Clinical trial results:
Sapphire: A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy Of Suprachoroidal CLS-TA in Conjunction with Intravitreal Aflibercept in Subjects with Retinal Vein Occlusion

Summary

EudraCT number	2016-004648-12
Trial protocol	GB HU DE ES AT PT DK PL IT
Global end of trial date	18 December 2018

Results information

Result version number	v1 (current)
This version publication date	05 March 2021
First version publication date	05 March 2021

Trial information

Trial identification

Sponsor protocol code	CLS1003-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02980874
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clearside Biomedical, Inc
Sponsor organisation address	900 North Point Parkway, Suite 200, Alpharetta, Georgia, United States, 30005
Public contact	Gina Debrah, Clearside Biomedical, Inc., 001 678254-2345, gina.debrah@clearsidebio.com
Scientific contact	Thomas Ciulla, MD, MBA, Clearside Biomedical, Inc., 001 678392-2318, thomas.ciulla@clearsidebio.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	18 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 December 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

This study was to demonstrate that suprachoroidal triamcinolone acetonide injectable suspension (CLS-TA) in conjunction with intravitreal aflibercept is superior to intravitreal aflibercept alone in the proportion of subjects demonstrating greater than or equal to (>=) 15 letter improvement in best corrected visual acuity (BCVA) two months from Baseline.

Protection of trial subjects:

The study was conducted in accordance with ethical principles that had their origin in the Declaration of Helsinki and were consistent with the International Council for Harmonisation Guideline for Good Clinical Practice, and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 February 2017
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	Poland: 10
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	Denmark: 3
Country: Number of subjects enrolled	Hungary: 7
Country: Number of subjects enrolled	Canada: 5
Country: Number of subjects enrolled	India: 32
Country: Number of subjects enrolled	Philippines: 3
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	United States: 365
Country: Number of subjects enrolled	Australia: 15
Worldwide total number of subjects	460
EEA total number of subjects	37

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)	196
From 65 to 84 years	238
85 years and over	26

Subject disposition

Recruitment

Recruitment details:

A total of 653 subjects were screened, of which 460 subjects were randomised into the study.

Pre-assignment

Screening details:

This study was conducted in subjects with macular edema and retinal vein occlusion.

Period 1

Period 1 title	Overall (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham

Arm description:

All subjects were to receive 3 unilateral suprachoroidal injections of 4 milligrams (mg) of CLS-TA in 100 microlitres (mcL) administered 12 weeks apart on Day 0, Week 12, and Week 24, in conjunction with 4 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received intravitreal sham procedures on Week 8, Week 16, and Week 20.

Arm type	Experimental
Investigational medicinal product name	CLS-TA
Investigational medicinal product code	
Other name	Triamcinolone acetonide injectable suspension
Pharmaceutical forms	Suspension for injection
Routes of administration	Intraocular use

Dosage and administration details:

Subjects were to receive 3 unilateral SC injections of CLS-TA administered 12 weeks apart in the study eye.

Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	Eylea
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects were to receive 4 unilateral injections of intravitreal aflibercept.

Arm title	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure

Arm description:

All subjects were to receive 7 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL administered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 suprachoroidal sham procedures administered 12 weeks apart on Day 0, Week 12, and Week 24.

Arm type	Active comparator

Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	Eylea
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects were to receive 7 unilateral injections of intravitreal aflibercept.

Number of subjects in period 1	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure
Started	231	229
Completed	128	127
Not completed	103	102
Adverse events (AEs)	2	7
Consent withdrawn by subject	7	2
Unknown study completion status	1	-
Other- Unspecified (included study termination)	88	88
Lost to follow-up	5	5

Baseline characteristics

Reporting groups	
Reporting group title	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham
Reporting group description:	
All subjects were to receive 3 unilateral suprachoroidal injections of 4 milligrams (mg) of CLS-TA in 100 microlitres (mcL) administered 12 weeks apart on Day 0, Week 12, and Week 24, in conjunction with 4 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received intravitreal sham procedures on Week 8, Week 16, and Week 20.	
Reporting group title	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure
Reporting group description:	
All subjects were to receive 7 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL administered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 suprachoroidal sham procedures administered 12 weeks apart on Day 0, Week 12, and Week 24.	

Reporting group values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure	Total
Number of subjects	231	229	460
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	66.4	64.9	
standard deviation	± 12.31	± 12.42	-
Gender categorical Units: Subjects			
Female	97	105	202
Male	134	124	258
Race Units: Subjects			
American Indian/Alaska Native	2	0	2
Asian	33	40	73
Black/African American	10	12	22
Native Hawaiian/Other Pacific Islander	1	0	1
White	181	177	358
Other	2	0	2
Unknown/Not reported	2	0	2

End points

End points reporting groups

Reporting group title	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham

Reporting group description:

All subjects were to receive 3 unilateral suprachoroidal injections of 4 milligrams (mg) of CLS-TA in 100 microlitres (mcL) administered 12 weeks apart on Day 0, Week 12, and Week 24, in conjunction with 4 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received intravitreal sham procedures on Week 8, Week 16, and Week 20.

Reporting group title	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure

Reporting group description:

All subjects were to receive 7 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL administered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 suprachoroidal sham procedures administered 12 weeks apart on Day 0, Week 12, and Week 24.

Primary: Percentage of Subjects Demonstrating >=15 Letter Improvement in Best Corrected Visual Acuity (BCVA) in the Study Eye From Baseline at Week 8

End point title	Percentage of Subjects Demonstrating >=15 Letter Improvement in Best Corrected Visual Acuity (BCVA) in the Study Eye From Baseline at Week 8

End point description:

BCVA was evaluated by Early Treatment of Diabetic Retinopathy Study (ETDRS) using standardized lighting and standardized lanes. The results were reported as the number of letters read. Visual acuity testing should precede any examination requiring contact with the eye. Analysis was performed on intent-to-treat (ITT) population that included all randomised subjects.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: Percentage of subjects				
number (confidence interval 95%)	49.4 (42.7 to 56.0)	55.5 (48.8 to 62.0)		

Statistical analyses

Statistical analysis title	CLS-TA+Aflibercept+Sham versus Aflibercept+Sham
Comparison groups	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham v Control:Intravitreal Aflibercept+Suprachoroidal Sham

	Procedure
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.187 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-6.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-15.2
upper limit	3

Notes:

[1] - The p-value was based on a CMH test for general association between treatment and response with stratification by type of retinal vein occlusion (BRVO, CRVO).

Secondary: Mean Change from Baseline in Best Corrected Visual Acuity

End point title	Mean Change from Baseline in Best Corrected Visual Acuity

End point description:

BCVA was evaluated by ETDRS using standardized lighting and standardized lanes. The results were reported as the number of letters read. Visual acuity testing should precede any examination requiring contact with the eye. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 8, and Week 24

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: Change in letters				
least squares mean (standard error)				
Week 8 (n=225,225)	14.8 (± 0.84)	17.8 (± 0.84)		
Week 24 (n=216,213)	15.5 (± 0.85)	20.5 (± 0.85)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Central Subfield Retinal Thickness (CST)

End point title	Mean Change From Baseline in Central Subfield Retinal Thickness (CST)

End point description:

CST was used to assess retinal thickness and disease characterisation and was measured by spectral domain optical coherence tomography (SD-OCT) at each visit. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Baseline, Week 8, and Week 24

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: Change in microns				
least squares mean (standard error)				
Week 8 (n=224,221)	-405.3 (± 3.96)	-403.4 (± 3.99)		
Week 24 (n=212,210)	-354.3 (± 8.01)	-416.2 (± 8.05)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point title	Number of Subjects with Treatment-Emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs)

End point description:

Adverse event (AE) was defined as the development of an undesirable medical condition or the deterioration of a pre-existing medical condition after or during exposure to a pharmaceutical product, whether or not considered causally related to the product. A serious adverse event (SAE) was an AE occurring during any study phase and at any dose of study treatment fulfilled one or more of the following: death, immediately life-threatening, in-patient hospitalisation or prolongation of existing hospitalisation, persistent or significant disability or incapacity, congenital abnormality or birth defect or important medical event. A TEAE was any AE (or SAE) occurring on or after the date of the first dose of study drug or worsening relative to the pre-treatment state. Analysis was performed on safety population that included all randomly assigned subjects who were administered at least 1 dose of the study treatment.

End point type	Secondary

End point timeframe:

From Baseline up to Week 48

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: subjects				
TEAEs	180	156		
TESAEs	25	28		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change From Baseline in Excess Retinal Thickness (ERT)

End point title	Mean Change From Baseline in Excess Retinal Thickness (ERT)

End point description:

Excess retinal thickness was defined as CST minus 300 microns, set to 1 micron if CST was less than or equal to 300 microns. Analysis was performed on ITT population.

End point type	Secondary

End point timeframe:

Baseline, Week 8

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: Change in microns				
least squares mean (standard error)				
Week 8	-356.2 (± 2.65)	-353.6 (± 2.67)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Additional Intravitreal Aflibercept Injections Administered From Week 8 Through Week 20

End point title	Percentage of Subjects With Additional Intravitreal Aflibercept Injections Administered From Week 8 Through Week 20

End point description:

Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for

specified category.

End point type	Secondary

End point timeframe:

Weeks 8, 16, and 20

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: percentage of subjects				
number (not applicable)				
Week 8 (n=225,226)	7.6	0		
Week 16 (n=220,215)	7.3	0		
Week 20 (n=216,219)	12	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Gaining >=0, >=5, >=10, and >=15 Best Corrected Visual Acuity

End point title	Number of Subjects Gaining >=0, >=5, >=10, and >=15 Best Corrected Visual Acuity

End point description:

BCVA was evaluated by ETDRS using standardized lighting and standardized lanes. The results were reported as the number of letters read. Visual acuity testing should precede any examination requiring contact with the eye. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Weeks 4, 8 and 48

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: subjects				
number (not applicable)				
Week 4- Subjects Gained >=0 (n=227,222)	210	213		

Week 4- Subjects Gained >=5 (n=227,222)	181	190		
Week 4- Subjects Gained >=10 (n=227,222)	127	149		
Week 4- Subjects Gained >=15 (n=227,222)	78	94		
Week 8- Subjects Gained >=0 (n=224,225)	212	217		
Week 8- Subjects Gained >=5 (n=224,225)	188	206		
Week 8- Subjects Gained >=10 (n=224,225)	153	172		
Week 8- Subjects Gained >=15 (n=224,225)	114	126		
Week 48- Subjects Gained >=0 (n=121,124)	98	110		
Week 48- Subjects Gained >=5 (n=121,124)	86	103		
Week 48- Subjects Gained >=10 (n=121,124)	67	94		
Week 48- Subjects Gained >=15 (n=121,124)	46	84		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Best Corrected Visual Acuity >70

End point title	Number of Subjects With Best Corrected Visual Acuity >70

End point description:

BCVA was evaluated by ETDRS using standardized lighting and standardized lanes. The results were reported as the number of letters read. Visual acuity testing should precede any examination requiring contact with the eye. Analysis was performed on ITT population in subjects with a baseline BCVA <=70 letters. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Weeks 4 and 8

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: subjects				
number (not applicable)				
Week 4 (n=227,220)	79	89		
Week 8 (n=224,223)	88	115		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Did Not Lose 15 or More Early Treatment of Diabetic Retinopathy Study Letters From Baseline

End point title	Percentage of Subjects Who Did Not Lose 15 or More Early Treatment of Diabetic Retinopathy Study Letters From Baseline

End point description:

Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Weeks 4, 8, 12, 16, 20, 24, 30, 36, 42 and 48

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	228	225		
Units: percentage of subjects				
number (confidence interval 95%)				
Week 4 (n=228,222)	0.9 (0.1 to 3.1)	0.9 (0.1 to 3.2)		
Week 8 (n=225,225)	0.9 (0.1 to 3.2)	0.4 (0.0 to 2.5)		
Week 12 (n=219,224)	1.4 (0.3 to 4.0)	0.9 (0.1 to 3.2)		
Week 16 (n=219,212)	1.8 (0.5 to 4.6)	0.9 (0.1 to 3.4)		
Week 20 (n=216,214)	3.2 (1.3 to 6.6)	0.0 (0.0 to 1.7)		
Week 24 (n=216,213)	2.3 (0.8 to 5.3)	1.9 (0.5 to 4.7)		
Week 30 (n=206,209)	2.4 (0.8 to 5.6)	2.4 (0.8 to 5.5)		
Week 36 (n=172,174)	3.5 (1.3 to 7.4)	3.4 (1.3 to 7.4)		
Week 42 (n=140,140)	4.3 (1.6 to 9.1)	2.1 (0.4 to 6.1)		
Week 48 (n=121,124)	4.1 (1.4 to 9.4)	4.8 (1.8 to 10.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Central Subfield Retinal Thickness <300

Microns at Every Study Visit

End point title	Percentage of Subjects with Central Subfield Retinal Thickness <300 Microns at Every Study Visit

End point description:

CST was used to assess retinal thickness and disease characterisation and was measured by Spectral Domain Optical Coherence Tomography (SD-OCT) at each visit. Analysis was performed on ITT population. Here 'n' signifies number of subjects with available data for specified category.

End point type	Secondary

End point timeframe:

Weeks 4 and 8

End point values	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	231	229		
Units: Percentage of subjects				
number (not applicable)				
Week 4 (n=214,214)	84.1	77.1		
Week 8 (n=217,217)	89.9	88.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline to Week 48

Adverse event reporting additional description:

Analysis was performed on safety population which consisted of all randomized subjects who received at least 1 dose of the study treatment.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham

Reporting group description:

All subjects were to receive 3 unilateral suprachoroidal injections of 4 mg of CLS-TA in 100 mcL administered 12 weeks apart on Day 0, Week 12, and Week 24, in conjunction with 4 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcL in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received intravitreal sham procedures on Week 8, Week 16, and Week 20.

Reporting group title	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure

Reporting group description:

All subjects were to receive 7 unilateral injections of intravitreal aflibercept of dose 2 mg in 50 mcLadministered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 suprachoroidal sham procedures administered 12 weeks apart on Day 0, Week 12, and Week 24.

Serious adverse events	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure	
Total subjects affected by serious adverse events			
subjects affected / exposed	25 / 231 (10.82%)	28 / 229 (12.23%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Ovarian cancer metastatic			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraganglion neoplasm malignant			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Squamous cell carcinoma			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic arteriosclerosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic stenosis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Abasia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	1 / 231 (0.43%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			

subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic pain			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostatomegaly			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 231 (0.43%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary congestion			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Major depression			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Investigations			
Intraocular pressure increased			
subjects affected / exposed	3 / 231 (1.30%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Alcohol poisoning			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple fractures			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (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 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Road traffic accident			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 231 (0.87%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 231 (0.00%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 231 (0.00%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Balance disorder			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
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	1 / 231 (0.43%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	1 / 231 (0.43%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemiplegia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 231 (0.87%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient global amnesia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 231 (0.00%)	3 / 229 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 231 (0.00%)	3 / 229 (1.31%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulcerative keratitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Visual acuity reduced			
subjects affected / exposed	2 / 231 (0.87%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Large intestinal obstruction			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 231 (0.43%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematuria			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (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			
Rotator cuff syndrome			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colonic abscess			

subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis C			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Perirectal abscess			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 231 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			

subjects affected / exposed	2 / 231 (0.87%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	2 / 231 (0.87%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lactic acidosis			
subjects affected / exposed	1 / 231 (0.43%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active: CLS-TA + Intravitreal Aflibercept + Intravitreal Sham	Control:Intravitreal Aflibercept+Suprachoroidal Sham Procedure	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	197 / 231 (85.28%)	116 / 229 (50.66%)	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	33 / 231 (14.29%)	9 / 229 (3.93%)	
occurrences (all)	51	13	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 231 (6.49%)	15 / 229 (6.55%)	
occurrences (all)	18	17	
Eye disorders			
Cataract			
subjects affected / exposed	21 / 231 (9.09%)	9 / 229 (3.93%)	
occurrences (all)	29	12	

Cataract subcapsular			
subjects affected / exposed	20 / 231 (8.66%)	3 / 229 (1.31%)	
occurrences (all)	22	3	
Conjunctival haemorrhage			
subjects affected / exposed	42 / 231 (18.18%)	28 / 229 (12.23%)	
occurrences (all)	65	31	
Eye pain			
subjects affected / exposed	20 / 231 (8.66%)	11 / 229 (4.80%)	
occurrences (all)	24	11	
Macular oedema			
subjects affected / exposed	8 / 231 (3.46%)	13 / 229 (5.68%)	
occurrences (all)	11	16	
Visual acuity reduced			
subjects affected / exposed	16 / 231 (6.93%)	6 / 229 (2.62%)	
occurrences (all)	18	7	
Vitreous detachment			
subjects affected / exposed	13 / 231 (5.63%)	9 / 229 (3.93%)	
occurrences (all)	16	10	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	9 / 231 (3.90%)	13 / 229 (5.68%)	
occurrences (all)	9	13	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
31 March 2017	The amendments were as follows: 1. Treatment provided during pro re nata (PRN) period restricted to aflibercept only, reference to the use of CLS-TA in the PRN period removed. 2. Inclusion criteria: updated minimum ETDRS BCVA to >=20 letters read. 3. Ophthalmic exclusion criteria: updated to exclude subjects that had received any intraocular or periocular corticosteroid injection, OZURDEX® implant, a RETISERT® implant, or an ILUVIEN® implant. 4. Ophthalmic exclusion criteria: updated to exclude subjects who had >3 macular laser photocoagulation treatments. 5. Addition of ophthalmic exclusion criteria: history of glaucoma, optic nerve head change consistent with glaucoma damage; or ocular hypertension in the study eye requiring more than one medication. 6. Addition of history of laser trabeculoplasty or MIGS surgery to ophthalmic exclusion criteria. 7. General exclusion criteria: updated to allow treatment of blood pressure prior to Baseline. 8. Addition of general exclusion criteria: history of any inflammatory or other medical condition that the investigator might reasonably anticipate would require treatment with high-dose corticosteroids (>10 mg/day oral prednisone or the equivalent) for >14 days. 9. Addition of instruction to collect IOP data on the fellow eye at all visits for comparison to the study eye IOP. 10. Rescue therapy criteria updated to start from Visit 4 (Week 8), and the criteria for additional treatment updated. 11. High dose systemic corticosteroids (>10 mg/day of prednisone or equivalent) for >14 days and Macular (grid/focal) laser added to prohibited medications/treatments.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
05 November 2018	The study was terminated as the primary (8-week) efficacy endpoint was not met. No additional benefit was observed for subjects receiving CLS-TA + aflibercept as compared to aflibercept monotherapy.	-

Notes:

Limitations and caveats

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

Due to the early termination of the trial by sponsor all planned study visits were not completed by all treated subjects; therefore, all planned data was not collected.

Notes: