



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 Due to Treatment-naïve Macular Edema Secondary to Retinal Vein Occlusion (RVO)

Summary

EudraCT number	2020-001061-37
Trial protocol	LV DE SK CZ FR HU IT
Global end of trial date	19 January 2023

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	KS301P103
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04592419
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-103 Trial Information , Kodiak Sciences Inc., ksi301clinical@kodiak.com
Scientific contact	KSI-CL-103 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	17 April 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 June 2022
Global end of trial reached?	Yes
Global end of trial date	19 January 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 administered every 8 weeks after 2 monthly doses is non-inferior to aflibercept 2 mg monthly with respect to mean change in BCVA from Day 1 to Week 24.

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	Israel: 13
Country: Number of subjects enrolled	Spain: 31
Country: Number of subjects enrolled	United States: 386
Country: Number of subjects enrolled	Poland: 38
Country: Number of subjects enrolled	Slovakia: 15
Country: Number of subjects enrolled	Czechia: 4
Country: Number of subjects enrolled	France: 21
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Latvia: 22
Worldwide total number of subjects	568
EEA total number of subjects	169

Notes:

Subjects enrolled per age group

In utero	0
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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)	268
From 65 to 84 years	271
85 years and over	29

Subject disposition

Recruitment

Recruitment details:

Participants were recruited from 138 sites in 11 countries.

Pre-assignment

Screening details:

The study comprised a screening period of 21 days.

Period 1

Period 1 title	Primary study period (Day 1 to Week 48)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

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

Arm description:

Intravitreal injection of KSI-301 (5 mg) at Day 1, Week 4, and once every 8 weeks through Week 20 followed by an individualized dosing regimen of intravitreal injection of KSI-301 (5 mg) from Week 24 to Week 44.

In the Extension Phase, participants randomized to KSI-301 (5 mg) in the Primary Study will continue to receive KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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
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Arm description:

Intravitreal injection of aflibercept (2 mg) once every 4 through Week 20 followed by an individualized dosing regimen of Intravitreal injection of Aflibercept (2 mg) once every 4 weeks from Week 24 to Week 44.

In the Extension Phase, participants randomized to aflibercept in the Primary Study will cross over to treatment with KSI-301 (5 mg). They will receive their first dose of KSI-301 (5 mg) at Week 48 and will receive additional treatment with KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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
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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	284	284
Completed	255	255
Not completed	29	29
Adverse event, serious fatal	3	1
Consent withdrawn by subject	7	13
Non-compliance with study schedule	-	1
Adverse event, non-fatal	7	2
Participant moved cities with no available site	-	1
Sponsor request	4	5
Participant left the country	2	-
Lost to follow-up	5	5
Progressive disease	1	1

Period 2

Period 2 title	Open label extension (Week 48 to 76)
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not applicable.

Arms

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

Arm description:

KSI-301 5 mg

Arm type	Experimental
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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
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Arm description:

Aflibercept 2 mg

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 2^[1]	KSI-301 5 mg	Aflibercept 2 mg
Started	216	228
Completed	135	130
Not completed	81	98
Adverse event, serious fatal	-	2
Consent withdrawn by subject	5	7
Non-compliance with study schedule	1	-
Adverse event, non-fatal	1	-
Sponsor request	73	84
Lost to follow-up	1	5

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: The original intent of the open label extension was to be an optional period for all patients that completed the primary study period. However, since the open label extension was terminated prior to all patients completing the primary (masked) study period, not all patients were eligible to participate in the extension period in addition to the patients that did not want to participate.

Baseline characteristics

Reporting groups

Reporting group title	KSI-301 5 mg
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Reporting group description:

Intravitreal injection of KSI-301 (5 mg) at Day 1, Week 4, and once every 8 weeks through Week 20 followed by an individualized dosing regimen of intravitreal injection of KSI-301 (5 mg) from Week 24 to Week 44.

In the Extension Phase, participants randomized to KSI-301 (5 mg) in the Primary Study will continue to receive KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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
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Reporting group description:

Intravitreal injection of aflibercept (2 mg) once every 4 through Week 20 followed by an individualized dosing regimen of Intravitreal injection of Aflibercept (2 mg) once every 4 weeks from Week 24 to Week 44.

In the Extension Phase, participants randomized to aflibercept in the Primary Study will cross over to treatment with KSI-301 (5 mg). They will receive their first dose of KSI-301 (5 mg) at Week 48 and will receive additional treatment with KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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	284	284	568
Age categorical			
Units: Subjects			
Adults (18-64 years)	126	142	268
From 65-84 years	144	127	271
85 years and over	14	15	29
Age continuous			
Units: years			
arithmetic mean	66.0	64.7	
standard deviation	± 11.76	± 11.32	-
Gender categorical			
Units: Subjects			
Female	141	138	279
Male	143	146	289
Race/Ethnicity			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	5	5	10
Black or African American	23	17	40
Native Hawaiian or Other Pacific Islander	0	0	0
White	240	245	485
Multiple	1	2	3

Other	4	3	7
Missing	11	11	22

Subject analysis sets

Subject analysis set title	All RVO Subtypes
Subject analysis set type	Full analysis

Subject analysis set description:

The Full Analysis Set is defined as all patients who received any treatment from Day 1 through Week 48.

Reporting group values	All RVO Subtypes		
Number of subjects	568		
Age categorical			
Units: Subjects			
Adults (18-64 years)	268		
From 65-84 years	271		
85 years and over	29		
Age continuous			
Units: years			
arithmetic mean	65.3		
standard deviation	± 11.55		
Gender categorical			
Units: Subjects			
Female	279		
Male	289		
Race/Ethnicity			
Units: Subjects			
American Indian or Alaska Native	1		
Asian	10		
Black or African American	40		
Native Hawaiian or Other Pacific Islander	0		
White	485		
Multiple	3		
Other	7		
Missing	22		

End points

End points reporting groups

Reporting group title	KSI-301 5 mg
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Reporting group description:

Intravitreal injection of KSI-301 (5 mg) at Day 1, Week 4, and once every 8 weeks through Week 20 followed by an individualized dosing regimen of intravitreal injection of KSI-301 (5 mg) from Week 24 to Week 44.

In the Extension Phase, participants randomized to KSI-301 (5 mg) in the Primary Study will continue to receive KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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
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Reporting group description:

Intravitreal injection of aflibercept (2 mg) once every 4 through Week 20 followed by an individualized dosing regimen of Intravitreal injection of Aflibercept (2 mg) once every 4 weeks from Week 24 to Week 44.

In the Extension Phase, participants randomized to aflibercept in the Primary Study will cross over to treatment with KSI-301 (5 mg). They will receive their first dose of KSI-301 (5 mg) at Week 48 and will receive additional treatment with KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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	KSI-301 5 mg
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Reporting group description:

KSI-301 5 mg

Reporting group title	Aflibercept 2 mg
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Reporting group description:

Aflibercept 2 mg

Subject analysis set title	All RVO Subtypes
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Subject analysis set type	Full analysis
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Subject analysis set description:

The Full Analysis Set is defined as all patients who received any treatment from Day 1 through Week 48.

Primary: Mean change in BCVA from Day 1 to Week 24 in BRVO Participants

End point title	Mean change in BCVA from Day 1 to Week 24 in BRVO Participants
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End point description:

Best Corrected Visual Acuity (BCVA) as a continuous variable measured at each study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA approach.

End point type	Primary
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End point timeframe:

Day 1 to Week 24

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	220	218		
Units: Letter read				
least squares mean (standard error)	14.2 (\pm 0.81)	15.6 (\pm 0.79)		

Statistical analyses

Statistical analysis title	Efficacy Analysis 1 (BRVO Participants)
Statistical analysis description:	
Primary Efficacy Analysis 1- Mean Change in BCVA from Baseline to Week 24 (Full Analysis Set - BRVO)	
Comparison groups	KSI-301 5 mg v Aflibercept 2 mg
Number of subjects included in analysis	438
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
P-value	= 0.0004 ^[2]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	95.02 %
sides	2-sided
lower limit	-3.11
upper limit	0.3
Variability estimate	Standard error of the mean
Dispersion value	0.87

Notes:

[1] - If the lower limit of the two-sided 95.02% CI for the difference between the two means is >-4.5 letters, noninferiority will be demonstrated. If noninferiority is demonstrated in participants with BRVO, a second analysis will assess noninferiority in the 'All RVO' (BRVO+CRVO) patients.

[2] - MMRM model with treatment, visit, treatment \times visit interaction, RVO subtype, baseline BCVA, disease duration, and geographical location as covariates.

Primary: Mean change in BCVA from Day 1 to Week 24 in All RVO Participants

End point title	Mean change in BCVA from Day 1 to Week 24 in All RVO Participants
End point description:	
BCVA as a continuous variable measured at each study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA approach.	
End point type	Primary
End point timeframe:	
Day 1 to Week 24	

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Letters read				
least squares mean (standard error)	13.0 (\pm 0.83)	15.5 (\pm 0.81)		

Statistical analyses

Statistical analysis title	Efficacy Analysis 2 (All RVO Participants)
Statistical analysis description:	
Primary Efficacy Analysis 2 - Mean Change in BCVA from Baseline to Week 24 (Full Analysis Set - All RVO Subtypes)	
Comparison groups	KSI-301 5 mg v Aflibercept 2 mg
Number of subjects included in analysis	568
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[3]
P-value	= 0.0243 ^[4]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	-2.5
Confidence interval	
level	95.02 %
sides	2-sided
lower limit	-4.24
upper limit	-0.71
Variability estimate	Standard error of the mean
Dispersion value	0.9

Notes:

[3] - If the lower limit of the two-sided 95.02% CI for the difference between the two means is >-4.5 letters, noninferiority will be demonstrated.

[4] - MMRM model with treatment, visit, treatment \times visit interaction, RVO subtype, baseline BCVA, disease duration, and geographical location as covariates

Secondary: Mean Change in BCVA (ETDRS Letters) from Baseline by Visit Over Time up to Week 48 for All RVO Participants

End point title	Mean Change in BCVA (ETDRS Letters) from Baseline by Visit Over Time up to Week 48 for All RVO Participants
End point description:	
BCVA as a continuous variable measured at each study visit using the Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA approach.	
End point type	Secondary
End point timeframe:	
Day 1 to Week 48	

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: ETDRS letters read				
arithmetic mean (standard deviation)				
Week 1 (n = 280, 275)	7.7 (± 9.25)	7.9 (± 7.74)		
Week 4 (n = 279, 275)	8.9 (± 9.89)	11.2 (± 10.01)		
Week 8 (n = 273, 278)	11.4 (± 10.38)	13.5 (± 9.78)		
Week 12 (n = 276, 277)	10.0 (± 12.58)	14.2 (± 10.05)		
Week 16 (n = 270, 272)	12.7 (± 11.99)	14.9 (± 10.52)		
Week 20 (n = 263, 269)	12.4 (± 12.29)	15.3 (± 11.86)		
Week 24 (n = 261, 267)	14.0 (± 11.42)	15.6 (± 11.54)		
Week 28 (n = 257, 264)	12.8 (± 11.85)	14.1 (± 12.9)		
Week 32 (n = 250, 257)	13.3 (± 11.55)	13.8 (± 12.46)		
Week 36 (n = 252, 259)	13.1 (± 11.52)	13.5 (± 11.96)		
Week 40 (n = 252, 257)	13.9 (± 11.51)	13.9 (± 12.87)		
Week 44 (n = 244, 256)	13.6 (± 11.26)	13.7 (± 13.11)		
Week 48 (n = 247, 252)	13.5 (± 12.10)	14.2 (± 13.64)		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Who Gain ≥5, ≥10 and ≥15 Letters from Baseline Over Time up to Week 48 for All RVO Participants

End point title	Proportion of Participants Who Gain ≥5, ≥10 and ≥15 Letters from Baseline Over Time up to Week 48 for All RVO Participants
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End point description:

Number of participants in each treatment arm who meet specified criteria at each visit from Week 1 through Week 48.

End point type	Secondary
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End point timeframe:

Day 1 to Week 48

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Participants				
Gain ≥5 letters, Week 1 (n = 280, 275)	176	176		
Gain ≥5 letters, Week 4 (n = 279, 275)	197	202		
Gain ≥5 letters, Week 8 (n = 273, 278)	211	233		
Gain ≥5 letters, Week 12 (n = 276, 277)	198	237		
Gain ≥5 letters, Week 16 (n = 270, 272)	222	240		
Gain ≥5 letters, Week 20 (n = 263, 269)	199	235		
Gain ≥5 letters, Week 24 (n = 261, 267)	215	233		
Gain ≥5 letters, Week 28 (n = 257, 264)	206	211		

Gain ≥ 5 letters, Week 32 (n = 250, 257)	200	213		
Gain ≥ 5 letters, Week 36 (n = 252, 259)	205	212		
Gain ≥ 5 letters, Week 40 (n = 252, 257)	210	215		
Gain ≥ 5 letters, Week 44 (n = 244, 256)	196	211		
Gain ≥ 5 letters, Week 48 (n = 247, 252)	199	206		
Gain ≥ 10 letters, Week 1 (n = 280, 275)	94	91		
Gain ≥ 10 letters, Week 4 (n = 279, 275)	120	145		
Gain ≥ 10 letters, Week 8 (n = 273, 278)	151	175		
Gain ≥ 10 letters, Week 12 (n = 276, 277)	141	179		
Gain ≥ 10 letters, Week 16 (n = 270, 272)	168	181		
Gain ≥ 10 letters, Week 20 (n = 263, 269)	168	183		
Gain ≥ 10 letters, Week 24 (n = 261, 267)	177	188		
Gain ≥ 10 letters, Week 28 (n = 257, 264)	160	168		
Gain ≥ 10 letters, Week 32 (n = 250, 257)	164	172		
Gain ≥ 10 letters, Week 36 (n = 252, 259)	158	162		
Gain ≥ 10 letters, Week 40 (n = 252, 257)	167	162		
Gain ≥ 10 letters, Week 44 (n = 244, 256)	156	164		
Gain ≥ 10 letters, Week 48 (n = 247, 252)	159	164		
Gain ≥ 15 letters, Week 1 (n = 280, 275)	46	49		
Gain ≥ 15 letters, Week 4 (n = 279, 275)	69	85		
Gain ≥ 15 letters, Week 8 (n = 273, 278)	92	111		
Gain ≥ 15 letters, Week 12 (n = 276, 277)	83	119		
Gain ≥ 15 letters, Week 16 (n = 270, 272)	109	131		
Gain ≥ 15 letters, Week 20 (n = 263, 269)	109	137		
Gain ≥ 15 letters, Week 24 (n = 261, 267)	121	138		
Gain ≥ 15 letters, Week 28 (n = 257, 264)	111	118		
Gain ≥ 15 letters, Week 32 (n = 250, 257)	113	113		
Gain ≥ 15 letters, Week 36 (n = 252, 259)	108	112		
Gain ≥ 15 letters, Week 40 (n = 252, 257)	107	120		
Gain ≥ 15 letters, Week 44 (n = 244, 256)	111	116		
Gain ≥ 15 letters, Week 48 (n = 247, 252)	112	120		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants Who Lost ≥ 5 , ≥ 10 and ≥ 15 Letters from Baseline Over Time up to Week 48 for All RVO Participants

End point title	Proportion of Participants Who Lost ≥ 5 , ≥ 10 and ≥ 15 Letters from Baseline Over Time up to Week 48 for All RVO Participants
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End point description:

Number of participants (n) in each treatment arm who meet specified criteria at each visit from Week 1 through Week 48.

End point type	Secondary
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End point timeframe:

Day 1 to Week 48

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Participants				
Lost ≥ 5 letters, Week 1 (n=280, 275)	5	6		
Lost ≥ 5 letters, Week 4 (n=279, 275)	19	7		
Lost ≥ 5 letters, Week 8 (n=273, 278)	14	3		
Lost ≥ 5 letters, Week 12 (n=276, 277)	18	3		
Lost ≥ 5 letters, Week 16 (n=270, 272)	13	5		
Lost ≥ 5 letters, Week 20 (n=263, 269)	17	8		
Lost ≥ 5 letters, Week 24 (n=261, 267)	13	7		
Lost ≥ 5 letters, Week 28 (n=257, 264)	16	10		
Lost ≥ 5 letters, Week 32 (n=250, 257)	14	9		
Lost ≥ 5 letters, Week 36 (n=252, 259)	16	11		
Lost ≥ 5 letters, Week 40 (n=252, 257)	13	14		
Lost ≥ 5 letters, Week 44 (n=244, 256)	10	15		
Lost ≥ 5 letters, Week 48 (n=247, 252)	18	15		
Lost ≥ 10 letters, Week 1 (n=280, 275)	3	1		
Lost ≥ 10 letters, Week 4 (n=279, 275)	4	1		
Lost ≥ 10 letters, Week 8 (n=273, 278)	6	1		
Lost ≥ 10 letters, Week 12 (n=276, 277)	9	0		
Lost ≥ 10 letters, Week 16 (n=270, 272)	6	2		
Lost ≥ 10 letters, Week 20 (n=263, 269)	10	5		
Lost ≥ 10 letters, Week 24 (n=261, 267)	4	4		
Lost ≥ 10 letters, Week 28 (n=257, 264)	9	8		
Lost ≥ 10 letters, Week 32 (n=250, 257)	9	7		
Lost ≥ 10 letters, Week 36 (n=252, 259)	10	4		
Lost ≥ 10 letters, Week 40 (n=252, 257)	9	8		
Lost ≥ 10 letters, Week 44 (n=244, 256)	6	9		
Lost ≥ 10 letters, Week 48 (n=247, 252)	9	9		
Lost ≥ 15 letters, Week 1 (n=280, 275)	2	0		
Lost ≥ 15 letters, Week 4 (n=279, 275)	2	1		
Lost ≥ 15 letters, Week 8 (n=273, 278)	1	0		
Lost ≥ 15 letters, Week 12 (n=276, 277)	6	0		

Lost ≥15 letters, Week 16 (n=270, 272)	5	1		
Lost ≥15 letters, Week 20 (n=263, 269)	4	2		
Lost ≥15 letters, Week 24 (n=261, 267)	1	2		
Lost ≥15 letters, Week 28 (n=257, 264)	5	5		
Lost ≥15 letters, Week 32 (n=250, 257)	4	6		
Lost ≥15 letters, Week 36 (n=252, 259)	2	2		
Lost ≥15 letters, Week 40 (n=252, 257)	3	5		
Lost ≥15 letters, Week 44 (n=244, 256)	3	6		
Lost ≥15 letters, Week 48 (n=247, 252)	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with BCVA Snellen Equivalent of 20/40 or Better from Baseline Over Time up to Week 48 for All RVO Participants

End point title	Proportion of Participants with BCVA Snellen Equivalent of 20/40 or Better from Baseline Over Time up to Week 48 for All RVO Participants
End point description: Number of participants (n) with BCVA Snellen Equivalent of 20/40 or Better from Baseline to Week 48. Snellen Equivalent of 20/40 is 69 ETDRS letters. Number of participants in each treatment arm who meet specified criteria at each visit from Baseline through Week 48.	
End point type	Secondary
End point timeframe: Day 1 to Week 48	

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Participants				
Baseline (n=284,284)	92	90		
Week 1 (n=280,275)	168	153		
Week 4 (n=279,275)	173	182		
Week 8 (n=273,278)	185	198		
Week 12 (n=276,277)	186	199		
Week 16 (n=270,272)	200	209		
Week 20 (n=263,269)	189	207		
Week 24 (n=261,267)	196	205		
Week 28 (n=257,264)	192	197		
Week 32 (n=250,257)	182	190		
Week 36 (n=252,259)	188	192		
Week 40 (n=252,257)	191	193		
Week 44 (n=244,256)	184	191		
Week 48 (n=247,252)	182	190		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with BCVA Snellen Equivalent of 20/200 or Worse from Baseline Over Time up to Week 48 for All RVO Participants)

End point title	Proportion of Participants with BCVA Snellen Equivalent of 20/200 or Worse from Baseline Over Time up to Week 48 for All RVO Participants)
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End point description:

Number of Participants (n) with BCVA Snellen Equivalent of 20/200 or Worse from Baseline to Week 48. Snellen Equivalent of 20/200 is 38 ETDRS letters. Number of participants in each treatment arm who meet specified criteria at each visit from Baseline through Week 48.

End point type	Secondary
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End point timeframe:

Day 1 to Week 48

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Participants				
Baseline (n=284, 284)	22	31		
Week 1 (n=280, 275)	9	12		
Week 4 (n=279, 275)	10	9		
Week 8 (n=273, 278)	6	5		
Week 12 (n=276, 277)	11	4		
Week 16 (n=270, 272)	7	7		
Week 20 (n=263, 269)	7	5		
Week 24 (n=261, 267)	2	4		
Week 28 (n=257, 264)	5	6		
Week 32 (n=250, 257)	3	5		
Week 36 (n=252, 259)	2	3		
Week 40 (n=252, 257)	2	7		
Week 44 (n=244, 256)	2	6		
Week 48 (n=247, 252)	5	8		

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Participants with Absence of Macular Edema from Baseline Over Time up to Week 48 for All RVO Participants

End point title	Proportion of Participants with Absence of Macular Edema from Baseline Over Time up to Week 48 for All RVO Participants
End point description: Macular Edema (ME) is assessed by optical coherence tomography (OCT) central subfield thickness (CST). A thickness of less than 325 microns is considered absence of ME. Proportion of participants with Absence of Macular Edema from Baseline to Week 48. Number of participants in each treatment arm who meet specified criteria at each visit from Week 1 through Week 48.	
End point type	Secondary
End point timeframe: Day 1 to Week 48	

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: Participants				
Baseline (n=284,284)	4	7		
Week 1 (n=278,274)	156	150		
Week 4 (n=279,276)	174	225		
Week 8 (n=273,277)	205	247		
Week 12 (n=275,276)	160	252		
Week 16 (n=270,272)	218	245		
Week 20 (n=262,268)	174	240		
Week 24 (n=261,266)	221	247		
Week 28 (n=258,263)	185	196		
Week 32 (n=252,256)	168	173		
Week 36 (n=249,258)	172	172		
Week 40 (n=252,255)	179	188		
Week 44 (n=240,255)	160	177		
Week 48 (n=245,251)	166	187		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in OCT Central Subfield Retinal Thickness (CST) from Baseline Over Time up to Week 48 for All RVO Participants

End point title	Mean Change in OCT Central Subfield Retinal Thickness (CST) from Baseline Over Time up to Week 48 for All RVO Participants
End point description: Mean change in OCT central subfield retinal thickness (CST) from baseline by visit over time (up to Week 48) for all RVO participants.	
End point type	Secondary
End point timeframe: Day 1 to Week 48	

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: micrometers (um)				
arithmetic mean (standard deviation)				
Week 1 (n = 278, 274)	-225.2 (± 152.87)	-255.9 (± 168.25)		
Week 4 (n = 279, 276)	-230.8 (± 181.37)	-294.2 (± 195.07)		
Week 8 (n = 273, 277)	-255.6 (± 190.4)	-310.1 (± 203.17)		
Week 12 (n = 275, 276)	-195.8 (± 213.7)	-314.8 (± 208.68)		
Week 16 (n = 270, 272)	-264.9 (± 204.77)	-321.0 (± 209.89)		
Week 20 (n = 262, 268)	-218.1 (± 203.88)	-323.0 (± 209.89)		
Week 24 (n = 261, 266)	-278.9 (± 192.68)	-326.6 (± 210.78)		
Week 28 (n = 258, 263)	-240.4 (± 200.78)	-273.9 (± 218.56)		
Week 32 (n = 252, 256)	-246.6 (± 200.99)	-269.7 (± 213.89)		
Week 36 (n = 249, 258)	-243.4 (± 198.13)	-258.6 (± 213.44)		
Week 40 (n = 252, 255)	-246.9 (± 193.79)	-274.9 (± 229.38)		
Week 44 (n = 240, 255)	-237.5 (± 189.3)	-258.3 (± 216.49)		
Week 48 (n = 245, 251)	-240.0 (± 203.97)	-278.8 (± 224.13)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change in OCT Center Point Retinal Thickness (CPT) From Baseline Over Time up to Week 48 for All RVO Participants

End point title	Mean Change in OCT Center Point Retinal Thickness (CPT) From Baseline Over Time up to Week 48 for All RVO Participants
End point description:	
Mean change in OCT center point retinal thickness (CPT) from baseline by visit over time (up to Week 48) for all RVO participants.	
End point type	Secondary
End point timeframe:	
Day 1 to Week 48	

End point values	KSI-301 5 mg	Aflibercept 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	284		
Units: micrometers (um)				
arithmetic mean (standard deviation)				
Week 1 (n = 278, 274)	-278.7 (± 186.23)	-320.9 (± 200.0)		
Week 4 (n = 279, 276)	-278.5 (± 212.92)	-358.4 (± 224.51)		
Week 8 (n = 273, 277)	-301.4 (± 220.72)	-373.9 (± 235.35)		
Week 12 (n = 275, 276)	-230.3 (± 248.92)	-377.6 (± 239.01)		
Week 16 (n = 270, 272)	-311.5 (± 237.01)	-381.3 (± 240.74)		
Week 20 (n = 262, 268)	-258.1 (± 236.58)	-385.4 (± 238.61)		
Week 24 (n = 261, 266)	-327.9 (± 223.13)	-387.5 (± 240.42)		
Week 28 (n = 258, 263)	-280.5 (± 232.22)	-328.0 (± 249.96)		
Week 32 (n = 252, 256)	-288.9 (± 229.60)	-322.4 (± 244.98)		
Week 36 (n = 249, 258)	-286.8 (± 229.63)	-308.1 (± 247.22)		
Week 40 (n = 252, 255)	-290.7 (± 220.56)	-328.7 (± 261.26)		
Week 44 (n = 240, 255)	-281.5 (± 221.38)	-306.6 (± 252.79)		
Week 48 (n = 245, 251)	-279.6 (± 231.43)	-331.6 (± 259.43)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From 1st dose of study drug to 76 weeks. Only SAEs caused by a protocol-mandated intervention were reported from time of ICD through 1st study intervention. From Day 1 through final safety follow up visit, all AE and SAE information were collected.

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, the Sponsor has reported under the Serious adverse events field "number of deaths resulting from adverse events" all deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the Investigator.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	KSI-301 5 mg
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Reporting group description:

Intravitreal injection of KSI-301 (5 mg) at Day 1, Week 4, and once every 8 weeks through Week 20 followed by an individualized dosing regimen of intravitreal injection of KSI-301 (5 mg) from Week 24 to Week 44.

In the Extension Phase, participants randomized to KSI-301 (5 mg) in the Primary Study will continue to receive KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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
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Reporting group description:

Intravitreal injection of aflibercept (2 mg) once every 4 through Week 20 followed by an individualized dosing regimen of Intravitreal injection of Aflibercept (2 mg) once every 4 weeks from Week 24 to Week 44.

In the Extension Phase, participants randomized to aflibercept in the Primary Study will cross over to treatment with KSI-301 (5 mg). They will receive their first dose of KSI-301 (5 mg) at Week 48 and will receive additional treatment with KSI-301 (5 mg) based on protocol-defined disease activity criteria.

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	KSI-301 5mg Extension Phase
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Reporting group description:

In the Extension Phase, participants randomized to KSI-301 (5 mg) in the Primary Study will continue to receive KSI-301 (5 mg) based on protocol-defined disease activity criteria.

In the Extension Phase, participants randomized to aflibercept in the Primary Study will cross over to treatment with KSI-301 (5 mg). They will receive their first dose of KSI-301 (5 mg) at Week 48 and will receive additional treatment with KSI-301 (5 mg) based on protocol-defined disease activity criteria.

Serious adverse events	KSI-301 5 mg	Aflibercept 2 mg	KSI-301 5mg Extension Phase
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 284 (12.68%)	23 / 284 (8.10%)	18 / 444 (4.05%)
number of deaths (all causes)	3	1	2
number of deaths resulting from adverse events	3	1	1

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Invasive ductal breast carcinoma			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Waldenstrom's macroglobulinaemia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Adenocarcinoma pancreas			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatocellular carcinoma			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Prostate cancer metastatic			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cancer			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bronchial neoplasm			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningioma			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sarcomatoid carcinoma of the lung			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 284 (0.35%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Giant cell arteritis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Essential hypertension			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Shock			

subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
General disorders and administration site conditions			
Non-cardiac chest pain			
subjects affected / exposed	0 / 284 (0.00%)	2 / 284 (0.70%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea exertional			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleuritic pain			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device malfunction			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Intraocular pressure increased - Study Eye			

subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Arthropod sting			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fractured sacrum			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 284 (0.00%)	2 / 284 (0.70%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hip fracture			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			

subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	2 / 284 (0.70%)	2 / 284 (0.70%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	2 / 284 (0.70%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrioventricular block			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 284 (0.00%)	2 / 284 (0.70%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery stenosis			

subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina unstable			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	2 / 284 (0.70%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolic encephalopathy			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Carpal tunnel syndrome			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral haemorrhage			

subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myelopathy			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dementia			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lacunar infarction			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nerve compression			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma - Study Eye			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lens dislocation - Study Eye			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment - Study Eye			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhegmatogenous retinal detachment - Study Eye			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vitritis - Study Eye			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal vein occlusion - Study Eye			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retinal detachment - Fellow Eye			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Gastroesophageal reflux disease			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Volvulus			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Large intestine polyp			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholestasis			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Nephrolithiasis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 284 (0.00%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	1 / 284 (0.35%)	2 / 284 (0.70%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	3 / 284 (1.06%)	1 / 284 (0.35%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
COVID-19 pneumonia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Furuncle			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	1 / 444 (0.23%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	2 / 444 (0.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vestibular neuronitis			
subjects affected / exposed	1 / 284 (0.35%)	0 / 284 (0.00%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Orchitis			
subjects affected / exposed	0 / 284 (0.00%)	1 / 284 (0.35%)	0 / 444 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	KSI-301 5 mg	Aflibercept 2 mg	KSI-301 5mg Extension Phase
Total subjects affected by non-serious adverse events			
subjects affected / exposed	73 / 284 (25.70%)	66 / 284 (23.24%)	53 / 444 (11.94%)
Vascular disorders			
Hypertension			
subjects affected / exposed	30 / 284 (10.56%)	26 / 284 (9.15%)	13 / 444 (2.93%)
occurrences (all)	31	28	13

Eye disorders Conjunctival haemorrhage - Study Eye subjects affected / exposed occurrences (all)	24 / 284 (8.45%) 27	22 / 284 (7.75%) 24	8 / 444 (1.80%) 8
Infections and infestations COVID-19 subjects affected / exposed occurrences (all)	30 / 284 (10.56%) 30	23 / 284 (8.10%) 23	32 / 444 (7.21%) 33

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 July 2020	Protocol Version 1.1 Changes from Version 1.0 include administrative revisions based on IRB pre-submission feedback of Version 1.0.
02 June 2021	Protocol Version 2.0 Changes from Version 1.1 include addition of a 20-week Extension Period; and addition of a China-specific enrolment plan.

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.

The open-label extension period of the study was terminated by the Sponsor once all participants had completed the last follow-up visit of the primary study (Week 52).

Notes: