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 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 Units: years			
arithmetic mean	62.6	62.9	
standard deviation	± 10.99	± 10.03	-
Gender Categorical Units: Subjects			
Female	48	49	97
Race 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