



Clinical trial results:

A dose-ranging study of intravitreal OPT-302 in combination with Ranibizumab, compared with Ranibizumab alone, in participants with neovascular age-related macular degeneration (wet AMD)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-002698-20 |
| Trial protocol | CZ LV GB ES IT |
| Global end of trial date | 14 May 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 30 May 2020 |
| First version publication date | 30 May 2020 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | OPT-302-1002 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03345082 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Opthea Limited |
| Sponsor organisation address | 650 Chapel Street, South Yarra, Australia, VIC 3141 |
| Public contact | Clinical Development, Opthea Limited, 61 398260399, clare.price@opthea.com |
| Scientific contact | Clinical Development, Opthea Limited, 61 398260399, clare.price@opthea.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 | 14 May 2019 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 14 May 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Determine the efficacy of two different doses of intravitreal OPT-302 when administered in combination with ranibizumab in participants with wet AMD

Protection of trial subjects:

This study was conducted in accordance with the International Council for Harmonization Guidelines for Good Clinical Practice and The Declaration of Helsinki as well as per United States (US) Food and Drug Administration (FDA) Human Participant Protection Regulations (Title 21 Code of Federal Regulations, Parts 50, 54, 56 & 312) and local regulations in each of the participating countries. Written informed consent was to be obtained from each potential study participant prior to the initiation of any study-related procedures. The investigator or designee had to explain to each participant the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, and any discomfort it may entail, and the alternative treatment options including standard of care.

The information sheet accompanying the informed consent form (ICF) was to be given by means of a standard written statement, written in non-technical language, approved by the relevant IEC/IRB, and potential participants were to be given sufficient time to adequately read the information and properly consider the potential risks, benefits, study-specific procedures and time commitments. The participant was to read and consider the consent statement before signing and dating it. A copy of the signed document was to be given to the participant and the original was to be retained by the investigator.

Background therapy:

All concomitant medications were to be reported and recorded in the eCRF (including prescribed and over-the-counter medications, vitamins, herbal remedies, other traditional preparations and any ocular preparations administered of any type) from the first Screening Visit through to the Week 24 Visit. Procedural medications, as mandated by the protocol, were not to be reported as concomitant medications. Additionally, use of restricted or excluded medications were to be recorded if they were used within the excluded periods prior to Screening. Where an ocular product or therapy was administered, the site of administration had to be included i.e., OD, OS or oculus uterque (OU; both eyes). The generic or trade name was to be recorded in the eCRF for products with one active ingredient.

Evidence for comparator:

Sham intravitreal injection, with ranibizumab 0.5 mg (50 µL), by intravitreal injection.

| | |
|---|------------------|
| Actual start date of recruitment | 09 November 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 165 |
| Country: Number of subjects enrolled | Italy: 31 |
| Country: Number of subjects enrolled | Israel: 46 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 37 |
| Country: Number of subjects enrolled | Spain: 19 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | Czech Republic: 14 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Hungary: 14 |
| Country: Number of subjects enrolled | Latvia: 22 |
| Worldwide total number of subjects | 366 |
| EEA total number of subjects | 155 |

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) | 31 |
| From 65 to 84 years | 254 |
| 85 years and over | 81 |

Subject disposition

Recruitment

Recruitment details:

This was a multicentre, randomised, parallel-group, sham-controlled, double-masked, dose-ranging study. Eligible participants were randomised to one of three treatment groups in a 1:1:1 ratio: intravitreal Ranibizumab 0.5 mg followed by OPT-302 0.5 mg or OPT-302 2.0 mg and intravitreal Ranibizumab 0.5 mg followed by a sham injection.

Pre-assignment

Screening details:

Screening included fundus imaging review by an Independent Reading Centre.

Period 1

| | |
|------------------------------|---------------------------|
| Period 1 title | Period 1 (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

Randomisation and double-masking were used to minimise bias arising from the assignment of participants to treatment groups, and the expectations of participants, investigators and individuals collecting data.

Arms

| | |
|------------------------------|-------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Ranibizumab 0.5 mg + OPT-302 0.5 mg |

Arm description:

Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by OPT-302 0.5 mg (50 µL) by intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles.

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Ranibizumab |
| Investigational medicinal product code | |
| Other name | Lucentis® |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intravitreal use |

Dosage and administration details:

Ranibizumab 0.5 mg solution for injection in prefilled syringe. Ranibizumab intravitreal injection was to be administered before the OPT-302 intravitreal injection. Intravitreal injection was given once every 4 weeks for six treatment cycles.

| | |
|--|------------------------|
| Investigational medicinal product name | OPT-302 |
| Investigational medicinal product code | OPT-302 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

OPT-302 0.5 mg solution for injection for intravitreal use. OPT-302 intravitreal injection was to be administered after Ranibizumab intravitreal injection. Intravitreal injection was given once every 4 weeks for six treatment cycles.

| | |
|------------------|-------------------------------------|
| Arm title | Ranibizumab 0.5 mg + OPT-302 2.0 mg |
|------------------|-------------------------------------|

Arm description:

Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by OPT-302 2.0 mg (50 µL) by intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--|
| Investigational medicinal product name | Ranibizumab |
| Investigational medicinal product code | |
| Other name | Lucentis® |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intravitreal use |

Dosage and administration details:

Ranibizumab 0.5 mg solution for injection in pre-filled syringe. Ranibizumab intravitreal injection was to be administered before the OPT-302 intravitreal injection. Intravitreal injection was given once every 4 weeks for six treatment cycles.

| | |
|--|------------------------|
| Investigational medicinal product name | OPT-302 |
| Investigational medicinal product code | OPT-302 |
| Other name | |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

OPT-302 2 mg solution for injection for intravitreal use. OPT-302 intravitreal injection was to be administered after Ranibizumab intravitreal injection. Intravitreal injection was given once every 4 weeks for six treatment cycle.

| | |
|------------------|---------------------------|
| Arm title | Ranibizumab 0.5 mg + Sham |
|------------------|---------------------------|

Arm description:

Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by a sham intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles.

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Ranibizumab |
| Investigational medicinal product code | |
| Other name | Lucentis® |
| Pharmaceutical forms | Solution for injection in pre-filled syringe |
| Routes of administration | Intravitreal use |

Dosage and administration details:

Ranibizumab 0.5 mg solution for injection in pre-filled syringe. Ranibizumab intravitreal injection was to be administered before sham injection procedure. Intravitreal injection was given once every 4 weeks for six treatment cycles.

| | |
|--|------------------|
| Investigational medicinal product name | Sham injection |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

Sham intravitreal injection was to be administered after Ranibizumab intravitreal injection. Intravitreal injection was given once every 4 weeks for six treatment cycles.

| Number of subjects in period 1 | Ranibizumab 0.5 mg + OPT-302 0.5 mg | Ranibizumab 0.5 mg + OPT-302 2.0 mg | Ranibizumab 0.5 mg + Sham |
|---------------------------------------|--|--|----------------------------------|
| Started | 122 | 123 | 121 |
| Completed | 112 | 120 | 116 |
| Not completed | 10 | 3 | 5 |
| Adverse event, serious fatal | - | - | 2 |
| Personal reasons | 1 | - | - |
| Consent withdrawn by subject | 7 | 3 | 2 |
| Withdrawn by the investigator | - | - | 1 |

| | | | |
|-------------------|---|---|---|
| Lost to follow-up | 2 | - | - |
|-------------------|---|---|---|

Baseline characteristics

Reporting groups

| | |
|---|-------------------------------------|
| Reporting group title | Ranibizumab 0.5 mg + OPT-302 0.5 mg |
| Reporting group description: | |
| Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by OPT-302 0.5 mg (50 µL) by intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles. | |
| Reporting group title | Ranibizumab 0.5 mg + OPT-302 2.0 mg |
| Reporting group description: | |
| Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by OPT-302 2.0 mg (50 µL) by intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles. | |
| Reporting group title | Ranibizumab 0.5 mg + Sham |
| Reporting group description: | |
| Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by a sham intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles. | |

| Reporting group values | Ranibizumab 0.5 mg + OPT-302 0.5 mg | Ranibizumab 0.5 mg + OPT-302 2.0 mg | Ranibizumab 0.5 mg + Sham |
|------------------------|-------------------------------------|-------------------------------------|---------------------------|
| Number of subjects | 122 | 123 | 121 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 7 | 11 | 13 |
| From 65-84 years | 85 | 86 | 83 |
| 85 years and over | 30 | 26 | 25 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 78.8 | 77.8 | 76.1 |
| full range (min-max) | 58 to 94 | 55 to 95 | 53 to 98 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 73 | 78 | 73 |
| Male | 49 | 45 | 48 |

| Reporting group values | Total | | |
|------------------------|-------|--|--|
| Number of subjects | 366 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 31 | | |
| From 65-84 years | 254 | | |
| 85 years and over | 81 | | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| full range (min-max) | - | | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 224 | | |
| Male | 142 | | |

Subject analysis sets

| | |
|----------------------------|-------------------|
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |

Subject analysis set description:

The safety population comprised all participants in the ITT population but excluded those who did not receive at least one dose of study product, i.e., OPT-302 and/or Ranibizumab. 365 subjects were treated (safety population). This population was employed to determine the safety endpoints.

| | |
|----------------------------|----------------------------------|
| Subject analysis set title | Intent-to-treat (ITT) population |
| Subject analysis set type | Intention-to-treat |

Subject analysis set description:

The intent-to-treat (ITT) population was to include all participants who were randomized into the study, irrespective of whether study product was administered or not. 366 subjects were randomized. This population was used to report participant disposition and to provide a sensitivity analysis of the primary endpoint only.

| | |
|----------------------------|--|
| Subject analysis set title | Modified intent-to-treat (mITT) population |
| Subject analysis set type | Modified intention-to-treat |

Subject analysis set description:

The modified intent-to-treat (mITT) population comprised all participants in the safety population but excluded any participant without a Baseline visual acuity score and/or any participant who did not return for at least one post-Baseline visit. mITT population included 362 subjects. This population was employed for all efficacy analyses.

| Reporting group values | Safety population | Intent-to-treat (ITT) population | Modified intent-to-treat (mITT) population |
|---------------------------------------|-------------------|----------------------------------|--|
| Number of subjects | 365 | 366 | 362 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 31 | 31 | 31 |
| From 65-84 years | 253 | 254 | 250 |
| 85 years and over | 81 | 81 | 81 |
| Age continuous Units: years | | | |
| arithmetic mean | 77.6 | 77.6 | 77.6 |
| full range (min-max) | 53 to 98 | 53 to 98 | 53 to 98 |
| Gender categorical Units: Subjects | | | |
| Female | 223 | 224 | 221 |
| Male | 142 | 142 | 141 |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Ranibizumab 0.5 mg + OPT-302 0.5 mg |
| Reporting group description: Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by OPT-302 0.5 mg (50 µL) by intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles. | |
| Reporting group title | Ranibizumab 0.5 mg + OPT-302 2.0 mg |
| Reporting group description: Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by OPT-302 2.0 mg (50 µL) by intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles. | |
| Reporting group title | Ranibizumab 0.5 mg + Sham |
| Reporting group description: Administered Ranibizumab 0.5 mg (50 µL) by intravitreal injection followed by a sham intravitreal injection. Administration was done every 4 weeks for 6 treatment cycles. | |
| Subject analysis set title | Safety population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population comprised all participants in the ITT population but excluded those who did not receive at least one dose of study product, i.e., OPT-302 and/or Ranibizumab. 365 subjects were treated (safety population). This population was employed to determine the safety endpoints. | |
| Subject analysis set title | Intent-to-treat (ITT) population |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: The intent-to-treat (ITT) population was to include all participants who were randomized into the study, irrespective of whether study product was administered or not. 366 subjects were randomized. This population was used to report participant disposition and to provide a sensitivity analysis of the primary endpoint only. | |
| Subject analysis set title | Modified intent-to-treat (mITT) population |
| Subject analysis set type | Modified intention-to-treat |
| Subject analysis set description: The modified intent-to-treat (mITT) population comprised all participants in the safety population but excluded any participant without a Baseline visual acuity score and/or any participant who did not return for at least one post-Baseline visit. mITT population included 362 subjects. This population was employed for all efficacy analyses. | |

Primary: Mean change from Baseline in ETDRS BCVA letters to Week 24 (Visit 8)

| | |
|--|--|
| End point title | Mean change from Baseline in ETDRS BCVA letters to Week 24 (Visit 8) |
| End point description: The primary efficacy outcome measure was changed in ETDRS BCVA at Week 24. Participants in the higher dose (OPT-302 2.0 mg) group showed a greater mean gain in ETDRS BCVA letters at Week 24 compared with sham (+14.22 vs. +10.84 letters) and this difference was statistically significant. Thus, the study met its primary endpoint in the higher dose group whilst the lower dose (OPT-302 0.5 mg) group was similar to sham. Intravitreal OPT-302 2.0 mg administered with Ranibizumab significantly improved mean visual acuity compared with Ranibizumab alone. | |
| End point type | Primary |
| End point timeframe: The primary endpoint is mean change from Baseline in Early Treatment Diabetic Retinopathy Study (ETDRS) best corrected visual acuity (BCVA) to Week 24 (Visit 8). It was based on the mITT population. | |

| End point values | Ranibizumab 0.5 mg + OPT- 302 0.5 mg | Ranibizumab 0.5 mg + OPT- 302 2.0 mg | Ranibizumab 0.5 mg + Sham | |
|-------------------------------------|--|--|---------------------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 122 | 121 | 119 | |
| Units: Observed values (letters) | | | | |
| least squares mean (standard error) | 9.44 (± 1.07) | 14.22 (± 1.06) | 10.84 (± 1.07) | |

Statistical analyses

| | |
|-----------------------------------|----------------------------|
| Statistical analysis title | SAS Version 9.4 (or later) |
|-----------------------------------|----------------------------|

Statistical analysis description:

Descriptive statistics included categorical data which were summarised in contingency tables presenting frequencies and percentages, and continuous data which were summarised number of missing values (Nmissing), number of non-missing values (n), mean, standard deviation (SD), standard error of the mean (SEM), 95% confidence interval (CI), median, minimum and maximum values.

| | |
|---|---|
| Comparison groups | Ranibizumab 0.5 mg + OPT-302 0.5 mg v Ranibizumab 0.5 mg + OPT-302 2.0 mg v Ranibizumab 0.5 mg + Sham |
| Number of subjects included in analysis | 362 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| Parameter estimate | Control of Alpha |
| Point estimate | 0.05 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.3 |
| upper limit | 6.27 |
| Variability estimate | Standard deviation |

Notes:

[1] - In order to preserve the level of significance, multiple comparisons were controlled using a Hochberg procedure. 95% confidence interval (CI) was constructed based on a Model for Repeated Measures which took into account the presence of missing data and yielded valid estimates under the assumption of data Missing at Random. With this procedure, the experiment-wise type I error rate was controlled at α (=0.05).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reporting was to begin from initiation of Screening (i.e., from the signing of the ICF) and continue throughout the study until the final study visit.

Adverse event reporting additional description:

A Data and Safety Monitoring Board was chartered to monitor the safety of all participants in this study by periodically reviewing unmasked summaries of safety data and assessing whether it was safe for the study to continue. The incidence of potentially related treatment-emergent adverse events (TEAEs) was similar across the three groups.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Ranibizumab 0.5 mg + OPT-302 0.5 mg |
|-----------------------|-------------------------------------|

Reporting group description: -

| | |
|-----------------------|-------------------------------------|
| Reporting group title | Ranibizumab 0.5 mg + OPT-302 2.0 mg |
|-----------------------|-------------------------------------|

Reporting group description: -

| | |
|-----------------------|---------------------------|
| Reporting group title | Ranibizumab 0.5 mg + Sham |
|-----------------------|---------------------------|

Reporting group description: -

| Serious adverse events | Ranibizumab 0.5 mg + OPT-302 0.5 mg | Ranibizumab 0.5 mg + OPT-302 2.0 mg | Ranibizumab 0.5 mg + Sham |
|---|-------------------------------------|-------------------------------------|---------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 120 (13.33%) | 9 / 124 (7.26%) | 10 / 121 (8.26%) |
| number of deaths (all causes) | 0 | 0 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 2 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Rectal cancer | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of lung | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| 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 | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal adenocarcinoma | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Vascular disorders | | | |
| Embolism arterial | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Surgical and medical procedures | | | |
| Gastric operation | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Immune system disorders | | | |
| Corneal graft rejection | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 | | | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic rhinosinusitis with nasal polyps | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Psychiatric disorders | | | |
| Confusional state | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Product issues | | | |
| Device dislocation | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (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 |
| Procedural vomiting | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (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 |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 2 / 121 (1.65%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 1 / 124 (0.81%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pericarditis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 flutter | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 2 / 124 (1.61%) | 0 / 121 (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 |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Syncope | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (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 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Corneal decompensation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Vitritis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| 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 haemorrhage | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Enteritis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Colonic abscess | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocarditis | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 0 / 124 (0.00%) | 1 / 121 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endophthalmitis | | | |
| subjects affected / exposed | 1 / 120 (0.83%) | 0 / 124 (0.00%) | 0 / 121 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (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 |
| Influenza | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (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 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 120 (0.00%) | 1 / 124 (0.81%) | 0 / 121 (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 |

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

| Non-serious adverse events | Ranibizumab 0.5 mg + OPT-302 0.5 mg | Ranibizumab 0.5 mg + OPT-302 2.0 mg | Ranibizumab 0.5 mg + Sham |
|---|--|--|--------------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 86 / 120 (71.67%) | 79 / 124 (63.71%) | 66 / 121 (54.55%) |
| Investigations | | | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 7 / 120 (5.83%) | 6 / 124 (4.84%) | 2 / 121 (1.65%) |
| occurrences (all) | 7 | 6 | 2 |
| Eye disorders | | | |
| Eye pain | | | |
| subjects affected / exposed | 25 / 120 (20.83%) | 18 / 124 (14.52%) | 20 / 121 (16.53%) |
| occurrences (all) | 25 | 18 | 20 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 20 / 120 (16.67%) | 17 / 124 (13.71%) | 16 / 121 (13.22%) |
| occurrences (all) | 20 | 17 | 16 |
| Vitreous floaters | | | |
| subjects affected / exposed | 11 / 120 (9.17%) | 9 / 124 (7.26%) | 5 / 121 (4.13%) |
| occurrences (all) | 11 | 9 | 5 |
| Eye irritation | | | |
| subjects affected / exposed | 8 / 120 (6.67%) | 8 / 124 (6.45%) | 7 / 121 (5.79%) |
| occurrences (all) | 8 | 8 | 7 |
| Foreign body sensation in eyes | | | |
| subjects affected / exposed | 4 / 120 (3.33%) | 4 / 124 (3.23%) | 8 / 121 (6.61%) |
| occurrences (all) | 4 | 4 | 8 |
| Lacrimation increased | | | |
| subjects affected / exposed | 5 / 120 (4.17%) | 7 / 124 (5.65%) | 3 / 121 (2.48%) |
| occurrences (all) | 5 | 7 | 3 |
| Ocular hyperaemia | | | |
| subjects affected / exposed | 6 / 120 (5.00%) | 4 / 124 (3.23%) | 3 / 121 (2.48%) |
| occurrences (all) | 6 | 4 | 3 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 23 November 2017 | Amendment 1, dated 23rd November 2017 (Protocol Version 2.0) - was released only in the US and Israel. Sections of the protocol including primary, secondary and exploratory objectives and endpoints, eligibility criteria, study procedures for discontinuation and pregnancy were further clarified. The Risk Assessment was updated with information concerning a bilateral amaurosis reported during Study OPT-302-1001 and potential teratogenicity of the anti-VEGF class of drugs. Progression of wet AMD in the Study Eye was added to the list of medical events that was to be reported as an AE. The facility to allow enrolment of additional participants if the calculated SD was significantly greater than the assumed SD; and/or if the overall rate of participants eligible for the mITT population was lower than estimated, was removed. Additional information on the approach to subgroup analyses were added to the efficacy analysis. |
| 13 December 2017 | Amendment, dated 13th December 2017 (Protocol Version 2.1) - was released and approved in the European countries only. Protocol Version 2.1 included all changes as per Protocol Version 2.0 with the following additional change: The option to store investigational product in a temperature-monitored refrigerator between 2°C to 8°C [35°F to 46°F]) was removed for European sites. Product was only to be stored in a temperature-monitored freezer (between -25°C to -15°C [-13°F to 5°F]). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None reported

Notes: