



Clinical trial results:

A Prospective, Randomized, Double-masked, Sham-controlled, Multi-center, Two-arm, Phase 3 Study to Evaluate the Efficacy and Safety of Intravitreal KSI-301 in Participants with Moderately Severe to Severe Non-proliferative Diabetic Retinopathy (NPDR)

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2020-001064-29 |
| Trial protocol | SK ES LV CZ |
| Global end of trial date | 31 August 2023 |

Results information

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

Trial information

Trial identification

| | |
|-----------------------|-----------|
| Sponsor protocol code | KS301P106 |
|-----------------------|-----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05066230 |
| 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-106 Trial Information, Kodiak Sciences Inc., ksi301clinical@kodiak.com |
| Scientific contact | KSI-CL-106 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 | 26 September 2023 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 03 August 2023 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 August 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To demonstrate that KSI-301 5 mg is superior to sham treatment, with respect to proportion of eyes improving ≥ 2 steps on Diabetic Retinopathy Severity Scale (DRSS) from baseline at Week 48.

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 | 30 August 2021 |
| 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: 1 |
| Country: Number of subjects enrolled | Slovakia: 2 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Czechia: 1 |
| Country: Number of subjects enrolled | United States: 243 |
| Worldwide total number of subjects | 253 |
| EEA total number of subjects | 10 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |

| | |
|----------------------|-----|
| Adults (18-64 years) | 191 |
| From 65 to 84 years | 62 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants were recruited based on physician referral at 52 medical centers between September 2021 and August 2022. The first participant was enrolled on 07 September 2021 and the last on 25 August 2022.

Pre-assignment

Screening details:

Of 560 enrolled participants, 253 met eligibility criteria and were randomized to treatment.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Primary Study (Through 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 - Treatment Group A |

Arm description:

Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92

| | |
|--|------------------------|
| 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 | Sham - Treatment Group B |
|------------------|--------------------------|

Arm description:

Sham injection on the same schedule as Treatment Group A

Sham injection: The sham injection 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 is performed to maintain masking of the study.

| | |
|---|-----------------|
| Arm type | Sham Comparator |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | KSI-301 - Treatment Group A | Sham - Treatment Group B |
|--------------------------------|-----------------------------|--------------------------|
| Started | 128 | 125 |
| Completed | 120 | 115 |
| Not completed | 8 | 10 |
| Adverse event, serious fatal | 1 | 1 |
| Consent withdrawn by subject | 4 | 2 |

| | | |
|------------------------------------|---|---|
| Non-compliance with study schedule | - | 1 |
| Adverse event, non-fatal | - | 3 |
| Participant relocated | 1 | - |
| Lost to follow-up | 2 | 3 |

Period 2

| | |
|------------------------------|--|
| Period 2 title | After Week 48 |
| Is this the baseline period? | No |
| 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 - Treatment Group A |

Arm description:

Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92

KSI-301: Intravitreal injection

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

Dosage and administration details:

5 mg via intravitreal injection

| | |
|------------------|--------------------------|
| Arm title | Sham - Treatment Group B |
|------------------|--------------------------|

Arm description:

Sham injection on the same schedule as Treatment Group A

Sham injection: The sham injection 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 is performed to maintain masking of the study.

| | |
|---|------|
| Arm type | Sham |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2 | KSI-301 - Treatment Group A | Sham - Treatment Group B |
|---------------------------------------|-----------------------------|--------------------------|
| Started | 120 | 115 |
| Completed | 0 | 0 |
| Not completed | 120 | 115 |
| Adverse event, serious fatal | 1 | - |
| Consent withdrawn by subject | - | 1 |

| | | |
|------------------------------------|-----|-----|
| Non-compliance with study schedule | 1 | - |
| Lost to follow-up | 3 | 3 |
| Sponsor Request | 115 | 111 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-----------------------------|
| Reporting group title | KSI-301 - Treatment Group A |
|-----------------------|-----------------------------|

Reporting group description:

Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92

| | |
|-----------------------|--------------------------|
| Reporting group title | Sham - Treatment Group B |
|-----------------------|--------------------------|

Reporting group description:

Sham injection on the same schedule as Treatment Group A

Sham injection: The sham injection 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 is performed to maintain masking of the study.

| Reporting group values | KSI-301 - Treatment Group A | Sham - Treatment Group B | Total |
|--|-----------------------------|--------------------------|-------|
| Number of subjects | 128 | 125 | 253 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 96 | 95 | 191 |
| From 65-84 years | 32 | 30 | 62 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous Units: years | | | |
| arithmetic mean | 56.4 | 57.0 | |
| standard deviation | ± 11.39 | ± 9.63 | - |
| Gender categorical Units: Subjects | | | |
| Female | 51 | 56 | 107 |
| Male | 77 | 69 | 146 |
| Race Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 2 | 2 |
| Asian | 3 | 3 | 6 |
| Black or African American | 13 | 23 | 36 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| White | 108 | 96 | 204 |
| Multiple | 2 | 0 | 2 |
| Other | 2 | 1 | 3 |
| Ethnicity Units: Subjects | | | |
| Hispanic or Latino | 57 | 52 | 109 |
| Not Hispanic or Latino | 71 | 73 | 144 |
| ETDRS Diabetic Retinopathy Severity Score at Baseline Units: Subjects | | | |
| DRSS Level ≤47 | 46 | 45 | 91 |
| DRSS Level ≥53 | 82 | 80 | 162 |

End points

End points reporting groups

| | |
|--|-----------------------------|
| Reporting group title | KSI-301 - Treatment Group A |
| Reporting group description: Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92 | |
| Reporting group title | Sham - Treatment Group B |
| Reporting group description: Sham injection on the same schedule as Treatment Group A Sham injection: The sham injection 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 is performed to maintain masking of the study. | |
| Reporting group title | KSI-301 - Treatment Group A |
| Reporting group description: Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92 KSI-301: Intravitreal injection | |
| Reporting group title | Sham - Treatment Group B |
| Reporting group description: Sham injection on the same schedule as Treatment Group A Sham injection: The sham injection 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 is performed to maintain masking of the study. | |
| Subject analysis set title | Primary Study |
| Subject analysis set type | Full analysis |
| Subject analysis set description: Full analysis set defined as all randomized subjects who received any study treatment (KSI-301 or sham) and have gradable DRSS value at baseline. Subjects will be analyzed according to their randomized treatment. | |

Primary: Percentage of Patients Improving ≥ 2 Steps on DRSS

| | |
|--|---|
| End point title | Percentage of Patients Improving ≥ 2 Steps on DRSS |
| End point description: Percentage of patients improving ≥ 2 steps on the Diabetic Retinopathy Severity Scale (DRSS) from baseline at Week 48 using last observation carried forward (LOCF) | |
| End point type | Primary |
| End point timeframe: Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|-----------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | 52 | 2 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 for Percentage of Patients |
| Comparison groups | KSI-301 - Treatment Group A v Sham - Treatment Group B |
| Number of subjects included in analysis | 253 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference of weighted percentage |
| Point estimate | 39.7 |
| Confidence interval | |
| level | 95.02 % |
| sides | 2-sided |
| lower limit | 31.3 |
| upper limit | 48.1 |

Notes:

[1] - Cochran-Mantel-Haentzel test stratified by baseline DRSS level (\leq level 47 vs. \geq level 53) and HbA1c level (\leq 8.5% vs. $>$ 8.5%)

Secondary: Percentage of Patients Developing Any Sight-Threatening Complication

| | |
|-----------------|--|
| End point title | Percentage of Patients Developing Any Sight-Threatening Complication |
|-----------------|--|

End point description:

Percentage of patients developing any of the following Sight-Threatening Complication: Proliferative Diabetic Retinopathy (PDR), Anterior segment neovascularization (ASNV), Vitreous hemorrhage or tractional retinal detachment believed to be due to PDR, or Diabetic Macular Edema (DME) from baseline through Week 48

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

End point timeframe:

Day 1 to Week 48

| | | | | |
|-----------------------------|-----------------------------|--------------------------|--|--|
| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | 3 | 26 | | |

Statistical analyses

| | |
|-----------------------------------|--|
| Statistical analysis title | Statistical Analysis 1 for Percentage of Patients |
| Comparison groups | KSI-301 - Treatment Group A v Sham - Treatment Group B |

| | |
|---|-----------------------------------|
| Number of subjects included in analysis | 253 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.0001 ^[2] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference of weighted percentage |
| Point estimate | -18.7 |
| Confidence interval | |
| level | 95.02 % |
| sides | 2-sided |
| lower limit | -26.2 |
| upper limit | -11.2 |

Notes:

[2] - Cochran-Mantel-Haenszel test stratified by baseline DRSS level (\leq level 47 vs. \geq level 53) and HbA1c level (\leq 8.5% vs. $>$ 8.5%).

Secondary: Percentage of Patients Improving ≥ 3 Steps on DRSS

| | |
|--|---|
| End point title | Percentage of Patients Improving ≥ 3 Steps on DRSS |
| End point description: | |
| Percentage of patients improving ≥ 3 steps on the Diabetic Retinopathy Severity Scale (DRSS) from baseline at Week 48 using last observation carried forward (LOCF) | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|-----------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | 7 | 0 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 for Percentage of Patients |
| Comparison groups | KSI-301 - Treatment Group A v Sham - Treatment Group B |
| Number of subjects included in analysis | 253 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0058 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference of weighted percentage |
| Point estimate | 5.6 |
| Confidence interval | |
| level | 95.02 % |
| sides | 2-sided |
| lower limit | 1.6 |
| upper limit | 9.5 |

Notes:

[3] - Cochran-Mantel-Haentzel test stratified by baseline DRSS level (\leq level 47 vs. \geq level 53), HbA1c level (\leq 8.5% vs. $>$ 8.5%).

Secondary: Percentage of Patients Developing PDR

| | |
|-----------------|---------------------------------------|
| End point title | Percentage of Patients Developing PDR |
|-----------------|---------------------------------------|

End point description:

Percentage of patients developing Proliferative Diabetic Retinopathy (PDR) from baseline through Week 48

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

End point timeframe:

Day 1 to Week 48

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|-----------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | 2 | 10 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Statistical Analysis 1 for Percentage of Patients |
| Comparison groups | KSI-301 - Treatment Group A v Sham - Treatment Group B |
| Number of subjects included in analysis | 253 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.0149 ^[4] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Difference of weighted percentage |
| Point estimate | -6.5 |
| Confidence interval | |
| level | 95.02 % |
| sides | 2-sided |
| lower limit | -11.8 |
| upper limit | -1.3 |

Notes:

[4] - Cochran-Mantel-Haentzel test stratified by baseline DRSS level (\leq level 47 vs. \geq level 53) and HbA1c level (\leq 8.5% vs. $>$ 8.5%).

Secondary: Percentage of Patients Developing PDR or ASNV

| | |
|-----------------|---|
| End point title | Percentage of Patients Developing PDR or ASNV |
|-----------------|---|

End point description:

Percentage of patients developing Proliferative Diabetic Retinopathy (PDR) or Anterior segment neovascularization (ASNV) from baseline through Week 48

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

End point timeframe:

Day 1 to Week 48

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|---|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | | | | |
| Percentage of Patients Developing PDR or ASNV | 2 | 10 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Developing Vitreous Hemorrhage or Tractional Retinal Detachment Believed to be Due to PDR

| | |
|------------------------|---|
| End point title | Percentage of Patients Developing Vitreous Hemorrhage or Tractional Retinal Detachment Believed to be Due to PDR |
| End point description: | Percentage of patients developing vitreous hemorrhage or tractional retinal detachment believed to be due to Proliferative Diabetic Retinopathy (PDR) from baseline through Week 48 |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|-----------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | 2 | 3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of patients developing DME

| | |
|------------------------|--|
| End point title | Percentage of patients developing DME |
| End point description: | Percentage of patients developing Diabetic Macular Edema (DME) from baseline through Week 48 |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|-----------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | 1 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients With a ≥ 2 -step or ≥ 3 -step Worsening on DRSS

| | |
|--|--|
| End point title | Percentage of Patients With a ≥ 2 -step or ≥ 3 -step Worsening on DRSS |
| End point description: | |
| Percentage of patients with a ≥ 2 -step or ≥ 3 -step worsening on the Diabetic Retinopathy Severity Scale (DRSS) from baseline at Week 48 using last observation carried forward (LOCF). The Diabetic Retinopathy Disease Severity Scale (DRSS) may be used to describe overall retinopathy severity as well as the change in severity over time. Severity range from level 10 (DR absent) to level 85 (advanced proliferative DR: posterior fundus obscured, or center of macula detached). | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|--|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| Patients with a ≥ 2 -step worsening on DRSS (n) | 1 | 5 | | |
| Patients with a ≥ 2 -step worsening on DRSS (%) | 0.78 | 4 | | |
| Patients with a ≥ 3 -step worsening on DRSS (n) | 0 | 3 | | |
| Patients with a ≥ 3 -step worsening on DRSS (%) | 0 | 2.4 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients Who Lost ≥5, ≥10, or ≥15 Letters in BCVA

| | |
|---|---|
| End point title | Percentage of Patients Who Lost ≥5, ≥10, or ≥15 Letters in BCVA |
| End point description: Percentage of patients who lost ≥5, ≥10, or ≥15 letters in Best-corrected Visual Acuity (BCVA) from baseline by visit over time | |
| End point type | Secondary |
| End point timeframe: Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|---|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Participants | | | | |
| number (not applicable) | | | | |
| lost ≥ 5 letters from baseline-Wk 8 (N analysed) | 127 | 123 | | |
| lost ≥ 5 letters from baseline-Wk 8 (n) | 8 | 15 | | |
| lost ≥ 5 letters from baseline-Wk 8 (%) | 6.3 | 12.2 | | |
| lost ≥ 5 letters from baseline-Wk 20 (N analysed) | 122 | 109 | | |
| lost ≥ 5 letters from baseline-Wk 20 (n) | 15 | 15 | | |
| lost ≥ 5 letters from baseline-Wk 20 (%) | 12.3 | 13.76 | | |
| lost ≥ 5 letters from baseline-Wk 32 (N analysed) | 117 | 99 | | |
| lost ≥ 5 letters from baseline-Wk 32 (n) | 17 | 10 | | |
| lost ≥ 5 letters from baseline-Wk 32 (%) | 14.53 | 10.1 | | |
| lost ≥ 5 letters from baseline-Wk 44 (N analysed) | 109 | 90 | | |
| lost ≥ 5 letters from baseline-Wk 44 (n) | 12 | 8 | | |
| lost ≥ 5 letters from baseline-Wk 44 (%) | 11.01 | 8.89 | | |
| lost ≥ 5 letters from baseline-Wk 48 (N analysed) | 114 | 91 | | |
| lost ≥ 5 letters from baseline-Wk 48 (n) | 14 | 11 | | |
| lost ≥ 5 letters from baseline-Wk 48 (%) | 12.28 | 12.09 | | |
| lost ≥10 letters from baseline-Wk 8 (N analysed) | 127 | 123 | | |
| lost ≥10 letters from baseline-Wk 8 (n) | 2 | 3 | | |
| lost ≥10 letters from baseline-Wk 8 (%) | 1.57 | 2.44 | | |
| lost ≥10 letters from baseline-Wk 20 (N analysed) | 122 | 109 | | |
| lost ≥10 letters from baseline-Wk 20 (n) | 2 | 4 | | |
| lost ≥10 letters from baseline-Wk 20 (%) | 1.64 | 3.67 | | |
| lost ≥10 letters from baseline-Wk 32 (N analysed) | 117 | 99 | | |
| lost ≥10 letters from baseline-Wk 32 (n) | 5 | 1 | | |

| | | | | |
|---|------|------|--|--|
| lost ≥10 letters from baseline-Wk 32 (%) | 4.27 | 1.01 | | |
| lost ≥10 letters from baseline-Wk 44 (N analysed) | 109 | 90 | | |
| lost ≥10 letters from baseline-Wk 44 (n) | 4 | 2 | | |
| lost ≥10 letters from baseline-Wk 44 (%) | 3.67 | 2.22 | | |
| lost ≥10 letters from baseline-Wk 48 (N analysed) | 114 | 91 | | |
| lost ≥10 letters from baseline-Wk 48 (n) | 5 | 1 | | |
| lost ≥10 letters from baseline-Wk 48 (%) | 4.39 | 1.1 | | |
| lost ≥15 letters from baseline-Wk 8 (N analysed) | 127 | 123 | | |
| lost ≥15 letters from baseline-Wk 8 (n) | 1 | 1 | | |
| lost ≥15 letters from baseline-Wk 8 (%) | 0.79 | 0.81 | | |
| lost ≥15 letters from baseline-Wk 20 (N analysed) | 122 | 109 | | |
| lost ≥15 letters from baseline-Wk 20 (n) | 1 | 1 | | |
| lost ≥15 letters from baseline-Wk 20 (%) | 0.82 | 0.92 | | |
| lost ≥15 letters from baseline-Wk 32 (N analysed) | 117 | 99 | | |
| lost ≥15 letters from baseline-Wk 32 (n) | 4 | 0 | | |
| lost ≥15 letters from baseline-Wk 32 (%) | 3.42 | 0 | | |
| lost ≥15 letters from baseline-Wk 44 (N analysed) | 109 | 90 | | |
| lost ≥15 letters from baseline-Wk 44 (n) | 0 | 0 | | |
| lost ≥15 letters from baseline-Wk 44 (%) | 0 | 0 | | |
| lost ≥15 letters from baseline-Wk 48 (N analysed) | 114 | 91 | | |
| lost ≥15 letters from baseline-Wk 48 (n) | 3 | 0 | | |
| lost ≥15 letters from baseline-Wk 48 (%) | 2.63 | 0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Levelopment of PDR, ASNV, or DME

| | |
|--|--|
| End point title | Time to First Levelopment of PDR, ASNV, or DME |
| End point description: | |
| Time to first development of Proliferative Diabetic Retinopathy (PDR), Anterior segment neovascularisation (ASNV), or Diabetic Macular Edema (DME) through Week 48 | |
| End point type | Secondary |
| End point timeframe: | |
| Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|---|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 ^[5] | 125 ^[6] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Time to 1st development of PDR, ASNV or DME | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[5] - 0 = Not available due to small number of PDR, ASNV and DME events

[6] - 0 = Not available due to small number of PDR, ASNV and DME events

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Development of PDR or ASNV

| | |
|------------------------|---|
| End point title | Time to First Development of PDR or ASNV |
| End point description: | Time to first development of Proliferative Diabetic Retinopathy (PDR) or Anterior Segment Neovascularization (ASNV) through Week 48 |
| End point type | Secondary |
| End point timeframe: | Day 1 to Week 48 |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|--|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 ^[7] | 125 ^[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Time to first development of PDR or ASNV | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[7] - 0 = Not available due to small number of PDR and ASNV events

[8] - 0 = Not available due to small number of PDR and ASNV events

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Development of Vitreous Hemorrhage or Tractional Retinal Detachment Believed to be Due to PDR

| | |
|------------------------|---|
| End point title | Time to First Development of Vitreous Hemorrhage or Tractional Retinal Detachment Believed to be Due to PDR |
| End point description: | Time to first development of vitreous hemorrhage (VH) or tractional retinal detachment (TRD) believed to be due to Proliferative Diabetic Retinopathy (PDR) through Week 48 |
| End point type | Secondary |

End point timeframe:

Day 1 to Week 48

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|--------------------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 ^[9] | 125 ^[10] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Time to 1st development of VH or TRD | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[9] - 0 = Not available due to small number of vitreous haemorrhage & tractional retinal detachment

[10] - 0 = Not available due to small number of vitreous haemorrhage & tractional retinal detachment

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change in OCT CST

| | |
|-----------------|------------------------|
| End point title | Mean Change in OCT CST |
|-----------------|------------------------|

End point description:

Mean change in Optical Coherence Tomography (OCT) central subfield retinal thickness (CST) from baseline by visit over time

| | |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Day 1 to Week 48

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|--------------------------------------|-----------------------------|--------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: Microns | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 (n = 127, 123) | -9.8 (± 10.64) | 4.5 (± 17.22) | | |
| Week 20 (n = 122, 109) | -12.8 (± 13.42) | 6.6 (± 28.99) | | |
| Week 32 (n = 117, 99) | -13.9 (± 14.88) | 5.2 (± 27.86) | | |
| Week 44 (n = 109, 90) | -8.9 (± 19.71) | -0.5 (± 17.12) | | |
| Week 48 (n = 114, 91) | -15.2 (± 16.35) | -0.7 (± 15.76) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change in BCVA

| | |
|---|---------------------|
| End point title | Mean Change in BCVA |
| End point description: Mean change in Best-corrected Visual Acuity (BCVA) from baseline by visit over time | |
| End point type | Other pre-specified |
| End point timeframe: Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|--------------------------------------|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 | 125 | | |
| Units: ETDRS Letters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 8 (n = 127, 123) | 1.3 (± 5.02) | 0.2 (± 4.80) | | |
| Week 20 (n = 122, 109) | 1.1 (± 5.22) | 0.3 (± 6.29) | | |
| Week 32 (n = 117, 99) | 0.9 (± 8.68) | 1.2 (± 4.87) | | |
| Week 44 (n = 109, 90) | 1.0 (± 5.63) | 1.6 (± 5.55) | | |
| Week 48 (n = 114, 91) | 1.1 (± 6.44) | 1.5 (± 5.49) | | |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Time to First Development of DME

| | |
|---|----------------------------------|
| End point title | Time to First Development of DME |
| End point description: Time to first development of Diabetic Macular Edema (DME) through Week 48 | |
| End point type | Other pre-specified |
| End point timeframe: Day 1 to Week 48 | |

| End point values | KSI-301 - Treatment Group A | Sham - Treatment Group B | | |
|----------------------------------|-----------------------------------|--------------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 128 ^[11] | 125 ^[12] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | | | | |
| Time to first development of DME | 0 (0 to 0) | 0 (0 to 0) | | |

Notes:

[11] - 0 = Not available due to small number of DME events

[12] - 0 = Not available due to small number of DME events

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) reported through the End of Study or Early Termination (ET)

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 23.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | KSI-301 - Treatment Group A (Day 1 to Week 48) |
|-----------------------|--|

Reporting group description:

Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92

KSI-301: Intravitreal injection

| | |
|-----------------------|--------------------------------------|
| Reporting group title | Treatment Group B (Day 1 to Week 48) |
|-----------------------|--------------------------------------|

Reporting group description:

Sham injection on the same schedule as Treatment Group A

Sham injection: The sham injection 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 is performed to maintain masking of the study.

| | |
|-----------------------|--|
| Reporting group title | KSI-301 - Treatment Group A (Post Week 48 to End of Study) |
|-----------------------|--|

Reporting group description:

Intravitreal injection of KSI-301 (5 mg): three initiating doses, and then every 24 weeks through Week 92

KSI-301: Intravitreal injection

| | |
|-----------------------|--|
| Reporting group title | Treatment Group B (Post Week 48 to End of Study) |
|-----------------------|--|

Reporting group description:

Sham injection on the same schedule as Treatment Group A

Sham injection: The sham injection 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 is performed to maintain masking of the study.

| Serious adverse events | KSI-301 - Treatment Group A (Day 1 to Week 48) | Treatment Group B (Day 1 to Week 48) | KSI-301 - Treatment Group A (Post Week 48 to End of Study) |
|---|--|--------------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 18 / 128 (14.06%) | 12 / 125 (9.60%) | 8 / 120 (6.67%) |
| number of deaths (all causes) | 1 | 1 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Hypertensive emergency | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 2 / 120 (1.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Impaired healing | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Fibula fracture | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 1 / 120 (0.83%) |
| 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 | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 2 / 128 (1.56%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Angina unstable | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Atrioventricular block | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 arrest | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Pulseless electrical activity | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Cerebral arteriosclerosis | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Eye disorders | | | |
| Retinal vein occlusion - Fellow Eye | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Gastrointestinal disorders | | | |
| Constipation | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Hepatobiliary disorders | | | |
| Gallbladder rupture | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin ulcer | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 0 / 120 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Localised infection | | | |
| subjects affected / exposed | 2 / 128 (1.56%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Osteomyelitis | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 2 / 125 (1.60%) | 2 / 120 (1.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Complicated appendicitis | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Infected cyst | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Septic shock | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 0 / 120 (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 |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Cellulitis staphylococcal | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Mycoplasma infection | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 1 / 125 (0.80%) | 0 / 120 (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 |
| Osteomyelitis acute | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 128 (0.00%) | 0 / 125 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 128 (0.78%) | 0 / 125 (0.00%) | 1 / 120 (0.83%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Treatment Group B (Post Week 48 to End of Study) | | |
|--|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 115 (2.61%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertensive emergency | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Impaired healing | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute pulmonary oedema | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Alcohol poisoning | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fibula fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tibia fracture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrioventricular block | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulseless electrical activity | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure chronic | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebral arteriosclerosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|-----------------|--|--|
| Deafness | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Retinal vein occlusion - Fellow Eye | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Gallbladder rupture | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Diabetic foot | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin ulcer | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 115 (0.87%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Renal failure | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Localised infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| COVID-19 pneumonia | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Complicated appendicitis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Infected cyst | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sepsis | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Urinary tract infection | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Appendicitis | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cellulitis staphylococcal | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mycoplasma infection | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Osteomyelitis acute | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | KSI-301 - Treatment Group A (Day 1 to Week 48) | Treatment Group B (Day 1 to Week 48) | KSI-301 - Treatment Group A (Post Week 48 to End of Study) |
|---|--|--------------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 49 / 128 (38.28%) | 51 / 125 (40.80%) | 15 / 120 (12.50%) |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 12 / 128 (9.38%) | 10 / 125 (8.00%) | 2 / 120 (1.67%) |
| occurrences (all) | 13 | 10 | 2 |
| Eye disorders | | | |
| Cataract - Study Eye | | | |
| subjects affected / exposed | 13 / 128 (10.16%) | 5 / 125 (4.00%) | 3 / 120 (2.50%) |
| occurrences (all) | 14 | 5 | 3 |
| Conjunctival haemorrhage - Study Eye | | | |
| subjects affected / exposed | 9 / 128 (7.03%) | 4 / 125 (3.20%) | 1 / 120 (0.83%) |
| occurrences (all) | 9 | 5 | 1 |
| Cataract - Fellow Eye | | | |
| subjects affected / exposed | 7 / 128 (5.47%) | 3 / 125 (2.40%) | 1 / 120 (0.83%) |
| occurrences (all) | 7 | 3 | 1 |
| Diabetic retinal oedema - Study Eye | | | |

| | | | |
|------------------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed | 2 / 128 (1.56%) | 18 / 125 (14.40%) | 3 / 120 (2.50%) |
| occurrences (all) | 2 | 19 | 3 |
| Diabetic retinopathy - Study Eye | | | |
| subjects affected / exposed | 2 / 128 (1.56%) | 8 / 125 (6.40%) | 1 / 120 (0.83%) |
| occurrences (all) | 2 | 8 | 1 |
| Infections and infestations | | | |
| COVID-19 | | | |
| subjects affected / exposed | 9 / 128 (7.03%) | 6 / 125 (4.80%) | 1 / 120 (0.83%) |
| occurrences (all) | 9 | 7 | 1 |
| Metabolism and nutrition disorders | | | |
| Diabetes mellitus | | | |
| subjects affected / exposed | 15 / 128 (11.72%) | 8 / 125 (6.40%) | 3 / 120 (2.50%) |
| occurrences (all) | 15 | 8 | 3 |

| | | | |
|--|--|--|--|
| Non-serious adverse events | Treatment Group B (Post Week 48 to End of Study) | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 115 (7.83%) | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 115 (0.87%) | | |
| occurrences (all) | 1 | | |
| Eye disorders | | | |
| Cataract - Study Eye | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences (all) | 0 | | |
| Conjunctival haemorrhage - Study Eye | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cataract - Fellow Eye | | | |
| subjects affected / exposed | 0 / 115 (0.00%) | | |
| occurrences (all) | 0 | | |
| Diabetic retinal oedema - Study Eye | | | |
| subjects affected / exposed | 3 / 115 (2.61%) | | |
| occurrences (all) | 3 | | |
| Diabetic retinopathy - Study Eye | | | |

| | | | |
|---|----------------------|--|--|
| subjects affected / exposed occurrences (all) | 3 / 115 (2.61%) 3 | | |
| Infections and infestations COVID-19 subjects affected / exposed occurrences (all) | 0 / 115 (0.00%) 0 | | |
| Metabolism and nutrition disorders Diabetes mellitus subjects affected / exposed occurrences (all) | 2 / 115 (1.74%) 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------|---|
| 17 May 2021 | Version 1.1 - Changes from Version 1.0 (original protocol) include: minor editorial and administrative revisions. |

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 after all participants completed Wk 48 safety follow-up due to demonstration of efficacy at the Week 48 Primary Analysis. Results were not reported for some endpoints due to insufficient sample size.

Notes: