Clinical trial results:
neoMONARCH: A Phase 2 Neoadjuvant Trial Comparing the Biological Effects of 2 Weeks of Abemaciclib (LY2835219) in Combination with Anastrozole to those of Abemaciclib Monotherapy and Anastrozole Monotherapy and Evaluating the Clinical Activity and Safety of a Subsequent 14 Weeks of Therapy with Abemaciclib in Combination with Anastrozole in Postmenopausal Women with Hormone Receptor Positive, HER2 Negative Breast Cancer

Summary

EudraCT number	2014-005486-75
Trial protocol	ES AT DE NL BE IT
Global end of trial date	12 February 2018

Results information

Result version number	v1 (current)
This version publication date	24 February 2019
First version publication date	24 February 2019

Trial information

Trial identification

Sponsor protocol code	I3Y-MC-JPBY

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02441946
WHO universal trial number (UTN)	-
Other trial identifiers	Trial ID: 15805

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon - Fri 9 AM - 5 PM EST , Eli Lilly and Company, 1 877-CTLilly,
Scientific contact	Available Mon - Fri 9 AM - 5 PM EST, Eli Lilly and Company, 1 877-285-4559,

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	12 February 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	12 February 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare the biological activity of abemaciclib in combination with anastrozole, abemaciclib monotherapy, and anastrozole monotherapy by assessing the percentage change from the baseline value in Ki67 expression after 2 weeks of therapy.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 3
Country: Number of subjects enrolled	Spain: 37
Country: Number of subjects enrolled	Austria: 26
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Germany: 15
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	United States: 80
Country: Number of subjects enrolled	Taiwan: 23
Country: Number of subjects enrolled	Korea, Republic of: 14
Country: Number of subjects enrolled	Italy: 11
Worldwide total number of subjects	224
EEA total number of subjects	103

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)	117
From 65 to 84 years	103
85 years and over	4

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants who had progressive disease at the end of the study but off study drug were considered to have completed the study. Participants were randomized to anastrozole, or abemaciclib, and abemaciclib + anastrozole in cycle 1. All participants received abemaciclib + anastrozole post cycle 1.

Period 1

Period 1 title	Cycle 1 Period 1 (2 Weeks)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Abemaciclib + Anastrozole

Arm description:

Participants were given 150 milligram (mg) of abemaciclib orally every 12 hours (Q12H) plus 1 mg of anastrozole orally once daily (QD) for 2 weeks.

Total treatment duration was 16 weeks. Cycle 1 lasts 14 days.

Arm type	Active comparator
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were given 150 mg of abemaciclib orally Q12H.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg of anastrozole orally QD for 2 weeks.

Arm title	Abemaciclib

Arm description:

Participants received 150 mg of abemaciclib orally Q12H for 2 weeks.

Total treatment duration was 16 weeks.

Cycle 1 lasts 14 days.

Arm type	Experimental
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 150 mg of abemaciclib orally Q12H for 2 weeks.

Arm title	Anastrozole

Arm description:

Participants received 1 mg of anastrozole orally QD for 2 weeks.

Total treatment duration was 16 weeks.

Cycle 1 lasts 14 days.

Arm type	Active comparator
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 1 mg of anastrozole orally QD for 2 weeks.

Number of subjects in period 1	Abemaciclib + Anastrozole	Abemaciclib	Anastrozole
Started	74	76	74
Received at least one dose of study drug	74	75	74
Completed	72	71	74
Not completed	2	5	0
Physician decision	1	-	-
Consent withdrawn by subject	-	3	-
Never Treated	-	1	-
Adverse event, non-fatal	1	1	-

Period 2

Period 2 title	Cycle 2 - 5 Period 2 (14 Weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

All 217 participants were treated with abemaciclib + anastrozole post cycle 1.

Arms

Arm title	Abemaciclib + Anastrozole

Arm description:

All participants received 150 mg of abemaciclib orally Q12H plus 1 mg of anastrozole orally QD for an additional 14 weeks.

Total treatment duration was 16 weeks.

Cycle 2 lasts 14 days.

Arm type	Active comparator
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants received 150 mg of abemaciclib orally Q12H for 14 weeks.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

1 mg of anastrozole orally QD for 2 weeks

Number of subjects in period 2	Abemaciclib + Anastrozole
Started	217
Received at Least One Dose of Study Drug	217
Completed	190
Not completed	27
Consent withdrawn by subject	9
Physician Decision	1
Adverse event, non-fatal	15
Noncompliance with study drug	1
Protocol deviation	1

Period 3

Period 3 title	Extension Period (8 Weeks)
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Abemaciclib + Anastrozole

Arm description:

150 mg of abemaciclib orally Q12H or 1 mg of anastrozole orally QD for 2 weeks.

All participants received 150 mg of abemaciclib orally Q12H plus 1 mg of anastrozole orally QD for an additional 8 weeks, after completed the mandatory 16 weeks of study treatment.

Total treatment duration was 24 weeks.

Arm type	Active comparator
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Participants were given 150 mg of abemaciclib orally Q12H.

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received 1 mg of anastrozole orally QD for 8 weeks.

All participants received 150 mg of abemaciclib orally Q12H plus 1 mg of anastrozole orally QD for an additional 8 weeks.

Total treatment duration was 24 weeks.

Number of subjects in period 3[1]	Abemaciclib + Anastrozole
Started	42
Completed	40
Not completed	2
Consent withdrawn by subject	1
Adverse event, non-fatal	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: All participants who did not discontinue continued to the extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Abemaciclib + Anastrozole

Reporting group description:

Participants were given 150 milligram (mg) of abemaciclib orally every 12 hours (Q12H) plus 1 mg of anastrozole orally once daily (QD) for 2 weeks.

Total treatment duration was 16 weeks. Cycle 1 lasts 14 days.

Reporting group title	Abemaciclib

Reporting group description:

Participants received 150 mg of abemaciclib orally Q12H for 2 weeks.

Total treatment duration was 16 weeks.

Cycle 1 lasts 14 days.

Reporting group title	Anastrozole

Reporting group description:

Participants received 1 mg of anastrozole orally QD for 2 weeks.

Total treatment duration was 16 weeks.

Cycle 1 lasts 14 days.

Reporting group values	Abemaciclib + Anastrozole	Abemaciclib	Anastrozole
Number of subjects	74	76	74
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	63.9	63.8	64.9
standard deviation	± 8.4	± 7.9	± 8.4
Gender categorical Units: Subjects			
Female	74	76	74
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	6	8	5
Not Hispanic or Latino	61	61	60
Unknown or Not Reported	7	7	9
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	12	16	16
Native Hawaiian or Other Pacific Islander	0	1	0
Black or African American	5	1	2
White	55	57	55
More than one race	1	1	1
Unknown or Not Reported	1	0	0

Region of Enrollment Units: Subjects			
Canada	0	3	1
Austria	10	4	12
Netherlands	1	0	2
Belgium	5	2	4
United States	26	28	26
Taiwan	5	7	11
Korea, Republic of Italy	5	7	2
Italy	4	3	4
Germany	5	6	4
Spain	13	16	8
Eastern Cooperative Oncology Group (ECOG) Units: Subjects			
0 (Fully Active)	69	70	64
1 (Restricted, able to do light sedentary work)	5	5	10
Unknown or Not Reported)	0	1	0
Ki67 at Baseline			
Tumor tissue collected through a core biopsy at baseline and at the end of cycle 1 was used to determine Ki67 expression. Ki67 expression is defined as the percent of cells staining positive by validated central assay.			
Units: Percent Cells Positive			
arithmetic mean	27.24	27.88	26.86
standard deviation	± 13.56	± 12.13	± 12.32

Reporting group values	Total		
Number of subjects	224		
Age categorical Units: Subjects			
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	224		
Male	0		
Ethnicity Units: Subjects			
Hispanic or Latino	19		
Not Hispanic or Latino	182		
Unknown or Not Reported	23		
Race Units: Subjects			
American Indian or Alaska Native	0		
Asian	44		

Native Hawaiian or Other Pacific Islander	1		
Black or African American	8		
White	167		
More than one race	3		
Unknown or Not Reported	1		
Region of Enrollment Units: Subjects			
Canada	4		
Austria	26		
Netherlands	3		
Belgium	11		
United States	80		
Taiwan	23		
Korea, Republic of Italy	14		
Italy	11		
Germany	15		
Spain	37		
Eastern Cooperative Oncology Group (ECOG) Units: Subjects			
0 (Fully Active)	203		
1 (Restricted, able to do light sedentary work)	20		
Unknown or Not Reported)	1		
Ki67 at Baseline			
Tumor tissue collected through a core biopsy at baseline and at the end of cycle 1 was used to determine Ki67 expression. Ki67 expression is defined as the percent of cells staining positive by validated central assay.			
Units: Percent Cells Positive			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

Reporting group title	Abemaciclib + Anastrozole

Reporting group description:

Participants were given 150 milligram (mg) of abemaciclib orally every 12 hours (Q12H) plus 1 mg of anastrozole orally once daily (QD) for 2 weeks.

Total treatment duration was 16 weeks. Cycle 1 lasts 14 days.

Reporting group title	Abemaciclib

Reporting group description:

Participants received 150 mg of abemaciclib orally Q12H for 2 weeks.

Total treatment duration was 16 weeks.

Cycle 1 lasts 14 days.

Reporting group title	Anastrozole

Reporting group description:

Participants received 1 mg of anastrozole orally QD for 2 weeks.

Total treatment duration was 16 weeks.

Cycle 1 lasts 14 days.

Reporting group title	Abemaciclib + Anastrozole

Reporting group description:

All participants received 150 mg of abemaciclib orally Q12H plus 1 mg of anastrozole orally QD for an additional 14 weeks.

Total treatment duration was 16 weeks.

Cycle 2 lasts 14 days.

Reporting group title	Abemaciclib + Anastrozole

Reporting group description:

150 mg of abemaciclib orally Q12H or 1 mg of anastrozole orally QD for 2 weeks.

All participants received 150 mg of abemaciclib orally Q12H plus 1 mg of anastrozole orally QD for an additional 8 weeks, after completed the mandatory 16 weeks of study treatment.

Total treatment duration was 24 weeks.

Subject analysis set title	Abemaciclib + Anastrozole
Subject analysis set type	Full analysis

Subject analysis set description:

All participants who received combination treatment post cycle 1.

Primary: Percent Change From Baseline to 2 Weeks in Ki67 Expression

End point title	Percent Change From Baseline to 2 Weeks in Ki67 Expression

End point description:

End point type	Primary

End point timeframe:

Baseline, 2 Weeks

End point values	Abemaciclib + Anastrozole	Abemaciclib	Anastrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	59[1]	52[2]	56[3]	
Units: Percent Change				
geometric mean (confidence interval 95%)	-93 (-95 to -90)	-91 (-93 to -87)	-63 (-73 to -49)	

Notes:

[1] - Geometric mean and confidence interval are percentages.

[2] - Participants with a valid baseline Ki67 of at least 5% and valid Ki67 at 2-weeks.

[3] - Participants with a valid baseline Ki67 of at least 5% and valid Ki67 at 2-weeks.

Statistical analyses

Statistical analysis title	Statistical Analysis Percent Change Ki67 (1)
Comparison groups	Abemaciclib + Anastrozole v Anastrozole
Number of subjects included in analysis	115
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 1-sided
Parameter estimate	Ratio of Geometric Means
Point estimate	0.19
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.13
upper limit	0.28

Statistical analysis title	Statistical Analysis Percent Change Ki67 (2)
Comparison groups	Abemaciclib v Anastrozole
Number of subjects included in analysis	108
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	t-test, 1-sided
Parameter estimate	Ratio of Geometric Mean
Point estimate	0.25
Confidence interval	
level	90 %
sides	2-sided
lower limit	0.17
upper limit	0.38

Secondary: Percentage of Participants With Pathologic Complete Response (pCR)

End point title	Percentage of Participants With Pathologic Complete Response (pCR)

End point description:

pCR is defined as absence of invasive cancer in the breast and sampled regional lymph nodes.

End point type	Secondary

End point timeframe:

16 Weeks

End point values	Abemaciclib + Anastrozole			
Subject group type	Reporting group			
Number of subjects analysed	190[4]			
Units: Percentage of Participants				
number (not applicable)	3.7			

Notes:

[4] - All participants who received combination treatment and underwent surgery after the end of treatment

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Response (CR) or Partial Response (PR): Clinical Objective Response

End point title	Percentage of Participants With Complete Response (CR) or Partial Response (PR): Clinical Objective Response

End point description:

The best overall response rate (ORR) is the percentage of participants with a best OR of CR or PR, according to Response Evaluation Criteria In Solid Tumors Criteria (RECIST) v1.1. ORR is recorded from the start of the study treatment until the earliest of objective progression or start of new anticancer therapy. A responder depends on target and non-target disease and the appearance of new lesions. CR is defined as the disappearance of all nontarget lesions. PR is at least a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. All lymph nodes are non-pathological or normal in size (<10mm short axis). Progressive disease (PD) is a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study, a relative increase of 20%, the sum must also demonstrate an absolute increase of 5 mm. Stable disease (SD) is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

End point type	Secondary

End point timeframe:

From Start of Treatment up to 16 Weeks

End point values	Abemaciclib + Anastrozole			
Subject group type	Subject analysis set			
Number of subjects analysed	224[5]			
Units: Percentage of Participants				
number (not applicable)	53.6			

Notes:

[5] - All participants who were randomized at study entry.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With Complete Radiologic Response or Partial Radiological Response: Radiological Response

End point title	Percentage of Participants With Complete Radiologic Response or Partial Radiological Response: Radiological Response

End point description:

Radiological response is the percentage of participants with CR, PR according to RECIST v.1.1. A responder is defined as any participant who exhibits a CR or PR. CR is the disappearance of all target lesions. PR is a 30% decrease in the sum of diameter of target lesions, taking as reference the baseline sum diameters. PD is 20% increase in the sum of diameters of target lesions taking as reference the smallest sum and the appearance of 1 or more new lesions. SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify as PD.

End point type	Secondary

End point timeframe:

From Start of Treatment Up to 16 Weeks

End point values	Abemaciclib + Anastrozole			
Subject group type	Subject analysis set			
Number of subjects analysed	224[6]			
Units: Percentage of Participants				
number (not applicable)	46.4			

Notes:

[6] - All participants who were randomized at study entry.

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 2 in EORTC QLQ-C30

End point title	Change from Baseline to Week 2 in EORTC QLQ-C30

End point description:

The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) questionnaire is a self-reported general cancer instrument consisting of 30 items covered by 1 of 3 dimensions:

global health status/quality of life (2 items), functional scales (15 total items addressing either physical, role, emotional, cognitive, or social functioning), and symptom scales (13 total items addressing either fatigue, nausea/vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, or financial impact)
EORTC QLQ-C30 data were scored on a scale ranging from 0 to 100 as described by Aaronson and colleagues (1993). A higher score represents a higher level of response. A lower score represents a lower level of response. Thus a high score for a functional scale or global health status represents a high level of functioning or health status. On the other hand, a high score for a symptom scale/item represents a high level of symptomatology.

End point type	Secondary

End point timeframe:

Baseline, 2 Weeks

End point values	Abemaciclib + Anastrozole	Abemaciclib	Anastrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	62[7]	66[8]	69[9]	
Units: units on a scale				
arithmetic mean (standard deviation)				
Global Health Status	-9.5 (± 17.9)	-7.6 (± 18.1)	-2.3 (± 13.4)	
Physical Functioning	-3.2 (± 10.2)	-5.5 (± 12.6)	-0.3 (± 7.5)	
Role Functioning	-11.3 (± 23.7)	-11.4 (± 24.0)	-2.2 (± 17.4)	
Emotional	5.4 (± 17.1)	3.5 (± 21.4)	1.3 (± 14.0)	
Cognitive	0.5 (± 12.4)	-2.0 (± 15.6)	-1.4 (± 11.0)	
Social Functioning	-8.3 (± 18.8)	-3.5 (± 16.7)	-0.7 (± 12.6)	
Fatigue	13.6 (± 23.2)	13.9 (± 22.6)	4.0 (± 12.8)	
Nausea/Vomiting	11.8 (± 17.7)	9.6 (± 12.4)	2.7 (± 7.4)	
Pain	4.8 (± 19.9)	3.5 (± 19.3)	2.9 (± 16.7)	
Dyspnea	1.1 (± 19.1)	0.5 (± 19.8)	-1.0 (± 12.7)	
Insomnia	-1.1 (± 19.1)	0.5 (± 29.5)	-1.9 (± 22.1)	
Appetite Loss	16.9 (± 28.3)	16.9 (± 27.5)	1.9 (± 15.0)	
Constipation	22.4 (± 31.5)	16.9 (± 31.2)	1.9 (± 15.0)	
Diarrhea	18.3 (± 29.4)	27.8 (± 25.9)	0.0 (± 15.1)	
Financial Impact	-2.8 (± 19.7)	2.0 (± 18.4)	0.0 (± 11.4)	

Notes:

[7] - n=61 for appetite loss and n=61 for constipation and n=60 for financial impact.

[8] - n=60 for constipation.

[9] - All participants who had evaluable EORTC QLQ-30 data.

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK): Apparent Clearance of Abemaciclib and Anastrozole

End point title	Pharmacokinetics (PK): Apparent Clearance of Abemaciclib and Anastrozole

End point description:

End point type	Secondary

End point timeframe:

Cycle(C)1, Day(D)1: 2 to 4 Hours (Hrs) Postdose; C1D14 (+2 Days) -4 Hours, Predose, 3 Hrs Postdose; C3D1-C5D28: Predose, 3+/- 0.5 Hrs Postdose

End point values	Abemaciclib + Anastrozole	Abemaciclib	Anastrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74[10]	75[11]	74[12]	
Units: Liters/Hour				
geometric mean (geometric coefficient of variation)	24.0 (± 32)	19.1 (± 55)	24.4 (± 61)	

Notes:

[10] - geometric coefficient of variation is a percentage.

[11] - geometric coefficient of variation is a percentage.

[12] - geometric coefficient of variation is a percentage.

Statistical analyses

No statistical analyses for this end point

Secondary: PK: Apparent Volume of Distribution of Abemaciclib and Anastrozole

End point title	PK: Apparent Volume of Distribution of Abemaciclib and Anastrozole

End point description:

End point type	Secondary

End point timeframe:

C1D1: 2 to 4 Hrs Postdose; C1D14 (+2 Days) -4 Hrs, Predose, 3 Hrs Postdose; C3D1-C5D28: Predose, 3+/- 0.5 Hrs Postdose

End point values	Abemaciclib + Anastrozole	Abemaciclib	Anastrozole	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	74[13]	75[14]	74[15]	
Units: Liters				
geometric mean (geometric coefficient of variation)	941 (± 53)	720 (± 58)	758 (± 49)	

Notes:

[13] - geometric coefficient of variation is a percentage.

[14] - geometric coefficient of variation is a percentage.

[15] - geometric coefficient of variation is a percentage.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to 24 Weeks	
Adverse event reporting additional description: I3Y-MC-JPBY	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.1

Reporting groups	
Reporting group title	Abemaciclib + Anastrozole 1 mg Cycle1
Reporting group description: -	
Reporting group title	Anastrozole Cycle1
Reporting group description: -	
Reporting group title	Abemaciclib Cycle1
Reporting group description: -	
Reporting group title	Abemaciclib + Anastrozole Post Cycle1 and Beyond
Reporting group description: -	

Serious adverse events	Abemaciclib + Anastrozole 1 mg Cycle1	Anastrozole Cycle1	Abemaciclib Cycle1
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 74 (1.35%)	0 / 74 (0.00%)	1 / 75 (1.33%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 74 (1.35%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 74 (1.35%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
blood creatinine increased			

alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
fracture			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
angina pectoris			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
seizure			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			

neutropenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 74 (1.35%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pancreatitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
hypoxia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
skin ulcer			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

chronic kidney disease			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
mastitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
dehydration			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypokalaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	0 / 75 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Abemaciclib + Anastrozole Post Cycle1 and Beyond		
Total subjects affected by serious adverse events			
subjects affected / exposed	16 / 217 (7.37%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
blood creatinine increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 217 (0.92%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
fracture			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	3 / 217 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
acute coronary syndrome			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

angina pectoris				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
myocardial infarction				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
seizure				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Blood and lymphatic system disorders				
neutropenia				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal disorders				
abdominal pain				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
pancreatitis				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory, thoracic and mediastinal disorders				

hypoxia				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Skin and subcutaneous tissue disorders				
skin ulcer				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
acute kidney injury				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
chronic kidney disease				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Psychiatric disorders				
anxiety				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
mastitis				
alternative dictionary used: MedDRA 19.1				
subjects affected / exposed	2 / 217 (0.92%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			

Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 217 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
dehydration			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
hypokalaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Abemaciclib + Anastrozole 1 mg Cycle1	Anastrozole Cycle1	Abemaciclib Cycle1
Total subjects affected by non-serious adverse events			
subjects affected / exposed	62 / 74 (83.78%)	17 / 74 (22.97%)	58 / 75 (77.33%)
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	4 / 74 (5.41%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	4	0	1
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 74 (2.70%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	3	0	1
blood creatinine increased			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	2 / 74 (2.70%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	2	0	1
weight decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	2 / 75 (2.67%)
occurrences (all)	0	0	2
Vascular disorders			
hot flush			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	3 / 74 (4.05%)	5 / 74 (6.76%)	2 / 75 (2.67%)
occurrences (all)	3	5	2
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 74 (1.35%)	1 / 74 (1.35%)	5 / 75 (6.67%)
occurrences (all)	1	1	5
dysgeusia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	4 / 74 (5.41%)	0 / 74 (0.00%)	5 / 75 (6.67%)
occurrences (all)	4	0	5
headache			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	3 / 74 (4.05%)	0 / 74 (0.00%)	5 / 75 (6.67%)
occurrences (all)	3	0	5
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	3 / 75 (4.00%)
occurrences (all)	0	0	3
leukopenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 74 (1.35%)	0 / 74 (0.00%)	3 / 75 (4.00%)
occurrences (all)	1	0	3
neutropenia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	2 / 74 (2.70%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	2	0	1
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	19 / 74 (25.68%)	3 / 74 (4.05%)	17 / 75 (22.67%)
occurrences (all)	20	4	18
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	13 / 74 (17.57%)	2 / 74 (2.70%)	7 / 75 (9.33%)
occurrences (all)	15	2	7
constipation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	27 / 74 (36.49%)	5 / 74 (6.76%)	26 / 75 (34.67%)
occurrences (all)	27	5	30
diarrhoea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	31 / 74 (41.89%)	2 / 74 (2.70%)	29 / 75 (38.67%)
occurrences (all)	34	2	33
dry mouth			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	1 / 74 (1.35%)	0 / 74 (0.00%)	5 / 75 (6.67%)
occurrences (all)	1	0	5
dyspepsia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	6 / 74 (8.11%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	6	0	1
nausea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	19 / 74 (25.68%)	2 / 74 (2.70%)	15 / 75 (20.00%)
occurrences (all)	19	2	15
stomatitis			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	2 / 74 (2.70%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	2	0	1
vomiting			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	5 / 74 (6.76%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	6	0	1
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	1 / 75 (1.33%)
occurrences (all)	0	0	1
pruritus			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	2 / 74 (2.70%)	1 / 74 (1.35%)	1 / 75 (1.33%)
occurrences (all)	2	1	1
rash			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	0 / 74 (0.00%)	0 / 74 (0.00%)	2 / 75 (2.67%)
occurrences (all)	0	0	2
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	5 / 74 (6.76%)	0 / 74 (0.00%)	13 / 75 (17.33%)
occurrences (all)	5	0	13

Non-serious adverse events	Abemaciclib + Anastrozole Post Cycle1 and Beyond		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	189 / 217 (87.10%)		
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	26 / 217 (11.98%)		
occurrences (all)	27		
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	22 / 217 (10.14%)		
occurrences (all)	23		
blood creatinine increased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	14 / 217 (6.45%)		
occurrences (all)	15		
weight decreased			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	15 / 217 (6.91%)		
occurrences (all)	17		
Vascular disorders			
hot flush			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	19 / 217 (8.76%)		
occurrences (all)	20		
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	8 / 217 (3.69%)		
occurrences (all)	10		
dysgeusia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	17 / 217 (7.83%)		
occurrences (all)	18		
headache			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	16 / 217 (7.37%)		
occurrences (all)	17		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	27 / 217 (12.44%)		
occurrences (all)	31		
leukopenia			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	19 / 217 (8.76%)		
occurrences (all)	22		
neutropenia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	45 / 217 (20.74%)		
occurrences (all)	58		
General disorders and administration site conditions			
fatigue			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	62 / 217 (28.57%)		
occurrences (all)	70		
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	30 / 217 (13.82%)		
occurrences (all)	34		
constipation			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	50 / 217 (23.04%)		
occurrences (all)	62		
diarrhoea			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	101 / 217 (46.54%)		
occurrences (all)	162		
dry mouth			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	7 / 217 (3.23%)		
occurrences (all)	8		
dyspepsia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	7 / 217 (3.23%)		
occurrences (all)	7		
nausea			
alternative dictionary used: MedDRA 19.1			

subjects affected / exposed	67 / 217 (30.88%)		
occurrences (all)	75		
stomatitis			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	19 / 217 (8.76%)		
occurrences (all)	21		
vomiting			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	25 / 217 (11.52%)		
occurrences (all)	32		
Skin and subcutaneous tissue disorders			
alopecia			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	12 / 217 (5.53%)		
occurrences (all)	12		
pruritus			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	20 / 217 (9.22%)		
occurrences (all)	21		
rash			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	22 / 217 (10.14%)		
occurrences (all)	24		
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 19.1			
subjects affected / exposed	33 / 217 (15.21%)		
occurrences (all)	36		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 December 2015	Amendment (a): updated the dosing guidance and clarify that blood cell growth factors are only to be used in a manner consistent with American Society of Clinical Oncology (ASCO) guidelines. Additional modifications duration of neoadjuvant therapy reference, clarified inclusion criterion lymph nodes and exclusion criterion loperamide hypersensitivity, extended treatment for patients experiencing clinical benefit, clarified cautions when coadministering cytochrome P450s, updated tumor measurement information and cycle 5 biopsy window, and clarified guidelines for ultrasound use, included information on biopsy after treatment discontinuation due to AE and added interim analyses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported