Clinical trial results:
A Prospective, Randomized, Double-masked, Active Comparator-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 Compared with Intravitreal Aflibercept in Participants with Visual Impairment Secondary to Treatment-naïve Diabetic Macular Edema (DME)

Summary

EudraCT number	2020-001063-82
Trial protocol	CZ HU FR IT
Global end of trial date	31 August 2023

Results information

Result version number	v1 (current)
This version publication date	22 September 2024
First version publication date	22 September 2024

Trial information

Trial identification

Sponsor protocol code	KS301P105

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04603937
WHO universal trial number (UTN)	-
Other trial identifiers	IND Number: 136167

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-105 Trial Information , Kodiak Sciences Inc., ksi301clinical@kodiak.com
Scientific contact	KSI-CL-105 Trial Information , Kodiak Sciences Inc., ksi301clinical@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 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 April 2023
Global end of trial reached?	Yes
Global end of trial date	31 August 2023
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 best corrected visual acuity (BCVA) from Day 1 to Year 1 (average of Weeks 48 and 52).

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, treatment with pan-retinal photocoagulation laser.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2020
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: 56
Country: Number of subjects enrolled	Czechia: 26
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Israel: 40
Country: Number of subjects enrolled	United States: 296
Worldwide total number of subjects	457
EEA total number of subjects	121

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)	270
From 65 to 84 years	187
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were recruited based on physician referral at 75 medical centers between September 2020 and January 2022. The first participant was enrolled on 30 September 2020 and the last on 31 January 2022.

Pre-assignment

Screening details:

Of 689 screened participants, 459 met eligibility criteria and were randomized to treatment. Two randomized subjects in KSI-301 arm never received treatment, so do not have reason for not completing treatment. Each participant contributed only one study eye to this study.

Period 1

Period 1 title	Primary Study Period (Day 1 to Week 64) (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

For masking purposes, sham injections will be administered at every monthly visit if an active treatment is not administered. To preserve masking, two investigators are required for this study. The masked Investigator will be responsible for the examinations and safety assessments. The unmasked Investigator will perform the injections and post-treatment assessments.

Arms

Are arms mutually exclusive?	Yes
Arm title	KSI-301 (Arm A)

Arm description:

Drug: KSI-301
Intravitreal injection

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:

Intravitreal injection of KSI-301 (5 mg) once every 4 weeks for 3 monthly doses followed by an individualized dosing regimen (every 8 to 24 weeks) via intravitreal injection from Week 16 to Week 100.

Arm title	Aflibercept (Arm B)

Arm description:

Ablibercept: Intravitreal injection

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:

Intravitreal injection of aflibercept (2 mg) once every 4 weeks for 5 monthly doses followed by aflibercept (2 mg) once every 8 weeks via intravitreal injection from Week 24 to 100.

Number of subjects in period 1	KSI-301 (Arm A)	Aflibercept (Arm B)
Started	229	228
Completed	210	205
Not completed	19	23
Adverse event, serious fatal	4	5
Consent withdrawn by subject	8	6
Physician decision	-	1
Adverse event, non-fatal	2	4
Subject withdrawn	-	1
Lost to follow-up	5	6

Baseline characteristics

Reporting groups	
Reporting group title	KSI-301 (Arm A)
Reporting group description: Drug: KSI-301 Intravitreal injection	
Reporting group title	Aflibercept (Arm B)
Reporting group description: Ablibercept: Intravitreal injection	

Reporting group values	KSI-301 (Arm A)	Aflibercept (Arm B)	Total
Number of subjects	229	228	457
Age categorical Units: Subjects			
Adults (18-64 years)	133	137	270
From 65-84 years	96	91	187
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	62.2	61.6	
standard deviation	± 9.34	± 9.90	-
Gender categorical Units: Subjects			
Female	97	79	176
Male	132	149	281
Race Units: Subjects			
White	194	201	395
Black or African American	22	12	34
Asian	3	1	4
American Indian or Alaska Native	0	1	1
Native Hawaiian or Other Pacific Islander	0	0	0
Other	3	2	5
Multiple	2	2	4
Not Reported	5	9	14
Ethnicity Units: Subjects			
Hispanic or Latino	42	58	100
Not Hispanic or Latino	182	161	343
Choose Not to Respond	5	9	14
BCVA in the Study Eye Units: Letters			
arithmetic mean	64.2	64.3	
standard deviation	± 11.43	± 11.21	-

End points

End points reporting groups	
Reporting group title	KSI-301 (Arm A)
Reporting group description: Drug: KSI-301 Intravitreal injection	
Reporting group title	Aflibercept (Arm B)
Reporting group description: Ablibercept: Intravitreal injection	

Primary: Mean Change in BCVA	
End point title	Mean Change in BCVA
End point description: Mean change in best-corrected visual acuity (BCVA) from baseline to the average of Weeks 60 and 64 (using Early Treatment Diabetic Retinopathy Study (ETDRS) Letters). 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: Day 1 to Week 64	

End point values	KSI-301 (Arm A)	Aflibercept (Arm B)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	229	228		
Units: ETDRS Letters				
least squares mean (standard error)				
Mean change in BCVA	6.7 (± 0.80)	11.5 (± 0.81)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Mean Change in BCVA
Comparison groups	KSI-301 (Arm A) v Aflibercept (Arm B)
Number of subjects included in analysis	457
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	-4.7

Confidence interval	
level	95.04 %
sides	2-sided
lower limit	-6.65
upper limit	-2.81
Variability estimate	Standard error of the mean
Dispersion value	0.97

Notes:

[1] - The maximum clinically acceptable true difference between KSI-301 and aflibercept participants to be considered non-inferior is 4.5 ETDRS letters, i.e. the non-inferiority margin

[2] - MMRM model with treatment, visit, treatment by visit interaction, randomization stratification factors, and continuous baseline BCVA and OCT CST

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time Frame Adverse Events (AEs) reported through Week 64 or Early Termination (ET) if occurred before Week 64.

Adverse event reporting additional description:

One subject randomized to KSI-301 treatment arm received incorrect treatment of Aflibercept, so was included in the Aflibercept treatment arm for safety analyses. Therefore, for adverse event reporting, there are 228 subjects in KSI-301 treatment arm and 229 subjects in Aflibercept treatment arm.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	KSI-301 (Arm A)

Reporting group description:

Drug: KSI-301
Intravitreal injection

Reporting group title	Aflibercept (Arm B)

Reporting group description:

Ablibercept: Intravitreal injection

Serious adverse events	KSI-301 (Arm A)	Aflibercept (Arm B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	53 / 228 (23.25%)	57 / 229 (24.89%)	
number of deaths (all causes)	4	6	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostate cancer			
subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acral lentiginous melanoma			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of lung			

subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			
subjects affected / exposed	0 / 228 (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			
Hypertensive crisis			
subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive urgency			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (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 / 228 (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	
Orthostatic hypotension			
subjects affected / exposed	0 / 228 (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	
Peripheral ischaemia			
subjects affected / exposed	0 / 228 (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	
Shock haemorrhagic			

subjects affected / exposed	0 / 228 (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	
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Asthenia			
subjects affected / exposed	0 / 228 (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	
Chest pain			
subjects affected / exposed	0 / 228 (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	
Oedema peripheral			
subjects affected / exposed	0 / 228 (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	
Pyrexia			
subjects affected / exposed	0 / 228 (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	
Reproductive system and breast disorders			
Prostatomegaly			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (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			
Respiratory failure			

subjects affected / exposed	3 / 228 (1.32%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia			
subjects affected / exposed	1 / 228 (0.44%)	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 embolism			
subjects affected / exposed	0 / 228 (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	
Acute respiratory failure			
subjects affected / exposed	0 / 228 (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	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hallucination			
subjects affected / exposed	0 / 228 (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	
Injury, poisoning and procedural complications			
Procedural pneumothorax			
subjects affected / exposed	1 / 228 (0.44%)	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 / 228 (0.44%)	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 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibula fracture			
subjects affected / exposed	0 / 228 (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	
Fracture			
subjects affected / exposed	0 / 228 (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	
Rib fracture			
subjects affected / exposed	0 / 228 (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	
Spinal compression fracture			
subjects affected / exposed	0 / 228 (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	
Traumatic haemothorax			
subjects affected / exposed	0 / 228 (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	
Wound dehiscence			
subjects affected / exposed	0 / 228 (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	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	3 / 228 (1.32%)	4 / 229 (1.75%)	
occurrences causally related to treatment / all	0 / 4	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	2 / 228 (0.88%)	3 / 229 (1.31%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure acute			
subjects affected / exposed	2 / 228 (0.88%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 228 (0.44%)	4 / 229 (1.75%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Angina unstable			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (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 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	1 / 228 (0.44%)	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 failure chronic			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			

subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (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 / 228 (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	
Acute coronary syndrome			
subjects affected / exposed	0 / 228 (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	
Angina pectoris			
subjects affected / exposed	0 / 228 (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	
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 228 (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	
Cardiomyopathy			
subjects affected / exposed	0 / 228 (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	
Ventricular fibrillation			
subjects affected / exposed	0 / 228 (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	
Nervous system disorders			
Carotid artery stenosis			
subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal ganglia haemorrhage			

subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalomalacia			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbosacral radiculopathy			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	0 / 228 (0.00%)	4 / 229 (1.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cerebrovascular accident			
subjects affected / exposed	0 / 228 (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	
Carotid artery aneurysm			
subjects affected / exposed	0 / 228 (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	
Haemorrhagic stroke			
subjects affected / exposed	0 / 228 (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	
Lacunar infarction			
subjects affected / exposed	0 / 228 (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	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 228 (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	
Blood loss anaemia			
subjects affected / exposed	0 / 228 (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	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 228 (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	
Eye disorders			
Cataract - Study Eye			
subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angle closure glaucoma - Fellow Eye			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract - Fellow Eye			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cataract subcapsular - Study Eye			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye haemorrhage - Fellow Eye			
subjects affected / exposed	1 / 228 (0.44%)	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 artery occlusion - Study Eye			

subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (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 - Fellow Eye			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular fibrosis - Study Eye			
subjects affected / exposed	0 / 228 (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	
Rhegmatogenous retinal detachment - Study Eye			
subjects affected / exposed	0 / 228 (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	
Vitreous haemorrhage - Fellow Eye			
subjects affected / exposed	0 / 228 (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	
Retinal detachment - Study Eye			
subjects affected / exposed	1 / 228 (0.44%)	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 vein occlusion - Study Eye			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Macular fibrosis - Fellow Eye			
subjects affected / exposed	0 / 228 (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			

Pancreatitis acute			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 228 (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	
Intestinal obstruction			
subjects affected / exposed	0 / 228 (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	
Irritable bowel syndrome			
subjects affected / exposed	0 / 228 (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	
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 228 (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	
Skin and subcutaneous tissue disorders			
Diabetic foot			
subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Henoch-Schonlein purpura			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin discolouration			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin ulcer			
subjects affected / exposed	0 / 228 (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	
Pemphigoid			
subjects affected / exposed	0 / 228 (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	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 228 (1.75%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	2 / 228 (0.88%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	2 / 228 (0.88%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			

subjects affected / exposed	0 / 228 (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	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc degeneration			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathic arthropathy			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Connective tissue inflammation			
subjects affected / exposed	0 / 228 (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	
Immune-mediated myositis			
subjects affected / exposed	0 / 228 (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	
Osteoarthritis			

subjects affected / exposed	0 / 228 (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	
Rhabdomyolysis			
subjects affected / exposed	0 / 228 (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	
Infections and infestations			
Pneumonia			
subjects affected / exposed	5 / 228 (2.19%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	3 / 228 (1.32%)	4 / 229 (1.75%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis chronic			
subjects affected / exposed	3 / 228 (1.32%)	3 / 229 (1.31%)	
occurrences causally related to treatment / all	0 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 228 (0.88%)	4 / 229 (1.75%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	1 / 228 (0.44%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 228 (0.44%)	2 / 229 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			

subjects affected / exposed	1 / 228 (0.44%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic foot infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocarditis bacterial			
subjects affected / exposed	1 / 228 (0.44%)	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 - Fellow Eye			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterococcal infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected skin ulcer			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			

subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess limb			
subjects affected / exposed	0 / 228 (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 / 228 (0.00%)	1 / 229 (0.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Endophthalmitis - Study Eye			
subjects affected / exposed	0 / 228 (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	
Helicobacter gastritis			

subjects affected / exposed	0 / 228 (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	
West Nile viral infection			
subjects affected / exposed	0 / 228 (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	
Metabolism and nutrition disorders			
Diabetic metabolic decompensation			
subjects affected / exposed	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	1 / 228 (0.44%)	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	1 / 228 (0.44%)	0 / 229 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	0 / 228 (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	
Hypovolaemia			
subjects affected / exposed	0 / 228 (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	

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

Non-serious adverse events	KSI-301 (Arm A)	Aflibercept (Arm B)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	113 / 228 (49.56%)	104 / 229 (45.41%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	23 / 228 (10.09%)	23 / 229 (10.04%)	
occurrences (all)	24	24	
Eye disorders			
Cataract - Study Eye			
subjects affected / exposed	33 / 228 (14.47%)	15 / 229 (6.55%)	
occurrences (all)	34	15	
Conjunctival haemorrhage - Study Eye			
subjects affected / exposed	22 / 228 (9.65%)	8 / 229 (3.49%)	
occurrences (all)	25	10	
Diabetic retinal oedema - Fellow Eye			
subjects affected / exposed	14 / 228 (6.14%)	24 / 229 (10.48%)	
occurrences (all)	16	25	
Cataract - Fellow Eye			
subjects affected / exposed	12 / 228 (5.26%)	12 / 229 (5.24%)	
occurrences (all)	12	12	
Diabetic retinal oedema - Study Eye			
subjects affected / exposed	12 / 228 (5.26%)	4 / 229 (1.75%)	
occurrences (all)	15	5	
Infections and infestations			
COVID-19			
subjects affected / exposed	32 / 228 (14.04%)	34 / 229 (14.85%)	
occurrences (all)	33	34	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	22 / 228 (9.65%)	22 / 229 (9.61%)	
occurrences (all)	23	23	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2022	Changes from Version 1.0 (original protocol) include the following: •The timing for evaluation of the primary objective was extended by 12weeks, from the average of Weeks 48 and 52 to the average of Weeks60 and 64. •The disease activity criteria were adjusted and simplified to remove subjectivity and allow for more uniform application of the criteria across all study subjects, as well as to account for patients with persistent retinal oedema that is not worsening.

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.

None specified.

Notes: