Clinical trial results:
Open-label, randomized, two–arm, controlled study to assess the efficacy, safety, and tolerability of intravitreal (IVT) aflibercept compared to laser photocoagulation in patients with retinopathy of prematurity (ROP)

Summary

EudraCT number	2018-002611-99
Trial protocol	CZ SE NL PT GB BE DE SK AT BG PL ES HU LT EE LV GR IT RO
Global end of trial date	12 February 2021

Results information

Result version number	v1 (current)
This version publication date	28 August 2021
First version publication date	28 August 2021

Trial information

Trial identification

Sponsor protocol code	BAY86-5321/20090

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04004208
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000236-PIP05-18
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	12 February 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 February 2021
Global end of trial reached?	Yes
Global end of trial date	12 February 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of aflibercept in subjects diagnosed with retinopathy of prematurity (ROP) in comparison to laser

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonization guideline E6: Good Clinical Practice. Before entering the study, the informed consent was read by and explained to all parent(s)/legally authorized representative(s) of the patients. Parent(s)/legally authorized representative(s) of the patients signed informed consent form and could withdraw their consent at any time without any disadvantage and without having to provide a reason for this decision. Only investigators qualified by training and experience were selected as appropriate experts to investigate the study drug.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 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	Argentina: 3
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Bulgaria: 9
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	Czechia: 5
Country: Number of subjects enrolled	Spain: 5
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	Greece: 5
Country: Number of subjects enrolled	Hong Kong: 1
Country: Number of subjects enrolled	Hungary: 2
Country: Number of subjects enrolled	Israel: 1
Country: Number of subjects enrolled	Italy: 4
Country: Number of subjects enrolled	Japan: 17
Country: Number of subjects enrolled	Korea, Republic of: 4

Country: Number of subjects enrolled	Malaysia: 1
Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Portugal: 5
Country: Number of subjects enrolled	Romania: 7
Country: Number of subjects enrolled	Russian Federation: 18
Country: Number of subjects enrolled	Singapore: 1
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	Sweden: 1
Country: Number of subjects enrolled	Turkey: 10
Country: Number of subjects enrolled	Taiwan: 3
Country: Number of subjects enrolled	Ukraine: 4
Worldwide total number of subjects	118
EEA total number of subjects	50

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	118
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:

Study was conducted at 64 centers in 27 countries or regions, between 25-SEP-2019 (first subject first visit) and 12-Feb-2021 (last subject last visit)

Pre-assignment

Screening details:

121 subjects were screened. 3 subjects were screen failures. 118 subjects were enrolled, 75 subjects were randomized to the aflibercept arm and 43 to the laser arm. 113 subjects were treated, 5 subjects randomized to the laser photocoagulation arm were withdrawn before receiving any study intervention.

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
Arm title	Aflibercept 0.4 mg

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	BAY86-5321
Other name	Eylea
Pharmaceutical forms	Solution for injection
Routes of administration	Intravitreal use

Dosage and administration details:

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 title	Laser photocoagulation

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	Laser Photocoagulation

No investigational medicinal product assigned in this arm

Number of subjects in period 1[1]	Aflibercept 0.4 mg	Laser photocoagulation
Started	75	38
Completed	68	36
Not completed	7	2
COVID-19 pandemic	1	-

Physician decision	1	-
Adverse event, non-fatal	1	1
Death	3	-
Withdrawal by parent/guardian	1	1

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 subjects enrolled was 118, however, the baseline data is presented for the 113 subjects treated.

Baseline characteristics

Reporting groups	
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.	
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 values	Aflibercept 0.4 mg	Laser photocoagulation	Total
Number of subjects	75	38	113
Age Categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	75	38	113
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			
Units: weeks			
arithmetic mean	26.43	26	
standard deviation	± 2.1	± 1.6	-
Gender Categorical Units: Subjects			
Female	34	19	53
Male	41	19	60
RACE Units: Subjects			
White	55	28	83
Black or African American	2	0	2
Asian Indian	0	2	2
Chinese	4	0	4
Japanese	10	6	16
Korean	2	1	3
Asian: Other	1	0	1
American Indian or Alaska Native	0	1	1
Multiple	1	0	1
ROP classification by investigator			

Units: Subjects			
Zone I excluding AP-ROP	15	7	22
Zone II excluding AP-ROP	46	26	72
AP-ROP: Zone I	12	4	16
AP-ROP: Zone II	2	1	3

End points

End points reporting groups

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.

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.

Primary: Proportion of subjects with absence of active ROP and unfavorable structural outcomes

End point title	Proportion of subjects with absence of active ROP and unfavorable structural outcomes

End point description:

Active ROP was defined as ROP requiring treatment. Unfavorable structural outcomes included retinal detachment, macular dragging, macular fold, or retrolental opacity.

End point type	Primary

End point timeframe:

At 24 weeks after starting study treatment

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Proportion of subjects				
number (not applicable)	0.855	0.821		

Statistical analyses

Statistical analysis title	Treatment difference %

Statistical analysis description:

Bayesian analysis with non-informative prior distributions. Calculation of two-sided 90% credible interval for the treatment difference (aflibercept – laser photocoagulation).

Comparison groups	Aflibercept 0.4 mg v Laser photocoagulation

Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
Parameter estimate	Difference in proportions
Point estimate	0.034
Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.08
upper limit	0.162

Notes:

[1] - Non inferiority margin is 5%.
Confidence interval actually refers to a credible interval based on the Bayesian analysis.

Secondary: Proportion of subjects requiring intervention with a second treatment modality

End point title	Proportion of subjects requiring intervention with a second treatment modality

End point description:

A second treatment modality for ROP was either rescue treatment or any other surgical or nonsurgical treatment for ROP

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Proportion of subjects				
number (not applicable)	0.072	0.096		

Statistical analyses

Statistical analysis title	Treatment difference %

Statistical analysis description:

Bayesian analysis with non-informative prior distributions. Calculation of two-sided 90% credible interval for the treatment difference (aflibercept – laser photocoagulation).

Comparison groups	Aflibercept 0.4 mg v Laser photocoagulation
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[2]
Parameter estimate	Difference in proportions
Point estimate	-0.023

Confidence interval	
level	90 %
sides	2-sided
lower limit	-0.11
upper limit	0.046

Notes:

[2] - Confidence interval actually refers to a credible interval based on the Bayesian analysis.

Secondary: Proportion of subjects with recurrence of ROP

End point title	Proportion of subjects with recurrence of ROP

End point description:

Subjects with recurrence of ROP were defined as subjects requiring re-treatment or rescue treatment after in the past the absence of treatment-requiring active ROP had been confirmed by the investigator.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Proportion of subjects				
number (not applicable)	0.161	0.063		

Statistical analyses

Statistical analysis title	Treatment difference %

Statistical analysis description:

Bayesian analysis with non-informative prior distributions. Calculation of two-sided 90% credible interval for the treatment difference (aflibercept – laser photocoagulation).

Comparison groups	Aflibercept 0.4 mg v Laser photocoagulation
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	other[3]
Parameter estimate	Difference in proportions
Point estimate	0.096
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.019
upper limit	0.175

Notes:

[3] - Confidence interval actually refers to a credible interval based on the Bayesian analysis.

Secondary: Exploration of ROP activity scale proposed by the International Neonatal Consortium

End point title	Exploration of ROP activity scale proposed by the International Neonatal Consortium

End point description:

Eyes were evaluated for change in ROP activitiy scale proposed by the International Neonatal Consortium (2018). ROP Activity Scale values of 0 to 7 are considered mild, 8 to 12 are moderate, and 13 to 22 are severe.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Scores on a scale				
arithmetic mean (standard deviation)				
Baseline	16.20 (± 2.81)	15.63 (± 3.53)		
Change from baseline to Week 24	-15.42 (± 4.46)	-14.77 (± 4.19)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with ocular Treatment-emergent Adverse Events (TEAEs)

End point title	Percentage of subjects with ocular Treatment-emergent Adverse Events (TEAEs)

End point description:

A treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) that was observed or reported after the first and not later than 30 days after the last administration of study treatment.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Percentage				
number (not applicable)	38.7	36.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with ocular Serious Adverse Events (SAEs)

End point title	Percentage of subjects with ocular Serious Adverse Events (SAEs)

End point description:

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 28

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Percentage				
number (not applicable)	13.3	7.9		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with systemic TEAEs

End point title	Percentage of subjects with systemic TEAEs

End point description:

A treatment-emergent adverse event (TEAE) was defined as an adverse event (AE) that was observed or reported after the first and not later than 30 days after the last administration of study treatment.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Percentage				
number (not applicable)	52.0	63.2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with systemic SAEs

End point title	Percentage of subjects with systemic SAEs

End point description:

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 28

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Subjects				
number (not applicable)	24.0	36.8		

Statistical analyses

No statistical analyses for this end point

Secondary: Concentrations of free aflibercept in plasma

End point title	Concentrations of free aflibercept in plasma[4]

End point description:

Blood samples for determination of aflibercept concentrations in plasma were collected in the aflibercept 0.4 mg arm at Day 1 (within 24 hours after injection), and at weeks 2 and 4, and if feasible also at weeks 8, 12 and 24. Statistics for week 8, 12, 24 not calculated as > 1/3 of the concentrations were below the lower limit of quantification.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

Notes:

[4] - 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: Concentrations of free aflibercept in plasma are only applicable for aflibercept 0.4 mg arm

End point values	Aflibercept 0.4 mg			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: ng/mL				
arithmetic mean (standard deviation)				
WEEK 0, DAY 1	480.607 (± 884.724)			
WEEK 2	218.965 (± 358.933)			

WEEK 4	133.093 (± 205.052)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with anti-drug antibodies (ADA)

End point title	Number of subjects with anti-drug antibodies (ADA)[5]

End point description:

Immunogenicity was characterized by anti-drug antibody (ADA) responses in patients in the aflibercept 0.4 mg arm. Serum samples were taken at baseline prior to the injection and at 12 weeks after injection. ADA titers were summarized for 3 categories: Low (titer <1,000); Moderate (1,000 ≤ titer ≤ 10,000); High (titer >10,000).

End point type	Secondary

End point timeframe:

Baseline and 12 weeks after aflibercept injection

Notes:

[5] - 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: Number of subjects with anti-drug antibodies (ADA) is only applicable for aflibercept 0.4 mg arm

End point values	Aflibercept 0.4 mg			
Subject group type	Reporting group			
Number of subjects analysed	75			
Units: Subjects				
Baseline	0			
Week 12	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with potential neutralizing antibodies (NAb)

End point title	Number of subjects with potential neutralizing antibodies

End point description:

NAb status was evaluated for the samples that were positive in the ADA assay and had sufficient volume to analyze.

End point type	Secondary

End point timeframe:

At 12 weeks after aflibercept injection

Notes:

[6] - 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: Number of subjects with potential neutralizing antibodies (NAb) is only applicable for aflibercept 0.4 mg arm

End point values	Aflibercept 0.4 mg			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Subjects				
Week 12	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of aflibercept administrations

End point title	Number of aflibercept administrations

End point description:

Total number of injections in both eyes.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Subjects				
0 aflibercept administration	0	34		
1 aflibercept administration	4	0		
2 aflibercept administrations	55	3		
3 aflibercept administrations	6	1		
4 aflibercept administrations	10	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of laser treatments

End point title	Number of laser treatments

End point description:

Total number of laser treatment in both eyes. If multiple sessions of laser treatment were necessary within 1 week from baseline, they were counted as a single treatment.

End point type	Secondary

End point timeframe:

From baseline (Day 1) up to week 24.

End point values	Aflibercept 0.4 mg	Laser photocoagulation		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	75	38		
Units: Subjects				
0 laser treatment	70	0		
1 laser treatment	3	4		
2 laser treatments	2	30		
3 laser treatments	0	1		
4 laser treatments	0	2		
6 laser treatments	0	1		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

After the first administration and not later than 30 days after the last administration of study treatment, up to 24 weeks.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

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.

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.

Serious adverse events	Laser photocoagulation	Aflibercept 0.4 mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 38 (26.32%)	9 / 75 (12.00%)	
number of deaths (all causes)	0	3	
number of deaths resulting from adverse events	0	1	
Investigations			
Intraocular pressure increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
C-reactive protein increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (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			
Overdose			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac disorders			
Pulmonary valve stenosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Corneal oedema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal detachment			
subjects affected / exposed	2 / 38 (5.26%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy of prematurity			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vitreous haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Necrotising colitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (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			
Apnoea			

subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia aspiration			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infantile apnoea			
subjects affected / exposed	2 / 38 (5.26%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	1 / 38 (2.63%)	2 / 75 (2.67%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctivitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinitis			

subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
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 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Laser photocoagulation	Aflibercept 0.4 mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 38 (60.53%)	53 / 75 (70.67%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Haemangioma of liver			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Crying			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Injection site haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	3 / 75 (4.00%)	
occurrences (all)	0	3	
Injection site reaction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	

Pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 38 (0.00%)	3 / 75 (4.00%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	2 / 38 (5.26%)	2 / 75 (2.67%)	
occurrences (all)	2	2	
Bronchopulmonary dysplasia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Laryngeal stenosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Nasal obstruction			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Tachypnoea			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Stridor			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Rhonchi			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Respiratory distress			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Pulmonary hypertension			

subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Chronic respiratory disease			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Investigations			
Cardiac murmur			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Intraocular pressure increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	3	
Oxygen saturation decreased			
subjects affected / exposed	0 / 38 (0.00%)	3 / 75 (4.00%)	
occurrences (all)	0	4	
Brain stem auditory evoked response abnormal			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	3	
Otoacoustic emissions test abnormal			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	3	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Post procedural oedema			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Multiple use of single-use product			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Congenital, familial and genetic disorders			

Cryptorchism			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Ankyloglossia congenital			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Congenital arterial malformation			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Laryngomalacia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Bradycardia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Sinus tachycardia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Developmental coordination disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Intraventricular haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Intraventricular haemorrhage neonatal			
subjects affected / exposed	1 / 38 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Thalamus haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Hypoxic-ischaemic encephalopathy			

subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Neonatal seizure			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	3	1	
Anaemia neonatal			
subjects affected / exposed	2 / 38 (5.26%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Splenomegaly			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Auditory disorder			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	4 / 75 (5.33%)	
occurrences (all)	0	6	
Conjunctival oedema			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	4	
Corneal oedema			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Eyelid oedema			
subjects affected / exposed	3 / 38 (7.89%)	2 / 75 (2.67%)	
occurrences (all)	5	4	
Iris adhesions			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Keratitis			

subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Retinal artery occlusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Lenticular opacities			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Retinal detachment			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Retinal vascular disorder			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Retinal haemorrhage			
subjects affected / exposed	5 / 38 (13.16%)	4 / 75 (5.33%)	
occurrences (all)	6	7	
Retinopathy of prematurity			
subjects affected / exposed	1 / 38 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	2	3	
Swelling of eyelid			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Vitreous haemorrhage			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Vitreous opacities			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Vitreoretinal traction syndrome			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Macular fibrosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Abdominal distension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Cheilitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Dysphagia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Enterocolitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Flatulence			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Gastric haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 38 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Inguinal hernia			
subjects affected / exposed	1 / 38 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	1	3	
Umbilical hernia			
subjects affected / exposed	3 / 38 (7.89%)	1 / 75 (1.33%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	

Hepatobiliary disorders			
Cholestasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Hepatic lesion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Eczema infantile			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Dermatitis diaper			
subjects affected / exposed	1 / 38 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	1	2	
Dermatitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Haemorrhage subcutaneous			
subjects affected / exposed	3 / 38 (7.89%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
Intertrigo			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Glycosuria			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Haematuria			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Proteinuria			
subjects affected / exposed	1 / 38 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Leukocyturia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			

Adrenomegaly			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Cushingoid			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Osteopenia			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Extremity contracture			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Infections and infestations			
Bacterial disease carrier			
subjects affected / exposed	2 / 38 (5.26%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Bacteriuria			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Bronchiolitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Conjunctivitis			
subjects affected / exposed	3 / 38 (7.89%)	3 / 75 (4.00%)	
occurrences (all)	5	5	
Cytomegalovirus infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Nasopharyngitis			

subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Rhinitis			
subjects affected / exposed	0 / 38 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
Sepsis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Urinary tract infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Oral fungal infection			
subjects affected / exposed	1 / 38 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
Rhinovirus infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Alkalosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
Hypoglycaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Metabolic acidosis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
Hypomagnesaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 June 2020	Pharmacokinetic samples were added at weeks 8, 12, and 24 to further characterize the PK profile in subjects treated with aflibercept, document the further elimination of free (pharmacologically active) aflibercept and bound aflibercept from plasma, and provide estimates of the elimination half-life.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported