Clinical trial results:
A multicenter, Investigator-Masked, Parallel Group, Randomized, Study of the Efficacy and Safety of Indomethacin 0.1% Eyedrops Compared with Ketorolac 0.5% Eyedrops in the Ocular Inflammation After Cataract Surgery.

Summary

EudraCT number	2007-004686-18
Trial protocol	FR PT DE
Global end of trial date	27 July 2009

Results information

Result version number	v1 (current)
This version publication date	27 August 2020
First version publication date	27 August 2020

Trial information

Trial identification

Sponsor protocol code	539

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Bausch & Lomb Incorporated
Sponsor organisation address	1400 North Goodman Street, Rochester, United States,
Public contact	Manager Clinical Science, Bausch&Lomb Dr Gerhard Mann chem.-Fabrik GmbH, Raphaele.SiouMermet@bausch.com
Scientific contact	Manager Clinical Science, Bausch&Lomb Dr Gerhard Mann chem.-Fabrik GmbH, Raphaele.SiouMermet@bausch.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 July 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 July 2009
Global end of trial reached?	Yes
Global end of trial date	27 July 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To show that indomethacin 0.1% eye drops are at least as effective as ketorolac 0.5% eye drops in the prevention of ocular inflammation (aqueous flare) following cataract surgery measured by laser Flare Meter 24 hours and 1 week after surgery.

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with Good Clinical Practices (GCPs), ICH guidelines (CPMP/ICH/135/95), applicable local regulations, and the Declaration of Helsinki (2004).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 July 2008
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	Poland: 20
Country: Number of subjects enrolled	Portugal: 9
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 67
Worldwide total number of subjects	123
EEA total number of subjects	123

Notes:

Subjects enrolled per age group

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

From 65 to 84 years	93
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Approximately 120 subjects (120 eyes), of either gender, 18 years of age or older, who planned to undergo cataract surgery by phacoemulsification were to be enrolled in this study. Potential subjects who met the eligibility requirements were to be scheduled for six study visits over a period of approximately 90 days.

Period 1

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

Blinding implementation details:

Subjects masked to treatment name

Arms

Are arms mutually exclusive?	Yes
Arm title	Indomethacin

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Indomethacin ophthalmic solution 0.1%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:

Subjects were to be instructed to instill one drop QID for three weeks, starting 24 hours prior to surgery.

Arm title	Ketorolac

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Ketorolac 0.5% ophthalmic solution
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ocular use

Dosage and administration details:

Subjects were to be instructed to instill one drop QID for three weeks, starting 24 hours prior to surgery.

Number of subjects in period 1	Indomethacin	Ketorolac
Started	59	64
Completed	55	57
Not completed	4	7
Consent withdrawn by subject	2	-
Adverse event, non-fatal	-	1
Other	-	2
Peroperative complication	-	1
Lost to follow-up	1	2
Protocol deviation	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Treatment

Reporting group description: -

Reporting group values	Treatment	Total	
Number of subjects	123	123	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	28	28	
From 65-84 years	93	93	
85 years and over	2	2	
Gender categorical Units: Subjects			
Female	69	69	
Male	54	54	

End points

End points reporting groups	
Reporting group title	Indomethacin
Reporting group description: -	
Reporting group title	Ketorolac
Reporting group description: -	

Primary: Aqueous Flare by LFM measurement at Day 1

End point title	Aqueous Flare by LFM measurement at Day 1
End point description:	
End point type	Primary
End point timeframe:	
Day 1	

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	43	43		
Units: ph/ms				
arithmetic mean (standard deviation)	18.50 (± 9.67)	16.25 (± 8.71)		

Statistical analyses

Statistical analysis title	Non-inferiority at Day 1
Comparison groups	Indomethacin v Ketorolac
Number of subjects included in analysis	86
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Mean difference (final values)
Point estimate	1.56
Confidence interval	
level	95 %
sides	1-sided
upper limit	5.5

Notes:

[1] - Non-inferiority of Indomethacin treatment was demonstrated if the upper limit of the 95% CI for the mean difference was less then than the upper limit of the non-inferiority margin (15).

Primary: Aqueous Flare by LFM measurement at Day 7

End point title	Aqueous Flare by LFM measurement at Day 7
End point description:	

End point type	Primary
End point timeframe:	
7 days	

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	42	41		
Units: ph/ms				
arithmetic mean (standard deviation)	11.88 (± 7.23)	15.01 (± 9.58)		

Statistical analyses

Statistical analysis title	Non-inferiority at 7 days
Comparison groups	Indomethacin v Ketorolac
Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Mean difference (final values)
Point estimate	-4.38
Confidence interval	
level	95 %
sides	1-sided
upper limit	-0.94

Notes:

[2] - Non-inferiority of Indomethacin treatment was demonstrated if the upper limit of the 95% CI for the mean difference was less than the upper limit of the non-inferiority margin (8).

Secondary: Aqueous Flare by LFM measurement at Day 30

End point title	Aqueous Flare by LFM measurement at Day 30
End point description:	

End point type	Secondary
End point timeframe:	
30 days	

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	59		
Units: ph/ms				
arithmetic mean (standard deviation)	9.20 (± 7.60)	8.94 (± 8.27)		

Statistical analyses

No statistical analyses for this end point

Secondary: Aqueous Flare by LFM measurement at Day 90

End point title	Aqueous Flare by LFM measurement at Day 90

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: ph/ms				
arithmetic mean (standard deviation)	7.70 (± 6.85)	8.12 (± 7.61)		

Statistical analyses

No statistical analyses for this end point

Secondary: Central retinal thickness at Day 30

End point title	Central retinal thickness at Day 30

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: um				
arithmetic mean (standard deviation)	221.6 (± 34.1)	232.1 (± 55.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Central retinal thickness at Day 90

End point title	Central retinal thickness at Day 90

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	55	57		
Units: um				
arithmetic mean (standard deviation)	227.9 (± 39.5)	227.5 (± 37.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Anterior Chamber Cells, > 50 cells

End point title	Slit Lamp Examination: Anterior Chamber Cells, > 50 cells

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Anterior Chamber Flare, Intense

End point title	Slit Lamp Examination: Anterior Chamber Flare, Intense

End point description:

End point type	Secondary

End point timeframe:
90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Conjunctival hyperaemia, Severe

End point title	Slit Lamp Examination: Conjunctival hyperaemia, Severe

End point description:

End point type	Secondary

End point timeframe:
90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Slit Lamp Examination: Perikeratic Circle, Severe

End point title	Slit Lamp Examination: Perikeratic Circle, Severe

End point description:

End point type	Secondary

End point timeframe:
90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Post Surgical Pain at Day 0

End point title	Post Surgical Pain at Day 0

End point description:

End point type	Secondary

End point timeframe:

Day 0

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects				
Absent	40	34		
Mild	16	25		
Moderate	3	2		
Severe	0	0		
Unbearable	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Post Surgical Pain at Day 1

End point title	Post Surgical Pain at Day 1

End point description:

End point type	Secondary

End point timeframe:

Day 1

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects				
Absent	42	46		
Mild	14	14		
Moderate	2	1		
Severe	1	0		
Unbearable	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Macula: Number of subjects with deterioration at Day 30

End point title	Fundoscopy, Macula: Number of subjects with deterioration at Day 30

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Retina: Number of subjects with deterioration at Day 30

End point title	Fundoscopy, Retina: Number of subjects with deterioration at Day 30

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Macula: Number of subjects with deterioration at Day 90

End point title	Fundoscopy, Macula: Number of subjects with deterioration at Day 90

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Fundoscopy, Retina: Number of subjects with deterioration at Day 90

End point title	Fundoscopy, Retina: Number of subjects with deterioration at Day 90

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of subjects using concomitant medications to treat inflammation related to cataract surgery

End point title	Proportion of subjects using concomitant medications to treat inflammation related to cataract surgery

End point description:

End point type	Secondary

End point timeframe:

90 days

End point values	Indomethacin	Ketorolac		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	61		
Units: Subjects	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
3 weeks	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	NA

Reporting groups	
Reporting group title	Indomethacin
Reporting group description: -	
Reporting group title	Ketorolac
Reporting group description: -	

Serious adverse events	Indomethacin	Ketorolac	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 59 (1.69%)	2 / 62 (3.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
IOL Subluxation			
subjects affected / exposed	0 / 59 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 59 (1.69%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cauda equina syndrome			
subjects affected / exposed	1 / 59 (1.69%)	0 / 62 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	0 / 59 (0.00%)	1 / 62 (1.61%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Indomethacin	Ketorolac	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 59 (5.08%)	3 / 62 (4.84%)	
Eye disorders			
Corneal oedema			
subjects affected / exposed	3 / 59 (5.08%)	3 / 62 (4.84%)	
occurrences (all)	3	3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2007	For the purpose of subject safety, an exclusion criterion was added to ensure that women met pregnancy prevention criteria immediately prior to and during the study.
15 July 2008	• To meet enrollment within specified timelines, the number of sites was increased from initially six to 11, the expectation that each site was to enroll an estimated 20 subjects was removed and the requirement that no more than 30% of the subjects could enroll at a single site was removed. As Germany is the country in the European Union that has the highest number of centres using the LFM this country was added to increase the number of sites, by addition of 5 sites. • Identified that the study was considered Phase III in Germany and Phase IV in France, Poland, and Portugal. Updated the protocol to note that the test article was commercially available in most of the countries where the study took place. • Tobramycin was added as a permitted therapy because gentamicin (an allowed therapy according to the original protocol) was not routinely used at some investigational sites. Gentamicin and tobramycin belong to the same class of antibiotics (aminoglycosides) and have similar characteristics. • Added that the Kowa FM 500, Kowa FC 1000, and Kowa FM 600 could be used for the flare measurements, because there is a high correlation of flare counts between the Kowa C 500 and Kowa C 1000 and the technical characteristics of the Kowa FM 500 and Kowa FM 600 are similar.
06 November 2008	• Changed the contact for reporting SAEs to be the Clinical Study Manager, who would then forward the information to Global Safety & Vigilance. • The Investigators were originally instructed to exclude subjects that had participated in a clinical study within 30 days before inclusion, but this was later added into the protocol as an exclusion criterion for further clarification. • As general anesthesia does not modify aqueous flare values, the inclusion criteria were changed to allow it as part of the cataract surgery. • Revised the exclusion criterion to exclude subjects who had diabetic retinopathy, as diabetes without retinopathy does not always increase blood-aqueous barrier permeability, and this was already covered in the inclusion criterion where preoperative flare values were to be ≤15 ph/ms. • Added Acetazolamide, Pilocarpin, and Intracameral anaesthesia to the disallowed medications list, as these modify flare values after their administration. • Removed the method of measuring bottle weights to assess treatment compliance since the amount of missing drops is not directly correlated to the number of drops used and would not offer a reliable representation of treatment compliance. • The Kowa FM 2000 was added to list of devices that could be used to gather flare measurements after the supplier confirmed the technical characteristics were similar to the Kowa FM 500, Kowa FC 1000, and Kowa FM 600.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported