



Clinical trial results:

A Phase 3, Double-Masked, Randomized Study of the Efficacy and Safety of Intravitreal Aflibercept Injection in Patients with Moderately Severe to Severe Nonproliferative Diabetic Retinopathy

Summary

EudraCT number	2016-002639-14
Trial protocol	HU DE GB
Global end of trial date	16 July 2019

Results information

Result version number	v1 (current)
This version publication date	14 July 2020
First version publication date	14 July 2020

Trial information

Trial identification

Sponsor protocol code	VGFTe-OD-1411
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02718326
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Road, Tarrytown, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com
Scientific contact	Clinical Trial Management, Regeneron Pharmaceuticals, Inc., clinicaltrials@regeneron.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 August 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	16 July 2019
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 assess the efficacy of intravitreal (IVT) aflibercept compared to sham treatment in the improvement of moderately severe to severe nonproliferative diabetic retinopathy (NPDR).

The secondary objectives of the study were:

- To characterize the safety of IVT aflibercept in subjects with moderately severe to severe NPDR
- To determine if IVT aflibercept will prevent the worsening of diabetic retinopathy and reduce the incidence of DME
- To determine the anatomic effects of IVT aflibercept in subjects with moderately severe to severe NPDR

Protection of trial subjects:

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the International Conference on Harmonisation (ICH) guidelines for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	29 March 2016
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	Germany: 5
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Hungary: 10
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	United States: 374
Worldwide total number of subjects	402
EEA total number of subjects	17

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	312
From 65 to 84 years	89
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment for this study was conducted in the following countries between 29 Mar 2016 and 07 Aug 2017: Germany, Hungary, Japan, the United Kingdom, and the United States. A total of 759 subjects were screened.

Pre-assignment

Screening details:

Out of 759, 402 subjects were randomized to receive 1 of 3 treatment groups in a 1:1:1 ratio stratified based on their Diabetic Retinopathy Severity Scale (DRSS) score (level 47 vs. level 53). Only 1 eye was selected as the study eye.

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Sham treatment

Arm description:

All subjects received sham injections in the study eye every 4 weeks (Q4) to week 16 (after 5 initial monthly sham injections), followed by sham injections Q8 to week 96.

Arm type	Sham injection
Investigational medicinal product name	Sham injection
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

Matching sham injections

Arm title	Intravitreal Aflibercept Injection (IAI) 2Q16
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Arm description:

All subjects received a 2 milligram (mg) Intravitreal Aflibercept Injection (IAI) in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96.

Arm type	Experimental
Investigational medicinal product name	Eylea
Investigational medicinal product code	
Other name	VEGF Trap-Eye
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

2mg every 16 weeks (2Q16)

Arm title	Intravitreal Aflibercept Injection (IAI) 2Q8
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Arm description:

All subjects received 2 mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.

Arm type	Experimental
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Investigational medicinal product name	Eylea
Investigational medicinal product code	
Other name	VEGF Trap-Eye
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

2 mg every 8 weeks (2Q8); PRN per protocol defined criteria from week 56 through 96

Number of subjects in period 1	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8
Started	133	135	134
Completed Week 52	109	122	124
Completed Week 100 (End of Study)	97	111	112
Completed	97	111	112
Not completed	36	24	22
Adverse event, serious fatal	8	1	2
Consent withdrawn by subject	4	9	6
Adverse event, non-fatal	4	9	-
Protocol Deviation	1	-	-
Pregnancy	1	-	-
Lost to follow-up	18	5	14

Baseline characteristics

Reporting groups

Reporting group title	Sham treatment
Reporting group description: All subjects received sham injections in the study eye every 4 weeks (Q4) to week 16 (after 5 initial monthly sham injections), followed by sham injections Q8 to week 96.	
Reporting group title	Intravitreal Aflibercept Injection (IAI) 2Q16
Reporting group description: All subjects received a 2 milligram (mg) Intravitreal Aflibercept Injection (IAI) in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96.	
Reporting group title	Intravitreal Aflibercept Injection (IAI) 2Q8
Reporting group description: All subjects received 2 mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.	

Reporting group values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8
Number of subjects	133	135	134
Age categorical Units: Subjects			
<40 years	11	14	10
≥40 - <65 years	94	92	91
≥65 years	28	29	33
Age Continuous Units: Years			
arithmetic mean	55.8	55.4	55.8
standard deviation	± 10.31	± 11.13	± 10.19
Sex: Female, Male Units:			
Female	64	60	53
Male	69	75	81
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	74	97	93
Hispanic or Latino	58	37	41
Not Reported	1	1	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	1	1	4
Asian	4	12	7
Native Hawaiian or Other Pacific Islander	0	1	1
Black or African American	13	16	12
White	107	99	104
More than one race	0	1	1
Not Reported	8	5	5
Baseline Diabetic Retinopathy Severity Score (DRSS)			
The Diabetic Retinopathy Disease Severity Scale (DRSS) may be used to describe overall retinopathy severity as well as the change in severity over time. Severity range from level 10 (DR absent) to level			

85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached).			
Units: Subjects			
Level 47 (Moderately Severe)	99	102	101
Level 53 (Severe)	34	33	33

Reporting group values	Total		
Number of subjects	402		
Age categorical			
Units: Subjects			
<40 years	35		
≥40 - <65 years	277		
≥65 years	90		
Age Continuous			
Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units:			
Female	177		
Male	225		
Ethnicity (NIH/OMB)			
Units: Subjects			
Not Hispanic or Latino	264		
Hispanic or Latino	136		
Not Reported	2		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	6		
Asian	23		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	41		
White	310		
More than one race	2		
Not Reported	18		
Baseline Diabetic Retinopathy Severity Score (DRSS)			
The Diabetic Retinopathy Disease Severity Scale (DRSS) may be used to describe overall retinopathy severity as well as the change in severity over time. Severity range from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached).			
Units: Subjects			
Level 47 (Moderately Severe)	302		
Level 53 (Severe)	100		

Subject analysis sets

Subject analysis set title	IAI 2 mg Groups Combined (2Q16 & 2Q8)
Subject analysis set type	Full analysis

Subject analysis set description:

IAI 2Q16: Subjects received a 2mg IAI in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96; IAI 2Q8: Subjects received 2mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.

Reporting group values	IAI 2 mg Groups Combined (2Q16 & 2Q8)		
Number of subjects	269		
Age categorical Units: Subjects			
<40 years	24		
≥40 - <65 years	183		
≥65 years	62		
Age Continuous Units: Years			
arithmetic mean	55.6		
standard deviation	± 10.66		
Sex: Female, Male Units:			
Female	113		
Male	156		
Ethnicity (NIH/OMB) Units: Subjects			
Not Hispanic or Latino	190		
Hispanic or Latino	78		
Not Reported	1		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	5		
Asian	19		
Native Hawaiian or Other Pacific Islander	2		
Black or African American	28		
White	203		
More than one race	2		
Not Reported	10		
Baseline Diabetic Retinopathy Severity Score (DRSS)			
The Diabetic Retinopathy Disease Severity Scale (DRSS) may be used to describe overall retinopathy severity as well as the change in severity over time. Severity range from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached).			
Units: Subjects			
Level 47 (Moderately Severe)	203		
Level 53 (Severe)	66		

End points

End points reporting groups

Reporting group title	Sham treatment
Reporting group description: All subjects received sham injections in the study eye every 4 weeks (Q4) to week 16 (after 5 initial monthly sham injections), followed by sham injections Q8 to week 96.	
Reporting group title	Intravitreal Aflibercept Injection (IAI) 2Q16
Reporting group description: All subjects received a 2 milligram (mg) Intravitreal Aflibercept Injection (IAI) in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96.	
Reporting group title	Intravitreal Aflibercept Injection (IAI) 2Q8
Reporting group description: All subjects received 2 mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.	
Subject analysis set title	IAI 2 mg Groups Combined (2Q16 & 2Q8)
Subject analysis set type	Full analysis
Subject analysis set description: IAI 2Q16: Subjects received a 2mg IAI in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96; IAI 2Q8: Subjects received 2mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.	

Primary: Percentage of Subjects Who Improved by ≥ 2 Steps from Baseline in the Diabetic Retinopathy Disease Severity Scale (DRSS) Score at Week 24 in the Combined 2Q16 and 2Q8 Groups

End point title	Percentage of Subjects Who Improved by ≥ 2 Steps from Baseline in the Diabetic Retinopathy Disease Severity Scale (DRSS) Score at Week 24 in the Combined 2Q16 and 2Q8 Groups
End point description: The Diabetic Retinopathy Disease Severity Scale (DRSS) may be used to describe overall retinopathy severity as well as the change in severity over time. Severity range from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached). Here, DRSS describes severity level 47 (moderately severe NPDR) and level 53 (severe NPDR) at week 24 from baseline. FAS included all randomized subjects who received any study treatment as assigned at baseline (as randomized). The missing data were imputed using last observation carried forward (LOCF) method.	
End point type	Primary
End point timeframe: At Week 24	

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	IAI 2 mg Groups Combined (2Q16 & 2Q8)
Subject group type	Reporting group	Reporting group	Reporting group	Subject analysis set
Number of subjects analysed	133	135	134	269
Units: Percentage of subjects				
number (not applicable)	6.0	61.5	55.2	58.4

Statistical analyses

Statistical analysis title	Sham treatment, IAI 2 mg Groups Combined
Comparison groups	Sham treatment v IAI 2 mg Groups Combined (2Q16 & 2Q8)
Number of subjects included in analysis	402
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	52.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	45.2
upper limit	59.5

Primary: Percentage of Subjects With a \geq 2-step Change at Week 52 in Diabetic Retinopathy Severity Scale (DRSS) From Baseline

End point title	Percentage of Subjects With a \geq 2-step Change at Week 52 in Diabetic Retinopathy Severity Scale (DRSS) From Baseline
End point description: The Diabetic Retinopathy Disease Severity Scale (DRSS) may be used to describe overall retinopathy severity as well as the change in severity over time. Severity range from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached). Here, DRSS describes severity level 47 (moderately severe NPDR) and level 53 (severe NPDR) at week 52 from baseline. FAS included all randomized subjects who received any study treatment as assigned at baseline (as randomized). The missing data were imputed using LOCF method.	
End point type	Primary
End point timeframe: At Week 52	

End point values	Sham treatment	Intravitreal Afibercept Injection (IAI) 2Q16	Intravitreal Afibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	135	134	
Units: Percentage of subjects				
number (not applicable)	15.0	65.2	79.9	

Statistical analyses

Statistical analysis title	Sham treatment, IAI 2Q16
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q16
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	50.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	40.1
upper limit	60.1

Statistical analysis title	Sham treatment, IAI 2Q18
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q8
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	64.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	55.8
upper limit	73.9

Secondary: Percentage of Subjects who Developed a Vision-Threatening Complication due to Diabetic Retinopathy at Week 52

End point title	Percentage of Subjects who Developed a Vision-Threatening Complication due to Diabetic Retinopathy at Week 52
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End point description:

Vision-threatening complications are defined as the composite outcome of proliferative diabetic retinopathy (PDR) (inclusive of subjects who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR) and anterior segment neovascularization (ASNV) (subjects with neovascularization of the iris [at least 2 cumulative clock hours], and/or definitive neovascularization of the iridocorneal angle). FAS included all randomized subjects who received any study treatment as

assigned at baseline (as randomized).

End point type	Secondary
End point timeframe:	
At Week 52	

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	135	134	
Units: Percentage of subjects				
number (not applicable)	20.3	3.7	3.0	

Statistical analyses

Statistical analysis title	Sham treatment, IAI 2Q8
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q8
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.7
upper limit	-9.9

Statistical analysis title	Sham treatment, IAI 2Q16
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q16
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	-16.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-24.2
upper limit	-9.1

Secondary: Percentage of Subjects who Developed Central Involved-Diabetic Macular Edema (CI-DME) at Week 52

End point title	Percentage of Subjects who Developed Central Involved-Diabetic Macular Edema (CI-DME) at Week 52
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End point description:

The percentage of subjects who developed CI-DME at week 52 were reported. FAS included all randomized subjects who received any study treatment as assigned at baseline (as randomized).

End point type	Secondary
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End point timeframe:

At Week 52

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	135	134	
Units: Percentage of subjects				
number (not applicable)	25.6	6.7	8.2	

Statistical analyses

Statistical analysis title	Sham treatment, IAI 2Q8
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q8
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	-17.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.2
upper limit	-8.5

Statistical analysis title	Sham treatment, IAI 2Q16
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q16

Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	-18.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-27.5
upper limit	-10.4

Secondary: Time to Development of any Neovascular Vision Threatening Complication (PDR/ASNV) through Week 52

End point title	Time to Development of any Neovascular Vision Threatening Complication (PDR/ASNV) through Week 52
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End point description:

Vision-threatening complication (VTC) is defined as the composite outcome of proliferative diabetic retinopathy (PDR) (inclusive of subjects who have vitreous hemorrhage or tractional retinal detachment believed to be due to PDR) and anterior segment neovascularization (ASNV) (subjects with neovascularization of the iris [at least 2 cumulative clock hours], and/or definitive neovascularization of the iridocorneal angle). Vision Threatening Complications include PDR/ASNV identified by investigators and Diabetic Retinopathy Scale Score (DRSS) >61. FAS included all randomized subjects who received any study treatment as assigned at baseline (as randomized). Subjects who did not have an event were censored at their last visit at or before the week 52 visit. Here, the value "99999" = Not evaluable due to small number of VTC events.

End point type	Secondary
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End point timeframe:

Baseline through week 52 (day 365)

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133 ^[1]	135 ^[2]	134 ^[3]	
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (371 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Notes:

[1] - 99999 = Not evaluable due to small number of VTC events.

[2] - 99999 = Not evaluable due to small number of VTC events.

[3] - 99999 = Not evaluable due to small number of VTC events.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Development of Central Involved-Diabetic Macular Edema (CI-

DME) through Week 52

End point title	Time to Development of Central Involved-Diabetic Macular Edema (CI-DME) through Week 52
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End point description:

Time to develop Central Involved-Diabetic Macular Edema (CI-DME) through week 52 reported. FAS included all randomized subjects who received any study treatment as assigned at baseline (as randomized). Subjects who did not have an event were censored at their last visit, at or before the week 52 visit. Here, the value "99999" = Not evaluable due to small number of CI-DME events.

End point type	Secondary
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End point timeframe:

Baseline through week 52 (day 365)

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133 ^[4]	135 ^[5]	134 ^[6]	
Units: Days				
median (inter-quartile range (Q1-Q3))	99999 (333 to 99999)	99999 (99999 to 99999)	99999 (99999 to 99999)	

Notes:

[4] - 99999 = Not evaluable due to small number of CI-DME events

[5] - 99999 = Not evaluable due to small number of CI-DME events

[6] - 99999 = Not evaluable due to small number of CI-DME events

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects who Received Panretinal Photocoagulation (PRP), Inclusive of Subjects Undergoing Vitrectomy With Endolaser, at Week 52

End point title	Percentage of Subjects who Received Panretinal Photocoagulation (PRP), Inclusive of Subjects Undergoing Vitrectomy With Endolaser, at Week 52
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End point description:

The percentage of subjects who received panretinal photocoagulation (PRP), inclusive of subjects undergoing vitrectomy with endolaser, at week 52 were reported. FAS included all randomized subjects who received any study treatment as assigned at baseline (as randomized).

End point type	Secondary
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End point timeframe:

At Week 52

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	135	134	
Units: Percentage of subjects				

number (not applicable)	6.8	0.7	0.7	
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Statistical analyses

Statistical analysis title	Sham treatment, IAI 2Q8
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q8
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0096
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	-1.5

Statistical analysis title	Sham treatment, IAI 2Q16
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q16
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0089
Method	Cochran-Mantel-Haenszel
Parameter estimate	percentage difference
Point estimate	-6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-10.5
upper limit	-1.6

Secondary: Area Under the Curve (AUC) for Change From Baseline in Best Corrected Visual Acuity (BCVA) at Week 52

End point title	Area Under the Curve (AUC) for Change From Baseline in Best Corrected Visual Acuity (BCVA) at Week 52
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End point description:

The area under the curve (AUC) is the area under the best corrected visual acuity (BCVA) versus time curve from baseline to week 52. Visual function of the study eye was assessed at a distance of 4 meters at every study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) Best Corrected Visual Acuity (BCVA) letter score. BCVA scale range is 0 (worst) to 100 (best). AUC was calculated as a weighted average based on total AUC (using the trapezoidal rule) divided by total duration in days. FAS

included all randomized subjects who received any study treatment as assigned at baseline (as randomized).

End point type	Secondary
End point timeframe:	
At week 52	

End point values	Sham treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	133	135	134	
Units: Scores on a scale				
arithmetic mean (standard deviation)	0.5 (\pm 3.01)	1.7 (\pm 3.50)	1.3 (\pm 3.49)	

Statistical analyses

Statistical analysis title	Sham treatment, IAI 2Q8
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q8
Number of subjects included in analysis	267
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0529
Method	ANOVA
Parameter estimate	Estimate for contrast
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.01
upper limit	1.6

Statistical analysis title	Sham treatment, IAI 2Q16
Comparison groups	Sham treatment v Intravitreal Aflibercept Injection (IAI) 2Q16
Number of subjects included in analysis	268
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0057
Method	ANOVA
Parameter estimate	Estimate for contrast
Point estimate	1.14

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.33
upper limit	1.94

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to week 100 regardless of seriousness or relationship to investigational product

Adverse event reporting additional description:

Reported adverse events are treatment-emergent adverse events (TEAEs) which are AEs that developed/worsened from baseline (day1) up to end of study (week 100).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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Reporting groups

Reporting group title	Sham Treatment
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Reporting group description:

All subjects received sham injections in the study eye every 4 weeks (Q4) to week 16 (after 5 initial monthly sham injections), followed by sham injections Q8 to week 96.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2Q16
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Reporting group description:

All subjects received a 2 milligram (mg) Intravitreal Aflibercept Injection (IAI) in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96.

Reporting group title	Intravitreal Aflibercept Injection (IAI) 2Q8
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Reporting group description:

All subjects received 2 mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.

Reporting group title	IAI 2 mg Groups Combined (2Q16 & 2Q8)
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Reporting group description:

IAI 2Q16: Subjects received a 2mg IAI in the study eye every 16 weeks (2Q16) (after 3 initial monthly doses and one 8-week interval) to week 96; IAI 2Q8: Subjects received 2mg IAI in the study eye every 8 weeks (2Q8) from day 1 up to week 48 (after 5 initial monthly doses), followed by a flexible treatment regimen with IAI 2 mg to week 96.

Serious adverse events	Sham Treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8
Total subjects affected by serious adverse events			
subjects affected / exposed	38 / 133 (28.57%)	38 / 135 (28.15%)	47 / 134 (35.07%)
number of deaths (all causes)	8	1	3
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric cancer			

subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Malignant melanoma			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatic carcinoma			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 metastatic			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Papillary thyroid cancer			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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			
Peripheral ischaemia			

subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Hypotension			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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			
Chest pain			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Non-cardiac chest pain			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Generalised oedema			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Pyrexia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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			

Acute respiratory failure			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 133 (1.50%)	1 / 135 (0.74%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary arterial hypertension			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 acidosis			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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 failure			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Pulmonary congestion			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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 hypertension			
subjects affected / exposed	2 / 133 (1.50%)	0 / 135 (0.00%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Psychiatric disorders			

Bipolar disorder			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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			
Blood glucose increased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood sodium decreased			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ankle fracture			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Fall			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fibula fracture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Meniscus injury			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Postoperative respiratory failure			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative thoracic procedure complication			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin laceration			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 arthropathy			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Ulna fracture			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Limb injury			

subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Pneumocephalus			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Subdural haematoma			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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 Study Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 disorders			
Coronary artery disease			
subjects affected / exposed	1 / 133 (0.75%)	5 / 135 (3.70%)	4 / 134 (2.99%)
occurrences causally related to treatment / all	0 / 1	0 / 5	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 133 (0.75%)	2 / 135 (1.48%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 133 (0.75%)	2 / 135 (1.48%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 133 (1.50%)	2 / 135 (1.48%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			
subjects affected / exposed	0 / 133 (0.00%)	2 / 135 (1.48%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure chronic			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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 ischaemia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Supraventricular tachycardia			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Acute coronary syndrome			

subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Cardiac failure			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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 cardiomyopathy			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Left ventricular dysfunction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Left ventricular failure			
subjects affected / exposed	2 / 133 (1.50%)	0 / 135 (0.00%)	0 / 134 (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
Pulseless electrical activity			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 133 (0.00%)	3 / 135 (2.22%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 3	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Brain stem stroke			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Cerebral infarction			

subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Hepatic encephalopathy			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemic unconsciousness			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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	3 / 133 (2.26%)	0 / 135 (0.00%)	0 / 134 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 133 (0.00%)	2 / 135 (1.48%)	0 / 134 (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
Eye disorders			
Visual acuity reduced Fellow Eye			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinal oedema Fellow Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular fibrosis Fellow Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Macular hole Fellow Eye			

subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion Fellow Eye			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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 impairment Fellow Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous adhesions Fellow Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	1 / 133 (0.75%)	1 / 135 (0.74%)	0 / 134 (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
Cataract Fellow Eye			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Iris neovascularisation Fellow Eye			
subjects affected / exposed	2 / 133 (1.50%)	0 / 135 (0.00%)	0 / 134 (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
Cystoid macular oedema Study Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Visual acuity reduced Study Eye			

subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitreous haemorrhage Study Eye			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic retinopathy Study Eye			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Iris neovascularisation Study Eye			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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 neovascularisation Study Eye			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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			
Diabetic gastroparesis			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Impaired gastric emptying			

subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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	1 / 133 (0.75%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Ileus			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Nausea			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 chronic			

subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Photosensitivity reaction			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	2 / 133 (1.50%)	1 / 135 (0.74%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
End stage renal disease			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urge incontinence			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Urinary retention			

subjects affected / exposed	1 / 133 (0.75%)	1 / 135 (0.74%)	0 / 134 (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
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 133 (0.75%)	2 / 135 (1.48%)	5 / 134 (3.73%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 6
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	2 / 133 (1.50%)	3 / 135 (2.22%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic foot infection			
subjects affected / exposed	0 / 133 (0.00%)	3 / 135 (2.22%)	0 / 134 (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
Sepsis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abscess limb			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	2 / 134 (1.49%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthritis bacterial			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Enterococcal bacteraemia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	4 / 133 (3.01%)	1 / 135 (0.74%)	0 / 134 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis acute			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
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 bacterial			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis syndrome			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Staphylococcal infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Staphylococcal osteomyelitis			

subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal skin infection			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Appendicitis			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Diabetic gangrene			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Infected skin ulcer			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Septic shock			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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	1 / 133 (0.75%)	0 / 135 (0.00%)	3 / 134 (2.24%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diabetic ketoacidosis			

subjects affected / exposed	0 / 133 (0.00%)	2 / 135 (1.48%)	0 / 134 (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
Hypoglycaemia			
subjects affected / exposed	0 / 133 (0.00%)	2 / 135 (1.48%)	0 / 134 (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
Diabetes mellitus			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gout			
subjects affected / exposed	0 / 133 (0.00%)	1 / 135 (0.74%)	0 / 134 (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
Hyperglycaemia			
subjects affected / exposed	0 / 133 (0.00%)	0 / 135 (0.00%)	1 / 134 (0.75%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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
Hypomagnesaemia			
subjects affected / exposed	1 / 133 (0.75%)	0 / 135 (0.00%)	0 / 134 (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

Serious adverse events	IAI 2 mg Groups Combined (2Q16 & 2Q8)		
Total subjects affected by serious adverse events			
subjects affected / exposed	85 / 269 (31.60%)		
number of deaths (all causes)	4		
number of deaths resulting from adverse events			

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma stage 0			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastric cancer			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Malignant melanoma			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pancreatic carcinoma			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transitional cell carcinoma metastatic			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Uterine leiomyoma			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Basal cell carcinoma			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Squamous cell carcinoma of skin subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral ischaemia subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arteriosclerosis subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypotension subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest pain subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Non-cardiac chest pain subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Asthenia subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Generalised oedema subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Pyrexia				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				
Acute respiratory failure				
subjects affected / exposed	2 / 269 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pleural effusion				
subjects affected / exposed	2 / 269 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Chronic obstructive pulmonary disease				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary arterial hypertension				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory acidosis				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory failure				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary congestion				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			

Pulmonary hypertension subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 269 (0.00%) 0 / 0 0 / 0		
Psychiatric disorders Bipolar disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 269 (0.37%) 0 / 1 0 / 0		
Investigations Blood glucose increased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 269 (0.37%) 0 / 1 0 / 0		
Blood sodium decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 269 (0.37%) 0 / 1 0 / 0		
Injury, poisoning and procedural complications Anaemia postoperative subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 269 (0.37%) 0 / 1 0 / 0		
Ankle fracture subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 269 (0.37%) 0 / 1 0 / 0		
Fall subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 269 (0.37%) 0 / 1 0 / 0		
Femur fracture			

subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Fibula fracture				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meniscus injury				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative respiratory failure				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Postoperative thoracic procedure complication				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Radius fracture				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin laceration				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tibia fracture				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Traumatic arthropathy				

subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ulna fracture			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Limb injury			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumocephalus			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Subdural haematoma			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Traumatic fracture Study Eye			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Coronary artery disease			
subjects affected / exposed	9 / 269 (3.35%)		
occurrences causally related to treatment / all	0 / 9		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	5 / 269 (1.86%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			

subjects affected / exposed	3 / 269 (1.12%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	2 / 269 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Cardiac failure acute				
subjects affected / exposed	2 / 269 (0.74%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Coronary artery stenosis				
subjects affected / exposed	2 / 269 (0.74%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure chronic				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Myocardial ischaemia				

subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular tachycardia			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Acute coronary syndrome			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular dysfunction			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Left ventricular failure			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulseless electrical activity			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular accident			

subjects affected / exposed	4 / 269 (1.49%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Brain stem stroke			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cerebral infarction			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic encephalopathy			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemic unconsciousness			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 269 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Visual acuity reduced Fellow Eye			
subjects affected / exposed	3 / 269 (1.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Diabetic retinal oedema Fellow Eye			

subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Macular fibrosis Fellow Eye				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Macular hole Fellow Eye				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Retinal vein occlusion Fellow Eye				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Visual impairment Fellow Eye				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous adhesions Fellow Eye				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vitreous haemorrhage Fellow Eye				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cataract Fellow Eye				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Iris neovascularisation Fellow Eye				

subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cystoid macular oedema Study Eye			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Visual acuity reduced Study Eye			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vitreous haemorrhage Study Eye			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diabetic retinopathy Study Eye			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Iris neovascularisation Study Eye			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Retinal neovascularisation Study Eye			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Diabetic gastroparesis			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dysphagia			

subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Faecaloma				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Impaired gastric emptying				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Small intestinal obstruction				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper gastrointestinal haemorrhage				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Ileus				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Nausea				

subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholecystitis chronic			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cholelithiasis			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	3 / 269 (1.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Photosensitivity reaction			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 269 (1.49%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Chronic kidney disease			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

End stage renal disease			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urge incontinence			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary retention			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	7 / 269 (2.60%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	6 / 269 (2.23%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
Diabetic foot infection			
subjects affected / exposed	3 / 269 (1.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	3 / 269 (1.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

Abscess limb				
subjects affected / exposed	2 / 269 (0.74%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Arthritis bacterial				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Enterococcal bacteraemia				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gastroenteritis viral				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Influenza				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Osteomyelitis acute				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia bacterial				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sepsis syndrome				

subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal infection				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal osteomyelitis				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Staphylococcal skin infection				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Urinary tract infection				
subjects affected / exposed	1 / 269 (0.37%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Appendicitis				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Diabetic gangrene				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infected skin ulcer				
subjects affected / exposed	0 / 269 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Septic shock				

subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	3 / 269 (1.12%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Diabetic ketoacidosis			
subjects affected / exposed	2 / 269 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hypoglycaemia			
subjects affected / exposed	2 / 269 (0.74%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Diabetes mellitus			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gout			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 269 (0.37%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypokalaemia			
subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypomagnesaemia			

subjects affected / exposed	0 / 269 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Sham Treatment	Intravitreal Aflibercept Injection (IAI) 2Q16	Intravitreal Aflibercept Injection (IAI) 2Q8
Total subjects affected by non-serious adverse events			
subjects affected / exposed	104 / 133 (78.20%)	104 / 135 (77.04%)	106 / 134 (79.10%)
Investigations			
Blood glucose increased			
subjects affected / exposed	7 / 133 (5.26%)	3 / 135 (2.22%)	7 / 134 (5.22%)
occurrences (all)	8	3	7
Glycosylated haemoglobin increased			
subjects affected / exposed	7 / 133 (5.26%)	9 / 135 (6.67%)	9 / 134 (6.72%)
occurrences (all)	7	9	9
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 133 (3.76%)	5 / 135 (3.70%)	8 / 134 (5.97%)
occurrences (all)	5	7	11
Vascular disorders			
Hypertension			
subjects affected / exposed	25 / 133 (18.80%)	28 / 135 (20.74%)	20 / 134 (14.93%)
occurrences (all)	28	32	23
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 133 (1.50%)	7 / 135 (5.19%)	8 / 134 (5.97%)
occurrences (all)	2	9	8
Eye disorders			
Blepharitis Fellow Eye			
subjects affected / exposed	1 / 133 (0.75%)	3 / 135 (2.22%)	7 / 134 (5.22%)
occurrences (all)	1	3	7
Cataract Fellow Eye			
subjects affected / exposed	4 / 133 (3.01%)	9 / 135 (6.67%)	4 / 134 (2.99%)
occurrences (all)	4	9	4
Conjunctival haemorrhage Fellow			

Eye			
subjects affected / exposed	6 / 133 (4.51%)	5 / 135 (3.70%)	8 / 134 (5.97%)
occurrences (all)	7	14	14
Diabetic retinal oedema Fellow Eye			
subjects affected / exposed	19 / 133 (14.29%)	17 / 135 (12.59%)	23 / 134 (17.16%)
occurrences (all)	25	24	27
Diabetic retinopathy Fellow Eye			
subjects affected / exposed	12 / 133 (9.02%)	13 / 135 (9.63%)	10 / 134 (7.46%)
occurrences (all)	13	14	10
Macular oedema Fellow Eye			
subjects affected / exposed	4 / 133 (3.01%)	7 / 135 (5.19%)	6 / 134 (4.48%)
occurrences (all)	4	7	6
Retinal exudates Fellow Eye			
subjects affected / exposed	8 / 133 (6.02%)	2 / 135 (1.48%)	6 / 134 (4.48%)
occurrences (all)	9	2	7
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	4 / 133 (3.01%)	8 / 135 (5.93%)	3 / 134 (2.24%)
occurrences (all)	4	12	3
Blepharitis Study Eye			
subjects affected / exposed	1 / 133 (0.75%)	2 / 135 (1.48%)	7 / 134 (5.22%)
occurrences (all)	1	2	7
Cataract Study Eye			
subjects affected / exposed	5 / 133 (3.76%)	8 / 135 (5.93%)	8 / 134 (5.97%)
occurrences (all)	5	8	8
Conjunctival haemorrhage Study Eye			
subjects affected / exposed	8 / 133 (6.02%)	18 / 135 (13.33%)	25 / 134 (18.66%)
occurrences (all)	14	27	34
Diabetic retinal oedema Study Eye			
subjects affected / exposed	43 / 133 (32.33%)	14 / 135 (10.37%)	19 / 134 (14.18%)
occurrences (all)	54	22	25
Diabetic retinopathy Study Eye			
subjects affected / exposed	22 / 133 (16.54%)	3 / 135 (2.22%)	5 / 134 (3.73%)
occurrences (all)	25	4	5
Eye pain Study Eye			
subjects affected / exposed	6 / 133 (4.51%)	11 / 135 (8.15%)	5 / 134 (3.73%)
occurrences (all)	8	13	5

Retinal exudates Study Eye subjects affected / exposed occurrences (all)	6 / 133 (4.51%) 7	5 / 135 (3.70%) 5	9 / 134 (6.72%) 9
Vitreous detachment Study Eye subjects affected / exposed occurrences (all)	4 / 133 (3.01%) 4	7 / 135 (5.19%) 7	7 / 134 (5.22%) 9
Vitreous floaters Study Eye subjects affected / exposed occurrences (all)	3 / 133 (2.26%) 3	7 / 135 (5.19%) 8	13 / 134 (9.70%) 13
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	3 / 133 (2.26%) 3	5 / 135 (3.70%) 5	7 / 134 (5.22%) 7
Nausea subjects affected / exposed occurrences (all)	8 / 133 (6.02%) 9	5 / 135 (3.70%) 5	6 / 134 (4.48%) 14
Infections and infestations			
Bronchitis subjects affected / exposed occurrences (all)	7 / 133 (5.26%) 7	9 / 135 (6.67%) 10	5 / 134 (3.73%) 5
Cellulitis subjects affected / exposed occurrences (all)	6 / 133 (4.51%) 6	5 / 135 (3.70%) 10	7 / 134 (5.22%) 7
Influenza subjects affected / exposed occurrences (all)	8 / 133 (6.02%) 8	10 / 135 (7.41%) 12	4 / 134 (2.99%) 4
Nasopharyngitis subjects affected / exposed occurrences (all)	15 / 133 (11.28%) 16	11 / 135 (8.15%) 16	11 / 134 (8.21%) 12
Urinary tract infection subjects affected / exposed occurrences (all)	16 / 133 (12.03%) 22	12 / 135 (8.89%) 13	11 / 134 (8.21%) 13
Metabolism and nutrition disorders			
Diabetes mellitus subjects affected / exposed occurrences (all)	13 / 133 (9.77%) 15	11 / 135 (8.15%) 11	8 / 134 (5.97%) 8

Non-serious adverse events	IAI 2 mg Groups Combined (2Q16 & 2Q8)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	210 / 269 (78.07%)		
Investigations			
Blood glucose increased			
subjects affected / exposed	10 / 269 (3.72%)		
occurrences (all)	10		
Glycosylated haemoglobin increased			
subjects affected / exposed	18 / 269 (6.69%)		
occurrences (all)	18		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	13 / 269 (4.83%)		
occurrences (all)	18		
Vascular disorders			
Hypertension			
subjects affected / exposed	48 / 269 (17.84%)		
occurrences (all)	55		
Nervous system disorders			
Headache			
subjects affected / exposed	15 / 269 (5.58%)		
occurrences (all)	17		
Eye disorders			
Blepharitis Fellow Eye			
subjects affected / exposed	10 / 269 (3.72%)		
occurrences (all)	10		
Cataract Fellow Eye			
subjects affected / exposed	13 / 269 (4.83%)		
occurrences (all)	13		
Conjunctival haemorrhage Fellow Eye			
subjects affected / exposed	13 / 269 (4.83%)		
occurrences (all)	28		
Diabetic retinal oedema Fellow Eye			
subjects affected / exposed	40 / 269 (14.87%)		
occurrences (all)	51		
Diabetic retinopathy Fellow Eye			

subjects affected / exposed	23 / 269 (8.55%)		
occurrences (all)	24		
Macular oedema Fellow Eye			
subjects affected / exposed	13 / 269 (4.83%)		
occurrences (all)	13		
Retinal exudates Fellow Eye			
subjects affected / exposed	8 / 269 (2.97%)		
occurrences (all)	9		
Vitreous haemorrhage Fellow Eye			
subjects affected / exposed	11 / 269 (4.09%)		
occurrences (all)	15		
Blepharitis Study Eye			
subjects affected / exposed	9 / 269 (3.35%)		
occurrences (all)	9		
Cataract Study Eye			
subjects affected / exposed	16 / 269 (5.95%)		
occurrences (all)	16		
Conjunctival haemorrhage Study Eye			
subjects affected / exposed	43 / 269 (15.99%)		
occurrences (all)	61		
Diabetic retinal oedema Study Eye			
subjects affected / exposed	33 / 269 (12.27%)		
occurrences (all)	47		
Diabetic retinopathy Study Eye			
subjects affected / exposed	8 / 269 (2.97%)		
occurrences (all)	9		
Eye pain Study Eye			
subjects affected / exposed	16 / 269 (5.95%)		
occurrences (all)	18		
Retinal exudates Study Eye			
subjects affected / exposed	14 / 269 (5.20%)		
occurrences (all)	14		
Vitreous detachment Study Eye			
subjects affected / exposed	14 / 269 (5.20%)		
occurrences (all)	16		
Vitreous floaters Study Eye			

subjects affected / exposed occurrences (all)	20 / 269 (7.43%) 21		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	12 / 269 (4.46%)		
occurrences (all)	12		
Nausea			
subjects affected / exposed	11 / 269 (4.09%)		
occurrences (all)	19		
Infections and infestations			
Bronchitis			
subjects affected / exposed	14 / 269 (5.20%)		
occurrences (all)	15		
Cellulitis			
subjects affected / exposed	12 / 269 (4.46%)		
occurrences (all)	17		
Influenza			
subjects affected / exposed	14 / 269 (5.20%)		
occurrences (all)	16		
Nasopharyngitis			
subjects affected / exposed	22 / 269 (8.18%)		
occurrences (all)	28		
Urinary tract infection			
subjects affected / exposed	23 / 269 (8.55%)		
occurrences (all)	26		
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	19 / 269 (7.06%)		
occurrences (all)	19		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	The purpose of this amendment was to incorporate the following changes and clarifications following discussions with the FDA: The primary outcome measure of the study became the proportion of patients who have improved by ≥ 2 steps from baseline in the Diabetic Retinopathy Severity Scale (DRSS) score at week 24 in the combined 2Q8 and 2Q16 groups, and at week 52 for each group separately. Secondary endpoints were modified slightly; a few have been separated into 2 endpoints. The 2Q8 group transitioned to a flexible dosing regimen based on the investigator's assessment of DRSS score beginning at week 56.
12 February 2016	The purpose of this amendment was to incorporate the following revisions in response to feedback from the Food and Drug Administration (FDA) and the Pharmaceuticals and Medical Devices Agency (PMDA): Revised the significance levels for testing of the secondary efficacy endpoints, per FDA feedback; Added a hemoglobin A1c (HbA1c) assessment at week 24, and fundus photography (FP) at week 8, per PMDA feedback
20 October 2016	The purpose of this amendment was to update exclusion criterion #16 to exclude women who were breastfeeding from participation in the study.
24 July 2018	The purpose of this amendment was to change the time point for evaluation of the secondary endpoints from week 100 to week 52.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported