EU Clinical Trials Register

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

Summary

EudraCT number	2014-003037-26
Trial protocol	HU AT BE ES DK FR
Global end of trial date	19 July 2019

Results information

Result version number	v1 (current)
This version publication date	14 June 2020
First version publication date	14 June 2020

Trial information

Trial identification

Sponsor protocol code	192024-091

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02247804
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@allergan.com
Scientific contact	Therapeutic Area, Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@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	19 July 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial is to evaluate the efficacy and safety of bimatoprost SR in participants 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	Australia: 21
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 3
Country: Number of subjects enrolled	Brazil: 23
Country: Number of subjects enrolled	Denmark: 8
Country: Number of subjects enrolled	Hong Kong: 3
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Israel: 14
Country: Number of subjects enrolled	Peru: 7
Country: Number of subjects enrolled	Philippines: 26
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Spain: 11
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 421
Worldwide total number of subjects	594
EEA total number of subjects	76

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)	310
From 65 to 84 years	278
85 years and over	6

Subject disposition

Recruitment

Recruitment details: -	

Pre-assignment

Screening details:

A total of 594 participants (198 participants in each treatment group) were enrolled.

Period 1

Period 1 title	Treatment Period 1
Is this the baseline period?	Yes
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 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	Intravitreal implant in applicator
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 administered 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	Intravitreal implant in applicator
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 administered 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 administered 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	198	198	198
Received (Sham or Bimatoprost SR)	193	197	197
Completed	176	194	190
Not completed	22	4	8
Adverse event, non-fatal	9	2	-
Protocol Deviation	-	-	1
Randomized but not Treated	5	1	1
Personal Reasons	7	1	2
Lost to follow-up	1	-	2
Lack of efficacy	-	-	2

Period 2

Period 2 title	Treatment Period 2
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 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	Intravitreal implant in applicator
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 administered 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	Intravitreal implant in applicator
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 administered 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 administered on Day 1, Week 16, and Week 32.

Number of subjects in period 2[1]	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Started	172	191	187
Completed	164	186	179
Not completed	8	5	8
Adverse event, non-fatal	6	3	3
Personal Reasons	2	1	1
Lost to follow-up	-	1	1
Reason not Specified	-	-	2
Lack of efficacy	-	-	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: 10 participants who completed Treatment Period 1, did not receive treatment in Treatment Period 2.

Period 3

Period 3 title	Treatment Period 3
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 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	Intravitreal implant in applicator
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 administered 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	Intravitreal implant in applicator
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 administered 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 administered 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	158	183	177
Completed	147	173	167
Not completed	11	10	10
Adverse event, non-fatal	4	3	3
Personal Reasons	4	3	2
Lost to follow-up	1	2	2
Reason not Specified	2	1	3
Lack of efficacy	-	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: 11 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 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 values	Bimatoprost SR 15 µg	Bimatoprost SR 10 µg	Timolol 0.5%: Comparator
Number of subjects	198	198	198
Age categorical			
Units: Subjects			
Adults (18-64 years)	100	103	107
From 65-84 years	95	93	90
85 years and over	3	2	1
Age Continuous			
Units: years			
arithmetic mean	62.5	62.6	62.5
standard deviation	± 13.0	± 11.5	± 11.0
Sex: Female, Male			
Units: participants			
Female	96	86	106
Male	102	112	92
Race/Ethnicity, Customized			
Units: Subjects			
White	122	123	130
Black or African American	30	31	21
Asian	12	17	16
Hispanic	27	23	25
Other	6	4	5
Not Reported	1	0	1
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: mm Hg			
arithmetic mean	24.76	24.64	24.63
full range (min-max)	18.0 to 32.0	21.5 to 32.0	16.0 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.			
Units: mm Hg			
arithmetic mean	23.56	23.29	23.19
full range (min-max)	19.0 to 32.0	19.0 to 32.0	16.0 to 32.0

Reporting group values	Total		
Number of subjects	594		
Age categorical			
Units: Subjects			
Adults (18-64 years)	310		
From 65-84 years	278		
85 years and over	6		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: participants			
Female	288		
Male	306		
Race/Ethnicity, Customized			
Units: Subjects			
White	375		
Black or African American	82		
Asian	45		
Hispanic	75		
Other	15		
Not Reported	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: mm Hg			
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.			
Units: mm Hg			
arithmetic mean			
full range (min-max)	-		

End points

End points 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.

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.

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.

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

End point title	Change from Baseline in IOP in the Study Eye at 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. Intent-to-treat (ITT) population was defined as all randomised participants. Number analysed is the number of participants with evaluable data at the given time point.

End point type	Primary

End point timeframe:

Baseline (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	198	198	198	
Units: millimeters of mercury (mm Hg)				
least squares mean (standard error)				
Change from Baseline:Hour 0,Week 12(n=185,192,191)	-6.46 (± 0.29)	-6.38 (± 0.28)	-6.05 (± 0.28)	
Change from Baseline:Hour 2,Week 12(n=183,192,191)	-7.18 (± 0.26)	-6.69 (± 0.25)	-6.48 (± 0.25)	

Statistical analyses

Statistical analysis title	Change from Baseline Week 12, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.295
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.36
Variability estimate	Standard error of the mean
Dispersion value	0.39

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 Week 12, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
P-value	= 0.3904
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.39

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 Week 12, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
P-value	= 0.0464
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.35

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 Week 12, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
P-value	= 0.5383
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.35

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. ITT population was defined as all randomised participants. Overall number of participants analysed is the number of 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	191	196	196	
Units: mm Hg				
least squares mean (standard error)	16.82 (± 0.25)	17.02 (± 0.25)	17.83 (± 0.25)	

Statistical analyses

Statistical analysis title	Week 2, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	387
Analysis specification	Pre-specified
Analysis type	non-inferiority[5]
P-value	= 0.0033
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.34

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 null 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 mm Hg 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	392
Analysis specification	Pre-specified
Analysis type	non-inferiority[6]
P-value	= 0.0187
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.34

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. ITT population was defined as all randomised participants. Overall number of participants analysed is the number of 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	191	196	196	
Units: mm Hg				
least squares mean (standard error)	16.48 (± 0.22)	16.42 (± 0.22)	17.33 (± 0.22)	

Statistical analyses

Statistical analysis title	Week 2, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	387
Analysis specification	Pre-specified
Analysis type	non-inferiority[7]
P-value	= 0.0057
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.31

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 null 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 mm Hg 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	392
Analysis specification	Pre-specified
Analysis type	non-inferiority[8]
P-value	= 0.0031
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.31
Variability estimate	Standard error of the mean
Dispersion value	0.3

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. ITT population was defined as all randomised participants. Overall number of participants analysed is the number of 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	188	197	194	
Units: mm Hg				
least squares mean (standard error)	17.08 (± 0.24)	16.88 (± 0.23)	17.71 (± 0.24)	

Statistical analyses

Statistical analysis title	Week 6, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	382
Analysis specification	Pre-specified
Analysis type	non-inferiority[9]
P-value	= 0.0547
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.32

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 null 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 mm Hg 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	391
Analysis specification	Pre-specified
Analysis type	non-inferiority[10]
P-value	= 0.0107
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.32

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. ITT population was defined as all randomised participants. Overall number of participants analysed is the number of 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	187	197	193	
Units: mm Hg				
least squares mean (standard error)	16.62 (± 0.23)	16.51 (± 0.22)	17.16 (± 0.23)	

Statistical analyses

Statistical analysis title	Week 6, Hour 2
Statistical analysis description:	

The null 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 mm Hg 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	380
Analysis specification	Pre-specified
Analysis type	non-inferiority[11]
P-value	= 0.086
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.32

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 null 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 mm Hg 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	390
Analysis specification	Pre-specified
Analysis type	non-inferiority[12]
P-value	= 0.0362
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.31

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. ITT population was defined as all randomised participants. Overall number of participants analysed is the number of 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	185	192	191	
Units: mm Hg				
least squares mean (standard error)	17.53 (± 0.29)	17.61 (± 0.28)	17.94 (± 0.28)	

Statistical analyses

Statistical analysis title	Week 12, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	376
Analysis specification	Pre-specified
Analysis type	non-inferiority[13]
P-value	= 0.295
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.17
upper limit	0.36
Variability estimate	Standard error of the mean
Dispersion value	0.39

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 null 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 mm Hg 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	383
Analysis specification	Pre-specified
Analysis type	non-inferiority[14]
P-value	= 0.3904
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.09
upper limit	0.43
Variability estimate	Standard error of the mean
Dispersion value	0.39

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. ITT population was defined as all randomised participants. Overall number of participants analysed is the number of participants with data available for analyses.

End point type	Primary

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	183	192	191	
Units: mm Hg				
least squares mean (standard error)	16.81 (± 0.26)	17.30 (± 0.25)	17.51 (± 0.25)	

Statistical analyses

Statistical analysis title	Week 12, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	374
Analysis specification	Pre-specified
Analysis type	non-inferiority[15]
P-value	= 0.0464
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.4
upper limit	-0.01
Variability estimate	Standard error of the mean
Dispersion value	0.35

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 null 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 mm Hg 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	383
Analysis specification	Pre-specified
Analysis type	non-inferiority[16]
P-value	= 0.5383
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.9
upper limit	0.47
Variability estimate	Standard error of the mean
Dispersion value	0.35

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. ITT population was defined as all randomized participants. Number analysed is the number of participants with evaluable data at the given timepoint.

End point type	Secondary

End point timeframe:

Baseline (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	198	198	198	
Units: mm Hg				
least squares mean (standard error)				
Change from Baseline:Hour 0,Week 2(n=191,196,196)	-7.17 (± 0.25)	-6.97 (± 0.25)	-6.17 (± 0.25)	
Change from Baseline:Hour 2,Week 2(n=191,196,196)	-7.52 (± 0.22)	-7.57 (± 0.22)	-6.67 (± 0.22)	
Change from Baseline:Hour 0,Week 6(n=188,197,194)	-6.91 (± 0.24)	-7.11 (± 0.23)	-6.29 (± 0.24)	
Change from Baseline:Hour 2,Week 6(n=187,197,193)	-7.37 (± 0.23)	-7.48 (± 0.22)	-6.83 (± 0.23)	

Statistical analyses

Statistical analysis title	Change from Baseline Week 2, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[17]
P-value	= 0.0033
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-1.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.68
upper limit	-0.34
Variability estimate	Standard error of the mean
Dispersion value	0.34

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 Week 2, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[18]
P-value	= 0.0187
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.47
upper limit	-0.13
Variability estimate	Standard error of the mean
Dispersion value	0.34

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 Week 2, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[19]
P-value	= 0.0057
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.45
upper limit	-0.25
Variability estimate	Standard error of the mean
Dispersion value	0.31

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 Week 2, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.0031
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.5
upper limit	-0.31
Variability estimate	Standard error of the mean
Dispersion value	0.3

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 Week 6, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[21]
P-value	= 0.0547
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.26
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.32

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 Week 6, Hour 0

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[22]
P-value	= 0.0107
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.46
upper limit	-0.19
Variability estimate	Standard error of the mean
Dispersion value	0.32

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 Week 6, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.086
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.54
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.16
upper limit	0.08
Variability estimate	Standard error of the mean
Dispersion value	0.32

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 Week 6, Hour 2

Statistical analysis description:

The null 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 mm Hg 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	396
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.0362
Method	MMRM
Parameter estimate	Least-squares Mean Difference
Point estimate	-0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.27
upper limit	-0.04
Variability estimate	Standard error of the mean
Dispersion value	0.31

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:

Safety population included all participants who received at least 1 dose 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	31 / 193 (16.06%)	25 / 197 (12.69%)	18 / 197 (9.14%)
number of deaths (all causes)	2	1	1
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intraductal proliferative breast lesion			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Basal cell carcinoma			

subjects affected / exposed	0 / 193 (0.00%)	2 / 197 (1.02%)	0 / 197 (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
Prostate cancer			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant melanoma			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Parathyroid tumour benign			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Hepatocellular carcinoma			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive breast carcinoma			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer recurrent			

subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
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

Internal haemorrhage

subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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

Varicose vein

subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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

Deep vein thrombosis

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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

Hypotension

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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

Peripheral arterial occlusive disease

subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
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

Chest pain

subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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

Respiratory, thoracic and mediastinal disorders

Pulmonary embolism

subjects affected / exposed	1 / 193 (0.52%)	1 / 197 (0.51%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute pulmonary oedema			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Pneumothorax spontaneous			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
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			
Femur fracture			
subjects affected / exposed	1 / 193 (0.52%)	1 / 197 (0.51%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Humerus fracture			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Radius fracture			

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Fall			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	2 / 197 (1.02%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Head injury			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 193 (1.04%)	0 / 197 (0.00%)	0 / 197 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Cardiac arrest			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Myocardial infarction			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Atrial fibrillation			

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Cardiac failure			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Bradycardia			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
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			
Cerebrovascular accident			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	2 / 197 (1.02%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Embolic stroke			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Headache			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Trigeminal neuralgia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Sciatica			

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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	12 / 193 (6.22%)	4 / 197 (2.03%)	0 / 197 (0.00%)
occurrences causally related to treatment / all	12 / 12	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Corneal oedema			
subjects affected / exposed	3 / 193 (1.55%)	2 / 197 (1.02%)	0 / 197 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iridocyclitis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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 touch			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Macular oedema			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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 tear			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Ulcerative keratitis			

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Uveitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Haemorrhoids			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric ulcer			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Intestinal obstruction			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Umbilical hernia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Diarrhoea			

subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Abdominal pain			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peptic ulcer			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hiatus hernia			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 193 (0.52%)	1 / 197 (0.51%)	0 / 197 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Musculoskeletal and connective tissue disorders			
Chondrocalcinosis pyrophosphate			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Osteoarthritis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Intervertebral disc protrusion			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Joint instability			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Clostridium difficile infection			
subjects affected / exposed	1 / 193 (0.52%)	0 / 197 (0.00%)	0 / 197 (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
Appendicitis perforated			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Diverticulitis			
subjects affected / exposed	0 / 193 (0.00%)	1 / 197 (0.51%)	0 / 197 (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
Gastroenteritis			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural sepsis			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Dehydration			
subjects affected / exposed	0 / 193 (0.00%)	0 / 197 (0.00%)	1 / 197 (0.51%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 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	143 / 193 (74.09%)	138 / 197 (70.05%)	105 / 197 (53.30%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	13 / 193 (6.74%)	20 / 197 (10.15%)	7 / 197 (3.55%)
occurrences (all)	17	28	13
Vascular disorders			
Hypertension			
subjects affected / exposed	17 / 193 (8.81%)	12 / 197 (6.09%)	8 / 197 (4.06%)
occurrences (all)	17	16	8
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 193 (4.15%)	14 / 197 (7.11%)	7 / 197 (3.55%)
occurrences (all)	10	16	7
Visual field defect			
subjects affected / exposed	4 / 193 (2.07%)	10 / 197 (5.08%)	5 / 197 (2.54%)
occurrences (all)	5	13	9
Eye disorders			
Conjunctival hyperaemia			
subjects affected / exposed	74 / 193 (38.34%)	60 / 197 (30.46%)	47 / 197 (23.86%)
occurrences (all)	193	180	139
Foreign body sensation in eyes			
subjects affected / exposed	31 / 193 (16.06%)	23 / 197 (11.68%)	12 / 197 (6.09%)
occurrences (all)	58	48	25
Eye pain			
subjects affected / exposed	28 / 193 (14.51%)	26 / 197 (13.20%)	12 / 197 (6.09%)
occurrences (all)	42	43	28
Eye irritation			

subjects affected / exposed	28 / 193 (14.51%)	18 / 197 (9.14%)	22 / 197 (11.17%)
occurrences (all)	66	45	62

Photophobia
subjects affected / exposed	23 / 193 (11.92%)	19 / 197 (9.64%)	4 / 197 (2.03%)
occurrences (all)	40	36	8

Corneal endothelial cell loss
subjects affected / exposed	20 / 193 (10.36%)	14 / 197 (7.11%)	0 / 197 (0.00%)
occurrences (all)	20	14	0

Conjunctival haemorrhage
subjects affected / exposed	19 / 193 (9.84%)	17 / 197 (8.63%)	16 / 197 (8.12%)
occurrences (all)	23	23	19

Iritis
subjects affected / exposed	19 / 193 (9.84%)	11 / 197 (5.58%)	1 / 197 (0.51%)
occurrences (all)	27	13	1

Dry eye
subjects affected / exposed	17 / 193 (8.81%)	19 / 197 (9.64%)	12 / 197 (6.09%)
occurrences (all)	32	35	24

Punctate keratitis
subjects affected / exposed	16 / 193 (8.29%)	12 / 197 (6.09%)	14 / 197 (7.11%)
occurrences (all)	30	36	40

Lacrimation increased
subjects affected / exposed	13 / 193 (6.74%)	10 / 197 (5.08%)	12 / 197 (6.09%)
occurrences (all)	22	15	22

Vision blurred
subjects affected / exposed	12 / 193 (6.22%)	10 / 197 (5.08%)	11 / 197 (5.58%)
occurrences (all)	20	21	21

Corneal oedema
subjects affected / exposed	12 / 193 (6.22%)	5 / 197 (2.54%)	2 / 197 (1.02%)
occurrences (all)	14	5	3

Anterior chamber cell
subjects affected / exposed	11 / 193 (5.70%)	9 / 197 (4.57%)	0 / 197 (0.00%)
occurrences (all)	16	11	0

Infections and infestations
Nasopharyngitis
subjects affected / exposed	13 / 193 (6.74%)	10 / 197 (5.08%)	14 / 197 (7.11%)
occurrences (all)	15	10	17

Influenza			
subjects affected / exposed	8 / 193 (4.15%)	13 / 197 (6.60%)	4 / 197 (2.03%)
occurrences (all)	8	15	4

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 August 2015	The following changes were implemented with Amendment 1: Protocol was amended to clarify some sections and to modify the inclusion/exclusion criteria.
16 March 2017	The following changes were implemented with Amendment 2: Protocol was amended to change the screening requirement for angle eligibility confirmation in the study eye, modify/clarify the inclusion/exclusion criteria, clarify the statistical analyses, and change additional procedures for participants with sickle cell disease from required to optional.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

 None reported