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	2020-001062-11
Trial protocol	DE LV SK HU IT
Global end of trial date	31 August 2023

Results information

Result version number	v1 (current)
This version publication date	08 September 2024
First version publication date	08 September 2024

Trial information

Trial identification

Sponsor protocol code	KS301P104

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04611152
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	KSI301P104 Trial Information, Kodiak Sciences Inc., ksi301clinical@kodiak.com
Scientific contact	KSI301P104 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	22 September 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 May 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	09 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	United States: 353
Country: Number of subjects enrolled	Slovakia: 25
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Germany: 10
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Latvia: 18
Worldwide total number of subjects	460
EEA total number of subjects	107

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)	274
From 65 to 84 years	183
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

Participants were recruited based on physician referral at 75 medical centers between September 2020 and February 2022. The first participant was enrolled on 30 September 2020 and the last on 16 February 2022.

Pre-assignment

Screening details:

Of 670 screened participants, 460 met eligibility criteria and were randomized to treatment.

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:

Masking

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:

Aflibercept: 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	230	230
Completed	205	212
Not completed	25	18
Adverse event, serious fatal	5	5
Consent withdrawn by subject	5	6
Adverse event, non-fatal	3	2
Lost to follow-up	11	2
Non-compliance with Study Schedule	1	3

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:	
Aflibercept: Intravitreal Injection	

Reporting group values	KSI-301 (Arm A)	Aflibercept (Arm B)	Total
Number of subjects	230	230	460
Age categorical Units: Subjects			
Adults (18-64 years)	138	136	274
From 65-84 years	91	92	183
85 years and over	1	2	3
Age continuous Units: years			
arithmetic mean	62	61.2	
standard deviation	± 9.73	± 10.61	-
Gender categorical Units: Subjects			
Female	80	87	167
Male	150	143	293
Race Units: Subjects			
White	204	200	404
Black or African American	21	21	42
Asian	3	3	6
American Indian or Alaska Native	1	1	2
Native Hawaiian or Other Pacific Islander	0	1	1
Other	1	4	5
Multiple	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	37	32	69
Not Hispanic or Latino	193	198	391
BCVA in the Study Eye, Letter Units: Letters			
arithmetic mean	66.4	66.6	
standard deviation	± 9.78	± 9.60	-

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:	
Aflibercept: Intravitreal Injection	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set defined as all randomized subjects who received any study treatment (KSI-301 or aflibercept). Subjects will be analyzed according to their randomized treatment.	

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)	
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	230	230		
Units: ETDRS Letters				
least squares mean (standard error)	5.6 (± 0.83)	9.5 (± 0.85)		

Statistical analyses

Statistical analysis title	Mean Change in BCVA
Comparison groups	KSI-301 (Arm A) v Aflibercept (Arm B)
Number of subjects included in analysis	460
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	= 0.4162 [2]
Method	Mixed models analysis
Parameter estimate	Adjusted mean difference
Point estimate	-3.8

Confidence interval	
level	95.04 %
sides	2-sided
lower limit	-5.47
upper limit	-2.17
Variability estimate	Standard error of the mean
Dispersion value	0.84

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:	
Adverse Events (AEs) reported through Week 64 or Early Termination (ET) if occurred before Week 64	
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:	
Aflibercept: Intravitreal Injection	

Serious adverse events	KSI-301 (Arm A)	Aflibercept (Arm B)	
Total subjects affected by serious adverse events			
subjects affected / exposed	61 / 230 (26.52%)	51 / 230 (22.17%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial cancer recurrent			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hodgkin's disease			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine neoplasm			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemangioma			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuroendocrine tumour			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cancer			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Hypertensive urgency			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral arterial occlusive disease			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arteriosclerosis			

subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive emergency			
subjects affected / exposed	0 / 230 (0.00%)	3 / 230 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Catheter site haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complication associated with device			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sudden death			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Reproductive system and breast disorders			
Prostatitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
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			
Respiratory failure			
subjects affected / exposed	3 / 230 (1.30%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			

subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute pulmonary oedema			
subjects affected / exposed	0 / 230 (0.00%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Behaviour disorder			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Medical observation			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
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			
Hip fracture			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning			

subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial bones fracture			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skull fracture			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular pseudoaneurysm			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 230 (0.00%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Burns third degree			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	5 / 230 (2.17%)	3 / 230 (1.30%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 2	0 / 2	
Coronary artery disease			
subjects affected / exposed	4 / 230 (1.74%)	5 / 230 (2.17%)	
occurrences causally related to treatment / all	0 / 4	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 230 (1.30%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 230 (0.43%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			

subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic valve incompetence			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arrhythmia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiorenal syndrome			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery occlusion			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			

subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute coronary syndrome			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrioventricular block			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive cardiomyopathy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic cardiomyopathy			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
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	3 / 230 (1.30%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 230 (0.87%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy			

subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haemorrhage			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Blood and lymphatic system disorders			
Lymphadenopathy mediastinal			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood loss anaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment - Fellow Eye			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 230 (0.43%)	3 / 230 (1.30%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 230 (0.43%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic pancreatitis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gastroparesis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (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 / 230 (0.00%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 230 (0.00%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhoids			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intra-abdominal fluid collection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Strangulated umbilical hernia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic cirrhosis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
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	4 / 230 (1.74%)	6 / 230 (2.61%)	
occurrences causally related to treatment / all	0 / 5	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Acute kidney injury			
subjects affected / exposed	1 / 230 (0.43%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
End stage renal disease			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease			
subjects affected / exposed	0 / 230 (0.00%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Psoriatic arthropathy			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 230 (0.00%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	5 / 230 (2.17%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis			
subjects affected / exposed	4 / 230 (1.74%)	3 / 230 (1.30%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	4 / 230 (1.74%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Sepsis			
subjects affected / exposed	3 / 230 (1.30%)	2 / 230 (0.87%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gangrene			
subjects affected / exposed	3 / 230 (1.30%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	3 / 230 (1.30%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic gangrene			
subjects affected / exposed	2 / 230 (0.87%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	2 / 230 (0.87%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 230 (0.87%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (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 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metapneumovirus infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteomyelitis acute			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endophthalmitis - Study Eye			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site infection			

subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Necrotising fasciitis			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
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 ketoacidosis			
subjects affected / exposed	3 / 230 (1.30%)	3 / 230 (1.30%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoglycaemia			
subjects affected / exposed	1 / 230 (0.43%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fluid overload			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 230 (0.43%)	0 / 230 (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 / 230 (0.43%)	0 / 230 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemic hyperosmolar nonketotic syndrome			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 230 (0.00%)	1 / 230 (0.43%)	
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 / 230 (0.00%)	1 / 230 (0.43%)	
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	126 / 230 (54.78%)	121 / 230 (52.61%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 230 (13.04%)	31 / 230 (13.48%)	
occurrences (all)	33	34	
Eye disorders			
Cataract - Study Eye			
subjects affected / exposed	35 / 230 (15.22%)	17 / 230 (7.39%)	
occurrences (all)	38	17	
Diabetic retinal oedema - Fellow Eye			
subjects affected / exposed	19 / 230 (8.26%)	21 / 230 (9.13%)	
occurrences (all)	19	22	
Conjunctival haemorrhage - Study Eye			

subjects affected / exposed	18 / 230 (7.83%)	15 / 230 (6.52%)	
occurrences (all)	21	21	
Cataract - Fellow Eye			
subjects affected / exposed	15 / 230 (6.52%)	12 / 230 (5.22%)	
occurrences (all)	15	12	
Dry eye - Study Eye			
subjects affected / exposed	13 / 230 (5.65%)	10 / 230 (4.35%)	
occurrences (all)	15	11	
Renal and urinary disorders			
Chronic kidney disease			
subjects affected / exposed	8 / 230 (3.48%)	14 / 230 (6.09%)	
occurrences (all)	8	14	
Infections and infestations			
COVID-19			
subjects affected / exposed	42 / 230 (18.26%)	33 / 230 (14.35%)	
occurrences (all)	45	36	
Nasopharyngitis			
subjects affected / exposed	8 / 230 (3.48%)	17 / 230 (7.39%)	
occurrences (all)	8	18	
Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	19 / 230 (8.26%)	17 / 230 (7.39%)	
occurrences (all)	19	18	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2022	Version 2.0 - Changes from Version 1.0 (original protocol) include the following: • The timing for evaluation of the primary objective was extended by 12 weeks, from the average of Weeks 48 and 52 to the average of Weeks 60 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 edema 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: