# 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<br>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<br>Units: years | | | |
| arithmetic mean | 62.5 | 62.6 | 62.5 |
| standard deviation | ± 13.0 | ± 11.5 | ± 11.0 |
| Sex: Female, Male<br>Units: participants | | | |
| Female | 96 | 86 | 106 |
| Male | 102 | 112 | 92 |
| Race/Ethnicity, Customized<br>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 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 | 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<br>subjects affected / exposed<br>occurrences (all) | 8 / 193 (4.15%)<br>8 | 13 / 197 (6.60%)<br>15 | 4 / 197 (2.03%)<br>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