# Clinical trial results:
# RAINBOW extension study: an extension study to evaluate the long-term efficacy and safety of RAnibizumab compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity

## Summary

| | |
|---|---|
| EudraCT number | 2014-004048-36 |
| Trial protocol | HU EE GB SK IT BE LT CZ DE AT SE GR DK FR HR PL |
| Global end of trial date | 21 April 2022 |

### Results information

| | |
|---|---|
| Result version number | v3 (current) |
| This version publication date | 03 February 2023 |
| First version publication date | 05 November 2022 |
| Version creation reason | • New data added to full data set<br>Alignment with CT.gov form due to major QA comment received |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | CRFB002H2301E1 |

### Additional study identifiers

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02640664 |
| WHO universal trial number (UTN) | - |

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.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 | 21 April 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 21 April 2022 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the visual function of patients, by assessing the visual acuity (VA) in the better-seeing eye at the patients' 5th birthday.

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.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 16 June 2016 |
| 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 | Austria: 4 |
| Country: Number of subjects enrolled | Estonia: 2 |
| Country: Number of subjects enrolled | France: 2 |
| Country: Number of subjects enrolled | Lithuania: 1 |
| Country: Number of subjects enrolled | Egypt: 1 |
| Country: Number of subjects enrolled | India: 23 |
| Country: Number of subjects enrolled | Japan: 25 |
| Country: Number of subjects enrolled | Malaysia: 2 |
| Country: Number of subjects enrolled | Saudi Arabia: 1 |
| Country: Number of subjects enrolled | Taiwan: 7 |
| Country: Number of subjects enrolled | United States: 15 |
| Country: Number of subjects enrolled | Czechia: 9 |
| Country: Number of subjects enrolled | Germany: 2 |
| Country: Number of subjects enrolled | Greece: 10 |
| Country: Number of subjects enrolled | Italy: 12 |
| Country: Number of subjects enrolled | Romania: 13 |
| Country: Number of subjects enrolled | Belgium: 10 |
| Country: Number of subjects enrolled | Croatia: 5 |
| Country: Number of subjects enrolled | Denmark: 1 |

| | |
|---|---|
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | Russian Federation: 18 |
| Country: Number of subjects enrolled | Slovakia: 1 |
| Country: Number of subjects enrolled | Turkey: 10 |
| Country: Number of subjects enrolled | United Kingdom: 4 |
| Worldwide total number of subjects | 180 |
| EEA total number of subjects | 74 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 3 |
| Infants and toddlers (28 days-23 months) | 177 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Study was carried out in Austria (2), Belgium (2), Croatia (1), Czech Republic (3), Denmark (1), Egypt (1), Estonia (1), France (2), Germany (1), Greece (3), Hungary (2), India (6), Italy (4), Japan (16), Lithuania (1), Malaysia (2), Romania (3), Russian Federation (5), Saudi Arabia (1), Slovakia (1), Taiwan (2), Turkey (3), UK (2), US (9)

### Pre-assignment

Screening details:

During Epoch 1 (starting at the baseline visit for the extension study up to 40 weeks from the baseline visit in the core study) participants continued to receive same treatment as in the core study. During Epoch 2 (starting at the end of Epoch 1 up to participant's 5th birthday) participants no longer received treatment.

### Period 1

| | |
|---|---|
| Period 1 title | Core study: Epoch 1 |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open-label study where the VA assessment at the child's 5th birthday visit was performed by an assessor who was masked to study treatment.

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Ranibizumab 0.2 mg |

Arm description:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| | |
|---|---|
| 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:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| | |
|---|---|
| **Arm title** | Ranibizumab 0.1 mg |

Arm description:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| | |
|---|---|
| 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:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| | |
|---|---|
| **Arm title** | Laser therapy |

| Arm description: | |
|---|---|
| Laser treatment to each eye on Day 1 (Baseline), with supplementary treatments allowed | |
| Arm type | laser ablation therapy |
| No investigational medicinal product assigned in this arm | |

| **Number of subjects in period 1** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy |
|---|---|---|---|
| Started | 61 | 65 | 54 |
| Completed | 60 | 65 | 53 |
| Not completed | 1 | 0 | 1 |
| Adverse event, serious fatal | - | - | 1 |
| Withdrawal of informed consent | 1 | - | - |

## Period 2

| Period 2 title | Extension study: Epoch 2 |
|---|---|
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Blinding implementation details:

This was an open-label study where the VA assessment at the child's 5th birthday visit was performed by an assessor who was masked to study treatment.

## Arms

| Are arms mutually exclusive? | Yes |
|---|---|
| **Arm title** | Ranibizumab 0.2 mg |

Arm description:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| 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:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| **Arm title** | Ranibizumab 0.1 mg |
|---|---|

Arm description:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| 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:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| | |
|---|---|
| **Arm title** | Laser therapy |

Arm description:

Laser treatment to each eye on Day 1 (Baseline), with supplementary treatments allowed

| | |
|---|---|
| Arm type | laser ablation therapy |

No investigational medicinal product assigned in this arm

| **Number of subjects in period 2** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy |
|---|---|---|---|
| Started | 60 | 65 | 53 |
| Completed | 54 | 55 | 47 |
| Not completed | 6 | 10 | 6 |
| Adverse event, serious fatal | - | - | 1 |
| Withdrawal of informed consent | 3 | 4 | 2 |
| Lost to follow-up | 3 | 4 | 1 |
| Subject/guardian decision | - | 2 | 2 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Ranibizumab 0.2 mg |
| Reporting group description: | |
| 1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required | |
| Reporting group title | Ranibizumab 0.1 mg |
| Reporting group description: | |
| 1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required | |
| Reporting group title | Laser therapy |
| Reporting group description: | |
| Laser treatment to each eye on Day 1 (Baseline), with supplementary treatments allowed | |

| Reporting group values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy |
|---|---|---|---|
| Number of subjects | 61 | 65 | 54 |
| Age categorical | | | |
| Age at extension baseline visit | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 61 | 65 | 54 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous | | | |
| Age at extension baseline visit | | | |
| Units: weeks | | | |
| arithmetic mean | 38.88 | 40.16 | 37.48 |
| standard deviation | ± 7.316 | ± 9.836 | ± 8.745 |
| Sex: Female, Male<br>Units: Participants | | | |
| Female | 32 | 35 | 27 |
| Male | 29 | 30 | 27 |
| Race/Ethnicity, Customized<br>Units: Subjects | | | |
| Caucasian | 38 | 40 | 32 |
| Black | 0 | 4 | 2 |
| Asian | 22 | 18 | 18 |
| Native American | 0 | 0 | 0 |
| Pacific Islander | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 |
| Other | 1 | 3 | 2 |

| **Reporting group values** | Total | | |
|---|---|---|---|
| Number of subjects | 180 | | |
| Age categorical | | | |
| Age at extension baseline visit | | | |
| Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | | |
| Newborns (0-27 days) | 0 | | |
| Infants and toddlers (28 days-23 months) | 180 | | |
| Children (2-11 years) | 0 | | |
| Adolescents (12-17 years) | 0 | | |
| Adults (18-64 years) | 0 | | |
| From 65-84 years | 0 | | |
| 85 years and over | 0 | | |
| Age Continuous | | | |
| Age at extension baseline visit | | | |
| Units: weeks | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: Participants | | | |
| Female | 94 | | |
| Male | 86 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Caucasian | 110 | | |
| Black | 6 | | |
| Asian | 58 | | |
| Native American | 0 | | |
| Pacific Islander | 0 | | |
| Unknown | 0 | | |
| Other | 6 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Ranibizumab 0.2 mg |
| Reporting group description: | |
| 1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required | |
| Reporting group title | Ranibizumab 0.1 mg |
| Reporting group description: | |
| 1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required | |
| Reporting group title | Laser therapy |
| Reporting group description: | |
| Laser treatment to each eye on Day 1 (Baseline), with supplementary treatments allowed | |
| Reporting group title | Ranibizumab 0.2 mg |
| Reporting group description: | |
| 1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required | |
| Reporting group title | Ranibizumab 0.1 mg |
| Reporting group description: | |
| 1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required | |
| Reporting group title | Laser therapy |
| Reporting group description: | |
| Laser treatment to each eye on Day 1 (Baseline), with supplementary treatments allowed | |

### Primary: Visual acuity (VA) of the better-seeing eye at the participant's fifth birthday visit – comparison between treatment arms

| | |
|---|---|
| End point title | Visual acuity (VA) of the better-seeing eye at the participant's fifth birthday visit – comparison between treatment arms |
| End point description: | |
| The VA assessment at the child's 5th birthday visit was performed using Early Treatment Diabetic Retinopathy Study (ETDRS) methodology. VA measurements were taken in a sitting position at an initial test distance of 3 meters using Lea Symbols charts. Scores represented the number of optotypes (Lea symbols) the participant identified and ranged from 0 to 100, with higher scores indicating better visual acuity. VA was tested in each eye, using the child's current refractive index. The better-seeing eye was defined as the eye with the higher ETDRS score at the 5th birthday visit. If both eyes had the same ETDRS score, then the right eye was assigned as the better-seeing eye. | |
| End point type | Primary |
| End point timeframe: | |
| at the participant's fifth birthday visit (maximum 5 years and 4 months post core baseline visit) | |

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 45 | 43 | 36 | |
| Units: Score | | | | |
| least squares mean (standard error) | 66.8 (± 1.95) | 64.6 (± 2.00) | 62.1 (± 2.18) | |

**Statistical analyses**

| **Statistical analysis title** | Ranibizumab 0.2 mg vs Laser |
|---|---|
| Comparison groups | Ranibizumab 0.2 mg v Laser therapy |
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 4.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.1 |
| upper limit | 10.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.93 |

| **Statistical analysis title** | Ranibizumab 0.2 mg vs Ranibizumab 0.1 mg |
|---|---|
| Comparison groups | Ranibizumab 0.2 mg v Ranibizumab 0.1 mg |
| Number of subjects included in analysis | 88 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.3 |
| upper limit | 7.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.79 |

| **Statistical analysis title** | Ranibizumab 0.1 mg vs Laser |
|---|---|
| Comparison groups | Ranibizumab 0.1 mg v Laser therapy |

| | |
|---|---|
| Number of subjects included in analysis | 79 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -3.4 |
| upper limit | 8.3 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 2.96 |

## Secondary: Number of participants with ocular adverse events (AEs) regardless of study treatment or procedure relationship by preferred term

| | |
|---|---|
| End point title | Number of participants with ocular adverse events (AEs) regardless of study treatment or procedure relationship by preferred term |

End point description:

Number of participants with ocular AEs starting during the core study and ongoing at extension baseline, or starting on/after extension baseline were reported.

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

End point timeframe:

throughout the study, approximately 5 years

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: Participants | 19 | 26 | 22 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with non-ocular adverse events regardless of study treatment or procedure relationship (greater than or equal to 3% in any arm) by preferred term

| | |
|---|---|
| End point title | Number of participants with non-ocular adverse events regardless of study treatment or procedure relationship (greater than or equal to 3% in any arm) by preferred term |

End point description:

Number of participants with non-ocular adverse events (AEs) regardless of study treatment or procedure relationship (greater than or equal to 3% in any arm) by preferred term were reported.

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

End point timeframe:

throughout the study, approximately 5 years

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: Participants | 46 | 53 | 46 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Visual acuity (VA) of the worse-seeing eye at the participant's fifth birthday visit – comparison between treatment arms

| End point title | Visual acuity (VA) of the worse-seeing eye at the participant's fifth birthday visit – comparison between treatment arms |
|---|---|

End point description:

The VA assessment at the child's 5th birthday visit was performed using Early Treatment Diabetic Retinopathy Study (ETDRS) methodology. VA measurements were taken in a sitting position at an initial test distance of 3 meters using Lea Symbols charts. Scores represented the number of optotypes (Lea symbols) the participant identified and ranged from 0 to 100, with higher scores indicating better visual acuity. VA was tested in each eye, using the child's current refractive index. The worse-seeing eye was the eye with a lower ETDRS score at the 5th birthday visit. If both eyes had the same ETDRS score, then the left eye was assigned as the worse-seeing eye.

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

End point timeframe:

at the participant's fifth birthday visit (maximum 5 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 45 | 42 | 36 | |
| Units: Score | | | | |
| least squares mean (standard error) | 60.2 (± 2.95) | 53.8 (± 3.05) | 52.2 (± 3.30) | |

## Statistical analyses

| **Statistical analysis title** | Ranibizumab 0.2 mg vs Laser |
|---|---|
| Comparison groups | Ranibizumab 0.2 mg v Laser therapy |

| | |
|---|---|
| Number of subjects included in analysis | 81 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.8 |
| upper limit | 16.7 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.42 |

| **Statistical analysis title** | Ranibizumab 0.1 mg vs Laser |
|---|---|
| Comparison groups | Ranibizumab 0.1 mg v Laser therapy |
| Number of subjects included in analysis | 78 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.3 |
| upper limit | 10.5 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.49 |

| **Statistical analysis title** | Ranibizumab 0.2 mg vs Ranibizumab 0.1 mg |
|---|---|
| Comparison groups | Ranibizumab 0.2 mg v Ranibizumab 0.1 mg |
| Number of subjects included in analysis | 87 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Method | ANOVA |
| Parameter estimate | Mean difference (net) |
| Point estimate | 6.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2 |
| upper limit | 14.8 |
| Variability estimate | Standard error of the mean |
| Dispersion value | 4.24 |

## Secondary: Number of participants with absence of active Retinopathy of Prematurity (ROP) at 40 weeks post core baseline visit

| End point title | Number of participants with absence of active Retinopathy of Prematurity (ROP) at 40 weeks post core baseline visit |
|---|---|

End point description:

The absence of active ROP in both eyes is defined by the absence of all of the following features: (1) Vessel dilatation of plus disease in at least 2 quardrants (some persisting tortuosity is allowed), (2) Extra-retina vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease.

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

End point timeframe:

at 40 weeks post core baseline visit

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 55 | 58 | 46 | |
| Units: Participants | | | | |
| Absence of active ROP | 55 | 58 | 46 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with absence of active Retinopathy of Prematurity (ROP) at 52 weeks post core baseline visit

| End point title | Number of participants with absence of active Retinopathy of Prematurity (ROP) at 52 weeks post core baseline visit |
|---|---|

End point description:

The absence of active ROP in both eyes is defined by the absence of all of the following features: (1) Vessel dilatation of plus disease in at least 2 quardrants (some persisting tortuosity is allowed), (2) Extra-retina vessels extending from the retina into the vitreous and judged to be a sign of active ROP disease.

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

End point timeframe:

at 52 weeks post core baseline visit

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 58 | 63 | 50 | |
| Units: Participants | 58 | 63 | 49 | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with absence of all ocular structural abnormalities at or before 40 weeks post baseline visit

| End point title | Number of participants with absence of all ocular structural abnormalities at or before 40 weeks post baseline visit |
|---|---|

End point description:

The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point: (1) Substantial temporal retinal vessel dragging causing abnormal structural features/macular Ectopia, (2) Retrolental membrane obscuring the view of the posterior pole, (3) Posterior retinal fold involving the macula, (4) Retinal detachment involving the macula

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

End point timeframe:

at or before 40 weeks post baseline visit

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 65 | 53 | |
| Units: Participants | 59 | 61 | 47 | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Number of participants with absence of all ocular structural abnormalities at or before the participant’s fifth birthday visit

| End point title | Number of participants with absence of all ocular structural abnormalities at or before the participant’s fifth birthday visit |
|---|---|

End point description:

The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point: (1) Substantial temporal retinal vessel dragging causing abnormal structural features/macular Ectopia, (2) Retrolental membrane obscuring the view of the posterior pole, (3) Posterior retinal fold involving the macula, (4) Retinal detachment involving the macula

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

End point timeframe:

at or before the participant’s fifth birthday visit (up to maximum 5 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 65 | 53 | |
| Units: Participants | 59 | 61 | 47 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with absence of individual ocular structural abnormalities at or before 40 weeks post baseline visit

| End point title | Number of participants with absence of individual ocular structural abnormalities at or before 40 weeks post baseline visit |
|---|---|

End point description:

The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point: (1) Substantial temporal retinal vessel dragging causing abnormal structural features/macular Ectopia, (2) Retrolental membrane obscuring the view of the posterior pole, (3) Posterior retinal fold involving the macula, (4) Retinal detachment involving the macula

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

End point timeframe:

at or before 40 weeks post baseline visit

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 65 | 53 | |
| Units: Participants | | | | |
| Absence of substantial temporal retinal vessel | 59 | 63 | 49 | |
| Absence of Retrolental membrane | 60 | 65 | 53 | |
| Absence of posterior retinal fold | 59 | 65 | 51 | |
| Absence of retinal detachment | 60 | 63 | 51 | |
| Abs of retinal detachment not involving the macula | 60 | 62 | 50 | |
| Absence of pre-retinal fibrosis | 58 | 60 | 49 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with absence of individual ocular structural abnormalities at or before the participant's fifth birthday visit

| End point title | Number of participants with absence of individual ocular structural abnormalities at or before the participant's fifth birthday visit |
|---|---|

End point description:

The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point: (1) Substantial temporal retinal vessel dragging causing abnormal structural features/macular Ectopia, (2) Retrolental membrane obscuring the view of the posterior pole, (3) Posterior retinal fold involving the macula, (4) Retinal detachment involving the macula

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

End point timeframe:

at or before the participant's fifth birthday visit (up to maximum 5 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 65 | 53 | |
| Units: Participants | | | | |
| Absence of temporal retinal vessel dragging | 59 | 63 | 49 | |
| Absence of Retrolental membrane | 60 | 65 | 52 | |
| Absence of posterior retinal fold | 59 | 65 | 51 | |
| Absence of retinal detachment | 60 | 63 | 50 | |
| Abs of retinal detachment not involving macula | 60 | 62 | 50 | |
| Absence of pre-retinal fibrosis | 58 | 59 | 48 | |
| Absence of optic disc pallor | 60 | 65 | 52 | |
| Absence of optic disc swelling | 60 | 65 | 53 | |
| Absence of pigmentary disturbance in the macula | 60 | 64 | 52 | |
| Absence of atrophic changes in macula | 60 | 65 | 51 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with absence of all ocular structural abnormalities at or before participant's 2 years corrected age visit

| End point title | Number of participants with absence of all ocular structural abnormalities at or before participant's 2 years corrected age visit |
|---|---|

End point description:

The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point: (1) Substantial temporal retinal vessel dragging causing abnormal structural features/macular Ectopia, (2) Retrolental membrane obscuring the view of the posterior pole, (3) Posterior retinal fold involving the macula, (4) Retinal detachment involving the macula

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

End point timeframe:

at or before participant’s 2 years corrected age visit (up to 2 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 65 | 53 | |
| Units: Participants | 59 | 61 | 47 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with absence of individual ocular structural abnormalities at or before participant’s 2 years corrected age visit

| End point title | Number of participants with absence of individual ocular structural abnormalities at or before participant’s 2 years corrected age visit |
|---|---|

End point description:

The absence of ocular structural abnormalities is defined by the absence of all of the following fundus features in both eyes at or before the given time point: (1) Substantial temporal retinal vessel dragging causing abnormal structural features/macular Ectopia, (2) Retrolental membrane obscuring the view of the posterior pole, (3) Posterior retinal fold involving the macula, (4) Retinal detachment involving the macula

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

End point timeframe:

at or before participant’s 2 years corrected age visit (up to 2 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 60 | 65 | 53 | |
| Units: Participants | | | | |
| Abs of temporal retinal vessel dragging | 59 | 63 | 49 | |
| Absence of Retrolental membrane | 60 | 65 | 52 | |
| Absence of posterior retinal fold | 59 | 65 | 51 | |
| Abs of retinal detachment involving the macula | 60 | 63 | 50 | |
| Abs of retinal detachment not involving the macula | 60 | 62 | 50 | |
| Absence of pre-retinal fibrosis | 58 | 59 | 48 | |
| Absence of optic disc pallor | 60 | 65 | 53 | |
| Absence of optic disc swelling | 60 | 65 | 53 | |
| Absence of pigmentary disturbance in the macula | 60 | 64 | 52 | |
| Absence of atrophic changes in macula | 60 | 65 | 52 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with recurrence of ROP up to 40 weeks post baseline visit in the core study

| End point title | Number of participants with recurrence of ROP up to 40 weeks post baseline visit in the core study |
|---|---|

End point description:

Recurrence of ROP was defined as ROP receiving any post-baseline intervention after the 1st study treatment in the core study. In the ranibizumab arms, post-baseline interventions were ranibizumab retreatment or switch to laser. In the laser arm, post-baseline interventions were supplementary laser treatments after 11 days post-baseline, or switch to ranibizumab; supplementary laser treatment within 11 days post-baseline was not counted as recurrence.

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

End point timeframe:

up to 40 weeks post baseline visit in the core study

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: Participants | 19 | 22 | 11 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with recurrence of ROP up to 52 weeks post baseline visit in the core study

| End point title | Number of participants with recurrence of ROP up to 52 weeks post baseline visit in the core study |
|---|---|

End point description:

Recurrence of ROP was defined as ROP receiving any post-baseline intervention after the 1st study treatment in the core study. In the ranibizumab arms, post-baseline interventions were ranibizumab retreatment or switch to laser. In the laser arm, post-baseline interventions were supplementary laser treatments after 11 days post-baseline, or switch to ranibizumab; supplementary laser treatment within 11 days post-baseline was not counted as recurrence. Beyond Week 40, participants did not receive any study intervention and no new data was collected after 40 weeks post core baseline visit.

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

End point timeframe:

up to 52 weeks post baseline visit in the core study

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: Participants | 19 | 22 | 11 | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of ranibizumab injections received per participant over the whole safety observation period

| End point title | Number of ranibizumab injections received per participant over the whole safety observation period |
|---|---|

End point description:

Number of ranibizumab injections received in the treatment of participants with ROP up to and including 40 weeks post baseline visit in the core study were reported.

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

End point timeframe:

up to and including 40 weeks post baseline visit in the core study

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 11 | |
| Units: Number of injections | | | | |
| arithmetic mean (standard deviation) | 2.5 (± 0.96) | 2.5 (± 1.06) | 2.4 (± 0.92) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Refraction status: Summary of participants at participant’s 2 years corrected age

| End point title | Refraction status: Summary of participants at participant’s 2 years corrected age |
|---|---|

End point description:

Summary of participants was reported to evaluate the refraction in each eye at the participant’s 2 years corrected age

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

End point timeframe:

at participant’s 2 years corrected age (maximum 2 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 57 | 54 | 47 | |
| Units: diopters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Best eye | -0.697 (± 2.7032) | -0.713 (± 2.6100) | -1.793 (± 4.1570) | |
| Worst eye | -0.825 (± 2.6575) | -0.829 (± 2.8346) | -1.516 (± 3.5652) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Refraction status: Summary of participants at the participant’s fifth birthday visit

| End point title | Refraction status: Summary of participants at the participant’s fifth birthday visit |
|---|---|

End point description:

Summary of participants was reported to evaluate the refraction in each eye at the participant’s fifth birthday visit

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

End point timeframe:

at the participant’s fifth birthday visit (maximum 5 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 52 | 55 | 45 | |
| Units: diopters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Best eye | -0.601 (± 2.8107) | -0.859 (± 2.7406) | -1.883 (± 4.4970) | |
| Worst eye | -0.904 (± 2.8501) | -1.074 (± 3.0405) | -1.706 (± 3.5740) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in weight at the participant’s 2 years’ corrected age

| End point title | Change from baseline in weight at the participant’s 2 years’ corrected age |
|---|---|

End point description:

Subject´s weight was reported to evaluate the physical development.

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

End point timeframe:

Baseline of the core study and at the subject’s 2 years’ corrected age (maximum 2 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 58 | 46 | |
| Units: grams | | | | |
| arithmetic mean (standard deviation) | | | | |
| Year 2 | 8695.9 (± 1406.58) | 8461.7 (± 1375.95) | 8840.6 (± 1643.80) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in weight at the participant’s fifth birthday

| End point title | Change from baseline in weight at the participant’s fifth birthday |
|---|---|

End point description:

Subject´s weight was reported to evaluate the physical development.

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

End point timeframe:

Baseline of the core study and at the subjects’ fifth birthday (maximum 5 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 52 | 54 | 45 | |
| Units: grams | | | | |
| arithmetic mean (standard deviation) | 14611.9 (± 3018.65) | 14324.7 (± 2616.96) | 14689.4 (± 3300.05) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Head Circumference

| End point title | Change from baseline in Head Circumference |
|---|---|

End point description:

Subject´s head circumference was reported to evaluate the physical development.

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

End point timeframe:

Baseline of the core study and at the subject’s 2 years’ corrected age (maximum 2 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 55 | 56 | 44 | |
| Units: cm | | | | |
| arithmetic mean (standard deviation) | 16.5 (± 2.60) | 16.2 (± 2.78) | 17.2 (± 2.81) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Sitting Diastolic Blood Pressure

| End point title | Change from baseline in Sitting Diastolic Blood Pressure |
|---|---|

End point description:

Subject´s Sitting Diastolic Blood Pressure was reported to evaluate the physical development.

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

End point timeframe:

Baseline of the core study and at the subject’s 2 years’ corrected age (maximum 2 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 38 | 33 | 31 | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 16.7 (± 14.92) | 13.6 (± 14.10) | 16.5 (± 12.14) | |

### Statistical analyses

No statistical analyses for this end point

## Secondary: Change from baseline in Sitting Systolic Blood Pressure

| End point title | Change from baseline in Sitting Systolic Blood Pressure |
|---|---|

End point description:

Subject´s Sitting Systolic Blood Pressure was reported to evaluate the physical development.

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

End point timeframe:

Baseline of the core study and at the subject's 2 years' corrected age (maximum 2 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 38 | 32 | 31 | |
| Units: mmHg | | | | |
| arithmetic mean (standard deviation) | 20.6 (± 16.13) | 16.2 (± 15.95) | 17.6 (± 12.75) | |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Number of participants with the summary of respiratory function status**

| End point title | Number of participants with the summary of respiratory function status |
|---|---|

End point description:

Number of participants with respiratory function status was reported

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

End point timeframe:

at the participants' fifth birthday visit (maximum 5 years and 4 months post core baseline visit)

| **End point values** | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: Participants | | | | |
| participants with Wheezing/whistling status | 6 | 4 | 2 | |
| participants with attacks of wheezing | 47 | 50 | 45 | |
| participants with frequency of sleep disturbance | 47 | 52 | 47 | |
| participants with wheezing limiting speech ability | 1 | 0 | 0 | |
| participants with dry cough status at night | 5 | 2 | 1 | |
| participants with presence of smoker at home | 15 | 8 | 4 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with hearing impairment of any type

| End point title | Number of participants with hearing impairment of any type |
|---|---|

End point description:

Number of participants with hearing function status was reported

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

End point timeframe:

at the participants' fifth birthday visit (maximum 5 years and 4 months post core baseline visit)

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: Participants | | | | |
| Participants with hearing impairment of any type | 2 | 2 | 4 | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Duration of hospitalization

| End point title | Duration of hospitalization |
|---|---|

End point description:

Duration of hospitalization (from birth to first hospital discharge home) was reported to evaluate the health status of the subject

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

End point timeframe:

From baseline of the core study up to 5 years and 4 months post core baseline visit

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 61 | 65 | 54 | |
| Units: days | | | | |
| arithmetic mean (standard deviation) | 111.1 (± 62.27) | 116.2 (± 78.10) | 95.7 (± 57.07) | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Weight at the time of first hospital discharge

| End point title | Weight at the time of first hospital discharge |
|---|---|

End point description:

Weight (gram) at the time of first hospital discharge was reported to evaluate the health status of the subject

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

End point timeframe:

From baseline of the core study up to 5 years and 4 months post core baseline visit

| End point values | Ranibizumab 0.2 mg | Ranibizumab 0.1 mg | Laser therapy | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 56 | 62 | 51 | |
| Units: gram | | | | |
| arithmetic mean (standard deviation) | 2910.9 (± 1359.34) | 2966.5 (± 1198.60) | 2658.7 (± 926.92) | |

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

throughout the study, up to approximately 5 years

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 25.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Ranibizumab 0.2 mg |

Reporting group description:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| | |
|---|---|
| Reporting group title | Laser |

Reporting group description:

Laser treatment to each eye on Day 1 (Baseline), with supplementary treatments allowed

| | |
|---|---|
| Reporting group title | Total |

Reporting group description:

Total of all the participants

| | |
|---|---|
| Reporting group title | Ranibizumab 0.1 mg |

Reporting group description:

1 intravitreal injection in both eyes on Day 1 (Baseline), with up to 2 re-treatments allowed for each eye if required

| Serious adverse events | Ranibizumab 0.2 mg | Laser | Total |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 21 / 61 (34.43%) | 26 / 54 (48.15%) | 74 / 180 (41.11%) |
| number of deaths (all causes) | 0 | 2 | 2 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pregnancy, puerperium and perinatal conditions | | | |
| Perinatal brain damage | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Developmental delay | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inflammation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 2 / 54 (3.70%) | 6 / 180 (3.33%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthma | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 54 (3.70%) | 6 / 180 (3.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | 0 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchial obstruction | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary dysplasia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|---|---|---|
| Bronchospasm | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercapnia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypoxia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Increased bronchial secretion | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngospasm | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasal discharge discolouration | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary vein stenosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory distress | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillar hypertrophy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Psychomotor retardation | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Oxygen saturation decreased | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural | | | |

| | | | |
|---|---|---|---|
| complications | | | |
| Endotracheal intubation complication | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Foreign body in respiratory tract | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Head injury | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital haematoma | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Congenital, familial and genetic disorders | | | |
| Cerebral palsy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coarctation of the aorta | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cryptorchism | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Bradycardia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Nervous system disorders | | | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile convulsion | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 54 (0.00%) | 5 / 180 (2.78%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 5 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Motor dysfunction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myoclonus | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nystagmus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periventricular leukomalacia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Quadriparesis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorder | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal detachment | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retinopathy of prematurity | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acetonaemic vomiting | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 54 (1.85%) | 4 / 180 (2.22%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Flatulence | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematemesis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haematochezia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ileus | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Inguinal hernia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mechanical ileus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising colitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 54 (3.70%) | 6 / 180 (3.33%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Portal hypertension | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rash papular | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urticarial vasculitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nephrolithiasis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Endocrine disorders | | | |
| Diabetes insipidus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial food poisoning | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchiolitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 54 (0.00%) | 7 / 180 (3.89%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 7 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 5 / 54 (9.26%) | 11 / 180 (6.11%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 12 | 0 / 18 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis viral | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Croup infectious | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterocolitis infectious | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epstein-Barr virus infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 54 (3.70%) | 3 / 180 (1.67%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis adenovirus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hand-foot-and-mouth disease | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpangina | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Laryngitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Leptospirosis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis viral | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parainfluenzae viral bronchitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 54 (1.85%) | 4 / 180 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 1 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pharyngitis streptococcal | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 4 / 54 (7.41%) | 10 / 180 (5.56%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 7 | 0 / 15 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia viral | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyelonephritis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 2 / 54 (3.70%) | 4 / 180 (2.22%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus bronchitis | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 54 (1.85%) | 2 / 180 (1.11%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| Streptococcal infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 54 (1.85%) | 3 / 180 (1.67%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral pharyngitis | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral tonsillitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 54 (1.85%) | 4 / 180 (2.22%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Electrolyte imbalance | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Failure to thrive | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperphosphatasaemia | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypophagia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 1 / 180 (0.56%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| **Serious adverse events** | Ranibizumab 0.1 mg | | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 27 / 65 (41.54%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Perinatal brain damage | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Developmental delay | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Inflammation | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |

| | | | | |
|---|---|---|---|---|
| Acute respiratory failure | | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Asthma | | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchial obstruction | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchopulmonary dysplasia | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Bronchospasm | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cough | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dyspnoea | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypercapnia | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hypoxia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 65 (3.08%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Increased bronchial secretion | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngospasm | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nasal discharge discolouration | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonitis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary hypertension | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pulmonary vein stenosis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory distress | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory failure | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 2 / 65 (3.08%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tonsillar hypertrophy | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Psychiatric disorders | | | | |
| Psychomotor retardation | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Investigations | | | | |
| Oxygen saturation decreased | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Injury, poisoning and procedural complications | | | | |
| Endotracheal intubation complication | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Foreign body in respiratory tract | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Head injury | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periorbital haematoma | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |

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|---|---|---|---|
| Congenital, familial and genetic disorders | | | |
| Cerebral palsy | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Coarctation of the aorta | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cryptorchism | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac arrest | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Cerebellar haemorrhage | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epilepsy | | | |

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|---|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Febrile convulsion | | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | | |
| occurrences causally related to treatment / all | 0 / 3 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hydrocephalus | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intracranial pressure increased | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Motor dysfunction | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Myoclonus | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Nystagmus | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periventricular leukomalacia | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Quadriparesis | | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorder | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal detachment | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinal haemorrhage | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Retinopathy of prematurity | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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|---|---|---|---|---|
| Acetonaemic vomiting | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Constipation | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Diarrhoea | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Flatulence | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrointestinal haemorrhage | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastrooesophageal reflux disease | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematemesis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Haematochezia | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ileus | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Inguinal hernia | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Mechanical ileus | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Necrotising colitis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Vomiting | | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | | |
| occurrences causally related to treatment / all | 0 / 4 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatobiliary disorders | | | | |
| Cholelithiasis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hepatic failure | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Portal hypertension | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Erythema multiforme | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rash papular | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urticarial vasculitis | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocrine disorders | | | |
| Diabetes insipidus | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|---|---|---|
| Musculoskeletal and connective tissue disorders | | | |
| Osteopenia | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Adenovirus infection | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bacterial food poisoning | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis viral | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Croup infectious | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|---|---|---|---|
| Ear infection | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Enterocolitis infectious | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Epstein-Barr virus infection | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis adenovirus | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis norovirus | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis rotavirus | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Gastroenteritis viral | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Hand-foot-and-mouth disease | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Herpangina | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Influenza | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Laryngitis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Leptospirosis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Lower respiratory tract infection | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Meningitis viral | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Otitis media acute | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Parainfluenzae viral bronchitis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Periorbital cellulitis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis | | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pharyngitis streptococcal | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia | | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | | | |
| occurrences causally related to treatment / all | 0 / 6 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia aspiration | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia respiratory syncytial viral | | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pneumonia viral | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Pyelonephritis | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory syncytial virus bronchiolitis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory syncytial virus bronchitis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory syncytial virus infection | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Respiratory tract infection viral | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Septic shock | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Streptococcal infection | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Tonsillitis | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Upper respiratory tract infection | | | | |

| | | | | |
|---|---|---|---|---|
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral infection | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral pharyngitis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral tonsillitis | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Viral upper respiratory tract infection | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Metabolism and nutrition disorders | | | | |
| Decreased appetite | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dehydration | | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Electrolyte imbalance | | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Failure to thrive | | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperphosphatasaemia | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypophagia | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 4 %

| **Non-serious adverse events** | Ranibizumab 0.2 mg | Laser | Total |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 41 / 61 (67.21%) | 40 / 54 (74.07%) | 127 / 180 (70.56%) |
| Nervous system disorders | | | |
| Febrile convulsion | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 3 / 54 (5.56%) | 8 / 180 (4.44%) |
| occurrences (all) | 3 | 4 | 10 |
| Nystagmus | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 1 / 54 (1.85%) | 5 / 180 (2.78%) |
| occurrences (all) | 1 | 1 | 6 |
| Seizure | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 2 / 54 (3.70%) | 5 / 180 (2.78%) |
| occurrences (all) | 4 | 2 | 6 |
| General disorders and administration site conditions | | | |
| Developmental delay | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 5 / 61 (8.20%) | 3 / 54 (5.56%) | 9 / 180 (5.00%) |
| occurrences (all) | 5 | 3 | 9 |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 10 / 54 (18.52%) | 27 / 180 (15.00%) |
| occurrences (all) | 6 | 23 | 59 |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 54 (1.85%) | 6 / 180 (3.33%) |
| occurrences (all) | 3 | 1 | 6 |
| Eye disorders | | | |
| Astigmatism | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 2 / 54 (3.70%) | 7 / 180 (3.89%) |
| occurrences (all) | 3 | 2 | 7 |
| Myopia | | | |
| subjects affected / exposed | 6 / 61 (9.84%) | 5 / 54 (9.26%) | 14 / 180 (7.78%) |
| occurrences (all) | 6 | 6 | 15 |
| Strabismus | | | |
| subjects affected / exposed | 10 / 61 (16.39%) | 12 / 54 (22.22%) | 34 / 180 (18.89%) |
| occurrences (all) | 11 | 12 | 38 |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 2 / 54 (3.70%) | 14 / 180 (7.78%) |
| occurrences (all) | 4 | 2 | 17 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 5 / 54 (9.26%) | 13 / 180 (7.22%) |
| occurrences (all) | 4 | 5 | 13 |
| Diarrhoea | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 5 / 54 (9.26%) | 13 / 180 (7.22%) |
| occurrences (all) | 4 | 6 | 17 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 2 / 54 (3.70%) | 5 / 180 (2.78%) |
| occurrences (all) | 0 | 2 | 13 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 3 / 54 (5.56%) | 14 / 180 (7.78%) |
| occurrences (all) | 7 | 6 | 25 |

| | | | |
|---|---|---|---|
| Bronchopulmonary dysplasia | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 4 / 54 (7.41%) | 9 / 180 (5.00%) |
| occurrences (all) | 2 | 5 | 10 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 0 / 54 (0.00%) | 4 / 180 (2.22%) |
| occurrences (all) | 1 | 0 | 10 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 1 / 54 (1.85%) | 6 / 180 (3.33%) |
| occurrences (all) | 2 | 2 | 10 |
| Skin and subcutaneous tissue disorders | | | |
| Dry skin | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 3 / 54 (5.56%) | 5 / 180 (2.78%) |
| occurrences (all) | 2 | 3 | 5 |
| Erythema | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 3 / 180 (1.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Rash | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 3 / 180 (1.67%) |
| occurrences (all) | 0 | 0 | 3 |
| Psychiatric disorders | | | |
| Autism spectrum disorder | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 54 (1.85%) | 5 / 180 (2.78%) |
| occurrences (all) | 3 | 1 | 5 |
| Musculoskeletal and connective tissue disorders | | | |
| Rickets | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 3 / 54 (5.56%) | 3 / 180 (1.67%) |
| occurrences (all) | 0 | 3 | 3 |
| Infections and infestations | | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 0 / 54 (0.00%) | 5 / 180 (2.78%) |
| occurrences (all) | 4 | 0 | 7 |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 3 / 54 (5.56%) | 5 / 180 (2.78%) |
| occurrences (all) | 1 | 3 | 6 |
| Bronchitis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 4 / 61 (6.56%) | 6 / 54 (11.11%) | 14 / 180 (7.78%) |
| occurrences (all) | 11 | 9 | 24 |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 4 / 54 (7.41%) | 10 / 180 (5.56%) |
| occurrences (all) | 2 | 4 | 10 |
| Ear infection | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 0 / 54 (0.00%) | 7 / 180 (3.89%) |
| occurrences (all) | 5 | 0 | 10 |
| Exanthema subitum | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 54 (1.85%) | 6 / 180 (3.33%) |
| occurrences (all) | 3 | 1 | 6 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 61 (1.64%) | 3 / 54 (5.56%) | 5 / 180 (2.78%) |
| occurrences (all) | 1 | 3 | 5 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 11 / 61 (18.03%) | 9 / 54 (16.67%) | 31 / 180 (17.22%) |
| occurrences (all) | 25 | 13 | 59 |
| Influenza | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 1 / 54 (1.85%) | 7 / 180 (3.89%) |
| occurrences (all) | 4 | 1 | 9 |
| Otitis media | | | |
| subjects affected / exposed | 7 / 61 (11.48%) | 3 / 54 (5.56%) | 12 / 180 (6.67%) |
| occurrences (all) | 9 | 3 | 14 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 61 (3.28%) | 5 / 54 (9.26%) | 10 / 180 (5.56%) |
| occurrences (all) | 2 | 9 | 15 |
| Pneumonia | | | |
| subjects affected / exposed | 5 / 61 (8.20%) | 0 / 54 (0.00%) | 6 / 180 (3.33%) |
| occurrences (all) | 6 | 0 | 7 |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 1 / 54 (1.85%) | 8 / 180 (4.44%) |
| occurrences (all) | 5 | 3 | 16 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 61 (4.92%) | 5 / 54 (9.26%) | 11 / 180 (6.11%) |
| occurrences (all) | 3 | 6 | 14 |
| Viral upper respiratory tract infection | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 61 (0.00%) | 0 / 54 (0.00%) | 3 / 180 (1.67%) |
| occurrences (all) | 0 | 0 | 5 |
| Metabolism and nutrition disorders | | | |
| Iron deficiency | | | |
| subjects affected / exposed | 4 / 61 (6.56%) | 4 / 54 (7.41%) | 8 / 180 (4.44%) |
| occurrences (all) | 5 | 4 | 9 |
| Malnutrition | | | |
| subjects affected / exposed | 0 / 61 (0.00%) | 1 / 54 (1.85%) | 4 / 180 (2.22%) |
| occurrences (all) | 0 | 1 | 4 |

| **Non-serious adverse events** | Ranibizumab 0.1 mg | | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 46 / 65 (70.77%) | | |
| Nervous system disorders | | | |
| Febrile convulsion | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | |
| occurrences (all) | 3 | | |
| Nystagmus | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences (all) | 4 | | |
| Seizure | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences (all) | 0 | | |
| General disorders and administration site conditions | | | |
| Developmental delay | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 11 / 65 (16.92%) | | |
| occurrences (all) | 30 | | |
| Immune system disorders | | | |
| Seasonal allergy | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | |
| occurrences (all) | 2 | | |
| Eye disorders | | | |
| Astigmatism | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed<br>occurrences (all)<br><br>Myopia<br>subjects affected / exposed<br>occurrences (all)<br><br>Strabismus<br>subjects affected / exposed<br>occurrences (all) | 2 / 65 (3.08%)<br>2<br><br>3 / 65 (4.62%)<br>3<br><br>12 / 65 (18.46%)<br>15 | | |
| Gastrointestinal disorders<br>Constipation<br>subjects affected / exposed<br>occurrences (all)<br><br>Gastrooesophageal reflux disease<br>subjects affected / exposed<br>occurrences (all)<br><br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Vomiting<br>subjects affected / exposed<br>occurrences (all) | <br><br>8 / 65 (12.31%)<br>11<br><br>4 / 65 (6.15%)<br>4<br><br>5 / 65 (7.69%)<br>7<br><br>3 / 65 (4.62%)<br>11 | | |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)<br><br>Bronchopulmonary dysplasia<br>subjects affected / exposed<br>occurrences (all)<br><br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)<br><br>Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all) | <br><br>6 / 65 (9.23%)<br>12<br><br>3 / 65 (4.62%)<br>3<br><br>3 / 65 (4.62%)<br>9<br><br>3 / 65 (4.62%)<br>6 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|---|---|---|
| Dry skin | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences (all) | 0 | | |
| Erythema | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences (all) | 3 | | |
| Rash | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences (all) | 3 | | |
| Psychiatric disorders | | | |
| Autism spectrum disorder | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences (all) | 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Rickets | | | |
| subjects affected / exposed | 0 / 65 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Bronchiolitis | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences (all) | 3 | | |
| COVID-19 | | | |
| subjects affected / exposed | 1 / 65 (1.54%) | | |
| occurrences (all) | 2 | | |
| Bronchitis | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | | |
| occurrences (all) | 4 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 4 / 65 (6.15%) | | |
| occurrences (all) | 4 | | |
| Ear infection | | | |
| subjects affected / exposed | 3 / 65 (4.62%) | | |
| occurrences (all) | 5 | | |
| Exanthema subitum | | | |
| subjects affected / exposed | 2 / 65 (3.08%) | | |
| occurrences (all) | 2 | | |

| | | | |
|---|---|---|---|
| Gastroenteritis viral<br>subjects affected / exposed<br>occurrences (all) | 1 / 65 (1.54%)<br>1 | | |
| Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all) | 11 / 65 (16.92%)<br>21 | | |
| Influenza<br>subjects affected / exposed<br>occurrences (all) | 2 / 65 (3.08%)<br>4 | | |
| Otitis media<br>subjects affected / exposed<br>occurrences (all) | 2 / 65 (3.08%)<br>2 | | |
| Pharyngitis<br>subjects affected / exposed<br>occurrences (all) | 3 / 65 (4.62%)<br>4 | | |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all) | 1 / 65 (1.54%)<br>1 | | |
| Respiratory tract infection viral<br>subjects affected / exposed<br>occurrences (all) | 4 / 65 (6.15%)<br>8 | | |
| Upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 65 (4.62%)<br>5 | | |
| Viral upper respiratory tract infection<br>subjects affected / exposed<br>occurrences (all) | 3 / 65 (4.62%)<br>5 | | |
| Metabolism and nutrition disorders<br>Iron deficiency<br>subjects affected / exposed<br>occurrences (all) | 0 / 65 (0.00%)<br>0 | | |
| Malnutrition<br>subjects affected / exposed<br>occurrences (all) | 3 / 65 (4.62%)<br>3 | | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 31 July 2018 | Introduced the collection of additional visual function data following EU national scientific advice meeting |
| 10 July 2019 | Included the requirement of masked VA assessments to be performed at the 5th birthday visit, following a request from the EMA. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported