Clinical trial results:
A randomized, single-blinded, multicenter, Phase IV study to compare systemic VEGF protein dynamics following monthly intravitreal injections of 0.5 mg ranibizumab versus 2 mg aflibercept until Week 12 in patients with neovascular (wet) age-related macular degeneration (TIDE AMD)

Summary

EudraCT number	2014-001182-27
Trial protocol	DE
Global end of trial date	08 June 2017

Results information

Result version number	v1 (current)
This version publication date	20 June 2018
First version publication date	20 June 2018

Trial information

Trial identification

Sponsor protocol code	CRFB002ADE27

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02257632
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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	08 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 June 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to compare systemic VEGF-A protein levels following monthly intravitreal injections of 0.5 mg ranibizumab for 3 months vs. monthly intravitreal injections of 2 mg aflibercept for 3 months, as measured by the area under the curve (AUC) from Baseline to Week 12.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 April 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	32

85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The study included adult patients with active, newly diagnosed, and untreated wAMD. In total, 41 patients were randomized. One patient was randomized unintendedly and not treated. This patient was not included in any analyses. A total of 40 patients were treated at 6 study sites across Germany. Patients were treated in an outpatient setting.

Pre-assignment

Screening details:

At Screening, the eligibility criteria were performed.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

6 monthly intravitreal injections of 0.5 mg ranibizumab

Arm type	Experimental
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

6 monthly intravitreal injections of 0.5 mg ranibizumab

Arm title	Group 2

Arm description:

3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab

Arm type	Active comparator
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraocular use

Dosage and administration details:

3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.
Justification: The study was performed in a single-blinded fashion. Only patients, staff performing BCVA assessments, CRC staff, laboratory staff, and data analysts remained blinded to the identity of the treatment from the time of randomization until database lock.

Number of subjects in period 1	Group 1	Group 2
Started	19	21
Full Analysis Set (FAS)	19	21
Safety Set (SAF)	19	21
Completed	18	19
Not completed	1	2
Adverse event, non-fatal	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
6 monthly intravitreal injections of 0.5 mg ranibizumab	
Reporting group title	Group 2
Reporting group description:	
3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab	

Reporting group values	Group 1	Group 2	Total
Number of subjects	19	21	40
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	3	3
From 65-84 years	18	14	32
85 years and over	1	4	5
Age Continuous			
Units: Years			
arithmetic mean	74.3	75.4	
standard deviation	± 5.50	± 8.94	-
Sex/Gender, Customized			
Units: Subjects			
Female|	11	10	21
Male|	8	11	19
Race/Ethnicity, Customized			
Units: Subjects			

End points

End points reporting groups	
Reporting group title	Group 1
Reporting group description:	
6 monthly intravitreal injections of 0.5 mg ranibizumab	
Reporting group title	Group 2
Reporting group description:	
3 monthly intravitreal injections of 2 mg aflibercept followed by 3 monthly intravitreal injections of 0.5 mg ranibizumab	

Primary: Standardized Area Under the Curve (AUC) for VEGF A levels by SIMOA (Quanterix's single molecule array) method for the comparative phase	
End point title	Standardized Area Under the Curve (AUC) for VEGF A levels by SIMOA (Quanterix's single molecule array) method for the comparative phase
End point description:	
The AUC was calculated using the trapezoidal rule, where all available measurement between Day 1 and Week 12 were used. The AUC was standardized by dividing the calculated value by the number of days from first to last measurement.	
End point type	Primary
End point timeframe:	
Baseline up to Week 12 visit (Days 1, 2, 8, 15, 29, 43, 57, 71, 85)	

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: pg/mL				
arithmetic mean (standard deviation)	18.78 (± 8.460)	33.95 (± 7.659)		

Statistical analyses

Statistical analysis title	AUC for VEGF A levels for the comparative phase
Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [1]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-14.98

Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.64
upper limit	-10.32

Notes:

[1] - missing Baseline VEGF-A level covariate values were imputed by the mean value of non-missing Baseline VEGF-A level from all other patients

Secondary: Systemic VEGF-A protein levels from study week 12 to 24

End point title	Systemic VEGF-A protein levels from study week 12 to 24

End point description:

Systemic VEGF-A protein levels in patients switching from monthly 2 mg aflibercept injections to monthly 0.5 mg ranibizumab compared to patients treated with monthly 0.5 mg ranibizumab from baseline (standardized area under the curve)

End point type	Secondary

End point timeframe:

From study week 12 to 24 (Days 85, 99, 113, 127, 141, 155, 169)

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: pg/mL				
arithmetic mean (standard deviation)	17.93 (± 5.316)	29.07 (± 7.863)		

Statistical analyses

Statistical analysis title	VEGF-A protein levels from study week 12 to 24
Comparison groups	Group 1 v Group 2
Number of subjects included in analysis	37
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001 [2]
Method	ANCOVA
Parameter estimate	Mean difference (final values)
Point estimate	-11.46
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.98
upper limit	-6.94

Notes:

[2] - missing Baseline VEGF-A level covariate values were imputed by the mean value of non-missing Baseline VEGF-A level from all the patients with values

Secondary: Systemic VEGF-A levels from study week 12 to 24 (change from baseline)

End point title	Systemic VEGF-A levels from study week 12 to 24 (change from baseline)

End point description:

Adjustment of systemic VEGF-A levels of patients switching from aflibercept to ranibizumab to levels comparable to baseline or to levels comparable as in patients treated from baseline with ranibizumab

End point type	Secondary

End point timeframe:

From study week 12 to 24

End point values	Group 1	Group 2		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	20		
Units: pg/ml				
arithmetic mean (standard deviation)				
Change from Baseline at Week 12|	-1.37 (± 5.369)	23.73 (± 13.700)		
Change from Baseline at Week 14|	-1.00 (± 6.128)	21.93 (± 15.638)		
Change from Baseline at Week 16|	-0.01 (± 4.675)	19.26 (± 16.432)		
Change from Baseline at Week 18|	1.99 (± 5.582)	11.61 (± 10.844)		
Change from Baseline at Week 20|	1.62 (± 6.460)	4.84 (± 11.065)		
Change from Baseline at Week 22|	0.66 (± 8.109)	2.45 (± 8.543)		
Change from Baseline at Week 24|	-1.18 (± 3.664)	0.96 (± 9.553)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Adverse event reporting additional description:

Adverse events that occurred in Group 2 are reported in Group 2 irrespective of treatment (Aflibercept, followed by ranibizumab)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Aflibercept 2 mg

Reporting group description:

Aflibercept 2 mg

Reporting group title	Ranibizumab 0.5 mg

Reporting group description:

Ranibizumab 0.5 mg

Serious adverse events	Aflibercept 2 mg	Ranibizumab 0.5 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 19 (15.79%)	3 / 21 (14.29%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign lung neoplasm			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			

subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Optic nerve cupping			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal pigment epithelial tear			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bone cyst			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Aflibercept 2 mg	Ranibizumab 0.5 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 19 (84.21%)	20 / 21 (95.24%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Vascular disorders			

Hypertension			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Intermittent claudication			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Jaw operation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fibrosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Influenza like illness			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Injection site pain			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Sensation of foreign body			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Bronchial wall thickening			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Oropharyngeal pain			

subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Pleural effusion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Pulmonary embolism			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Investigations			
Blood pressure increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Body temperature increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Electrocardiogram abnormal			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Haemoglobin E present			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Intraocular pressure increased			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	1	4	
Mean cell haemoglobin concentration increased			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Mean cell haemoglobin increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Hand fracture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Cardiac disorders			
Aortic valve disease			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Aortic valve incompetence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Atrial fibrillation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Cardiac discomfort			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Cardiac fibrillation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Cardiovascular disorder			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Mitral valve incompetence			

subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Sinus bradycardia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Tricuspid valve incompetence			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	2 / 19 (10.53%)	1 / 21 (4.76%)	
occurrences (all)	3	1	
Monoparesis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Anterior chamber cell			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	2	
Blepharitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Choroidal neovascularisation			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Conjunctival erosion			

subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Conjunctival haemorrhage			
subjects affected / exposed	4 / 19 (21.05%)	6 / 21 (28.57%)	
occurrences (all)	4	9	
Conjunctival hyperaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Corneal erosion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	2	2	
Eye discharge			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Eyelid oedema			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Foreign body sensation in eyes			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	3	
Lacrimation increased			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Macular fibrosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Metamorphopsia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Ocular discomfort			

subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Pinguecula			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Retinal fibrosis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Retinal scar			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Subretinal fluid			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Vision blurred			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Visual acuity reduced			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Visual impairment			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	2	
Vitreous detachment			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Vitreous floaters			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	2	2	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Melanosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Photosensitivity reaction			
subjects affected / exposed	0 / 19 (0.00%)	2 / 21 (9.52%)	
occurrences (all)	0	2	
Sebaceous gland disorder			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Thyroid mass			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Back pain			

subjects affected / exposed	2 / 19 (10.53%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Fibromyalgia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Muscular weakness			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Neck pain			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Spinal column stenosis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 21 (4.76%)	
occurrences (all)	1	1	
Conjunctivitis			
subjects affected / exposed	1 / 19 (5.26%)	2 / 21 (9.52%)	
occurrences (all)	1	2	
Gastroenteritis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Herpes simplex			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Hordeolum			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	

Influenza			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 19 (21.05%)	4 / 21 (19.05%)	
occurrences (all)	5	6	
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 21 (4.76%)	
occurrences (all)	0	1	
Hyperglycaemia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	
Iron deficiency			
subjects affected / exposed	1 / 19 (5.26%)	0 / 21 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 April 2015	Exclusion criterion no. 4 was changed so that only patients with Type 1 or Type 2 diabetes mellitus with HbA1c > 10% (> 86 mmol/mol) at Screening were excluded from the study. Rationale: a large proportion of wAMD patients who suffered from adult-onset diabetes had the possibility to be included in the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported