NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Ranibizumab

Trial Indication(s)

Retinopathy of prematurity (ROP)

Protocol Number

CRFB002H2301

Protocol Title

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

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: December 2015 (Actual)
Primary Completion Date: December 2017 (Actual)
Study Completion Date: December 2017 (Actual)

Reason for Termination (If applicable)

Not applicable

Study Design/Methodology

This was a randomized, multicenter, open-label, 3-arm, parallel-group, superiority study evaluating the efficacy and safety of intravitreal ranibizumab 0.1 mg, intravitreal ranibizumab 0.2 mg, and laser therapy (ratio 1:1:1) for the treatment of ROP. The study consisted of a screening period (screening and randomization could occur up to 3 days before the administration of the first investigational treatment), followed by a treatment and follow-up period (Day 1 to Day 169).

Centers

87 centers in 26 countries: Lithuania(1), France(2), Hungary(2), Belgium(2), Croatia(2), Austria(2), Estonia(1), Italy(4), India(6), Japan(17), United Kingdom(3), Greece(3), Czech Republic(3), Turkey(6), Denmark(1), Taiwan(2), Malaysia(2), Germany(2), Poland(2), Russia(5), Slovakia (Slovak Republic)(1), United States(12), Romania(3), Egypt(1), Mexico(1), Saudi Arabia(1)

Objectives:

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.

Key secondary objectives were:

- To demonstrate that intravitreal ranibizumab 0.1 mg has superior efficacy to laser therapy in the treatment of ROP as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting investigational treatment
- To demonstrate that intravitreal ranibizumab 0.2 mg had superior efficacy to intravitreal ranibizumab 0.1 mg in the treatment of ROP as measured by the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting investigational treatment

Other secondary objectives were:

- To evaluate the time to intervention with a second modality for ROP or development of unfavorable structural outcome or death
- To evaluate the recurrence of ROP receiving any post-baseline intervention at 24 weeks or before
- To evaluate the ocular and systemic safety of intravitreal ranibizumab 0.1 mg and 0.2 mg in the treatment of ROP as assessed by ocular examination, monitoring of adverse events (AEs) throughout the study, and by the assessment of length, weight, head circumference and lower leg length at Baseline, Day 85, and Day 169
- To evaluate the systemic pharmacokinetics (PK) of intravitreal ranibizumab in patients with ROP, as evaluated by sparse-sampling population PK methods
- To evaluate the effects of investigational treatment on systemic vascular endothelial growth factor (VEGF) levels in patients with ROP, as evaluated by sparse-sampling population concentration-response methods
- To assess the number of ranibizumab administrations needed in the treatment of patients with ROP

Test Product (s), Dose(s), and Mode(s) of Administration

Intravitreal injections of ranibizumab 0.1 mg and ranibizumab 0.2 mg.
Patients received their randomized treatment on Day 1. Re-treatment with ranibizumab for either eye occurred for worsening of ROP at least 28 days after the previous ranibizumab treatment in that eye. Up to 2 re-treatments with ranibizumab per eye to treat ROP recurrence were allowed.

Reference therapy consisted of laser ablation therapy (referred to hereafter as laser therapy).

Statistical Methods

A sequential testing procedure was used for primary and key secondary comparisons All hypotheses were tested at a pre-specified level of significance (two-sided α=0.05).
Missing data to be used for the statistical inference of the primary variable was imputed by eye. Imputation of missing data was only undertaken if the value of the primary variable was missing.
The primary analysis of the hypotheses was undertaken after imputing missing values related to the occurrence of active ROP and unfavorable structural outcomes at Week 24, assuming the following:

- If the last non-missing value of a criterion was “success”, then the missing value of the criterion at Week 24 remained missing
- If the last non-missing value of a criterion was “failure” then the missing value of the component at Week 24 was imputed as ”failure”

The imputed value of the primary variable was then derived from the imputed values of the individual components. The primary analysis was undertaken after imputing missing values of the primary variable at 24 weeks.
All secondary efficacy analyses were performed based on observed data unless otherwise specified. No imputation of missing data was undertaken on secondary efficacy variables.
No interim analysis was performed.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- preterm infants with a birth weight of less than 1500 g
- bilateral ROP with one of the following retinal findings in each eye: Zone I, stage 1+, 2+, 3 or 3+ disease, or Zone II, stage 3+ disease, or Aggressive posterior retinopathy of prematurity (AP-ROP)

Exclusion Criteria:
- ROP disease characteristic in either eye other than that listed above at the time of the first investigational treatment
- A history of hypersensitivity (either the patient or the mother) to any of the investigational treatments or to drugs of similar chemical classes
- Had received any previous surgical or nonsurgical treatment for ROP (e.g., ablative laser therapy or cryotherapy, vitrectomy)
- Had been previously exposed to any intravitreal or systemic anti-VEGF agent (either the patient or the mother during this child’s pregnancy)
- Had used (either the patient or the mother) other investigational drugs as part of another clinical study (other than vitamins and minerals) within 30 days or within 5 half-lives of the other investigational drug, whichever was longer

- Had ocular structural abnormalities that were assessed by the Investigator to have had a clinically significant impact on study assessments
- Had active ocular infection within 5 days before or on the day of first investigational treatment
- Had a history of hydrocephalus requiring treatment
- Had a history of any other neurological conditions that are assessed by the Investigator to have a significant risk of severe impact on visual function
- Had any other medical conditions or clinically significant comorbidities or personal circumstances that were assessed by the Investigator to have a clinically relevant impact on study participation, any of the study procedures, or on efficacy assessments (e.g., poor life expectancy, pupil not able to be adequately dilated, unable to comply with the visit schedule)

Participant Flow Table

Treatment (Day 1 - Baseline)

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Started	74	77	74
Safety Set	73	76	69
VEGF Set	19	26	51
PK Set	49	46	0
Completed	73	76	69
Not Completed	1	1	5
Subj/Guardian Decision	0	0	2
Physician Decision	1	1	1
Lost to Follow-up	0	0	1
Adverse Event	0	0	1

Follow-Up Phase (up to Day 169)

	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	1	0	0
Subject/Guardian Decision	1	0	1
Death	4	4	4
Withdrawal of Consent	1	1	0

Baseline Characteristics

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy	Total
Number of Participants [units: participants]	74	77	74	225
Age Continuous[1] (units: Weeks) Mean ± Standard Deviation				
	25.8±2.25	26.5±2.57	26.2±2.59	26.1±2.48
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)				
Female	41	40	37	118
Male	33	37	37	107

Race (NIH/OMB)
(units: Participants)
Count of Participants (Not Applicable)

American Indian or Alaska Native	0	0	0	0
Asian	27	22	23	72
Native Hawaiian or Other Pacific Islander	0	0	0	0
Black or African American	0	4	3	7
White	43	45	45	133
More than one race	0	0	0	0
Unknown or Not Reported	4	6	3	13

[1] Gestational age at birth (weeks)

Summary of Efficacy

Primary and key secondary objectives

- The highest treatment success (defined as absence of active ROP and absence of unfavorable structural outcomes measured at Week 24) with 80.0% was observed in the ranibizumab 0.2 mg group, compared to 75.0% in the ranibizumab 0.1 mg group and 66.2% in the laser group. The difference between ranibizumab 0.2 mg and laser was clinically relevant with an OR of 2.19 (95% CI [0.9932, 4.8235]), indicating that patients treated with ranibizumab 0.2 mg were 2 times more likely to achieve treatment success compared with laser therapy, even though the primary endpoint did not demonstrate statistical significance as the one-sided p-value (p=0.0254) was marginally above the significance level of 0.025.

Other secondary objectives

- A lower proportion of patients in both ranibizumab groups compared to the laser group required intervention for ROP in either eye at or before the 24-week assessment visit with a treatment modality other than the modality of the study treatment received at Baseline (i.e. patients who switched treatment; 11 patients (14.9%) for ranibizumab 0.2 mg and 13 patients (16.9%) for ranibizumab 0.1 mg vs. 18 patients (24.3%) for laser).

- Active ROP in either eye at the 24-week assessment visit was only reported in the ranibizumab 0.1 mg group (3 patients, 4.3%) but not in the ranibizumab 0.2 mg and laser groups.
- Unfavorable structural outcomes in either eye at or before the 24-week assessment visit were less common in the ranibizumab 0.2 mg group (1 patient, 1.4%) than in the ranibizumab 0.1 mg (5 patients, 6.7%) and laser (7 patients, 10.1%) groups.
- The proportion of patients with recurrence of ROP receiving any post-baseline intervention at or before 24 weeks (i.e. ranibizumab re-treatment or switch to laser in the ranibizumab groups, switch to ranibizumab treatment in the laser group) was comparable in both ranibizumab groups (23 patients (31.1%) for ranibizumab 0.2 mg and 24 patients (31.2%) for ranibizumab 0.1 mg). In the laser group, 14 patients (18.9%) received post-baseline study treatment.
- A similar proportion of patients in all treatment groups died at or before the 24-week assessment (4 patients (5.4%) in the ranibizumab 0.2 mg group, 4 patients (5.2%) in the ranibizumab 0.1 mg group, and 4 patients (5.4%) in the laser group).

Pharmacokinetic/pharmacodynamic and immunogenicity results

- After intravitreal administration, ranibizumab was detected in serum, with highest mean concentrations generally achieved on Day 1, within 24 hours after injection.
- Mean ranibizumab serum concentrations on Day 1 were approximately twice as high in the ranibizumab 0.2 mg group compared to the ranibizumab 0.1 mg group.
- Across treatment groups, there was a trend for a reduction in systemic VEGF concentrations between Day 1 and Day 15, with return toward Baseline by Day 29.
- Similar VEGF profiles were observed for ranibizumab- and laser-treated patients, despite there was a high variability in the VEGF data.

Primary Outcome Result(s)

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	74	77	74
Percentage of Participants with absence of active ROP			

and absence of unfavorable structural outcomes in both eyes at Week 24 (units: Percentage of Participants)			
	80.0	75.0	66.2

Statistical Analysis

Groups	Ranibizumab 0.2 mg, Ranibizumab 0.1 mg, Laser therapy	
Superiority		The primary efficacy variable was treatment success, defined as the absence of active ROP and absence of unfavorable structural outcomes in both eyes 24 weeks after starting study treatment.
P Value	0.0254	
Method	Cochran-Mantel-Haenszel	
Odds Ratio (OR)	2.19	
95 % Confidence Interval 2-Sided	0.9932 to 4.8235	

Secondary Outcome Result(s)

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	74	77	74
Percentage of Participants requiring Interventions with a second modality for ROP at Week 24 (units: Percentage of participants)			
	14.9	16.9	24.3

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	74	77	74
Number of Participants Experiencing an Event, from the first study treatment to the last study visit (units: Participants)			
	14	18	23

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

Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy

Number of Participants Analyzed [units: participants]	74	77	74
Percentage of Participants having recurrent ROP and receiving any post-baseline intervention at or before Week 24 (units: Percentage of participants)			
All participants	31.1	31.2	18.9
ZONE I	35.7	53.3	28.6
ZONE II	28.3	17.4	13.0

Percent of Participants with Ocular Adverse Events by Primary System Organ (SOCs) at Week 24

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	73	76	69
Percent of Participants with Ocular Adverse Events by Primary System Organ (SOCs) at Week 24 (units: Percent of participants)			
Mild	23.3	32.9	17.4
Moderate	4.1	6.6	13.0
Severe	2.7	1.3	2.9

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg
Number of Participants Analyzed [units: participants]	49	46

Mean change in Ranibizumab concentration in Pharmacokinetic serum samples over time at Day 1, Day 15 and Day 29 (units: picogram/milliliter (pg/mL)) Mean ± Standard Deviation		
Day 1 (Baseline)	24700.0 ± 52400.00	12100.0 ± 25500.0
Day 15	5830.0 ± 4750.0	27700.0 ± 144000
Day 29	1810.0 ± 2990.0	732.0 ± 535.0

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

	Ranibizumab 0.2 mg	**Ranibizumab 0.1 mg**	**Laser therapy**
Number of Participants Analyzed [units: participants]	19	26	51
Mean change in Vascular Endothelial Growth Factor (VEGF) levels over time at Day 1, Day 15 and Day 29 (units: picogram/milliliter (pg/mL)) Mean ± Standard Deviation			
Day 1	239.0 ± 226.0	230.0 ± 224.0	232.0 ± 240.0
Day 1 / no treatment modality switch	239.0 ± 226.0	239.0 ± 233.0	233.0 ± 245.0
Day 15	466.0 ± 1500.0	118.0 ± 129.0	180.0 ± 214.0
Day 15 / no treatment modality switch	498.0 ± 1560.0	124.0 ± 134.0	177.0 ± 224.0
Day 29	117.0 ± 84.0	176.0 ± 142.0	161.0 ± 132.0
Day 29 / no treatment modality switch	117.0 ± 84.0	139.0 ± 75.3	163.0 ± 138.0

Total Number of Ranibizumab Injections received at Week 24

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	73	76	69
Total Number of Ranibizumab Injections received at Week 24 (units: Injections)			
	73	76	13

Percent of Participants with Non-Ocular Adverse Events by Primary System Organ (SOCs) at Week 24

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	73	76	69
Percent of Participants with Non-Ocular Adverse Events by Primary System Organ (SOCs) at Week 24 (units: Percent of participants)			
Mild	37.0	27.6	31.9
Moderate	24.7	34.2	27.5
Severe	23.3	19.7	17.4

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy

Number of Participants Analyzed [units: participants]	73	76	69
Mean change from Baseline in Vital signs (Body Length, Head Circumference and Knee to Heel Length) at Day 85 and Day 169 (units: centimeter (cm)) Mean ± Standard Deviation			
Day 85 / Body Length	10.1 ± 2.59	11.0 ± 3.33	11.1 ± 3.65
Day 169 / Body Length	18.7 ± 3.28	18.6 ± 3.66	19.0 ± 4.50
Day 85 / Head Circumference	6.9 ± 1.96	6.5 ± 2.31	7.2 ± 2.13
Day 169 / Head Circumference	10.4 ± 2.12	10.3 ± 2.56	10.6 ± 2.61
Day 85 / Knee to Heel Length	2.9 ± 1.90	3.1 ± 1.65	3.1 ± 2.02
Day 169 / Knee to Heel Length	5.4 ± 2.86	5.1 ± 2.19	5.3 ± 2.15

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	73	76	69
Mean change from Baseline in Vital signs (Weight) at Day 85 and Day 169 (units: gram (g)) Mean ± Standard Deviation			
Day 85 / Weight	2198.9 ± 615.68	2149.9 ± 754.27	2182.7 ± 612.70
Day 169 / Weight	3794.3 ± 782.48	3716.7 ± 897.15	3826.0 ± 882.17

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

	Ranibizumab 0.2 mg	Ranibizumab 0.1 mg	Laser therapy
Number of Participants Analyzed [units: participants]	73	76	69
Mean change from Baseline in Vital signs (Sitting Blood Pressure) at Day 85 and Day 169 (units: millimeters of mercury (mmHg)) Mean ± Standard Deviation			
Day 85 / Sitting Diastolic Blood Pressure	8.1 ± 14.66	7.0 ± 14.25	9.8 ± 16.95
Day 85 / Sitting Systolic Blood Pressure	6.3 ± 15.85	9.4 ± 15.73	15.5 ± 16.85
Day 169 / Sitting Diastolic Blood Pressure	11.5 ± 15.60	11.8 ± 14.42	14.7 ± 17.05
Day 169 / Sitting Systolic Blood Pressure	10.2 ± 16.15	11.2 ± 13.45	17.7 ± 19.35

Summary of Safety

Exposure

- In the 2 ranibizumab groups, over 3/4 of patients (78.1% and 77.6%) did not require any ranibizumab re-treatment; in the laser group, 13 patients received ranibizumab (i.e., they switched to ranibizumab treatment), with a mean of 2.2 injections/patient.

Ocular AEs

- Overall, 76 patients (34.9%) experienced ocular AEs, with no clinically relevant differences between treatment groups. The most frequent ocular AE overall was retinal hemorrhage (23 patients, 10.6%), followed by conjunctival hemorrhage (14 patients, 6.4%), conjunctivitis (10 patients, 4.6%), and ROP (8 patients, 3.7%).

- The majority of ocular AEs were mild or moderate in severity; severe ocular AEs were reported for 2 patients (2.7%) in the ranibizumab 0.2 mg group, 1 patient (1.3%) in the ranibizumab 0.1 mg group, and 2 patients (2.9%) in the laser group.
- The most common related ocular AE, conjunctival hemorrhage, occurred more frequently with ranibizumab compared to laser (6 patients (8.2%) and 6 patients (7.9%) vs. 2 patients (2.9%)). All other related ocular AEs occurred with low incidences (< 3% overall) and in comparable proportions of patients across treatment groups.
- Overall, 9 patients (4.1%) experienced at least one ocular SAE. There were no clinically relevant differences between treatment groups; the most frequent ocular SAE was ROP (2.8% overall).
- There were no ocular AEs leading to permanent study discontinuation.

Non-ocular AEs

- Overall, 177 patients (81.2%) experienced non-ocular AEs, with no clinically relevant differences between treatment groups; the most frequent non-ocular AEs by PT were pyrexia (19 patients, 8.7%), dermatitis diaper (18 patients, 8.3%), anemia (18 patients, 8.3%), and nasopharyngitis (18 patients, 8.3%).
- Severe non-ocular AEs were reported for 44 patients (20.2%) overall (17 patients (23.3%) for ranibizumab 0.2 mg, 15 patients (19.7%) for ranibizumab 0.1 mg, 12 patients (17.4%) for laser), with no relevant differences between treatment groups. The majority of these severe AEs occurred in 1 or 2 patients only.
- The incidence of non-ocular SAEs was similar across treatment groups (70 patients, 32.1% overall); the most common non-ocular SAEs by PT were pneumonia, bronchiolitis, and bronchopulmonary dysplasia (all 6 patients (2.8%) overall), followed by apnea and respiratory failure (both 4 patients (1.8%) overall).
- The only non-ocular AE suspected to be related to study treatment was an SAE of respiratory failure (with fatal outcome) in the ranibizumab 0.1 mg group.
- Overall, 12 patients (5.5%) died during the study, with proportions similar across treatment groups (4 patients in each group). Except for 1 event of respiratory failure, none of the events leading to death was suspected by the Investigator to be related to study treatment.
- In addition to the 12 patients with death, 1 patient (in the ranibizumab 0.2 mg group; 1.4%) experienced a non-ocular AE of gastroenteritis leading to permanent study discontinuation.

Safety Results

All-Cause Mortality

	Ranibizumab 0.2 mg N = 73	Ranibizumab 0.1 mg N = 76	Laser N = 69
Total participants affected	4 (5.48%)	4 (5.26%)	4 (5.80%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit).
Additional Description	Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events fields "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.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment

	Ranibizumab 0.2 mg N = 73	Ranibizumab 0.1 mg N = 76	Laser N = 69
Total participants affected	26 (35.62%)	24 (31.58%)	24 (34.78%)
Blood and lymphatic system disorders			
Anaemia	1 (1.37%)	0 (0.00%)	0 (0.00%)

Cardiac disorders			
Arrhythmia	0 (0.00%)	1 (1.32%)	0 (0.00%)
Cardiac arrest	0 (0.00%)	1 (1.32%)	1 (1.45%)
Cardiac failure	0 (0.00%)	1 (1.32%)	0 (0.00%)
Cardiogenic shock	0 (0.00%)	1 (1.32%)	0 (0.00%)
Cardiopulmonary failure	1 (1.37%)	1 (1.32%)	0 (0.00%)
Cardio-respiratory arrest	0 (0.00%)	2 (2.63%)	0 (0.00%)
Congenital, familial and genetic disorders			
Hydrocele	0 (0.00%)	0 (0.00%)	1 (1.45%)
Ileal atresia	1 (1.37%)	0 (0.00%)	0 (0.00%)
Eye disorders			
Cataract	1 (1.37%)	0 (0.00%)	0 (0.00%)
Exophthalmos	0 (0.00%)	1 (1.32%)	0 (0.00%)
Eye disorder	0 (0.00%)	1 (1.32%)	0 (0.00%)
Retinopathy of prematurity	2 (2.74%)	1 (1.32%)	3 (4.35%)
Gastrointestinal disorders			
Abdominal discomfort	1 (1.37%)	0 (0.00%)	0 (0.00%)
Diarrhoea	0 (0.00%)	2 (2.63%)	0 (0.00%)
Gastrointestinal haemorrhage	1 (1.37%)	0 (0.00%)	0 (0.00%)
Gastrooesophageal reflux disease	0 (0.00%)	1 (1.32%)	1 (1.45%)
Ileal perforation	1 (1.37%)	0 (0.00%)	0 (0.00%)
Ileus	0 (0.00%)	1 (1.32%)	0 (0.00%)

Incarcerated inguinal hernia	2 (2.74%)	0 (0.00%)	0 (0.00%)
Inguinal hernia	1 (1.37%)	2 (2.63%)	0 (0.00%)
Necrotising colitis	0 (0.00%)	3 (3.95%)	0 (0.00%)
Vomiting	0 (0.00%)	1 (1.32%)	2 (2.90%)
General disorders and administration site conditions			
Cyst	1 (1.37%)	0 (0.00%)	0 (0.00%)
No adverse event	0 (0.00%)	1 (1.32%)	0 (0.00%)
Hepatobiliary disorders			
Hepatic failure	0 (0.00%)	1 (1.32%)	1 (1.45%)
Infections and infestations			
Bronchiolitis	2 (2.74%)	4 (5.26%)	0 (0.00%)
Bronchitis	1 (1.37%)	0 (0.00%)	1 (1.45%)
Conjunctivitis	0 (0.00%)	0 (0.00%)	1 (1.45%)
Cytomegalovirus infection	0 (0.00%)	0 (0.00%)	1 (1.45%)
Endophthalmitis	0 (0.00%)	1 (1.32%)	0 (0.00%)
Enterococcal sepsis	1 (1.37%)	0 (0.00%)	0 (0.00%)
Escherichia urinary tract infection	1 (1.37%)	0 (0.00%)	0 (0.00%)
Gastroenteritis	1 (1.37%)	0 (0.00%)	1 (1.45%)
Klebsiella sepsis	1 (1.37%)	0 (0.00%)	0 (0.00%)
Lower respiratory tract infection viral	0 (0.00%)	1 (1.32%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	2 (2.63%)	0 (0.00%)

Orbital infection	0 (0.00%)	1 (1.32%)	0 (0.00%)
Peritonitis	1 (1.37%)	0 (0.00%)	0 (0.00%)
Pneumonia	4 (5.48%)	0 (0.00%)	2 (2.90%)
Pneumonia bacterial	0 (0.00%)	0 (0.00%)	1 (1.45%)
Pneumonia respiratory syncytial viral	0 (0.00%)	0 (0.00%)	1 (1.45%)
Pneumonia staphylococcal	1 (1.37%)	0 (0.00%)	0 (0.00%)
Respiratory syncytial virus bronchiolitis	0 (0.00%)	0 (0.00%)	1 (1.45%)
Respiratory tract infection	0 (0.00%)	1 (1.32%)	0 (0.00%)
Rhinovirus infection	0 (0.00%)	0 (0.00%)	1 (1.45%)
Roseola	1 (1.37%)	0 (0.00%)	0 (0.00%)
Sepsis	0 (0.00%)	1 (1.32%)	2 (2.90%)
Septic shock	1 (1.37%)	1 (1.32%)	0 (0.00%)
Staphylococcal infection	0 (0.00%)	0 (0.00%)	1 (1.45%)
Staphylococcal sepsis	1 (1.37%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	0 (0.00%)	1 (1.32%)	0 (0.00%)
Urinary tract infection	1 (1.37%)	0 (0.00%)	0 (0.00%)
Viral infection	1 (1.37%)	1 (1.32%)	1 (1.45%)
Injury, poisoning and procedural complications			
Gastrointestinal stoma complication	1 (1.37%)	0 (0.00%)	1 (1.45%)
Greenstick fracture	1 (1.37%)	0 (0.00%)	0 (0.00%)
Investigations			

Blood potassium increased	0 (0.00%)	1 (1.32%)	0 (0.00%)
Oxygen saturation decreased	0 (0.00%)	0 (0.00%)	1 (1.45%)
Weight decreased	1 (1.37%)	0 (0.00%)	0 (0.00%)
Metabolism and nutrition disorders			
Dehydration	1 (1.37%)	0 (0.00%)	0 (0.00%)
Failure to thrive	1 (1.37%)	0 (0.00%)	0 (0.00%)
Hypernatraemia	0 (0.00%)	1 (1.32%)	0 (0.00%)
Hyperphosphatasaemia	1 (1.37%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Bone disorder	1 (1.37%)	0 (0.00%)	0 (0.00%)
Osteopenia	0 (0.00%)	0 (0.00%)	1 (1.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma	1 (1.37%)	1 (1.32%)	0 (0.00%)
Nervous system disorders			
Brain oedema	2 (2.74%)	0 (0.00%)	0 (0.00%)
Cerebellar haemorrhage	1 (1.37%)	0 (0.00%)	0 (0.00%)
Cerebral cyst	0 (0.00%)	0 (0.00%)	1 (1.45%)
Cognitive disorder	0 (0.00%)	1 (1.32%)	0 (0.00%)
Hydrocephalus	1 (1.37%)	0 (0.00%)	1 (1.45%)
Nystagmus	1 (1.37%)	0 (0.00%)	0 (0.00%)
Partial seizures	1 (1.37%)	0 (0.00%)	0 (0.00%)

Pregnancy, puerperium and perinatal conditions			
Perinatal brain damage	0 (0.00%)	0 (0.00%)	2 (2.90%)
Psychiatric disorders			
Breath holding	0 (0.00%)	1 (1.32%)	0 (0.00%)
Psychomotor retardation	0 (0.00%)	1 (1.32%)	0 (0.00%)
Renal and urinary disorders			
Renal failure	0 (0.00%)	1 (1.32%)	1 (1.45%)
Tubulointerstitial nephritis	0 (0.00%)	0 (0.00%)	1 (1.45%)
Respiratory, thoracic and mediastinal disorders			
Apnoea	0 (0.00%)	2 (2.63%)	2 (2.90%)
Aspiration	1 (1.37%)	0 (0.00%)	0 (0.00%)
Atelectasis	0 (0.00%)	0 (0.00%)	1 (1.45%)
Bronchopulmonary dysplasia	2 (2.74%)	2 (2.63%)	2 (2.90%)
Cough	0 (0.00%)	0 (0.00%)	1 (1.45%)
Dyspnoea	0 (0.00%)	1 (1.32%)	0 (0.00%)
Pneumonia aspiration	0 (0.00%)	1 (1.32%)	0 (0.00%)
Pulmonary hypertension	0 (0.00%)	0 (0.00%)	1 (1.45%)
Pulmonary vein stenosis	0 (0.00%)	1 (1.32%)	1 (1.45%)
Respiratory arrest	0 (0.00%)	1 (1.32%)	0 (0.00%)
Respiratory distress	1 (1.37%)	1 (1.32%)	0 (0.00%)
Respiratory failure	0 (0.00%)	3 (3.95%)	1 (1.45%)
Respiratory symptom	0 (0.00%)	0 (0.00%)	1 (1.45%)

Tracheomalacia	0 (0.00%)	1 (1.32%)	0 (0.00%)
Wheezing	0 (0.00%)	0 (0.00%)	1 (1.45%)
Skin and subcutaneous tissue disorders			
Purpura	1 (1.37%)	0 (0.00%)	0 (0.00%)
Social circumstances			
Dependence on oxygen therapy	1 (1.37%)	0 (0.00%)	0 (0.00%)
Vascular disorders			
Haemodynamic instability	0 (0.00%)	0 (0.00%)	1 (1.45%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit).
Additional Description	Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events fields "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.
Source Vocabulary for Table Default	MedDRA (20.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	4%

Ranibizumab 0.2 mg N = 73	**Ranibizumab 0.1 mg N = 76**	**Laser N = 69**

Total participants affected	43 (58.90%)	47 (61.84%)	37 (53.62%)
Blood and lymphatic system disorders			
Anaemia	4 (5.48%)	8 (10.53%)	5 (7.25%)
Anaemia neonatal	2 (2.74%)	4 (5.26%)	1 (1.45%)
Cardiac disorders			
Bradycardia	2 (2.74%)	5 (6.58%)	1 (1.45%)
Eye disorders			
Conjunctival haemorrhage	6 (8.22%)	6 (7.89%)	2 (2.90%)
Retinal haemorrhage	6 (8.22%)	10 (13.16%)	7 (10.14%)
Vitreous haemorrhage	0 (0.00%)	4 (5.26%)	0 (0.00%)
Gastrointestinal disorders			
Diarrhoea	4 (5.48%)	0 (0.00%)	1 (1.45%)
Gastrooesophageal reflux disease	5 (6.85%)	5 (6.58%)	4 (5.80%)
Inguinal hernia	3 (4.11%)	0 (0.00%)	2 (2.90%)
Vomiting	2 (2.74%)	4 (5.26%)	2 (2.90%)
General disorders and administration site conditions			
Pyrexia	9 (12.33%)	6 (7.89%)	4 (5.80%)
Infections and infestations			
Conjunctivitis	1 (1.37%)	6 (7.89%)	2 (2.90%)
Nasopharyngitis	7 (9.59%)	5 (6.58%)	4 (5.80%)

Pneumonia	1 (1.37%)	1 (1.32%)	6 (8.70%)
Rhinitis	3 (4.11%)	0 (0.00%)	2 (2.90%)
Sepsis	1 (1.37%)	0 (0.00%)	3 (4.35%)
Upper respiratory tract infection	6 (8.22%)	3 (3.95%)	1 (1.45%)
Urinary tract infection	3 (4.11%)	2 (2.63%)	2 (2.90%)
Musculoskeletal and connective tissue disorders			
Osteopenia	0 (0.00%)	4 (5.26%)	1 (1.45%)
Respiratory, thoracic and mediastinal disorders			
Apnoea	1 (1.37%)	4 (5.26%)	1 (1.45%)
Bronchopulmonary dysplasia	2 (2.74%)	3 (3.95%)	4 (5.80%)
Bronchospasm	3 (4.11%)	0 (0.00%)	1 (1.45%)
Cough	4 (5.48%)	2 (2.63%)	1 (1.45%)
Skin and subcutaneous tissue disorders			
Dermatitis diaper	8 (10.96%)	6 (7.89%)	4 (5.80%)

Other Relevant Findings

Other safety assessments

- No safety concerns arose from results in laboratory safety assessments.
- Treatment groups were similar in terms of body length, weight, head circumference, knee to heal length at Day 85 and Day 169 of the study. No clinically significant differences were observed for vital signs at Day 85 and Day 169.

Conclusion:

The highest treatment success with 80.0% was observed in the ranibizumab 0.2 mg group of preterm neonates with ROP. Patients treated with ranibizumab 0.2 mg were 2 times more likely to achieve treatment success compared with laser therapy, which is considered clinically relevant.

Ranibizumab treatment is safe and well tolerated in patients with ROP. The observed safety profile was as expected in a preterm population, and ocular SAEs were generally consistent with the established profile for ranibizumab in adults.

Date of Clinical Trial Report

13-Apr-2018