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: