



Clinical trial results:

Phase 1b/2a study of OPT-302 in combination with aflibercept for persistent central-involved diabetic macular edema

Summary

EudraCT number	2018-003298-90
Trial protocol	LV
Global end of trial date	11 June 2020

Results information

Result version number	v1 (current)
This version publication date	16 June 2022
First version publication date	16 June 2022

Trial information

Trial identification

Sponsor protocol code	OPT-302-1003
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03397264
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Opthea Limited
Sponsor organisation address	Level 4, 650 Chapel Street, South Yarra, Australia, 3141
Public contact	Clinical Development, Opthea Ltd, 61 398260399, annette.leahy@opthea.com
Scientific contact	Clinical Development, Opthea Ltd, 61 398260399, annette.leahy@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	17 August 2020
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Phase 1b and 2a: To evaluate the safety and tolerability of OPT-302 intravitreal (IVT) injection in combination with IVT aflibercept in participants with central-involved Diabetic Macular Edema (DME)

Phase 2b: To assess the response rate (≥ 5 letter gain in Best Corrected Visual Acuity [BCVA] from baseline to week 12 according to ETDRS criteria) in participants with persistent central-involved DME receiving combination OPT-302 and aflibercept treatment

Protection of trial subjects:

The study was conducted in accordance with the protocol and the following guidelines and regulations:

- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice;
- The Declaration of Helsinki;
- United States (US) Food and Drug Administration (FDA) Human Participant Protection Regulations (Title 21 Code of Federal Regulations, Parts 50, 54, 56 & 312);
- Local regulations in each of the participating countries.

Before entering the study, the participant information and informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Latvia: 9
Country: Number of subjects enrolled	Israel: 34
Country: Number of subjects enrolled	Australia: 9
Country: Number of subjects enrolled	United States: 101
Worldwide total number of subjects	153
EEA total number of subjects	9

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)	96
From 65 to 84 years	55
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Nil

Period 1

Period 1 title	Phase 2a (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
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Arm title	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302
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Arm description:

2.0 mg aflibercept followed by 2.0 mg OPT-302 (0.05 mL each), both by intravitreal injection.

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

Dosage and administration details:

2.0 mg OPT-302 administered via Intravitreal Injection every 4 weeks x 3 treatments

Investigational medicinal product name	aflibercept
Investigational medicinal product code	
Other name	Eylea
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

2.0 mg intravitreal aflibercept every 4 weeks x 3 treatments

Arm title	Phase 2a: 2.0 mg aflibercept with sham
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Arm description:

2.0 mg aflibercept (0.05 mL) followed by sham, both by intravitreal injection.

Arm type	Sham IVT injection
Investigational medicinal product name	Sham Intravitreal Injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Pharmaceutical dose form not applicable
Routes of administration	Route of administration not applicable

Dosage and administration details:

Sham Intravitreal injection administered every 4 weeks x 3 treatments

Number of subjects in period 1^[1]	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302	Phase 2a: 2.0 mg aflibercept with sham
Started	96	48
Completed	89	47
Not completed	7	1
Adverse event, non-fatal	1	-
Lost to follow-up	2	1
Protocol deviation	2	-
not specified	2	-

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: This was a two part study: a Ph1b open-label (unblinded) dose escalation (n=9) and Ph2a randomised (blinded) dose expansion study (n=144). A total of 153 participants were enrolled/randomised into the two different parts of the study. The baseline period represents the Ph2a randomised blinded dose expansion study (n=144) due to limitations of the EudraCT system to accommodate the blinded and unblinded phases of this study protocol.

Baseline characteristics

Reporting groups

Reporting group title	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302
Reporting group description: 2.0 mg aflibercept followed by 2.0 mg OPT-302 (0.05 mL each), both by intravitreal injection.	
Reporting group title	Phase 2a: 2.0 mg aflibercept with sham
Reporting group description: 2.0 mg aflibercept (0.05 mL) followed by sham, both by intravitreal injection.	

Reporting group values	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302	Phase 2a: 2.0 mg aflibercept with sham	Total
Number of subjects	96	48	144
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	58	32	90
From 65-84 years	36	16	52
85 years and over	2	0	2
Gender categorical Units: Subjects			
Female	36	18	54
Male	60	30	90

End points

End points reporting groups

Reporting group title	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302
Reporting group description: 2.0 mg aflibercept followed by 2.0 mg OPT-302 (0.05 mL each), both by intravitreal injection.	
Reporting group title	Phase 2a: 2.0 mg aflibercept with sham
Reporting group description: 2.0 mg aflibercept (0.05 mL) followed by sham, both by intravitreal injection.	
Subject analysis set title	Primary Per Protocol
Subject analysis set type	Per protocol
Subject analysis set description: This population was defined as the first 72 evaluable participants in the 2.0 mg OPT-302 with 2.0 mg aflibercept group from the PP population in the Phase 2a Study. Evaluable participants represent a subset of participants who were randomised, received the intended study product (a total of 3 scheduled intravitreal injections approximately once every 4 weeks), and could be evaluated for study outcomes	
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 excluding those who did not receive at least one dose of study product(s) (aflibercept or OPT-302). Participants were analysed according to the treatment that they actually received.	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description: The PP population comprised participants in the Safety population who were compliant with the study product, and who were considered sufficiently compliant with the protocol.	

Primary: Response Rate - Proportion of Participants Achieving a ≥ 5 letter Gain

End point title	Response Rate - Proportion of Participants Achieving a ≥ 5 letter Gain ^{[1][2]}
End point description: Response rate defined as the proportion of participants receiving the combination of OPT-302 and aflibercept achieving at least a 5 letter gain in BCVA at week 12 compared to Baseline according to the ETDRS criteria	
End point type	Primary
End point timeframe: Baseline to Week 12	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: A one stage design was used for the primary endpoint based on the pre-specified response rate (38%) of a total of 72 evaluable patients receiving aflibercept + OPT-302. Clinical activity was concluded if ≥ 27 of 72 patients receiving 2 mg OPT-302 + 2 mg aflibercept had a ≥ 5 letter gain in BCVA from baseline to week 12; Type I and II error rates were set to 5% and with probability of at least 90%. The primary endpoint was met: response rate was 52.8% (95% CI: 41.2%; 64.3%).

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: As per protocol the study was a non-comparative, one stage design used for the primary outcome, with a pre-specified primary efficacy end point of a ≥ 5 letter vision gain (BCVA). OPT-302 combination therapy would be considered to have a clinical activity if ≥ 27 of 72 participants had a ≥ 5 letter gain from baseline to Week 12. The treatment response rate was selected because it represents a clinically relevant improvement in previously treated participants, based on published studies.

End point values	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302			
Subject group type	Reporting group			
Number of subjects analysed	72			
Units: Participants	38			

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in BCVA

End point title	Mean Change in BCVA
End point description: Mean Change in Best Corrected Visual Acuity (BCVA) Score. BCVA measured in accordance with Early Treatment Diabetic Retinopathy Score (ETDRS) criteria.	
End point type	Secondary
End point timeframe: Baseline to Week 12	

End point values	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302	Phase 2a: 2.0 mg aflibercept with sham		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	40		
Units: μm				
arithmetic mean (standard error)	5.9 (\pm 0.79)	6.1 (\pm 0.96)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in CST

End point title	Mean Change in CST
End point description: Mean change in Central Subfield Thickness (CST) on spectral domain coherence tomography (SD-OCT)	
End point type	Secondary
End point timeframe: Baseline to Week 12	

End point values	Phase 2a: 2.0 mg aflibercept with 2.0 mg OPT-302	Phase 2a: 2.0 mg aflibercept with sham		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	74	39		
Units: μm				
arithmetic mean (standard error)	-52.2 (\pm 10.28)	-34.9 (\pm 12.01)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline to Week 12

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Ph 1b: 2.0 mg Aflibercept with 0.3 mg OPT-302
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Reporting group description:

2.0 mg aflibercept intravitreal injection (0.05 mL) followed by 0.3 mg OPT-302 intravitreal injection (0.5mL) every 4 weeks for 3 treatments

Reporting group title	Ph 1b: 2.0 mg Aflibercept with 1.0 mg OPT-302
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Reporting group description: -

Reporting group title	Ph 1b: 2.0 mg Aflibercept with 2.0 mg OPT-302
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Reporting group description: -

Reporting group title	Ph 2a: 2.0 mg Aflibercept with 2.0 mg OPT-302
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Reporting group description: -

Reporting group title	Ph 2a: 2.0 mg Aflibercept with Sham
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Reporting group description: -

Serious adverse events	Ph 1b: 2.0 mg Aflibercept with 0.3 mg OPT-302	Ph 1b: 2.0 mg Aflibercept with 1.0 mg OPT-302	Ph 1b: 2.0 mg Aflibercept with 2.0 mg OPT-302
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	0 / 3 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 3 (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
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 3 (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 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post Operative Wound infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 3 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Ph 2a: 2.0 mg Aflibercept with 2.0 mg OPT-302	Ph 2a: 2.0 mg Aflibercept with Sham	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 95 (8.42%)	1 / 49 (2.04%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			

subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Ulcer			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Impaired gastric emptying			
subjects affected / exposed	0 / 95 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			

subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 95 (0.00%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	2 / 95 (2.11%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post Operative Wound infection			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 95 (0.00%)	1 / 49 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 95 (1.05%)	0 / 49 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ph 1b: 2.0 mg Aflibercept with 0.3 mg OPT-302	Ph 1b: 2.0 mg Aflibercept with 1.0 mg OPT-302	Ph 1b: 2.0 mg Aflibercept with 2.0 mg OPT-302
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 3 (66.67%)	1 / 3 (33.33%)	1 / 3 (33.33%)
Investigations			
Intraocular pressure increased			

subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Eye disorders			
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1	1 / 3 (33.33%) 1
Punctate keratitis subjects affected / exposed occurrences (all)	1 / 3 (33.33%) 1	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0	0 / 3 (0.00%) 0

Non-serious adverse events	Ph 2a: 2.0 mg Aflibercept with 2.0 mg OPT-302	Ph 2a: 2.0 mg Aflibercept with Sham	
Total subjects affected by non-serious adverse events subjects affected / exposed	36 / 95 (37.89%)	15 / 49 (30.61%)	
Investigations			
Intraocular pressure increased subjects affected / exposed occurrences (all)	13 / 95 (13.68%) 13	3 / 49 (6.12%) 3	
Eye disorders			
Conjunctival haemorrhage subjects affected / exposed occurrences (all)	19 / 95 (20.00%) 19	6 / 49 (12.24%) 6	
Punctate keratitis subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2	3 / 49 (6.12%) 3	
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	2 / 95 (2.11%) 2	3 / 49 (6.12%) 3	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 February 2018	<ul style="list-style-type: none">• A four to six week Run In phase for potential participants who received prior bevacizumab therapy was added• The number of study sites was increased• CST inclusion criteria was revised.
15 May 2018	<ul style="list-style-type: none">• The eligibility criteria for the Run In phase were revised• The number of study sites was increased• CST inclusion criterion revised• The duration of DME history inclusion criteria was revised.
02 August 2018	<ul style="list-style-type: none">• Sections of the protocol were updated to accommodate study expansion into the EU e.g. contraception requirements.• Updated sections in the protocol for clarification and consistency.
25 March 2020	Changes to incorporate flexibility due to the COVID-19 pandemic.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported