Clinical trial results:
Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration (BEACON Study)

Summary

EudraCT number	2013-003320-36
Trial protocol	DE IT
Global end of trial date	30 March 2018

Results information

Result version number	v1 (current)
This version publication date	11 May 2019
First version publication date	11 May 2019

Trial information

Trial identification

Sponsor protocol code	190342-038

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02087085
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	30 March 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 March 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to assess the safety and efficacy of the brimonidine intravitreal implant in participants with geographic atrophy (GA) due to age-related macular degeneration.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 May 2014
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	Italy: 55
Country: Number of subjects enrolled	United Kingdom: 23
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	France: 26
Country: Number of subjects enrolled	United States: 149
Country: Number of subjects enrolled	Australia: 34
Worldwide total number of subjects	310
EEA total number of subjects	127

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)	17

From 65 to 84 years	242
85 years and over	51

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 576 participants were screened, and 310 participants were enrolled and randomised to receive either 400 µg brimonidine implant or sham treatment.

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	Investigator, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	400 µg Brimonidine Implant

Arm description:

400 µg brimonidine implant in the study eye, administered by intravitreal injections using the Brimonidine Drug Delivery System (Brimo DDS®) applicator every 3 months from Baseline (Day 1) through Month 21.

Arm type	Experimental
Investigational medicinal product name	Brimonidine free base
Investigational medicinal product code	AGN-190342
Other name	
Pharmaceutical forms	Implant
Routes of administration	Intravitreal use

Dosage and administration details:

400 µg brimonidine implant in the study eye using Brimo DDS® applicator on Day 1, and every 3 months through Month 21.

Arm title	Sham

Arm description:

Sham treatment (control) in the study eye, administered by intravitreal injections using a needleless drug delivery system (DDS) applicator every 3 months from Baseline (Day 1) through Month 21.

Arm type	Sham comparator
Investigational medicinal product name	Sham
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Intravitreal use

Dosage and administration details:

Sham treatment with needleless applicator (no implant) to the study eye on Day 1, and every 3 months through Month 21.

Number of subjects in period 1	400 µg Brimonidine Implant	Sham
Started	154	156
Completed	34	40
Not completed	120	116
Adverse Event	10	14
Withdrawal by Subject	9	11
Study Terminated by Sponsor	87	80
Lost to follow-up	6	4
Other Miscellaneous Reasons	3	4
Lack of efficacy	4	3
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	400 µg Brimonidine Implant
Reporting group description:	
400 µg brimonidine implant in the study eye, administered by intravitreal injections using the Brimonidine Drug Delivery System (Brimo DDS®) applicator every 3 months from Baseline (Day 1) through Month 21.	
Reporting group title	Sham
Reporting group description:	
Sham treatment (control) in the study eye, administered by intravitreal injections using a needleless drug delivery system (DDS) applicator every 3 months from Baseline (Day 1) through Month 21.	

Reporting group values	400 µg Brimonidine Implant	Sham	Total
Number of subjects	154	156	310
Age categorical Units: Subjects			
18-64 years	13	4	17
65-84 years	116	126	242
85 years and over	25	26	51
Age Continuous Units: years			
arithmetic mean	76.9	77.0	
standard deviation	± 7.89	± 7.24	-
Sex: Female, Male Units: Subjects			
Female	101	91	192
Male	53	65	118
Race/Ethnicity, Customized Units: Subjects			
White	153	156	309
Black or African American	1	0	1
Geographic Atrophy (GA) Lesion Area by Fundus Autofluorescence (FAF)			
GA lesion area was measured in mm^2 by FAF and analysis of FAF images was performed by the central reading centre. Modified intent-to-treat (mITT) population included all randomised and treated participants with baseline and at least 1 postbaseline assessment for GA lesion area by FAF.			
Units: millimetres squared (mm^2) arithmetic mean standard deviation	±	±	-

Subject analysis sets	
Subject analysis set title	400 µg Brimonidine Implant
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
400 µg brimonidine implant in the study eye, administered by intravitreal injections using the Brimonidine Drug Delivery System (Brimo DDS®) applicator every 3 months from Baseline (Day 1) through Month 21.	
Subject analysis set title	Sham
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Sham treatment (control) in the study eye, administered by intravitreal injections using a needleless DDS applicator every 3 months from Baseline (Day 1) through Month 21.

Reporting group values	400 µg Brimonidine Implant	Sham	
Number of subjects	149	154	
Age categorical Units: Subjects			
18-64 years			
65-84 years			
85 years and over			
Age Continuous Units: years			
arithmetic mean			
standard deviation	±	±	
Sex: Female, Male Units: Subjects			
Female			
Male			
Race/Ethnicity, Customized Units: Subjects			
White			
Black or African American			
Geographic Atrophy (GA) Lesion Area by Fundus Autofluorescence (FAF)			
GA lesion area was measured in mm^2 by FAF and analysis of FAF images was performed by the central reading centre. Modified intent-to-treat (mITT) population included all randomised and treated participants with baseline and at least 1 postbaseline assessment for GA lesion area by FAF.			
Units: millimetres squared (mm^2)			
arithmetic mean	5.1611	5.4761	
standard deviation	± 3.7016	± 3.5961	

End points

End points reporting groups

Reporting group title	400 µg Brimonidine Implant
Reporting group description:	
400 µg brimonidine implant in the study eye, administered by intravitreal injections using the Brimonidine Drug Delivery System (Brimo DDS®) applicator every 3 months from Baseline (Day 1) through Month 21.	
Reporting group title	Sham
Reporting group description:	
Sham treatment (control) in the study eye, administered by intravitreal injections using a needleless drug delivery system (DDS) applicator every 3 months from Baseline (Day 1) through Month 21.	
Subject analysis set title	400 µg Brimonidine Implant
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
400 µg brimonidine implant in the study eye, administered by intravitreal injections using the Brimonidine Drug Delivery System (Brimo DDS®) applicator every 3 months from Baseline (Day 1) through Month 21.	
Subject analysis set title	Sham
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Sham treatment (control) in the study eye, administered by intravitreal injections using a needleless DDS applicator every 3 months from Baseline (Day 1) through Month 24.	

Primary: Change From Baseline in Geographic Atrophy (GA) Lesion Area of the Study Eye as Assessed by Fundus Autofluorescence (FAF) at Month 24

End point title	Change From Baseline in Geographic Atrophy (GA) Lesion Area of the Study Eye as Assessed by Fundus Autofluorescence (FAF) at Month 24
End point description:	
GA lesion area was measured in mm^2 by FAF in the study eye and was quantified by the central reading centre. The study eye was defined as the eye that met inclusion/exclusion criteria with the worst standard Best Correct Visual Acuity (BCVA). If the BCVA in both eyes was similar the right eye was selected as the study eye. A positive change from baseline indicates an increase in size of GA lesion area (worsening; disease progression). Mixed model for repeated measures (MMRM) was used for analysis. Participants from the modified intent-to-treat (mITT) population, all randomised and treated participants with baseline and at least 1 postbaseline assessment for GA lesion area by FAF, with data available for analysis at Month 24.	
End point type	Primary
End point timeframe:	
Baseline (Day 1) to Month 24	

End point values	400 µg Brimonidine Implant	Sham		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	90		
Units: mm^2				
least squares mean (standard error)	3.1455 (± 0.1377)	3.5044 (± 0.1359)		

Statistical analyses

Statistical analysis title	400 µg Brimonidine Implant vs Sham
Comparison groups	400 µg Brimonidine Implant v Sham
Number of subjects included in analysis	176
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.047 [1]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.3589
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.7132
upper limit	-0.0047
Variability estimate	Standard error of the mean
Dispersion value	0.1804

Notes:

[1] - MMRM model included treatment group, study region, analysis visit and treatment-by-visit interaction as factors and baseline value and baseline value-by-analysis visit interaction as covariates.

Secondary: Change From Baseline in Standard Best Corrected Visual Acuity (BCVA) Score as Assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) Chart at Month 24

End point title	Change From Baseline in Standard Best Corrected Visual Acuity (BCVA) Score as Assessed by Early Treatment Diabetic Retinopathy Study (ETDRS) Chart at Month 24

End point description:

BCVA was measured using an eye chart (ETDRS) and was reported as the number of letters read correctly (ranging from 0 to 100 letters) in the study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). The study eye was defined as the eye that met inclusion/exclusion criteria with the worst standard BCVA. If the BCVA in both eyes was similar the right eye was selected as the study eye. A positive change from baseline indicates an improvement and a negative change from baseline indicates a worsening. MMRM was used for analysis. Participants from the mITT population, all randomised and treated participants with baseline and at least 1 postbaseline assessment for GA lesion area by FAF, with data available for analysis for this endpoint at Month 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Month 24

End point values	400 µg Brimonidine Implant	Sham		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: letters read correctly				
least squares mean (standard error)	-10.9 (± 1.0)	-9.7 (± 1.0)		

Statistical analyses

Statistical analysis title	400 µg Brimonidine Implant vs Sham
Comparison groups	400 µg Brimonidine Implant v Sham
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.39 [2]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.9
upper limit	1.5
Variability estimate	Standard error of the mean
Dispersion value	1.4

Notes:

[2] - MMRM model included treatment group, study region, analysis visit and treatment-by-visit interaction as factors and baseline value and baseline value-by-analysis visit interaction as covariates.

Secondary: Change From Baseline in Low Luminance BCVA Score as Assessed by ETDRS Chart at Month 24

End point title	Change From Baseline in Low Luminance BCVA Score as Assessed by ETDRS Chart at Month 24

End point description:

Low Luminance BCVA was measured by placing a 2.0 log unit neutral density filter over the best correction for that eye and having the participant read the normally illuminated ETDRS chart and was reported as the number of letters read correctly (ranging from 0 to 100 letters) in the study eye. The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). The study eye was defined as the eye that met inclusion/exclusion criteria with the worst standard BCVA. If the BCVA in both eyes was similar the right eye was selected as the study eye. A positive change from baseline indicates an improvement and a negative change from baseline indicates a worsening. MMRM was used for analysis. Participants from the mITT population, all randomised and treated participants with baseline and at least 1 postbaseline assessment for GA lesion area by FAF, with data available for analysis for this endpoint at Month 24.

End point type	Secondary

End point timeframe:

Baseline (Day 1) to Month 24

End point values	400 µg Brimonidine Implant	Sham		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	81	82		
Units: letters read correctly				
least squares mean (standard error)	-8.1 (± 1.0)	-6.7 (± 1.0)		

Statistical analyses

Statistical analysis title	400 µg Brimonidine Implant vs Sham
Comparison groups	400 µg Brimonidine Implant v Sham
Number of subjects included in analysis	163
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.301 [3]
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-1.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.2
upper limit	1.3
Variability estimate	Standard error of the mean
Dispersion value	1.4

Notes:

[3] - MMRM model included treatment group, study region, analysis visit and treatment-by-visit interaction as factors and baseline value and baseline value-by-analysis visit interaction as covariates.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose of study drug to date of last visit (up to approximately 33 months)	
Adverse event reporting additional description:	
Safety population included all participants who received at least 1 administration of study treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups	
Reporting group title	400 µg Brimonidine Implant
Reporting group description:	
400 µg brimonidine implant in the study eye, administered by intravitreal injections using the Brimonidine Drug Delivery System (DDS) every 3 months from Baseline (Day 1) through Month 21.	
Reporting group title	Sham
Reporting group description:	
Sham treatment (control) in the study eye, administered by intravitreal injections using a needleless DDS Applicator every 3 months from Baseline (Day 1) through Month 21.	

Serious adverse events	400 µg Brimonidine Implant	Sham	
Total subjects affected by serious adverse events			
subjects affected / exposed	48 / 154 (31.17%)	37 / 156 (23.72%)	
number of deaths (all causes)	5	6	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	2 / 154 (1.30%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma			
subjects affected / exposed	2 / 154 (1.30%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of skin			
subjects affected / exposed	2 / 154 (1.30%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Adenocarcinoma gastric			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Desmoplastic melanoma			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal melanoma			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lip neoplasm malignant stage unspecified			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to peritoneum			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestine adenocarcinoma			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adrenal gland cancer			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
B-cell lymphoma			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cancer			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant neoplasm of unknown primary site			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Hypertensive crisis			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral artery aneurysm			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis superficial			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 154 (0.00%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Uterine prolapse			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 154 (0.65%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Acute respiratory failure			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 154 (0.00%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Psychiatric disorders			
Alcohol withdrawal syndrome			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delirium			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device dislocation			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	2 / 154 (1.30%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural intestinal perforation			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Flail chest			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Laceration			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 154 (0.00%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendon rupture			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	0 / 154 (0.00%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic haemothorax			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 154 (1.95%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	3 / 154 (1.95%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			

subjects affected / exposed	3 / 154 (1.95%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 154 (1.95%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 0	
Coronary artery disease			
subjects affected / exposed	2 / 154 (1.30%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus node dysfunction			
subjects affected / exposed	2 / 154 (1.30%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block complete			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiopulmonary failure			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nervous system disorders			
Brain stem ischaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Presyncope			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dementia alzheimer's type			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Encephalopathy			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Iron deficiency anaemia			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Visual acuity reduced			
subjects affected / exposed	2 / 154 (1.30%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	2 / 154 (1.30%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal tear			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal vein occlusion			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anterior capsule contraction			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pancreatitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hiatus hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inguinal hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spigelian hernia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			

Cholecystitis			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis chronic			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Intertrigo			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bladder outlet obstruction			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	2 / 154 (1.30%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acquired claw toe			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 154 (0.65%)	2 / 156 (1.28%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Back pain			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoporosis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spondylolisthesis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 154 (1.95%)	3 / 156 (1.92%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis bacterial			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial pyelonephritis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			

subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			

subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 154 (0.65%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 154 (0.65%)	0 / 156 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 154 (0.00%)	1 / 156 (0.64%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	400 µg Brimonidine Implant	Sham	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	79 / 154 (51.30%)	61 / 156 (39.10%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	5 / 154 (3.25%)	10 / 156 (6.41%)	
occurrences (all)	6	11	
Vascular disorders			
Hypertension			
subjects affected / exposed	8 / 154 (5.19%)	11 / 156 (7.05%)	
occurrences (all)	8	12	
Nervous system disorders			
Headache			
subjects affected / exposed	8 / 154 (5.19%)	4 / 156 (2.56%)	
occurrences (all)	8	5	
Eye disorders			

Vitreous floaters			
subjects affected / exposed	29 / 154 (18.83%)	1 / 156 (0.64%)	
occurrences (all)	30	1	
Conjunctival haemorrhage			
subjects affected / exposed	21 / 154 (13.64%)	11 / 156 (7.05%)	
occurrences (all)	27	13	
Visual impairment			
subjects affected / exposed	12 / 154 (7.79%)	6 / 156 (3.85%)	
occurrences (all)	16	11	
Eye pain			
subjects affected / exposed	11 / 154 (7.14%)	9 / 156 (5.77%)	
occurrences (all)	11	11	
Visual acuity reduced			
subjects affected / exposed	9 / 154 (5.84%)	6 / 156 (3.85%)	
occurrences (all)	11	10	
Dry eye			
subjects affected / exposed	8 / 154 (5.19%)	6 / 156 (3.85%)	
occurrences (all)	12	12	
Ocular discomfort			
subjects affected / exposed	8 / 154 (5.19%)	1 / 156 (0.64%)	
occurrences (all)	8	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	12 / 154 (7.79%)	12 / 156 (7.69%)	
occurrences (all)	18	17	
Urinary tract infection			
subjects affected / exposed	3 / 154 (1.95%)	15 / 156 (9.62%)	
occurrences (all)	3	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 March 2014	Amendment 1: The study design was updated to reflect changes in timing of selected procedures, additional data collection in the nonstudy eye (3-field confocal scanning laser ophthalmoscopy (cSLO) exams), and the addition of blood samples for modelling of disease progression by gene expression analysis. In addition, roflumilast was added as a prohibited medication and clarifications were made throughout the protocol.
27 August 2014	Amendment 2: Updates were made to the inclusion and exclusion criteria (specifically the addition of inclusion criterion #6 requiring the presence of drusen as assessed with fundus photography and/or spectral-domain optical coherence tomography (SD-OCT) at Screening and the modification of exclusion criterion #14 to exclude participants with a history of glaucoma who might had had visual field deficits). The study design was updated to reflect the addition of corneal curvature assessment, the removal of blood draw for pharmacokinetic (PK) at Months 9 and 24, and the requirement that complete ophthalmic examinations include: external examination of the eye and adnexa, screening for eyelid/pupil responsiveness, slit-lamp biomicroscopy, indirect ophthalmoscopy, dilated fundus examination, and intraocular pressure (IOP) assessment. The following other efficacy measure was added: "GA lesion area growth in the fellow eye, as assessed with FAF and quantified by the central reading centre (CRC)," and scotopic microperimetry was changed to scotopic/mesopic microperimetry.
30 September 2014	Amendment 3: The number of sites was revised from approximately 15 to 20 to approximately 15 to 30 and inclusion criteria were updated to reflect looser restrictions for participant eligibility in order to facilitate participant recruitment. In addition, visit windows for corneal curvature assessments were adjusted for participant convenience, and other minor clarifications were made.
08 October 2014	Amendment 4: The maximum lesion size was increased from 12.5 mm^2 to 18mm^2. The visit window for Screening Visit 2 was changed from -19 to -2 days to -20 to -2 days for participant and investigator convenience. In addition, several corrections and clarifications were made.
14 January 2015	Amendment 5: Several revisions were made to reflect that microperimetry would only be conducted at selected sites in participants who qualified and consented to the procedure in order to ease participant recruitment; loss of retinal sensitivity was removed from the clinical hypotheses and retinal sensitivity was changed to the other efficacy endpoint, rather than a secondary efficacy endpoint. In addition, a possible interim analysis of the first 50% of participants that completed Month 18 was added in order to facilitate earlier project planning.
13 May 2015	Amendment 6: To facilitate participant recruitment, the number of sites was increased from approximately 30 to approximately 40 and the inclusion criterion requiring that the study eye have a BCVA better than or equal to 55 letters (20/80 Snellen equivalent) was changed to require a BCVA better than or equal to 45 letters (20/125 Snellen equivalent). A second interim analysis was planned to be carried out when 100% of participants had completed Month 18. Updates were also made to reflect that standard and low luminance BCVA would be assessed in both eyes, rather than the study eye only, at Baseline and Months 12 and 24, and that these BCVA assessments would be done prior to pupil dilation, as pupil dilation temporarily reduces visual acuity. In addition, cSLO quantitative fundus autofluorescence (Qfaf) (central field) was changed to be an assessment performed in participants who participated in the microperimetry procedure only, and in the study eye only, rather than both eyes.

23 May 2017	Amendment 7: Updates were made to reflect the following changes to efficacy measures and analyses: area of reticular drusen was changed to presence or absence of reticular drusen (given difficulty of measuring the area), the primary efficacy analysis method was changed from an analysis of covariance to an MMRM in order to attain greater statistical power, near-IR measurement was changed from 7-field to 3-field, genotyping was changed from analysis of specific changes to genome-wide variations, use of a Goldmann applanation tonometer for IOP measurements was changed to recommended instead of required, last observation carried forward analyses were removed, per-protocol population was removed, and it was specified that analyses performed on the mITT population would be based on the randomised treatment. In addition, the interim analysis that was planned to be carried out when 100% of participants completed Month 18 was dropped from the planned analyses. Several clarifications and corrections were also made throughout the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported