



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

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

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 2 / 75 (2.67%) 2 | |
| Neonatal seizure subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 38 (5.26%) 3 | 1 / 75 (1.33%) 1 | |
| Anaemia neonatal subjects affected / exposed occurrences (all) | 2 / 38 (5.26%) 2 | 0 / 75 (0.00%) 0 | |
| Splenomegaly subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Ear and labyrinth disorders | | | |
| Auditory disorder subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 | 0 / 75 (0.00%) 0 | |
| Eye disorders | | | |
| Conjunctival haemorrhage subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 4 / 75 (5.33%) 6 | |
| Conjunctival oedema subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 2 / 75 (2.67%) 4 | |
| Corneal oedema subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 2 | 0 / 75 (0.00%) 0 | |
| Eyelid oedema subjects affected / exposed occurrences (all) | 3 / 38 (7.89%) 5 | 2 / 75 (2.67%) 4 | |
| Iris adhesions subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 | 0 / 75 (0.00%) 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 occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Cushingoid subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Osteopenia subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 2 / 75 (2.67%) 2 | |
| Extremity contracture subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Infections and infestations | | | |
| Bacterial disease carrier subjects affected / exposed occurrences (all) | 2 / 38 (5.26%) 2 | 0 / 75 (0.00%) 0 | |
| Bacteriuria subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 | 0 / 75 (0.00%) 0 | |
| Bronchiolitis subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Conjunctivitis subjects affected / exposed occurrences (all) | 3 / 38 (7.89%) 5 | 3 / 75 (4.00%) 5 | |
| Cytomegalovirus infection subjects affected / exposed occurrences (all) | 1 / 38 (2.63%) 1 | 0 / 75 (0.00%) 0 | |
| Ear infection subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 1 | |
| Infection subjects affected / exposed occurrences (all) | 0 / 38 (0.00%) 0 | 1 / 75 (1.33%) 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