Clinical trial results:
TOPAZ: A Randomized, Masked, Controlled Trial to Study the Safety and Efficacy of Suprachoroidal CLS-TA in Combination With an Intravitreal Anti-VEGF Agent in Subjects With Retinal Vein Occlusion

Summary

EudraCT number	2017-002089-37
Trial protocol	GB HU EE
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	CLS1003-302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03203447
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Clearside Biomedical, Inc.
Sponsor organisation address	900 North Point Parkway, Suite 200, Alpharetta, United States, GA 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 in pharmacologic treatment naïve subjects with retinal vein occlusion (RVO), suprachoroidal (SC) triamcinolone acetonide injectable suspension (CLS-TA) administered with an intravitreal (IVT) anti-Vascular endothelial growth factor (anti-VEGF) agent was superior to an IVT anti-VEGF agent alone using a best corrected visual acuity (BCVA) outcome.

Protection of trial subjects:

The study was conducted in accordance with the ethical principles stated in the Declaration of Helsinki and the International Council on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	02 March 2018
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	Australia: 5
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 121
Country: Number of subjects enrolled	United States: 197
Worldwide total number of subjects	325
EEA total number of subjects	2

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)	167
From 65 to 84 years	146
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

325 subjects were randomized in study. 3 subjects were randomized but not received treatment. Therefore, efficacy data, based on intent-to-treat population, included all 325 subjects, while adverse event data, based on safety population, subjects received 1 or more treatments, included 322 subjects. Study was terminated due to sponsor discretion.

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	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham

Arm description:

All subjects were to receive 3 unilateral SC 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 an IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 millilitres [mL] or bevacizumab 1.25 mg in 0.05 mL) in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received IVT 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 administer with 3 unilateral SC injections of CLS-TA for 12 weeks apart at Day 0, Week 12 and Week 24 in the study eye.

Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects were to administer with 4 unilateral injections of IVT ranibizumab at Day 0, Week 4, Week 12 and Week 24.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects were to administer with 4 unilateral injections of IVT bevacizumab at Day 0, Week 4, Week 12 and Week 24.

Arm title	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure

Arm description:

All subjects were to receive 7 unilateral injections of IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 mL or bevacizumab 1.25 mg in 0.05 mL) administered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 sham SC procedures administered 12 weeks apart on Day 0, Week 12, and Week 24 in the study eye.

Arm type	Active comparator
Investigational medicinal product name	Ranibizumab
Investigational medicinal product code	
Other name	Lucentis
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects were to administer with 7 unilateral injections of ranibizumab administered 4 weeks apart at Day 0, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	Avastin
Pharmaceutical forms	Injection
Routes of administration	Intravitreal use

Dosage and administration details:

Subjects were to administer with 7 unilateral injections of bevacizumab administered 4 weeks apart at Day 0, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24.

Number of subjects in period 1	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure
Started	162	163
Treated	160	162
Completed	0	0
Not completed	162	163
Consent withdrawn by subject	2	1
Study Termination	156	150
Unknown	3	2
Lost to follow-up	1	10

Baseline characteristics

Reporting groups	
Reporting group title	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham
Reporting group description:	
All subjects were to receive 3 unilateral SC 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 an IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 millilitres [mL] or bevacizumab 1.25 mg in 0.05 mL) in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received IVT sham procedures on Week 8, Week 16, and Week 20.	
Reporting group title	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure
Reporting group description:	
All subjects were to receive 7 unilateral injections of IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 mL or bevacizumab 1.25 mg in 0.05 mL) administered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 sham SC procedures administered 12 weeks apart on Day 0, Week 12, and Week 24 in the study eye.	

Reporting group values	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure	Total
Number of subjects	162	163	325
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.7	62.7	
standard deviation	± 13.03	± 12.29	-
Gender categorical Units: Subjects			
Female	82	70	152
Male	80	93	173
Race Units: Subjects			
Asian	73	70	143
Black or African American	6	3	9
Native Hawaiian or Other Pacific Islander	1	2	3
White	78	85	163
Other	2	1	3
Unknown/Not reported	1	2	3
Not applicable	1	0	1

End points

End points reporting groups

Reporting group title	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham

Reporting group description:

All subjects were to receive 3 unilateral SC 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 an IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 millilitres [mL] or bevacizumab 1.25 mg in 0.05 mL) in the study eye on Day 0, Week 4, Week 12 and Week 24. Subjects also received IVT sham procedures on Week 8, Week 16, and Week 20.

Reporting group title	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure

Reporting group description:

All subjects were to receive 7 unilateral injections of IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 mL or bevacizumab 1.25 mg in 0.05 mL) administered 4 weeks apart on Day 0, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24 along with 3 sham SC procedures administered 12 weeks apart on Day 0, Week 12, and Week 24 in the study eye.

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

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

End point description:

BCVA were measured using an eye chart and reported as the number of letters read correctly (ranging from 0 to 100 letters). The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). An increase in the number of letters read correctly indicated improved vision. Analysis was performed on ITT population.

End point type	Primary

End point timeframe:

Baseline, Week 8

End point values	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	163		
Units: percentage of subjects				
number (confidence interval 95%)	39.5 (31.9 to 47.5)	46.6 (38.8 to 54.6)		

Statistical analyses

Statistical analysis title	Active versus Control
Comparison groups	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham v Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure

Number of subjects included in analysis	325
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.191 [1]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Percentage Difference
Point estimate	-7.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.9
upper limit	3.6

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 in the Study Eye

End point title	Mean Change From Baseline in Best Corrected Visual Acuity in the Study Eye

End point description:

BCVA is measured using an eye chart and is reported as the number of letters read correctly (ranging from 0 to 100 letters). The lower the number of letters read correctly on the eye chart, the worse the vision (or visual acuity). An increase in the number of letters read correctly means that vision has improved. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category. In the below table, 99999 represents that data was not collected for the specified endpoint because there was no subject assessed at the particular time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 30 and 36

End point values	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	163		
Units: letters				
least squares mean (standard error)				
Week 4 (n = 146, 152)	11.2 (± 0.85)	12.1 (± 0.84)		
Week 8 (n = 116, 112)	14.3 (± 0.93)	15.5 (± 0.94)		
Week 12 (n = 77, 74)	14.1 (± 1.06)	17.1 (± 1.08)		
Week 16 (n = 49, 50)	16.2 (± 1.25)	19.4 (± 1.24)		
Week 20 (n = 28, 31)	15.5 (± 1.55)	20.9 (± 1.49)		
Week 24 (n = 16, 17)	13.8 (± 1.96)	20.7 (± 1.91)		
Week 30 (n = 5, 5)	14.2 (± 3.32)	25.1 (± 3.32)		
Week 36 (n =2, 0)	17.0 (± 5.15)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in Central Subfield Retinal Thickness (CST) in the Study Eye

End point title	Mean Change from Baseline in Central Subfield Retinal Thickness (CST) in the Study Eye

End point description:

Mean Change from Baseline in CST in the study eye were assessed. Analysis was performed on ITT population. Here, 'n' = number of subjects analysed for each specified category. In the below table, 99999 represents that data was not collected for the specified endpoint because there was no subject assessed at the particular time point.

End point type	Secondary

End point timeframe:

Baseline, Weeks 4, 8, 12, 16, 20, 24, 30, and 36

End point values	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	162	159		
Units: microns				
least squares mean (standard error)				
Week 4 (n = 146, 151)	-368.4 (± 9.07)	-319.9 (± 9.00)		
Week 8 (n = 115, 109)	-386.4 (± 9.76)	-338.9 (± 9.96)		
Week 12 (n= 75, 74)	-328.9 (± 11.11)	-349.9 (± 11.19)		
Week 16 (n = 49, 50)	-403.2 (± 12.76)	-356.9 (± 12.72)		
Week 20 (n = 27, 31)	-398.8 (± 15.85)	-373.3 (± 15.08)		
Week 24 (n = 16, 17)	-353.6 (± 19.60)	-374.7 (± 19.12)		
Week 30 (n = 4, 5)	-417.5 (± 36.59)	-356.3 (± 32.76)		
Week 36 (n = 2, 0)	-387.2 (± 50.86)	99999 (± 99999)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline through Week 48

Adverse event reporting additional description:

Analysis was performed on the safety population that consisted of all randomised 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	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham

Reporting group description:

All subjects were to receive 3 unilateral SC injections of 4 mg of CLS-TA 100 mcL, in conjunction with 4 unilateral injections of an IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 mL or bevacizumab 1.25 mg in 0.05 mL) in the study eye along with the sham IVT procedures.

Reporting group title	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure

Reporting group description:

All subjects were to receive 7 unilateral injections of IVT anti-VEGF agent (either ranibizumab 0.5 mg in 0.05 mL or bevacizumab 1.25 mg in 0.05 mL) along with 3 sham SC procedures in the study eye.

Serious adverse events	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 160 (0.63%)	3 / 162 (1.85%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 160 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure congestive			
subjects affected / exposed	1 / 160 (0.63%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			

subjects affected / exposed	0 / 160 (0.00%)	1 / 162 (0.62%)	
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			
Pulmonary embolism			
subjects affected / exposed	0 / 160 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 160 (0.63%)	0 / 162 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 160 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 160 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 160 (0.00%)	1 / 162 (0.62%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	CLS-TA + Intravitreal Anti-VEGF agent + Intravitreal Sham	Intravitreal Anti-VEGF agent + Suprachoroidal Sham procedure	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 160 (6.88%)	1 / 162 (0.62%)	

Investigations Intraocular pressure increased subjects affected / exposed occurrences (all)	11 / 160 (6.88%) 14	1 / 162 (0.62%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2017	Following changes were made: Various formatting changes done throughout the protocol; 'aflibercept' replaced with 'intravitreal anti-VEGF agent' or 'IVT anti-VEGF agent' including of Lucentis and Avastin. Removed the post injection slit lamp ophthalmoscopy assessment from Appendix A to reflect common clinical procedures.
25 January 2018	Following changes were made: Clarified the distinction between serious and severe adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 December 2018	The Sponsor terminated the study prior to completion of enrollment due to the failure of companion phase 3 study (CLS1003-301).	-

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, 325 of the planned 460 were enrolled. All planned study visits were not completed by all treated subjects; therefore, all planned data was not collected.

Notes: