



Clinical trial results:

A Phase 2A Open-Label Trial to Assess the Safety of Zimura™ (Anti-C5) Administered in Combination With Lucentis® 0.5 mg in Treatment Naïve Subjects with Neovascular Age Related Macular Degeneration

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2017-003923-31 |
| Trial protocol | LV HU |
| Global end of trial date | 18 October 2018 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 03 December 2021 |
| First version publication date | 03 December 2021 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | OPH2007 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03362190 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | IVERIC bio, Inc. (formerly Ophthotech Corporation) |
| Sponsor organisation address | Five Penn Plaza, Suite 2372, New York, United States, |
| Public contact | Medical Director, IVERIC bio, Inc., clinicaltrials@ivericbio.com |
| Scientific contact | Medical Director, IVERIC bio, Inc., clinicaltrials@ivericbio.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 | 18 October 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 18 October 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 18 October 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the safety of intravitreal Zimura™ administered in combination with Lucentis® in treatment naïve subjects with NVAMD

Protection of trial subjects:

The study was conducted in full compliance with the principles of the Declaration of Helsinki and in line with the principles outlined in the Guideline for Good Clinical Practice (GCP), the International Council for Harmonisation (ICH) Tripartite Guideline (May 1997). Before initiation of the study, the protocol and the subject informed consent provisions were reviewed and approved by the appropriate independent ethics committees (IECs) for each of the centers involved in the study. Study initiation at each site began only after receiving written approval from the IEC. Prior to study entry, all subjects were informed fully of the nature and aims of the study. Ample time was provided for the subjects to read the subject information sheet and ask any questions regarding the investigational drug. Subjects were informed that their participation was voluntary and that they could withdraw from the study at any time for any reason without incurring any penalty or withholding of treatment on the part of the investigator. Before receiving any treatment related to this study, all subjects provided their written informed consent.

Background therapy: -

Evidence for comparator: -

| | |
|---|-----------------|
| Actual start date of recruitment | 02 October 2017 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 45 |
| Country: Number of subjects enrolled | Hungary: 13 |
| Country: Number of subjects enrolled | Latvia: 6 |
| Worldwide total number of subjects | 64 |
| EEA total number of subjects | 19 |

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) | 5 |
| From 65 to 84 years | 49 |
| 85 years and over | 10 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Inclusion: active subfoveal NVAMD, ≥ 50 years

Exclusion: severe cardiac disease, major surgical procedure < 1 month of trial entry, clinically significant laboratory value, treatment with investigational agent < 60 days of trial, women who are pregnant or nursing, known relevant serious allergies, prior AMD treatment (excl vitamin/mineral supplement)

Period 1

| | |
|------------------------------|-----------------------------------|
| Period 1 title | Treatment period (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|----------|
| Arm title | Cohort 1 |
|------------------|----------|

Arm description:

Monthly administration of Lucentis 0.5 mg followed 2 days later by Zimura 4mg

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Zimura |
| Investigational medicinal product code | |
| Other name | avacincaptad pegol |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

2 x 2 mg intravitreal injections in the study eye, administered once per month for 6 doses in total. Zimura injections were administered 2 days after the Lucentis injections.

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

Dosage and administration details:

0.5 mg/intravitreal injection in the study eye, administered once per month for 6 doses in total.

| | |
|------------------|----------|
| Arm title | Cohort 2 |
|------------------|----------|

Arm description:

Monthly administration of Zimura 2mg + Lucentis 0.5 mg administered (given on the same day)

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Zimura |
| Investigational medicinal product code | |
| Other name | avacincaptad pegol |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

1 x 2 mg intravitreal injections in the study eye, administered once per month for 6 doses in total. Zimura injections were administered on the same day as the Lucentis injections.

| | |
|---|------------------------|
| Investigational medicinal product name | Lucentis |
| Investigational medicinal product code | |
| Other name | ranibizumab |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |
| Dosage and administration details: | |
| 0.5 mg/intravitreal injection in the study eye, administered once per month for 6 doses in total. | |
| Arm title | Cohort 3 |

Arm description:

Zimura 2mg + Lucentis 0.5 mg

Induction Phase (Day 1 - Month 2): Monthly administration of Zimura 2mg + Lucentis 0.5 mg given on the same day followed 14 days later with Zimura 2mg (Total: 6 doses of Zimura & 3 doses of Lucentis)

Maintenance Phase (Month 3-5): Monthly administration of Zimura 2mg + Lucentis 0.5mg given on the same day (Total: 3 doses of Zimura and 3 doses of Lucentis)

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Zimura |
| Investigational medicinal product code | |
| Other name | avacincaptad pegol |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

1 x 2 mg intravitreal injections in the study eye, administered every 14 days for 3 months (Induction Phase) and once per month for the subsequent 3 months (Maintenance Phase). When applicable, Zimura injections were administered on the same day as the Lucentis injections.

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

Dosage and administration details:

0.5 mg/intravitreal injection in the study eye, administered once per month for 6 doses in total.

| | |
|------------------|----------|
| Arm title | Cohort 4 |
|------------------|----------|

Arm description:

Zimura 2mg + Lucentis 0.5 mg

Induction Phase (Day 1 - Month 2): Monthly administration of Zimura 2mg + Lucentis 0.5 mg given on the same day followed 14 days later with Zimura 2mg (Total: 6 doses of Zimura & 3 doses Lucentis)

Maintenance Phase (Month 3-5): Monthly administration of Zimura 2mg followed 2 days later by Zimura 2mg + Lucentis 0.5mg (Total: 6 doses of Zimura & 3 doses Lucentis)

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Zimura |
| Investigational medicinal product code | |
| Other name | avacincaptad pegol |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

1 x 2 mg intravitreal injections in the study eye, administered every 14 days for 3 months (Induction Phase) and twice per month (2 days apart) for the subsequent 3 months (Maintenance Phase). When applicable, Zimura injections were administered on the same day as the Lucentis injections (day 0 during the Induction Phase and Day 2 during the Maintenance Phase).

| | |
|--|-------------|
| Investigational medicinal product name | Lucentis |
| Investigational medicinal product code | |
| Other name | ranibizumab |

| | |
|--------------------------|------------------------|
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intravitreal use |

Dosage and administration details:

0.5 mg/intravitreal injection in the study eye, administered once per month for 6 doses in total (Day 0 during the Induction Phase and Day 2 during the Maintenance Phase).

| Number of subjects in period 1 | Cohort 1 | Cohort 2 | Cohort 3 |
|---------------------------------------|----------|----------|----------|
| Started | 10 | 10 | 22 |
| Completed | 10 | 10 | 22 |
| Not completed | 0 | 0 | 0 |
| Consent withdrawn by subject | - | - | - |
| Adverse event, non-fatal | - | - | - |

| Number of subjects in period 1 | Cohort 4 |
|---------------------------------------|----------|
| Started | 22 |
| Completed | 20 |
| Not completed | 2 |
| Consent withdrawn by subject | 1 |
| Adverse event, non-fatal | 1 |

Baseline characteristics

Reporting groups

| | |
|---|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: | |
| Monthly administration of Lucentis 0.5 mg followed 2 days later by Zimura 4mg | |
| Reporting group title | Cohort 2 |
| Reporting group description: | |
| Monthly administration of Zimura 2mg + Lucentis 0.5 mg administered (given on the same day) | |
| Reporting group title | Cohort 3 |
| Reporting group description: | |
| Zimura 2mg + Lucentis 0.5 mg | |
| Induction Phase (Day 1 - Month 2): Monthly administration of Zimura 2mg + Lucentis 0.5 mg given on the same day followed 14 days later with Zimura 2mg (Total: 6 doses of Zimura & 3 doses of Lucentis) | |
| Maintenance Phase (Month 3-5): Monthly administration of Zimura 2mg + Lucentis 0.5mg given on the same day (Total: 3 doses of Zimura and 3 doses of Lucentis) | |
| Reporting group title | Cohort 4 |
| Reporting group description: | |
| Zimura 2mg + Lucentis 0.5 mg | |
| Induction Phase (Day 1 - Month 2): Monthly administration of Zimura 2mg + Lucentis 0.5 mg given on the same day followed 14 days later with Zimura 2mg (Total: 6 doses of Zimura & 3 doses Lucentis) | |
| Maintenance Phase (Month 3-5): Monthly administration of Zimura 2mg followed 2 days later by Zimura 2mg + Lucentis 0.5mg (Total: 6 doses of Zimura & 3 doses Lucentis) | |

| Reporting group values | Cohort 1 | Cohort 2 | Cohort 3 |
|----------------------------------|----------|----------|----------|
| Number of subjects | 10 | 10 | 22 |
| Age categorical | | | |
| Units: Subjects | | | |
| ≤ 18 years | 0 | 0 | 0 |
| 18-64 years | 2 | 0 | 2 |
| ≥ 65 years | 8 | 10 | 20 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 73.7 | 77.9 | 74.1 |
| standard deviation | ± 11.27 | ± 6.62 | ± 7.41 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 8 | 14 |
| Male | 6 | 2 | 8 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 0 | 0 | 1 |
| Not Hispanic or Latino | 10 | 10 | 21 |
| Unknown or Not Reported | 0 | 0 | 0 |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 |

| | | | |
|---|-------|-------|-------|
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 0 | 0 | 0 |
| White | 10 | 10 | 22 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 0 | 0 | 0 |
| ETDRS Visual Acuity - Study Eye | | | |
| Units: Number of letters read | | | |
| arithmetic mean | 53.9 | 51.5 | 52.5 |
| standard deviation | ± 9.0 | ± 5.4 | ± 9.4 |

| | | | |
|---|----------|-------|--|
| Reporting group values | Cohort 4 | Total | |
| Number of subjects | 22 | 64 | |
| Age categorical | | | |
| Units: Subjects | | | |
| ≤ 18 years | 0 | 0 | |
| 18-64 years | 1 | 5 | |
| ≥ 65 years | 21 | 59 | |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 78.1 | - | |
| standard deviation | ± 7.40 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 12 | 38 | |
| Male | 10 | 26 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 2 | |
| Not Hispanic or Latino | 21 | 62 | |
| Unknown or Not Reported | 0 | 0 | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Black or African American | 0 | 0 | |
| White | 22 | 64 | |
| More than one race | 0 | 0 | |
| Unknown or Not Reported | 0 | 0 | |
| ETDRS Visual Acuity - Study Eye | | | |
| Units: Number of letters read | | | |
| arithmetic mean | 53.2 | - | |
| standard deviation | ± 9.9 | - | |

End points

End points reporting groups

| | |
|---|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: Monthly administration of Lucentis 0.5 mg followed 2 days later by Zimura 4mg | |
| Reporting group title | Cohort 2 |
| Reporting group description: Monthly administration of Zimura 2mg + Lucentis 0.5 mg administered (given on the same day) | |
| Reporting group title | Cohort 3 |
| Reporting group description: Zimura 2mg + Lucentis 0.5 mg | |
| Induction Phase (Day 1 - Month 2): Monthly administration of Zimura 2mg + Lucentis 0.5 mg given on the same day followed 14 days later with Zimura 2mg (Total: 6 doses of Zimura & 3 doses of Lucentis) | |
| Maintenance Phase (Month 3-5): Monthly administration of Zimura 2mg + Lucentis 0.5mg given on the same day (Total: 3 doses of Zimura and 3 doses of Lucentis) | |
| Reporting group title | Cohort 4 |
| Reporting group description: Zimura 2mg + Lucentis 0.5 mg | |
| Induction Phase (Day 1 - Month 2): Monthly administration of Zimura 2mg + Lucentis 0.5 mg given on the same day followed 14 days later with Zimura 2mg (Total: 6 doses of Zimura & 3 doses Lucentis) | |
| Maintenance Phase (Month 3-5): Monthly administration of Zimura 2mg followed 2 days later by Zimura 2mg + Lucentis 0.5mg (Total: 6 doses of Zimura & 3 doses Lucentis) | |

Primary: Systemic Adverse Events

| | |
|---|--|
| End point title | Systemic Adverse Events ^[1] |
| End point description: Number of subjects with systemic treatment-emergent Adverse Events (with calculated percentage) | |
| End point type | Primary |
| End point timeframe: 6 months | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was a safety study and no formal hypothesis testing was performed.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|-----------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 10 | 22 | 22 |
| Units: subjects | | | | |
| all causalities (subjects) | 6 | 5 | 5 | 11 |
| all causalities (%) | 60 | 50 | 23 | 50 |
| related to study drugs (subjects) | 0 | 0 | 0 | 0 |
| related to study drugs (%) | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Ophthalmic Adverse Events

End point title Ophthalmic Adverse Events^[2]

End point description:

Number of subjects with ophthalmic Adverse Events (with calculated percentage)

End point type Primary

End point timeframe:

6 months

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: This was a safety study and no formal hypothesis testing was performed.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 10 | 22 | 22 |
| Units: subjects | | | | |
| all causalities - study eye (subjects) | 8 | 4 | 11 | 15 |
| all causalities - study eye (%) | 80 | 40 | 50 | 68 |
| all causalities - fellow eye (subjects) | 1 | 1 | 0 | 2 |
| all causalities - fellow eye (%) | 10 | 10 | 0 | 9 |
| related to inject procedure - study eye (subjects) | 8 | 4 | 10 | 12 |
| related to inject procedure - study eye (%) | 80 | 40 | 45 | 55 |
| related to inject procedure - fellow eye (subject) | 0 | 0 | 0 | 0 |
| related to inject procedure - fellow eye (%) | 0 | 0 | 0 | 0 |
| related to study drugs - study eye (subjects) | 0 | 0 | 0 | 0 |
| related to study drugs - study eye (%) | 0 | 0 | 0 | 0 |
| related to study drugs - fellow eye (subjects) | 0 | 0 | 0 | 0 |
| related to study drugs - fellow eye (%) | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Change from baseline - ECG

End point title Change from baseline - ECG

End point description:

Number of patients with a change in ECG parameters from Baseline to Month 6

End point type Other pre-specified

End point timeframe:

6 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 10 | 22 | 22 |
| Units: subjects | | | | |
| No change (subjects) | 7 | 5 | 18 | 12 |
| No change (%) | 70 | 50 | 82 | 55 |
| Not Clinically Significant Change (subjects) | 3 | 5 | 3 | 6 |
| Not Clinically Significant Change (%) | 30 | 50 | 14 | 27 |
| Clinically Significant Change (subjects) | 0 | 0 | 0 | 1 |
| Clinically Significant Change (%) | 0 | 0 | 0 | 5 |
| Missing (subjects) | 0 | 0 | 1 | 3 |
| Missing (%) | 0 | 0 | 5 | 14 |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change from Baseline - Study Eye ETDRS Visual Acuity

| | |
|-----------------|---|
| End point title | Mean Change from Baseline - Study Eye ETDRS Visual Acuity |
|-----------------|---|

End point description:

Mean change from Baseline to Month 6 in the number of letters read by the study eye using the ETDRS Visual Acuity charts. Higher ETDRS letters represents better vision and a larger change in ETDRS letters represents better functioning.

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

End point timeframe:

6 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 10 | 22 | 22 |
| Units: number of letters read | | | | |
| arithmetic mean (standard deviation) | 9.0 (± 11.0) | 10.2 (± 18.7) | 10.7 (± 10.3) | 9.9 (± 8.2) |

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Mean Change from Baseline - Vital Signs

| | |
|-----------------|---|
| End point title | Mean Change from Baseline - Vital Signs |
|-----------------|---|

End point description:

Mean change from Baseline to Month 6 in the following parameters: Pulse (beats/minute), blood pressure (mmHg), and respiration rate (breaths/minute)

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

End point timeframe:

6 months

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 10 | 10 | 22 | 22 |
| Units: units | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pulse (beats/min) | -5.2 (± 5.92) | -2.0 (± 6.77) | 0.7 (± 11.22) | 0.1 (± 6.75) |
| Systolic blood pressure (mmHg) | -12.0 (± 15.04) | 0.7 (± 8.92) | -1.9 (± 14.92) | -5.8 (± 18.24) |
| Diastolic blood pressure (mmHg) | -3.2 (± 7.93) | -7.9 (± 12.32) | -4.7 (± 11.83) | -0.4 (± 8.24) |
| Respiration rate (breaths/min) | 0.6 (± 1.35) | -2.0 (± 3.77) | -1.0 (± 2.01) | -0.2 (± 2.31) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From start of treatment until Month 6 (end of study)

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 21.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 2 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 3 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 4 |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------------|-----------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 22 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 22 (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 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 22 (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 |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 22 (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 |

| | | | |
|---|----------------|--|--|
| Serious adverse events | Cohort 4 | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 22 (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 | Cohort 1 | Cohort 2 | Cohort 3 |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 10 / 10 (100.00%) | 7 / 10 (70.00%) | 10 / 22 (45.45%) |
| Investigations | | | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | 0 / 10 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 2 | 0 | 1 |
| Contusion | | | |

| | | | |
|---|-----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Corneal abrasion subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Laceration subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Vascular disorders Hypertension subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Nervous system disorders Syncope subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 10 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Eye disorders Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 6 / 10 (60.00%) 14 | 1 / 10 (10.00%) 1 | 5 / 22 (22.73%) 6 |
| Vitreous floaters subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 0 / 10 (0.00%) 0 | 3 / 22 (13.64%) 3 |
| Conjunctival hyperaemia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 1 / 10 (10.00%) 1 | 1 / 22 (4.55%) 1 |
| Punctate keratitis subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | 1 / 10 (10.00%) 1 | 1 / 22 (4.55%) 1 |
| Eye pain subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 3 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Corneal oedema subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Ocular discomfort | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 0 | 1 |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 0 | 1 | 2 |
| Cataract | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 0 | 1 |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Visual impairment | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Neovascular age-related macular degeneration | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Subretinal fibrosis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vitreous opacities | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | 1 / 10 (10.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |

| | | | |
|--|----------------------|----------------------|---------------------|
| subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Hiatus hernia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Rash subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Urticaria subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Psychiatric disorders Anxiety subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 2 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Herpes zoster subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Tooth infection subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | 1 / 10 (10.00%) 1 | 0 / 22 (0.00%) 0 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | 0 / 10 (0.00%) 0 | 0 / 22 (0.00%) 0 |

| | | | |
|------------------------------------|-----------------|----------------|----------------|
| Metabolism and nutrition disorders | | | |
| Vitamin B complex deficiency | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | 0 / 10 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| Non-serious adverse events | Cohort 4 | | |
|---|------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 22 (59.09%) | | |
| Investigations | | | |
| Intraocular pressure increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 2 | | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Contusion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Corneal abrasion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Laceration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Nervous system disorders | | | |
| Syncope | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye disorders | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 6 / 22 (27.27%) | | |
| occurrences (all) | 12 | | |
| Vitreous floaters | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 3 | | |
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 5 | | |
| Punctate keratitis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 2 | | |
| Eye pain | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | | |
| occurrences (all) | 6 | | |
| Corneal oedema | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 3 | | |
| Ocular discomfort | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Vitreous detachment | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |
| Lacrimation increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | | |
| occurrences (all) | 1 | | |

| | | | |
|---|----------------|--|--|
| Visual impairment | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | | |
| occurrences (all) | 2 | | |
| Neovascular age-related macular degeneration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Retinal artery occlusion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Subretinal fibrosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vitreous opacities | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hiatus hernia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urticaria | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Anxiety | | | |

| | | | |
|--|---|--|--|
| subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | | |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) Upper respiratory tract infection subjects affected / exposed occurrences (all) Herpes zoster subjects affected / exposed occurrences (all) Tooth infection subjects affected / exposed occurrences (all) Urinary tract infection subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 1 / 22 (4.55%) 1 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 | | |
| Metabolism and nutrition disorders Vitamin B complex deficiency subjects affected / exposed occurrences (all) Vitamin D deficiency subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 0 / 22 (0.00%) 0 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported