



Clinical trial results:

Randomized, Controlled, Multi-Center Study to Assess the Efficacy, Safety, and Tolerability of Intravitreal Aflibercept Compared to Laser Photocoagulation in Patients with Retinopathy of Prematurity

Summary

EudraCT number	2019-001764-29
Trial protocol	HU SK CZ BG BE PT GR RO
Global end of trial date	18 August 2022

Results information

Result version number	v1 (current)
This version publication date	02 March 2023
First version publication date	02 March 2023

Trial information

Trial identification

Sponsor protocol code	VGFTe-ROP-1920
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04101721
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Regeneron Pharmaceuticals, Inc.
Sponsor organisation address	777 Old Saw Mill River Rd., Tarrytown, NY, United States, 10591
Public contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.com
Scientific contact	Clinical Trials Administrator, Regeneron Pharmaceuticals, Inc., 001 844-734-6643, clinicaltrials@regeneron.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 August 2022
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	18 August 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to assess the efficacy of aflibercept compared to laser in patients diagnosed with retinopathy of prematurity (ROP). The secondary objectives of the study are to assess the need for a second treatment modality, to assess the recurrence of ROP in the study and to assess the safety and tolerability of aflibercept.

Protection of trial subjects:

It is the responsibility of both the sponsor and the investigator(s) to ensure that this clinical study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with the ICH guidelines for GCP and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 October 2019
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	Bulgaria: 5
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Korea, Republic of: 1
Country: Number of subjects enrolled	Romania: 2
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Taiwan: 1
Country: Number of subjects enrolled	Thailand: 50
Country: Number of subjects enrolled	Turkey: 9
Country: Number of subjects enrolled	United States: 37
Country: Number of subjects enrolled	Viet Nam: 5
Worldwide total number of subjects	127
EEA total number of subjects	7

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	127
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: -

Pre-assignment

Screening details:

137 participants were screened, 127 participants were randomized (94 participants to aflibercept and 33 to laser). 120 participants were treated (93 aflibercept, 27 laser), 7 were withdrawn before receiving any study intervention (aflibercept arm: 1 by parent/guardian; laser arm: 1 physician decision, 5 by parent/guardian).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
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Arm title	Laser photocoagulation
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Arm description:

Laser treatment to each eligible eye at baseline (Day 1), with supplementary laser treatments allowed. Multiple sessions within one week from baseline were counted as a single treatment. One or both eyes could be treated.

Arm type	Procedure/surgery
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No investigational medicinal product assigned in this arm

Arm title	Aflibercept 0.4 mg
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Arm description:

One intravitreal injection of aflibercept 0.4 mg (0.01 mL) per eligible eye at baseline (Day 1), with up to 2 re-injections at the same single dose allowed for each eligible eye if required and interval since last aflibercept injection was 28 or more days. One or both eyes could be treated.

Arm type	Experimental
Investigational medicinal product name	Aflibercept
Investigational medicinal product code	VEGF Trap-Eye
Other name	EYLEA
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

0.4 mg (0.01 mL) at baseline and up to 2 additional treatments

Number of subjects in period 1 ^[1]	Laser photocoagulation	Aflibercept 0.4 mg
Started	27	93
Completed	26	87
Not completed	1	6
Adverse event, serious fatal	-	1
Withdrawal By Parent/Guardian	1	2
Lost to follow-up	-	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The worldwide number of participants enrolled was 127, however, the baseline data are presented for the 120 participants treated.

Baseline characteristics

Reporting groups

Reporting group title	Laser photocoagulation
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Reporting group description:

Laser treatment to each eligible eye at baseline (Day 1), with supplementary laser treatments allowed. Multiple sessions within one week from baseline were counted as a single treatment. One or both eyes could be treated.

Reporting group title	Aflibercept 0.4 mg
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Reporting group description:

One intravitreal injection of aflibercept 0.4 mg (0.01 mL) per eligible eye at baseline (Day 1), with up to 2 re-injections at the same single dose allowed for each eligible eye if required and interval since last aflibercept injection was 28 or more days. One or both eyes could be treated.

Reporting group values	Laser photocoagulation	Aflibercept 0.4 mg	Total
Number of subjects	27	93	120
Age Categorical			
Units: Participants			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	27	93	120
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			
Chronological Age at Randomization			
Units: weeks			
arithmetic mean	11.09	9.76	
standard deviation	± 4.338	± 3.149	-
Gender Categorical			
Units: Participants			
Female	10	52	62
Male	17	41	58
Race			
Units: Subjects			
White	11	26	37
Black or African American	2	6	8
Asian	13	44	57
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Other	1	12	13
Not Reported	0	5	5
ROP Status by Investigator			
ROP (retinopathy of prematurity) classified by the investigator according to the International Classification for Retinopathy of Prematurity in at least one eye with one of the following retinal findings:			

Zone I, or Zone II, or AP(aggressive posterior)-ROP (Zone I, Zone II). Zone I is the innermost zone of the retina centered around the optic disc, surrounded by the more peripheral Zone II. AP-ROP is a rapidly progressive form of ROP, with posterior location, most commonly observed in Zone I, less common in posterior Zone II. AP-ROP, if untreated, usually progresses to retinal detachment.

Units: Subjects			
Zone I	5	16	21
Zone II	20	68	88
AP-ROP	2	9	11

End points

End points reporting groups

Reporting group title	Laser photocoagulation
Reporting group description: Laser treatment to each eligible eye at baseline (Day 1), with supplementary laser treatments allowed. Multiple sessions within one week from baseline were counted as a single treatment. One or both eyes could be treated.	
Reporting group title	Aflibercept 0.4 mg
Reporting group description: One intravitreal injection of aflibercept 0.4 mg (0.01 mL) per eligible eye at baseline (Day 1), with up to 2 re-injections at the same single dose allowed for each eligible eye if required and interval since last aflibercept injection was 28 or more days. One or both eyes could be treated.	

Primary: Percentage of participants with absence of active retinopathy of prematurity (ROP) and unfavorable structural outcomes from baseline to week 52 of chronological age

End point title	Percentage of participants with absence of active retinopathy of prematurity (ROP) and unfavorable structural outcomes from baseline to week 52 of chronological age
End point description: Active ROP was ROP requiring treatment and unfavorable structural outcome was defined as retinal detachment, macular dragging, macular fold, or retrolental opacity. (For participants with both eyes enrolled in the study, both eyes must meet the endpoint). Full analysis set (FAS): All randomized participants who received any study treatment. Analysis on the FAS will be performed according to the treatment assigned at baseline (as randomized).	
End point type	Primary
End point timeframe: Baseline to week 52 of chronological age	

End point values	Laser photocoagulation	Aflibercept 0.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: Percentage of participants				
number (not applicable)	77.8	79.6		

Statistical analyses

Statistical analysis title	Treatment difference (aflibercept vs. laser)
Statistical analysis description: Difference with confidence interval (CI) is calculated using Mantel-Haenszel weighting scheme adjusted by baseline ROP status.	
Comparison groups	Laser photocoagulation v Aflibercept 0.4 mg

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	non-inferiority ^[1]
Parameter estimate	Adjusted difference
Point estimate	1.81
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-15.71
upper limit	19.33

Notes:

[1] - Non-inferiority margin is 5%

Secondary: Percentage of participants requiring intervention with a second treatment modality from baseline to week 52 of chronological age

End point title	Percentage of participants requiring intervention with a second treatment modality from baseline to week 52 of chronological age
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End point description:

Second treatment modality includes any treatment in addition to that assigned to the participant at baseline. This includes per-protocol rescue treatment (laser for aflibercept group, aflibercept for laser group), anti-VEGF agents not part of study protocol (e.g., bevacizumab, ranibizumab, commercially-available aflibercept not provided as study medication), or any ocular surgery for the management of any retinal pathology secondary to ROP (e.g., vitrectomy, scleral buckle for retinal detachments). (FAS)

End point type	Secondary
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End point timeframe:

Baseline to to week 52 of chronological age

End point values	Laser photocoagulation	Aflibercept 0.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: Percentage of participants				
number (not applicable)	18.5	15.1		

Statistical analyses

Statistical analysis title	Treatment difference (aflibercept vs. laser)
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Statistical analysis description:

Difference with confidence interval (CI) is calculated using Mantel-Haenszel weighting scheme adjusted by baseline ROP status.

Comparison groups	Laser photocoagulation v Aflibercept 0.4 mg
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Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted difference
Point estimate	-3.66
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-19.86
upper limit	12.54

Secondary: Percentage of participants with recurrence of ROP through week 52 of chronological age

End point title	Percentage of participants with recurrence of ROP through week 52 of chronological age
End point description:	
Recurrence of disease is defined as the reappearance of the disease requiring further treatment (including retreatment or rescue), where both "presence of ROP" and "presence of active ROP requiring treatment" are marked as "Yes", after initial regression. Here, the initial regression is defined as, at a particular visit, absence of ROP or ROP treatment not required for active ROP, i.e., presence of ROP is marked as "No" or the presence of active ROP requiring treatment is marked as "No." (FAS)	
End point type	Secondary
End point timeframe:	
Baseline to week 52 of chronological age	

End point values	Laser photocoagulation	Aflibercept 0.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: Percentage of participants				
number (not applicable)	29.6	39.8		

Statistical analyses

Statistical analysis title	Treatment difference (aflibercept vs. laser)
Statistical analysis description:	
Difference with confidence interval (CI) is calculated using Mantel-Haenszel weighting scheme adjusted by baseline ROP status	
Comparison groups	Laser photocoagulation v Aflibercept 0.4 mg

Number of subjects included in analysis	120
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Adjusted difference
Point estimate	10.1
Confidence interval	
level	95.1 %
sides	2-sided
lower limit	-9.83
upper limit	30.02

Secondary: Percentage of participants with ocular treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)

End point title	Percentage of participants with ocular treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (TESAEs)
End point description: Safety analysis set (SAF): All randomized participants who received any study treatment (active or laser); it is based on the treatment actually received (as treated)	
End point type	Secondary
End point timeframe: Baseline to Week 52 of chronological age	

End point values	Laser photocoagulation	Aflibercept 0.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: Percentage of participants				
number (not applicable)				
% Ocular TEAEs	25.9	18.3		
% Ocular TESAEs	11.1	6.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of participants with systematic (non-ocular) TEAEs and TESAEs

End point title	Percentage of participants with systematic (non-ocular) TEAEs and TESAEs
End point description: SAF: All randomized participants who received any study treatment (active or laser); it is based on the treatment actually received (as treated)	
End point type	Secondary

End point timeframe:

Baseline to Week 52 of chronological age

End point values	Laser photocoagulation	Aflibercept 0.4 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	27	93		
Units: Percentage of participants				
number (not applicable)				
% Systematic TEAEs	51.9	47.3		
% Systematic TESAEs	7.4	12.9		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From signing of ICF to end of study (week 52 of chronological age visit)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	25.0
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Reporting groups

Reporting group title	Laser photocoagulation
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Reporting group description:

Laser treatment to each eligible eye at baseline (Day 1), with supplementary laser treatments allowed. Multiple sessions within one week from baseline were counted as a single treatment. One or both eyes could be treated.

Reporting group title	Aflibercept 0.4 mg
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Reporting group description:

One intravitreal injection of aflibercept 0.4 mg (0.01 mL) per eligible eye at baseline (Day 1), with up to 2 reinjections at the same single dose allowed for each eligible eye if required and interval since last aflibercept injection was 28 or more days. One or both eyes could be treated.

Serious adverse events	Laser photocoagulation	Aflibercept 0.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)	32 / 93 (34.41%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Investigations			
Oxygen saturation decreased			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Anaesthetic complication pulmonary			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative respiratory distress			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Prophylaxis against dehydration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Removal of foreign body from gastrointestinal tract			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Partial seizures			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lethargy			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Eye disorders			
Retinal detachment Study Eye			

subjects affected / exposed	2 / 27 (7.41%)	6 / 93 (6.45%)	
occurrences causally related to treatment / all	0 / 3	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage Study Eye			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrophy of globe Study Eye			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maculopathy Study Eye			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Corneal infiltrates Study Eye			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal scar Study Eye			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	1 / 27 (3.70%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			

subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Apnoeic attack			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choking			

subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Apnoea			
subjects affected / exposed	2 / 27 (7.41%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic respiratory disease			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 27 (3.70%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia viral			
subjects affected / exposed	1 / 27 (3.70%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neonatal infection			

subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device site infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis viral			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 27 (0.00%)	2 / 93 (2.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	1 / 27 (3.70%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device malfunction			

subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Poor feeding infant			
subjects affected / exposed	0 / 27 (0.00%)	1 / 93 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overfeeding of infant			
subjects affected / exposed	1 / 27 (3.70%)	0 / 93 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Laser photocoagulation	Aflibercept 0.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 27 (44.44%)	40 / 93 (43.01%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 27 (7.41%)	1 / 93 (1.08%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	4 / 27 (14.81%)	4 / 93 (4.30%)	
occurrences (all)	4	6	
Eye disorders			
Conjunctival haemorrhage Study Eye			
subjects affected / exposed	0 / 27 (0.00%)	5 / 93 (5.38%)	
occurrences (all)	0	7	
Strabismus Study Eye			

subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	6 / 93 (6.45%) 9	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	4 / 27 (14.81%)	4 / 93 (4.30%)	
occurrences (all)	5	4	
Gastrooesophageal reflux disease			
subjects affected / exposed	2 / 27 (7.41%)	5 / 93 (5.38%)	
occurrences (all)	2	5	
Inguinal hernia			
subjects affected / exposed	3 / 27 (11.11%)	4 / 93 (4.30%)	
occurrences (all)	3	4	
Umbilical hernia			
subjects affected / exposed	0 / 27 (0.00%)	5 / 93 (5.38%)	
occurrences (all)	0	5	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	2 / 27 (7.41%)	1 / 93 (1.08%)	
occurrences (all)	2	1	
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 27 (0.00%)	7 / 93 (7.53%)	
occurrences (all)	0	7	
Cough			
subjects affected / exposed	2 / 27 (7.41%)	3 / 93 (3.23%)	
occurrences (all)	2	3	
Wheezing			
subjects affected / exposed	2 / 27 (7.41%)	1 / 93 (1.08%)	
occurrences (all)	2	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	2 / 27 (7.41%)	5 / 93 (5.38%)	
occurrences (all)	2	8	
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	2 / 27 (7.41%)	2 / 93 (2.15%)	
occurrences (all)	2	2	

Infections and infestations Bacterial disease carrier subjects affected / exposed occurrences (all)	2 / 27 (7.41%) 2	1 / 93 (1.08%) 1	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 27 (0.00%) 0	6 / 93 (6.45%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 July 2019	Updated statistical sections to describe the Per Protocol Set (PPS) analysis, which is required for noninferiority studies. Removed reference to pooled analyses (with the Bayer sister study) as this is no longer planned; Clarified that collection of demographic and baseline data includes relevant maternal history; Clarified that the hearing test will be performed once only, at any time prior to discharge from the neonatal intensive care unit (NICU); Clarified that a second central nervous system imaging will be carried out prior to discharge from the NICU; Removed description of volumes for blood sampling, as this information is referenced in other study document(s); Added brief description of the RAINBOW study (in retinopathy of prematurity) for clarity

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported