



## Clinical trial results:

**A randomized, double-masked, 48-week, parallel group, placebo-controlled, proof of concept study to investigate the efficacy and safety of RG7774 in patients with diabetes mellitus Type 1 or Type 2 with treatment naive diabetic retinopathy**

### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2019-002067-10 |
| Trial protocol           | GB SK PL       |
| Global end of trial date | 19 July 2023   |

### Results information

|                                |                |
|--------------------------------|----------------|
| Result version number          | v1 (current)   |
| This version publication date  | 01 August 2024 |
| First version publication date | 01 August 2024 |

### Trial information

#### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | BP41321 |
|-----------------------|---------|

#### Additional study identifiers

|                                    |                   |
|------------------------------------|-------------------|
| ISRCTN number                      | -                 |
| ClinicalTrials.gov id (NCT number) | NCT04265261       |
| WHO universal trial number (UTN)   | -                 |
| Other trial identifiers            | CANBERRA: BP41321 |

Notes:

### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | F. Hoffmann-La Roche AG   |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, 4058   |
| Public contact               | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com |
| Scientific contact           | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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                       | 28 September 2023 |
| Is this the analysis of the primary completion data? | No                |

|                                  |              |
|----------------------------------|--------------|
| Global end of trial reached?     | Yes          |
| Global end of trial date         | 19 July 2023 |
| Was the trial ended prematurely? | No           |

Notes:

## General information about the trial

Main objective of the trial:

To assess the safety, tolerability, and effect of oral administration of RG7774 on the severity of diabetic retinopathy (DR) in participants with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) and good vision

Protection of trial subjects:

All participants were required to sign an Informed Consent Form

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 05 June 2020 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 2       |
| Country: Number of subjects enrolled | Spain: 9           |
| Country: Number of subjects enrolled | United Kingdom: 10 |
| Country: Number of subjects enrolled | Poland: 10         |
| Country: Number of subjects enrolled | Slovakia: 1        |
| Country: Number of subjects enrolled | United States: 107 |
| Worldwide total number of subjects   | 139                |
| EEA total number of subjects         | 20                 |

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) | 109 |
| From 65 to 84 years  | 30  |
| 85 years and over    | 0   |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Participants with diabetes mellitus Type 1 or 2 with treatment-naïve diabetic retinopathy

### Period 1

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

### Arms

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

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Placebo |
|------------------|---------|

Arm description:

Participants received an oral dose of placebo matched to RG7774 once daily (QD)

|  |                    |
|--|--------------------|
| Arm type                               | Placebo            |
| Investigational medicinal product name | Placebo            |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received oral placebo once daily

|                  |                      |
|------------------|----------------------|
| <b>Arm title</b> | Vicasinabin 30 mg QD |
|------------------|----------------------|

Arm description:

Participants received 30 mg of oral RG7774 QD

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Vicasinabin        |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received 30 mg of oral vicasinabin once daily

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | Vicasinabin 200 mg QD |
|------------------|-----------------------|

Arm description:

Participants received 200 mg of oral RG7774 QD

|  |                    |
|--|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Vicasinabin        |
| Investigational medicinal product code |                    |
| Other name                             |                    |
| Pharmaceutical forms                   | Film-coated tablet |
| Routes of administration               | Oral use           |

Dosage and administration details:

Participants received 200 mg of oral vicasinabin once daily

| <b>Number of subjects in period 1</b> | Placebo | Vicasinabin 30 mg QD | Vicasinabin 200 mg QD |
|---------------------------------------|---------|----------------------|-----------------------|
| Started                               | 47      | 48                   | 44                    |
| Completed                             | 37      | 43                   | 36                    |
| Not completed                         | 10      | 5                    | 8                     |
| Adverse event, serious fatal          | 1       | -                    | -                     |
| Consent withdrawn by subject          | 2       | 1                    | 4                     |
| Physician decision                    | -       | -                    | 1                     |
| Non-Compliance with Study Drug        | 1       | 1                    | -                     |
| Adverse event, non-fatal              | 2       | -                    | -                     |
| Protocol Deviation                    | -       | 2                    | -                     |
| Lost to follow-up                     | 4       | 1                    | 3                     |

## Baseline characteristics

### Reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | Placebo               |
| Reporting group description:  |                       |
| Participants received an oral dose of placebo matched to RG7774 once daily (QD) |                       |
| Reporting group title   | Vicasinabin 30 mg QD  |
| Reporting group description:  |                       |
| Participants received 30 mg of oral RG7774 QD                                   |                       |
| Reporting group title   | Vicasinabin 200 mg QD |
| Reporting group description:  |                       |
| Participants received 200 mg of oral RG7774 QD                                  |                       |

| Reporting group values                    | Placebo | Vicasinabin 30 mg QD | Vicasinabin 200 mg QD |
|---|---------|----------------------|-----------------------|
| Number of subjects                        | 47      | 48                   | 44                    |
| Age categorical                           |         |                      |                       |
| Units: Subjects                           |         |                      |                       |
| Adults (18-64 years)                      | 35      | 39                   | 35                    |
| From 65-84 years                          | 12      | 9                    | 9                     |
| Age Continuous                            |         |                      |                       |
| Units: Years                              |         |                      |                       |
| arithmetic mean                           | 58.9    | 57.3                 | 56.5                  |
| standard deviation                        | ± 9.3   | ± 10.0               | ± 10.5                |
| Sex: Female, Male                         |         |                      |                       |
| Units: Participants                       |         |                      |                       |
| Female                                    | 17      | 18                   | 16                    |
| Male                                      | 30      | 30                   | 28                    |
| Ethnicity (NIH/OMB)                       |         |                      |                       |
| Units: Subjects                           |         |                      |                       |
| Hispanic or Latino                        | 14      | 18                   | 15                    |
| Not Hispanic or Latino                    | 32      | 30                   | 29                    |
| Unknown or Not Reported                   | 1       | 0                    | 0                     |
| Race (NIH/OMB)                            |         |                      |                       |
| Units: Subjects                           |         |                      |                       |
| American Indian or Alaska Native          | 0       | 0                    | 0                     |
| Asian                                     | 2       | 2                    | 3                     |
| Native Hawaiian or Other Pacific Islander | 0       | 0                    | 0                     |
| Black or African American                 | 5       | 0                    | 4                     |
| White                                     | 40      | 46                   | 35                    |
| More than one race                        | 0       | 0                    | 0                     |
| Unknown or Not Reported                   | 0       | 0                    | 2                     |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 139   |  |  |
| Age categorical        |       |  |  |
| Units: Subjects        |       |  |  |
| Adults (18-64 years)   | 109   |  |  |
| From 65-84 years       | 30    |  |  |

|   |     |  |  |
|---|-----|--|--|
| Age Continuous<br>Units: Years<br>arithmetic mean<br>standard deviation | -   |  |  |
| Sex: Female, Male<br>Units: Participants                                |     |  |  |
| Female  | 51  |  |  |
| Male  | 88  |  |  |
| Ethnicity (NIH/OMB)<br>Units: Subjects                                  |     |  |  |
| Hispanic or Latino  | 47  |  |  |
| Not Hispanic or Latino  | 91  |  |  |
| Unknown or Not Reported   | 1   |  |  |
| Race (NIH/OMB)<br>Units: Subjects                                       |     |  |  |
| American Indian or Alaska Native  | 0   |  |  |
| Asian   | 7   |  |  |
| Native Hawaiian or Other Pacific Islander                               | 0   |  |  |
| Black or African American   | 9   |  |  |
| White   | 121 |  |  |
| More than one race  | 0   |  |  |
| Unknown or Not Reported   | 2   |  |  |

## End points

### End points reporting groups

|   |                       |
|---|-----------------------|
| Reporting group title   | Placebo               |
| Reporting group description:  |                       |
| Participants received an oral dose of placebo matched to RG7774 once daily (QD) |                       |
| Reporting group title   | Vicasinabin 30 mg QD  |
| Reporting group description:  |                       |
| Participants received 30 mg of oral RG7774 QD                                   |                       |
| Reporting group title   | Vicasinabin 200 mg QD |
| Reporting group description:  |                       |
| Participants received 200 mg of oral RG7774 QD                                  |                       |

### Primary: Proportion of Participants with $\geq$ 2-Step Improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS) from Baseline at Week 36 Measured in the Study Eye

|   |   |
|---|---|
| End point title   | Proportion of Participants with $\geq$ 2-Step Improvement in the Early Treatment Diabetic Retinopathy Study (ETDRS) DR Severity Scale (DRSS) from Baseline at Week 36 Measured in the Study Eye |
| End point description:  |   |
| The ETDRS DRSS is a standardized grading test to measure diabetic retinopathy progression, where higher scores indicate a higher risk of vision loss. The DRSS ranges from level 10 (no diabetic retinopathy) to level 85 (advanced diabetic retinopathy) |   |
| End point type  | Primary   |
| End point timeframe:  |   |
| Week 36   |   |

| End point values                 | Placebo             | Vicasinabin 30 mg QD | Vicasinabin 200 mg QD |  |
|----------------------------------|---------------------|----------------------|-----------------------|--|
| Subject group type               | Reporting group     | Reporting group      | Reporting group       |  |
| Number of subjects analysed      | 38                  | 42                   | 35                    |  |
| Units: Percentage                |                     |                      |                       |  |
| number (confidence interval 95%) | 7.89 (2.72 to 20.8) | 9.52 (3.77 to 22.07) | 5.71 (1.58 to 18.61)  |  |

### Statistical analyses

|                            |                                |
|----------------------------|--------------------------------|
| Statistical analysis title | Placebo vs Vicasinabin 30 mg   |
| Comparison groups          | Placebo v Vicasinabin 30 mg QD |



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 80                      |
| Analysis specification                  | Pre-specified           |
| Analysis type                           |                         |
| P-value                                 | = 0.8586                |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Risk difference (RD)    |
| Point estimate                          | 1.19                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | -11.86                  |
| upper limit                             | 14.23                   |

|   |                                 |
|---|---------------------------------|
| <b>Statistical analysis title</b>       | Placebo vs Vicasinabin 200 mg   |
| Comparison groups                       | Placebo v Vicasinabin 200 mg QD |
| Number of subjects included in analysis | 73                              |
| Analysis specification                  | Pre-specified                   |
| Analysis type                           |                                 |
| P-value                                 | = 0.6388                        |
| Method                                  | Cochran-Mantel-Haenszel         |
| Parameter estimate                      | Risk difference (RD)            |
| Point estimate                          | -2.93                           |
| Confidence interval                     |                                 |
| level                                   | 95 %                            |
| sides                                   | 2-sided                         |
| lower limit                             | -15.18                          |
| upper limit                             | 9.31                            |

### Primary: Percentage of Participants with Adverse Events (AEs)

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with Adverse Events (AEs) <sup>[1]</sup> |
|-----------------|---|

End point description:

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

End point timeframe:

Up to 1 year (baseline through follow-up period)

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: There was no formal statistical analyses deemed necessary for this endpoint.

| End point values                  | Placebo         | Vicasinabin 30 mg QD | Vicasinabin 200 mg QD |  |
|-----------------------------------|-----------------|----------------------|-----------------------|--|
| Subject group type                | Reporting group | Reporting group      | Reporting group       |  |
| Number of subjects analysed       | 47              | 48                   | 43                    |  |
| Units: Percentage of participants |                 |                      |                       |  |
| number (not applicable)           | 72.3            | 64.6                 | 81.4                  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Time-to-Event for Vision-Threatening DR in the Study Eye

|                 |  |
|-----------------|--|
| End point title | Time-to-Event for Vision-Threatening DR in the Study Eye |
|-----------------|--|

End point description:

Vision-threatening DR was defined as anterior segment neovascularization (ASNV), new proliferative diabetic retinopathy (PDR), new diabetic macular edema (DME), and pre-existing DME requiring treatment. Time-to-event was defined as the time where 50% of the population develops a DR vision-threatening event.

9999 indicates that either the Kaplan-Meier percentile time has not been achieved or that the percentile is at a boundary of the observed range and no upper or lower 95% CI can be found.

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

End point timeframe:

Up to Day 277

| End point values                 | Placebo              | Vicasinabin 30 mg QD  | Vicasinabin 200 mg QD |  |
|----------------------------------|----------------------|-----------------------|-----------------------|--|
| Subject group type               | Reporting group      | Reporting group       | Reporting group       |  |
| Number of subjects analysed      | 47                   | 48                    | 43                    |  |
| Units: Days                      |                      |                       |                       |  |
| number (confidence interval 95%) | 9999 (257.0 to 9999) | 267.0 (254.0 to 9999) | 9999 (260.0 to 9999)  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Incidence of new Anterior Segment Neovascularization (ASNV), new Proliferative Diabetic Retinopathy (PDR), new Diabetic Macular Edema (DME), and Pre-Existing DME Requiring Intervention in the Study Eye

|                 |   |
|-----------------|---|
| End point title | Incidence of new Anterior Segment Neovascularization (ASNV), new Proliferative Diabetic Retinopathy (PDR), new Diabetic Macular Edema (DME), and Pre-Existing DME Requiring Intervention in the Study Eye |
|-----------------|---|

End point description:

This is a descriptive summary of the incidence of new ASNV, new PDR, and both new and pre-existing DME, all of which indicate disease progression.

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

End point timeframe:

Week 36

| End point values                     | Placebo           | Vicasinabin 30 mg QD | Vicasinabin 200 mg QD |  |
|--------------------------------------|-------------------|----------------------|-----------------------|--|
| Subject group type                   | Reporting group   | Reporting group      | Reporting group       |  |
| Number of subjects analysed          | 47                | 48                   | 43                    |  |
| Units: Percentage of participants    |                   |                      |                       |  |
| number (confidence interval 95%)     |                   |                      |                       |  |
| New ASNV                             | 0 (0.0 to 9.4)    | 0 (0.0 to 9.2)       | 0 (0.0 to 10.2)       |  |
| New PDR                              | 0 (0.0 to 9.4)    | 6.3 (1.6 to 18.2)    | 0 (0.0 to 10.2)       |  |
| New DME                              | 0 (0.0 to 9.4)    | 4.2 (0.7 to 15.4)    | 0 (0.0 to 10.2)       |  |
| Pre-existing DME requiring treatment | 4.3 (0.7 to 15.7) | 10.4 (3.9 to 23.4)   | 6.8 (1.8 to 20.1)     |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Change from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye at Week 36

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Best Corrected Visual Acuity (BCVA) in the Study Eye at Week 36 |
|-----------------|---|

End point description:

BCVA was measured by a qualified VA examiner prior to pupil dilation using modified ETDRS Charts 1, 2, and R. The adjusted mean is reported for each group.

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

End point timeframe:

Baseline; Week 36

| End point values                 | Placebo             | Vicasinabin 30 mg QD | Vicasinabin 200 mg QD |  |
|----------------------------------|---------------------|----------------------|-----------------------|--|
| Subject group type               | Reporting group     | Reporting group      | Reporting group       |  |
| Number of subjects analysed      | 47                  | 48                   | 43                    |  |
| Units: Number of letters         |                     |                      |                       |  |
| arithmetic mean (standard error) | 0.12 ( $\pm$ 0.747) | -0.45 ( $\pm$ 0.697) | -0.22 ( $\pm$ 0.744)  |  |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Approximately 3 years

Adverse event reporting additional description:

All-cause mortality includes the entire study population.

SAE and NSAE reporting includes the safety population, which included all participants who gave informed consent and received at least one dose of study medication. Participants in the safety population were grouped according to the actual treatment received.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 26.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Participants received an oral dose of placebo matched to RG7774 once daily (QD)

|                       |                       |
|-----------------------|-----------------------|
| Reporting group title | Vicasinabin 200 mg QD |
|-----------------------|-----------------------|

Reporting group description:

Participants received 200 mg of oral RG7774 QD

|                       |                      |
|-----------------------|----------------------|
| Reporting group title | Vicasinabin 30 mg QD |
|-----------------------|----------------------|

Reporting group description:

Participants received 30 mg of oral RG7774 QD

| Serious adverse events                            | Placebo         | Vicasinabin 200 mg QD | Vicasinabin 30 mg QD |
|---|-----------------|-----------------------|----------------------|
| Total subjects affected by serious adverse events |                 |                       |                      |
| subjects affected / exposed                       | 8 / 47 (17.02%) | 5 / 43 (11.63%)       | 3 / 48 (6.25%)       |
| number of deaths (all causes)                     | 1               | 0                     | 0                    |
| number of deaths resulting from adverse events    | 0               | 0                     | 0                    |
| Vascular disorders                                |                 |                       |                      |
| Intermittent claudication                         |                 |                       |                      |
| subjects affected / exposed                       | 1 / 47 (2.13%)  | 0 / 43 (0.00%)        | 0 / 48 (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 disorders                                 |                 |                       |                      |
| Coronary artery disease                           |                 |                       |                      |
| subjects affected / exposed                       | 0 / 47 (0.00%)  | 1 / 43 (2.33%)        | 0 / 48 (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                |
| Atrioventricular block second degree              |                 |                       |                      |

|  |                |                |                |
|--|----------------|----------------|----------------|
| subjects affected / exposed                          | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| General disorders and administration site conditions |                |                |                |
| Chest pain   |                |                |                |
| subjects affected / exposed                          | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| Immune system disorders                              |                |                |                |
| Anaphylactic reaction                                |                |                |                |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 1 / 43 (2.33%) | 0 / 48 (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 tear   |                |                |                |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 1 / 43 (2.33%) | 0 / 48 (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          |
| Diabetic retinopathy                                 |                |                |                |
| subjects affected / exposed                          | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 2 / 48 (4.17%) |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0          | 0 / 2          |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0          | 0 / 0          |
| Gastrointestinal disorders                           |                |                |                |
| Pancreatitis   |                |                |                |
| subjects affected / exposed                          | 0 / 47 (0.00%) | 1 / 43 (2.33%) | 0 / 48 (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          |
| Reproductive system and breast disorders             |                |                |                |
| Endometrial hyperplasia                              |                |                |                |
| subjects affected / exposed                          | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| Hepatobiliary disorders                              |                |                |                |
| Biliary colic  |                |                |                |

|   |                |                |                |
|---|----------------|----------------|----------------|
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| Psychiatric disorders                           |                |                |                |
| Anxiety   |                |                |                |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 0 / 43 (0.00%) | 1 / 48 (2.08%) |
| occurrences causally related to treatment / all | 0 / 0          | 0 / 0          | 0 / 1          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |
| Infections and infestations                     |                |                |                |
| Osteomyelitis                                   |                |                |                |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 43 (2.33%) | 0 / 48 (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          |
| Sepsis  |                |                |                |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| Localised infection                             |                |                |                |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| Extradural abscess                              |                |                |                |
| subjects affected / exposed                     | 0 / 47 (0.00%) | 1 / 43 (2.33%) | 0 / 48 (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                                      |                |                |                |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 0 / 43 (0.00%) | 0 / 48 (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          |
| COVID-19  |                |                |                |
| subjects affected / exposed                     | 1 / 47 (2.13%) | 1 / 43 (2.33%) | 0 / 48 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 1          | 0 / 0          |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0          | 0 / 0          |

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

| <b>Non-serious adverse events</b>                     | Placebo          | Vicasinabin 200 mg QD | Vicasinabin 30 mg QD |
|---|------------------|-----------------------|----------------------|
| Total subjects affected by non-serious adverse events |                  |                       |                      |
| subjects affected / exposed                           | 13 / 47 (27.66%) | 15 / 43 (34.88%)      | 21 / 48 (43.75%)     |
| Vascular disorders                                    |                  |                       |                      |
| Hypertension  |                  |                       |                      |
| subjects affected / exposed                           | 2 / 47 (4.26%)   | 1 / 43 (2.33%)        | 3 / 48 (6.25%)       |
| occurrences (all)                                     | 2                | 1                     | 3                    |
| Nervous system disorders                              |                  |                       |                      |
| Headache  |                  |                       |                      |
| subjects affected / exposed                           | 3 / 47 (6.38%)   | 2 / 43 (4.65%)        | 2 / 48 (4.17%)       |
| occurrences (all)                                     | 5                | 2                     | 2                    |
| Eye disorders   |                  |                       |                      |
| Diabetic retinal oedema                               |                  |                       |                      |
| subjects affected / exposed                           | 3 / 47 (6.38%)   | 6 / 43 (13.95%)       | 8 / 48 (16.67%)      |
| occurrences (all)                                     | 3                | 7                     | 13                   |
| Diabetic retinopathy                                  |                  |                       |                      |
| subjects affected / exposed                           | 3 / 47 (6.38%)   | 1 / 43 (2.33%)        | 5 / 48 (10.42%)      |
| occurrences (all)                                     | 3                | 2                     | 5                    |
| Vitreous haemorrhage                                  |                  |                       |                      |
| subjects affected / exposed                           | 1 / 47 (2.13%)   | 2 / 43 (4.65%)        | 3 / 48 (6.25%)       |
| occurrences (all)                                     | 2                | 3                     | 3                    |
| Gastrointestinal disorders                            |                  |                       |                      |
| Constipation  |                  |                       |                      |
| subjects affected / exposed                           | 3 / 47 (6.38%)   | 0 / 43 (0.00%)        | 0 / 48 (0.00%)       |
| occurrences (all)                                     | 4                | 0                     | 0                    |
| Infections and infestations                           |                  |                       |                      |
| COVID-19  |                  |                       |                      |
| subjects affected / exposed                           | 1 / 47 (2.13%)   | 5 / 43 (11.63%)       | 3 / 48 (6.25%)       |
| occurrences (all)                                     | 1                | 5                     | 3                    |
| Nasopharyngitis                                       |                  |                       |                      |
| subjects affected / exposed                           | 1 / 47 (2.13%)   | 0 / 43 (0.00%)        | 3 / 48 (6.25%)       |
| occurrences (all)                                     | 4                | 0                     | 3                    |
| Metabolism and nutrition disorders                    |                  |                       |                      |
| Type 2 diabetes mellitus                              |                  |                       |                      |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 47 (2.13%) | 1 / 43 (2.33%) | 4 / 48 (8.33%) |
| occurrences (all)           | 1              | 1              | 4              |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 17 December 2019 | <ul style="list-style-type: none"><li>- The exploratory assessments of contrast sensitivity and visual field were clarified to only be required from sites with appropriate capabilities.</li><li>- An additional exploratory objective was added to explore the use of an advanced, artificial intelligence-based analytics tool to assess clinically relevant features.</li><li>- An inclusion criterion was removed for consistency with the exclusion criteria.</li><li>- It was clarified that the determination of natural progression of disease versus an adverse event (AE) was to be based upon Investigator opinion.</li></ul>  |
| 13 November 2020 | <ul style="list-style-type: none"><li>- Operational procedures on Day 1 assessment were clarified.</li><li>- An additional exploratory objective was added to explore potential effects of vicasinabin on glycemic status.</li><li>- Operational updates related to COVID-19 were implemented, including a new assessment.</li><li>- Clarifications and additional examples were added to both the inclusion and exclusion criteria.</li><li>- The screen failure process was clarified.</li><li>- Brolucizumab use was made to be an exception from permitted therapies and excluded as rescue treatment.</li><li>- Disease-related AEs were further defined; clarifications were made to the number of assessments needed in case of rescue treatments for disease-related events; and follow up for disease-related AEs was specifically delineated.</li><li>- Disease-related AEs (e.g., amputations, ulcers, diabetes-related surgery) and sight-threatening events (e.g., decrease of &gt; 30 letters in visual acuity [VA] score, severe intraocular inflammation) were added as Adverse Events of Special Interest (AESIs); sight-threatening events were added under the definition of serious adverse events (SAEs).</li><li>- Sample size and the efficacy analysis method were clarified, and a sensitivity analysis was added in case the amount of missing data exceeded 10% of all expected data.</li></ul> |
| 03 February 2021 | <ul style="list-style-type: none"><li>- An exclusion criterion regarding the location of an implantation of intraocular lens for the study eye was modified.</li><li>- COVID-19 positive participants were added to the exclusion criteria.</li><li>- The timing of additional visits for warfarin-taking participants was clarified.</li></ul>  |
| 15 June 2021     | <ul style="list-style-type: none"><li>- The number of assessments and duration of patient visits were reduced.</li><li>- Entry Criteria were modified to increase enrollment: an additional Diabetic Retinopathy Severity Scale (DRSS) rescreening was added, the glycosylated hemoglobin (HbA1c) threshold was increased to 12%, prior periocular pharmacological intervention was excluded, and participants without active hepatitis B virus or hepatitis C virus (HBC) and participants enrolled in other retinal/ovular clinical trials may be permitted in select circumstances.</li><li>- The screen failure process was modified to allow participants who had previously failed according to outdated inclusion/exclusion criteria.</li><li>- The process for evaluating ECG results was standardized.</li><li>- Missing data treatment and the assessment of related efficacy estimates was clarified to be detailed in an external technical document.</li></ul>  |

Notes:

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## **Interruptions (globally)**

Were there any global interruptions to the trial? No

## **Limitations and caveats**

None reported