# Clinical trial results:
# A Phase 2, Randomized, Open-Label, Two-arm Study to Assess the Efficacy and Safety of the Epigenetic Modifying Effects of CC-486 (Oral Azacitidine) in Combination With Fulvestrant in Postmenopausal Women with ER+, HER2- Metastatic Breast Cancer Who Have Progressed on an Aromatase Inhibitor

## Summary

| | |
|---|---|
| EudraCT number | 2014-003220-52 |
| Trial protocol | BE ES DE FR IT |
| Global end of trial date | 21 November 2017 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 06 December 2018 |
| First version publication date | 06 December 2018 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | CC-486-BRSTM-001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02374099 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Celgene Corporation |
| Sponsor organisation address | 86 Morris Avenue, Summit, United States, 07901 |
| Public contact | Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com |
| Scientific contact | Ileana Elias, Celgene Corporation, 01 647-968-4300, ilelias@celgene.com |

Notes:

**Paediatric regulatory details**

| | |
|---|---|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 02 March 2018 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 21 November 2017 |
| Was the trial ended prematurely? | Yes |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of the study is to evaluate the efficacy of CC-486 in combination with fulvestrant relative to fulvestrant monotherapy, by estimation of the hazard ratio of progression free survival (PFS).

Protection of trial subjects:

The study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 15 March 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 | France: 15 |
| Country: Number of subjects enrolled | Italy: 23 |
| Country: Number of subjects enrolled | United States: 17 |
| Country: Number of subjects enrolled | Belgium: 13 |
| Country: Number of subjects enrolled | Germany: 8 |
| Country: Number of subjects enrolled | Spain: 21 |
| Worldwide total number of subjects | 97 |
| EEA total number of subjects | 80 |

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) | 54 |

| | |
|---|---|
| From 65 to 84 years | 43 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 35 sites in Spain, Germany, Belgium, Italy and the United States.

### Pre-assignment

Screening details:

The study enrolled adult, postmenopausal women, with metastatic breast cancer who progressed on an aromatase inhibitor. Participants were randomly assigned in a 1:1 ratio to one of two treatment arms to CC-486 tablets and fulvestrant or fulvestrant alone.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | CC-486 and Fulvestrant |

Arm description:

Participants received CC-486 tablets by mouth (PO) daily (QD) on days 1-21 of each 28 day treatment cycle and fulvestrant 500 mg by intramuscular injection (IM) on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up withdrawal of consent, or lost to follow-up.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | CC-486 |
| Investigational medicinal product code | |
| Other name | Oral Azacitidine |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

300 mg of CC-486 tablets by mouth daily (QD) on days 1-21 of each 28 day-cycle

| | |
|---|---|
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | Faslodex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

500 mg fulvestrant administered by intramuscular (IM) injection on days 1 and 15 of cycle 1 and on day 1 of subsequent cycles.

| | |
|---|---|
| **Arm title** | Fulvestrant |

Arm description:

Participants received fulvestrant 500 mg by intramuscular injection on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | Faslodex |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

500 mg fulvestrant administered by intramuscular (IM) injection on days 1 and 15 of cycle 1 and on day 1 of subsequent cycles.

| **Number of subjects in period 1** | CC-486 and Fulvestrant | Fulvestrant |
|---|---|---|
| Started | 48 | 49 |
| Participants Treated | 46 | 48 |
| Completed | 0 | 0 |
| Not completed | 48 | 49 |
| Consent withdrawn by subject | 5 | 1 |
| Randomized, but not treated | 2 | 1 |
| Adverse event, non-fatal | 1 | - |
| Progressive Disease | 35 | 40 |
| Miscellaneous | 2 | 3 |
| Study Terminated by Sponsor | 3 | 4 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | CC-486 and Fulvestrant |
| Reporting group description: | |
| Participants received CC-486 tablets by mouth (PO) daily (QD) on days 1-21 of each 28 day treatment cycle and fulvestrant 500 mg by intramuscular injection (IM) on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up withdrawal of consent, or lost to follow-up. | |
| Reporting group title | Fulvestrant |
| Reporting group description: | |
| Participants received fulvestrant 500 mg by intramuscular injection on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up. | |

| Reporting group values | CC-486 and Fulvestrant | Fulvestrant | Total |
|---|---|---|---|
| Number of subjects | 48 | 49 | 97 |
| Age Categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| 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) | 29 | 25 | 54 |
| From 65-84 years | 19 | 24 | 43 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous<br>Units: years | | | |
| arithmetic mean | 62.6 | 62.9 | |
| standard deviation | ± 10.99 | ± 10.03 | - |
| Gender Categorical<br>Units: Subjects | | | |
| Female | 48 | 49 | 97 |
| Race<br>Units: Subjects | | | |
| White | 34 | 39 | 73 |
| Asian | 0 | 1 | 1 |
| American Indian/Alaska Native | 1 | 0 | 1 |
| Not Collected or Reported | 13 | 9 | 22 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) | | | |
| ECOG performance status is used by doctors and researchers to assess how a subject's disease is progressing, assess how the disease affects the daily living activities of the subject and determine appropriate treatment and prognosis. 0 = Fully Active (Most Favorable Activity); 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, No self-care (Least Favorable Activity) | | | |
| Units: Subjects | | | |
| 0 = Fully Active | 36 | 21 | 57 |

| | | | |
|---|---|---|---|
| 1 = Restrictive but ambulatory | 12 | 28 | 40 |
| 2 = = Ambulatory but unable to work | 0 | 0 | 0 |
| 3 = Limited Self Care | 0 | 0 | 0 |
| Time from Primary Diagnosis of Breast Cancer to Study Randomization | | | |
| Units: months | | | |
| arithmetic mean | 119.05 | 95.57 | |
| standard deviation | ± 70.322 | ± 76.434 | - |
| Duration of Prior Hormonal Anti-Cancer Therapy | | | |
| Units: Months | | | |
| arithmetic mean | 31.39 | 35.84 | |
| standard deviation | ± 14.830 | ± 27.409 | - |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | CC-486 and Fulvestrant |
| Reporting group description: | |
| Participants received CC-486 tablets by mouth (PO) daily (QD) on days 1-21 of each 28 day treatment cycle and fulvestrant 500 mg by intramuscular injection (IM) on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up withdrawal of consent, or lost to follow-up. | |
| Reporting group title | Fulvestrant |
| Reporting group description: | |
| Participants received fulvestrant 500 mg by intramuscular injection on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up. | |

### Primary: Kaplan-Meier Estimate of Progression Free Survival (PFS)

| | |
|---|---|
| End point title | Kaplan-Meier Estimate of Progression Free Survival (PFS) |
| End point description: | |
| Progression-free survival was defined as the duration from the date of randomization to the date of disease progression based on investigator's assessment using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 or death (from any cause), whichever occurred first. Per RECIST 1.1, progressive disease (PD) was defined as at least a 20% increase in the sum of diameters of target or non-target lesions from nadir or appearance of a new lesion. The Intent-to-treat (ITT) population included all randomized participants regardless of whether the participant received any investigational product (IP) or had any efficacy assessments collected. | |
| End point type | Primary |
| End point timeframe: | |
| From the date of randomization of study drug to the date of the cut off date of 13 December 2016; follow-up for PFS was 21 months | |

| End point values | CC-486 and Fulvestrant | Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 49 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.49 (2.07 to 8.25) | 5.46 (3.58 to 7.36) | | |

### Statistical analyses

| | |
|---|---|
| **Statistical analysis title** | Statistical Analysis 1 |
| Comparison groups | CC-486 and Fulvestrant v Fulvestrant |

| | |
|---|---|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[1] |
| P-value | = 0.599 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.87 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 1.42 |

Notes:

[1] - Hazard ratio and associated two-sided 95% confidence intervals (CI) were estimated by the Cox proportional hazard models.

## Secondary: Percentage of Participants who Achieved a Confirmed Complete Response (CR) or Partial Response (PR) to Treatment (Objective Response Rate) Based On the Investigator Assessment

| | |
|---|---|
| End point title | Percentage of Participants who Achieved a Confirmed Complete Response (CR) or Partial Response (PR) to Treatment (Objective Response Rate) Based On the Investigator Assessment |

End point description:

Overall response rate was defined as the percentage of participants who achieved a confirmed complete response or partial response based on RECIST Version 1.1 criteria. RECIST criteria v 1.1 defined a CR as the disappearance of all target lesions and a PR with at least a 30% decrease in the sum of diameters of target lesions from baseline. The two-sided 95% exact binomial CI each arm was estimated by the Clopper-Pearson method. The Intent-to-treat population included all randomized participants regardless of whether the participant received any IP or had any efficacy assessments collected.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Disease response was assessed every 8 weeks, for the first 24 weeks, then every 12 weeks until DP; from date of randomization of study drug to the data cut-off date of 13 December 2016; follow-up for overall response was 21 months.

| **End point values** | CC-486 and Fulvestrant | Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 49 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 8.3 (2.32 to 19.98) | 2.0 (0.05 to 10.85) | | |

## Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | CC-486 and Fulvestrant v Fulvestrant |

| | |
|---|---|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[2] |
| P-value | = 0.1479 |
| Method | Fisher exact |
| Parameter estimate | Difference in Response Rates |
| Point estimate | 6.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.47 |
| upper limit | 15.06 |

Notes:

[2] - The two-sided 95% confidence interval for the difference in ORR was estimated by the Wilson method.

## Secondary: Percentage of Participants who Achieved a Confirmed CR, PR or Stable Disease (SD) for ≥ 24 Weeks (Clinical Benefit Rate) by Investigator Assessment

| | |
|---|---|
| End point title | Percentage of Participants who Achieved a Confirmed CR, PR or Stable Disease (SD) for ≥ 24 Weeks (Clinical Benefit Rate) by Investigator Assessment |

End point description:

Percentage of participants with CR or PR or SD was defined per RECIST criteria v 1.1 as a CR that includes a disappearance of all target lesions, a PR was defined as having at least a 30% decrease in the sum of diameters of target lesions from baseline and SD as neither sufficient shrinkage to qualify for PR nor sufficient increase of lesions to qualify for progressive disease. The two-sided 95% exact binomial CI each arm was estimated by the Clopper-Pearson method. The ITT population included all randomized participants regardless of whether the participant received any IP or had any efficacy assessments collected.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Disease response was assessed every 8 weeks, for the first 24 weeks, then every 12 weeks until DP; from date of randomization of study drug to data cut-off date of 13 December 2016; follow-up for clinical benefit response was 21 months.

| **End point values** | CC-486 and Fulvestrant | Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 49 | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 31.3 (18.66 to 46.25) | 30.6 (18.25 to 45.42) | | |

### Statistical analyses

| **Statistical analysis title** | Statistical Analysis 1 |
|---|---|
| Comparison groups | CC-486 and Fulvestrant v Fulvestrant |

| | |
|---|---|
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[3] |
| P-value | = 0.1732 |
| Method | Fisher exact |
| Parameter estimate | Difference in clinical benefit rate |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.76 |
| upper limit | 19.04 |

Notes:

[3] - The two-sided 95% confidence interval for the difference in clinical benefit rate was estimated by the Wilson method.

## Secondary: Kaplan Meier Estimate of Overall Survival

| | |
|---|---|
| End point title | Kaplan Meier Estimate of Overall Survival |

End point description:

Overall survival was defined as the time from the date of randomization to the date of death (from any cause). All participants who were lost to follow up prior to the end of the study or who were withdrawn from the study were censored at the time of last contact. The ITT population included all randomized participants regardless of whether the participant received any IP or had any efficacy assessments collected. 99999 indicates overall survival was not estimable due to the data not being mature at the time of the data cut off date. The median OS was not reached.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

From the date of randomization of study drug to the data cut off date of 13 December 2016; participants were followed for overall survival for 21 months

| End point values | CC-486 and Fulvestrant | Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 49 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (13.7 to 99999) | 99999 (10.7 to 99999) | | |

### Statistical analyses

| Statistical analysis title | Statistical Analysis 1 |
|---|---|
| Comparison groups | CC-486 and Fulvestrant v Fulvestrant |
| Number of subjects included in analysis | 97 |
| Analysis specification | Pre-specified |
| Analysis type | superiority[4] |
| P-value | = 0.2725 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.59 |

| Confidence interval | |
|---|---|
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.23 |
| upper limit | 1.53 |

Notes:

[4] - Hazard Ratio and associated two-sided 95% CI were estimated by the Cox proportional hazard model.

## Secondary: Kaplan Meier Estimate of Duration of Response

| End point title | Kaplan Meier Estimate of Duration of Response |
|---|---|

End point description:

Duration of response was defined as the time from the first tumor assessment when the confirmed CR/PR criterion was first met to the date of disease progression, based on investigator's assessment following RECIST Version 1.1 criteria. Only participants who had a confirmed CR or PR response are included in the analysis. 99999 indicates the median duration of response was not estimable due to the data not being mature at the time of the data cut off date.

| End point type | Secondary |
|---|---|

End point timeframe:

From the date of randomization of study drug to the data cut off of 13 December 2016; follow-up for duration of response was 21 months.

| **End point values** | CC-486 and Fulvestrant | Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 48 | 49 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (6.61 to 99999) | 99999 (99999 to 99999) | | |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAEs)

| End point title | Number of Participants with Treatment Emergent Adverse Events (TEAEs) |
|---|---|

End point description:

Treatment-emergent adverse events (TEAEs) were defined as any AEs that begin or worsen with an onset date on or after the date of the first dose of IP through 28 days after the last dose. A serious AE (SAE) = any AE which results in death; is life-threatening; requires inpatient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; constitutes an important medical event. The severity of AEs were graded based on the participant's symptoms according to the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0); AEs were evaluated for severity as follows: Grade 1 = Mild – transient or mild discomfort; no medical intervention required; Grade 2 = Moderate – mild to moderate limitation in activity; Grade 3 = Severe; Grade 4 = Life threatening; Grade 5 = Death. The safety population includes all randomized participants who received at least 1 dose of IP.

| End point type | Secondary |
|---|---|

End point timeframe:

Randomization to 28 days after the last dose of IP; those AEs known at any time thereafter being

related to IP; up to the last subject last visit of 21 November 2017; TEAE follow-up occurred up to 155 weeks and 2 days

| **End point values** | CC-486 and Fulvestrant | Fulvestrant | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 48 | | |
| Units: participants | | | | |
| TEAE | 46 | 48 | | |
| Grade 3 or 4 TEAE | 32 | 15 | | |
| Grade 5 TEAE (Death) | 2 | 1 | | |
| Serious TEAE | 10 | 7 | | |
| TEAE Leading to Stopping Any Study Drug | 14 | 1 | | |
| TEAE Leading to Dose Reduction Any Study Drug | 19 | 0 | | |
| TEAE Leading to Interruption Any Study Drug | 22 | 3 | | |
| Treatment-Related TEAE | 46 | 30 | | |
| Treatment-Related TEAE Grade 3 or 4 TEAE | 29 | 2 | | |
| Treatment-Related TEAE Grade 5 | 0 | 0 | | |
| Treatment-Related Serious TEAE | 4 | 0 | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Randomization to 28 days after the last dose of IP; those AEs known at any time thereafter being related to IP; up to final cut off date of the last subject last visit of 21 November 2017.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

### Reporting groups

| | |
|---|---|
| Reporting group title | CC-486 and Fulvestrant |

Reporting group description:

Participants received CC-486 tablets by mouth (PO) daily (QD) on days 1-21 of each 28 day treatment cycle and fulvestrant 500 mg by intramuscular injection (IM) on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up withdrawal of consent, or lost to follow-up.

| | |
|---|---|
| Reporting group title | Fulvestrant |

Reporting group description:

Participants received fulvestrant 500 mg by intramuscular injection on days 1 and 15 of cycle 1 and on day 1 only in subsequent cycles until disease progression, start of new anticancer therapy, death, withdrawal of consent, or lost to follow-up.

| Serious adverse events | CC-486 and Fulvestrant | Fulvestrant | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 7 / 48 (14.58%) | |
| number of deaths (all causes) | 2 | 1 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (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 | | | |
| Cervical myelopathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (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 | | | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Constipation | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal necrosis | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Nausea | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small intestinal obstruction | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Vomiting | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic failure | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neck pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal osteoarthritis | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 1 / 48 (2.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 0 / 48 (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** | CC-486 and Fulvestrant | Fulvestrant | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 46 (97.83%) | 44 / 48 (91.67%) | |
| Investigations | | | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 48 (10.42%) | |
| occurrences (all) | 1 | 10 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 48 (6.25%) | |
| occurrences (all) | 0 | 4 | |
| Weight decreased | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 1 / 48 (2.08%) | |
| occurrences (all) | 3 | 1 | |
| White blood cell count decreased | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 46 (6.52%) | 0 / 48 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 5 / 48 (10.42%) | |
| occurrences (all) | 4 | 5 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 4 / 48 (8.33%) | |
| occurrences (all) | 3 | 6 | |
| Headache | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 5 / 48 (10.42%) | |
| occurrences (all) | 7 | 7 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 48 (6.25%) | |
| occurrences (all) | 1 | 4 | |
| Neutropenia | | | |
| subjects affected / exposed | 10 / 46 (21.74%) | 0 / 48 (0.00%) | |
| occurrences (all) | 22 | 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 16 / 46 (34.78%) | 10 / 48 (20.83%) | |
| occurrences (all) | 28 | 13 | |
| Fatigue | | | |
| subjects affected / exposed | 13 / 46 (28.26%) | 12 / 48 (25.00%) | |
| occurrences (all) | 18 | 16 | |
| Injection site pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 5 / 48 (10.42%) | |
| occurrences (all) | 1 | 5 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 48 (6.25%) | |
| occurrences (all) | 1 | 5 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 2 / 48 (4.17%) | |
| occurrences (all) | 5 | 2 | |

| | | | |
|---|---|---|---|
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 2 / 48 (4.17%) | |
| occurrences (all) | 6 | 2 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 1 / 48 (2.08%) | |
| occurrences (all) | 7 | 1 | |
| Constipation | | | |
| subjects affected / exposed | 19 / 46 (41.30%) | 10 / 48 (20.83%) | |
| occurrences (all) | 26 | 10 | |
| Diarrhoea | | | |
| subjects affected / exposed | 20 / 46 (43.48%) | 6 / 48 (12.50%) | |
| occurrences (all) | 53 | 11 | |
| Nausea | | | |
| subjects affected / exposed | 35 / 46 (76.09%) | 14 / 48 (29.17%) | |
| occurrences (all) | 73 | 16 | |
| Vomiting | | | |
| subjects affected / exposed | 33 / 46 (71.74%) | 5 / 48 (10.42%) | |
| occurrences (all) | 56 | 5 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 4 / 48 (8.33%) | |
| occurrences (all) | 5 | 6 | |
| Dyspnoea | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 7 / 48 (14.58%) | |
| occurrences (all) | 4 | 8 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 0 / 48 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 46 (0.00%) | 3 / 48 (6.25%) | |
| occurrences (all) | 0 | 3 | |
| Insomnia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 46 (4.35%) | 4 / 48 (8.33%) | |
| occurrences (all) | 2 | 4 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 6 / 46 (13.04%) | 9 / 48 (18.75%) | |
| occurrences (all) | 9 | 11 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 7 / 48 (14.58%) | |
| occurrences (all) | 3 | 8 | |
| Bone pain | | | |
| subjects affected / exposed | 5 / 46 (10.87%) | 6 / 48 (12.50%) | |
| occurrences (all) | 7 | 7 | |
| Muscle spasms | | | |
| subjects affected / exposed | 4 / 46 (8.70%) | 1 / 48 (2.08%) | |
| occurrences (all) | 4 | 1 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 48 (6.25%) | |
| occurrences (all) | 1 | 5 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 2 / 46 (4.35%) | 7 / 48 (14.58%) | |
| occurrences (all) | 3 | 11 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 4 / 48 (8.33%) | |
| occurrences (all) | 1 | 4 | |
| Pain in extremity | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 6 / 48 (12.50%) | |
| occurrences (all) | 4 | 6 | |
| Infections and infestations | | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 4 / 48 (8.33%) | |
| occurrences (all) | 3 | 4 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 46 (6.52%) | 3 / 48 (6.25%) | |
| occurrences (all) | 3 | 4 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|---|---|---|
| Decreased appetite | | | |
| subjects affected / exposed | 13 / 46 (28.26%) | 8 / 48 (16.67%) | |
| occurrences (all) | 18 | 9 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 1 / 46 (2.17%) | 3 / 48 (6.25%) | |
| occurrences (all) | 1 | 4 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 04 December 2014 | Provided additional dose modification criteria for renal dysfunction related toxicities as requested and agreed to with the FDA and in order to be consistent with other CC-486 clinical study protocols. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported