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 – APOLLO Study

Summary

EudraCT number	2013-000552-18
Trial protocol	CZ BG
Global end of trial date	02 June 2015

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	769

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01749904
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bausch & Lomb Incorporated
Sponsor organisation address	1400 N Goodman St, Rochester, NY, United States, 14609
Public contact	Director of Clinical Operations, Bausch & Lomb Incorporated, 011 9733606389, tuyen.ong@bausch.com
Scientific contact	Director of Clinical Operations, Bausch & Lomb Incorporated, 011 9733606389, tuyen.ong@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	02 June 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 June 2015
Global end of trial reached?	Yes
Global end of trial date	02 June 2015
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 ophthalmic solution 0.024% once daily (QD) was noninferior 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 E6(R1), the US Code of Federal Regulations (CFR) dealing with clinical studies (Title 21 CFR Parts 11, 50, 54, 56, and 312); Title 42 US Code 282(j); the ethical principles in the Declaration of Helsinki; and applicable local regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 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	United States: 356
Country: Number of subjects enrolled	Bulgaria: 37
Country: Number of subjects enrolled	Czech Republic: 27
Worldwide total number of subjects	420
EEA total number of subjects	64

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)	207

From 65 to 84 years	207
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Of the 420 subjects randomized, 418 instilled at least one dose of study medication and were included in the safety population, whereas one subject did not have any post-baseline efficacy reading, hence 417 subjects were included in the Intent-to-treat population.

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	Investigator, Subject

Arms

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

Arm description:

BOL-303259-X ophthalmic solution QD (PM) and vehicle QD (AM) administered for 3 months (Visit 6) into the study eye(s). BOL-303259-X: Topical ocular BOL-303259-X will be administered QD in the evening and its vehicle administered QD in the morning for 3 months (Visit 6). BOL-303259-X: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months from Visit 6 through Visit 9 (1 year)

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

Dosage and administration details:

Topical ocular vehicle will be administered QD in the morning.

Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Topical ocular BOL-303259-X will be administered QD in the evening.

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 for 3 months (Visit 6). BOL-303259-X: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months from Visit 6 through Visit 9 (1 year)

Arm type	Active comparator
Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months.	
Investigational medicinal product name	Timolol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol will be administered BID once in the morning and once in the evening.

Number of subjects in period 1	BOL-303259-X	Timolol
Started	286	134
Completed	264	123
Not completed	22	11
Consent withdrawn by subject	6	1
Adverse event, non-fatal	4	5
Investigator decision	1	2
Failure to follow study procedures	2	2
Other than specified	7	1
Lost to follow-up	2	-

Baseline characteristics

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 (Visit 6) into the study eye(s). BOL-303259-X: Topical ocular BOL-303259-X will be administered QD in the evening and its vehicle administered QD in the morning for 3 months (Visit 6). BOL-303259-X: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months from Visit 6 through Visit 9 (1 year)	
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 for 3 months (Visit 6). BOL-303259-X: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months from Visit 6 through Visit 9 (1 year)	

Reporting group values	BOL-303259-X	Timolol	Total
Number of subjects	286	134	420
Age categorical Units: Subjects			
Age Continuous Units: years			
arithmetic mean	64.7	63.1	
standard deviation	± 10.33	± 11.21	-
Sex: Female, Male Units: Subjects			
Female	168	78	246
Male	118	56	174
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	30	13	43
Not Hispanic or Latino	256	121	377
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	64	24	88
White	219	109	328
More than one race	0	0	0
Unknown or Not Reported	2	0	2

End points

End points 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 (Visit 6) into the study eye(s). BOL-303259-X: Topical ocular BOL-303259-X will be administered QD in the evening and its vehicle administered QD in the morning for 3 months (Visit 6). BOL-303259-X: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months from Visit 6 through Visit 9 (1 year)

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 for 3 months (Visit 6). BOL-303259-X: All participants will receive topical ocular BOL-303259-X QD in the evening for an additional 9 months from Visit 6 through Visit 9 (1 year)

Subject analysis set title	BOL-303259-X Safety Extension Phase
Subject analysis set type	Full 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 9 months from Visit 6 through Visit 9 (1 year) during the open label safety extension phase

Primary: Mean IOP

End point title	Mean IOP

End point description:

Mean intraocular pressure (IOP) in 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). 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	284	133		
Units: millimetres of mercury (mmHg)				
least squares mean (standard deviation)				
8 am week 2 (n=282,133)	18.61 (± 3.544)	19.84 (± 3.651)		
12 pm week 2 (n=282,131)	18.00 (± 3.376)	19.37 (± 3.696)		
4 pm week 2 (n=281,131)	18.09 (± 3.293)	19.20 (± 3.359)		
8 am week 6 (n=283,133)	18.59 (± 3.525)	19.63 (± 3.243)		
12 pm week 6 (n=283,131)	17.84 (± 3.305)	19.09 (± 3.230)		
4 pm week 6 (n=284,131)	17.82 (± 3.513)	19.09 (± 3.492)		
8 am Month 3 (n=283,133)	18.71 (± 3.382)	19.73 (± 2.230)		

12 pm Month 3 (n=283,131)	17.88 (± 3.409)	19.15 (± 3.311)		
4 pm Month 3 (n=284,131)	17.83 (± 3.521)	19.15 (± 3.643)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Timolol v BOL-303259-X
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.01 [2]
Method	ANCOVA

Notes:

[1] - The 2 treatments were compared for each time point by visit. LS mean of each treatment group, the difference in the LS mean, and the 2-sided 95% CI for the difference were obtained. Non-inferiority could be claimed if the upper limit of the CIs <1.5 mmHg at all time points of each visit and <1.00 mmHg for at least 5 out of the 9 time points. If non-inferiority was determined, superiority at each time point could be claimed if the upper limit of the 95% CI<0 mmHg at all time points of each visit.

[2] - The ANCOVA results for the comparison of LS means of mean IOP between treatment groups demonstrated non-inferiority of BOL-303259-X to timolol and also superiority of BOL-303259-X to timolol.

Secondary: Response Rate - IOP ≤ 18 mmHg

End point title	Response Rate - IOP ≤ 18 mmHg

End point description:

Percentage of participants with IOP ≤18 mmHg consistently at all 9 time points in the first 3 months. 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	284	133		
Units: participants	65	15		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOL-303259-X v Timolol

Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.005
Method	Chi-squared

Secondary: Response Rate - IOP reduction ≥ 25%

End point title	Response Rate - IOP reduction ≥ 25%

End point description:

Percentage of participants with IOP reduction ≥ 25% consistently at all 9 time points in the first 3 months. Intent-to-treat 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	284	133		
Units: participants	99	26		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	BOL-303259-X v Timolol
Number of subjects included in analysis	417
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.001
Method	Chi-squared

Other pre-specified: Number of participants with Ocular and Systemic Adverse Events

End point title	Number of participants with Ocular and Systemic Adverse Events

End point description:

Following assessments through Visit 6 (Month 3), all participants, irrespective of previous randomization, converted to a single open label safety arm receiving BOL-303259-X QD in the evening. Adverse events were recorded throughout the comparative efficacy phase and open label extension phase. Safety population (analyzed as treated). Of the 420 subjects randomized, 418 instilled at least one dose of study medication and were included in the safety population; one subject randomized to BOL-303259-X received timolol in the efficacy phase and was therefore analyzed as part of the timolol treatment group. Hence, actual number of subjects analyzed for this endpoint are: 283 and 135 for BOL-303259-X and timolol arms, respectively.

End point type	Other pre-specified

End point timeframe:
12 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	284	134	385	
Units: participants				
>/= 1 nonocular AE	36	19	62	
>/= 1 ocular (Study eye) AE	38	16	46	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

1 year

Adverse event reporting additional description:

Safety Population (analyzed as treated). 1 subject randomized to BOL-303259-X received timolol and was therefore analyzed as part of the timolol group in the efficacy phase of the study. 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	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

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	BOL-303259-X Safety extension phase

Reporting group 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 9 months from Visit 6 through Visit 9 (1 year) during the open label safety extension phase

Serious adverse events	Timolol	BOL-303259-X	BOL-303259-X Safety extension phase
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 135 (1.48%)	3 / 283 (1.06%)	8 / 385 (2.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Recurrence of breast cancer			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Right upper lobe lung cancer			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Injury, poisoning and procedural complications			
Spider bite			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 135 (0.74%)	0 / 283 (0.00%)	0 / 385 (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			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Ankle fracture			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Fracture of right femoral neck			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	1 / 283 (0.35%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	1 / 283 (0.35%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leg disco-ordination			
alternative dictionary used: MedDRA 13.0			

subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Aphasia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
General disorders and administration site conditions			
Dislocation of intraocular lens			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Immune system disorders			
Allergic angioedema due to Motrin			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Food allergy			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Respiratory, thoracic and mediastinal disorders			
Chest pain			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	1 / 283 (0.35%)	0 / 385 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Hydronephrosis			

alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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
Musculoskeletal and connective tissue disorders			
Torn rotator cuff			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	1 / 135 (0.74%)	0 / 283 (0.00%)	0 / 385 (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
Infections and infestations			
Pneumonia			
alternative dictionary used: MedDRA 13.0			
subjects affected / exposed	0 / 135 (0.00%)	0 / 283 (0.00%)	1 / 385 (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

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

Non-serious adverse events	Timolol	BOL-303259-X	BOL-303259-X Safety extension phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 135 (2.22%)	11 / 283 (3.89%)	5 / 385 (1.30%)
Eye disorders			
Eye irritation			
subjects affected / exposed	3 / 135 (2.22%)	11 / 283 (3.89%)	5 / 385 (1.30%)
occurrences (all)	3	11	5

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 February 2013	Significant changes included following: • Revision of a criterion to exclude subjects who had previously received latanoprostene bunod ophthalmic solution from participating in study; • Addition of a exclusion to exclude subjects with a current cancer diagnosis from participating in study; • Correction to exclusion criterion regarding the Best-Corrected Visual Acuity (BCVA); • Addition of the requirement of a visual fields 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 fluorescein agent, and visual fields for ease of performing assessments at study sites; • Revision that conjunctival hyperemia assessment did not have to be performed as part of the slit-lamp examination and should precede the slit-lamp examination; • Specification of which assessments had to be performed by an ophthalmologist; • Clarification that specular microscopy was to be performed only on the study eye; • Correction that mydriatic drugs were not to be used until after all vision testing was completed; • Revision of the instructions for AE and serious adverse event monitoring for increased subject safety; • Text revisions for clarification of the study endpoints, the timing of dosing, the inclusion and exclusion criteria, which subjects 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 subjects required to undergo a washout period, that study drug instillation was to be done by the subject, when subject 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	Significant changes included 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 that specular microscopy was to be performed in the study eye and at select US sites only; • Clarification of period during which diclofenac was disallowed.
13 August 2013	Significant changes included the following: • Clarification of the inclusion criterion regarding acceptable contraceptive methods for female subjects and male subjects with partners of childbearing potential.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported