Clinical trial results:
Safety and Efficacy of Abicipar Pegol (AGN-150998) in Patients With Neovascular Age-related Macular Degeneration (SEQUOIA Study)

Summary

EudraCT number	2014-004580-20
Trial protocol	HU NL IT DK PL
Global end of trial date	06 June 2019

Results information

Result version number	v1 (current)
This version publication date	22 June 2020
First version publication date	22 June 2020

Trial information

Trial identification

Sponsor protocol code	150998-006

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02462486
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan, Inc
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire SL7 1YL, United Kingdom, SL7 1YL
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@Allergan.com
Scientific contact	Therapeutic Area, Head, Allergan plc, 001 862-261-7000, IR-CTRegistration@allergan.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	06 June 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 June 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the study is safety and efficacy of abicipar pegol in participants with neovascular age-related macular degeneration.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 June 2015
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	Denmark: 18
Country: Number of subjects enrolled	United Kingdom: 77
Country: Number of subjects enrolled	Hungary: 100
Country: Number of subjects enrolled	Italy: 57
Country: Number of subjects enrolled	Netherlands: 16
Country: Number of subjects enrolled	Poland: 98
Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Canada: 27
Country: Number of subjects enrolled	Japan: 92
Country: Number of subjects enrolled	Peru: 5
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	United States: 383
Country: Number of subjects enrolled	South Africa: 5
Worldwide total number of subjects	949
EEA total number of subjects	366

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)	93
From 65 to 84 years	692
85 years and over	164

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 949 participants were enrolled in the study.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Abicipar pegol 2 mg (2Q8)

Arm description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 8, followed by injections every 8 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.

Arm type	Experimental
Investigational medicinal product name	Abicipar pegol
Investigational medicinal product code	
Other name	AGN-150998
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection.

Investigational medicinal product name	Sham Procedure
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Intravitreal use

Dosage and administration details:

Sham injection.

Arm title	Abicipar pegol 2 mg (2Q12)

Arm description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 12, followed by injections every 12 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.

Arm type	Experimental
Investigational medicinal product name	Abicipar pegol
Investigational medicinal product code	
Other name	AGN-150998
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection.

Investigational medicinal product name	Sham Procedure
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in needle-free injector
Routes of administration	Intravitreal use

Dosage and administration details:

Sham injection.

Arm title	Ranibizumab (rQ4)

Arm description:

Ranibizumab (Lucentis®) was administered to the study eye by intravitreal injection every 4 weeks from Day 1 through Week 96.

Arm type	Active comparator
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis®
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Intravitreal injection.

Number of subjects in period 1	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)
Started	316	315	318
Completed	222	223	266
Not completed	94	92	52
Screen Failure:Missed Exclusion Criteria	1	1	3
Consent withdrawn by subject	25	22	19
Adverse event, non-fatal	53	48	21
Lost to follow-up	3	4	2
Reason Not Completed	3	4	3
Lack of efficacy	6	12	3
Protocol deviation	3	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Abicipar pegol 2 mg (2Q8)
Reporting group description:	
Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 8, followed by injections every 8 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.	
Reporting group title	Abicipar pegol 2 mg (2Q12)
Reporting group description:	
Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 12, followed by injections every 12 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.	
Reporting group title	Ranibizumab (rQ4)
Reporting group description:	
Ranibizumab (Lucentis®) was administered to the study eye by intravitreal injection every 4 weeks from Day 1 through Week 96.	

Reporting group values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)
Number of subjects	316	315	318
Age categorical Units: Subjects			
Adults (18-64 years)	34	29	30
From 65-84 years	223	233	236
85 years and over	59	53	52
Age Continuous Units: years			
arithmetic mean	75.9	76.2	75.9
standard deviation	± 8.6	± 8.3	± 8.4
Sex: Female, Male Units: participants			
Female	179	174	185
Male	137	141	133
Race/Ethnicity, Customized Units: Subjects			
White	266	266	264
Black	2	4	3
Asian	39	35	41
Hispanic	7	8	9
Other	2	0	0
Not Reported	0	1	1
Unknown	0	1	0
Best Corrected Visual Acuity (BCVA)			
BCVA was measured using an eye chart and is reported as number of letters read correctly using Early Treatment of Diabetic Retinopathy Study (ETDRS) Scale (0 to 100 letters) in study eye. Lower number of letters read correctly, worse the vision. Study eye: eye that meets entry criteria. If both eyes met all of entry criteria, eye with worse BCVA at baseline (Day 1) was selected. If values for both eyes were identical, participant selected non-dominant eye, or else right eye was selected.			
Units: letters			
arithmetic mean	57.2	56.4	57.1

standard deviation	± 12.3	± 12.5	± 12.3
Central Retinal Thickness (CRT)			
CRT was assessed using spectral domain optical coherence tomography (SD-OCT), a non-invasive diagnostic system that provides high-resolution imaging sections of retina. SD-OCT was performed in study eye after pupil dilation.Study eye was defined as the eye that meets the entry criteria. If both the eyes met all of the entry criteria, the eye with worse BCVA at baseline (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. [n=316,314,318]			
Units: microns			
arithmetic mean	380.3	378.2	382.4
standard deviation	± 117.9	± 123.8	± 130.3
National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)			
NEI-VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. Responses of individual participants were recorded as scores that ranged between 0 (worst) to 100 (best vision related function) with higher scale indicating better vision related function. The overall composite score is then calculated by averaging over all 11 vision-targeted subscale scores, excluding the general health score. Overall composite score was calculated based on mean of non-missing subscales.			
Units: score on a scale			
arithmetic mean	78.4	78.3	77.3
standard deviation	± 14.6	± 14.4	± 15.6

Reporting group values	Total		
Number of subjects	949		
Age categorical Units: Subjects			
Adults (18-64 years)	93		
From 65-84 years	692		
85 years and over	164		
Age Continuous Units: years arithmetic mean standard deviation	- -		
Sex: Female, Male Units: participants			
Female	538		
Male	411		
Race/Ethnicity, Customized Units: Subjects			
White	796		
Black	9		
Asian	115		
Hispanic	24		
Other	2		
Not Reported	2		
Unknown	1		
Best Corrected Visual Acuity (BCVA)			
BCVA was measured using an eye chart and is reported as number of letters read correctly using Early Treatment of Diabetic Retinopathy Study (ETDRS) Scale (0 to 100 letters) in study eye. Lower number of letters read correctly, worse the vision. Study eye: eye that meets entry criteria. If both eyes met all of entry criteria, eye with worse BCVA at baseline (Day 1) was selected. If values for both eyes were identical, participant selected non-dominant eye, or else right eye was selected.			
Units: letters arithmetic mean standard deviation	 -		

Central Retinal Thickness (CRT)			
CRT was assessed using spectral domain optical coherence tomography (SD-OCT), a non-invasive diagnostic system that provides high-resolution imaging sections of retina. SD-OCT was performed in study eye after pupil dilation.Study eye was defined as the eye that meets the entry criteria. If both the eyes met all of the entry criteria, the eye with worse BCVA at baseline (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. [n=316,314,318]			
Units: microns arithmetic mean standard deviation	- -		
National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)			
NEI-VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. Responses of individual participants were recorded as scores that ranged between 0 (worst) to 100 (best vision related function) with higher scale indicating better vision related function. The overall composite score is then calculated by averaging over all 11 vision-targeted subscale scores, excluding the general health score. Overall composite score was calculated based on mean of non-missing subscales.			
Units: score on a scale arithmetic mean standard deviation	- -		

Subject analysis sets

Subject analysis set title	Abicipar pegol 2 mg (2Q8)
Subject analysis set type	Per protocol

Subject analysis set description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 8, followed by injections every 8 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered. Per-protocol (PP) population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

Subject analysis set title	Abicipar pegol 2 mg (2Q12)
Subject analysis set type	Per protocol

Subject analysis set description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 12, followed by injections every 12 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered. PP population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

Subject analysis set title	Ranibizumab (rQ4)
Subject analysis set type	Per protocol

Subject analysis set description:

Ranibizumab (Lucentis®) was administered to the study eye by intravitreal injection every 4 weeks from Day 1 through Week 96. PP population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

Reporting group values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)
Number of subjects	267	265	299
Age categorical Units: Subjects			
Adults (18-64 years) From 65-84 years 85 years and over			

Age Continuous Units: years arithmetic mean standard deviation	± 	± 	±
Sex: Female, Male Units: participants Female Male			
Race/Ethnicity, Customized Units: Subjects White Black Asian Hispanic Other Not Reported Unknown			
Best Corrected Visual Acuity (BCVA)			
BCVA was measured using an eye chart and is reported as number of letters read correctly using Early Treatment of Diabetic Retinopathy Study (ETDRS) Scale (0 to 100 letters) in study eye. Lower number of letters read correctly, worse the vision. Study eye: eye that meets entry criteria. If both eyes met all of entry criteria, eye with worse BCVA at baseline (Day 1) was selected. If values for both eyes were identical, participant selected non-dominant eye, or else right eye was selected.			
Units: letters arithmetic mean standard deviation	 57.8 ± 12.1	 56.3 ± 12.5	 57.0 ± 12.3
Central Retinal Thickness (CRT)			
CRT was assessed using spectral domain optical coherence tomography (SD-OCT), a non-invasive diagnostic system that provides high-resolution imaging sections of retina. SD-OCT was performed in study eye after pupil dilation.Study eye was defined as the eye that meets the entry criteria. If both the eyes met all of the entry criteria, the eye with worse BCVA at baseline (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. [n=316,314,318]			
Units: microns arithmetic mean standard deviation	 ±	 ±	 ±
National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25)			
NEI-VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. Responses of individual participants were recorded as scores that ranged between 0 (worst) to 100 (best vision related function) with higher scale indicating better vision related function. The overall composite score is then calculated by averaging over all 11 vision-targeted subscale scores, excluding the general health score. Overall composite score was calculated based on mean of non-missing subscales.			
Units: score on a scale arithmetic mean standard deviation	 ±	 ±	 ±

End points

End points reporting groups

Reporting group title	Abicipar pegol 2 mg (2Q8)

Reporting group description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 8, followed by injections every 8 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.

Reporting group title	Abicipar pegol 2 mg (2Q12)

Reporting group description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 12, followed by injections every 12 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.

Reporting group title	Ranibizumab (rQ4)

Reporting group description:

Ranibizumab (Lucentis®) was administered to the study eye by intravitreal injection every 4 weeks from Day 1 through Week 96.

Subject analysis set title	Abicipar pegol 2 mg (2Q8)
Subject analysis set type	Per protocol

Subject analysis set description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 8, followed by injections every 8 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered. Per-protocol (PP) population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

Subject analysis set title	Abicipar pegol 2 mg (2Q12)
Subject analysis set type	Per protocol

Subject analysis set description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 12, followed by injections every 12 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered. PP population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

Subject analysis set title	Ranibizumab (rQ4)
Subject analysis set type	Per protocol

Subject analysis set description:

Ranibizumab (Lucentis®) was administered to the study eye by intravitreal injection every 4 weeks from Day 1 through Week 96. PP population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

Primary: Percentage of Participants with Stable Vision

End point title	Percentage of Participants with Stable Vision

End point description:

Stable vision was vision loss of fewer than 15 letters in BCVA from baseline (BL). BCVA was measured using an eye chart and was reported as number of letters read correctly using ETDRS Scale (0 to 100 letters) in study eye. Lower number of letters read correctly on eye chart, worse vision (or visual acuity). Increase in number of letters read correctly means that vision has improved. Study eye was defined as eye that meets entry criteria. If both eyes met all of entry criteria, eye with worse BCVA at BL (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. Per-protocol (PP) population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately.

End point type	Primary

End point timeframe:

Baseline to Week 52

End point values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	267	265	299	
Units: percentage of participants				
number (not applicable)	94.8	91.3	96.0	

Statistical analyses

Statistical analysis title	Percentage of Participants with Stable Vision

Statistical analysis description:

For hypothesis testing, if the lower limit of the 95.1% confidence interval for the difference between an abicipar group and ranibizumab is greater than or equal to -10%, non-inferiority of abicipar group is established.

Comparison groups	Abicipar pegol 2 mg (2Q8) v Ranibizumab (rQ4)
Number of subjects included in analysis	566
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Percentage Difference
Point estimate	-1.2
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-5
upper limit	2.4

Notes:

[1] - The 95.1% CI for the weighted difference were calculated based on the Newcombe method using the Cochran-Mantel-Haenszel weights and baseline BCVA (≤55 vs >55 letters) as stratification factor.

Statistical analysis title	Percentage of Participants with Stable Vision

Statistical analysis description:

For hypothesis testing, if the lower limit of the 95.1% confidence interval for the difference between an abicipar group and ranibizumab is greater than or equal to -10%, non-inferiority of abicipar group is established.

Comparison groups	Ranibizumab (rQ4) v Abicipar pegol 2 mg (2Q12)
Number of subjects included in analysis	564
Analysis specification	Pre-specified
Analysis type	non-inferiority[2]
Parameter estimate	Percentage Difference
Point estimate	-4.6
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-9
upper limit	-0.5

Notes:

[2] - The 95.1% CI for the weighted difference were calculated based on the Newcombe method using the Cochran-Mantel-Haenszel weights and baseline BCVA (≤55 vs >55 letters) as stratification factor.

Secondary: Mean Change from Baseline in Best-corrected Visual Acuity (BCVA) in the Study Eye

End point title	Mean Change from Baseline in Best-corrected Visual Acuity (BCVA) in the Study Eye

End point description:

BCVA was measured using an eye chart and is reported as the number of letters read correctly using the ETDRS Scale (0 to 100 letters) in the study eye. The lower the number of letters read correctly, the worse the vision (or visual acuity). An increase in the number of letters read correctly means that vision has improved. Mixed-effect model for repeated measures (MMRM) analysis was used. Study eye was defined as the eye that meets the entry criteria. If both the eyes met all of the entry criteria, the eye with worse BCVA at baseline (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. PP population included all randomized and treated participants without any protocol deviations that impacted the primary efficacy variable and with treatment compliance to represent the intended regimen adequately. Number analyzed is the number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	248	251	287	
Units: letters				
arithmetic mean (standard deviation)	8.3 (± 14.3)	7.3 (± 13.8)	8.3 (± 11.8)	

Statistical analyses

Statistical analysis title	Mean Change from Baseline in BCVA at Week 52

Statistical analysis description:

For hypothesis testing, non-inferiority of abicipar is established if the lower limit of the CI is > - 5.0 letters.

Comparison groups	Abicipar pegol 2 mg (2Q8) v Ranibizumab (rQ4)
Number of subjects included in analysis	535
Analysis specification	Pre-specified
Analysis type	non-inferiority[3]
Parameter estimate	Least Squares (LS) Mean Difference
Point estimate	-0.2
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-2.4
upper limit	2
Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[3] - MMRM included treatment, region, BL BCVA, BL CRT ≤400 or >400, choroidal neovascularization lesion type, visit, visit-by-BL BCVA interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

Statistical analysis title	Mean Change from Baseline in BCVA at Week 52

Statistical analysis description:

For hypothesis testing, non-inferiority of abicipar is established if the lower limit of the CI is > - 5.0 letters.

Comparison groups	Abicipar pegol 2 mg (2Q12) v Ranibizumab (rQ4)
Number of subjects included in analysis	538
Analysis specification	Pre-specified
Analysis type	non-inferiority[4]
Parameter estimate	LS Mean Difference
Point estimate	-1.6
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-3.8
upper limit	0.6
Variability estimate	Standard error of the mean
Dispersion value	1.1

Notes:

[4] - MMRM included treatment, region, BL BCVA, BL CRT ≤400 or >400, choroidal neovascularization lesion type, visit, visit-by-BL BCVA interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

Secondary: Mean Change from Baseline in Central Retinal Thickness (CRT) in the Study Eye

End point title	Mean Change from Baseline in Central Retinal Thickness (CRT) in the Study Eye

End point description:

CRT was assessed using spectral domain optical coherence tomography (SD-OCT), a non-invasive diagnostic system that provides high-resolution imaging sections of the retina. SD-OCT was performed in the study eye after pupil dilation. A negative change from Baseline indicates improvement and a positive change from baseline indicates worsening. Study eye is defined as the eye that meets the entry criteria. If both the eyes met all of the entry criteria, the eye with worse BCVA at baseline (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. MMRM analysis was used. Intent-to-treat (ITT) Population included all randomized participants. Number analyzed is the number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	248	256	286	
Units: microns				
arithmetic mean (standard deviation)	-146.8 (± 118.1)	-141.7 (± 127.1)	-147.1 (± 126.2)	

Statistical analyses

Statistical analysis title	Mean Change from Baseline in CRT at Week 52

Statistical analysis description:

Superiority of abicipar was demonstrated if the lower limit of CI for the treatment difference was greater than zero.

Comparison groups	Ranibizumab (rQ4) v Abicipar pegol 2 mg (2Q8)
Number of subjects included in analysis	534
Analysis specification	Pre-specified
Analysis type	superiority[5]
Parameter estimate	LS Mean Difference
Point estimate	3.5
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-7.1
upper limit	14
Variability estimate	Standard error of the mean
Dispersion value	5.4

Notes:

[5] - MMRM included treatment, region, BL BCVA, BL CRT, choroidal neovascularization lesion type, visit, visit-by-baseline CRT interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix.

Statistical analysis title	Mean Change from Baseline in CRT at Week 52

Statistical analysis description:

Superiority of abicipar was demonstrated if the lower limit of CI for the treatment difference was greater than zero.

Comparison groups	Abicipar pegol 2 mg (2Q12) v Ranibizumab (rQ4)
Number of subjects included in analysis	542
Analysis specification	Pre-specified
Analysis type	superiority[6]
Parameter estimate	LS Mean Difference
Point estimate	5.9
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-4.7
upper limit	16.5
Variability estimate	Standard error of the mean
Dispersion value	5.4

Notes:

[6] - MMRM included treatment, region, BL BCVA, BL CRT, choroidal neovascularization lesion type, visit, visit-by-baseline CRT interaction, and treatment-by-visit interaction term as covariates using an unstructured covariance matrix

Secondary: Percentage of Participants with BCVA Gain of More Than 15 Letters From Baseline in the Study Eye

End point title	Percentage of Participants with BCVA Gain of More Than 15 Letters From Baseline in the Study Eye

End point description:

BCVA was measured using an eye chart and is reported as number of letters read correctly using the Early Treatment of Diabetic Retinopathy Study (ETDRS) Scale (ranging from 0 to 100 letters) in study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). An increase in the number of letters read correctly means that vision has improved. The percentage of participants with a BCVA gain of more than 15 letters are noted. Study eye was defined as the eye that meets the entry criteria. If both the eyes met all of the entry criteria, the eye with worse BCVA at baseline (Day 1) was selected. If BCVA values for both eyes were identical then participant had to select the non-dominant eye, or else right eye was selected as study eye. ITT Population included all randomized participants. Number analyzed is the number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	316	315	318	
Units: percentage of participants				
number (not applicable)	28.2	24.4	26.7	

Statistical analyses

Statistical analysis title	Participants with BCVA Gain of >15 Letters

Statistical analysis description:

The 95.1% CI for the weighted difference were calculated based on the Newcombe method using the Cochran-Mantel-Haenszel weights and baseline BCVA (≤55 vs >55 letters) as the stratification factor.

Comparison groups	Abicipar pegol 2 mg (2Q8) v Ranibizumab (rQ4)
Number of subjects included in analysis	634
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage Difference
Point estimate	1.4
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-5.5
upper limit	8.4

Statistical analysis title	Participants with BCVA Gain of >15 Letters

Statistical analysis description:

The 95.1% CI for the weighted difference were calculated based on the Newcombe method using the Cochran-Mantel-Haenszel weights and baseline BCVA (≤55 vs >55 letters) as the stratification factor.

Comparison groups	Abicipar pegol 2 mg (2Q12) v Ranibizumab (rQ4)

Number of subjects included in analysis	633
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Percentage Difference
Point estimate	-2.3
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-9.1
upper limit	4.5

Secondary: Mean Change from Baseline in the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) Composite Score

End point title	Mean Change from Baseline in the National Eye Institute Visual Functioning Questionnaire-25 (NEI-VFQ-25) Composite Score

End point description:

NEI-VFQ-25 consists of 25 vision-targeted questions that represent 11 vision-related quality of life subscales and one general health item. Responses of individual participants were recorded as scores that ranged between 0 (worst) to 100 (best vision related function) with higher scale indicating better vision. Overall composite score is then calculated by averaging over all 11 vision-targeted subscale scores, excluding general health score. Overall composite score was calculated based on mean of non-missing subscales. Study eye: eye that meets entry criteria. If both eyes met all of entry criteria, eye with worse BCVA at baseline (day 1) was selected. If BCVA values for both eyes were identical then participant had to select non-dominant eye, or else right eye was selected as study eye. A positive change from baseline indicates improvement. MMRM analysis was used. ITT population included all randomized participants. Number analyzed is the number of participants with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 52

End point values	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	254	261	287	
Units: scores on a scale				
least squares mean (standard error)	2.8 (± 0.7)	2.4 (± 0.7)	4.4 (± 0.7)	

Statistical analyses

Statistical analysis title	Mean Change from Baseline in NEI-VFQ-25 at Week 52

Statistical analysis description:

Superiority of abicipar was demonstrated if the lower limit of CI for the treatment difference was greater than zero.

Comparison groups	Abicipar pegol 2 mg (2Q8) v Ranibizumab (rQ4)

Number of subjects included in analysis	541
Analysis specification	Pre-specified
Analysis type	superiority[7]
Parameter estimate	LS Mean Difference
Point estimate	-1.6
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-3.5
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[7] - MMRM included treatment group, region, baseline BCVA in the study eye, baseline VFQ score, visit, and treatment-by-visit interaction as fixed covariates using an unstructured covariance matrix.

Statistical analysis title	Mean Change from Baseline in NEI-VFQ-25 at Week 52

Statistical analysis description:

Superiority of abicipar was demonstrated if the lower limit of CI for the treatment difference was greater than zero.

Comparison groups	Abicipar pegol 2 mg (2Q12) v Ranibizumab (rQ4)
Number of subjects included in analysis	548
Analysis specification	Pre-specified
Analysis type	superiority[8]
Parameter estimate	LS Mean Difference
Point estimate	-2
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-3.9
upper limit	-0.1
Variability estimate	Standard error of the mean
Dispersion value	1

Notes:

[8] - MMRM included treatment group, region, baseline BCVA in the study eye, baseline VFQ score, visit, and treatment-by-visit interaction as fixed covariates using an unstructured covariance matrix.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose up to last dose (Up to Week 104)	
Adverse event reporting additional description:	
Safety population included all treated participants.	
Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Abicipar pegol 2 mg (2Q8)

Reporting group description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 8, followed by injections every 8 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.

Reporting group title	Abicipar pegol 2 mg (2Q12)

Reporting group description:

Abicipar pegol 2 mg was administered to the study eye by intravitreal injection on Day 1, Week 4, and Week 12, followed by injections every 12 weeks through Week 96. Scheduled visits occurred every 4 weeks. To maintain masking, sham was administered to the study eye at scheduled visits where abicipar was not administered.

Reporting group title	Ranibizumab (rQ4)

Reporting group description:

Ranibizumab (Lucentis®) was administered to the study eye by intravitreal injection every 4 weeks from Day 1 through Week 96.

Serious adverse events	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)
Total subjects affected by serious adverse events			
subjects affected / exposed	94 / 313 (30.03%)	83 / 314 (26.43%)	78 / 315 (24.76%)
number of deaths (all causes)	11	6	7
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 313 (0.64%)	3 / 314 (0.96%)	6 / 315 (1.90%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Squamous cell carcinoma			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung adenocarcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal cancer metastatic			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Small cell lung cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Keratoacanthoma			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metastases to liver			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Retroperitoneal neoplasm metastatic			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thyroid cancer			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transitional cell carcinoma			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelodysplastic syndrome			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	0 / 315 (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
Bladder neoplasm			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Colorectal cancer metastatic			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Lung adenocarcinoma stage IV			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Meningioma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Small cell lung cancer metastatic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Squamous cell carcinoma of head and neck			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Pancreatic carcinoma			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Bladder transitional cell carcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Bowen’s disease			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Hepatic cancer			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Oropharyngeal squamous cell carcinoma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Plasma cell myeloma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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 cancer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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			
Hypertension			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic stenosis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertensive crisis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock haemorrhagic			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	0 / 315 (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
Blood pressure inadequately controlled			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Deep vein thrombosis			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic aneurysm rupture			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lymphoedema			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Peripheral artery aneurysm			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
General disorders and administration site conditions			
Peripheral swelling			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Death			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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			
Drug hypersensitivity			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Reproductive system and breast disorders			
Gynaecomastia			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostatomegaly			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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	2 / 313 (0.64%)	3 / 314 (0.96%)	3 / 315 (0.95%)
occurrences causally related to treatment / all	0 / 4	0 / 4	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Dyspnoea			
subjects affected / exposed	1 / 313 (0.32%)	2 / 314 (0.64%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Emphysema			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax spontaneous			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Pleural effusion			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (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
Epistaxis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Asthma			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Haemoptysis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Psychiatric disorders			
Hallucination			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental status changes			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depression			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Investigations			
Troponin increased			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intraocular pressure increased			
subjects affected / exposed	1 / 313 (0.32%)	2 / 314 (0.64%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Heart rate decreased			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Monoclonal immunoglobulin present			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Blood glucose abnormal			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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 pressure increased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Pulmonary function test decreased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Urine electrolytes decreased			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 313 (0.64%)	3 / 314 (0.96%)	3 / 315 (0.95%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femoral neck fracture			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Animal bite			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cervical vertebral fracture			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Concussion			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple fractures			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Scrotal haematoma			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Synovial rupture			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Traumatic liver injury			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular pseudoaneurysm			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	0 / 315 (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
Foot fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Hand fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Incisional hernia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Lower limb fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Periprosthetic fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Road traffic accident			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Skin laceration			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Skin wound			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Wrist fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Femur fracture			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	0 / 315 (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
Head injury			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	0 / 315 (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
Rib fracture			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	3 / 313 (0.96%)	5 / 314 (1.59%)	5 / 315 (1.59%)
occurrences causally related to treatment / all	0 / 3	0 / 5	0 / 5
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Atrial fibrillation			

subjects affected / exposed	2 / 313 (0.64%)	3 / 314 (0.96%)	5 / 315 (1.59%)
occurrences causally related to treatment / all	0 / 3	0 / 3	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			
subjects affected / exposed	1 / 313 (0.32%)	2 / 314 (0.64%)	3 / 315 (0.95%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Bradycardia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 313 (0.00%)	4 / 314 (1.27%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Acute myocardial infarction			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial oedema			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 313 (0.32%)	2 / 314 (0.64%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial ischaemia			
subjects affected / exposed	2 / 313 (0.64%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aortic valve disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Aortic valve incompetence			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Aortic valve stenosis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Atrioventricular block second degree			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Coronary artery occlusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Mitral valve incompetence			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Sinus bradycardia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Tachycardia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	3 / 315 (0.95%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 313 (0.00%)	3 / 314 (0.96%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem stroke			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar radiculopathy			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraesthesia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Piriformis syndrome			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Amnesia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Dizziness			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Hypoaesthesia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Optic neuritis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peroneal nerve palsy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Radiculopathy			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Vertebral artery occlusion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Carotid artery occlusion			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Carotid artery stenosis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Carpal tunnel syndrome			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Cerebral infarction			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Ischaemic stroke			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Speech disorder			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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 dementia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (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
Iron deficiency anaemia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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 positional			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniere’s disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	5 / 315 (1.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment			
subjects affected / exposed	3 / 313 (0.96%)	0 / 314 (0.00%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	2 / 313 (0.64%)	3 / 314 (0.96%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal fibrosis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal pigment epithelial tear			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uveitis			

subjects affected / exposed	7 / 313 (2.24%)	4 / 314 (1.27%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	7 / 7	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vasculitis			
subjects affected / exposed	4 / 313 (1.28%)	4 / 314 (1.27%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	4 / 4	4 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced			
subjects affected / exposed	1 / 313 (0.32%)	3 / 314 (0.96%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	2 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitritis			
subjects affected / exposed	4 / 313 (1.28%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	4 / 4	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Iridocyclitis			
subjects affected / exposed	2 / 313 (0.64%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal artery occlusion			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Age-related macular degeneration			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Autoimmune uveitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Choroidal neovascularisation			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Neovascular age-related macular degeneration			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Retinal vein occlusion			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anterior chamber inflammation			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Keratitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Macular hole			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Serous retinal detachment			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Alcoholic pancreatitis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulum			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal perforation			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritoneal haemorrhage			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 313 (0.00%)	2 / 314 (0.64%)	0 / 315 (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
Intestinal obstruction			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Pancreatitis acute			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Vomiting			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain upper			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Constipation			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Duodenal ulcer			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Gastrointestinal ulcer haemorrhage			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Large intestine polyp			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Pharyngo-oesophageal diverticulum			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Renal and urinary disorders			
Nephrolithiasis			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (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
Haematuria			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Musculoskeletal and connective tissue disorders			
Osteoarthritis			

subjects affected / exposed	2 / 313 (0.64%)	1 / 314 (0.32%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rotator cuff syndrome			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone loss			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscular weakness			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (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
Back pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Flank pain			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Foot fracture			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Haemarthrosis			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Muscle spasms			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Spinal column stenosis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Spondylolisthesis			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Synovial cyst			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Bursitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Trigger finger			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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	4 / 313 (1.28%)	3 / 314 (0.96%)	8 / 315 (2.54%)
occurrences causally related to treatment / all	0 / 4	0 / 3	0 / 11
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 1
Diverticulitis			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	2 / 315 (0.63%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	5 / 313 (1.60%)	4 / 314 (1.27%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	5 / 5	5 / 5	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal abscess			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteritis infective			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis viral			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
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 infection			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infective aortitis			

subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	1 / 313 (0.32%)	1 / 314 (0.32%)	0 / 315 (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
Cytomegalovirus infection			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Pneumonia escherichia			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Pyelonephritis acute			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Septic shock			

subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	3 / 313 (0.96%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	2 / 313 (0.64%)	0 / 314 (0.00%)	0 / 315 (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
Cellulitis staphylococcal			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Clostridium difficile colitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea infectious			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Gastroenteritis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Infectious colitis			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Pulmonary sepsis			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 313 (0.64%)	2 / 314 (0.64%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 313 (0.00%)	0 / 314 (0.00%)	1 / 315 (0.32%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malnutrition			
subjects affected / exposed	0 / 313 (0.00%)	1 / 314 (0.32%)	0 / 315 (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
Fluid overload			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Hypoglycaemia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Hypokalaemia			
subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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
Vitamin B12 deficiency			

subjects affected / exposed	1 / 313 (0.32%)	0 / 314 (0.00%)	0 / 315 (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

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

Non-serious adverse events	Abicipar pegol 2 mg (2Q8)	Abicipar pegol 2 mg (2Q12)	Ranibizumab (rQ4)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	168 / 313 (53.67%)	166 / 314 (52.87%)	166 / 315 (52.70%)
Investigations			
Intraocular pressure increased			
subjects affected / exposed	29 / 313 (9.27%)	29 / 314 (9.24%)	20 / 315 (6.35%)
occurrences (all)	48	58	50
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 313 (4.15%)	14 / 314 (4.46%)	22 / 315 (6.98%)
occurrences (all)	15	16	23
Vascular disorders			
Hypertension			
subjects affected / exposed	18 / 313 (5.75%)	22 / 314 (7.01%)	16 / 315 (5.08%)
occurrences (all)	19	25	21
Nervous system disorders			
Headache			
subjects affected / exposed	11 / 313 (3.51%)	18 / 314 (5.73%)	17 / 315 (5.40%)
occurrences (all)	13	18	25
Eye disorders			
Eye pain			
subjects affected / exposed	37 / 313 (11.82%)	35 / 314 (11.15%)	36 / 315 (11.43%)
occurrences (all)	53	50	69
Conjunctival haemorrhage			
subjects affected / exposed	24 / 313 (7.67%)	29 / 314 (9.24%)	29 / 315 (9.21%)
occurrences (all)	32	35	49
Conjunctival hyperaemia			
subjects affected / exposed	17 / 313 (5.43%)	15 / 314 (4.78%)	23 / 315 (7.30%)
occurrences (all)	21	19	30
Neovascular age-related macular degeneration			

subjects affected / exposed	18 / 313 (5.75%)	25 / 314 (7.96%)	21 / 315 (6.67%)
occurrences (all)	18	25	21
Vitreous floaters			
subjects affected / exposed	27 / 313 (8.63%)	30 / 314 (9.55%)	17 / 315 (5.40%)
occurrences (all)	41	45	25
Vitreous detachment			
subjects affected / exposed	16 / 313 (5.11%)	17 / 314 (5.41%)	11 / 315 (3.49%)
occurrences (all)	21	19	12
Visual acuity reduced			
subjects affected / exposed	17 / 313 (5.43%)	15 / 314 (4.78%)	6 / 315 (1.90%)
occurrences (all)	18	16	8
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	33 / 313 (10.54%)	35 / 314 (11.15%)	40 / 315 (12.70%)
occurrences (all)	46	46	60
Influenza			
subjects affected / exposed	19 / 313 (6.07%)	15 / 314 (4.78%)	22 / 315 (6.98%)
occurrences (all)	21	17	26
Urinary tract infection			
subjects affected / exposed	22 / 313 (7.03%)	21 / 314 (6.69%)	12 / 315 (3.81%)
occurrences (all)	31	33	12

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 March 2015	Following changes were implemented with Amendment 1: •Moved Ocular Exclusion Criteria (Either Eye) to immediately follow General Exclusion Criteria •Revised exclusion criterion 8: Active ocular/intraocular infection at baseline (day 1) •Revised exclusion criterion 9: History of recurrent or currently active ocular/intraocular inflammation (eg, uveitis) at baseline (day 1) •Added ocular exclusion criterion 10: History or clinical evidence of diabetic retinopathy, diabetic macular edema (DME) or any retinal vascular disease other than age-related macular degeneration (AMD) at screening •Reorganized list of Ocular Exclusion Criteria (Study Eye) •Added ocular exclusion criterion (study eye) 11: Presence of choroidal neovascularization (CNV) other than AMD at screening •Added ocular exclusion criterion (study eye) #16: Prior use of ocular anti-VEGF agents for neovascular eye diseases other than AMD •Clarified pre-treatment administration preparation protocol to include use of 5% povidone iodine irrigation/saline flush, periocular 10% povidone iodine, topical antibiotics instilled 15, 10, and 5 minutes prior to treatment administration, and topical anesthesia. Removed dispensing of participants administered antibiotic drops •Revised Randomization/Stratification as follows: participants were randomized by region to 3 treatment groups (2Q8, 2Q12, and rQ4). Within each region, allocation to treatment groups was stratified by the following 3 factors using at a ratio of 1:1:1 •Added draw blood samples for immunogenicity analysis (Week 4 only) •Removed National Eye Institute Visual Functioning Questionnaire (25 questions) (NEI-VFQ-25) vision related subscale scores from secondary analyses •Modified footnote g to require immunogenicity sample collection when a significant treatment-related adverse event is noted •Added footnote p: "Visit dates and visit windows are calculated from actual date of baseline study treatment administration".
28 April 2016	Following changes were implemented with Amendment 2: •Study duration from 100 to 104 weeks throughout protocol •Revised inclusion criterion: Presence of active subfoveal and/or juxtafoveal CNV secondary to AMD assessed by fluorescein angiogram. In addition, presence of retinal fluid on optical coherence tomography (OCT) and/or fluorescein leakage under the fovea as assessed by investigator at screening and confirmed by central reading center prior to baseline•Revised exclusion criterion: Active periocular, ocular, or /intraocular infection at baseline•Revised exclusion criterion: Previous or concurrent macular laser treatment •Revised exclusion criterion: Structural damage to the center of macula that is likely to preclude improvement in BCVA assessed by investigator at screening and confirmed by central reading center prior to baseline including any of following: Macular hole stage 3 or 4 Atrophy of retinal pigment epithelium (RPE) Retinal fibrosis or scarring •Added Week 104 as study exit or early termination visit, week 100 was a study assessment visit without study treatment for all treatment groups •Visit windows for Weeks 4 through 24, Weeks 28 through 48, Weeks 52 through 96, and Weeks 100 through 104/early exit has been changed from ±5 days to ±7 days; accompanying footnote "p" was updated to include that minimum interval between 2 study visits ≥ 20 days •Updated the minimum and maximum number of visits scheduled •Updated to include purpose of monitoring •Updated exclusion criterion to refer to povidone iodine solution •Added clarification to criteria for escape to standard of care: Persistent fluid by OCT, judged to be cause of BCVA loss.

28 April 2016	•Updated: Participants who escape to standard of care were required to complete the study exit procedures indicated at week 100 104/early exit visit and were reevaluated at subsequent follow-up visits: 1) 4 or 8 weeks, 2) approximately 16 weeks, and 3) approximately 52 and 100 weeks after baseline for BCVA, CRT, and adverse event assessment •Added: In addition, a post-injection safety follow-up phone call (up to 3 days following the office visit) should be performed for all enrolled participants after the administration of each study treatment. Postinjection safety follow-up may be completed in-office for participants who participate in blood sample collection for PK analysis •Added that if non-inferiority for both abicipar arms is established, that superiority testing of abicipar over ranibizumab was performed •Analysis updated to be based on ANCOVA with baseline BCVA as a covariate •Updated to describe additional analyses if non-inferiority for both abicipar arms is established • Updated week 100 visit procedures to reflect changes to Table 1 based on addition of week 104/exit visit •New section to list visit procedures at week 104/early exit •Updated as follows: Participants who discontinue early due to other reasons was required to complete the study exit procedures indicated at the week 104/early exit visit and were reevaluated at the subsequent follow-up visits: 1) approximately 16 weeks after the last study medication injection for immunogenicity, BCVA, CRT, and adverse events assessments, and 2) approximately 52 and 100 weeks after baseline for BCVA, CRT, and adverse event assessments.
23 February 2017	The following changes were implemented with Amendment 3 •Participation in long-term safety study: - footnote "o" in Table 1, -last bullet regarding an offer to evaluate participation in a long-term safety study •Updated to reflect the current template language with regards to conducting the study in accordance with applicable laws and regulations.
10 April 2018	The following changes were implemented with Amendment 4: •Changed the analysis population for the non-inferiority test of the primary and the key secondary efficacy variable of BCVA mean change from intent-to-treat (ITT) to Per protocol (PP); ITT analysis for non-inferiority was performed as well but was considered as sensitivity analysis •Added MMRM for analysis of secondary efficacy (continuous) variables as the primary method; ANCOVA was performed as well but was considered as sensitivity analysis •Removed subgroup analyses section.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported