EU Clinical Trials Register

Clinical trial results:
Open-label Phase-4 study to examine the change of vision-related quality of life in subjects with diabetic macular edema (DME) during treatment with intravitreal injections of 2 mg aflibercept according to EU label for the first year of treatment

Summary

EudraCT number	2014-005119-17
Trial protocol	HU CZ SK IT LT ES PT FR DE AT GB
Global end of trial date	09 August 2017

Results information

Result version number	v1 (current)
This version publication date	12 August 2018
First version publication date	12 August 2018

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/17850

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02581995
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, D-51368 Leverkusen, Germany,
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	09 August 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 August 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to evaluate the change in vision-related quality of life (VRQoL) (National Eye Institute Visual Function Questionnaire-25 [NEI VFQ-25] total score) in subjects with diabetic macular edema (DME) during the first year of treatment with aflibercept according to the european union product information (EU-PI) for treatment of DME.

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 Council for 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	Canada: 20
Country: Number of subjects enrolled	Czech Republic: 42
Country: Number of subjects enrolled	Austria: 10
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 21
Country: Number of subjects enrolled	Hungary: 127
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Lithuania: 14
Country: Number of subjects enrolled	Poland: 94
Country: Number of subjects enrolled	Portugal: 30
Country: Number of subjects enrolled	Slovakia: 87
Country: Number of subjects enrolled	Spain: 53
Country: Number of subjects enrolled	Switzerland: 5
Country: Number of subjects enrolled	United Kingdom: 18
Worldwide total number of subjects	560
EEA total number of subjects	535

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)	272
From 65 to 84 years	285
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple study centers in 14 countries, between 19 November 2015 (first subject first visit) and 09 August 2017 (last subject last visit).

Pre-assignment

Screening details:

Overall, 676 subjects were screened. Of them, 116 subjects did not complete screening: 100 failed screening; 8 withdrew, 1 had an adverse event, 1 subject was lost to follow-up and 6 were not assigned to treatment for other reasons. A total of 560 subjects were assigned to treatment and 31 subjects discontinued the study prematurely.

Period 1

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

Arms

Arm title	Aflibercept

Arm description:

Subjects were treated according to the EU-PI for treatment of DME for the first year of treatment and received 1 dose of 2 mg aflibercept injected intravitreally (IVT) every 4 weeks for 5 consecutive doses, followed by dosing every 8 weeks thereafter until the end of the 52 week treatment period.

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

Dosage and administration details:

Subjects were treated according to the EU-PI for treatment of DME for the first year of treatment and received 1 dose of 2 mg aflibercept injected IVT every 4 weeks for 5 consecutive doses, followed by dosing every 8 weeks thereafter until the end of the 52 week treatment period.

Number of subjects in period 1	Aflibercept
Started	560
Completed	529
Not completed	31
Physician decision	1
Death	4
Other	3
Adverse event	6
Lost to follow-up	5
Withdrawal by subject	12

Baseline characteristics

Reporting groups

Reporting group title	Aflibercept
Reporting group description:	

Subjects were treated according to the EU-PI for treatment of DME for the first year of treatment and received 1 dose of 2 mg aflibercept injected intravitreally (IVT) every 4 weeks for 5 consecutive doses, followed by dosing every 8 weeks thereafter until the end of the 52 week treatment period.

Reporting group values	Aflibercept	Total	
Number of subjects	560	560	
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	64.3		
standard deviation	± 9.3	-	
Sex: Female, Male			
Units: Subjects			
Female	224	224	
Male	336	336	
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	4	4	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	3	3	
White	519	519	
More than one race	0	0	
Unknown or Not Reported	34	34	
DRSS (Diabetic retinopathy severity score)			

The following severities are possible. 10 = Diabetic retinopathy (DR) absent, 14 = DR questionable, 15 = DR questionable, 20 = Microaneurysms only, 35 = Mild Non-proliferative diabetic retinopathy (NPDR), 43 = Moderate NPDR, 47 = Moderately severe NPDR, 53 = Severe NPDR, 61 = Mild Proliferative diabetic retinopathy (PDR), 65 = Moderate PDR, 71 = High-risk PDR, 75 = High-risk PDR, 81 = Advanced PDR: fundus partially obscured, center of macula attached, 85 = Advanced PDR: posterior fundus obscured, or center of macula detached, 90 = cannot grade, even sufficiently for level 81 or 85.

Units: Subjects			
10 - DR absent	0	0	
15 - DR questionable	2	2	
35 - Mild NPDR	148	148	
43 - Moderate NPDR	185	185	
47 - Moderately severe NPDR	153	153	
53 - Severe NPDR	48	48	
61 - Mild PDR	8	8	
65 - Moderate PDR	8	8	
71 - High-risk PDR	2	2	
90 - Cannot grade	6	6	

Central Retinal Thickness (CRT)			
The CRT was recorded at the study eye only. Subjects received active treatment (intravitreal aflibercept) for the study eye and received close medical supervision.			
Units: microns			
arithmetic mean	464.81		
standard deviation	± 136.21	-	
Best Corrected Visual Acuity (BCVA)			
The BCVA was recorded at the study eye only. Subjects received active treatment (intravitreal aflibercept) for the study eye and received close medical supervision.			
Units: score on a scale			
arithmetic mean	61.5		
standard deviation	± 10.9	-	
NEI VFQ-25 total score			
The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, example: a score of 50 represents 50% of the highest possible score.			
Units: score on a scale			
arithmetic mean	70.122		
standard deviation	± 19.243	-	
NEI VFQ-25 near activities subscale			
Items within each sub-scale are averaged together to create the 12 sub-scale Scores. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered. Evaluating this parameter included subjects from the full analysis set (N= 553).			
Units: score on a scale			
arithmetic mean	62.967		
standard deviation	± 23.479	-	
NEI VFQ-25 distant activities subscale			
Items within each sub-scale are averaged together to create the 12 sub-scale Scores. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered. Evaluating this parameter included subjects from the full analysis set (N= 553).			
Units: score on a scale			
arithmetic mean	71.964		
standard deviation	± 23.973	-	
Pre-injection Intraocular Pressure Units: millimeter of mercury (mmHg)			
arithmetic mean	16.2		
standard deviation	± 3.0	-	
Systolic Blood Pressure Units: millimeter of mercury (mmHg)			
arithmetic mean	138.1		
standard deviation	± 13.6	-	
Diastolic Blood Pressure Units: millimeter of mercury (mmHg)			
arithmetic mean	77.7		
standard deviation	± 9.4	-	
Heart Rate Units: beats per minute (beats/min)			
arithmetic mean	75.1		
standard deviation	± 10.1	-	

Body Temperature Units: celsius			
arithmetic mean	36.37		
standard deviation	± 0.38	-	

End points

End points reporting groups

Reporting group title	Aflibercept

Reporting group description:

Subjects were treated according to the EU-PI for treatment of DME for the first year of treatment and received 1 dose of 2 mg aflibercept injected intravitreally (IVT) every 4 weeks for 5 consecutive doses, followed by dosing every 8 weeks thereafter until the end of the 52 week treatment period.

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

Subject analysis set description:

FAS included all subjects who received at least one injection of study drug and completed the baseline and at least one post-baseline NEI VFQ-25 questionnaire (N= 553).

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

Subject analysis set description:

SAF included all subjects who received at least 1 injection of study drug (N= 560).

Primary: Change from Baseline to Week 52 in NEI VFQ-25 Total Score

End point title	Change from Baseline to Week 52 in NEI VFQ-25 Total Score[1]

End point description:

National eye institute 25-item visual function questionnaire (NEI VFQ-25) is a condition-specific measure which was designed to capture the specific impact of vision loss on health-related quality of life (HRQoL). The calculation for NEI VFQ-25 sub-scale scores and total score was performed according to the "NEI VFQ-25 Scoring Algorithm – August 2000". The NEI VFQ-25 consists of a base set of 25 vision-targeted questions representing 11 vision-related constructs, plus an additional single-item general health rating question. All items are scored so that a high score represents better functioning. Each item is then converted to a 0 to 100 scale so that the lowest and highest possible scores are set at 0 and 100 points, respectively. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score.

End point type	Primary

End point timeframe:

Baseline, Week 52

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Descriptive statistics were done, no inferential statistical analyses were performed.

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	553[2]			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	6.106 (5.303 to 6.909)			

Notes:

[2] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the NEI VFQ 25 Near Activities Subscale

End point title	Change from Baseline to Week 52 in the NEI VFQ 25 Near Activities Subscale

End point description:

NEI VFQ-25 is a condition-specific measure which was designed to capture the specific impact of vision loss on HRQoL. The calculation for NEI VFQ-25 sub-scale scores and total score was performed according to the "NEI VFQ-25 Scoring Algorithm – August 2000". Items within each sub-scale are averaged together to create the 12 sub-scale Scores. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	553[3]			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	11.370 (10.108 to 12.632)			

Notes:

[3] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in the NEI VFQ 25 Distant Activities Subscale

End point title	Change from Baseline to Week 52 in the NEI VFQ 25 Distant Activities Subscale

End point description:

NEI VFQ-25 is a condition-specific measure which was designed to capture the specific impact of vision loss on HRQoL. The calculation for NEI VFQ-25 sub-scale scores and total score was performed according to the "NEI VFQ-25 Scoring Algorithm – August 2000". Items within each sub-scale are averaged together to create the 12 sub-scale Scores. Items that are left blank (missing data) are not taken into account when calculating the scale scores. Sub-scales with at least one item answered can be used to generate a sub-scale score. Hence, scores represent the average for all items in the subscale that the respondent answered.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	553[4]			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	7.331 (6.118 to 8.545)			

Notes:

[4] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Best Corrected Visual Acuity (BCVA) (Early Treatment Diabetic Retinopathy Study [ETDRS] letter score])

End point title	Change from Baseline to Week 52 in Best Corrected Visual Acuity (BCVA) (Early Treatment Diabetic Retinopathy Study [ETDRS] letter score])

End point description:

Visual function was assessed using the ETDRS protocol (Early Treatment Diabetic Retinopathy Study Research Group 1985) starting at 4 meters. The values might range from 0 to 100. A higher score represents better functioning.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	553[5]			
Units: score on a scale				
arithmetic mean (confidence interval 95%)	10.0 (9.5 to 10.6)			

Notes:

[5] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 52 in Central Retinal Thickness (CRT) Measured by Optical Coherence Tomography (OCT)

End point title	Change from Baseline to Week 52 in Central Retinal Thickness (CRT) Measured by Optical Coherence Tomography (OCT)

End point description:

The CRT was recorded at the study eye only. Subjects received active treatment (intravitreal aflibercept) for the study eye and received close medical supervision. Retinal and lesion characteristics were evaluated using spectral domain optical coherence tomography (OCT). For all visits where the OCT procedure was scheduled, images were captured and read by the investigator. All OCTs were electronically archived at the study sites as part of the source documentation.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	553[6]			
Units: microns				
arithmetic mean (confidence interval 95%)	-175.38 (-184.93 to -165.82)			

Notes:

[6] - FAS

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Progressing to Greater or Equal to (>=) 61 on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) as Assessed by Fundus Photography (FP)

End point title	Proportion of Subjects Progressing to Greater or Equal to (>=) 61 on the ETDRS Diabetic Retinopathy Severity Scale (DRSS) as Assessed by Fundus Photography (FP)

End point description:

The ETDRS DRSS was assessed by FP according to the following scale for both eyes. The following severities are possible. 10 = Diabetic retinopathy (DR) absent, 14 = DR questionable, 15 = DR questionable, 20 = Micro-aneurysms only, 35 = Mild Non-proliferative diabetic retinopathy (NPDR), 43 = Moderate NPDR, 47 = Moderately severe NPDR, 53 = Severe NPDR, 61 = Mild Proliferative diabetic retinopathy (PDR), 65 = Moderate PDR, 71 = High-risk PDR, 75 = High-risk PDR, 81 = Advanced PDR: fundus partially obscured, center of macula attached, 85 = Advanced PDR: posterior fundus obscured, or center of macula detached, 90 = cannot grade, even sufficiently for level 81 or 85.

End point type	Secondary

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	489[7]			
Units: percentage of subjects				
number (not applicable)	0.4			

Notes:

[7] - Subjects in the FAS with gradable baseline and Week 52 FP and a DRSS of less than (<) 61 at baseline

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Pre-injection Intraocular Pressure for Study Eye Every 4 Weeks

End point title	Change from Baseline in Pre-injection Intraocular Pressure for Study Eye Every 4 Weeks

End point description:

Intraocular pressure (IOP) was measured using applanation tonometry Goldmann, Tonopen or approved alternative). The same method of intraocular pressure measurement was used in each participant throughout the study. For the measurement of intraocular pressure, a local anesthetic combined with fluorescein was applied topically to the eye being tested (example: one drop of oxybuprocain plus fluorescein). In the below table, pre-injection intraocular pressure for study eye was reported and 'n' signifies number od subjects who were evaluable for this measure at given time point.

End point type	Other pre-specified

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 24, 32, 40, 48, 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	560[8]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)				
Change at Week 4 (n= 552)	-0.4 (± 2.9)			
Change at Week 8 (n= 545)	-0.3 (± 2.9)			
Change at Week 12 (n= 547)	-0.5 (± 2.9)			
Change at Week 16 (n= 548)	-0.3 (± 2.9)			
Change at Week 24 (n= 542)	-0.2 (± 3.0)			
Change at Week 32 (n= 541)	-0.1 (± 3.0)			
Change at Week 40 (n= 533)	0.0 (± 3.0)			
Change at Week 48 (n= 532)	0.0 (± 3.0)			
Change at Week 52 (n= 527)	0.1 (± 3.1)			

Notes:

[8] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Systolic Blood Pressure at Week 52

End point title	Change from Baseline in Systolic Blood Pressure at Week 52

End point description:

Systolic blood pressure was measured in a consistent and standardized way according to locally established practice.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	560[9]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)	-0.1 (± 15.1)			

Notes:

[9] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Diastolic Blood Pressure at Week 52

End point title	Change from Baseline in Diastolic Blood Pressure at Week 52
End point description:	
Diastolic blood pressure was measured in a consistent and standardized way according to locally established practice.	
End point type	Other pre-specified
End point timeframe:	
Baseline, Week 52	

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	560[10]			
Units: millimeter of mercury (mmHg)				
arithmetic mean (standard deviation)	-0.3 (± 9.9)			

Notes:

[10] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Heart Rate at Week 52

End point title	Change from Baseline in Heart Rate at Week 52
End point description:	
Heart rate was measured in a consistent and standardized way according to locally established practice.	
End point type	Other pre-specified
End point timeframe:	
Baseline, Week 52	

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	560[11]			
Units: beats per minute (beats/min)				
arithmetic mean (standard deviation)	-1.0 (± 9.5)			

Notes:

[11] - SAF

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from Baseline in Body Temperature at Week 52

End point title	Change from Baseline in Body Temperature at Week 52

End point description:

Temperature was measured in a consistent and standardized way according to locally established practice.

End point type	Other pre-specified

End point timeframe:

Baseline, Week 52

End point values	Aflibercept			
Subject group type	Reporting group			
Number of subjects analysed	560[12]			
Units: celsius				
arithmetic mean (standard deviation)	-0.04 (± 0.41)			

Notes:

[12] - SAF

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:	
From start of study treatment up to 30 days after the last injection of study treatment	
Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Aflibercept

Reporting group description:

Subjects were treated according to the EU-PI for treatment of DME for the first year of treatment and received 1 dose of 2 mg aflibercept injected IVT every 4 weeks for 5 consecutive doses, followed by dosing every 8 weeks thereafter until the end of the 52 week treatment period.

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: There was no non-serious treatment-emergent adverse events reported by ≥ 5% of subjects.

Serious adverse events	Aflibercept		
Total subjects affected by serious adverse events			
subjects affected / exposed	66 / 560 (11.79%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	5		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to lymph nodes			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to peritoneum			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastatic malignant melanoma			

subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Small cell lung cancer			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Arteriosclerosis			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral arterial occlusive disease			
subjects affected / exposed	2 / 560 (0.36%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Hypertensive crisis			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peripheral vascular disorder			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Umbilical hernia repair			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitrectomy			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast			

disorders				
Prostatitis				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Pulmonary embolism				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea exertional				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
Depression				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Major depression				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Suicide attempt				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Echocardiogram abnormal				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza A virus test positive				

subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Carbon monoxide poisoning			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femoral neck fracture			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Humerus fracture			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Inflammation of wound			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	2 / 560 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Atrioventricular block				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Bundle branch block right				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Cardiac failure chronic				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac failure congestive				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardio-respiratory arrest				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiopulmonary failure				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiovascular insufficiency				

subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Mitral valve incompetence				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Nervous system disorders				
Cerebrovascular accident				
subjects affected / exposed	3 / 560 (0.54%)			
occurrences causally related to treatment / all	1 / 3			
deaths causally related to treatment / all	0 / 0			
Lacunar stroke				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Transient ischaemic attack				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vascular encephalopathy				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 1			
Eye disorders				
Anterior chamber inflammation				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Cataract subcapsular				

subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Posterior capsule opacification			
subjects affected / exposed	2 / 560 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitritis			
subjects affected / exposed	2 / 560 (0.36%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal hernia			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Peptic ulcer haemorrhage			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatitis acute			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Umbilical hernia			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			

Cholelithiasis				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Chronic kidney disease				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic nephropathy				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Pain in extremity				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Anal abscess				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Boutonneuse fever				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cellulitis				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Diabetic foot infection				

subjects affected / exposed	2 / 560 (0.36%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Endophthalmitis			
subjects affected / exposed	3 / 560 (0.54%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Erysipelas			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Osteomyelitis			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parotitis			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 560 (1.07%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Pyelonephritis chronic			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Septic shock			
subjects affected / exposed	1 / 560 (0.18%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Diabetic ketoacidosis			

subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Diabetic metabolic decompensation				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hyperkalaemia				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Type 1 diabetes mellitus				
subjects affected / exposed	1 / 560 (0.18%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Type 2 diabetes mellitus				
subjects affected / exposed	2 / 560 (0.36%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

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

Non-serious adverse events	Aflibercept		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 560 (0.00%)		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 September 2015	The following modifications were made in this amendment: •An update was made to inclusion criterion: use of adequate contraception (definition based on the judgment of the investigator) replaced with use of highly effective contraception (definition based clinical trials facilitation group [CTFG] from 15 September 2014) •Updates were made to pregnancy testing requirements: serum test binding was required at the screening visit (urine dipstick was not an alternative as per original protocol); urine dipstick test added for baseline visit. A requirement for serum pregnancy test within 7 days before first injection of medication was added •An update was made to inclusion criteria: "written informed consent" complemented by "signed" •Special warnings from EU-PI (most recent version number) were added to information on dosage and administration of the study drug •Smoking history was added to the medical history •Total and high-density lipoprotein cholesterol were added to the laboratory safety parameters

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

IOP, AEs, vital signs in clinical trial application (CTA) (E.5.2) were not secondary endpoints of clinical study protocol (CSP). Proportion of subjects progressing to >= 61 ETDRS of DRSS was a secondary endpoint of the CSP missing in the CTA (E.5.2).

Notes: