



Clinical trial results:

A Randomized, Multicenter, Single-Masked, Parallel-Group Dose Finding Study Comparing the Safety and Efficacy of BOL-303259-X (0.006%, 0.012%, 0.024% and 0.040%) to Latanoprost 0.005% in Subjects With Open Angle Glaucoma or Ocular Hypertension

Summary

EudraCT number	2010-022178-14
Trial protocol	PL CZ BG
Global end of trial date	20 December 2011

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	659
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01223378
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Dr. Gerhard Mann Chem.-Pharm. Fabrik GmbH/Bausch & Lomb
Sponsor organisation address	Brunsbütteler Damm 165-173, Berlin, Germany, 13581
Public contact	Study Manager, Dr. Gerhard Mann Chem.-Pharm. Fabrik GmbH/Bausch & Lomb, natasa.orlic-pleyer@bausch.com
Scientific contact	Study Manager, Dr. Gerhard Mann Chem.-Pharm. Fabrik GmbH/Bausch & Lomb, natasa.orlic-pleyer@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	20 December 2011
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2011
Global end of trial reached?	Yes
Global end of trial date	20 December 2011
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to determine the most effective drug concentration(s) of BOL-303259-X in the reduction of intraocular pressure (IOP) in order to support further clinical development of an appropriate dose with regard to efficacy, and ocular and systemic safety.

Protection of trial subjects:

This study was conducted in compliance with the protocol and in accordance with Good Clinical Practice (GCP), as described in the International Conference on Harmonisation (ICH) Guidelines for Good Clinical Practice (GCP) ICH E6 (R1), 21CFR Parts 11, 50, 54, 56, and 312, 42 USC 282(j), applicable local regulations, and the Declaration of Helsinki and its amendments.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	13 December 2010
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: 269
Country: Number of subjects enrolled	Bulgaria: 90
Country: Number of subjects enrolled	Poland: 35
Country: Number of subjects enrolled	Czech Republic: 19
Worldwide total number of subjects	413
EEA total number of subjects	144

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)	246
From 65 to 84 years	163
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

First subject enrolled on 13 Dec 2010, Last subject exited on 20 Dec 2011. This study was conducted at 23 clinical sites (US [15 sites], Bulgaria [3 sites], Poland [3 sites], and Czech Republic [2 sites]).

Pre-assignment

Screening details:

Subjects who were currently under treatment with an IOP-lowering medication at Visit 1 were required to discontinue the IOP medication during the washout period (minimum of 28 days) between Visit 1 and Visit 3.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BOL-303259-X 0.006%

Arm description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.006%, once daily (QD) 28 days

Arm type	Experimental
Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Topical use

Dosage and administration details:

ophthalmic solution, various concentrations, once daily (QD) 28 days

Arm title	BOL-303259-X 0.012%
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Arm description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.012%, once daily (QD) 28 days

Arm type	Experimental
Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Topical use

Dosage and administration details:

ophthalmic solution, various concentrations, once daily (QD) 28 days

Arm title	BOL-303259-X 0.024%
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Arm description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.024%, once daily (QD) 28 days

Arm type	Experimental
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Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Topical use

Dosage and administration details:

ophthalmic solution, various concentrations, once daily (QD) 28 days

Arm title	BOL-303259-X 0.040%
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Arm description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.040%, once daily (QD) 28 days

Arm type	Experimental
Investigational medicinal product name	BOL-303259-X
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Topical use

Dosage and administration details:

ophthalmic solution, various concentrations, once daily (QD) 28 days

Arm title	Latanoprost
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Arm description:

ophthalmic solution

Latanoprost: 0.005% ophthalmic solution, QD 28 days

Arm type	Active comparator
Investigational medicinal product name	Latanoprost
Investigational medicinal product code	
Other name	Xalatan
Pharmaceutical forms	Eye drops, solution
Routes of administration	Topical use

Dosage and administration details:

0.005% ophthalmic solution, QD 28 days

Notes:

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

Justification: Investigator was the one party that was blinded.

Number of subjects in period 1	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%
Started	82	85	83
Completed	76	81	80
Not completed	6	4	3
Failure to follow the required study procedures	1	1	1
Consent withdrawn by subject	1	-	-
Adverse event, non-fatal	3	1	1
Other than specified	1	1	1
Lost to follow-up	-	1	-

Number of subjects in period 1	BOL-303259-X 0.040%	Latanoprost
Started	81	82

Completed	80	79
Not completed	1	3
Failure to follow the required study procedures	-	-
Consent withdrawn by subject	1	1
Adverse event, non-fatal	-	1
Other than specified	-	1
Lost to follow-up	-	-

Baseline characteristics

Reporting groups

Reporting group title	BOL-303259-X 0.006%
Reporting group description:	
ophthalmic solution	
Experimental: BOL-303259-X: ophthalmic solution, 0.006%, once daily (QD) 28 days	
Reporting group title	BOL-303259-X 0.012%
Reporting group description:	
ophthalmic solution	
Experimental: BOL-303259-X: ophthalmic solution, 0.012%, once daily (QD) 28 days	
Reporting group title	BOL-303259-X 0.024%
Reporting group description:	
ophthalmic solution	
Experimental: BOL-303259-X: ophthalmic solution, 0.024%, once daily (QD) 28 days	
Reporting group title	BOL-303259-X 0.040%
Reporting group description:	
ophthalmic solution	
Experimental: BOL-303259-X: ophthalmic solution, 0.040%, once daily (QD) 28 days	
Reporting group title	Latanoprost
Reporting group description:	
ophthalmic solution	
Latanoprost: 0.005% ophthalmic solution, QD 28 days	

Reporting group values	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%
Number of subjects	82	85	83
Age Categorical			
Units: Subjects			

Age Continuous			
Units: years			
arithmetic mean	60.9	61.6	60.8
standard deviation	± 11.39	± 9.58	± 11.47
Gender Categorical			
Units: Subjects			
Female	56	46	57
Male	26	39	26
Ethnicity			
Units: Subjects			
Hispanic or Latino	5	2	8
Not Hispanic or Latino	77	83	75
Unknown or Not Reported	0	0	0
Race			
Units: Subjects			
American Indian or Alaska Native	0	1	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	21	23	21
White	61	61	62

More than one race	0	0	0
Unknown or Not Reported	0	0	0

Reporting group values	BOL-303259-X 0.040%	Latanoprost	Total
Number of subjects	81	82	413
Age Categorical Units: Subjects			

Age Continuous Units: years arithmetic mean standard deviation	60.3 ± 12.89	61.0 ± 11.92	-
Gender Categorical Units: Subjects			
Female	43	53	255
Male	38	29	158
Ethnicity Units: Subjects			
Hispanic or Latino	6	11	32
Not Hispanic or Latino	75	71	381
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	0	0	1
Asian	1	0	1
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	23	16	104
White	56	66	306
More than one race	0	0	0
Unknown or Not Reported	1	0	1

End points

End points reporting groups

Reporting group title	BOL-303259-X 0.006%
Reporting group description: ophthalmic solution Experimental: BOL-303259-X: ophthalmic solution, 0.006%, once daily (QD) 28 days	
Reporting group title	BOL-303259-X 0.012%
Reporting group description: ophthalmic solution Experimental: BOL-303259-X: ophthalmic solution, 0.012%, once daily (QD) 28 days	
Reporting group title	BOL-303259-X 0.024%
Reporting group description: ophthalmic solution Experimental: BOL-303259-X: ophthalmic solution, 0.024%, once daily (QD) 28 days	
Reporting group title	BOL-303259-X 0.040%
Reporting group description: ophthalmic solution Experimental: BOL-303259-X: ophthalmic solution, 0.040%, once daily (QD) 28 days	
Reporting group title	Latanoprost
Reporting group description: ophthalmic solution Latanoprost: 0.005% ophthalmic solution, QD 28 days	

Primary: Change in Mean Diurnal IOP at Visit 6 (Day 28)

End point title	Change in Mean Diurnal IOP at Visit 6 (Day 28)
End point description: Determine the most effective drug concentration(s) of BOL-303259-X in the reduction of intraocular pressure (IOP) and compared to latanoprost. Intent-to-treat population, observed data (study eye).	
End point type	Primary
End point timeframe: Baseline and Visit 6 (Day 28)	

End point values	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%	BOL-303259-X 0.040%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	81	83	83	80
Units: mm Hg				
arithmetic mean (standard deviation)	-7.829 ($\pm$ 2.823)	-8.295 ($\pm$ 2.864)	-8.952 ($\pm$ 3.337)	-8.894 ($\pm$ 2.666)

End point values	Latanoprost			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: mm Hg				

arithmetic mean (standard deviation)	-7.800 ($\pm$ 2.834)			
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Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Results obtained from an analysis of covariance model with treatment effect and baseline IOP.	
Comparison groups	Latanoprost v BOL-303259-X 0.006%
Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9125
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.048
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.817
upper limit	0.914

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Results obtained from an analysis of covariance model with treatment effect and baseline IOP.	
Comparison groups	BOL-303259-X 0.012% v Latanoprost
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2575
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	0.496
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.364
upper limit	1.357

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Results obtained from an analysis of covariance model with treatment effect and baseline IOP.	
Comparison groups	BOL-303259-X 0.024% v Latanoprost

Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0051
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.234
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.373
upper limit	2.095

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Results obtained from an analysis of covariance model with treatment effect and baseline IOP.	
Comparison groups	BOL-303259-X 0.040% v Latanoprost
Number of subjects included in analysis	160
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0089
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	1.161
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.292
upper limit	2.03

Secondary: Change in Mean Diurnal IOP at Visits 4, 5, and 7	
End point title	Change in Mean Diurnal IOP at Visits 4, 5, and 7
End point description:	
Determine the most effective drug concentration(s) of BOL-303259-X in the reduction of intraocular pressure (IOP) and compared to latanoprost. Intent-to-treat population, observed data (study eye).	
End point type	Secondary
End point timeframe:	
Baseline and Visit 4 (Day 7), Visit 5 (day 14), and Visit 7 (Day 29)	

End point values	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%	BOL-303259-X 0.040%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	81	80
Units: mm Hg				
arithmetic mean (standard deviation)				
Visit 4 (Day 7) (n=79,82,81,80,80)	-6.850 (± 2.768)	-7.707 (± 3.192)	-8.230 (± 3.286)	-8.456 (± 2.892)
Visit 5 (Day 14) (n=76,80,80,80,79)	-7.607 (± 2.204)	-7.934 (± 3.065)	-8.859 (± 3.300)	-8.606 (± 2.878)
Visit 7 (Day 29) (n=76,81,80,80,79)	-6.188 (± 2.782)	-6.202 (± 3.001)	-7.177 (± 3.615)	-6.846 (± 3.135)

End point values	Latanoprost			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: mm Hg				
arithmetic mean (standard deviation)				
Visit 4 (Day 7) (n=79,82,81,80,80)	-7.325 (± 2.699)			
Visit 5 (Day 14) (n=76,80,80,80,79)	-7.719 (± 3.035)			
Visit 7 (Day 29) (n=76,81,80,80,79)	-6.276 (± 2.941)			

Statistical analyses

No statistical analyses for this end point

Secondary: IOP ≤18mm Hg

End point title	IOP ≤18mm Hg
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End point description:

Determine the number of subjects with mean diurnal IOP ≤18 mm Hg with BOL-303259-X versus latanoprost ophthalmic solution. Intent-to-treat population, observed data (study eye).

End point type	Secondary
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End point timeframe:

Visit 4 (Day 7), Visit 5 (day 14), Visit 6 (Day 28) and Visit 7 (Day 29)

End point values	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%	BOL-303259-X 0.040%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	85	83	81
Units: participants				
Visit 4 (Day 7) (n=79,82,81,80,80)	30	37	47	46
Visit 5 (Day 14) (n=76,80,80,80,79)	34	42	52	45
Visit 6 (Day 28) (n=81,83,83,80,80)	41	44	57	51

Visit 7 (Day 29) (n=76,81,80,80,79)	25	24	37	25
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End point values	Latanoprost			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: participants				
Visit 4 (Day 7) (n=79,82,81,80,80)	29			
Visit 5 (Day 14) (n=76,80,80,80,79)	39			
Visit 6 (Day 28) (n=81,83,83,80,80)	38			
Visit 7 (Day 29) (n=76,81,80,80,79)	23			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IOP at Specified Time Points (8 AM, 12 PM, 4 PM) at Visit 6 (Day 28)

End point title	Change in IOP at Specified Time Points (8 AM, 12 PM, 4 PM) at Visit 6 (Day 28)
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End point description:

The change in the observed mean study eye IOP from baseline (Visit 3, Day 1) at specified time points (8 AM, 12 PM, 4 PM) at Visit 6 (Day 28). Intent to treat, data as observed (study eye).

End point type	Secondary
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End point timeframe:

Baseline and Visit 6 (Day 28)

End point values	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%	BOL-303259-X 0.040%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82	85	83	81
Units: mm Hg				
arithmetic mean (standard deviation)				
Change from Baseline (8 am) (n=81,83,83,80,80)	-8.42 (± 3.69)	-8.91 (± 3.24)	-9.46 (± 4.01)	-9.61 (± 2.95)
Change from Baseline (12 pm) (n=79,83,82,80,79)	-7.82 (± 3.34)	-8.33 (± 3.35)	-8.98 (± 3.50)	-8.60 (± 3.23)
Change from Baseline (4 pm) (n=79,83,82,80,79)	-7.23 (± 2.97)	-7.65 (± 3.37)	-8.59 (± 3.54)	-8.47 (± 3.28)

End point values	Latanoprost			
Subject group type	Reporting group			
Number of subjects analysed	82			
Units: mm Hg				

arithmetic mean (standard deviation)				
Change from Baseline (8 am) (n=81,83,83,80,80)	-8.76 (± 3.24)			
Change from Baseline (12 pm) (n=79,83,82,80,79)	-7.63 (± 3.55)			
Change from Baseline (4 pm) (n=79,83,82,80,79)	-6.99 (± 3.52)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change in IOP at Specified Time Points (8 AM, 12 PM, 4 PM) at Visits 4, 5, and 7 (Days 7, 14, and 29)

End point title	Change in IOP at Specified Time Points (8 AM, 12 PM, 4 PM) at Visits 4, 5, and 7 (Days 7, 14, and 29)
End point description:	The change in the observed mean study eye IOP from baseline (Visit 3, Day 1) at specified time points (points 8 AM, 12 PM, and 4 PM) at Visits 4, 5, and 7 (Days 7, 14, and 29). Intent-to-treat, observed data (study eye).
End point type	Secondary
End point timeframe:	Baseline and Visits 4, 5 and 7 (Days 7, 14, and 29)

End point values	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%	BOL-303259-X 0.040%
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	79	82	81	80
Units: mm Hg				
arithmetic mean (standard deviation)				
Visit 4 (Day 7) (8 am) (n=79,82,81,80,80)	-7.203 (± 3.634)	-8.396 (± 3.935)	-8.667 (± 3.827)	-8.869 (± 3.384)
Visit 4 (Day 7) (12 pm) (n=79,82,81,80,80)	-6.665 (± 3.046)	-7.823 (± 3.409)	-8.247 (± 3.643)	-8.219 (± 3.338)
Visit 4 (Day 7) (4 pm) (n=79,82,81,80,80)	-6.684 (± 3.246)	-6.902 (± 3.371)	-7.778 (± 3.479)	-8.281 (± 3.172)
Visit 5 (Day 14) (8 am) (n=76,80,80,80,79)	-8.270 (± 3.399)	-8.538 (± 3.518)	-9.569 (± 3.597)	-9.006 (± 3.031)
Visit 5 (Day 14) (12 pm) (n=76,80,80,80,79)	-7.500 (± 2.653)	-8.381 (± 3.518)	-8.700 (± 3.579)	-8.556 (± 3.529)
Visit 5 (Day 14) (4 pm) (n=76,79,79,80,79)	-7.053 (± 2.519)	-6.905 (± 3.354)	-8.310 (± 3.667)	-8.256 (± 3.410)
Visit 7 (Day 29) (8 am) (n=76,81,80,80,79)	-6.969 (± 3.245)	-6.796 (± 3.379)	-7.675 (± 4.198)	-7.406 (± 3.26)
Visit 7 (Day 29) (12 pm) (n=76,81,80,79,79)	-6.039 (± 3.591)	-6.235 (± 3.626)	-7.119 (± 3.791)	-6.791 (± 3.246)
Visit 7 (Day 29) (4 pm) (n=73,81,80,78,79)	-5.575 (± 3.464)	-5.574 (± 3.615)	-6.738 (± 3.769)	-6.090 (± 4.142)

End point values	Latanoprost			
Subject group type	Reporting group			
Number of subjects analysed	80			
Units: mm Hg				
arithmetic mean (standard deviation)				
Visit 4 (Day 7) (8 am) (n=79,82,81,80,80)	-8.125 (± 2.826)			
Visit 4 (Day 7) (12 pm) (n=79,82,81,80,80)	-7.200 (± 3.386)			
Visit 4 (Day 7) (4 pm) (n=79,82,81,80,80)	-6.650 (± 3.312)			
Visit 5 (Day 14) (8 am) (n=76,80,80,80,79)	-8.519 (± 3.444)			
Visit 5 (Day 14) (12 pm) (n=76,80,80,80,79)	-7.519 (± 3.437)			
Visit 5 (Day 14) (4 pm) (n=76,79,79,80,79)	-7.120 (± 3.744)			
Visit 7 (Day 29) (8 am) (n=76,81,80,80,79)	-7.006 (± 3.131)			
Visit 7 (Day 29) (12 pm) (n=76,81,80,79,79)	-6.108 (± 3.228)			
Visit 7 (Day 29) (4 pm) (n=73,81,80,78,79)	-5.715 (± 3.514)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

The period of observation for collection of AEs extended from the time the subject gave informed consent until the last study visit (Visit 7).

Adverse event reporting additional description:

The safety population included one less subject in the BOL-303259-X 0.012% group than the ITT population. Hence the safety population included 412 subjects in total whereas the ITT population included 413 in total.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	13.0
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Reporting groups

Reporting group title	BOL-303259-X 0.006%
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Reporting group description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.006%, once daily (QD) 28 days

Reporting group title	BOL-303259-X 0.012%
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Reporting group description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.012%, once daily (QD) 28 days

Reporting group title	BOL-303259-X 0.024%
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Reporting group description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.024%, once daily (QD) 28 days

Reporting group title	BOL-303259-X 0.040%
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Reporting group description:

ophthalmic solution

Experimental: BOL-303259-X: ophthalmic solution, 0.040%, once daily (QD) 28 days

Reporting group title	Latanoprost
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Reporting group description:

ophthalmic solution

Latanoprost: 0.005% ophthalmic solution, QD 28 days

Serious adverse events	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 82 (1.22%)	0 / 84 (0.00%)	0 / 83 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
Cardiac disorders			
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Gastrointestinal disorders			
Gastric Ulcer Hemorrhage	Additional description: Bleeding gastric ulcer		
subjects affected / exposed	0 / 82 (0.00%)	0 / 84 (0.00%)	0 / 83 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric Ulcer	Additional description: Gastric Ulcer		
subjects affected / exposed	1 / 82 (1.22%)	0 / 84 (0.00%)	0 / 83 (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
Gastrointestinal Hemorrhage	Additional description: Gastrointestinal bleed		
subjects affected / exposed	1 / 82 (1.22%)	0 / 84 (0.00%)	0 / 83 (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

Serious adverse events	BOL-303259-X 0.040%	Latanoprost	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 81 (0.00%)	2 / 82 (2.44%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Cardiac disorders			
Acute myocardial infarction	Additional description: Acute myocardial infarction		
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastric Ulcer Hemorrhage	Additional description: Bleeding gastric ulcer		
subjects affected / exposed	0 / 81 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer	Additional description: Gastric Ulcer		
subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal Hemorrhage	Additional description: Gastrointestinal bleed		

subjects affected / exposed	0 / 81 (0.00%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BOL-303259-X 0.006%	BOL-303259-X 0.012%	BOL-303259-X 0.024%
Total subjects affected by non-serious adverse events			
subjects affected / exposed	14 / 82 (17.07%)	17 / 84 (20.24%)	13 / 83 (15.66%)
Eye disorders			
Ocular hyperemia			
subjects affected / exposed	1 / 82 (1.22%)	5 / 84 (5.95%)	2 / 83 (2.41%)
occurrences (all)	1	5	2
Instillation site pain			
subjects affected / exposed	12 / 82 (14.63%)	14 / 84 (16.67%)	10 / 83 (12.05%)
occurrences (all)	12	15	10
Eye irritation			
subjects affected / exposed	1 / 82 (1.22%)	2 / 84 (2.38%)	3 / 83 (3.61%)
occurrences (all)	1	3	3

Non-serious adverse events	BOL-303259-X 0.040%	Latanoprost	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	20 / 81 (24.69%)	9 / 82 (10.98%)	
Eye disorders			
Ocular hyperemia			
subjects affected / exposed	4 / 81 (4.94%)	7 / 82 (8.54%)	
occurrences (all)	5	7	
Instillation site pain			
subjects affected / exposed	14 / 81 (17.28%)	5 / 82 (6.10%)	
occurrences (all)	15	6	
Eye irritation			
subjects affected / exposed	5 / 81 (6.17%)	0 / 82 (0.00%)	
occurrences (all)	5	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 October 2010	Changes made included the following: - Replaced "BOL-303259-X latanoprostinod" with "BOL 303259-X" since latanoprostinod is not an approved compound name. - Increased the baseline IOP in the study to be able to examine the difference between the IOP-lowering effects of the test article and the active comparator, one of the 3 mean/median IOP measurements in Inclusion Criterion was changed from ≥ 24 mmHg to ≥ 26 mmHg at a minimum of 1 time point in the same eye. - Removed the requirement for a negative urine pregnancy test at Visit 2 (mid-washout). - Maximum central corneal thickness was changed from 600 μm to 590 μm in Exclusion Criterion to avoid enrolling subjects with artificially highly IOPs. - Added "in either eye" to Exclusion Criterion to clarify that subjects with very narrow angles, angle closure, congenital and secondary glaucoma, and history of angle closure in either eye should be excluded. - Removed instructions to perform vital signs in the standing position. - Added a description of the subject dosing instruction sheet. - Removed events occurring from any failure of expected pharmacological action from the definition of an AE since this was a dose-ranging study and collection of lack of effect events was not required. - Revised serious adverse event definition to be more consistent with global standards. - Clarified that non-serious AEs that were ongoing upon early discontinuation from the study were also to be followed by the Investigator for 30 days after the subject exited the study. - Removed the Snellen fraction information from the Recording and Scoring of logMar values.
27 October 2010	Changes included the following: - Revised Inclusion Criterion to indicate that the mean/median IOP should be ≤ 32 mmHg in both eyes at all 3 measurement time points. - Revised Exclusion Criterion to include subjects expected to require treatment with systemic corticosteroids. - Removed performing vital signs in the standing position from the Study Procedures section in the synopsis and removed the description of collecting measurements for different body postures in Appendix. - Clarified that the unmasked designee should weight study medication bottles and dispense study medication. - Clarified that the comparator's screw cap was turquoise in the US and white in the EU. - Clarified that if the 2 systolic or diastolic values of the blood pressure measurements differed by more than 5 mmHg, a third reading should be taken and the average of the 3 measurements should be averaged.

18 May 2011	Changes included the following: - Revised the maximum allowed central corneal thickness in either eye in Exclusion Criterion from 590 µm to 600 µm. After review of the screening failures in this study, a high rate of exclusion was shown to be due to the maximum allowed central corneal thickness of 590 µm. Although increased central corneal thickness may give artificially high IOP measurements, an increase of 10 µm is very small and its effect on IOP would be minimal and negligible. This change did not affect the study objective or endpoints and did not create any safety concerns for the study subjects. - Removed calcium channel blockers as an example medication that could interact with the safety or efficacy of a NO-donating compound from the disallowed therapies in Exclusion Criterion. The subject population in this study was older by nature, tended to have hypertension, and had higher rates of calcium channel blocker use, as shown during screening. Since the interim safety data review of the enrolled and dosed subjects showed no safety signals for hypotension, the study drug was not expected to potentiate the hypotensive effect of calcium channel blockers used in the study. To be able to have a good representation of the general glaucoma population, calcium channel blocker use was permitted in the study.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported