



Clinical trial results:

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

Summary

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

Results information

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

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | KSI-CL-102 |
|-----------------------|------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Kodiak Sciences Inc. |
| Sponsor organisation address | 1200 Page Mill Road, Palo Alto, CA, United States, 94304 |
| Public contact | KSI-CL-102 Trial Information, Kodiak Sciences Inc, KSI-CL-102@kodiak.com |
| Scientific contact | KSI-CL-102 Trial Information, Kodiak Sciences Inc, KSI-CL-102@kodiak.com |

Notes:

Paediatric regulatory details

| | |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 27 May 2022 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 17 November 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 26 April 2022 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

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

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 08 October 2019 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Slovakia: 21 |
| Country: Number of subjects enrolled | Spain: 9 |
| Country: Number of subjects enrolled | Czechia: 29 |
| Country: Number of subjects enrolled | Germany: 3 |
| Country: Number of subjects enrolled | Latvia: 15 |
| Country: Number of subjects enrolled | United States: 464 |
| Worldwide total number of subjects | 557 |
| EEA total number of subjects | 93 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 | 0 |

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

Subject disposition

Recruitment

Recruitment details:

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

Pre-assignment

Screening details:

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

Period 1

| | |
|------------------------------|---------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Assessor |

Blinding implementation details:

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

Arms

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

Arm description:

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

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

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

Dosage and administration details:

5 mg via intravitreal injection

| | |
|------------------|------------------|
| Arm title | Aflibercept 2 mg |
|------------------|------------------|

Arm description:

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

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

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

Dosage and administration details:

2 mg via intravitreal injection

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

Baseline characteristics

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | KSI-301 5 mg |
|-----------------------|--------------|

Reporting group description:

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

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

| | |
|-----------------------|------------------|
| Reporting group title | Aflibercept 2 mg |
|-----------------------|------------------|

Reporting group description:

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

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

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

End points

End points reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | KSI-301 5 mg |
|-----------------------|--------------|

Reporting group description:

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

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

| | |
|-----------------------|------------------|
| Reporting group title | Aflibercept 2 mg |
|-----------------------|------------------|

Reporting group description:

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

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

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

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

End point description:

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

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Year 1

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

Statistical analyses

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

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

Notes:

[1] - The maximum clinically acceptable true difference between KSI-301 and aflibercept participants to be considered non-inferior is 4 ETDRS letters, i.e. the non-inferiority margin (NI) is 4 letters.

[2] - MMRM model with treatment, visit, treatment by visit interaction, categories for baseline BCVA, BCVA-low luminance VA baseline, geographical location.

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1

Notes:

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

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1

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

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

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

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Year 1

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

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

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

Adverse event reporting additional description:

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

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.1 |

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | KSI-301 5 mg |
|-----------------------|--------------|

Reporting group description:

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

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

| | |
|-----------------------|------------------|
| Reporting group title | Aflibercept 2 mg |
|-----------------------|------------------|

Reporting group description:

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

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

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

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

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

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

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

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

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

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

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

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

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 277 (0.00%) | 1 / 280 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | 1 / 280 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 277 (0.36%) | 0 / 280 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | KSI-301 5 mg | Aflibercept 2 mg | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 82 / 277 (29.60%) | 84 / 280 (30.00%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 15 / 277 (5.42%) | 16 / 280 (5.71%) | |
| occurrences (all) | 15 | 16 | |
| Eye disorders | | | |
| Neovascular age-related macular degeneration - Fellow Eye | | | |
| subjects affected / exposed | 19 / 277 (6.86%) | 26 / 280 (9.29%) | |
| occurrences (all) | 19 | 26 | |
| Retinal haemorrhage - Study Eye | | | |
| subjects affected / exposed | 17 / 277 (6.14%) | 4 / 280 (1.43%) | |
| occurrences (all) | 18 | 5 | |
| Cataract - Study Eye | | | |
| subjects affected / exposed | 15 / 277 (5.42%) | 10 / 280 (3.57%) | |
| occurrences (all) | 15 | 10 | |
| Conjunctival haemorrhage - Study Eye | | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

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

Notes: