Clinical trial results:
Managing neovascular age-related macular degeneration (nAMD) over 2 years with a Treat and Extend (T&E) regimen of 2 mg intravitreal aflibercept - a randomized, open-label, active-controlled, parallel-group phase IV/IIIb study (ARIES)

Summary

EudraCT number	2014-003132-39
Trial protocol	GB ES FR IT
Global end of trial date	26 April 2019

Results information

Result version number	v1 (current)
This version publication date	08 May 2020
First version publication date	08 May 2020

Trial information

Trial identification

Sponsor protocol code	BAY 86-5321/17508

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02581891
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	27 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess whether 2 mg Intravitreal (IVT) aflibercept administered in an early-start T&E regimen (initiated after the first 8-weekly treatment interval) is non-inferior to 2 mg IVT aflibercept administered in a late-start T&E regimen (initiated at the end of Year 1, per current label at that time) in subjects with nAMD.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Conference on Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent form was read by and explained to all subjects. Participating subjects signed informed consent form and could withdraw from the study at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 November 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 34
Country: Number of subjects enrolled	Canada: 30
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 48
Country: Number of subjects enrolled	Hungary: 80
Country: Number of subjects enrolled	Italy: 46
Country: Number of subjects enrolled	Spain: 24
Country: Number of subjects enrolled	United Kingdom: 16
Worldwide total number of subjects	287
EEA total number of subjects	257

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)	26
From 65 to 84 years	212
85 years and over	49

Subject disposition

Recruitment

Recruitment details:

This study was conducted from 19-Nov-2015 (First Patient First Visit) to 26-Apr-2019 (Last Patient Last Visit).

Pre-assignment

Screening details:

A total of 443 participants were enrolled in this study. Of these, 156 participants were screening failures and did not enter the treatment period. Of the 287 treated participants, 16 were treated during the initiation phase, but were not randomized to a treatment arm after the initiation phase.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Early-start T&E arm

Arm description:

All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 to Week 104 participants randomized to Early-start T&E arm (Treat and Extend arm) received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	Eylea
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

The volume of injection was 50 µL (0.05 mL) for the 2 mg aflibercept dose, and was administered via IVT injection to the study eye.

Arm title	Late-start T&E arm

Arm description:

All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 participants randomized to Late-start T&E arm received four 2Q8 injections. In Year 2 starting at Week 48, participants received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	BAY86-5321
Other name	Eylea
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

The volume of injection was 50 µL (0.05 mL) for the 2 mg aflibercept dose, and was administered via IVT injection to the study eye.

Number of subjects in period 1[1]	Early-start T&E arm	Late-start T&E arm
Started	135	136
Completed treatment	120	117
Completed	119	117
Not completed	16	19
Discontinued during followup	1	-
Adverse event, serious fatal	3	4
Consent withdrawn by subject	4	5
Physician decision	-	1
Adverse event, non-fatal	4	6
Other Reasons	3	1
Lost to follow-up	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Sixteen participants who were treated in initiation phase were not randomized and allocated to a treatment arm.

Baseline characteristics

Reporting groups	
Reporting group title	Early-start T&E arm
Reporting group description:	
All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 to Week 104 participants randomized to Early-start T&E arm (Treat and Extend arm) received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.	
Reporting group title	Late-start T&E arm
Reporting group description:	
All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 participants randomized to Late-start T&E arm received four 2Q8 injections. In Year 2 starting at Week 48, participants received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.	

Reporting group values	Early-start T&E arm	Late-start T&E arm	Total
Number of subjects	135	136	271
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	16	9	25
From 65-84 years	95	106	201
85 years and over	24	21	45
Age Continuous Units: Years			
arithmetic mean	76	76.9	
standard deviation	± 8.8	± 8.2	-
Sex: Female, Male Units: Participants			
Female	81	73	154
Male	54	63	117
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	1	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	131	127	258
More than one race	0	0	0
Unknown or Not Reported	1	8	9
Ethnicity (NIH/OMB) Units: Subjects			

Hispanic or Latino	3	7	10
Not Hispanic or Latino	126	122	248
Unknown or Not Reported	6	7	13
Baseline BCVA letters scores (study eye)			
BCVA = best corrected visual acuity			
Units: letters			
arithmetic mean	60.2	61.3	
standard deviation	± 12.1	± 10.8	-
Baseline CRT			
CRT = central retinal thickness			
Units: µm			
arithmetic mean	443.7	448.3	
standard deviation	± 120.0	± 133.1	-
BCVA letters scores at Week 16 (study eye)			
BCVA = best corrected visual acuity			
Units: letters			
arithmetic mean	66.7	69.6	
standard deviation	± 13.0	± 11.6	-
CRT at Week 16 (study eye)			
CRT = central retinal thickness			
Units: µm			
arithmetic mean	321.4	322.5	
standard deviation	± 93.4	± 104.0	-

End points

End points reporting groups

Reporting group title	Early-start T&E arm

Reporting group description:

All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 to Week 104 participants randomized to Early-start T&E arm (Treat and Extend arm) received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.

Reporting group title	Late-start T&E arm

Reporting group description:

All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 participants randomized to Late-start T&E arm received four 2Q8 injections. In Year 2 starting at Week 48, participants received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.

Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis

Subject analysis set description:

The FAS included all randomized subjects who received any study drug and have a BCVA assessment at Week 16 and at least 1 additional post-Week 16 BCVA assessment. The FAS were analyzed "as randomized".

Subject analysis set title	Per-protocol Set (PPS)
Subject analysis set type	Per protocol

Subject analysis set description:

The PPS includes all subjects in the FAS without any major protocol deviation. Additionally, injection-intensive subjects who needed injections at shorter intervals than 2Q8 between Week 16 and Week 52 were excluded from the PPS.

Subject analysis set title	Safety Analysis Set (SAF)
Subject analysis set type	Safety analysis

Subject analysis set description:

The SAF includes all subjects who received any study drug under this protocol. In the safety analysis subjects who dropped out after start of treatment before randomization were described only in "total", since no allocation of such subjects to a treatment arm is possible.

Primary: Change in BCVA as measured by the ETDRS letter score

End point title	Change in BCVA as measured by the ETDRS letter score

End point description:

BCVA (best corrected visual acuity) was measured by the ETDRS (Early Treatment Diabetic Retinopathy Study) letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters; a higher score represents better functioning.

End point type	Primary

End point timeframe:

From Week 16 to Week 104

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[1]	104[2]		
Units: Letters correctly read				
arithmetic mean (standard deviation)	-2.1 (± 11.4)	-0.4 (± 8.4)		

Notes:
[1] - PPS
[2] - PPS

Statistical analyses

Statistical analysis title	Analysis of covariance for BCVA change
Comparison groups	Early-start T&E arm v Late-start T&E arm
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0162
Method	ANCOVA
Parameter estimate	LS means difference
Point estimate	-2.0199
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.747
upper limit	0.7073
Variability estimate	Standard error of the mean
Dispersion value	1.3833

Secondary: Percentage of participants maintaining vision (<3 lines loss) at Week 104 compared with baseline

End point title	Percentage of participants maintaining vision (<3 lines loss) at Week 104 compared with baseline

End point description:

Participants maintained 3 lines (15 letters) vision loss in BCVA (Best-corrected visual acuity) as measured by the ETDRS (Early Treatment Diabetic Retinopathy Study) letter.

End point type	Secondary

End point timeframe:

at Week 104

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[3]	104[4]		
Units: Percentage				
number (not applicable)	93.4	96.2		

Notes:
[3] - PPS
[4] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Change in BCVA from baseline to Week 52, baseline to Week 104, and Week 16 to Week 52

End point title	Change in BCVA from baseline to Week 52, baseline to Week 104, and Week 16 to Week 52

End point description:

BCVA (best corrected visual acuity) was measured by the ETDRS (Early Treatment Diabetic Retinopathy Study) letter score of 73 to 25 (= Acuity of 20/40 to 20/320) in the study eye at 4 meters; a higher score represents better functioning.

End point type	Secondary

End point timeframe:

from baseline to Week 52, baseline to Week 104, and Week 16 to Week 52

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[5]	104[6]		
Units: Letters				
arithmetic mean (standard deviation)				
From baseline to Week 52	7.8 (± 9.4)	10.2 (± 9.3)		
From baseline to Week 104	4.3 (± 13.4)	7.9 (± 11.9)		
From Week 16 to Week 52	1.3 (± 6.4)	2.0 (± 5.3)		

Notes:

[5] - PPS

[6] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants maintaining vision (<3 lines loss) at Week 52 compared with baseline

End point title	Percentage of participants maintaining vision (<3 lines loss) at Week 52 compared with baseline

End point description:

Participants maintained 3 lines (15 letters) vision loss in BCVA (Best-corrected visual acuity) as measured by the ETDRS (Early Treatment Diabetic Retinopathy Study) letter.

End point type	Secondary

End point timeframe:

At week 52

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[7]	104[8]		
Units: Percentage				
number (not applicable)	100.0	100.0		

Notes:

[7] - PPS

[8] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants gained 3-line at Week 52 and Week 104 compared with baseline

End point title	Percentage of participants gained 3-line at Week 52 and Week 104 compared with baseline

End point description:

Participants gained 3 lines (15 letters) in BCVA (Best-corrected visual acuity) as measured by the ETDRS (Early Treatment Diabetic Retinopathy Study) letter.

End point type	Secondary

End point timeframe:

At Week 52 and Week 104

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[9]	104[10]		
Units: Percentage				
number (not applicable)				
Week 52	19.8	27.9		
Week 104	18.9	22.1		

Notes:

[9] - PPS

[10] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Change in Central Retinal Thickness (CRT)

End point title	Change in Central Retinal Thickness (CRT)

End point description:

CRT were evaluated using spectral domain Optical coherence tomograph (OCT).

End point type	Secondary

End point timeframe:

From baseline to Week 52, baseline to Week 104, Week 16 to Week 52, and Week 16 to Week 104

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[11]	104[12]		
Units: Letters				
arithmetic mean (standard deviation)				
From baseline to Week 52	-164.9 (± 117.3)	-167.1 (± 117.1)		
From baseline to Week 104	-161.6 (± 135.6)	-158.6 (± 125.1)		
From Week 16 to Week 52	-28.5 (± 56.3)	-28.7 (± 54.0)		
From Week 16 to Week 104	-25.1 (± 68.9)	-20.2 (± 70.0)		

Notes:

[11] - PPS

[12] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of study drug injections from baseline to Week 52 and baseline to Week 104

End point title	Number of study drug injections from baseline to Week 52 and baseline to Week 104

End point description:

End point type	Secondary

End point timeframe:

At Week 52 and Week 104

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[13]	104[14]		
Units: injections				
arithmetic mean (standard deviation)				
Week 52	7.1 (± 0.8)	8.0 (± 0.2)		
Week 104	12.0 (± 2.3)	13.0 (± 1.8)		

Notes:

[13] - PPS

[14] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of last treatment interval

End point title	Duration of last treatment interval

End point description:

End point type	Secondary

End point timeframe:

Early-Start T&E: from week 16 up to Week 104 or early termination; Late-Start T&E: From end of Year 1 up to Week 104 or early termination

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[15]	104[16]		
Units: Weeks				
arithmetic mean (standard deviation)	11.5445 (± 3.7336)	11.3819 (± 3.6845)		

Notes:

[15] - PPS

[16] - PPS

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants requiring retreatment at 8 weeks, 10 weeks, 12 weeks, 14 weeks, and 16 weeks as the last treatment interval

End point title	Percentage of participants requiring retreatment at 8 weeks, 10 weeks, 12 weeks, 14 weeks, and 16 weeks as the last treatment interval

End point description:

End point type	Secondary

End point timeframe:

at 8 weeks, 10 weeks, 12 weeks, 14 weeks, and 16 weeks

End point values	Early-start T&E arm	Late-start T&E arm		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	106[17]	104[18]		
Units: percentage				
number (not applicable)				
<8 weeks	5.7	7.7		
8 weeks	27.4	29.8		
10 weeks	19.8	10.6		
12 weeks	8.5	13.5		
14 weeks	8.5	11.5		
16 weeks	25.5	25.0		
>16 weeks	4.7	1.9		

Notes:
[17] - PPS
[18] - PPS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment-emergent adverse events (TEAEs) were AEs that started after the first application of aflibercept up to 30 days after last study drug Injection in the study. TEAEs were collected Week 0 till End of study/Week 104 or early termination.

Adverse event reporting additional description:

Below adverse events were reported based on Safety Analysis Set (SAF), which included all participants who received any study drug in this study. The participants who dropped out after start of treatment before randomization were not allocated to a treatment arm, but were included in this SAF.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Early-start T&E arm

Reporting group description:

All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 to Week 104 participants randomized to Early-start T&E arm (Treat and Extend arm) received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.

Reporting group title	Late-start T&E arm

Reporting group description:

All participants during the initiation phase received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4, and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks) at Week 16. From Week 16 participants randomized to Late-start T&E arm received four 2Q8 injections. In Year 2 starting at Week 48, participants received treatment in individualized intervals of between 8 to16 weeks based on anatomical criteria.

Reporting group title	Treated, but not randomized

Reporting group description:

Participants were treated during the initiation phase, received Aflibercept (Eylea, BAY86-5321) 3 doses at Weeks 0, 4 and 8 followed by one dose 2Q8 (2 mg administered every 8 weeks)at Week 16, but were not randomized to a treatment arm after the initiation phase.

Serious adverse events	Early-start T&E arm	Late-start T&E arm	Treated, but not randomized
Total subjects affected by serious adverse events			
subjects affected / exposed	29 / 135 (21.48%)	35 / 136 (25.74%)	3 / 16 (18.75%)
number of deaths (all causes)	3	4	0
number of deaths resulting from adverse events	1	2	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			

subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Bladder neoplasm			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Breast cancer			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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 myeloid leukaemia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Lung neoplasm malignant			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Lung neoplasm			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Epithelioid mesothelioma			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Papillary renal cell carcinoma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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			
Aortic aneurysm			

subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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 dissection			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Haematoma			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Hypovolaemic shock			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Intermittent claudication			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Deep vein thrombosis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Extremity necrosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Peripheral artery stenosis			

subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Surgical and medical procedures			
Implantable defibrillator replacement			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
General disorders and administration site conditions			
Hernia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Pyrexia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Cough			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Dyspnoea			

subjects affected / exposed	0 / 135 (0.00%)	2 / 136 (1.47%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Psychiatric disorders			
Suicide attempt			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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			
Concussion			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Facial bones fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Hip fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Rib fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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

Splenic rupture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Traumatic fracture			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Inflammation of wound			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Pelvic fracture			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	1 / 16 (6.25%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Atrial flutter			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	2 / 135 (1.48%)	0 / 136 (0.00%)	0 / 16 (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
Cor pulmonale acute			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Coronary artery stenosis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Myocardial infarction			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Pericardial haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Ventricular tachycardia			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Congestive cardiomyopathy			

subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Cardiac valve disease			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Cerebrovascular accident			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	2 / 16 (12.50%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhagic stroke			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Hemiplegia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Vertebrobasilar insufficiency			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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			

Eye inflammation			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Retinal artery embolism			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Visual acuity reduced			
subjects affected / exposed	0 / 135 (0.00%)	2 / 136 (1.47%)	0 / 16 (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
Visual impairment			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Eyelid cyst			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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 disorders			
Abdominal pain			
subjects affected / exposed	2 / 135 (1.48%)	0 / 136 (0.00%)	0 / 16 (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
Constipation			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Duodenal ulcer perforation			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Gastritis			

subjects affected / exposed	1 / 135 (0.74%)	1 / 136 (0.74%)	0 / 16 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Haematochezia			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Ileus			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Inguinal hernia			
subjects affected / exposed	2 / 135 (1.48%)	1 / 136 (0.74%)	0 / 16 (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
Intestinal perforation			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Pancreatitis acute			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Small intestinal obstruction			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Large intestine polyp			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Noninfective sialoadenitis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Biliary colic			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Cholangitis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Cholecystitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Cholecystitis acute			
subjects affected / exposed	2 / 135 (1.48%)	2 / 136 (1.47%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			

subjects affected / exposed	1 / 135 (0.74%)	1 / 136 (0.74%)	0 / 16 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
End stage renal disease			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Intervertebral disc disorder			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Fracture pain			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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			
Bronchitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Cystitis			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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

Influenza			
subjects affected / exposed	2 / 135 (1.48%)	0 / 136 (0.00%)	0 / 16 (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
Pneumonia			
subjects affected / exposed	3 / 135 (2.22%)	5 / 136 (3.68%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pseudomonal			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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
Sepsis			
subjects affected / exposed	1 / 135 (0.74%)	1 / 136 (0.74%)	0 / 16 (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
Enterococcal sepsis			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (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
Infective exacerbation of chronic obstructive airways disease			
subjects affected / exposed	3 / 135 (2.22%)	0 / 136 (0.00%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenovirus infection			
subjects affected / exposed	1 / 135 (0.74%)	0 / 136 (0.00%)	0 / 16 (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			
Fluid overload			
subjects affected / exposed	0 / 135 (0.00%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Early-start T&E arm	Late-start T&E arm	Treated, but not randomized
Total subjects affected by non-serious adverse events			
subjects affected / exposed	93 / 135 (68.89%)	80 / 136 (58.82%)	10 / 16 (62.50%)
Injury, poisoning and procedural complications			
Foreign body in eye			
subjects affected / exposed	0 / 135 (0.00%)	0 / 136 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Post procedural swelling			
subjects affected / exposed	0 / 135 (0.00%)	0 / 136 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1
Vascular disorders			
Hypertension			
subjects affected / exposed	13 / 135 (9.63%)	11 / 136 (8.09%)	0 / 16 (0.00%)
occurrences (all)	15	11	0
Eye disorders			
Blepharitis			
subjects affected / exposed	2 / 135 (1.48%)	11 / 136 (8.09%)	0 / 16 (0.00%)
occurrences (all)	6	25	0
Cataract			
subjects affected / exposed	9 / 135 (6.67%)	8 / 136 (5.88%)	0 / 16 (0.00%)
occurrences (all)	14	13	0
Cataract nuclear			
subjects affected / exposed	2 / 135 (1.48%)	7 / 136 (5.15%)	0 / 16 (0.00%)
occurrences (all)	4	16	0
Conjunctival haemorrhage			
subjects affected / exposed	20 / 135 (14.81%)	18 / 136 (13.24%)	0 / 16 (0.00%)
occurrences (all)	26	20	0
Corneal erosion			
subjects affected / exposed	5 / 135 (3.70%)	2 / 136 (1.47%)	1 / 16 (6.25%)
occurrences (all)	6	3	1

Dry eye			
subjects affected / exposed	6 / 135 (4.44%)	11 / 136 (8.09%)	0 / 16 (0.00%)
occurrences (all)	11	18	0
Erythema of eyelid			
subjects affected / exposed	0 / 135 (0.00%)	0 / 136 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Macular degeneration			
subjects affected / exposed	6 / 135 (4.44%)	5 / 136 (3.68%)	1 / 16 (6.25%)
occurrences (all)	6	5	1
Punctate keratitis			
subjects affected / exposed	10 / 135 (7.41%)	5 / 136 (3.68%)	1 / 16 (6.25%)
occurrences (all)	23	9	1
Retinal haemorrhage			
subjects affected / exposed	4 / 135 (2.96%)	6 / 136 (4.41%)	2 / 16 (12.50%)
occurrences (all)	4	7	2
Swelling of eyelid			
subjects affected / exposed	0 / 135 (0.00%)	0 / 136 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	2
Visual acuity reduced			
subjects affected / exposed	21 / 135 (15.56%)	17 / 136 (12.50%)	1 / 16 (6.25%)
occurrences (all)	24	19	1
Visual impairment			
subjects affected / exposed	8 / 135 (5.93%)	4 / 136 (2.94%)	0 / 16 (0.00%)
occurrences (all)	11	4	0
Vitreous floaters			
subjects affected / exposed	8 / 135 (5.93%)	4 / 136 (2.94%)	0 / 16 (0.00%)
occurrences (all)	8	5	0
Vitreous adhesions			
subjects affected / exposed	1 / 135 (0.74%)	2 / 136 (1.47%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Choroidal neovascularisation			
subjects affected / exposed	7 / 135 (5.19%)	5 / 136 (3.68%)	0 / 16 (0.00%)
occurrences (all)	7	5	0
Retinal pigment epithelial tear			
subjects affected / exposed	3 / 135 (2.22%)	2 / 136 (1.47%)	1 / 16 (6.25%)
occurrences (all)	3	2	1

Neovascular age-related macular degeneration			
subjects affected / exposed	15 / 135 (11.11%)	14 / 136 (10.29%)	1 / 16 (6.25%)
occurrences (all)	15	14	1
Macular fibrosis			
subjects affected / exposed	2 / 135 (1.48%)	6 / 136 (4.41%)	1 / 16 (6.25%)
occurrences (all)	2	6	1
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	8 / 135 (5.93%)	1 / 136 (0.74%)	0 / 16 (0.00%)
occurrences (all)	9	1	0
Musculoskeletal pain			
subjects affected / exposed	1 / 135 (0.74%)	2 / 136 (1.47%)	1 / 16 (6.25%)
occurrences (all)	1	2	1
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	0 / 135 (0.00%)	3 / 136 (2.21%)	1 / 16 (6.25%)
occurrences (all)	0	3	1
Influenza			
subjects affected / exposed	11 / 135 (8.15%)	12 / 136 (8.82%)	0 / 16 (0.00%)
occurrences (all)	12	13	0
Nasopharyngitis			
subjects affected / exposed	18 / 135 (13.33%)	17 / 136 (12.50%)	0 / 16 (0.00%)
occurrences (all)	21	22	0
Metabolism and nutrition disorders			
Dyslipidaemia			
subjects affected / exposed	0 / 135 (0.00%)	0 / 136 (0.00%)	1 / 16 (6.25%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 February 2016	Major modifications included the following: • The special case of a diagnosis of "completely dry" was added to the early start T&E arm, • anatomical criteria for extending the treatment intervals were clarified, • the option of not extending the treatment interval, even if all anatomical criteria are met, was removed, • the specification of Choroidal neovascularization (CNV) lesions were simplified (Inclusion criterion 3), and the percentage of total lesions for scar or fibrosis was reduced (Exclusion criterion 6).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported