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	v2
This version publication date	29 December 2022
First version publication date	05 November 2022
Version creation reason	

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	Belgium: 10
Country: Number of subjects enrolled	Croatia: 5
Country: Number of subjects enrolled	Czechia: 9
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Egypt: 1
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 23
Country: Number of subjects enrolled	Italy: 12
Country: Number of subjects enrolled	Japan: 25
Country: Number of subjects enrolled	Lithuania: 1
Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Romania: 13
Country: Number of subjects enrolled	Russian Federation: 18

Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Slovakia: 1
Country: Number of subjects enrolled	Taiwan: 7
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	United States: 15
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 Units: Participants			
Female	32	35	27
Male	29	30	27
Race/Ethnicity, Customized 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 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. 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 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 patient identified. 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 letter score, then the left eye is 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	Total

Reporting group description:

Total of all the participants

Reporting group title	Laser

Reporting group description:

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

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	Total	Laser
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 61 (34.43%)	74 / 180 (41.11%)	26 / 54 (48.15%)
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%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
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 / 180 (0.56%)	1 / 54 (1.85%)
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%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inflammation			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	6 / 180 (3.33%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 3	0 / 7	0 / 3
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%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 61 (1.64%)	6 / 180 (3.33%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 2	0 / 9	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchial obstruction			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercapnia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 61 (0.00%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Increased bronchial secretion			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Laryngospasm			
subjects affected / exposed	2 / 61 (3.28%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nasal discharge discolouration			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonitis			

subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary hypertension			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary vein stenosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory distress			
subjects affected / exposed	0 / 61 (0.00%)	2 / 180 (1.11%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 61 (0.00%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tonsillar hypertrophy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 61 (1.64%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foreign body in respiratory tract			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital haematoma			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coarctation of the aorta			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Bradycardia			

subjects affected / exposed	1 / 61 (1.64%)	2 / 180 (1.11%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	5 / 180 (2.78%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	1 / 61 (1.64%)	2 / 180 (1.11%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Motor dysfunction			

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

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

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

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

subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nephrolithiasis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bacterial food poisoning			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	7 / 180 (3.89%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	3 / 61 (4.92%)	11 / 180 (6.11%)	5 / 54 (9.26%)
occurrences causally related to treatment / all	0 / 3	0 / 18	0 / 12
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Croup infectious			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear infection			
subjects affected / exposed	1 / 61 (1.64%)	2 / 180 (1.11%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterocolitis infectious			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epstein-Barr virus infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	3 / 180 (1.67%)	2 / 54 (3.70%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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%)	2 / 180 (1.11%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpangina			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leptospirosis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meningitis viral			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Otitis media acute			
subjects affected / exposed	1 / 61 (1.64%)	2 / 180 (1.11%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Parainfluenzae viral bronchitis			
subjects affected / exposed	1 / 61 (1.64%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Periorbital cellulitis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis			
subjects affected / exposed	1 / 61 (1.64%)	4 / 180 (2.22%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	1 / 4	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pharyngitis streptococcal			

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

subjects affected / exposed	1 / 61 (1.64%)	2 / 180 (1.11%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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 / 180 (0.56%)	1 / 54 (1.85%)
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%)	3 / 180 (1.67%)	1 / 54 (1.85%)
occurrences causally related to treatment / all	0 / 2	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 61 (0.00%)	1 / 180 (0.56%)	1 / 54 (1.85%)
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%)	1 / 180 (0.56%)	0 / 54 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral tonsillitis			

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

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

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			

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			

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				

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		

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

subjects affected / exposed	5 / 61 (8.20%)	9 / 180 (5.00%)	3 / 54 (5.56%)
occurrences (all)	5	9	3
Pyrexia			
subjects affected / exposed	6 / 61 (9.84%)	27 / 180 (15.00%)	10 / 54 (18.52%)
occurrences (all)	6	59	23
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 61 (4.92%)	6 / 180 (3.33%)	1 / 54 (1.85%)
occurrences (all)	3	6	1
Eye disorders			
Astigmatism			
subjects affected / exposed	3 / 61 (4.92%)	7 / 180 (3.89%)	2 / 54 (3.70%)
occurrences (all)	3	7	2
Myopia			
subjects affected / exposed	6 / 61 (9.84%)	14 / 180 (7.78%)	5 / 54 (9.26%)
occurrences (all)	6	15	6
Strabismus			
subjects affected / exposed	10 / 61 (16.39%)	34 / 180 (18.89%)	12 / 54 (22.22%)
occurrences (all)	11	38	12
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 61 (6.56%)	14 / 180 (7.78%)	2 / 54 (3.70%)
occurrences (all)	4	17	2
Diarrhoea			
subjects affected / exposed	3 / 61 (4.92%)	13 / 180 (7.22%)	5 / 54 (9.26%)
occurrences (all)	4	17	6
Gastrooesophageal reflux disease			
subjects affected / exposed	4 / 61 (6.56%)	13 / 180 (7.22%)	5 / 54 (9.26%)
occurrences (all)	4	13	5
Vomiting			
subjects affected / exposed	0 / 61 (0.00%)	5 / 180 (2.78%)	2 / 54 (3.70%)
occurrences (all)	0	13	2
Respiratory, thoracic and mediastinal disorders			
Bronchopulmonary dysplasia			
subjects affected / exposed	2 / 61 (3.28%)	9 / 180 (5.00%)	4 / 54 (7.41%)
occurrences (all)	2	10	5

Cough			
subjects affected / exposed	5 / 61 (8.20%)	14 / 180 (7.78%)	3 / 54 (5.56%)
occurrences (all)	7	25	6
Dyspnoea			
subjects affected / exposed	1 / 61 (1.64%)	4 / 180 (2.22%)	0 / 54 (0.00%)
occurrences (all)	1	10	0
Rhinorrhoea			
subjects affected / exposed	2 / 61 (3.28%)	6 / 180 (3.33%)	1 / 54 (1.85%)
occurrences (all)	2	10	2
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	2 / 61 (3.28%)	5 / 180 (2.78%)	3 / 54 (5.56%)
occurrences (all)	2	5	3
Erythema			
subjects affected / exposed	0 / 61 (0.00%)	3 / 180 (1.67%)	0 / 54 (0.00%)
occurrences (all)	0	3	0
Rash			
subjects affected / exposed	0 / 61 (0.00%)	3 / 180 (1.67%)	0 / 54 (0.00%)
occurrences (all)	0	3	0
Psychiatric disorders			
Autism spectrum disorder			
subjects affected / exposed	3 / 61 (4.92%)	5 / 180 (2.78%)	1 / 54 (1.85%)
occurrences (all)	3	5	1
Musculoskeletal and connective tissue disorders			
Rickets			
subjects affected / exposed	0 / 61 (0.00%)	3 / 180 (1.67%)	3 / 54 (5.56%)
occurrences (all)	0	3	3
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 61 (3.28%)	5 / 180 (2.78%)	0 / 54 (0.00%)
occurrences (all)	4	7	0
Bronchitis			
subjects affected / exposed	4 / 61 (6.56%)	14 / 180 (7.78%)	6 / 54 (11.11%)
occurrences (all)	11	24	9
COVID-19			

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

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

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 occurrences (all) Myopia subjects affected / exposed occurrences (all) Strabismus subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2 3 / 65 (4.62%) 3 12 / 65 (18.46%) 15		
Gastrointestinal disorders Constipation subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gastrooesophageal reflux disease subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 8 / 65 (12.31%) 11 5 / 65 (7.69%) 7 4 / 65 (6.15%) 4 3 / 65 (4.62%) 11		
Respiratory, thoracic and mediastinal disorders Bronchopulmonary dysplasia subjects affected / exposed occurrences (all) Cough subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	 3 / 65 (4.62%) 3 6 / 65 (9.23%) 12 3 / 65 (4.62%) 9 3 / 65 (4.62%) 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		
Bronchitis			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
COVID-19			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences (all)	2		
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 subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Influenza subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 4		
Nasopharyngitis subjects affected / exposed occurrences (all)	11 / 65 (16.92%) 21		
Otitis media subjects affected / exposed occurrences (all)	2 / 65 (3.08%) 2		
Pharyngitis subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 4		
Pneumonia subjects affected / exposed occurrences (all)	1 / 65 (1.54%) 1		
Respiratory tract infection viral subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 8		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 5		
Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 5		
Metabolism and nutrition disorders Iron deficiency subjects affected / exposed occurrences (all)	0 / 65 (0.00%) 0		
Malnutrition subjects affected / exposed occurrences (all)	3 / 65 (4.62%) 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