Clinical trial results:
The Efficacy and Safety of Bimatoprost SR in Patients With Open-angle Glaucoma or Ocular Hypertension

Summary

EudraCT number	2014-003186-24
Trial protocol	GB CZ DE IT NL PT
Global end of trial date	22 July 2020

Results information

Result version number	v1 (current)
This version publication date	16 May 2021
First version publication date	16 May 2021

Trial information

Trial identification

Sponsor protocol code	192024-092

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02250651
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Marlow International, The Parkway, Marlow, Buckinghamshire, United Kingdom, SL7 1YL
Public contact	EU Regulatory Dept, Allergan Limited, +44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	EU Regulatory Dept, Allergan Limited, +44 1628 494444, ml-eu_reg_affairs@allergan.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	22 July 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	22 July 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate the efficacy and safety of bimatoprost sustained-release (SR) in patients with open-angle glaucoma or ocular hypertension. The study includes a 12-month treatment period with an 8-month extended follow-up.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 December 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	8 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Czechia: 14
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Italy: 10
Country: Number of subjects enrolled	United Kingdom: 18
Country: Number of subjects enrolled	Argentina: 45
Country: Number of subjects enrolled	Canada: 23
Country: Number of subjects enrolled	Colombia: 28
Country: Number of subjects enrolled	Egypt: 7
Country: Number of subjects enrolled	Malaysia: 5
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Korea, Republic of: 11
Country: Number of subjects enrolled	Turkey: 6
Country: Number of subjects enrolled	United States: 324
Worldwide total number of subjects	528
EEA total number of subjects	33

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)	285
From 65 to 84 years	237
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 528 participants (176 participants in each treatment group) were enrolled.

Period 1

Period 1 title	Treatment Period 1 (Day 1 to Week 15)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Bimatoprost SR 15 µg

Arm description:

Study Eye: bimatoprost sustained-release (SR) 15 micrograms (µg) administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Experimental
Investigational medicinal product name	Bimatoprost SR
Investigational medicinal product code	
Other name	AGN-192024
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Ophthalmic use

Dosage and administration details:

Bimatoprost SR administered in the study eye on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol Vehicle (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol vehicle administered once in the morning and once in the evening for up to 20 months.

Arm title	Bimatoprost SR 10 µg

Arm description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Experimental
Investigational medicinal product name	Bimatoprost SR
Investigational medicinal product code	
Other name	AGN-192024
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Ophthalmic use

Dosage and administration details:

Bimatoprost SR administered in the study eye on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol Vehicle (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol vehicle administered once in the morning and once in the evening for up to 20 months.

Arm title	Timolol 0.5%: Comparator

Arm description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Active comparator
Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details: Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.	
Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Number of subjects in period 1	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Started	176	176	176
Received Sham or Bimatoprost SR	176	175	173
Completed	172	170	165
Not completed	4	6	11
Adverse Event	-	2	2
Protocol Deviation	1	-	-
Randomized but not Treated	-	1	3
Personal Reasons	2	3	5
Lost to follow-up	1	-	-
Reason not Specified	-	-	1

Period 2

Period 2 title	Treatment Period 2 (Week 16 to Week 31)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bimatoprost SR 15 µg

Arm description:

Study Eye: bimatoprost sustained-release (SR) 15 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Experimental

Investigational medicinal product name	Bimatoprost SR
Investigational medicinal product code	
Other name	AGN-192024
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Ophthalmic use

Dosage and administration details:

Bimatoprost SR administered in the study eye on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol Vehicle (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol vehicle administered once in the morning and once in the evening for up to 20 months.

Arm title	Bimatoprost SR 10 µg

Arm description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Experimental
Investigational medicinal product name	Bimatoprost SR
Investigational medicinal product code	
Other name	AGN-192024
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Ophthalmic use

Dosage and administration details:

Bimatoprost SR administered in the study eye on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedured on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol Vehicle (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol vehicle administered once in the morning and once in the evening for up to 20 months.

Arm title	Timolol 0.5%: Comparator

Arm description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Active comparator
Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] administered on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Number of subjects in period 2[1]	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Started	165	168	165
Completed	159	162	160
Not completed	6	6	5
Adverse Event	4	1	-
Protocol Deviation	-	1	-
Personal Reasons	2	3	2
Lost to follow-up	-	-	3
Reason not Specified	-	1	-

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 9 participants who completed Treatment Period 1, did not receive treatment in Treatment

Period 2.

Period 3

Period 3 title	Treatment Period 3 (Week 32 to Week 52)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Bimatoprost SR 15 µg

Arm description:

Study Eye: bimatoprost sustained-release (SR) 15 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Experimental
Investigational medicinal product name	Bimatoprost SR
Investigational medicinal product code	
Other name	AGN-192024
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Ophthalmic use

Dosage and administration details:

Bimatoprost SR administered in the study eye on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol Vehicle (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol vehicle administered once in the morning and once in the evening for up to 20 months.

Arm title	Bimatoprost SR 10 µg

Arm description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20

months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Experimental
Investigational medicinal product name	Bimatoprost SR
Investigational medicinal product code	
Other name	AGN-192024
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Ophthalmic use

Dosage and administration details:

Bimatoprost SR administered in the study eye on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Investigational medicinal product name	Timolol Vehicle (placebo)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol vehicle administered once in the morning and once in the evening for up to 20 months.

Arm title	Timolol 0.5%: Comparator

Arm description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Arm type	Active comparator
Investigational medicinal product name	Timolol 0.5%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Eye drops, solution
Routes of administration	Ophthalmic use

Dosage and administration details:

Timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Investigational medicinal product name	Sham: Applicator Without Needle
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Ophthalmic use

Dosage and administration details:

Sham [without needle] procedure on Day 1, Week 16, and Week 32.

Number of subjects in period 3[2]	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Started	147	156	159
Completed	138	152	154
Not completed	9	4	5
Adverse Event	4	1	1
Personal Reasons	2	-	2
Lost to follow-up	1	2	1
Reason not Specified	2	1	1

Notes:

[2] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: 19 participants who completed Treatment Period 2, did not receive treatment in Treatment Period 3.

Baseline characteristics

Reporting groups	
Reporting group title	Bimatoprost SR 15 µg
Reporting group description:	
Study Eye: bimatoprost sustained-release (SR) 15 micrograms (µg) administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.	
Reporting group title	Bimatoprost SR 10 µg
Reporting group description:	
Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.	
Reporting group title	Timolol 0.5%: Comparator
Reporting group description:	
Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.	

Reporting group values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Number of subjects	176	176	176
Age categorical Units: Subjects			
Adults (18-64 years)	87	94	104
From 65-84 years	88	80	69
85 years and over	1	2	3
Age Continuous Units: years			
arithmetic mean	63.8	62.5	61.4
standard deviation	± 10.7	± 12.7	± 12.4
Sex: Female, Male Units: participants			
Female	91	90	88
Male	85	86	88
Race/Ethnicity, Customized Units: Subjects			
White	116	115	104
Black or African and American	19	20	36
Asian	6	11	13
Hispanic	27	22	21
Other	8	8	2
Intraocular Pressure (IOP) at Hour 0			
IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye.			
Units: millimeters of mercury (mmHg)			
arithmetic mean	24.39	24.28	24.46
full range (min-max)	18.0 to 32.0	15.0 to 32.0	17.0 to 32.0

Intraocular Pressure (IOP) at Hour 2			
IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. The number of participants in the subject analysis set is the number of participants with data available for IOP at Baseline.			
Units: mmHg			
arithmetic mean	23.41		23.43
full range (min-max)	18.5 to 32.0		15.0 to 32.0

Reporting group values	Total		
Number of subjects	528		
Age categorical Units: Subjects			
Adults (18-64 years)	285		
From 65-84 years	237		
85 years and over	6		
Age Continuous Units: years arithmetic mean standard deviation	--		
Sex: Female, Male Units: participants			
Female	269		
Male	259		
Race/Ethnicity, Customized Units: Subjects			
White	335		
Black or African and American	75		
Asian	30		
Hispanic	70		
Other	18		
Intraocular Pressure (IOP) at Hour 0			
IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye.			
Units: millimeters of mercury (mmHg) arithmetic mean full range (min-max)	--		
Intraocular Pressure (IOP) at Hour 2			
IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. The number of participants in the subject analysis set is the number of participants with data available for IOP at Baseline.			
Units: mmHg arithmetic mean full range (min-max)	--		

Subject analysis sets	
Subject analysis set title	Bimatoprost SR 10 µg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group values	Bimatoprost SR 10 µg		
Number of subjects	175		
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years arithmetic mean standard deviation	 ±		
Sex: Female, Male Units: participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Black or African and American Asian Hispanic Other			
Intraocular Pressure (IOP) at Hour 0			
IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye.			
Units: millimeters of mercury (mmHg) arithmetic mean full range (min-max)			
Intraocular Pressure (IOP) at Hour 2			
IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. The number of participants in the subject analysis set is the number of participants with data available for IOP at Baseline.			
Units: mmHg arithmetic mean full range (min-max)	 23.24 14.0 to 32.0		

End points

End points reporting groups

Reporting group title	Bimatoprost SR 15 µg

Reporting group description:

Study Eye: bimatoprost sustained-release (SR) 15 micrograms (µg) administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Bimatoprost SR 10 µg

Reporting group description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Timolol 0.5%: Comparator

Reporting group description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Bimatoprost SR 15 µg

Reporting group description:

Study Eye: bimatoprost sustained-release (SR) 15 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Bimatoprost SR 10 µg

Reporting group description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Timolol 0.5%: Comparator

Reporting group description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Bimatoprost SR 15 µg

Reporting group description:

Study Eye: bimatoprost sustained-release (SR) 15 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Bimatoprost SR 10 µg

Reporting group description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Timolol 0.5%: Comparator

Reporting group description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Subject analysis set title	Bimatoprost SR 10 µg
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Primary: Change from Baseline in Intraocular Pressure (IOP) in the Study Eye to Week 12 (Hours 0 and 2)

End point title	Change from Baseline in Intraocular Pressure (IOP) in the Study Eye to Week 12 (Hours 0 and 2)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. A mixed-effects model with repeated measures (MMRM) was used for analyses. A negative change from baseline indicates an improvement and a positive change from baseline indicates a worsening. Participants from the Intent-to-treat (ITT) Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Baseline (Up to 3 days prior to Day 1 at Hours 0 and 2) to Week 12 (Hours 0 and 2)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	176	176	
Units: millimeters of mercury (mmHg)				
least squares mean (standard error)				
Change from Baseline:Week 12,Hour 0(n=168,169,165)	-6.47 (± 0.30)	-6.18 (± 0.30)	-6.11 (± 0.30)	
Change from Baseline:Week 12,Hour 2(n=168,168,165)	-7.16 (± 0.28)	-6.72 (± 0.28)	-6.36 (± 0.29)	

Statistical analyses

Statistical analysis title	Change from Baseline at Week 12, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Week 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.3738
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.36

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.41

Notes:

[1] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 12, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Week 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.8514
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.73
Variability estimate	Standard error of the mean
Dispersion value	0.41

Notes:

[2] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 12, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Week 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.0401
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[3] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 12, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Week 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.3621
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[4] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Primary: IOP in the Study Eye at Week 2 (Hour 0)

End point title	IOP in the Study Eye at Week 2 (Hour 0)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Week 2 (Hour 0)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	172	172	
Units: mmHg				
least squares mean (standard error)	16.74 (± 0.27)	16.92 (± 0.27)	17.50 (± 0.27)	

Statistical analyses

Statistical analysis title	Week 2, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	= 0.0382
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[5] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Week 2, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.1133
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.58

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[6] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Primary: IOP in the Study Eye at Week 2 (Hour 2)

End point title	IOP in the Study Eye at Week 2 (Hour 2)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Week 2 (Hour 2)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	170	172	172	
Units: mmHg				
least squares mean (standard error)	16.09 (± 0.25)	16.48 (± 0.25)	17.19 (± 0.25)	

Statistical analyses

Statistical analysis title	Week 2, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	342
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.0013
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	-0.43
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[7] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Week 2, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	344
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	= 0.0364
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[8] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Primary: IOP in the Study Eye at Week 6 (Hour 0)

End point title	IOP in the Study Eye at Week 6 (Hour 0)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Week 6 (Hour 0)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	171	168	
Units: mmHg				
least squares mean (standard error)	17.05 (± 0.28)	16.93 (± 0.28)	17.51 (± 0.29)	

Statistical analyses

Statistical analysis title	Week 6, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	= 0.2304
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[9] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Week 6, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	= 0.1272
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[10] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Primary: IOP in the Study Eye at Week 6 (Hour 2)

End point title	IOP in the Study Eye at Week 6 (Hour 2)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Week 6 (Hour 2)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	172	171	168	
Units: mmHg				
least squares mean (standard error)	16.13 (± 0.26)	16.53 (± 0.26)	17.18 (± 0.27)	

Statistical analyses

Statistical analysis title	Week 6, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	340
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.0038
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[11] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Week 6, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	339
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	= 0.0741
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[12] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Primary: IOP in the Study Eye at Week 12 (Hour 0)

End point title	IOP in the Study Eye at Week 12 (Hour 0)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Week 12 (Hour 0)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168	169	166	
Units: mmHg				
least squares mean (standard error)	17.39 (± 0.30)	17.68 (± 0.30)	17.75 (± 0.30)	

Statistical analyses

Statistical analysis title	Week 12, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.3738
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.44
Variability estimate	Standard error of the mean
Dispersion value	0.41

Notes:

[13] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Week 12, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	= 0.8514
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.88
upper limit	0.73
Variability estimate	Standard error of the mean
Dispersion value	0.41

Notes:

[14] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Primary: IOP in the Study Eye at Week 12 (Hour 2)

End point title	IOP in the Study Eye at Week 12 (Hour 2)

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Primary

End point timeframe:

Week 12 (Hour 2)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	168	169	166	
Units: mmHg				
least squares mean (standard error)	16.70 (± 0.28)	17.15 (± 0.28)	17.50 (± 0.29)	

Statistical analyses

Statistical analysis title	Week 12, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	= 0.0401
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.8

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.57
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[15] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Week 12, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared non-inferior to timolol 0.5% if the upper limit of the 95% CI was ≤ 1.5 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	335
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	= 0.3621
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.36
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	0.41
Variability estimate	Standard error of the mean
Dispersion value	0.39

Notes:

[16] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Secondary: Change from Baseline in IOP in the Study Eye

End point title	Change from Baseline in IOP in the Study Eye

End point description:

IOP is a measurement of the fluid pressure inside the study eye. Measurements were taken at Hours 0 and 2. The study eye is defined as the eye that meets the entry criteria. If both eyes meet the entry criteria, the eye with the higher IOP at Baseline Hour 0 will be selected as the study eye. If both eyes had the same IOP at Hour 0, then the right eye was designated as the study eye. MMRM was used for analyses. A negative change from baseline indicates an improvement and a positive change from baseline indicates a worsening. Participants from the ITT Population, all randomized participants, with data available for analyses.

End point type	Secondary

End point timeframe:

Baseline (Up to 3 days prior to Day 1 at Hours 0 and 2) to Weeks 2 and 6 (Hours 0 and 2)

End point values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	176	176	176	
Units: mmHg				
least squares mean (standard error)				
Change from Baseline:Week 2,Hour 0(n=170,172,171)	-7.12 (± 0.27)	-6.94 (± 0.27)	-6.36 (± 0.27)	
Change from Baseline:Week 2,Hour 2(n=170,171,171)	-7.77 (± 0.25)	-7.38 (± 0.25)	-6.67 (± 0.25)	
Change from Baseline:Week 6,Hour 0(n=172,171,167)	-6.81 (± 0.28)	-6.93 (± 0.28)	-6.35 (± 0.29)	
Change from Baseline:Week 6,Hour 2(n=172,170,167)	-7.74 (± 0.26)	-7.33 (± 0.26)	-6.69 (± 0.27)	

Statistical analyses

Statistical analysis title	Change from Baseline at Week 2, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0382
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.48
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[17] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 2, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.1133
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.58
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.29
upper limit	0.14
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[18] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 2, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0013
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	-0.43
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[19] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 2, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0364
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.38
upper limit	-0.05
Variability estimate	Standard error of the mean
Dispersion value	0.34

Notes:

[20] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 6, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.2304
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.22
upper limit	0.29
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[21] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 6, Hour 0

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.1272
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.59
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.34
upper limit	0.17
Variability estimate	Standard error of the mean
Dispersion value	0.38

Notes:

[22] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 6, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 15 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 15 µg v Timolol 0.5%: Comparator
Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.0038
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.76
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[23] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Statistical analysis title	Change from Baseline at Week 6, Hour 2

Statistical analysis description:

The hypothesis was that bimatoprost SR 10 µg was to be declared superior to timolol 0.5% if the upper limit of the 95% CI was <0 mmHg for all scheduled timepoints (Hours 0 and 2 at Weeks 2, 6, 12).

Comparison groups	Bimatoprost SR 10 µg v Timolol 0.5%: Comparator

Number of subjects included in analysis	352
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.0741
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.36
upper limit	0.06
Variability estimate	Standard error of the mean
Dispersion value	0.36

Notes:

[24] - MMRM analyses was used with response variable:IOP time-matched change from baseline;Fixed factors: Treatment,timepoint,treatment-by-timepoint interaction and baseline IOP stratification; Covariate:Time-matched baseline IOP and timepoint by time-matched baseline IOP interaction. Unstructured covariance matrix was used.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First dose of study drug to last visit (Up to approximately 20 months)

Adverse event reporting additional description:

All-cause Mortality: Intent-to-treat Population included all randomized participants. Serious and Other Adverse Events: Safety Population included all participants who received at least 1 administration of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Bimatoprost SR 15 µg

Reporting group description:

Study Eye: bimatoprost SR 15 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Bimatoprost SR 10 µg

Reporting group description:

Study Eye: bimatoprost SR 10 µg administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol vehicle administered once in the morning and once in the evening for up to 20 months. Non-Study Eye: sham administration on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Reporting group title	Timolol 0.5%: Comparator

Reporting group description:

Study Eye and Non-Study Eye: sham administered on Day 1 (Period 1), Week 16 (Period 2), and Week 32 (Period 3); timolol 0.5% administered once in the morning and once in the evening for up to 20 months.

Serious adverse events	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 176 (20.45%)	22 / 175 (12.57%)	16 / 173 (9.25%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer	Additional description: Number of participants at risk are male participants as this adverse event is specific to males.		
subjects affected / exposed[1]	2 / 85 (2.35%)	0 / 85 (0.00%)	1 / 88 (1.14%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	2 / 176 (1.14%)	0 / 175 (0.00%)	0 / 173 (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
Breast cancer stage I			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Hepatocellular carcinoma			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Metastases to liver			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Natural killer-cell leukaemia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Waldenstrom’s macroglobulinaemia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Bronchial carcinoma			

subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Oropharyngeal squamous cell carcinoma			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Follicular thyroid cancer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestine carcinoma metastatic			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Penetrating aortic ulcer			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
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			

Death			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Immune system disorders			
Sarcoidosis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Reproductive system and breast disorders			
Menorrhagia	Additional description: Number of participants at risk are female participants as this adverse event is specific to females.		
subjects affected / exposed[2]	0 / 91 (0.00%)	1 / 90 (1.11%)	0 / 85 (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
Ovarian cyst	Additional description: Number of participants at risk are female participants as this adverse event is specific to females.		
subjects affected / exposed[3]	0 / 91 (0.00%)	1 / 90 (1.11%)	0 / 85 (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
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Depression			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Schizophrenia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
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			
Jaw fracture			

subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Procedural pain			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Fall			
subjects affected / exposed	0 / 176 (0.00%)	2 / 175 (1.14%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femur fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Humerus fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Rib fracture			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Subdural haematoma			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Product administered at inappropriate site			

subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 176 (0.57%)	1 / 175 (0.57%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Angina unstable			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Coronary artery disease			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Cardiac failure congestive			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
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			
Encephalopathy			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Transient ischaemic attack			
subjects affected / exposed	0 / 176 (0.00%)	2 / 175 (1.14%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
VIth nerve paralysis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Eye disorders			
Corneal endothelial cell loss			
subjects affected / exposed	9 / 176 (5.11%)	3 / 175 (1.71%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	8 / 9	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal oedema			
subjects affected / exposed	2 / 176 (1.14%)	1 / 175 (0.57%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	2 / 2	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Macular oedema			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pterygium			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Corneal decompensation			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Visual impairment			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Retinal tear			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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 disorders			
Ascites			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pancreatitis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Rectal haemorrhage			

subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Vomiting			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	2 / 173 (1.16%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticular perforation			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholangitis acute			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Cholelithiasis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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			
End stage renal disease			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Acute kidney injury			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Micturition urgency			

subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
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			
Osteoarthritis			
subjects affected / exposed	3 / 176 (1.70%)	0 / 175 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Haemarthrosis			
subjects affected / exposed	0 / 176 (0.00%)	1 / 175 (0.57%)	0 / 173 (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
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 176 (1.70%)	0 / 175 (0.00%)	0 / 173 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Appendicitis			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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

Hypoglycaemia			
subjects affected / exposed	1 / 176 (0.57%)	0 / 175 (0.00%)	0 / 173 (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
Hyperkalaemia			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic acidosis			
subjects affected / exposed	0 / 176 (0.00%)	0 / 175 (0.00%)	1 / 173 (0.58%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number of participants at risk are female participants as this adverse event is specific to males.
[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number of participants at risk are female participants as this adverse event is specific to females.
[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed to this adverse event. These numbers are expected to be equal.
Justification: Number of participants at risk are female participants as this adverse event is specific to females.

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

Non-serious adverse events	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Total subjects affected by non-serious adverse events			
subjects affected / exposed	133 / 176 (75.57%)	103 / 175 (58.86%)	72 / 173 (41.62%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	17 / 176 (9.66%)	15 / 175 (8.57%)	6 / 173 (3.47%)
occurrences (all)	27	26	10
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	73 / 176 (41.48%)	48 / 175 (27.43%)	20 / 173 (11.56%)
occurrences (all)	218	148	51
Corneal endothelial cell loss			
subjects affected / exposed	38 / 176 (21.59%)	12 / 175 (6.86%)	2 / 173 (1.16%)
occurrences (all)	39	13	3
Eye pain			

subjects affected / exposed	23 / 176 (13.07%)	12 / 175 (6.86%)	9 / 173 (5.20%)
occurrences (all)	40	20	12
Corneal oedema			
subjects affected / exposed	21 / 176 (11.93%)	5 / 175 (2.86%)	0 / 173 (0.00%)
occurrences (all)	24	5	0
Foreign body sensation in eyes			
subjects affected / exposed	19 / 176 (10.80%)	18 / 175 (10.29%)	2 / 173 (1.16%)
occurrences (all)	35	27	4
Dry eye			
subjects affected / exposed	18 / 176 (10.23%)	12 / 175 (6.86%)	7 / 173 (4.05%)
occurrences (all)	35	25	20
Conjunctival haemorrhage			
subjects affected / exposed	17 / 176 (9.66%)	20 / 175 (11.43%)	15 / 173 (8.67%)
occurrences (all)	24	32	24
Punctate keratitis			
subjects affected / exposed	14 / 176 (7.95%)	10 / 175 (5.71%)	8 / 173 (4.62%)
occurrences (all)	27	23	15
Photophobia			
subjects affected / exposed	13 / 176 (7.39%)	13 / 175 (7.43%)	0 / 173 (0.00%)
occurrences (all)	32	20	0
Eye irritation			
subjects affected / exposed	13 / 176 (7.39%)	10 / 175 (5.71%)	9 / 173 (5.20%)
occurrences (all)	27	17	15
Anterior chamber cell			
subjects affected / exposed	13 / 176 (7.39%)	6 / 175 (3.43%)	1 / 173 (0.58%)
occurrences (all)	14	9	1
Ocular discomfort			
subjects affected / exposed	11 / 176 (6.25%)	3 / 175 (1.71%)	1 / 173 (0.58%)
occurrences (all)	14	4	4
Iritis			
subjects affected / exposed	9 / 176 (5.11%)	8 / 175 (4.57%)	0 / 173 (0.00%)
occurrences (all)	11	12	0
Lacrimation increased			
subjects affected / exposed	9 / 176 (5.11%)	7 / 175 (4.00%)	1 / 173 (0.58%)
occurrences (all)	16	12	2
Vision blurred			

subjects affected / exposed	7 / 176 (3.98%)	11 / 175 (6.29%)	1 / 173 (0.58%)
occurrences (all)	11	16	2
Blepharitis			
subjects affected / exposed	7 / 176 (3.98%)	10 / 175 (5.71%)	5 / 173 (2.89%)
occurrences (all)	12	18	10
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 176 (5.11%)	12 / 175 (6.86%)	14 / 173 (8.09%)
occurrences (all)	16	15	15

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 August 2015	The following changes were implemented with Amendment 1: Modified inclusion and exclusion criteria. Updated the number of study sites. Clarified when required surgical procedures could be performed in the fellow eye. Defined a time frame and requirements for the validity of the qualifications provided by the reading center. Clarified that participants were to be followed for 12 months after their last Bimatoprost SR (or Sham) administration for safety purposes.
16 March 2017	The following changes were implemented with Amendment 2: Revised the screening requirement for angle eligibility confirmation in the study eye to the use of a standard clinical evaluation, modified/clarified the inclusion/exclusion criteria, clarified the statistical analyses, and changed additional procedures for participants with sickle cell disease from required to optional.
05 June 2018	The following changes were implemented with Amendment 3: The number of participants to enroll was reduced from 600 (200 per group) to approximately 510 (170 per group) as the observed premature discontinuation rate and IOP variability was lower than initially assumed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported