



## Clinical trial results:

**A 6-month multicenter, randomized, double-masked phase IIIb-study comparing the efficacy and safety of Lucentis (ranibizumab) intravitreal injections versus Ozurdex (dexamethasone) intravitreal implant in patients with visual impairment due to macular edema following central retinal vein occlusion (CRVO)**

**Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.novfor> complete trial results.**

## Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2011-001020-38  |
| Trial protocol           | DE GB HU CZ PL  |
| Global end of trial date | 21 January 2014 |

## Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 15 July 2018 |
| First version publication date | 15 July 2018 |

## Trial information

### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | CRFB002EDE18 |
|-----------------------|--------------|

### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01396083 |
| WHO universal trial number (UTN)   | -           |

Notes:

## Sponsors

|                              |                                                               |
|------------------------------|---------------------------------------------------------------|
| Sponsor organisation name    | Novartis Pharma AG                                            |
| Sponsor organisation address | CH-4002, Basel, Switzerland,                                  |
| Public contact               | Cinical Disclosure Office, Novartis Pharma AG, 41 613241111 , |
| Scientific contact           | Cinical Disclosure Office, Novartis Pharma AG, 41 613241111 , |

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                                | No |

|                                |
|--------------------------------|
| 1901/2006 apply to this trial? |
|--------------------------------|

Notes:

### Results analysis stage

|                                                      |                 |
|------------------------------------------------------|-----------------|
| Analysis stage                                       | Final           |
| Date of interim/final analysis                       | 21 January 2014 |
| Is this the analysis of the primary completion data? | No              |
| Global end of trial reached?                         | Yes             |
| Global end of trial date                             | 21 January 2014 |
| Was the trial ended prematurely?                     | No              |

Notes:

### General information about the trial

Main objective of the trial:

The primary objective is to show that ranibizumab (administered in an individualized treatment regimen) has superior efficacy and safety compared to dexamethasone implant (Ozurdex®) over a 6 month period.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial. In addition, only one eye was chosen as the study eye. If both eyes were eligible, the eye with the worse VA as assessed at the baseline visit was selected for study treatment, unless, based on medical reasons, the investigator deemed the other eye to be more appropriate for study treatment. Only the study eye was treated with either of the study drugs.

Background therapy: -

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 15 June 2011 |
| 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: 9          |
| Country: Number of subjects enrolled | United Kingdom: 53 |
| Country: Number of subjects enrolled | Germany: 176       |
| Country: Number of subjects enrolled | Hungary: 5         |
| Worldwide total number of subjects   | 243                |
| EEA total number of subjects         | 243                |

Notes:

#### Subjects enrolled per age group

|                                        |   |
|----------------------------------------|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|                                          |     |
|------------------------------------------|-----|
| wk                                       |     |
| 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)                     | 104 |
| From 65 to 84 years                      | 124 |
| 85 years and over                        | 15  |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Three-hundred-twenty-five patients were screened for study eligibility at 66 German and European study sites while 82 patients failed screening (multiple reasons per patient were possible). In total, 243 patients were randomized.

### 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, Monitor, Data analyst, Assessor |

### Arms

|                              |             |
|------------------------------|-------------|
| Are arms mutually exclusive? | Yes         |
| <b>Arm title</b>             | Ranibizumab |

Arm description:

Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.

|                                        |                  |
|----------------------------------------|------------------|
| Arm type                               | Experimental     |
| Investigational medicinal product name | Ranibizumab      |
| Investigational medicinal product code | RFB002           |
| Other name                             |                  |
| Pharmaceutical forms                   | Injection        |
| Routes of administration               | Intravitreal use |

Dosage and administration details:

0.5 mg/0.05 ml solution to be injected intravitreally

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

Arm description:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.

|                                        |                   |
|----------------------------------------|-------------------|
| Arm type                               | Active comparator |
| Investigational medicinal product name | dexamethasone     |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intravitreal use  |

Dosage and administration details:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release (LAR) over 6 months) at baseline and sham-injections thereafter.

| <b>Number of subjects in period 1</b> | Ranibizumab | Dexamethasone |
|---------------------------------------|-------------|---------------|
| Started                               | 124         | 119           |
| Completed                             | 113         | 72            |
| Not completed                         | 11          | 47            |
| Abnormal laboratory value(s)          | 1           | -             |
| Consent withdrawn by subject          | 4           | 5             |
| Unsatisfactory therapeutic effect     | 2           | 13            |
| Administrative problems               | 1           | -             |
| Adverse Event(s)                      | 2           | 28            |
| Lost to follow-up                     | 1           | -             |
| Protocol deviation                    | -           | 1             |

## Baseline characteristics

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Ranibizumab |
|-----------------------|-------------|

Reporting group description:

Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.

|                       |               |
|-----------------------|---------------|
| Reporting group title | Dexamethasone |
|-----------------------|---------------|

Reporting group description:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.

| Reporting group values                                                                                                                          | Ranibizumab | Dexamethasone | Total |
|-------------------------------------------------------------------------------------------------------------------------------------------------|-------------|---------------|-------|
| Number of subjects                                                                                                                              | 124         | 119           | 243   |
| Age categorical                                                                                                                                 |             |               |       |
| Units: Subjects                                                                                                                                 |             |               |       |
| ≤65 years                                                                                                                                       | 59          | 52            | 111   |
| >65 years                                                                                                                                       | 65          | 67            | 132   |
| Age continuous                                                                                                                                  |             |               |       |
| The EMA result system autopopulates the "-" and will not allow the entry of the mean age for the trial, which is 66.1 (standard deviation 11.9) |             |               |       |
| Units: years                                                                                                                                    |             |               |       |
| arithmetic mean                                                                                                                                 | 65.3        | 66.9          |       |
| standard deviation                                                                                                                              | ± 11.4      | ± 12.4        | -     |
| Gender categorical                                                                                                                              |             |               |       |
| Units: Subjects                                                                                                                                 |             |               |       |
| Female                                                                                                                                          | 52          | 46            | 98    |
| Male                                                                                                                                            | 72          | 73            | 145   |

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |               |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------|
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Ranibizumab   |
| Reporting group description:<br>Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment. |               |
| Reporting group title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        | Dexamethasone |
| Reporting group description:<br>Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.                                                                                                                                                                                                                                                                                                                                    |               |

### Primary: Mean Average best corrected visual acuity (BCVA) Change From Month 1 Through Month 6 to Baseline

|                                                                                                                                                                                                                                                                                                                                  |                                                                                                  |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                  | Mean Average best corrected visual acuity (BCVA) Change From Month 1 Through Month 6 to Baseline |
| End point description:<br>BCVA score was based on the number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart assessed at a starting distance of 4 meters. An ETDRS visual acuity score of 85 is approximately 20/20. An increased score indicates improvement in acuity. |                                                                                                  |
| End point type                                                                                                                                                                                                                                                                                                                   | Primary                                                                                          |
| End point timeframe:<br>The average of the changes in BCVA (letters) from baseline to any post-baseline visit, i.e. the mean of six differences to baseline for the six post-baseline visits at Month 1 to 6.                                                                                                                    |                                                                                                  |

| End point values                             | Ranibizumab            | Dexamethasone       |  |  |
|----------------------------------------------|------------------------|---------------------|--|--|
| Subject group type                           | Reporting group        | Reporting group     |  |  |
| Number of subjects analysed                  | 124 <sup>[1]</sup>     | 119 <sup>[2]</sup>  |  |  |
| Units: letters                               |                        |                     |  |  |
| least squares mean (confidence interval 95%) | 12.86 (10.24 to 15.48) | 2.96 (0.27 to 5.64) |  |  |

Notes:

[1] - Full analysis set , Last observation carried forward (LOCF)

[2] - Full analysis set, Last observation carried forward (LOCF)

### Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                             |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Statistical analysis title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Full Analysis Set           |
| Statistical analysis description:<br>The Full Analysis Set consisted of all patients from the Randomized Set who had received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned. The null-hypothesis to be rejected was that there is no difference in the change of BCVA (letters), averaged over all post-baseline visits, between patients under ranibizumab and those under dexamethasone. |                             |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Ranibizumab v Dexamethasone |

|                                         |                            |
|-----------------------------------------|----------------------------|
| Number of subjects included in analysis | 243                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | < 0.0001                   |
| Method                                  | ANCOVA                     |
| Parameter estimate                      | Mean difference (net)      |
| Point estimate                          | 9.91                       |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 6.51                       |
| upper limit                             | 13.3                       |

Notes:

[3] - The primary analysis was performed by an analysis of covariance (ANCOVA) model with average change in BCVA (letters) from Visit 1 through Visit 6 as dependent variable, and with the factors center, treatment, and covariate baseline BCVA as predictors.

### Secondary: Mean BCVA Change at Month 6

|                                                                                                                                                                                                                                                                                                                                                                         |                             |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                         | Mean BCVA Change at Month 6 |
| End point description:                                                                                                                                                                                                                                                                                                                                                  |                             |
| To compare the mean BCVA change at Month 6 from Baseline in patients treated with dexamethasone versus ranibizumab. The analysis was performed by an analysis of covariance (ANCOVA) model with average change in BCVA (letters) from Visit 1 through Visit 6 as dependent variable, and with the factors center, treatment, and covariate baseline BCVA as predictors. |                             |
| End point type                                                                                                                                                                                                                                                                                                                                                          | Secondary                   |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                    |                             |
| Baseline, month 6                                                                                                                                                                                                                                                                                                                                                       |                             |

| End point values                             | Ranibizumab            | Dexamethasone        |  |  |
|----------------------------------------------|------------------------|----------------------|--|--|
| Subject group type                           | Reporting group        | Reporting group      |  |  |
| Number of subjects analysed                  | 124                    | 119                  |  |  |
| Units: letters                               |                        |                      |  |  |
| least squares mean (confidence interval 95%) | 14.78 (11.24 to 18.32) | -3.17 (-6.8 to 0.46) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Patients Gaining / Losing ≥ 15 / 10 / 5 Letters

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                                           |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Number of Patients Gaining / Losing ≥ 15 / 10 / 5 Letters |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                           |
| BCVA score was based on the number of letters read correctly on the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart assessed at a starting distance of 4 meters. An ETDRS visual acuity score of 85 is approximately 20/20. An increased score indicates improvement in acuity. This outcome assessed the number of participants who gained 15, 10 or 5 more letters of visual acuity at month 6 as compared with baseline. This analysis is done on the full analysis set (FAS) which consisted of all patients from the Randomized Set (RS) who had received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat |                                                           |

principle, patients were analyzed according to the treatment assigned.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, 6 months   |           |

| End point values            | Ranibizumab        | Dexamethasone      |  |  |
|-----------------------------|--------------------|--------------------|--|--|
| Subject group type          | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed | 124 <sup>[4]</sup> | 119 <sup>[5]</sup> |  |  |
| Units: patients             |                    |                    |  |  |
| Gain ≥ 15 letters           | 73                 | 22                 |  |  |
| Loss of ≥ 15 letters        | 1                  | 31                 |  |  |
| Gain ≥ 10 letters           | 89                 | 38                 |  |  |
| Loss of ≥ 10 letters        | 4                  | 35                 |  |  |
| Gain ≥ 5 letters            | 104                | 54                 |  |  |
| Loss of ≥ 5 letters         | 5                  | 40                 |  |  |

Notes:

[4] - Full Analysis Set

[5] - Full Analysis Set

## Statistical analyses

No statistical analyses for this end point

## Secondary: Time to Achieve a Significant Improvement ≥ 15 Letters

|                 |                                                        |
|-----------------|--------------------------------------------------------|
| End point title | Time to Achieve a Significant Improvement ≥ 15 Letters |
|-----------------|--------------------------------------------------------|

End point description:

The time was analyzed by the Kaplan-Maier-Method, adjusting the calculation for dropouts. This was based on the full analysis set (FAS), which consisted of all patients from the Randomized Set (RS) who had received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analyzed according to the treatment assigned. For the dexamethasone treatment group, 99999.9 represents not applicable data because EudraCT system is not accepting "NA" for not available/not applicable data.

|                      |           |
|----------------------|-----------|
| End point type       | Secondary |
| End point timeframe: |           |
| Baseline, Month 6    |           |

| End point values                 | Ranibizumab     | Dexamethasone      |  |  |
|----------------------------------|-----------------|--------------------|--|--|
| Subject group type               | Reporting group | Reporting group    |  |  |
| Number of subjects analysed      | 124             | 119                |  |  |
| Units: Days                      |                 |                    |  |  |
| median (confidence interval 95%) | 62 (56 to 91)   | 98 (63 to 99999.9) |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change Over Time in BCVA (letters)

|                 |                                    |
|-----------------|------------------------------------|
| End point title | Change Over Time in BCVA (letters) |
|-----------------|------------------------------------|

End point description:

The analysis was performed by an analysis of covariance (ANCOVA) model with average change in BCVA (letters) from Visit 1 through Visit 6 as dependent variable, and with the factors center, treatment and covariate baseline BCVA as predictors, for the Full Analysis Set (FAS) and last observation carried forward (LOCF).

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

End point timeframe:

Baseline, month 6

| End point values                             | Ranibizumab            | Dexamethason<br>e     |  |  |
|----------------------------------------------|------------------------|-----------------------|--|--|
| Subject group type                           | Reporting group        | Reporting group       |  |  |
| Number of subjects analysed                  | 124                    | 119                   |  |  |
| Units: letters                               |                        |                       |  |  |
| least squares mean (confidence interval 95%) |                        |                       |  |  |
| Month 1                                      | 9.77 (7.27 to 12.27)   | 9.54 (6.98 to 12.1)   |  |  |
| Month 2                                      | 12.25 (9.59 to 14.91)  | 11.04 (8.31 to 13.76) |  |  |
| Month 3                                      | 14.04 (10.92 to 17.16) | 4.99 (1.79 to 8.18)   |  |  |
| Month 4                                      | 12.76 (9.48 to 16.04)  | -1.73 (-5.09 to 1.63) |  |  |
| Month 5                                      | 13.57 (10.25 to 16.89) | -2.92 (-6.33 to 0.48) |  |  |
| Month 6                                      | 14.78 (11.24 to 18.32) | -3.17 (-6.8 to 0.46)  |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Change Over Time of the Central Retinal Thickness (CRT)

|                 |                                                         |
|-----------------|---------------------------------------------------------|
| End point title | Change Over Time of the Central Retinal Thickness (CRT) |
|-----------------|---------------------------------------------------------|

End point description:

Retinal thickness was measured using Optical Coherence Tomography (OCT). Data presented are the course of CRT ( $\mu\text{m}$ ) over time from baseline to month 6, assessed by investigator (Full Analysis Set/Last Observation Carried Forward).

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

End point timeframe:

Baseline, month 6

| End point values                                  | Ranibizumab           | Dexamethason<br>e     |  |  |
|---------------------------------------------------|-----------------------|-----------------------|--|--|
| Subject group type                                | Reporting group       | Reporting group       |  |  |
| Number of subjects analysed                       | 124                   | 119                   |  |  |
| Units: $\mu\text{m}$                              |                       |                       |  |  |
| arithmetic mean (standard deviation)              |                       |                       |  |  |
| Change Over Time of the Central Retinal Thickness | -376.7 ( $\pm$ 274.9) | -168.7 ( $\pm$ 288.3) |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the Quality of Life According to the National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) Questionnaires

|                 |                                                                                                                                  |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|
| End point title | Changes in the Quality of Life According to the National Eye Institute Visual Function Questionnaire (NEI-VFQ 25) Questionnaires |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------|

End point description:

The VFQ-25 composite and subscale scores range from 0 to 100, a higher score indicating better functioning. The 12 subscales in the VFQ-25 are general health, general vision, ocular pain, near activities, distance activities, social function, mental health, role difficulties, dependency, driving, color vision, and peripheral vision. The scores on the subscales were added together for a total score, which ranged from 0 to 100. A higher score indicated improvement in quality of life due to vision function. An overall composite score can be calculated and is provided.

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

End point timeframe:

Composite score Baseline, 6 months

| End point values                        | Ranibizumab     | Dexamethason<br>e |  |  |
|-----------------------------------------|-----------------|-------------------|--|--|
| Subject group type                      | Reporting group | Reporting group   |  |  |
| Number of subjects analysed             | 121             | 118               |  |  |
| Units: Score on a scale                 |                 |                   |  |  |
| arithmetic mean (standard deviation)    |                 |                   |  |  |
| Changes in the NEI-VFQ 25 Questionnaire | 6 ( $\pm$ 12.1) | 2 ( $\pm$ 10.9)   |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the Quality of Life According to the Short Form (36) Health Survey (SF-36) Questionnaires

|                                                                                                                                          |                                                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                          | Changes in the Quality of Life According to the Short Form (36) Health Survey (SF-36) Questionnaires |
| End point description:<br>SF-36 summary measures are norm-based scores with mean = 50 and SD = 10. Higher scores indicate better health. |                                                                                                      |
| End point type                                                                                                                           | Secondary                                                                                            |
| End point timeframe:<br>Baseline, month 6                                                                                                |                                                                                                      |

| End point values                     | Ranibizumab     | Dexamethasone   |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 116             | 113             |  |  |
| Units: Units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| SF-36 physical component (n=116,113) | -0.7 (± 6.3)    | 0.4 (± 6.6)     |  |  |
| SF-36 mental component (n=116,113)   | 2.4 (± 8.7)     | 0.4 (± 9.2)     |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Changes in the Quality of Life According to Euro Quality of Life (EQ-5D) Questionnaires

|                                                                                                                                                  |                                                                                         |
|--------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| End point title                                                                                                                                  | Changes in the Quality of Life According to Euro Quality of Life (EQ-5D) Questionnaires |
| End point description:<br>The EQ-5D visual analog scale ranges from 0 to 100, 0 representing the worst and 100 the best imaginable health state. |                                                                                         |
| End point type                                                                                                                                   | Secondary                                                                               |
| End point timeframe:<br>Baseline, month 6                                                                                                        |                                                                                         |

| End point values                     | Ranibizumab     | Dexamethasone   |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 119             | 114             |  |  |
| Units: Units on a scale              |                 |                 |  |  |
| arithmetic mean (standard deviation) |                 |                 |  |  |
| Changes in QOL according to EQ-5D    | 0.1 (± 13.2)    | 2 (± 14.8)      |  |  |

### Statistical analyses

No statistical analyses for this end point

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**Secondary: Increase Rate of Intraocular Pressure (IOP): number of patients with  $\geq 10\%$  increase in IOP compared to baseline (safety set)**

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|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Increase Rate of Intraocular Pressure (IOP): number of patients with $\geq 10\%$ increase in IOP compared to baseline (safety set) |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The number of patients with  $\geq 10\%$  increase in Internal Ocular Pressure (IOP) compared to baseline at any post-baseline visit.

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

End point timeframe:

Baseline, month 6

| End point values            | Ranibizumab     | Dexamethasone   |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 124             | 119             |  |  |
| Units: Patients             |                 |                 |  |  |
| Any post-baseline visit     | 94              | 105             |  |  |

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**Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

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

### Dictionary used

|                    |        |
|--------------------|--------|
| Dictionary name    | MedDRA |
| Dictionary version | 16.1   |

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | Ranibizumab |
|-----------------------|-------------|

Reporting group description:

Randomized patients received injections of 0.5 mg ranibizumab according to the proposed European label: consecutive monthly intravitreal injections with 0.5 mg ranibizumab until visual acuity (VA) stability was achieved, followed by a PRN (pro re nata/taken as needed) re-treatment if there was a decline from stable VA levels due to macular edema. Stability could be confirmed when a patient's VA was stable for three consecutive monthly assessments performed while on ranibizumab treatment.

|                       |               |
|-----------------------|---------------|
| Reporting group title | Dexamethasone |
|-----------------------|---------------|

Reporting group description:

Patients randomized to dexamethasone received a single intravitreal implant (700 µg; long acting release [LAR] over 6 months) at baseline and sham-injections thereafter.

| Serious adverse events                                              | Ranibizumab      | Dexamethasone     |  |
|---------------------------------------------------------------------|------------------|-------------------|--|
| Total subjects affected by serious adverse events                   |                  |                   |  |
| subjects affected / exposed                                         | 10 / 124 (8.06%) | 16 / 119 (13.45%) |  |
| number of deaths (all causes)                                       | 0                | 0                 |  |
| number of deaths resulting from adverse events                      | 0                | 0                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                   |  |
| ADENOCARCINOMA OF COLON                                             |                  |                   |  |
| subjects affected / exposed                                         | 0 / 124 (0.00%)  | 1 / 119 (0.84%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| GASTROINTESTINAL CARCINOMA                                          |                  |                   |  |
| subjects affected / exposed                                         | 0 / 124 (0.00%)  | 1 / 119 (0.84%)   |  |
| occurrences causally related to treatment / all                     | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all                          | 0 / 0            | 0 / 0             |  |
| RENAL NEOPLASM                                                      |                  |                   |  |

|                                                      |                 |                 |  |
|------------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Vascular disorders                                   |                 |                 |  |
| HYPERTENSION                                         |                 |                 |  |
| subjects affected / exposed                          | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| ASTHENIA                                             |                 |                 |  |
| subjects affected / exposed                          | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| FATIGUE                                              |                 |                 |  |
| subjects affected / exposed                          | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders             |                 |                 |  |
| PROSTATITIS                                          |                 |                 |  |
| subjects affected / exposed                          | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Investigations                                       |                 |                 |  |
| INTRAOCULAR PRESSURE DECREASED (Study eye)           |                 |                 |  |
| subjects affected / exposed                          | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| INTRAOCULAR PRESSURE INCREASED (Study eye)           |                 |                 |  |
| subjects affected / exposed                          | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| PROSTATIC SPECIFIC ANTIGEN INCREASED                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| WEIGHT DECREASED                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| UPPER LIMB FRACTURE                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| WRIST FRACTURE                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| ADENOMATOUS POLYPOSIS COLI                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| ANGINA PECTORIS                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| ATRIAL FIBRILLATION                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| CARDIAC FAILURE                                 |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| MITRAL VALVE INCOMPETENCE                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| HEADACHE                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| RADIAL NERVE PALSY                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| TRANSIENT ISCHAEMIC ATTACK                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| DEAFNESS                                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| CONJUNCTIVAL HYPERAEMIA (Study eye)             |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| CORNEAL OEDEMA (Study eye)                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| EYE PAIN (Study eye)                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| GLAUCOMA (Study eye)                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 3 / 119 (2.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| HYPHAEMA (Study eye)                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 3 / 119 (2.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| IRIS NEOVASCULARISATION (Study eye)             |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 4 / 119 (3.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| MACULAR OEDEMA (Study eye)                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 2 / 119 (1.68%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| RETINAL ARTERY OCCLUSION (Study eye)            |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| RETINAL VEIN OCCLUSION (Study eye)              |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| VISUAL ACUITY REDUCED (Study eye)               |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 3 / 119 (2.52%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| VITREOUS HAEMORRHAGE (Study eye)                |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| ABDOMINAL HERNIA                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| COLITIS                                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| GASTRODUODENAL ULCER                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| OESOPHAGEAL RUPTURE                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| UMBILICAL HERNIA                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| BACK PAIN                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| CYSTITIS                                        |                 |                 |  |

|                                                 |                 |                 |  |
|-------------------------------------------------|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>DIVERTICULITIS</b>                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>PNEUMONIA</b>                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 0 / 119 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>SOFT TISSUE INFECTION</b>                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 124 (0.00%) | 1 / 119 (0.84%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

Frequency threshold for reporting non-serious adverse events: 2.5 %

| <b>Non-serious adverse events</b>                     | Ranibizumab       | Dexamethasone     |  |
|-------------------------------------------------------|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events |                   |                   |  |
| subjects affected / exposed                           | 77 / 124 (62.10%) | 99 / 119 (83.19%) |  |
| <b>Investigations</b>                                 |                   |                   |  |
| <b>BLOOD GLUCOSE INCREASED</b>                        |                   |                   |  |
| subjects affected / exposed                           | 4 / 124 (3.23%)   | 2 / 119 (1.68%)   |  |
| occurrences (all)                                     | 4                 | 2                 |  |
| <b>INTRAOCULAR PRESSURE INCREASED (Fellow eye)</b>    |                   |                   |  |
| subjects affected / exposed                           | 0 / 124 (0.00%)   | 3 / 119 (2.52%)   |  |
| occurrences (all)                                     | 0                 | 3                 |  |
| <b>INTRAOCULAR PRESSURE INCREASED (Study eye)</b>     |                   |                   |  |
| subjects affected / exposed                           | 7 / 124 (5.65%)   | 38 / 119 (31.93%) |  |
| occurrences (all)                                     | 10                | 41                |  |
| <b>Vascular disorders</b>                             |                   |                   |  |
| <b>HYPERTENSION</b>                                   |                   |                   |  |

|                                                                                                                        |                         |                         |  |
|------------------------------------------------------------------------------------------------------------------------|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                                                                       | 5 / 124 (4.03%)<br>6    | 3 / 119 (2.52%)<br>3    |  |
| VASCULAR SHUNT (Study eye)<br>subjects affected / exposed<br>occurrences (all)                                         | 1 / 124 (0.81%)<br>1    | 3 / 119 (2.52%)<br>3    |  |
| Nervous system disorders<br>HEADACHE<br>subjects affected / exposed<br>occurrences (all)                               | 7 / 124 (5.65%)<br>9    | 10 / 119 (8.40%)<br>11  |  |
| General disorders and administration<br>site conditions<br>PYREXIA<br>subjects affected / exposed<br>occurrences (all) | 0 / 124 (0.00%)<br>0    | 3 / 119 (2.52%)<br>3    |  |
| Eye disorders<br>ABNORMAL SENSATION IN EYE<br>(Study eye)<br>subjects affected / exposed<br>occurrences (all)          | 6 / 124 (4.84%)<br>8    | 8 / 119 (6.72%)<br>9    |  |
| CONJUNCTIVAL HAEMORRHAGE<br>(Study eye)<br>subjects affected / exposed<br>occurrences (all)                            | 16 / 124 (12.90%)<br>18 | 13 / 119 (10.92%)<br>13 |  |
| DRY EYE (Fellow eye)<br>subjects affected / exposed<br>occurrences (all)                                               | 4 / 124 (3.23%)<br>4    | 1 / 119 (0.84%)<br>1    |  |
| DRY EYE (Study eye)<br>subjects affected / exposed<br>occurrences (all)                                                | 4 / 124 (3.23%)<br>4    | 4 / 119 (3.36%)<br>5    |  |
| EYE IRRITATION (Study eye)<br>subjects affected / exposed<br>occurrences (all)                                         | 4 / 124 (3.23%)<br>5    | 3 / 119 (2.52%)<br>5    |  |
| EYE PAIN (Study eye)<br>subjects affected / exposed<br>occurrences (all)                                               | 15 / 124 (12.10%)<br>22 | 14 / 119 (11.76%)<br>16 |  |
| FOREIGN BODY SENSATION IN EYES<br>(Study eye)                                                                          |                         |                         |  |

|                                          |                   |                   |
|------------------------------------------|-------------------|-------------------|
| subjects affected / exposed              | 6 / 124 (4.84%)   | 6 / 119 (5.04%)   |
| occurrences (all)                        | 6                 | 6                 |
| GLAUCOMA (Study eye)                     |                   |                   |
| subjects affected / exposed              | 0 / 124 (0.00%)   | 5 / 119 (4.20%)   |
| occurrences (all)                        | 0                 | 5                 |
| IRIS NEOVASCULARISATION (Study eye)      |                   |                   |
| subjects affected / exposed              | 0 / 124 (0.00%)   | 5 / 119 (4.20%)   |
| occurrences (all)                        | 0                 | 5                 |
| LACRIMATION INCREASED (Study eye)        |                   |                   |
| subjects affected / exposed              | 6 / 124 (4.84%)   | 8 / 119 (6.72%)   |
| occurrences (all)                        | 7                 | 8                 |
| MACULAR ISCHAEMIA (Study eye)            |                   |                   |
| subjects affected / exposed              | 0 / 124 (0.00%)   | 3 / 119 (2.52%)   |
| occurrences (all)                        | 0                 | 3                 |
| MACULAR OEDEMA (Study eye)               |                   |                   |
| subjects affected / exposed              | 13 / 124 (10.48%) | 19 / 119 (15.97%) |
| occurrences (all)                        | 14                | 21                |
| OCULAR HYPERAEMIA (Study eye)            |                   |                   |
| subjects affected / exposed              | 14 / 124 (11.29%) | 15 / 119 (12.61%) |
| occurrences (all)                        | 27                | 20                |
| OCULAR HYPERTENSION (Study eye)          |                   |                   |
| subjects affected / exposed              | 0 / 124 (0.00%)   | 6 / 119 (5.04%)   |
| occurrences (all)                        | 0                 | 10                |
| OPTIC DISC VASCULAR DISORDER (Study eye) |                   |                   |
| subjects affected / exposed              | 5 / 124 (4.03%)   | 0 / 119 (0.00%)   |
| occurrences (all)                        | 5                 | 0                 |
| RETINAL EXUDATES (Study eye)             |                   |                   |
| subjects affected / exposed              | 2 / 124 (1.61%)   | 4 / 119 (3.36%)   |
| occurrences (all)                        | 2                 | 4                 |
| RETINAL ISCHAEMIA (Study eye)            |                   |                   |
| subjects affected / exposed              | 1 / 124 (0.81%)   | 6 / 119 (5.04%)   |
| occurrences (all)                        | 1                 | 6                 |
| RETINAL VASCULAR DISORDER (Study eye)    |                   |                   |

|                                                 |                 |                   |  |
|-------------------------------------------------|-----------------|-------------------|--|
| subjects affected / exposed                     | 2 / 124 (1.61%) | 5 / 119 (4.20%)   |  |
| occurrences (all)                               | 2               | 5                 |  |
| VISUAL ACUITY REDUCED (Study eye)               |                 |                   |  |
| subjects affected / exposed                     | 8 / 124 (6.45%) | 19 / 119 (15.97%) |  |
| occurrences (all)                               | 10              | 19                |  |
| VISUAL IMPAIRMENT (Study eye)                   |                 |                   |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) | 6 / 119 (5.04%)   |  |
| occurrences (all)                               | 2               | 6                 |  |
| VITREOUS DETACHMENT (Study eye)                 |                 |                   |  |
| subjects affected / exposed                     | 5 / 124 (4.03%) | 3 / 119 (2.52%)   |  |
| occurrences (all)                               | 5               | 3                 |  |
| VITREOUS FLOATERS (Study eye)                   |                 |                   |  |
| subjects affected / exposed                     | 5 / 124 (4.03%) | 11 / 119 (9.24%)  |  |
| occurrences (all)                               | 6               | 11                |  |
| Gastrointestinal disorders                      |                 |                   |  |
| DIARRHOEA                                       |                 |                   |  |
| subjects affected / exposed                     | 6 / 124 (4.84%) | 2 / 119 (1.68%)   |  |
| occurrences (all)                               | 7               | 2                 |  |
| NAUSEA                                          |                 |                   |  |
| subjects affected / exposed                     | 4 / 124 (3.23%) | 3 / 119 (2.52%)   |  |
| occurrences (all)                               | 4               | 4                 |  |
| Musculoskeletal and connective tissue disorders |                 |                   |  |
| ARTHRALGIA                                      |                 |                   |  |
| subjects affected / exposed                     | 2 / 124 (1.61%) | 3 / 119 (2.52%)   |  |
| occurrences (all)                               | 3               | 3                 |  |
| BACK PAIN                                       |                 |                   |  |
| subjects affected / exposed                     | 7 / 124 (5.65%) | 4 / 119 (3.36%)   |  |
| occurrences (all)                               | 7               | 4                 |  |
| Infections and infestations                     |                 |                   |  |
| BRONCHITIS                                      |                 |                   |  |
| subjects affected / exposed                     | 1 / 124 (0.81%) | 3 / 119 (2.52%)   |  |
| occurrences (all)                               | 1               | 3                 |  |
| NASOPHARYNGITIS                                 |                 |                   |  |
| subjects affected / exposed                     | 9 / 124 (7.26%) | 12 / 119 (10.08%) |  |
| occurrences (all)                               | 9               | 16                |  |

|                                                                             |                      |                      |  |
|-----------------------------------------------------------------------------|----------------------|----------------------|--|
| URINARY TRACT INFECTION<br>subjects affected / exposed<br>occurrences (all) | 1 / 124 (0.81%)<br>1 | 4 / 119 (3.36%)<br>4 |  |
|-----------------------------------------------------------------------------|----------------------|----------------------|--|

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
|------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 24 June 2011     | This amendment was introduced to include: <ul style="list-style-type: none"><li>• Addition of country-specific requirements regarding the use of contraception and pregnancy advice within the United Kingdom</li><li>• Addition of the use of antimicrobial drops for 3 days before any visit when an injection was scheduled to be performed as required by local or country-specific practices,</li><li>• Addition of minor changes including some typographical errors</li></ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 10 October 2011  | As Lucentis (ranibizumab) became commercially available in May 2011 for the treatment of RVO, the protocol amendment was made to allow for usage of both commercially available Lucentis (according to local requirements and approvals) as well as ranibizumab clinical trial stock.<br>Furthermore, changes were made concerning the study drug preparation procedure in that for sham injections empty vials were no longer provided. In order to maintain the masking only the syringe, either empty in the case of sham-injections or pre-filled in the case of ranibizumab injections, were visible to the patient in the room of study drug administration; study drug withdrawal took place in a separate room or area, such that the patient remained masked to treatment. This procedure was in line with usual medical practice.<br>Finally, administrative errors have been corrected.<br>The following sections of the protocol had been changed: Investigational and control drugs, Dispensing the study drug, Assessment schedule, Treatment procedures |
| 12 December 2011 | Amendment was made to consolidate the changes made in the two previous amendments in a single amended protocol. Additionally, minor changes and corrections were made: Efficacy, Assessment schedule.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |

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.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use <https://www.novctrd.com/CtrdWeb/home.nov> for complete trial results.

Notes: