



Clinical trial results:

RAINBOW study: a randomized, controlled study evaluating the efficacy and safety of RAnibizumab compared with laser therapy for the treatment of INfants BOrn prematurely With retinopathy of prematurity
Summary

EudraCT number	2014-003041-10
Trial protocol	IT EE LT HU BE AT DE GB HR FR SK CZ GR DK FI PL
Global end of trial date	14 December 2017

Results information

Result version number	v1
This version publication date	21 June 2018
First version publication date	21 June 2018

Trial information

Trial identification

Sponsor protocol code	CRFB002H2301
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02375971
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-000527-PIP04-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	14 December 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 December 2017
Global end of trial reached?	Yes
Global end of trial date	14 December 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to demonstrate that intravitreal ranibizumab 0.2 mg had superior efficacy to laser therapy in the treatment of retinopathy of prematurity (ROP) as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting study treatment.

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	30 December 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 10
Country: Number of subjects enrolled	Croatia: 7
Country: Number of subjects enrolled	Czech Republic: 9
Country: Number of subjects enrolled	Denmark: 1
Country: Number of subjects enrolled	Egypt: 3
Country: Number of subjects enrolled	Estonia: 2
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Greece: 10
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	India: 29
Country: Number of subjects enrolled	Italy: 14
Country: Number of subjects enrolled	Japan: 29
Country: Number of subjects enrolled	Lithuania: 1

Country: Number of subjects enrolled	Malaysia: 2
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Poland: 3
Country: Number of subjects enrolled	Romania: 16
Country: Number of subjects enrolled	Russian Federation: 20
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: 14
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	225
EEA total number of subjects	93

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	225
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted in 87 sites: Austria(2), Belgium(2), Croatia(2), Czech Republic(3), Denmark(1), Egypt(1), Estonia(1), France(2), Germany(2), Greece(3), Hungary(2), India(6), Italy(4), Japan(17), Lithuania(1), Malaysia(2), Mexico(1), Poland(2), Romania(3), Russia(5), Saudi Arabia(1), Slovakia(1), Taiwan(2), Turkey(6), UK(3) and USA(12).

Pre-assignment

Screening details:

One patient was discontinued prior to receiving any study treatment and was later re-randomized; this patient is counted twice in the Randomized Set (FAS) (225). The number of unique participants randomized in the study is 224.

Period 1

Period 1 title	Treatment (Day 1 - Baseline)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

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	Solution for 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
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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	Solution for 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
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Arm description:

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

Arm type	Laser therapy (eye)
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	74	77	74
Safety Set	73	76	69
VEGF Set	19 ^[1]	26 ^[2]	51 ^[3]
PK Set	49 ^[4]	46 ^[5]	0 ^[6]
Completed	73	76	69
Not completed	1	1	5
Subj/Guardian Decision	-	-	2
Physician decision	1	1	1
Adverse event, non-fatal	-	-	1
Lost to follow-up	-	-	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Patients in 'Started' = All randomized patients to whom treatment had been assigned (FAS). Patients in 'Safety Set' = At least 1 application of investigational treatment and a 1 post baseline safety assessment. Patients in 'VEGF Set' = All patients who provided valid Vascular endothelial growth factor (VEGF) plasma samples. Patients in 'PK Set' = All patients who provided Pharmacokinetics (PK) serum samples. Patients in 'Completed' = All patients who completed the treatment phase.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Patients in 'Started' = All randomized patients to whom treatment had been assigned (FAS). Patients in 'Safety Set' = At least 1 application of investigational treatment and a 1 post baseline safety assessment. Patients in 'VEGF Set' = All patients who provided valid Vascular endothelial growth factor (VEGF) plasma samples. Patients in 'PK Set' = All patients who provided Pharmacokinetics (PK) serum samples. Patients in 'Completed' = All patients who completed the treatment phase.

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Patients in 'Started' = All randomized patients to whom treatment had been assigned (FAS). Patients in 'Safety Set' = At least 1 application of investigational treatment and a 1 post baseline safety assessment. Patients in 'VEGF Set' = All patients who provided valid Vascular endothelial growth factor (VEGF) plasma samples. Patients in 'PK Set' = All patients who provided Pharmacokinetics (PK) serum samples. Patients in 'Completed' = All patients who completed the treatment phase.

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Patients in 'Started' = All randomized patients to whom treatment had been assigned (FAS). Patients in 'Safety Set' = At least 1 application of investigational treatment and a 1 post baseline safety assessment. Patients in 'VEGF Set' = All patients who provided valid Vascular endothelial growth factor (VEGF) plasma samples. Patients in 'PK Set' = All patients who provided Pharmacokinetics (PK) serum samples. Patients in 'Completed' = All patients who completed the treatment phase.

[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Patients in 'Started' = All randomized patients to whom treatment had been assigned (FAS). Patients in 'Safety Set' = At least 1 application of investigational treatment and a 1 post baseline safety assessment. Patients in 'VEGF Set' = All patients who provided valid Vascular endothelial growth factor (VEGF) plasma samples. Patients in 'PK Set' = All patients who provided Pharmacokinetics (PK) serum samples. Patients in 'Completed' = All patients who completed the treatment phase.

[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Patients in 'Started' = All randomized patients to whom treatment had been assigned (FAS). Patients in 'Safety Set' = At least 1 application of investigational treatment and a 1 post baseline safety assessment. Patients in 'VEGF Set' = All patients who provided valid Vascular endothelial growth factor (VEGF) plasma samples. Patients in 'PK Set' = All patients who provided Pharmacokinetics (PK) serum samples. Patients in 'Completed' = All patients who completed the treatment phase.

Period 2

Period 2 title	Follow-Up Phase (up to Day 169)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

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	Solution for 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
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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	Solution for 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
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Arm description:

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

Arm type	Laser therapy (eye)
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	73	76	69
Completed	66	71	64
Not completed	7	5	5
Adverse event, serious fatal	4	4	4
Withdrawal of Consent	1	1	-
Adverse event, non-fatal	1	-	-
Subject/Guardian Decision	1	-	1

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	74	77	74
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	74	77	74
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
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			
Gestational age at birth (weeks)			
Units: Weeks			
arithmetic mean	25.8	26.5	26.2
standard deviation	± 2.25	± 2.57	± 2.59
Sex: Female, Male			
Units: Subjects			
Female	41	40	37
Male	33	37	37
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	27	22	23
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	4	3
White	43	45	45
More than one race	0	0	0
Unknown or Not Reported	4	6	3

Reporting group values	Total		
Number of subjects	225		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	225		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	0		
From 65-84 years	0		
85 years and over	0		
Age Continuous			
Gestational age at birth (weeks)			
Units: Weeks			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	118		
Male	107		
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0		
Asian	72		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	7		
White	133		
More than one race	0		
Unknown or Not Reported	13		

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: Percentage of Participants with absence of active ROP and absence of unfavorable structural outcomes in both eyes at Week 24

End point title	Percentage of Participants with absence of active ROP and absence of unfavorable structural outcomes in both eyes at Week 24
End point description: To achieve this outcome, patients must fulfill all the following criteria, 1) survival, 2) no intervention with a second modality for ROP, 3) absence of active ROP and 4) absence of unfavorable structural outcome. Retinopathy of prematurity (ROP) is a pathologic process that occurs in the incompletely vascularized, developing retina of low birth-weight preterm neonates.	
End point type	Primary
End point timeframe: Week 24	

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	74	77	74	
Units: Percentage of Participants				
number (not applicable)	80.0	75.0	66.2	

Statistical analyses

Statistical analysis title	Primary objective
Comparison groups	Ranibizumab 0.2 mg v Ranibizumab 0.1 mg v Laser therapy
Number of subjects included in analysis	225
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0254
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	2.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9932
upper limit	4.8235

Secondary: Percentage of Participants requiring Interventions with a second modality for ROP at Week 24

End point title	Percentage of Participants requiring Interventions with a second modality for ROP at Week 24
End point description:	
Intervention for ROP in either eye at or before the 24-week assessment visit with a treatment modality other than the modality of the first study treatment. Only descriptive analysis done.	
End point type	Secondary
End point timeframe:	
Week 24	

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	74	77	74	
Units: Percentage of participants				
number (not applicable)	14.9	16.9	24.3	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Experiencing an Event, from the first study treatment to the last study visit

End point title	Number of Participants Experiencing an Event, from the first study treatment to the last study visit
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End point description:

An event was defined as death, treatment switch, or the first occurrence of unfavorable structural outcomes in either eye. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Day 1 (after initiation of study treatment) up to study exit (Day 169)

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	74	77	74	
Units: Participants	14	18	23	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants having recurrent ROP and receiving any post-baseline intervention at or before Week 24

End point title	Percentage of Participants having recurrent ROP and receiving any post-baseline intervention at or before Week 24
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End point description:

Recurrence of ROP is defined as subjects receiving any post-baseline intervention in either eye at or before 24 weeks (ranibizumab re-treatment or switch to laser in the ranibizumab groups, switch to ranibizumab treatment in the laser group). Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Week 24

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	74	77	74	
Units: Percentage of participants				
number (not applicable)				
All participants	31.1	31.2	18.9	
ZONE I	35.7	53.3	28.6	
ZONE II	28.3	17.4	13.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Ocular Adverse Events by Primary System Organ (SOCs) at Week 24

End point title	Number of Ocular Adverse Events by Primary System Organ (SOCs) at Week 24
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End point description:

Number of Ocular Adverse Events regardless of Study Treatment and Procedure Relationship by Primary System Organ (SOCs) reported categorically (Mild, Moderate, Severe) 24 weeks after the first study treatment. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Week 24

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	73	76	69	
Units: Ocular Adverse Events (AEs)				
number (not applicable)				
Mild	23.3	32.9	17.4	
Moderate	4.1	6.6	13.0	
Severe	2.7	1.3	2.9	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Ranibizumab concentration in Pharmacokinetic serum samples over time at Day 1, Day 15 and Day 29

End point title	Mean change in Ranibizumab concentration in Pharmacokinetic serum samples over time at Day 1, Day 15 and Day 29 ^[1]
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End point description:

Blood samples for the determination of ranibizumab concentrations were collected in the Ranibizumab treatment arms only at the following time points: within 24 hours after the first administration of ranibizumab, at Day 15 and at Day 29. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Day 1 (Baseline), Day 15 and Day 29

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Blood samples for the determination of ranibizumab concentrations were collected in the Ranibizumab treatment arms only.

End point values	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	49 ^[2]	46 ^[3]		
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Day 1 (Baseline) (n=43,43)	24700.0 (± 52400.00)	12100.0 (± 25500.0)		
Day 15 (n=45,36)	5830.0 (± 4750.0)	27700.0 (± 144000)		
Day 29 (n=31,24)	1810.0 (± 2990.0)	732.0 (± 535.0)		

Notes:

[2] - n = number of participants in the PK set.

[3] - n = number of participants in the PK set.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change in Vascular Endothelial Growth Factor (VEGF) levels over time at Day 1, Day 15 and Day 29

End point title	Mean change in Vascular Endothelial Growth Factor (VEGF) levels over time at Day 1, Day 15 and Day 29
End point description:	
Blood samples for the determination of systemic VEGF levels were collected at the following time points: before the first investigational treatment, at Day 15 and at Day 29. Only descriptive analysis done.	
End point type	Secondary
End point timeframe:	
Day 1 (Baseline), Day 15 and Day 29	

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	19 ^[4]	26 ^[5]	51 ^[6]	
Units: picogram/milliliter (pg/mL)				
arithmetic mean (standard deviation)				
Day 1 (n=17,21,46)	239.0 (± 226.0)	230.0 (± 224.0)	232.0 (± 240.0)	
D1 / no treatment modality switch (n=17,18,41)	239.0 (± 226.0)	239.0 (± 233.0)	233.0 (± 245.0)	
Day 15 (n=15,26,44)	466.0 (± 1500.0)	118.0 (± 129.0)	180.0 (± 214.0)	
D15 / no treatment modality switch (n=14,23,38)	498.0 (± 1560.0)	124.0 (± 134.0)	177.0 (± 224.0)	
Day 29 (n=13,18,30)	117.0 (± 84.0)	176.0 (± 142.0)	161.0 (± 132.0)	
D29 / no treatment modality switch (n=13,15,27)	117.0 (± 84.0)	139.0 (± 75.3)	163.0 (± 138.0)	

Notes:

[4] - n = number of participants in the VEGF Set.

[5] - n = number of participants in the VEGF Set.

[6] - n = number of participants in the VEGF Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Total Number of Ranibizumab Injections received at Week 24

End point title	Total Number of Ranibizumab Injections received at Week 24
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End point description:

Patients randomized to receive Ranibizumab 0.1 mg or 0.2 mg received a single dose of intravitreal Ranibizumab to each eye on Day 1 (Baseline). Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Week 24

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	73	76	69	
Units: Injections	73	76	13	

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Non-Ocular Adverse Events by Primary System Organ (SOCs) at Week 24

End point title	Number of Non-Ocular Adverse Events by Primary System Organ (SOCs) at Week 24
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End point description:

Number of Non-Ocular Adverse Events regardless of Study Treatment and Procedure Relationship by Primary System Organ (SOCs) reported categorically (Mild, Moderate, Severe) 24 weeks after the first study treatment. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Week 24

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	73	76	69	
Units: Non-Ocular Adverse Events (AEs)				
number (not applicable)				
Mild	37.0	27.6	31.9	
Moderate	24.7	34.2	27.5	
Severe	23.3	19.7	17.4	

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Vital signs (Body Length, Head Circumference and Knee to Heel Length) at Day 85 and Day 169

End point title	Mean change from Baseline in Vital signs (Body Length, Head Circumference and Knee to Heel Length) at Day 85 and Day 169
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End point description:

Body Length, Head Circumference and Knee to Heel Length were assessed. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Baseline, Day 85, Day 169

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	73 ^[7]	76 ^[8]	69 ^[9]	
Units: centimeter (cm)				
arithmetic mean (standard deviation)				
Day 85 / Body Length (n=61,63,60)	10.1 (± 2.59)	11.0 (± 3.33)	11.1 (± 3.65)	
Day 169 / Body Length (n=62,62,57)	18.7 (± 3.28)	18.6 (± 3.66)	19.0 (± 4.50)	
Day 85 / Head Circumference (n=62,62,59)	6.9 (± 1.96)	6.5 (± 2.31)	7.2 (± 2.13)	
Day 169 / Head Circumference (n=62,62,57)	10.4 (± 2.12)	10.3 (± 2.56)	10.6 (± 2.61)	
Day 85 / Knee to Heel Length (n=55,51,52)	2.9 (± 1.90)	3.1 (± 1.65)	3.1 (± 2.02)	
Day 169 / Knee to Heel Length (n=53,52,52)	5.4 (± 2.86)	5.1 (± 2.19)	5.3 (± 2.15)	

Notes:

[7] - n = number of participants in the Safety Set.

[8] - n = number of participants in the Safety Set.

[9] - n = number of participants in the Safety Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Vital signs (Weight) at Day 85 and Day 169

End point title	Mean change from Baseline in Vital signs (Weight) at Day 85 and Day 169
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End point description:

Body weight was measured. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Baseline, Day 85, Day 169

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	73 ^[10]	76 ^[11]	69 ^[12]	
Units: gram (g)				
arithmetic mean (standard deviation)				
Day 85 / Weight (n=63,66,60)	2198.9 (± 615.68)	2149.9 (± 754.27)	2182.7 (± 612.70)	
Day 169 / Weight (n=62,62,60)	3794.3 (± 782.48)	3716.7 (± 897.15)	3826.0 (± 882.17)	

Notes:

[10] - n = number of participants in the Safety Set.

[11] - n = number of participants in the Safety Set.

[12] - n = number of participants in the Safety Set.

Statistical analyses

No statistical analyses for this end point

Secondary: Mean change from Baseline in Vital signs (Sitting Blood Pressure) at Day 85 and Day 169

End point title	Mean change from Baseline in Vital signs (Sitting Blood Pressure) at Day 85 and Day 169
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End point description:

Blood Pressure measurements were not required by the protocol. Instead, the most recent Systolic and Diastolic Blood Pressure expressed in millimeters of mercury (mmHg) measured as part of the routine clinical care were used. Only descriptive analysis done.

End point type	Secondary
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End point timeframe:

Baseline, Day 85, Day 169

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	73 ^[13]	76 ^[14]	69 ^[15]	
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Day 85 / Sitting Diastolic BP (n=47,46,41)	8.1 (± 14.66)	7.0 (± 14.25)	9.8 (± 16.95)	
Day 85 / Sitting Systolic BP (n=47,46,41)	6.3 (± 15.85)	9.4 (± 15.73)	15.5 (± 16.85)	
Day 169 / Sitting Diastolic BP (n=45,46,40)	11.5 (± 15.60)	11.8 (± 14.42)	14.7 (± 17.05)	

Day 169 / Sitting Systolic BP (n=45,46,40)	10.2 (± 16.15)	11.2 (± 13.45)	17.7 (± 19.35)	
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Notes:

[13] - n = number of participants in the Safety Set.

[14] - n = number of participants in the Safety Set.

[15] - n = number of participants in the Safety Set.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe for AE

Adverse event reporting additional description:

AE additional description

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	20.1
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Reporting groups

Reporting group title	Ranibizumab 0.2 mg
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Reporting group description:

Ranibizumab 0.2 mg

Reporting group title	Ranibizumab 0.1 mg
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Reporting group description:

Ranibizumab 0.1 mg

Reporting group title	Laser
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Reporting group description:

Laser

Serious adverse events	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser
Total subjects affected by serious adverse events			
subjects affected / exposed	26 / 73 (35.62%)	24 / 76 (31.58%)	24 / 69 (34.78%)
number of deaths (all causes)	4	4	4
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	1 / 73 (1.37%)	1 / 76 (1.32%)	0 / 69 (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
Vascular disorders			
Haemodynamic instability			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pregnancy, puerperium and perinatal conditions			
Perinatal brain damage			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Cyst			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
No adverse event			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Social circumstances			
Dependence on oxygen therapy			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 73 (0.00%)	2 / 76 (2.63%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspiration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atelectasis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchopulmonary dysplasia			

subjects affected / exposed	2 / 73 (2.74%)	2 / 76 (2.63%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cough			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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 aspiration			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Pulmonary hypertension			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary vein stenosis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory arrest			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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	1 / 73 (1.37%)	1 / 76 (1.32%)	0 / 69 (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 failure			

subjects affected / exposed	0 / 73 (0.00%)	3 / 76 (3.95%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	1 / 3	0 / 1
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 1
Respiratory symptom			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tracheomalacia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Wheezing			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Breath holding			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Psychomotor retardation			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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			
Blood potassium increased			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Oxygen saturation decreased			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Weight decreased			

subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Greenstick fracture			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Hydrocele			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ileal atresia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Cardiac failure			

subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardio-respiratory arrest			
subjects affected / exposed	0 / 73 (0.00%)	2 / 76 (2.63%)	0 / 69 (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
Cardiogenic shock			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 73 (1.37%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Nervous system disorders			
Brain oedema			
subjects affected / exposed	2 / 73 (2.74%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cerebellar haemorrhage			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral cyst			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cognitive disorder			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Hydrocephalus			

subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nystagmus			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Partial seizures			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Cataract			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Exophthalmos			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorder			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Retinopathy of prematurity			
subjects affected / exposed	2 / 73 (2.74%)	1 / 76 (1.32%)	3 / 69 (4.35%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			

Abdominal discomfort				
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Diarrhoea				
subjects affected / exposed	0 / 73 (0.00%)	2 / 76 (2.63%)	0 / 69 (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	
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Gastrooesophageal reflux disease				
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	1 / 69 (1.45%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Ileal perforation				
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Ileus				
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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	
Incarcerated inguinal hernia				
subjects affected / exposed	2 / 73 (2.74%)	0 / 76 (0.00%)	0 / 69 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0	
Inguinal hernia				
subjects affected / exposed	1 / 73 (1.37%)	2 / 76 (2.63%)	0 / 69 (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	
Necrotising colitis				

subjects affected / exposed	0 / 73 (0.00%)	3 / 76 (3.95%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 2	0 / 0
Vomiting			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Skin and subcutaneous tissue disorders			
Purpura			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 1
Tubulointerstitial nephritis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Bone disorder			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteopenia			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	2 / 73 (2.74%)	4 / 76 (5.26%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Conjunctivitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytomegalovirus infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endophthalmitis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterococcal sepsis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Klebsiella sepsis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Nasopharyngitis			
subjects affected / exposed	0 / 73 (0.00%)	2 / 76 (2.63%)	0 / 69 (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
Orbital infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	4 / 73 (5.48%)	0 / 76 (0.00%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pneumonia bacterial			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia respiratory syncytial viral			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia staphylococcal			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory syncytial virus bronchiolitis			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Rhinovirus infection			
subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Roseola			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	2 / 69 (2.90%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 2
Septic shock			
subjects affected / exposed	1 / 73 (1.37%)	1 / 76 (1.32%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Staphylococcal infection			

subjects affected / exposed	0 / 73 (0.00%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Staphylococcal sepsis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Urinary tract infection			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 73 (1.37%)	1 / 76 (1.32%)	1 / 69 (1.45%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Failure to thrive			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypernatraemia			
subjects affected / exposed	0 / 73 (0.00%)	1 / 76 (1.32%)	0 / 69 (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
Hyperphosphatasemia			

subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	0 / 69 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser
Total subjects affected by non-serious adverse events			
subjects affected / exposed	43 / 73 (58.90%)	47 / 76 (61.84%)	37 / 69 (53.62%)
Cardiac disorders			
Bradycardia			
subjects affected / exposed	2 / 73 (2.74%)	5 / 76 (6.58%)	1 / 69 (1.45%)
occurrences (all)	2	7	2
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	4 / 73 (5.48%)	8 / 76 (10.53%)	5 / 69 (7.25%)
occurrences (all)	5	9	7
Anaemia neonatal			
subjects affected / exposed	2 / 73 (2.74%)	4 / 76 (5.26%)	1 / 69 (1.45%)
occurrences (all)	2	4	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	9 / 73 (12.33%)	6 / 76 (7.89%)	4 / 69 (5.80%)
occurrences (all)	12	7	4
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	6 / 73 (8.22%)	6 / 76 (7.89%)	2 / 69 (2.90%)
occurrences (all)	12	8	3
Retinal haemorrhage			
subjects affected / exposed	6 / 73 (8.22%)	10 / 76 (13.16%)	7 / 69 (10.14%)
occurrences (all)	10	15	10
Vitreous haemorrhage			
subjects affected / exposed	0 / 73 (0.00%)	4 / 76 (5.26%)	0 / 69 (0.00%)
occurrences (all)	0	6	0
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	4 / 73 (5.48%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences (all)	5	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	5 / 73 (6.85%)	5 / 76 (6.58%)	4 / 69 (5.80%)
occurrences (all)	5	5	4
Inguinal hernia			
subjects affected / exposed	3 / 73 (4.11%)	0 / 76 (0.00%)	2 / 69 (2.90%)
occurrences (all)	3	0	2
Vomiting			
subjects affected / exposed	2 / 73 (2.74%)	4 / 76 (5.26%)	2 / 69 (2.90%)
occurrences (all)	2	5	2
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 73 (1.37%)	4 / 76 (5.26%)	1 / 69 (1.45%)
occurrences (all)	1	7	1
Bronchopulmonary dysplasia			
subjects affected / exposed	2 / 73 (2.74%)	3 / 76 (3.95%)	4 / 69 (5.80%)
occurrences (all)	2	3	4
Bronchospasm			
subjects affected / exposed	3 / 73 (4.11%)	0 / 76 (0.00%)	1 / 69 (1.45%)
occurrences (all)	3	0	1
Cough			
subjects affected / exposed	4 / 73 (5.48%)	2 / 76 (2.63%)	1 / 69 (1.45%)
occurrences (all)	4	2	1
Skin and subcutaneous tissue disorders			
Dermatitis diaper			
subjects affected / exposed	8 / 73 (10.96%)	6 / 76 (7.89%)	4 / 69 (5.80%)
occurrences (all)	10	6	4
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	0 / 73 (0.00%)	4 / 76 (5.26%)	1 / 69 (1.45%)
occurrences (all)	0	4	1
Infections and infestations			
Conjunctivitis			

subjects affected / exposed	1 / 73 (1.37%)	6 / 76 (7.89%)	2 / 69 (2.90%)
occurrences (all)	2	11	4
Nasopharyngitis			
subjects affected / exposed	7 / 73 (9.59%)	5 / 76 (6.58%)	4 / 69 (5.80%)
occurrences (all)	7	8	6
Pneumonia			
subjects affected / exposed	1 / 73 (1.37%)	1 / 76 (1.32%)	6 / 69 (8.70%)
occurrences (all)	2	1	6
Rhinitis			
subjects affected / exposed	3 / 73 (4.11%)	0 / 76 (0.00%)	2 / 69 (2.90%)
occurrences (all)	3	0	2
Sepsis			
subjects affected / exposed	1 / 73 (1.37%)	0 / 76 (0.00%)	3 / 69 (4.35%)
occurrences (all)	2	0	3
Upper respiratory tract infection			
subjects affected / exposed	6 / 73 (8.22%)	3 / 76 (3.95%)	1 / 69 (1.45%)
occurrences (all)	8	4	1
Urinary tract infection			
subjects affected / exposed	3 / 73 (4.11%)	2 / 76 (2.63%)	2 / 69 (2.90%)
occurrences (all)	4	2	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 August 2015	Amendment 1: The main purpose of amendment 1 is to: • Include additional safety assessments as requested by Health Authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees during the clinical trial application process. This will enhance the safety monitoring. • Amend the exclusion criteria to improve clarity. The exclusion criteria #2 was deleted because it was redundant with e.g. exclusion 11. The exclusion criteria #11 was amended to clarify that clinically significant comorbidities are exclusionary only if they are assessed by the investigator to have a clinically relevant impact on study participation, any of the study procedures, or on efficacy assessments. • Better align the rescue procedures and criteria with current clinical practice including changes to the definition of ROP disease that is unchanged, has minimally improved or has worsened. • Retain patients in the trial for further follow-up in the instances when they are administered with prohibited treatment. This will ensure an appropriate safety monitoring of these patients.
01 February 2017	Amendment 2: The main purpose of amendment 2 is to reduce the number from 300 patients planned to be treated in the study to approximately 180 patients planned to be randomized following approval by the European Medicine Agency to modify an agreed Paediatric Investigation Plan (PIP).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported