Clinical trial results:
A Phase 2, Randomized, Placebo-controlled, Double-masked Study to Assess Safety and Efficacy of Multiple Doses of IONIS-FB-LRX, an Antisense Inhibitor of Complement Factor B, in Patients With Geographic Atrophy Secondary to Age-related Macular Degeneration (AMD)

Summary

EudraCT number	2020-005174-94
Trial protocol	CZ NL ES AT
Global end of trial date	12 June 2024

Results information

Result version number	v1 (current)
This version publication date	29 June 2025
First version publication date	29 June 2025

Trial information

Trial identification

Sponsor protocol code	ISIS 696844-CS5

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03815825
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ionis Pharmaceuticals, Inc.
Sponsor organisation address	2855 Gazelle Court, Carlsbad, United States, 92010
Public contact	Ionis Pharmaceuticals, Inc., Ionis Clinical Trial Information, +1 760-603-2346, globalregulatoryaffairs@ionis.com
Scientific contact	Ionis Pharmaceuticals, Inc., Ionis Clinical Trial Information, +1 760-603-2346, globalregulatoryaffairs@ionis.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	12 June 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 April 2024
Global end of trial reached?	Yes
Global end of trial date	12 June 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study was to evaluate the effect of IONIS-FB-LRX (ISIS 696844) on the rate of change of the area of geographic atrophy (GA) secondary to age-related macular degeneration (AMD) measured by fundus autofluorescence (FAF).

Protection of trial subjects:

Each subject, or legally acceptable representative, signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 March 2019
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	United States: 210
Country: Number of subjects enrolled	Australia: 38
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Canada: 14
Country: Number of subjects enrolled	Spain: 30
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	Poland: 16
Worldwide total number of subjects	329
EEA total number of subjects	67

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)	28
From 65 to 84 years	244
85 years and over	57

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 79 investigative sites in the United States (US), Australia, Spain, Canada, Austria, Poland, and the Czech Republic from 04 March 2019 to 12 June 2024.

Pre-assignment

Screening details:

A total of 332 subjects with GA secondary to AMD were randomised and 329 received at least 1 dose of either ISIS 696844 or placebo. As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects. Number reported are the subjects who completed the 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	Subject, Investigator, Monitor, Data analyst, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	ISIS 696844 40 mg

Arm description:

Subjects received a loading dose of ISIS 696844, 40 milligrams (mg), subcutaneously (SC) at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose every 4 weeks up to Week 45.

Arm type	Experimental
Investigational medicinal product name	ISIS 696844
Investigational medicinal product code	
Other name	IONIS-FB-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 696844, 40 mg, was administered SC at Weeks 1, 3, and 5 (on Days 1, 15 and 29), followed by 1 dose, Q4W up to Week 45.

Arm title	ISIS 696844 70 mg

Arm description:

Subjects received a loading dose of ISIS 696844, 70 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.

Arm type	Experimental
Investigational medicinal product name	ISIS 696844
Investigational medicinal product code	
Other name	IONIS-FB-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 696844, 70 mg, was administered SC at Weeks 1, 3, and 5 (on Days 1, 15 and 29), followed by 1 dose, Q4W up to Week 45.

Arm title	ISIS 696844 100 mg

Arm description:

Subjects received a loading dose of ISIS 696844, 100 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.

Arm type	Experimental

Investigational medicinal product name	ISIS 696844
Investigational medicinal product code	
Other name	IONIS-FB-LRx
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

ISIS 696844, 100 mg, was administered SC at Weeks 1, 3, and 5 (on Days 1, 15 and 29), followed by 1 dose, Q4W up to Week 45.

Arm title	Pooled Placebo

Arm description:

Subjects received matching placebo, either 40 mg, 70 mg, or 100 mg, SC at Weeks 1,3 and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Matching placebo, either 40 mg, 70 mg, or 100 mg, was administered SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, Q4W up to Week 45.

Number of subjects in period 1	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg
Started	104	105	14
Completed	92	96	14
Not completed	12	9	0
Consent withdrawn by subject	3	3	-
Reason Not Specified	2	-	-
Ineligibility	1	-	-
Adverse Event or Serious Adverse Event	6	6	-

Number of subjects in period 1	Pooled Placebo
Started	106
Completed	97
Not completed	9
Consent withdrawn by subject	3
Reason Not Specified	-
Ineligibility	-
Adverse Event or Serious Adverse Event	6

Baseline characteristics

Reporting groups	
Reporting group title	ISIS 696844 40 mg
Reporting group description:	
Subjects received a loading dose of ISIS 696844, 40 milligrams (mg), subcutaneously (SC) at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose every 4 weeks up to Week 45.	
Reporting group title	ISIS 696844 70 mg
Reporting group description:	
Subjects received a loading dose of ISIS 696844, 70 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.	
Reporting group title	ISIS 696844 100 mg
Reporting group description:	
Subjects received a loading dose of ISIS 696844, 100 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.	
Reporting group title	Pooled Placebo
Reporting group description:	
Subjects received matching placebo, either 40 mg, 70 mg, or 100 mg, SC at Weeks 1,3 and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.	

Reporting group values	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg
Number of subjects	104	105	14
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	76.2	75.6	72.3
standard deviation	± 8.20	± 8.37	± 6.90
Gender categorical Units: Subjects			
Male	37	41	8
Female	67	64	6
Ethnicity Units: Subjects			
Hispanic or Latino	2	1	0
Not Hispanic or Latino	102	104	14
Race Units: Subjects			
White	102	103	14
Black	0	1	0
Other Race	2	1	0
GA Area Measured by FAF in Study Eye at Baseline			
Baseline was defined as the average of Week -2 (Screening Period 2) and Week 1 (Day 1 pre-dose) assessments.			
Units: square millimeters (mm2)/365.25 days			
arithmetic mean	7.4498	7.7186	8.4266
standard deviation	± 4.1358	± 3.8793	± 3.9372

Reporting group values	Pooled Placebo	Total	
Number of subjects	106	329	
Age Categorical Units: Subjects			

Age continuous Units: years			
arithmetic mean	77.6		
standard deviation	± 8.17	-	
Gender categorical Units: Subjects			
Male	47	133	
Female	59	196	
Ethnicity Units: Subjects			
Hispanic or Latino	2	5	
Not Hispanic or Latino	104	324	
Race Units: Subjects			
White	106	325	
Black	0	1	
Other Race	0	3	
GA Area Measured by FAF in Study Eye at Baseline			
Baseline was defined as the average of Week -2 (Screening Period 2) and Week 1 (Day 1 pre-dose) assessments.			
Units: square millimeters (mm2)/365.25 days			
arithmetic mean	7.6762		
standard deviation	± 4.1123	-	

End points

End points reporting groups

Reporting group title	ISIS 696844 40 mg
Reporting group description:	
Subjects received a loading dose of ISIS 696844, 40 milligrams (mg), subcutaneously (SC) at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose every 4 weeks up to Week 45.	
Reporting group title	ISIS 696844 70 mg
Reporting group description:	
Subjects received a loading dose of ISIS 696844, 70 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.	
Reporting group title	ISIS 696844 100 mg
Reporting group description:	
Subjects received a loading dose of ISIS 696844, 100 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.	
Reporting group title	Pooled Placebo
Reporting group description:	
Subjects received matching placebo, either 40 mg, 70 mg, or 100 mg, SC at Weeks 1,3 and 5 (on Days 1, 15, and 29), followed by 1 dose, every 4 weeks up to Week 45.	

Primary: Mean Rate of Change From Baseline in GA Area at Week 49 by FAF - Study Eye

End point title	Mean Rate of Change From Baseline in GA Area at Week 49 by FAF - Study Eye
End point description:	
The mean rate of change in GA growth was measured by FAF images as determined by the central reading center (CRC). Intent-to-treat (ITT) population included all subjects who were randomized and received at least one dose of the study drug. Baseline was defined as value at Week -2 (Screening Period 2), if available. Otherwise, the last available measurement prior to the first dose will be used as the baseline. As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects. CNV = choroidal neovascularization.	
End point type	Primary
End point timeframe:	
Baseline to Week 49	

End point values	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	105	14	106
Units: mm2/365.25 days				
least squares mean (standard error)	1.9375 (± 0.1316)	2.1059 (± 0.1278)	2.0139 (± 0.3448)	2.1885 (± 0.1271)

Statistical analyses

Statistical analysis title	ISIS 696844 40 mg vs Pooled Placebo

Statistical analysis description:

Random effects model with treatment group, interaction between treatment group & time, stage of subjects randomized, status of exudative CNV in fellow eye as factors & time & rate of change in the GA area during screening as covariates. Random effects include the intercept and slope (time) with an unstructured covariance matrix, with all other variables as fixed effects. The within patient error was assumed to be independent and normally distributed with variance component as the covariance stru

Comparison groups	ISIS 696844 40 mg v Pooled Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.171
Method	Random Effect Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.251
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.611
upper limit	0.1091
Variability estimate	Standard error of the mean
Dispersion value	0.183

Statistical analysis title	ISIS 696844 100 mg vs Pooled Placebo

Statistical analysis description:

Random effects model with treatment group, interaction between treatment group & time, stage of subjects randomized, status of exudative CNV in fellow eye as factors & time & rate of change in the GA area during screening as covariates. Random effects include the intercept & slope (time) with an unstructured covariance matrix with all other variables as fixed effects. The within patient error was assumed to be independent & normally distributed with variance component as the covariance structure

Comparison groups	ISIS 696844 100 mg v Pooled Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.635
Method	Random Effect Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.1745
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8976
upper limit	0.5486
Variability estimate	Standard error of the mean
Dispersion value	0.3675

Statistical analysis title	ISIS 696844 70 mg vs Pooled Placebo

Statistical analysis description:

Random effects model with treatment group, interaction between treatment group & time, stage of subjects randomized, status of exudative CNV in fellow eye as factors & time & rate of change in the GA

area during screening as covariates. Random effects include the intercept & slope (time) with an unstructured covariance matrix with all other variables as fixed effects. The within patient error was assumed to be independent & normally distributed with variance component as the covariance structure

Comparison groups	ISIS 696844 70 mg v Pooled Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.647
Method	Random Effect Model
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.0826
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4372
upper limit	0.2721
Variability estimate	Standard error of the mean
Dispersion value	0.1802

Secondary: Absolute Change From Baseline in the GA Area as Measured by FAF - Study Eye

End point title	Absolute Change From Baseline in the GA Area as Measured by FAF - Study Eye

End point description:

The absolute change in GA area was measured by FAF images as determined by the CRC. ITT population included all subjects who were randomized and received at least one dose of the study drug. Subjects analyzed are the number of subjects in ITT population. As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects. MMRM = Mixed Model for Repeated Measures.

End point type	Secondary

End point timeframe:

Baseline, Week 57

End point values	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	105	14	106
Units: mm2				
least squares mean (standard error)	2.2528 (± 0.1476)	2.3590 (± 0.1422)	2.3548 (± 0.3753)	2.4539 (± 0.1433)

Statistical analyses

Statistical analysis title	ISIS 696844 40 mg vs Pooled Placebo

Statistical analysis description:

MMRM with treatment group, study visit, interaction between treatment group & study visit, baseline GA area, rate of change in GA area during Screening, stage of subjects randomized & status of exudative

CNV in fellow eye as independent variables. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	ISIS 696844 40 mg v Pooled Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.312
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.201
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.5914
upper limit	0.1894
Variability estimate	Standard error of the mean
Dispersion value	0.1983

Statistical analysis title	ISIS 696844 100 mg vs Pooled Placebo

Statistical analysis description:

MMRM with treatment group, study visit, interaction between treatment group & study visit, baseline GA area, rate of change in GA area during Screening, stage of subjects randomized & status of exudative CNV in fellow eye as independent variables. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	ISIS 696844 100 mg v Pooled Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.806
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.099
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.8926
upper limit	0.6945
Variability estimate	Standard error of the mean
Dispersion value	0.4032

Statistical analysis title	ISIS 696844 70 mg vs Pooled Placebo

Statistical analysis description:

MMRM with treatment group, study visit, interaction between treatment group & study visit, baseline GA area, rate of change in GA area during Screening, stage of subjects randomized & status of exudative CNV in fellow eye as independent variables. An unstructured covariance matrix was used to model the within-subject errors.

Comparison groups	ISIS 696844 70 mg v Pooled Placebo

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.627
Method	MMRM
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.0948
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.478
upper limit	0.2884
Variability estimate	Standard error of the mean
Dispersion value	0.1947

Secondary: Percent Change From Baseline in Levels of Factor B (FB) in Plasma at Steady State

End point title	Percent Change From Baseline in Levels of Factor B (FB) in Plasma at Steady State

End point description:

ITT population included all subjects who were randomized and received at least one dose of the study drug. Baseline was defined as the average of Week -2 (Screening Period 2) and Week 1 (Day 1 pre-dose) assessments. Steady-state levels of complement factors or complement activity were defined as the average of available data from Week 33 to Week 49 assessments.
As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects. ANCOVA = Analysis of Covariance.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	105	14	106
Units: percent change				
least squares mean (standard error)	-63.0 (± 1.70)	-68.8 (± 1.61)	-66.9 (± 3.75)	2.1 (± 1.67)

Statistical analyses

Statistical analysis title	ISIS 696844 40 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomised, baseline GA area, rate of change in GA area during Screening, and baseline plasma FB level as covariates.

Comparison groups	ISIS 696844 40 mg v Pooled Placebo

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-65.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-68.8
upper limit	-61.5
Variability estimate	Standard error of the mean
Dispersion value	1.87

Statistical analysis title	ISIS 696844 100 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomised, baseline GA area, rate of change in GA area during Screening, and baseline plasma FB level as covariates.

Comparison groups	ISIS 696844 100 mg v Pooled Placebo
Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-69
Confidence interval	
level	95 %
sides	2-sided
lower limit	-77.3
upper limit	-60.8
Variability estimate	Standard error of the mean
Dispersion value	4.19

Statistical analysis title	ISIS 696844 70 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomised, baseline GA area, rate of change in GA area during Screening, and baseline plasma FB level as covariates.

Comparison groups	ISIS 696844 70 mg v Pooled Placebo

Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-70.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	-74.5
upper limit	-67.3
Variability estimate	Standard error of the mean
Dispersion value	1.84

Secondary: Percent Change From Baseline in Levels of Serum Complement Alternative Pathway Function (AH50) Activity at Steady State

End point title	Percent Change From Baseline in Levels of Serum Complement Alternative Pathway Function (AH50) Activity at Steady State

End point description:

ITT population included all subjects who were randomized and received at least one dose of the study drug. Baseline was defined as the average of Week -2 (Screening Period 2) and Week 1 (Day 1 pre-dose) assessments. Steady-state levels of complement factors or complement activity were defined as the average of available data from Week 33 to Week 49 assessments. As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	105	14	106
Units: percent change				
least squares mean (standard error)	-22.4 (± 2.03)	-33.7 (± 1.93)	-34.2 (± 4.46)	-1.3 (± 1.98)

Statistical analyses

Statistical analysis title	ISIS 696844 40 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening, and baseline AH50 level as covariates.

Comparison groups	ISIS 696844 40 mg v Pooled Placebo

Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-21.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-25.5
upper limit	-16.7
Variability estimate	Standard error of the mean
Dispersion value	2.23

Statistical analysis title	ISIS 696844 70 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening, and baseline AH50 level as covariates.

Comparison groups	ISIS 696844 70 mg v Pooled Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-32.5
Confidence interval	
level	95 %
sides	2-sided
lower limit	-36.8
upper limit	-28.2
Variability estimate	Standard error of the mean
Dispersion value	2.19

Statistical analysis title	ISIS 696844 100 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening, and baseline AH50 level as covariates.

Comparison groups	ISIS 696844 100 mg v Pooled Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-33
Confidence interval	
level	95 %
sides	2-sided
lower limit	-42.8
upper limit	-23.2
Variability estimate	Standard error of the mean
Dispersion value	4.98

Notes:

[1] - ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomised, baseline GA area, rate of change in GA area during Screening, and baseline plasma FB level as covariates.

Secondary: Absolute Change From Baseline in Low Luminance Visual Acuity (LLVA) - Study Eye

End point title	Absolute Change From Baseline in Low Luminance Visual Acuity (LLVA) - Study Eye

End point description:

Visual function assessments included LLVA assessment in study eye only. LLVA was measured on Early Treatment of Diabetic Retinopathy Study (ETDRS) chart and a 2.0 log unit neutral density filter at a starting distance of 4 meters (performed prior to dilating eyes). The letter score ranges from 0 (worse score) to 100 (best score), and a gain in LLVA from baseline indicates an improvement in visual acuity. The Markov Chain Monte Carlo (MCMC) method was used to impute missing LLVA score by treatment group based on following variable list for imputations: baseline, week 25 and week 49 LLVA scores, Stage of subjects randomized, status of exudative CNV in the fellow eye (Absence vs Presence), baseline GA area & rate of change in GA area during Screening. ITT population included all subjects who were randomized & received at least one dose of the study drug. As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects.

End point type	Secondary

End point timeframe:

Baseline, Week 49

End point values	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg	Pooled Placebo
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	104	105	14	106
Units: score on a scale				
least squares mean (standard error)	-2.1 (± 1.38)	-1.9 (± 1.32)	2.6 (± 3.02)	-3.1 (± 1.36)

Statistical analyses

Statistical analysis title	ISIS 696844 40 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening,

and baseline LLVA score as covariates.

Comparison groups	ISIS 696844 40 mg v Pooled Placebo
Number of subjects included in analysis	210
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.53
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2
upper limit	4
Variability estimate	Standard error of the mean
Dispersion value	1.53

Statistical analysis title	ISIS 696844 70 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening, and baseline LLVA score as covariates.

Comparison groups	ISIS 696844 70 mg v Pooled Placebo
Number of subjects included in analysis	211
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.421 [2]
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	1.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.7
upper limit	4.2
Variability estimate	Standard error of the mean
Dispersion value	1.51

Notes:

[2] - ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening, and baseline LLVA score as covariates.

Statistical analysis title	ISIS 696844 100 mg vs Pooled Placebo

Statistical analysis description:

ANCOVA model with treatment group and status of exudative CNV in the fellow eye (Absence vs Presence), stage of subjects randomized, baseline GA area, rate of change in GA area during Screening, and baseline LLVA score as covariates.

Comparison groups	ISIS 696844 100 mg v Pooled Placebo

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.098
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	5.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1
upper limit	12.3
Variability estimate	Standard error of the mean
Dispersion value	3.4

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to Week 57 (treatment period up to Week 45, safety follow-up period up to Week 57)

Adverse event reporting additional description:

Safety population included all subjects who were randomised and received at least one dose of the study drug. As pre-specified, for purposes of analyses, data for placebo subjects were pooled for comparison to ISIS 696844-treated subjects.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	ISIS 696844 40 mg

Reporting group description:

Subjects received a loading dose of ISIS 696844, 40 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose Q4W up to Week 45.

Reporting group title	ISIS 696844 70 mg

Reporting group description:

Subjects received a loading dose of ISIS 696844, 70 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, Q4W up to Week 45.

Reporting group title	ISIS 696844 100 mg

Reporting group description:

Subjects received a loading dose of ISIS 696844, 100 mg, SC at Weeks 1, 3, and 5 (on Days 1, 15, and 29), followed by 1 dose, Q4W up to Week 45.

Reporting group title	Pooled Placebo

Reporting group description:

Subjects received matching placebo, either 40 mg, 70 mg, or 100 mg, SC at Weeks 1,3 and 5 (on Days 1, 15, and 29), followed by 1 dose, Q4W up to Week 45.

Serious adverse events	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 104 (17.31%)	12 / 105 (11.43%)	1 / 14 (7.14%)
number of deaths (all causes)	1	0	0
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Lung neoplasm malignant			

subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Pancreatic carcinoma			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Gastric cancer			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Benign uterine neoplasm			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal cell carcinoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma of colon			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Peripheral artery stenosis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Haematoma			

subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Hypertensive urgency			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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			
Pulmonary embolism			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea at rest			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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 respiratory failure			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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 oedema			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Confusional state			

subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Depression			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Suicidal ideation			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Vascular graft thrombosis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Femur fracture			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
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 respiratory failure			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			

Coronary artery disease			
subjects affected / exposed	2 / 104 (1.92%)	2 / 105 (1.90%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 104 (0.96%)	1 / 105 (0.95%)	0 / 14 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Atrial flutter			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Bradycardia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Angina pectoris			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Acute myocardial infarction			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Angina unstable			

subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Presyncope			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Paraesthesia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Dizziness			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Syncope			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Normocytic anaemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Autoimmune haemolytic anaemia			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood loss anaemia			

subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Gastric polyps			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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
Colitis microscopic			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Lumbar spinal stenosis			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spondylolisthesis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal stenosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Device related infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Pyelonephritis			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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

Diverticulitis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	0 / 14 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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			
Hypokalaemia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Dehydration			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	0 / 14 (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
Hyponatraemia			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	0 / 14 (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

Serious adverse events	Pooled Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 106 (15.09%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lung neoplasm malignant			

subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Pancreatic carcinoma				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Gastric cancer				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Breast cancer				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Benign uterine neoplasm				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Basal cell carcinoma				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Adenocarcinoma of colon				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Vascular disorders				
Peripheral artery stenosis				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Haematoma				

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hypertensive urgency			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dyspnoea at rest			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Acute respiratory failure			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pulmonary oedema			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Confusional state			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Vascular graft thrombosis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Femur fracture			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rib fracture			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Postoperative respiratory failure			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			

Coronary artery disease				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	2 / 106 (1.89%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Atrial flutter				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Myocardial infarction				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina pectoris				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Acute myocardial infarction				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Angina unstable				

subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Transient ischaemic attack			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Presyncope			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Paraesthesia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dizziness			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Normocytic anaemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Autoimmune haemolytic anaemia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood loss anaemia			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Gastric polyps			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Colitis microscopic			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Small intestinal obstruction			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Eczema			
subjects affected / exposed	0 / 106 (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	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nephrolithiasis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Lumbar spinal stenosis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Intervertebral disc protrusion			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spondylolisthesis			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal stenosis			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Device related infection			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pyelonephritis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

Diverticulitis			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Urinary tract infection			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Dehydration			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Hyponatraemia			
subjects affected / exposed	0 / 106 (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	ISIS 696844 40 mg	ISIS 696844 70 mg	ISIS 696844 100 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	74 / 104 (71.15%)	71 / 105 (67.62%)	13 / 14 (92.86%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	3
Squamous cell carcinoma			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	3

Basal cell carcinoma			
subjects affected / exposed	2 / 104 (1.92%)	2 / 105 (1.90%)	2 / 14 (14.29%)
occurrences (all)	4	2	2
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Extravasation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	4 / 104 (3.85%)	6 / 105 (5.71%)	0 / 14 (0.00%)
occurrences (all)	5	6	0
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Depression			
subjects affected / exposed	1 / 104 (0.96%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Investigations			
Blood creatinine increased			
subjects affected / exposed	8 / 104 (7.69%)	3 / 105 (2.86%)	0 / 14 (0.00%)
occurrences (all)	10	4	0

White blood cells urine positive			
subjects affected / exposed	3 / 104 (2.88%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	3	3	1
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 104 (3.85%)	3 / 105 (2.86%)	3 / 14 (21.43%)
occurrences (all)	4	3	3
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 104 (0.00%)	3 / 105 (2.86%)	2 / 14 (14.29%)
occurrences (all)	0	6	3
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 104 (0.00%)	3 / 105 (2.86%)	2 / 14 (14.29%)
occurrences (all)	0	3	2
Platelet count decreased			
subjects affected / exposed	5 / 104 (4.81%)	2 / 105 (1.90%)	2 / 14 (14.29%)
occurrences (all)	10	2	2
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 104 (0.96%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	1	2	2
Hepatic enzyme increased			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Red blood cells urine positive			
subjects affected / exposed	2 / 104 (1.92%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	2	0	2
Transaminases increased			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Urinary sediment present			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
Alanine aminotransferase increased			
subjects affected / exposed	1 / 104 (0.96%)	7 / 105 (6.67%)	2 / 14 (14.29%)
occurrences (all)	1	7	3
Injury, poisoning and procedural complications			

Skin laceration			
subjects affected / exposed	1 / 104 (0.96%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	1	4	1
Ligament sprain			
subjects affected / exposed	2 / 104 (1.92%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	2	2	1
Head injury			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fall			
subjects affected / exposed	6 / 104 (5.77%)	4 / 105 (3.81%)	1 / 14 (7.14%)
occurrences (all)	6	5	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	4 / 104 (3.85%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	4	1	1
Bundle branch block right			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Supraventricular extrasystoles			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 104 (3.85%)	6 / 105 (5.71%)	0 / 14 (0.00%)
occurrences (all)	4	8	0
Sciatica			
subjects affected / exposed	1 / 104 (0.96%)	1 / 105 (0.95%)	2 / 14 (14.29%)
occurrences (all)	1	1	2
Dizziness			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Eye disorders			
SE or FE: Visual acuity reduced			
subjects affected / exposed	7 / 104 (6.73%)	5 / 105 (4.76%)	0 / 14 (0.00%)
occurrences (all)	7	5	0
Study Eye (SE) or Fellow Eye (FE):			

Dry age-related macular degeneration			
subjects affected / exposed	11 / 104 (10.58%)	4 / 105 (3.81%)	1 / 14 (7.14%)
occurrences (all)	14	4	1
SE or FE: Choroidal neovascularisation			
subjects affected / exposed	4 / 104 (3.85%)	6 / 105 (5.71%)	1 / 14 (7.14%)
occurrences (all)	4	6	1
SE or FE: Posterior capsule opacification			
subjects affected / exposed	3 / 104 (2.88%)	6 / 105 (5.71%)	1 / 14 (7.14%)
occurrences (all)	6	6	2
SE or FE: Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
SE or FE: Conjunctivitis allergic			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
SE or FE: Epiretinal membrane			
subjects affected / exposed	3 / 104 (2.88%)	3 / 105 (2.86%)	2 / 14 (14.29%)
occurrences (all)	3	3	2
SE or FE: Vitreous detachment			
subjects affected / exposed	6 / 104 (5.77%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	6	2	1
SE or FE: Visual impairment			
subjects affected / exposed	5 / 104 (4.81%)	5 / 105 (4.76%)	2 / 14 (14.29%)
occurrences (all)	6	5	2
SE or FE: Dry eye			
subjects affected / exposed	1 / 104 (0.96%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
SE or FE: Retinal pigmentation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
SE or FE: Retinal oedema			
subjects affected / exposed	3 / 104 (2.88%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
SE or FE: Retinal haemorrhage			

subjects affected / exposed	5 / 104 (4.81%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	5	2	1
SE or FE: Retinal cyst			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
SE or FE: Subretinal fluid			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	2
SE or FE: Subretinal hyperreflective exudation			
subjects affected / exposed	0 / 104 (0.00%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	0	2	2
SE or FE: Vitreous floaters			
subjects affected / exposed	2 / 104 (1.92%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
SE only: Dry age-related macular degeneration			
subjects affected / exposed	7 / 104 (6.73%)	1 / 105 (0.95%)	0 / 14 (0.00%)
occurrences (all)	8	1	0
SE only: Choroidal neovascularisation			
subjects affected / exposed	2 / 104 (1.92%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
SE only: Posterior capsule opacification			
subjects affected / exposed	3 / 104 (2.88%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	3	3	1
SE only: Subretinal hyperreflective exudation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
SE only: Vitreous detachment			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
SE only: Epiretinal membrane			
subjects affected / exposed	0 / 104 (0.00%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
SE only: Subretinal fluid			

subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
SE only: Retinal pigmentation			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
SE only: Retinal haemorrhage			
subjects affected / exposed	4 / 104 (3.85%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	4	1	1
SE only: Retinal cyst			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	0	1	1
SE only: Visual impairment			
subjects affected / exposed	3 / 104 (2.88%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	3	2	1
SE only: Vitreous floaters			
subjects affected / exposed	1 / 104 (0.96%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	1	2	1
FE only: Dry age-related macular degeneration			
subjects affected / exposed	5 / 104 (4.81%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	5	1	1
FE only: Posterior capsule opacification			
subjects affected / exposed	3 / 104 (2.88%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	3	2	1
FE only: Visual impairment			
subjects affected / exposed	2 / 104 (1.92%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	2	2	1
FE only: Epiretinal membrane			
subjects affected / exposed	3 / 104 (2.88%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	3	0	1
FE only: Retinal oedema			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
FE only: Subretinal fluid			

subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
FE only: Subretinal hyperreflective exudation			
subjects affected / exposed	0 / 104 (0.00%)	2 / 105 (1.90%)	1 / 14 (7.14%)
occurrences (all)	0	2	1
Both eyes (OU): Conjunctivitis allergic			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
OU: Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
OU: Dry eye			
subjects affected / exposed	1 / 104 (0.96%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	1	1	1
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	3 / 104 (2.88%)	4 / 105 (3.81%)	1 / 14 (7.14%)
occurrences (all)	4	4	1
Diarrhoea			
subjects affected / exposed	3 / 104 (2.88%)	4 / 105 (3.81%)	1 / 14 (7.14%)
occurrences (all)	3	4	1
Abdominal discomfort			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Rash			
subjects affected / exposed	4 / 104 (3.85%)	5 / 105 (4.76%)	2 / 14 (14.29%)
occurrences (all)	6	5	2
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	8 / 104 (7.69%)	7 / 105 (6.67%)	0 / 14 (0.00%)
occurrences (all)	9	7	0
Back pain			
subjects affected / exposed	5 / 104 (4.81%)	6 / 105 (5.71%)	0 / 14 (0.00%)
occurrences (all)	5	8	0
Pain in extremity			
subjects affected / exposed	2 / 104 (1.92%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
Intervertebral disc compression			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Fibromyalgia			
subjects affected / exposed	1 / 104 (0.96%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	1	0	1
Infections and infestations			
Cystitis			
subjects affected / exposed	2 / 104 (1.92%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	2	3	1
Upper respiratory tract infection			
subjects affected / exposed	1 / 104 (0.96%)	2 / 105 (1.90%)	2 / 14 (14.29%)
occurrences (all)	1	2	2
Nasopharyngitis			
subjects affected / exposed	8 / 104 (7.69%)	5 / 105 (4.76%)	0 / 14 (0.00%)
occurrences (all)	9	5	0
Urinary tract infection			
subjects affected / exposed	13 / 104 (12.50%)	7 / 105 (6.67%)	1 / 14 (7.14%)
occurrences (all)	15	11	1
COVID-19			
subjects affected / exposed	14 / 104 (13.46%)	15 / 105 (14.29%)	1 / 14 (7.14%)
occurrences (all)	14	15	1
Onychomycosis			
subjects affected / exposed	0 / 104 (0.00%)	0 / 105 (0.00%)	1 / 14 (7.14%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	4 / 104 (3.85%)	3 / 105 (2.86%)	1 / 14 (7.14%)
occurrences (all)	5	5	1

Localised infection			
subjects affected / exposed	0 / 104 (0.00%)	1 / 105 (0.95%)	1 / 14 (7.14%)
occurrences (all)	0	1	1

Non-serious adverse events	Pooled Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	70 / 106 (66.04%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Squamous cell carcinoma of skin			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Squamous cell carcinoma			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Basal cell carcinoma			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Vascular disorders			
Orthostatic hypotension			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Injection site reaction			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Extravasation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Reproductive system and breast disorders			
Genital rash			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Cough			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	9		
Psychiatric disorders			
Insomnia			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Depression			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Investigations			
Blood creatinine increased			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
White blood cells urine positive			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	4		
Blood creatine phosphokinase increased			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	2		
Gamma-glutamyltransferase increased			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Platelet count decreased			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Blood alkaline phosphatase increased			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	7		

Hepatic enzyme increased subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Red blood cells urine positive subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2		
Transaminases increased subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Urinary sediment present subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Injury, poisoning and procedural complications Skin laceration subjects affected / exposed occurrences (all)	2 / 106 (1.89%) 2		
Ligament sprain subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Head injury subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Fall subjects affected / exposed occurrences (all)	5 / 106 (4.72%) 5		
Cardiac disorders Atrial fibrillation subjects affected / exposed occurrences (all)	3 / 106 (2.83%) 3		
Bundle branch block right subjects affected / exposed occurrences (all)	0 / 106 (0.00%) 0		
Supraventricular extrasystoles			

subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 106 (4.72%)		
occurrences (all)	5		
Sciatica			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Dizziness			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Eye disorders			
SE or FE: Visual acuity reduced			
subjects affected / exposed	7 / 106 (6.60%)		
occurrences (all)	8		
Study Eye (SE) or Fellow Eye (FE): Dry age-related macular degeneration			
subjects affected / exposed	10 / 106 (9.43%)		
occurrences (all)	10		
SE or FE: Choroidal neovascularisation			
subjects affected / exposed	6 / 106 (5.66%)		
occurrences (all)	6		
SE or FE: Posterior capsule opacification			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	4		
SE or FE: Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
SE or FE: Conjunctivitis allergic			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
SE or FE: Epiretinal membrane			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	3		

SE or FE: Vitreous detachment				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
SE or FE: Visual impairment				
subjects affected / exposed	5 / 106 (4.72%)			
occurrences (all)	5			
SE or FE: Dry eye				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE or FE: Retinal pigmentation				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE or FE: Retinal oedema				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
SE or FE: Retinal haemorrhage				
subjects affected / exposed	2 / 106 (1.89%)			
occurrences (all)	2			
SE or FE: Retinal cyst				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE or FE: Subretinal fluid				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE or FE: Subretinal hyperreflective exudation				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE or FE: Vitreous floaters				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE only: Dry age-related macular degeneration				
subjects affected / exposed	5 / 106 (4.72%)			
occurrences (all)	5			
SE only: Choroidal neovascularisation				

subjects affected / exposed	2 / 106 (1.89%)			
occurrences (all)	2			
SE only: Posterior capsule opacification				
subjects affected / exposed	2 / 106 (1.89%)			
occurrences (all)	2			
SE only: Subretinal hyperreflective exudation				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE only: Vitreous detachment				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
SE only: Epiretinal membrane				
subjects affected / exposed	2 / 106 (1.89%)			
occurrences (all)	2			
SE only: Subretinal fluid				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE only: Retinal pigmentation				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE only: Retinal haemorrhage				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE only: Retinal cyst				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
SE only: Visual impairment				
subjects affected / exposed	1 / 106 (0.94%)			
occurrences (all)	1			
SE only: Vitreous floaters				
subjects affected / exposed	0 / 106 (0.00%)			
occurrences (all)	0			
FE only: Dry age-related macular degeneration				

subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
FE only: Posterior capsule opacification			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
FE only: Visual impairment			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
FE only: Epiretinal membrane			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
FE only: Retinal oedema			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
FE only: Subretinal fluid			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
FE only: Subretinal hyperreflective exudation			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Both eyes (OU): Conjunctivitis allergic			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
OU: Detachment of retinal pigment epithelium			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
OU: Dry eye			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Diarrhoea			

subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Abdominal discomfort			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Urticaria			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 106 (6.60%)		
occurrences (all)	7		
Back pain			
subjects affected / exposed	4 / 106 (3.77%)		
occurrences (all)	4		
Pain in extremity			
subjects affected / exposed	2 / 106 (1.89%)		
occurrences (all)	2		
Intervertebral disc compression			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Fibromyalgia			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Infections and infestations			
Cystitis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Upper respiratory tract infection			
subjects affected / exposed	1 / 106 (0.94%)		
occurrences (all)	1		
Nasopharyngitis			

subjects affected / exposed	12 / 106 (11.32%)		
occurrences (all)	15		
Urinary tract infection			
subjects affected / exposed	11 / 106 (10.38%)		
occurrences (all)	13		
COVID-19			
subjects affected / exposed	16 / 106 (15.09%)		
occurrences (all)	16		
Onychomycosis			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		
Sinusitis			
subjects affected / exposed	3 / 106 (2.83%)		
occurrences (all)	3		
Localised infection			
subjects affected / exposed	0 / 106 (0.00%)		
occurrences (all)	0		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 June 2020	The following changes were made as per amendment 1: 1. Extended duration of Screening Period 1 to accommodate the need for subjects and/or sites to delay randomisation for a variety of reasons, including COVID-19 exposure 2. Updated the description of repeating procedures and calculation of the rate of GA area growth for stratification purposes 3. Revised inclusion and exclusion criteria
01 November 2022	The following changes were made as per amendment 2: 1. Revised inclusion and exclusion criteria 2. Added a second interim analyses for assessment of efficacy and safety endpoints when ≥50% of subjects had reached the Week 49 visit
15 May 2023	The following changes were made as per amendment 3: 1. Changed the primary efficacy endpoint from absolute change in GA area to rate of growth (slope) 2. Added a secondary objective and corresponding endpoint to evaluate the effect of ISIS 696844 on the absolute change in GA area measured by FAF

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported