



Clinical trial results:

A multicenter, randomized, double-blind, phase II study to evaluate the tolerability of an induction dose escalation of everolimus in patients with metastatic breast cancer

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2014-005126-35 |
| Trial protocol | DE |
| Global end of trial date | 19 January 2021 |

Results information

| | |
|-----------------------------------|---|
| Result version number | v1 (current) |
| This version publication date | 09 September 2022 |
| First version publication date | 09 September 2022 |
| Summary attachment (see zip file) | DESIREE_CSR_Synopsis (CSR_DESIREE_final_Synopsis.pdf) |

Trial information

Trial identification

| | |
|-----------------------|---------------|
| Sponsor protocol code | GBG86-DESIREE |
|-----------------------|---------------|

Additional study identifiers

| | |
|------------------------------------|-------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02387099 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Novartis: CRAD001JDE60T |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | GBG Forschungs GmbH |
| Sponsor organisation address | Martin Behaim Str. 12, Neu-Isenburg, Germany, 63263 |
| Public contact | Medicine and Research, GBG Forschungs GmbH, publications@gbg.de |
| Scientific contact | Medicine and Research, GBG Forschungs GmbH, publications@gbg.de |

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? | No |

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 September 2021 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 19 January 2021 |
| Global end of trial reached? | Yes |
| Global end of trial date | 19 January 2021 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the cumulative rate of stomatitis grade 2-4 (WHO's oral toxicity scale (OTS)) at 12 weeks after start of treatment using a conventional and a dose-escalating schema of everolimus in combination with exemestane in patients with metastatic breast cancer and progression or relapse after non-steroidal aromatase-inhibitor treatment.

Protection of trial subjects:

The trial protocol including amendments, the patient information and the informed consent were reviewed and approved from a properly constituted IRB/IEC for each site prior to the study start. The trial was in compliance with the International Conference on Harmonization (ICH) - Harmonized Tripartite Guideline for Good Clinical Practice (GCP) (E6), and the Commission Directives in the European Community as well as with the applicable German national laws and regulations, and with Declaration of Helsinki and its revisions in all aspects of preparation, monitoring, reporting, auditing, and archiving.

Background therapy:

exemestane treatment

Evidence for comparator:

Standard of Care (SoC)

| | |
|---|---------------|
| Actual start date of recruitment | 01 April 2015 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------|
| Country: Number of subjects enrolled | Germany: 156 |
| Worldwide total number of subjects | 156 |
| EEA total number of subjects | 156 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| 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) | 81 |
| From 65 to 84 years | 73 |
| 85 years and over | 2 |

Subject disposition

Recruitment

Recruitment details:

Between June 2015 and October 2020, 208 patients were screened, 160 patients were randomised to receive either EVE esc (80 patients) or EVE 10mg (80 patients), and 156 started treatment.

Pre-assignment

Screening details:

Postmenopausal women with locally advanced or metastatic HR+/HER2- BC not amenable to curative treatment by surgery or radiotherapy alone and without indication for chemotherapy (e.g. symptomatic visceral metastasis).

Period 1

| | |
|------------------------------|--|
| Period 1 title | overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

After a dose escalation period of 3 weeks which was double-blinded (blinded phase), the interventional part of the study was completed and the patient continued on prescribed everolimus as part of SoC (open-label phase).

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | EVE esc |

Arm description:

A total of 80 patients were randomised to receive dose escalating schema of everolimus (EVE esc) in combination with exemestane and started treatment. 22 patients completed 24 weeks treatment with everolimus and 23 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | Afinitor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

week 1: 3x2.5 mg placebo and 1x2.5 mg everolimus;
week 2: 2x2.5 mg placebo and 2x2.5 mg everolimus;
week 3: 1x2.5 mg placebo and 3x2.5 mg everolimus;
weeks 4-24: 4x2.5 mg everolimus (open-label).

| | |
|------------------|----------|
| Arm title | EVE 10mg |
|------------------|----------|

Arm description:

A total of 80 patients were randomised to receive a conventional schema of 10 mg of everolimus (EVE 10mg) in combination with exemestane, 76 started treatment (4 patients did not start study treatment: one due to multiple brain metastases, 2 due to too long drug delivery time before start of study treatment, and one due to withdrew informed consent). 26 patients completed 24 weeks treatment with everolimus and 22 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

| | |
|--|------------|
| Investigational medicinal product name | Everolimus |
| Investigational medicinal product code | |
| Other name | Afinitor |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Standard administration schedule of everolimus /everolimus-placebo: 10 mg/day (4 tablets of 2.5 mg), orally administrated

| Number of subjects in period 1 | EVE esc | EVE 10mg |
|---------------------------------------|---------|----------|
| Started | 80 | 76 |
| Completed | 22 | 26 |
| Not completed | 58 | 50 |
| Adverse event, serious fatal | 1 | 3 |
| Adverse event, non-fatal | 8 | 10 |
| patient/investigation decision | 10 | 12 |
| disease progression | 39 | 25 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | EVE esc |
|-----------------------|---------|

Reporting group description:

A total of 80 patients were randomised to receive dose escalating schema of everolimus (EVE esc) in combination with exemestane and started treatment. 22 patients completed 24 weeks treatment with everolimus and 23 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

| | |
|-----------------------|----------|
| Reporting group title | EVE 10mg |
|-----------------------|----------|

Reporting group description:

A total of 80 patients were randomised to receive a conventional schema of 10 mg of everolimus (EVE 10mg) in combination with exemestane, 76 started treatment (4 patients did not start study treatment: one due to multiple brain metastases, 2 due to too long drug delivery time before start of study treatment, and one due to withdrew informed consent). 26 patients completed 24 weeks treatment with everolimus and 22 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

| Reporting group values | EVE esc | EVE 10mg | Total |
|------------------------|---------|----------|-------|
| Number of subjects | 80 | 76 | 156 |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 40 | 41 | 81 |
| From 65-84 years | 38 | 35 | 73 |
| 85 years and over | 2 | 0 | 2 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 80 | 76 | 156 |
| Male | 0 | 0 | 0 |

End points

End points reporting groups

| | |
|-----------------------|---------|
| Reporting group title | EVE esc |
|-----------------------|---------|

Reporting group description:

A total of 80 patients were randomised to receive dose escalating schema of everolimus (EVE esc) in combination with exemestane and started treatment. 22 patients completed 24 weeks treatment with everolimus and 23 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

| | |
|-----------------------|----------|
| Reporting group title | EVE 10mg |
|-----------------------|----------|

Reporting group description:

A total of 80 patients were randomised to receive a conventional schema of 10 mg of everolimus (EVE 10mg) in combination with exemestane, 76 started treatment (4 patients did not start study treatment: one due to multiple brain metastases, 2 due to too long drug delivery time before start of study treatment, and one due to withdrew informed consent). 26 patients completed 24 weeks treatment with everolimus and 22 completed 24 weeks treatment with exemestane. Note, the number of patients started treatment is given for "started".

Primary: Rate of stomatitis episodes grade ≥ 2 at 12 weeks

| | |
|-----------------|--|
| End point title | Rate of stomatitis episodes grade ≥ 2 at 12 weeks |
|-----------------|--|

End point description:

The primary endpoint was the rate of stomatitis episodes grade ≥ 2 within the first 12 weeks of treatment start. Patients with first episode of grade ≥ 2 stomatitis which occurred during 12-week period after start of everolimus were included in the numerator of the cumulative rate. Patients in whom the occurrence of stomatitis could not be assessed during 12-week period due to premature treatment discontinuation as a results of adverse events (AEs), patient's or investigator's decision were considered as having an episode of stomatitis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

12 weeks

| End point values | EVE esc | EVE 10mg | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 80 | 76 | | |
| Units: percent | | | | |
| number (confidence interval 95%) | | | | |
| Stomatitis episodes | 28.8 (19.2 to 40.0) | 46.1 (34.5 to 57.9) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | Rate of stomatitis episodes - differences |
|----------------------------|---|

Statistical analysis description:

Primary endpoint analysis was performed in the modified intent-to-treat (mITT) analysis set including all randomised patients who started therapy.

| | |
|-------------------|--------------------|
| Comparison groups | EVE esc v EVE 10mg |
|-------------------|--------------------|

| | |
|---|----------------------------|
| Number of subjects included in analysis | 156 |
| Analysis specification | Pre-specified |
| Analysis type | superiority ^[1] |
| P-value | = 0.039 |
| Method | Chi-squared corrected |
| Parameter estimate | absolute differences |
| Point estimate | -17.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -32.3 |
| upper limit | -2.3 |

Notes:

[1] - Differences in the rates of stomatitis episodes were tested using a continuity-corrected χ^2 -test ($\alpha=0.20$)

| | |
|-----------------------------------|--|
| Statistical analysis title | Rate of stomatitis episodes - odds ratio |
|-----------------------------------|--|

Statistical analysis description:

The primary endpoint analysis was performed on the modified intent-to-treat (mITT) analysis set including all randomized patients who started therapy. Odds ratios (OR) with the 95% CI are displayed.

| | |
|---|----------------------------|
| Comparison groups | EVE esc v EVE 10mg |
| Number of subjects included in analysis | 156 |
| Analysis specification | Post-hoc |
| Analysis type | superiority ^[2] |
| P-value | = 0.011 ^[3] |
| Method | Regression, Logistic |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 0.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.2 |
| upper limit | 0.81 |

Notes:

[2] - Multivariate logistic regression analysis adjusted for age, ECOG PS, BMI, and number of previous therapy lines for mBC

[3] - multivariate logistic regression analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events occurring during the 24-week treatment period were reported.

Adverse event reporting additional description:

AEs are reported per patient during the complete treatment duration for the overall safety population. Non-serious AEs any grade per patient occurring more frequently (> 20%) are presented. Note, overall number of single AE occurrences per term was not assessed, only per patient; SAEs are reported regardless of causality

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | EVE esc |
|-----------------------|---------|

Reporting group description:

dose escalating schema of everolimus in combination with exemestane. Note, one patient who was randomized to EVE esc arm received EVE 10mg during the first 3 weeks of treatment and therefore this patient was analysed in the EVE 10mg arm (EVE esc N=79)

| | |
|-----------------------|----------|
| Reporting group title | EVE 10mg |
|-----------------------|----------|

Reporting group description:

Conventional dosing schedule of everolimus starting with 10 mg at first dose in combination with exemestane. Note, one patient who was randomized to EVE esc arm received EVE 10mg during the first 3 weeks of treatment and therefore this patient was analysed in the EVE 10mg arm. Another patient in the EVE 10mg was excluded from the safety analysis due to uncompleted safety documentation (missing data) (EVE 10mg N=76)

| Serious adverse events | EVE esc | EVE 10mg | |
|---|------------------|------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 23 / 79 (29.11%) | 22 / 76 (28.95%) | |
| number of deaths (all causes) | 1 | 3 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Lymphoedema | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|----------------|--|
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Surgical and medical procedures | | | |
| Bone operation | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenterostomy | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleurodesis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 4 / 76 (5.26%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 3 / 76 (3.95%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 3 / 79 (3.80%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (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 | | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 3 / 76 (3.95%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ascites | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 2 / 76 (2.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 2 / 76 (2.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyloric stenosis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Jaundice | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Cystitis haemorrhagic | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydronephrosis | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis norovirus | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotitis | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngeal abscess | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 79 (2.53%) | 0 / 76 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound infection | | | |
| subjects affected / exposed | 0 / 79 (0.00%) | 1 / 76 (1.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 79 (1.27%) | 0 / 76 (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 | EVE esc | EVE 10mg | |
|---|-------------------|-------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 79 / 79 (100.00%) | 76 / 76 (100.00%) | |
| Investigations | | | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 41 / 79 (51.90%) | 36 / 76 (47.37%) | |
| occurrences (all) | 41 | 36 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 63 / 79 (79.75%) | 55 / 76 (72.37%) | |
| occurrences (all) | 63 | 55 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 53 / 79 (67.09%) | 41 / 76 (53.95%) | |
| occurrences (all) | 53 | 41 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 24 / 79 (30.38%) | 31 / 76 (40.79%) | |
| occurrences (all) | 24 | 31 | |
| Weight decreased | | | |
| subjects affected / exposed | 16 / 79 (20.25%) | 22 / 76 (28.95%) | |
| occurrences (all) | 16 | 22 | |
| serum cholestrol increased | | | |
| subjects affected / exposed | 61 / 79 (77.22%) | 65 / 76 (85.53%) | |
| occurrences (all) | 61 | 65 | |
| LDL/HDL ratio increased | | | |
| subjects affected / exposed | 41 / 79 (51.90%) | 55 / 76 (72.37%) | |
| occurrences (all) | 41 | 55 | |
| LDL/HDL ratio decreased | | | |
| subjects affected / exposed | 76 / 79 (96.20%) | 71 / 76 (93.42%) | |
| occurrences (all) | 76 | 71 | |
| Nervous system disorders | | | |

| | | | |
|--|------------------------|------------------------|--|
| Headache subjects affected / exposed occurrences (all) | 24 / 79 (30.38%) 24 | 17 / 76 (22.37%) 17 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 59 / 79 (74.68%) 59 | 62 / 76 (81.58%) 62 | |
| Leukopenia subjects affected / exposed occurrences (all) | 53 / 79 (67.09%) 53 | 51 / 76 (67.11%) 51 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 29 / 79 (36.71%) 29 | 36 / 76 (47.37%) 36 | |
| Neutropenia subjects affected / exposed occurrences (all) | 33 / 79 (41.77%) 33 | 29 / 76 (38.16%) 29 | |
| General disorders and administration site conditions | | | |
| Fatigue subjects affected / exposed occurrences (all) | 42 / 79 (53.16%) 42 | 40 / 76 (52.63%) 40 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 28 / 79 (35.44%) 28 | 19 / 76 (25.00%) 19 | |
| Nausea subjects affected / exposed occurrences (all) | 23 / 79 (29.11%) 23 | 26 / 76 (34.21%) 26 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 24 / 79 (30.38%) 24 | 21 / 76 (27.63%) 21 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 16 / 79 (20.25%) 16 | 23 / 76 (30.26%) 23 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|---|------------------------|------------------------|--|
| Arthralgia subjects affected / exposed occurrences (all) | 18 / 79 (22.78%) 18 | 22 / 76 (28.95%) 22 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 22 / 79 (27.85%) 22 | 16 / 76 (21.05%) 16 | |
| Hypertriglyceridaemia subjects affected / exposed occurrences (all) | 58 / 79 (73.42%) 58 | 55 / 76 (72.37%) 55 | |
| Hypoglycaemia subjects affected / exposed occurrences (all) | 16 / 79 (20.25%) 16 | 9 / 76 (11.84%) 9 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 45 / 79 (56.96%) 45 | 46 / 76 (60.53%) 46 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported