Clinical trial results:
A Phase 2b/3, Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center Study to Investigate the Efficacy and Safety of Repeated Intravitreal Administration of KSI-301 in Subjects With Neovascular (Wet) Age-related Macular Degeneration

Summary

EudraCT number	2018-003428-35
Trial protocol	LV GB DE CZ SK PL ES IT
Global end of trial date	26 April 2022

Results information

Result version number	v1 (current)
This version publication date	13 July 2024
First version publication date	13 July 2024

Trial information

Trial identification

Sponsor protocol code	KSI-CL-102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04049266
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Kodiak Sciences Inc.
Sponsor organisation address	1200 Page Mill Road, Palo Alto, CA, United States, 94304
Public contact	KSI-CL-102 Trial Information, Kodiak Sciences Inc, KSI-CL-102@kodiak.com
Scientific contact	KSI-CL-102 Trial Information, Kodiak Sciences Inc, KSI-CL-102@kodiak.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	27 May 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	17 November 2021
Global end of trial reached?	Yes
Global end of trial date	26 April 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that KSI-301 5 mg is non-inferior to aflibercept 2 mg with respect to mean change in BCVA from Day 1 to Year 1. Year 1 is defined as the mean of the Week 48 and 52 measurements.

Protection of trial subjects:

The study followed the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All local regulatory requirements pertinent to safety of trial subjects were followed during the conduct of the trial. At the Investigator's discretion, rescue therapy (standard of care) was available. to participants with loss of ≥ 15 BCVA ETDRS letters compared to Day 1.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 October 2019
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: 16
Country: Number of subjects enrolled	Slovakia: 21
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	Czechia: 29
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Latvia: 15
Country: Number of subjects enrolled	United States: 464
Worldwide total number of subjects	557
EEA total number of subjects	93

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	41
From 65 to 84 years	427
85 years and over	89

Subject disposition

Recruitment

Recruitment details:

Participants were recruited based on physician referral at 72 medical centers between September 2019 and November 2020. The first participant was enrolled on 08 October 2019 and the last on 24 November 2020.

Pre-assignment

Screening details:

Of 785 participants screened, 559 were randomized to treatment. Two randomized subjects (one subject in KSI-301 arm and one subject in aflibercept arm) never received treatment, so do not have reason for not completing 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, Assessor

Blinding implementation details:

A masked evaluating investigator will be responsible for subject care except the injections and the safety assessment following the injections. An unmasked treating investigator will perform the injections and assess patient safety following the injections.

Arms

Are arms mutually exclusive?	Yes
Arm title	KSI-301 5 mg

Arm description:

Drug: KSI-301 5 mg. KSI-301 5 mg will be administered by intravitreal injection into the study eye at 12, 16, and 20 weeks intervals as specified in the study protocol.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Arm type	Experimental
Investigational medicinal product name	Tarcocimab tedromer
Investigational medicinal product code	KSI-301
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

5 mg via intravitreal injection

Arm title	Aflibercept 2 mg

Arm description:

Drug: Aflibercept 2 mg. Aflibercept 2 mg will be administered by intravitreal injection into the study eye once every 4 weeks for 3 consecutive months, followed by once every 8 weeks.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Arm type	Active comparator

Investigational medicinal product name	Aflibercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

2 mg via intravitreal injection

Number of subjects in period 1	KSI-301 5 mg	Aflibercept 2 mg
Started	277	280
Completed	240	254
Not completed	37	26
Adverse event, serious fatal	3	8
Consent withdrawn by subject	6	10
Physician decision	1	-
Adverse event, non-fatal	13	1
Other	1	-
Non-compliance with study drug	-	3
Lost to follow-up	2	2
Progressive disease	11	2

Baseline characteristics

Reporting groups

Reporting group title	KSI-301 5 mg

Reporting group description:

Drug: KSI-301 5 mg. KSI-301 5 mg will be administered by intravitreal injection into the study eye at 12, 16, and 20 weeks intervals as specified in the study protocol.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Reporting group title	Aflibercept 2 mg

Reporting group description:

Drug: Aflibercept 2 mg. Aflibercept 2 mg will be administered by intravitreal injection into the study eye once every 4 weeks for 3 consecutive months, followed by once every 8 weeks.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Reporting group values	KSI-301 5 mg	Aflibercept 2 mg	Total
Number of subjects	277	280	557
Age categorical Units: Subjects			
Adults (18-64 years)	18	23	41
From 65-84 years	215	212	427
85 years and over	44	45	89
Age continuous Units: years			
arithmetic mean	76.6	76.2	
standard deviation	± 7.35	± 8.27	-
Gender categorical Units: Subjects			
Female	178	168	346
Male	99	112	211
Ethnicity Units: Subjects			
Hispanic or Latino	17	9	26
Not Hispanic or Latino	260	271	531
Unknown or Not Reported	0	0	0
Race Units: Subjects			
American Indian or Alaska Native	1	1	2
Asian	4	5	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	271	272	543
More than one race	0	0	0
Unknown or Not Reported	0	1	1

End points

End points reporting groups

Reporting group title	KSI-301 5 mg

Reporting group description:

Drug: KSI-301 5 mg. KSI-301 5 mg will be administered by intravitreal injection into the study eye at 12, 16, and 20 weeks intervals as specified in the study protocol.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Reporting group title	Aflibercept 2 mg

Reporting group description:

Drug: Aflibercept 2 mg. Aflibercept 2 mg will be administered by intravitreal injection into the study eye once every 4 weeks for 3 consecutive months, followed by once every 8 weeks.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Primary: Change From Baseline in BCVA in the Study Eye Averaged Over Weeks 48 and 52, Full Analysis Set Year 1

End point title	Change From Baseline in BCVA in the Study Eye Averaged Over Weeks 48 and 52, Full Analysis Set Year 1

End point description:

Best Corrected Visual Acuity (BCVA) was measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters. The BCVA letter score ranges from 0 to 100 (best score), and a gain in BCVA letter score from baseline indicates an improvement in visual acuity.

End point type	Primary

End point timeframe:

Year 1

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	280		
Units: ETDRS Letters				
least squares mean (standard error)	1 (± 0.78)	7 (± 0.77)		

Statistical analyses

Statistical analysis title	KSI-301 5 mg Q12W-Q20W, Aflibercept 2 mg Q8W
Comparison groups	KSI-301 5 mg v Aflibercept 2 mg

Number of subjects included in analysis	557
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	> 0.9999 [2]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-6
Confidence interval	
level	95.03 %
sides	2-sided
lower limit	-8
upper limit	-4
Variability estimate	Standard error of the mean
Dispersion value	1.01

Notes:

[1] - The maximum clinically acceptable true difference between KSI-301 and aflibercept participants to be considered non-inferior is 4 ETDRS letters, i.e. the non-inferiority margin (NI) is 4 letters.
[2] - MMRM model with treatment, visit, treatment by visit interaction, categories for baseline BCVA, BCVA-low luminance VA baseline, geographical location.

Secondary: Proportion of Subjects on KSI-301 Arm With a Once Every 12-Weeks, 16-Weeks or 20-Weeks Treatment Interval

End point title	Proportion of Subjects on KSI-301 Arm With a Once Every 12-Weeks, 16-Weeks or 20-Weeks Treatment Interval[3]

End point description:

Number of subjects on KSI-301 arm achieving a Once Every 12-Weeks, 16-Weeks or 20-Weeks Treatment Interval based on individualized treatment response

End point type	Secondary

End point timeframe:

Year 1

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: For the study design for Study KSI-CL-102 (DAZZLE), only the KSI-301 arm had once every 12-weeks, 16-weeks or 20-weeks treatment interval. All patients in Aflibercept arm received treatment at fixed interval of once every 8-weeks. Therefore, this endpoint applies to the KSI-301 arm only and the statistics are meant to be descriptive only.

End point values	KSI-301 5 mg			
Subject group type	Reporting group			
Number of subjects analysed	234			
Units: Subjects				
Number of participants on the KSI-301 Q12W	71			
Number of participants on the KSI-301 Q16W	24			
Number of participants on the KSI-301 Q20W	139			

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Gaining ≥ 5, ≥10 and ≥15 Letters in BCVA From Baseline in the Study Eye, Full Analysis Set Year 1

End point title	Proportion of Subjects Gaining ≥ 5, ≥10 and ≥15 Letters in BCVA From Baseline in the Study Eye, Full Analysis Set Year 1

End point description:

Categorical improvements in Best Corrected Visual Acuity (BCVA) of clinically relevant BCVA measurements corresponding to 1, 2 and 3 lines of the ETDRS vision testing chart

End point type	Secondary

End point timeframe:

Year 1

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	254		
Units: Subjects				
Gain >=5 ETDRS Letters at Year 1	103	148		
Gain >=10 ETDRS Letters at Year 1	66	87		
Gain >=15 ETDRS Letters at Year 1	31	46		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects Who Achieving BCVA Snellen Equivalent of 20/40 or Better in the Study Eye at Year 1

End point title	Proportion of Subjects Who Achieving BCVA Snellen Equivalent of 20/40 or Better in the Study Eye at Year 1

End point description:

Best Corrected Visual Acuity (BCVA) was measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters. The BCVA letter score ranges from 0 to 100 (best score), and a gain in BCVA letter score from baseline indicates an improvement in visual acuity. BCVA Snellen equivalent of 20/40 was defined as ≥69 ETDRS letters

End point type	Secondary

End point timeframe:

Year 1

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	254		
Units: Subjects	119	165		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With BCVA Snellen Equivalent of 20/200 or Worse in the Study Eye at Year 1

End point title	Proportion of Subjects With BCVA Snellen Equivalent of 20/200 or Worse in the Study Eye at Year 1

End point description:

Best Corrected Visual Acuity (BCVA) was measured on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart at a starting distance of 4 meters. The BCVA letter score ranges from 0 to 100 (best score), and a gain in BCVA letter score from baseline indicates an improvement in visual acuity. BCVA Snellen equivalent of 20/200 or Worse was defined as BCVA ≤ 38 ETDRS Letters.

End point type	Secondary

End point timeframe:

Year 1

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	238	254		
Units: Subjects	13	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in OCT Central Subfield Retinal Thickness (CST) From Day 1

End point title	Mean Change in OCT Central Subfield Retinal Thickness (CST) From Day 1

End point description:

Central subfield thickness (CST) was defined as the distance between the internal limiting membrane (ILM) and the retinal pigment epithelium (RPE) as assessed by a central reading center.

End point type	Secondary

End point timeframe:

Year 1

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	277	280		
Units: Microns				
arithmetic mean (standard deviation)	-96.1 (± 123.39)	-134.1 (± 111.17)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) reported through Week 52 or Early Termination (ET) if occurred before Week 52.

Adverse event reporting additional description:

Safety results for the KSI-301 5mg arm are presented together as patients treated with Q12W dosing received 6 total doses in Year 1 and the patients treated with Q20W dosing received 5 total doses in Year 1. Therefore, presenting all treatment intervals together provides a more robust dataset to evaluate the safety profile of KSI-301.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	KSI-301 5 mg

Reporting group description:

Drug: KSI-301 5 mg. KSI-301 5 mg will be administered by intravitreal injection into the study eye at 12, 16, and 20 weeks intervals as specified in the study protocol.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Reporting group title	Aflibercept 2 mg

Reporting group description:

Drug: Aflibercept 2 mg. Aflibercept 2 mg will be administered by intravitreal injection into the study eye once every 4 weeks for 3 consecutive months, followed by once every 8 weeks.

Drug: Sham Procedure. The sham is a procedure that mimics an intravitreal injection. It involves pressing the blunt end of an empty syringe (without a needle) against the anesthetized eye. It will be administered to participants in both treatments arms at applicable visits to maintain masking.

Serious adverse events	KSI-301 5 mg	Aflibercept 2 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	35 / 277 (12.64%)	33 / 280 (11.79%)	
number of deaths (all causes)	4	8	
number of deaths resulting from adverse events	1	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign gastric neoplasm			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Invasive ductal breast carcinoma			

subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer recurrent			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Jugular vein thrombosis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			

Chest discomfort			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Perforated ulcer			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (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	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Prostatic varices			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	1 / 277 (0.36%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchiectasis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hiccups			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary hypertension			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device occlusion			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 277 (0.36%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ilium fracture			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Spinal compression fracture			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral neck fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	2 / 277 (0.72%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 277 (0.36%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericarditis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular extrasystoles			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease			
subjects affected / exposed	0 / 277 (0.00%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ischaemic stroke			
subjects affected / exposed	2 / 277 (0.72%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 277 (0.36%)	3 / 280 (1.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery occlusion			

subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhagic stroke			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic encephalopathy			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient aphasia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal haemorrhage - Study Eye			
subjects affected / exposed	2 / 277 (0.72%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neovascular age-related macular			

degeneration - Study Eye			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhegmatogenous retinal detachment - Study Eye			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 277 (0.36%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal dilatation			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peptic ulcer			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Bile duct stone			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (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			
Renal failure			

subjects affected / exposed	2 / 277 (0.72%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 277 (0.36%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 277 (0.36%)	3 / 280 (1.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Clostridium difficile colitis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis - Study Eye			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (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	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 277 (0.00%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	0 / 277 (0.00%)	2 / 280 (0.71%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus infection			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cystitis			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
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	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 277 (0.00%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 277 (0.36%)	1 / 280 (0.36%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 277 (0.36%)	0 / 280 (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	KSI-301 5 mg	Aflibercept 2 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	82 / 277 (29.60%)	84 / 280 (30.00%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	15 / 277 (5.42%)	16 / 280 (5.71%)	
occurrences (all)	15	16	
Eye disorders			
Neovascular age-related macular degeneration - Fellow Eye			
subjects affected / exposed	19 / 277 (6.86%)	26 / 280 (9.29%)	
occurrences (all)	19	26	
Retinal haemorrhage - Study Eye			
subjects affected / exposed	17 / 277 (6.14%)	4 / 280 (1.43%)	
occurrences (all)	18	5	
Cataract - Study Eye			
subjects affected / exposed	15 / 277 (5.42%)	10 / 280 (3.57%)	
occurrences (all)	15	10	
Conjunctival haemorrhage - Study Eye			

subjects affected / exposed occurrences (all)	13 / 277 (4.69%) 14	24 / 280 (8.57%) 30	
Infections and infestations Urinary tract infection subjects affected / exposed occurrences (all)	15 / 277 (5.42%) 18	16 / 280 (5.71%) 18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2020	Protocol Version 2.0 Major change from Version 1.0 (original protocol) was increased sample size.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study was terminated early by the Sponsor because the study did not meet the primary endpoint. Thus, not all participants in this study completed the full duration of treatment.

Notes: