Clinical trial results:
A Randomized, Multicenter, Double-Masked, Parallel-Group Study Comparing the Safety and Efficacy of BOL-303259-X 0.024% (Latanoprostene Bunod) Ophthalmic Solution With Timolol Maleate Ophthalmic Solution 0.5% in Subjects With Open-Angle Glaucoma or Ocular Hypertension

Summary

EudraCT number	2013-000553-45
Trial protocol	GB DE IT
Global end of trial date	26 November 2014

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	770

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01749930
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bausch & Lomb Incorporated
Sponsor organisation address	400 Somerset Corporate Blvd., Bridgewater, United States, 08807
Public contact	Director, Medical Affairs, Bausch & Lomb Incorporated, 011 585 7323284, Heleen.DeCory@bausch.com
Scientific contact	Director, Medical Affairs, Bausch & Lomb Incorporated, 011 585 7323284, Heleen.DeCory@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	26 November 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 November 2014
Global end of trial reached?	Yes
Global end of trial date	26 November 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to demonstrate that the mean intraocular pressure (IOP) reduction after 3 months (90 days) of treatment with latanoprostene bunod (LBN) ophthalmic solution 0.024% once daily (QD) is non-inferior to timolol maleate 0.5% twice daily (BID).

Protection of trial subjects:

This study was conducted in compliance with the study protocol and in accordance with Good Clinical Practices (GCPs), as described in the International Conference on Harmonisation (ICH) Harmonized Tripartite Guidelines for GCP, the US Code of Federal Regulations dealing with clinical studies (21 CFR Parts 11, 50, 54, 56, and 312), the ethical principles in the Declaration of Helsinki, and applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 January 2013
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	Germany: 6
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	United States: 407
Worldwide total number of subjects	420
EEA total number of subjects	13

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)	195
From 65 to 84 years	220
85 years and over	5

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants receiving an IOP-lowering medication before study start underwent a washout period. Participants were randomized in a 2:1 ratio on Day 0 to receive LBN ophthalmic solution 0.024% QD and vehicle QD or timolol maleate 0.5% BID. After Month 3 visit assessments, participants from both arms received LBN ophthalmic solution 0.024% QD only.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BOL-303259-X

Arm description:

BOL-303259-X ophthalmic solution QD (evening [PM]) and vehicle QD (morning [AM]) administered for 3 months (Visit 6) into the study eye(s). BOL-303259-X: BOL-303259-X will be administered QD in the evening and its vehicle administered QD in the morning.
BOL-303259-X: All participants will receive a topical ocular BOL-303259-X QD in the evening from 3 months (Visit 6) through 6 months (Visit7).

Arm type	Experimental
Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

BOL-303259-X was administered as per the dose and schedule specified in the respective arms.

Arm title	Timolol

Arm description:

Timolol maleate ophthalmic solution, 0.5%, administered BID for 3 months (Visit 6) into study eye(s).
Timolol: Timolol will be administered BID once in the morning and once in the evening.
BOL-303259-X: All participants will receive a topical ocular BOL-303259-X QD in the evening from 3 months (Visit 6) through 6 months (Visit7).

Arm type	Active comparator
Investigational medicinal product name	Timolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ear/eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol was administered as per the dose and schedule specified in the respective arms.

Number of subjects in period 1	BOL-303259-X	Timolol
Started	283	137
Completed	253	125
Not completed	30	12
Adverse event, serious fatal	1	-
Randomized in error	1	-
Physician decision	1	-
Consent withdrawn by subject	5	2
Adverse event, non-fatal	5	4
Failure to follow study procedures	6	3
Administrative issue	1	-
Lost to follow-up	1	1
Other Unspecified	9	2

Baseline characteristics

Reporting groups	
Reporting group title	BOL-303259-X
Reporting group description:	
BOL-303259-X ophthalmic solution QD (evening [PM]) and vehicle QD (morning [AM]) administered for 3 months (Visit 6) into the study eye(s). BOL-303259-X: BOL-303259-X will be administered QD in the evening and its vehicle administered QD in the morning. BOL-303259-X: All participants will receive a topical ocular BOL-303259-X QD in the evening from 3 months (Visit 6) through 6 months (Visit7).	
Reporting group title	Timolol
Reporting group description:	
Timolol maleate ophthalmic solution, 0.5%, administered BID for 3 months (Visit 6) into study eye(s). Timolol: Timolol will be administered BID once in the morning and once in the evening. BOL-303259-X: All participants will receive a topical ocular BOL-303259-X QD in the evening from 3 months (Visit 6) through 6 months (Visit7).	

Reporting group values	BOL-303259-X	Timolol	Total
Number of subjects	283	137	420
Age categorical Units: Subjects			
Adults (18-64 years)	131	64	195
65 years and over	152	73	225
Age Continuous Units: years			
arithmetic mean	64.8	64.1	
standard deviation	± 9.83	± 9.68	-
Sex: Female, Male Units: Subjects			
Female	165	79	244
Male	118	58	176
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	37	19	56
Not Hispanic or Latino	246	118	364
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	0	1
Asian	4	2	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	70	46	116
White	208	89	297
More than one race	0	0	0
Unknown or Not Reported	0	0	0

End points

End points reporting groups

Reporting group title	BOL-303259-X

Reporting group description:

BOL-303259-X ophthalmic solution QD (evening [PM]) and vehicle QD (morning [AM]) administered for 3 months (Visit 6) into the study eye(s). BOL-303259-X: BOL-303259-X will be administered QD in the evening and its vehicle administered QD in the morning.
BOL-303259-X: All participants will receive a topical ocular BOL-303259-X QD in the evening from 3 months (Visit 6) through 6 months (Visit7).

Reporting group title	Timolol

Reporting group description:

Timolol maleate ophthalmic solution, 0.5%, administered BID for 3 months (Visit 6) into study eye(s). Timolol: Timolol will be administered BID once in the morning and once in the evening.
BOL-303259-X: All participants will receive a topical ocular BOL-303259-X QD in the evening from 3 months (Visit 6) through 6 months (Visit7).

Subject analysis set title	BOL-303259-X Safety Extension Phase
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Following completion of the efficacy phase, all subjects were converted to BOL-303259-X ophthalmic solution QD (PM) and vehicle QD (AM) for an additional 3 months during the open label safety extension phase

Primary: Mean IOP

End point title	Mean IOP

End point description:

Mean intraocular pressure (IOP) in the study eye measured at the specified time points: 8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3). Population included the Intent-to-treat population with last observation carried forward (LOCF).

End point type	Primary

End point timeframe:

8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3)

End point values	BOL-303259-X	Timolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	135		
Units: mm Hg				
least squares mean (standard deviation)				
8 am week 2 (n=275, 134)	19.17 (± 3.748)	19.61 (± 3.092)		
12 pm week 2 (n=270, 134)	18.46 (± 3.327)	19.22 (± 3.241)		
4 pm week 2 (n=270, 134)	18.10 (± 3.135)	18.79 (± 3.022)		
8 am week 6 (n=277, 135)	18.67 (± 3.272)	19.59 (± 3.324)		
12 pm week 6 (n=271, 135)	18.02 (± 3.073)	18.86 (± 3.169)		
4 pm week 6 (n=271, 135)	17.87 (± 3.114)	18.85 (± 3.415)		
8 am Month 3 (n=277, 135)	18.68 (± 3.195)	19.56 (± 3.318)		

12 pm Month 3 (n=271, 135)	17.92 (± 3.119)	19.21 (± 3.129)		
4 pm Month 3 (n=271, 135)	17.72 (± 3.153)	19.06 (± 3.002)		

Statistical analyses

Statistical analysis title	BOL-303259-X versus Timolol
Comparison groups	BOL-303259-X v Timolol
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.216 [1]
Method	ANCOVA

Notes:

[1] - The ANCOVA results for the comparison of LS means of mean IOP between treatment groups demonstrated noninferiority of BOL-303259-X to timolol. Superiority of BOL-303259-X to timolol was demonstrated at 8 of 9 time points (exception at 8 am Week 2).

Secondary: IOP ≤18 mmHg

End point title	IOP ≤18 mmHg

End point description:

Number of participants with IOP ≤18 mmHg consistently at all 9 time points in the first 3 months. Population included the Intent-to-treat population with LOCF.

End point type	Secondary

End point timeframe:

8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3)

End point values	BOL-303259-X	Timolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	135		
Units: participants	49	15		

Statistical analyses

Statistical analysis title	BOL-303259-X versus Timolol
Comparison groups	BOL-303259-X v Timolol
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.084
Method	Chi-squared

Secondary: IOP Reduction ≥25%

End point title	IOP Reduction ≥25%

End point description:

Number of participants with IOP reduction ≥25% consistently at all 9 time points in the first 3 months. Population included the Intent-to-treat population with LOCF.

End point type	Secondary

End point timeframe:

8 AM, 12 PM, and 4 PM at Visit 4 (Week 2), Visit 5 (Week 6), and Visit 6 (Month 3)

End point values	BOL-303259-X	Timolol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	135		
Units: participants	86	25		

Statistical analyses

Statistical analysis title	BOL-303259-X versus Timolol
Comparison groups	BOL-303259-X v Timolol
Number of subjects included in analysis	412
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.007
Method	Chi-squared

Other pre-specified: Number of Participants with Ocular and Systemic Adverse Events (AEs)

End point title	Number of Participants with Ocular and Systemic Adverse Events (AEs)

End point description:

Following assessments through 3 months (Visit 6), all participants, irrespective of previous randomization, converted to a single open label safety arm receiving BOL-303259-X QD in the evening for an additional 3 months through Visit 7. Adverse events were recorded throughout the comparative efficacy phase and open label extension phase. Population included the Safety population. Of the subjects randomized, 415 instilled at least one dose of study medication and were included in the safety population.

End point type	Other pre-specified

End point timeframe:

6 months

End point values	BOL-303259-X	Timolol	BOL-303259-X Safety Extension Phase	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	279	136	384	
Units: participants				
>/= 1 nonocular AE	36	18	23	
>/= 1 ocular (Study eye) AE	66	18	53	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

6 months

Adverse event reporting additional description:

Safety Population (analyzed as treated). Of the subjects randomized, 415 instilled at least one dose of study medication and were included in the safety population. All subjects were converted to BOL-303259-X during the safety extension phase and AEs reported during that phase are presented below as a third arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	13.0

Reporting groups

Reporting group title	BOL-303259-X

Reporting group description:

BOL-303259-X ophthalmic solution QD (PM) and vehicle QD (AM) administered for 3 months into the study eye during the efficacy phase

Reporting group title	Timolol

Reporting group description:

Timolol maleate ophthalmic solution, 0.5%, administered BID for 3 months into study eye during the efficacy phase.

Reporting group title	BOL-303259-X Safety extension phase

Reporting group description:

Following completion of the efficacy phase, all subjects were converted to BL-303259-X ophthalmic solution QD (PM) and vehicle QD (AM) for an additional 3 months during the open label extension phase

Serious adverse events	BOL-303259-X	Timolol	BOL-303259-X Safety extension phase
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 279 (1.43%)	0 / 136 (0.00%)	2 / 384 (0.52%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Left shoulder subluxation of acromioclavicular joint			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scapular fracture			

subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	2 / 279 (0.72%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural hermorrhage			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Closed dislocation of finger			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Closed fracture of distal end of ulna			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Uncontrolled hypertension			
subjects affected / exposed	0 / 279 (0.00%)	0 / 136 (0.00%)	1 / 384 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chest pain			

subjects affected / exposed	0 / 279 (0.00%)	0 / 136 (0.00%)	1 / 384 (0.26%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Other convulsions			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subarachnoid hemorrhage			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelethiasis			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Pain in joint (shoulder)			
subjects affected / exposed	1 / 279 (0.36%)	0 / 136 (0.00%)	0 / 384 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	BOL-303259-X	Timolol	BOL-303259-X Safety extension phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 279 (17.92%)	12 / 136 (8.82%)	32 / 384 (8.33%)
Eye disorders			
Conjunctival hyperemia			
subjects affected / exposed	25 / 279 (8.96%)	1 / 136 (0.74%)	18 / 384 (4.69%)
occurrences (all)	32	1	19
Eye irritation			

subjects affected / exposed	20 / 279 (7.17%)	6 / 136 (4.41%)	8 / 384 (2.08%)
occurrences (all)	20	7	8
Eye pain			
subjects affected / exposed	16 / 279 (5.73%)	5 / 136 (3.68%)	6 / 384 (1.56%)
occurrences (all)	16	6	7

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2013	Changes to the protocol include the following: • Addition of the requirement of a visual field's assessment for eligibility. • Clarification that assessment of the primary objective after 3 months of treatment was to be done after 90 days of treatment. • Ophthalmoscopy was not required to be performed under dilation. • Revision of the order of performing pachymetry, slit-lamp examination, IOP measurements, installation of the fluorescein agent, and visual fields for ease of performing assessments at the study sites. • Specification of which assessments had to be performed by an ophthalmologist. • Revision of the instructions for AE and serious AE monitoring for increased participant safety. • Text revisions for clarification of the study endpoints, the timing of dosing, the inclusion and exclusion criteria, which participants were required to undergo a washout period, the washout period required for different IOP-lowering medications (including addition of a tabular summary), the study schedule for participants required to undergo a washout period, that study drug instillation was to be done by the participant, when participant dosing instructions should have been dispensed, that the pachymetry test was to be performed by a calibrated ultrasonic pachymeter, and the details of the statistical methods to be used.
02 August 2013	Changes to the protocol include the following: • Text revisions for clarification of exclusion criteria. • Updated the number of investigative sites participating in the study (increased from 30 to 45 sites). • Revision of the instructions for unmasking in the event of an emergency, to be in line with ICH guidance and standards of practice. • Clarification of period during which diclofenac was disallowed.
13 August 2013	Changes to the protocol include the following: •Clarification of an inclusion criterion.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported