Clinical trial results:
monarcHER: A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib plus Trastuzumab with or without Fulvestrant to Standard-of-Care Chemotherapy of Physician?s Choice plus Trastuzumab in Women with HR+, HER2+ Locally Advanced or Metastatic Breast Cancer

Summary

EudraCT number	2015-003400-24
Trial protocol	ES GR BE GB DE IT
Global end of trial date	09 November 2023
Results information	
Result version number	v2 (current)
This version publication date	20 November 2024
First version publication date	24 April 2020
Version creation reason	• New data added to full data set New Data added to full data set

Trial information

Trial identification	
Sponsor protocol code	I3Y-MC-JPBZ
Additional study identifiers	
ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02675231
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 15804

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 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

Notes:

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

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 November 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 November 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the effectiveness of abemaciclib plus trastuzumab with or without fulvestrant versus trastuzumab plus physicians choice standard of care chemotherapy in women with hormone receptor positive (HR+), human epidermal growth factor receptor 2 positive (HER2+) locally advanced or metastatic breast cancer after prior exposure to at least two HER2-directed therapies for advanced disease.

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	23 May 2016
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	Argentina: 19
Country: Number of subjects enrolled	United States: 45
Country: Number of subjects enrolled	United Kingdom: 28
Country: Number of subjects enrolled	Spain: 17
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Canada: 10
Country: Number of subjects enrolled	Korea, Republic of: 30
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Italy: 9
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Australia: 8
Country: Number of subjects enrolled	France: 27
Country: Number of subjects enrolled	Germany: 7

Worldwide total number of subjects	237
EEA total number of subjects	111

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)	185
From 65 to 84 years	52
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

In the Subject disposition, completers included participants who either died due to any cause or were alive and on the study at the conclusion but off treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant

Arm description:

150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Arm type	Experimental
Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	LY2835219
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle

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

Dosage and administration details:

500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Arm title	150 mg Abemaciclib + 8 mg/kg Trastuzumab

Arm description:

150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Arm type	Experimental

Investigational medicinal product name	Abemaciclib
Investigational medicinal product code	
Other name	LY2835219
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

150 mg abemaciclib given orally Q12H of a 21-day cycle.

Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Arm title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Arm description:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician’s choice administered according to product label.

Arm type	Active comparator
Investigational medicinal product name	Trastuzumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Investigational medicinal product name	Standard of Care Single Agent Chemotherapy
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Standard-of-care single-agent chemotherapy of physician’s choice administered according to product label

Number of subjects in period 1	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Started	79	79	79
Received at Least One Dose of Drug	78	77	72 [1]
Completed	74	71	74
Not completed	5	8	5
Consent withdrawn by subject	2	4	2
Lost to follow-up	3	4	3

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: The milestone is added to represent the treated participants.

Baseline characteristics

Reporting groups	
Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant
Reporting group description:	
150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.	
Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab
Reporting group description:	
150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.	
Reporting group title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Reporting group description:	
8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician's choice administered according to product label.	

Reporting group values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects	79	79	79
Age categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	54.34	54.99	56.77
standard deviation	± 10.25	± 11.08	± 12.37
Gender categorical			
Units: Subjects			
Female	79	79	79
Male	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	14	11	12
Not Hispanic or Latino	58	52	56
Unknown or Not Reported	7	16	11
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	1	1
Asian	15	10	10
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	2	4
White	55	53	55
More than one race	0	0	1
Unknown or Not Reported	6	13	8
Region of Enrollment			

Units: Subjects			
Argentina	9	7	3
United States	20	8	17
United Kingdom	9	9	10
Spain	6	8	3
Greece	1	1	2
Canada	2	4	4
South Korea	11	9	10
Belgium	5	7	7
Brazil	3	1	4
Italy	2	5	2
Mexico	2	1	3
Australia	2	4	2
France	6	13	8
Germany	1	2	4

Reporting group values	Total		
Number of subjects	237		
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	237		
Male	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	37		
Not Hispanic or Latino	166		
Unknown or Not Reported	34		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	2		
Asian	35		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	9		
White	163		
More than one race	1		
Unknown or Not Reported	27		
Region of Enrollment Units: Subjects			
Argentina	19		
United States	45		
United Kingdom	28		
Spain	17		
Greece	4		

Canada	10		
South Korea	30		
Belgium	19		
Brazil	8		
Italy	9		
Mexico	6		
Australia	8		
France	27		
Germany	7		

End points

End points reporting groups

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant

Reporting group description:

150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.

Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab

Reporting group description:

150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.

Reporting group title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Reporting group description:

8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician’s choice administered according to product label.

Primary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

PFS time was measured from the date of randomization to the date of investigator-determined objective progression as defined by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, or death from any cause. Progressive Disease (PD) was at least a 20% increase in sum of the diameters of target lesions, with reference being the smallest sum on study and an absolute increase of at least 5 mm, or unequivocal progression of non-target lesions, or 1 or more new lesions. If a participant does not have a complete baseline disease assessment, then the PFS time was censored at the date of first dose, regardless of whether or not objectively determined disease progression or death has been observed for the participant. If a participant was not known to have died or have objective progression as of data inclusion cutoff date for the analysis, the PFS time was censored at the last adequate tumor assessment date. Analysis Population Description (APD) included all enrolled participants.

End point type	Primary

End point timeframe:

Baseline to Progressive Disease or Death from Any Cause (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79[1]	79[2]	79[3]	
Units: Months				
median (confidence interval 95%)	8.3 (5.9 to 12.6)	5.7 (4.2 to 7.2)	5.7 (5.4 to 6.9)	

Notes:

[1] - Censored participants: =23

[2] - Censored participants: =18

[3] - Censored participants: =27

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (≥) 80% power assuming a Hazard ration (HR) of 0·667 at an experiment-wise 2-sided alpha level of 0·2.

Comparison groups	8 mg/kg Trastuzumab + Standard of Care Chemotherapy v 150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	= 0.0506 [5]
Method	Logrank

Notes:

[4] - PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (≥) 80% power assuming a Hazard ration (HR) of 0·667 at an experiment-wise 2-sided alpha level of 0·2.
[5] - This is statistically significant at the pre-specified 2-sided alpha of 0·2

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (≥) 80% power assuming a Hazard ration (HR) of 0·667 at an experiment-wise 2-sided alpha level of 0·2.

Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority[6]
P-value	= 0.7695
Method	Logrank

Notes:

[6] - PFS analysis was planned after approximately 165 PFS events occurred in the enrolled population, yielding greater than or equal to (≥) 80% power assuming a Hazard ration (HR) of 0·667 at an experiment-wise 2-sided alpha level of 0·2.

Secondary: Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR): Objective Response Rate (ORR)

End point title	Percentage of Participants Achieving Complete Response (CR) or Partial Response (PR): Objective Response Rate (ORR)

End point description:

ORR was the percentage of participants achieving a best overall response (BOR) of complete response (CR) or partial response (PR) as per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the longest diameters (LD) of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. APD included all enrolled participants.

End point type	Secondary

End point timeframe:

Baseline to Objective Disease Progression (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: Percentage of participants				
number (confidence interval 95%)	32.9 (22.5 to 43.3)	13.9 (6.3 to 21.6)	13.9 (6.3 to 21.6)	

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DoR)

End point title	Duration of Response (DoR)

End point description:

DoR was the time from the date of first evidence of complete response or partial response to the date of objective progression or the date of death due to any cause, whichever is earlier. CR and PR were defined using the RECIST v1.1. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. If a responder was not known to have died or have objective progression as of the data inclusion cutoff date, duration of response was censored at the last adequate tumor assessment date. APD included all enrolled participants who received at least one dose of study drug and achieved CR or PR. 99999=NA because for 8 mg/kg Trastuzumab + Standard of Care Chemotherapy, the median and upper limit of the 95% CI was not calculated due to the high censoring rate.

End point type	Secondary

End point timeframe:

Date of CR or PR to Date of Objective Disease Progression or Death from Any Cause (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	26[7]	11[8]	11[9]	
Units: Months				
median (confidence interval 95%)	12.5 (6.5 to 23.5)	9.5 (2.8 to 22.7)	99999 (4.1 to 99999)	

Notes:

[7] - Censored participants: =12

[8] - Censored participants: =3

[9] - Censored participants: =11
99999 = NA.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Best Overall Response of CR, PR, or Stable Disease (SD): Disease Control Rate (DCR)

End point title	Percentage of Participants with a Best Overall Response of CR, PR, or Stable Disease (SD): Disease Control Rate (DCR)

End point description:

Disease Control Rate (DCR) was the percentage of participants with a best overall response of CR, PR, or Stable Disease (SD) as per Response using RECIST v1.1 criteria. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions, no progression of non-target lesions, and no appearance of new lesions. APD included all enrolled participants.

End point type	Secondary

End point timeframe:

Baseline to Objective Disease Progression (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: Percentage of participants				
number (confidence interval 95%)	78.5 (69.4 to 87.5)	74.7 (65.1 to 84.3)	67.1 (56.7 to 77.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Best Overall Response of CR, PR, or SD with Duration of SD for at Least 6 Months: Clinical Benefit Rate (CBR)

End point title	Percentage of Participants with Best Overall Response of CR, PR, or SD with Duration of SD for at Least 6 Months: Clinical Benefit Rate (CBR)

End point description:

Clinical benefit rate defined as percentage of participants with best overall response of CR, PR, or SD with a duration of at least 6 months. CR, PR, or SD were defined using RECIST, v1.1 criteria. CR defined as the disappearance of all target and non-target lesions and no appearance of new lesions. PR defined

as at least a 30% decrease in the sum of the LD of target lesions (taking as reference the baseline sum LD), no progression of non-target lesions, and no appearance of new lesions. SD was neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD for target lesions, no progression of non-target lesions, and no appearance of new lesions. Percentage of participants = (participants with CR+PR+SD with a duration of at least 6 months /number of participants enrolled) *100. APD included all enrolled participants.

End point type	Secondary

End point timeframe:

Date of CR, PR or SD to 6 Months Post CR, PR or SD (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: Percentage of participants				
number (confidence interval 95%)	58.2 (47.4 to 69.1)	45.6 (34.6 to 56.6)	38.0 (27.3 to 48.7)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pain and Symptom Burden Assessment on the Modified Brief Pain Inventory-Short Form (mBPI-sf)

End point title	Change from Baseline in Pain and Symptom Burden Assessment on the Modified Brief Pain Inventory-Short Form (mBPI-sf)

End point description:

The mBPI-sf is an 11-item instrument used as a multiple-item measure of cancer pain intensity. In addition to pain intensity (4 items), the mBPI-sf is designed for participants to record the presence of pain in general, pain relief, and pain interference with function (general activity, mood, ability to walk, ability to perform normal work, relations with others, sleep, enjoyment of life). Responses for the mBPI-sf items are captured through the use of 11-point numeric rating scales anchored at 0 (no pain or does not interfere) and 10 (pain as bad as you can imagine or completely interferes). The mBPI-sf recall period is 24 hours and typical completion time for this instrument is less than 5 minutes. Mean Interference Score data is reported here. Least square (LS) Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all enrolled participants.

End point type	Secondary

End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79	79	79	
Units: units on a scale				
least squares mean (standard error)	0 (± 0.18)	0.20 (± 0.18)	0.31 (± 0.19)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.232 [10]
Method	MMRM Model

Notes:

[10] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Secondary: Change from Baseline in Symptom Burden on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

End point title	Change from Baseline in Symptom Burden on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-C30 (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30 v3.0 was a self-administered questionnaire with multidimensional scales that measures 5 functional domains (physical, role, cognitive, emotional, and social), global health status, and symptom scales of fatigue, pain, nausea and vomiting, dyspnea, loss of appetite, insomnia, constipation and diarrhea, and financial difficulties. A linear transformation is applied to standardize the raw scores to range between 0 and 100 per developer guidelines. For functional domains and global health status, higher scores represent a better level of functioning. For symptoms scales, higher scores represented a greater degree of symptoms. LS Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all randomized participants who received at least one dose of study drug with baseline and post-baseline EORTC QLQ-C30 data for each EORTC QLQ-C30 items.

End point type	Secondary

End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	72	69	
Units: units on a scale				
least squares mean (standard error)				
Global health status	-2.9 (± 1.6)	-5.9 (± 1.7)	-1.9 (± 1.8)	
Functional scale: Physical functioning	-1.0 (± 1.6)	-4.4 (± 1.6)	-4.5 (± 1.7)	
Functional scale: Role functioning	-2.7 (± 2.2)	-5.0 (± 2.3)	-8.2 (± 2.4)	
Functional scale: Emotional functioning	2.4 (± 1.7)	-0.4 (± 1.8)	1.1 (± 1.8)	
Functional scale: Cognitive functioning	-1.8 (± 1.4)	-1.1 (± 1.5)	-1.6 (± 1.6)	
Functional scale: Social functioning	-0.9 (± 1.9)	-0.9 (± 1.9)	-2.4 (± 2.0)	
Symptom scale: Fatigue	1.8 (± 1.9)	7.0 (± 2.0)	4.7 (± 2.1)	
Symptom scale: Nausea and vomiting	6.3 (± 1.4)	5.6 (± 1.4)	2.2 (± 1.5)	
Symptom scale: Pain	-2.5 (± 2.1)	3.1 (± 2.1)	4.3 (± 2.2)	
Symptom scale: Dyspnoea	0.7 (± 1.9)	2.9 (± 2.0)	3.7 (± 2.1)	
Symptom scale: Insomnia	-4.4 (± 2.1)	-1.6 (± 2.2)	2.0 (± 2.3)	
Symptom scale: Appetite loss	6.3 (± 2.3)	5.5 (± 2.4)	2.4 (± 2.5)	
Symptom scale: Constipation	-6.3 (± 1.9)	-10.5 (± 1.9)	-3.4 (± 2.0)	
Symptom scale: Diarrhoea	21.5 (± 2.2)	25.3 (± 2.3)	2.2 (± 2.4)	
Symptom scale: Financial difficulties	0.8 (± 2.0)	-1.9 (± 2.1)	-3.2 (± 2.2)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1: Global health status
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.689 [11]
Method	MMRM Model

Notes:

[11] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 2: Functional scale: Physical
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.141 [12]
Method	MMRM Model

Notes:

[12] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 3: Functional scale: Role
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.095 [13]
Method	MMRM Model

Notes:

[13] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical analysis 4:Functional scale: Emotional
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.591 [14]
Method	MMRM Model

Notes:

[14] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 5: Functional scale:Cognitive
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.935 [15]
Method	MMRM Model

Notes:

[15] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical analysis 6: Functional scale: Social
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.578 [16]
Method	MMRM Model

Notes:

[16] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 7: Symptom scale: Fatigue
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.308 [17]
Method	MMRM Model

Notes:

[17] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 8 : Symptom: Nausea, vomiting
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.043 [18]
Method	MMRM Model

Notes:

[18] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 9: Symptom scale: Pain
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [19]
Method	MMRM Model

Notes:

[19] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 10: Symptom scale: Dyspnoea
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.276 [20]
Method	MMRM Model

Notes:

[20] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 11: Symptom scale: Insomnia
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.041 [21]
Method	MMRM Model

Notes:

[21] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 12: Symptom: Appetite loss
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.262 [22]
Method	MMRM Model

Notes:

[22] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 13:Symptom scale:Constipation
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[23]
P-value	= 0.285
Method	MMRM Model

Notes:

[23] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 14: Symptom scale: Diarrhoea
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [24]
Method	MMRM Model

Notes:

[24] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 15: Symptom scale: Financial
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.18 [25]
Method	MMRM Model

Notes:

[25] - p-values are from Type 3 sums of squares mixed models repeated measures model (MMRM): Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Secondary: Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score

End point title	Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Index Score

End point description:

The EQ-5D-5L is a standardized instrument for use as a measure of self-reported health status. Participants completed the 5-level (no problem, slight problem, moderate problem, severe problem, and inability or extreme problem), 5-dimension (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) questionnaire concerning their current health state. Five dimensions of health status are each assessed with 5 response options and scored as a composite index which were anchored on a scale of 0 to 1 with a higher score representing better health status.LS Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all enrolled participants who received at least one dose of study drug with baseline and post-baseline EQ-5D 5L data.

End point type	Secondary

End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	72	68	
Units: units on a scale				
least squares mean (standard error)	0.01 (± 0.02)	-0.01 (± 0.02)	-0.04 (± 0.02)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.033 [26]
Method	MMRM Model

Notes:

[26] - p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Statistical analysis title	Statistical Analysis 2
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	140
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.275 [27]
Method	MMRM Model

Notes:

[27] - p-values are from Type 3 sums of squares mixed models repeated measures model: Change from baseline = Treatment + Visit + Treatment*Visit + Baseline.

Secondary: Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Visual Analogue Scale (VAS)

End point title	Change From Baseline on the EuroQol 5-Dimension, 5-Level Questionnaire (EQ-5D-5L) Visual Analogue Scale (VAS)

End point description:

European Quality of Life-5 Dimensions-5 Level (EQ-5D-5L) is a standardized measure of health status of the participant. The EQ-5D-5L is assessed using a visual analog scale (VAS) that ranged from 0 to 100 millimeter (mm), where 0 is the worst health you can imagine and 100 is the best health you can imagine. A higher score indicates better health state. LS Mean value was controlled for Treatment, visit, Treatment*Visit and baseline. APD included all enrolled participants who received at least one dose of study drug with baseline and post-baseline EQ-5D 5L VAS data.

End point type	Secondary

End point timeframe:

Baseline, 30 Days After Treatment Discontinuation (Up To 36 Months)

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	72	71	70	
Units: millimeter (mm)				
least squares mean (standard error)	0.61 (± 1.4)	-1.64 (± 1.4)	-0.61 (± 1.5)	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy

Number of subjects included in analysis	142
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.546
Method	MMRM Model

Statistical analysis title	Statistical Analysis 2
Comparison groups	8 mg/kg Trastuzumab + Standard of Care Chemotherapy v 150 mg Abemaciclib + 8 mg/kg Trastuzumab
Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	superiority[28]
P-value	= 0.62
Method	MMRM Model

Notes:

[28] - EQ 5D-5L Visual Analog Scale Score

Secondary: Pharmacokinetics (PK): Minimum Steady State Concentration (Cmin,ss) of Abemaciclib and its Metabolites (M2 and M20)

End point title	Pharmacokinetics (PK): Minimum Steady State Concentration (Cmin,ss) of Abemaciclib and its Metabolites (M2 and M20)[29]

End point description:

Minimum Steady State Concentration (Cmin,ss) of Abemaciclib and Its Metabolites (M2 and M20) was evaluated. M2 and M20 are 2 major active metabolites of abemaciclib.

End point type	Secondary

End point timeframe:

Cycle(C)1 Day(D)1,C1D15, C2D1, C2D8, C3D1,C3D15, C4D1, C5D1:pre-dose; C1D1, C2D1, C3D1, C4D1, C5D1:post-dose

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: The outcome is specific to Abemaciclib and its Metabolites

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	77	71		
Units: nanogram/milliliter (ng/mL)				
geometric mean (geometric coefficient of variation)				
Abemaciclib	134 (± 77)	155 (± 53)		
M2	72.0 (± 120)	96.5 (± 120)		
M20	136 (± 120)	181 (± 130)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants With 1 Year Overall Survival (OS)

End point title	Percentage of Participants With 1 Year Overall Survival (OS)

End point description:

OS is defined as the time from the date of randomization until death from any cause. For participants not known to have died by the data-inclusion cutoff date, OS is censored at the last date they were known to be alive. For each treatment arm OS rate at 1 year from the date of randomization was determined using the OS times and was estimated using the Kaplan-Meier method. APD included all randomized participants (including the censored participants).

End point type	Secondary

End point timeframe:

Randomization to date of death from any cause assessed at 1 year

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79[30]	79[31]	79[32]	
Units: percentage of participants				
number (confidence interval 95%)	77.2 (65.9 to 85.2)	77.4 (66.1 to 85.3)	69.8 (57.5 to 79.1)	

Notes:

[30] - Censored participants: = 62

[31] - Censored participants: = 62

[32] - Censored participants: = 58

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified by the number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer and the status of disease (measurable vs. non-measurable).

Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.241
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	1.3

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Stratified by the number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer and the status of disease (measurable vs. non-measurable).	
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.313
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.72
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.38
upper limit	1.36

Secondary: Percentage of Participants With 2 Year OS

End point title	Percentage of Participants With 2 Year OS
End point description:	
OS is defined as the time from the date of randomization until death from any cause. For participants not known to have died by the data-inclusion cutoff date, OS is censored at the last date they were known to be alive. For each treatment arm OS rate at 2 years from the date of randomization was determined using the OS times and was estimated using the Kaplan-Meier method. APD included all randomized participants (including the censored participants).	
End point type	Secondary
End point timeframe:	
Randomization to date of death from any cause assessed at 2 years	

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79[33]	79[34]	79[35]	
Units: percentage of participants				
number (confidence interval 95%)	55.8 (43.5 to 66.4)	55.7 (43.4 to 66.3)	43.0 (30.9 to 54.5)	

Notes:

[33] - Censored participants: = 47

[34] - Censored participants: = 47

[35] - Censored participants: = 41

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Stratified by the number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer and the status of disease (measurable vs. non-measurable).	
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.104
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.08

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Stratified by the number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer and the status of disease (measurable vs. non-measurable).	
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.12
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.1

Secondary: Percentage of Participants With 3 Year OS

End point title	Percentage of Participants With 3 Year OS

End point description:

OS is defined as the time from the date of randomization until death from any cause. For participants not known to have died by the data-inclusion cutoff date, OS is censored at the last date they were known to be alive. For each treatment arm OS rate at 3 years from the date of randomization was determined using the OS times and was estimated using the Kaplan-Meier method. APD included all randomized participants (including the censored participants).

End point type	Secondary

End point timeframe:

Randomization to date of death from any cause assessed at 3 years

End point values	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	150 mg Abemaciclib + 8 mg/kg Trastuzumab	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	79[36]	79[37]	79[38]	
Units: percentage of participants				
number (confidence interval 95%)	46.7 (34.7 to 57.9)	40.2 (28.6 to 51.5)	29.9 (19.1 to 41.3)	

Notes:

[36] - Censored participants: = 41

[37] - Censored participants: = 37

[38] - Censored participants: = 33

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Stratified by the number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer and the status of disease (measurable vs. non-measurable).

Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.049
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Stratified by the number of previous regimens (excluding single-agent endocrine therapy) for advanced breast cancer and the status of disease (measurable vs. non-measurable).	
Comparison groups	150 mg Abemaciclib + 8 mg/kg Trastuzumab v 8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Number of subjects included in analysis	158
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.153
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.74
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.12

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Baseline till end of follow-up (Up to 6.5 years)	
Adverse event reporting additional description:	
All enrolled participants who received at least one dose of study drug.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups	
Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant
Reporting group description:	
150 milligram (mg) abemaciclib given orally every 12 hours (Q12H) of a 21-day cycle; plus 8 milligram per kilogram (mg/kg) trastuzumab intravenous (IV) infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle; plus 500 mg fulvestrant intramuscularly (IM) on day 1, 15 and 29 and then once every 4 weeks thereafter.	
Reporting group title	8 mg/kg Trastuzumab + Standard of Care Chemotherapy
Reporting group description:	
8 mg/kg trastuzumab IV infusion on Day 1 of a 21-day cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle plus standard of care single agent chemotherapy of physician’s choice administered according to product label.	
Reporting group title	150 mg Abemaciclib + 8 mg/kg Trastuzumab
Reporting group description:	
150 mg abemaciclib given orally Q12H of a 21-day cycle; plus 8 mg/kg trastuzumab IV infusion on Day 1 of the cycle then a 6 mg/kg maintenance dose IV infusion on Day 1 of each subsequent cycle.	

Serious adverse events	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	150 mg Abemaciclib + 8 mg/kg Trastuzumab
Total subjects affected by serious adverse events			
subjects affected / exposed	24 / 78 (30.77%)	14 / 72 (19.44%)	15 / 77 (19.48%)
number of deaths (all causes)	52	53	55
number of deaths resulting from adverse events			
General disorders and administration site conditions			
chest pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pain			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
malaise			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pyrexia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
drug hypersensitivity			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
vaginal haemorrhage			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
acute respiratory distress syndrome			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
dyspnoea			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
epistaxis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
interstitial lung disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pleural effusion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
respiratory failure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
pulmonary embolism			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pneumothorax			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

pneumonitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
anxiety			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
depression			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
confusional state			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
femur fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hip fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
spinal compression fracture			

alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (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
radiation pneumonitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
cardio-respiratory arrest			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
pericardial effusion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
cerebral haemorrhage			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
dizziness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
headache			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
febrile neutropenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	3 / 72 (4.17%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 1	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
neutropenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
leukopenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (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
ascites			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
constipation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
diarrhoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
faecaloma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ileus			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
intestinal obstruction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

vomiting			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
stomatitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (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
Hepatobiliary disorders			
bile duct stone			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
cholangitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
jaundice cholestatic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	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 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract obstruction			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary retention			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
back pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
osteonecrosis of jaw			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
musculoskeletal pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
musculoskeletal chest pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
cellulitis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
clostridium difficile colitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ear infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
fungal infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (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
gastroenteritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
herpes zoster			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
influenza			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

pneumonia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	2 / 77 (2.60%)
occurrences causally related to treatment / all	1 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
meningitis viral			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lymphangitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lower respiratory tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
soft tissue infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
sepsis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	3 / 72 (4.17%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 1	2 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract infection			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
hypokalaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	150 mg Abemaciclib + 8 mg/kg Trastuzumab + 500 mg Fulvestrant	8 mg/kg Trastuzumab + Standard of Care Chemotherapy	150 mg Abemaciclib + 8 mg/kg Trastuzumab
Total subjects affected by non-serious adverse events			
subjects affected / exposed	76 / 78 (97.44%)	68 / 72 (94.44%)	75 / 77 (97.40%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
lipoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
tumour pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Vascular disorders			
axillary vein thrombosis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
blood pressure fluctuation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
haematoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
hot flush			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	6 / 78 (7.69%)	2 / 72 (2.78%)	3 / 77 (3.90%)
occurrences (all)	9	2	3
hypotension			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
hypertension			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	2 / 72 (2.78%)	4 / 77 (5.19%)
occurrences (all)	4	2	6
lymphoedema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	2	2	0
peripheral venous disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
vascular pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0

Surgical and medical procedures			
bladder catheter removal			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
breast reconstruction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
central venous catheterisation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
nail operation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
radiotherapy to brain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
removal of foreign body			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
tooth extraction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	1	3	0
General disorders and administration site conditions			
axillary pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
chest discomfort			

alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
catheter site pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
catheter site swelling			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
chest pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	2	1	2
complication associated with device			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
chills			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	5	0	1
face oedema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
fatigue			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	45 / 78 (57.69%)	32 / 72 (44.44%)	41 / 77 (53.25%)
occurrences (all)	66	39	57
feeling of body temperature change			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
gravitational oedema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
gait disturbance			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
generalised oedema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
influenza like illness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	6 / 77 (7.79%)
occurrences (all)	3	0	15
injection site discomfort			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
injection site reaction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	2 / 72 (2.78%)	1 / 77 (1.30%)
occurrences (all)	4	2	1
malaise			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	3 / 77 (3.90%)
occurrences (all)	1	1	3
mucosal dryness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

mucosal inflammation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	4 / 72 (5.56%)	3 / 77 (3.90%)
occurrences (all)	2	6	4
necrosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
non-cardiac chest pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	7	1	1
oedema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
oedema peripheral			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	7 / 72 (9.72%)	6 / 77 (7.79%)
occurrences (all)	10	8	9
pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	3	2	2
peripheral swelling			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
pyrexia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	13 / 78 (16.67%)	11 / 72 (15.28%)	5 / 77 (6.49%)
occurrences (all)	18	17	8
swelling face			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
seasonal allergy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1
Reproductive system and breast disorders			
breast discharge			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
breast haemorrhage			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
breast pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	3	1	2
cystocele			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
genital rash			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
pelvic pain			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
vulvovaginal dryness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
vaginal discharge			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
vaginal haemorrhage			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
catarrh			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
cough			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	21 / 78 (26.92%)	9 / 72 (12.50%)	12 / 77 (15.58%)
occurrences (all)	31	13	14
dysphonia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
dyspnoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	15 / 78 (19.23%)	13 / 72 (18.06%)	7 / 77 (9.09%)
occurrences (all)	21	14	9
dyspnoea exertional			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
epistaxis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	6 / 78 (7.69%)	5 / 72 (6.94%)	7 / 77 (9.09%)
occurrences (all)	9	5	11
hypoxia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
laryngeal inflammation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
lung disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
lower respiratory tract congestion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
nasal mucosal disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
nasal inflammation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
nasal dryness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

nasal discomfort			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
nasal discharge discolouration			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
nasal congestion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	4	1	0
oropharyngeal pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	3 / 72 (4.17%)	1 / 77 (1.30%)
occurrences (all)	3	3	1
paranasal sinus hypersecretion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
pleural effusion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
pneumonitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
productive cough			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	2
pulmonary oedema			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
pulmonary embolism			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
rhinorrhoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	3 / 72 (4.17%)	3 / 77 (3.90%)
occurrences (all)	1	3	4
rhinitis allergic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	9	1	1
sneezing			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
tachypnoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
throat irritation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
wheezing			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Psychiatric disorders			
abulia			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
anxiety			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	5 / 72 (6.94%)	3 / 77 (3.90%)
occurrences (all)	2	6	3
confusional state			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
depression			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 78 (8.97%)	3 / 72 (4.17%)	3 / 77 (3.90%)
occurrences (all)	9	3	3
insomnia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	5 / 72 (6.94%)	6 / 77 (7.79%)
occurrences (all)	4	5	9
libido decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
panic attack			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 78 (8.97%)	8 / 72 (11.11%)	6 / 77 (7.79%)
occurrences (all)	8	17	9
aspartate aminotransferase increased			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	10 / 78 (12.82%)	8 / 72 (11.11%)	7 / 77 (9.09%)
occurrences (all)	11	22	10
bilirubin conjugated increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
blood alkaline phosphatase increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 78 (8.97%)	2 / 72 (2.78%)	1 / 77 (1.30%)
occurrences (all)	7	3	1
blood bilirubin decreased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
blood bilirubin increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	4 / 72 (5.56%)	2 / 77 (2.60%)
occurrences (all)	5	8	2
blood bilirubin unconjugated increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
blood chloride increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
blood creatinine increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	10 / 78 (12.82%)	0 / 72 (0.00%)	11 / 77 (14.29%)
occurrences (all)	15	0	14
body temperature increased alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

c-reactive protein increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
cell marker increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
electrocardiogram repolarisation abnormality			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
ejection fraction decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	3 / 72 (4.17%)	1 / 77 (1.30%)
occurrences (all)	0	4	1
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	3 / 77 (3.90%)
occurrences (all)	1	2	3
glomerular filtration rate decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
grip strength decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
hepatic enzyme increased			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
liver function test abnormal			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
monocyte count decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
monocyte count increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
weight increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
weight decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	6 / 78 (7.69%)	2 / 72 (2.78%)	5 / 77 (6.49%)
occurrences (all)	10	2	5
vitamin d decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Injury, poisoning and procedural complications			
arthropod bite			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
contusion			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
fibula fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
fall			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	3 / 77 (3.90%)
occurrences (all)	4	1	4
femoral neck fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
foreign body			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
hip fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
infusion related reaction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	4	0
joint injury			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
procedural pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	2	0

radiation skin injury			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
skin abrasion			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
spinal compression fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
skin laceration			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
thermal burn			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
thoracic vertebral fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
tooth fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
spinal fracture			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			

atrial fibrillation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
atrioventricular block first degree			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
cardiac failure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
cardiomegaly			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
bradycardia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
left atrial enlargement			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
left ventricular dysfunction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
palpitations			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	3	1	0
pericardial effusion			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
sinus tachycardia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1
tachycardia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	3	1	0
Nervous system disorders			
balance disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
cerebral thrombosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
dizziness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	3 / 72 (4.17%)	10 / 77 (12.99%)
occurrences (all)	7	3	14
dysarthria			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
dysgeusia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	2 / 72 (2.78%)	4 / 77 (5.19%)
occurrences (all)	4	4	4
facial paresis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
headache			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	13 / 78 (16.67%)	15 / 72 (20.83%)	11 / 77 (14.29%)
occurrences (all)	19	18	16
hemiparesis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
lethargy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	3	2	0
loss of consciousness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
memory impairment			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
migraine			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
nerve compression			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
neuropathy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	15 / 72 (20.83%)	7 / 77 (9.09%)
occurrences (all)	5	20	8

peripheral motor neuropathy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	3
psychomotor skills impaired			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
presyncope			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
radiculopathy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
seizure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
sinus headache			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
spinal cord compression			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
somnolence			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
stupor			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
syncope			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
taste disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	2	3	0
tension headache			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
tremor			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	1	1	3
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	30 / 78 (38.46%)	16 / 72 (22.22%)	20 / 77 (25.97%)
occurrences (all)	47	19	25
anaemia macrocytic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
febrile neutropenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	3 / 72 (4.17%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
iron deficiency anaemia			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
leukocytosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
leukopenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	18 / 78 (23.08%)	10 / 72 (13.89%)	9 / 77 (11.69%)
occurrences (all)	27	58	13
lymphocytosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
lymphopenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	6 / 78 (7.69%)	4 / 72 (5.56%)	4 / 77 (5.19%)
occurrences (all)	7	16	5
neutropenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	38 / 78 (48.72%)	26 / 72 (36.11%)	27 / 77 (35.06%)
occurrences (all)	72	88	59
neutrophilia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
thrombocytopenia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	23 / 78 (29.49%)	5 / 72 (6.94%)	23 / 77 (29.87%)
occurrences (all)	33	20	42
Ear and labyrinth disorders			
deafness			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
ear pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	4	2	0
middle ear inflammation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
otorrhoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
vertigo			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	2 / 77 (2.60%)
occurrences (all)	1	2	2
Eye disorders			
blepharitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
blindness			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
cataract			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
cataract nuclear			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
conjunctival hyperaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
conjunctival irritation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
conjunctivitis allergic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
diplopia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1
dry eye			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	3 / 77 (3.90%)
occurrences (all)	4	2	3
eye discharge			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
eye disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
eye irritation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1

eye pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	1	2	0
eye pruritus			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
intraocular haematoma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
lacrimation increased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 78 (8.97%)	2 / 72 (2.78%)	5 / 77 (6.49%)
occurrences (all)	8	2	5
ocular hyperaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
periorbital oedema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
vision blurred			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	1 / 72 (1.39%)	3 / 77 (3.90%)
occurrences (all)	4	1	3
visual acuity reduced			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
visual impairment			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
xerophthalmia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
abdominal distension			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	6 / 78 (7.69%)	0 / 72 (0.00%)	3 / 77 (3.90%)
occurrences (all)	9	0	3
abdominal pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	24 / 78 (30.77%)	16 / 72 (22.22%)	19 / 77 (24.68%)
occurrences (all)	35	20	26
anal incontinence			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
anorectal discomfort			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
aphthous ulcer			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	1 / 77 (1.30%)
occurrences (all)	0	2	1
ascites			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	1 / 77 (1.30%)
occurrences (all)	0	2	1
abdominal rigidity			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
defaecation urgency			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
colitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
constipation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	11 / 78 (14.10%)	15 / 72 (20.83%)	8 / 77 (10.39%)
occurrences (all)	13	19	9
diarrhoea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	62 / 78 (79.49%)	18 / 72 (25.00%)	60 / 77 (77.92%)
occurrences (all)	169	33	163
dry mouth			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	4 / 72 (5.56%)	5 / 77 (6.49%)
occurrences (all)	5	7	6
dyspepsia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	8 / 78 (10.26%)	6 / 72 (8.33%)	7 / 77 (9.09%)
occurrences (all)	15	8	8
dysphagia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
enterocolitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

gastric ulcer			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
gastritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	5	1	1
gastrointestinal disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
gastrointestinal toxicity			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	5	1	1
gingival bleeding			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	1	1	3
gingival pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
glossodynia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
flatulence			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
haemorrhoidal haemorrhage			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
haemorrhoids			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
haematochezia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
ileus			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
lip swelling			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
mouth ulceration			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	6	2	0
nausea			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	38 / 78 (48.72%)	26 / 72 (36.11%)	32 / 77 (41.56%)
occurrences (all)	56	36	48
oral dysaesthesia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0

oesophageal pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
pancreatitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
proctalgia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
rectal haemorrhage			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
toothache			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
stomatitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	8 / 72 (11.11%)	7 / 77 (9.09%)
occurrences (all)	4	13	9
vomiting			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	22 / 78 (28.21%)	11 / 72 (15.28%)	22 / 77 (28.57%)
occurrences (all)	33	13	27
Hepatobiliary disorders			
cholestasis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
hepatic cytolysis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
hepatotoxicity			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
jaundice			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
portal vein thrombosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
pseudocirrhosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
acne			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
alopecia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	8 / 78 (10.26%)	8 / 72 (11.11%)	7 / 77 (9.09%)
occurrences (all)	9	8	8
blister			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
cutaneous lupus erythematosus			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
dermatitis acneiform			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
dermatitis allergic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
dermatitis contact			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
dry skin			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	4 / 72 (5.56%)	4 / 77 (5.19%)
occurrences (all)	5	4	4
eczema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences (all)	3	0	2
erythema			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	3 / 72 (4.17%)	1 / 77 (1.30%)
occurrences (all)	0	3	2
hyperhidrosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
intertrigo			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0

nail dystrophy			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
nail disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	4 / 77 (5.19%)
occurrences (all)	2	1	4
nail discolouration			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
nail bed disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
nail ridging			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
night sweats			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
onychomadesis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
onycholysis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
onychoclasis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	4 / 78 (5.13%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	4	0	1
pain of skin			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences (all)	3	0	4
palmar-plantar erythrodysaesthesia syndrome			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	13 / 72 (18.06%)	1 / 77 (1.30%)
occurrences (all)	0	20	2
papule			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
photosensitivity reaction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
petechiae			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
prurigo			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
pruritus			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	12 / 78 (15.38%)	3 / 72 (4.17%)	9 / 77 (11.69%)
occurrences (all)	17	3	9
purpura			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0

rash			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	15 / 78 (19.23%)	9 / 72 (12.50%)	14 / 77 (18.18%)
occurrences (all)	19	13	20
sensitive skin			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
skin discolouration			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
skin ulcer			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
skin reaction			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
skin irritation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
skin fissures			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	0	4	0
skin exfoliation			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
skin disorder			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
stasis dermatitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
urticaria			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	4
xeroderma			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Renal and urinary disorders			
acute kidney injury			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	8
bladder disorder			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
bladder pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
bladder tamponade			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
chronic kidney disease			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
cystitis noninfective			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	2
dysuria			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
haematuria			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	1	2	0
incontinence			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
nephropathy toxic			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
nephrolithiasis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
pollakiuria			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	2 / 77 (2.60%)
occurrences (all)	1	0	3
polyuria			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1

renal failure			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
urinary incontinence			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
urinary retention			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	14 / 78 (17.95%)	11 / 72 (15.28%)	12 / 77 (15.58%)
occurrences (all)	21	16	14
arthritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	2	1
bone pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	7 / 72 (9.72%)	3 / 77 (3.90%)
occurrences (all)	1	10	3
back pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	6 / 78 (7.69%)	6 / 72 (8.33%)	12 / 77 (15.58%)
occurrences (all)	11	8	14
costochondritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
flank pain			
alternative dictionary used:			

MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	3	1	1
haematoma muscle			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
inguinal mass			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
joint range of motion decreased			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
limb discomfort			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
muscle spasms			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	2 / 72 (2.78%)	3 / 77 (3.90%)
occurrences (all)	5	2	3
myalgia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 78 (8.97%)	10 / 72 (13.89%)	7 / 77 (9.09%)
occurrences (all)	9	11	8
musculoskeletal pain			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	2	1	1
musculoskeletal chest pain			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	1 / 77 (1.30%)
occurrences (all)	1	2	1
muscular weakness alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
muscle twitching alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
neck pain alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	2 / 72 (2.78%)	3 / 77 (3.90%)
occurrences (all)	1	2	4
osteonecrosis alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
osteoporosis alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
pain in extremity alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	8 / 72 (11.11%)	5 / 77 (6.49%)
occurrences (all)	4	11	6
pain in jaw alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
osteonecrosis of jaw alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	2	0	1

plantar fasciitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
covid-19			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
bronchitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
candida infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
catheter site infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
cellulitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
conjunctivitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	2	1	2
device related infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	2	1	0
ear infection			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
folliculitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
fungal skin infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
gastroenteritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	4 / 72 (5.56%)	0 / 77 (0.00%)
occurrences (all)	5	5	0
gastroenteritis norovirus			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
herpes zoster			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
infected bite			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
infected dermal cyst			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
influenza			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	2 / 72 (2.78%)	5 / 77 (6.49%)
occurrences (all)	6	2	5

kidney infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
lip infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	2
lymphangitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
lower respiratory tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	5	0	0
localised infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
nail infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
nasopharyngitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	2 / 72 (2.78%)	3 / 77 (3.90%)
occurrences (all)	5	2	3
oral infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
oral candidiasis			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
onychomycosis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
paronychia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
pharyngotonsillitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
pharyngitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	3	1	2
pneumonia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	3	1	2
postoperative wound infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
pyelonephritis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
sepsis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0

rhinitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	4 / 78 (5.13%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	4	1	2
respiratory tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
rash pustular			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
spinal cord infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
sinusitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	1	1	2
skin infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
tooth abscess			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
tooth infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
upper respiratory tract infection			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	12 / 78 (15.38%)	8 / 72 (11.11%)	4 / 77 (5.19%)
occurrences (all)	19	12	5
urinary tract infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	8 / 78 (10.26%)	6 / 72 (8.33%)	10 / 77 (12.99%)
occurrences (all)	16	9	24
vaginal infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	2	1	1
vascular device infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
viral infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	3	0	1
viral sinusitis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
vulvovaginal candidiasis			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
wound infection			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed	19 / 78 (24.36%)	13 / 72 (18.06%)	16 / 77 (20.78%)
occurrences (all)	26	15	20
dehydration			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	4 / 72 (5.56%)	2 / 77 (2.60%)
occurrences (all)	3	4	2
hypernatraemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	4	0
hypercalcaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	1 / 77 (1.30%)
occurrences (all)	2	1	1
hyperchloraemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	3	0
hypercholesterolaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
hyperglycaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	4 / 72 (5.56%)	1 / 77 (1.30%)
occurrences (all)	1	9	3
hyperkalaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	5 / 78 (6.41%)	1 / 72 (1.39%)	3 / 77 (3.90%)
occurrences (all)	6	1	3
hyperuricaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	2 / 72 (2.78%)	0 / 77 (0.00%)
occurrences (all)	0	4	0

hypoalbuminaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	2 / 72 (2.78%)	2 / 77 (2.60%)
occurrences (all)	2	2	2
hypocalcaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	1 / 78 (1.28%)	4 / 72 (5.56%)	2 / 77 (2.60%)
occurrences (all)	1	5	2
hypoglycaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
hypokalaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	7 / 78 (8.97%)	4 / 72 (5.56%)	7 / 77 (9.09%)
occurrences (all)	18	5	14
hypomagnesaemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
hyponatraemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	2 / 78 (2.56%)	1 / 72 (1.39%)	2 / 77 (2.60%)
occurrences (all)	3	1	3
hypophosphataemia			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	3 / 78 (3.85%)	0 / 72 (0.00%)	0 / 77 (0.00%)
occurrences (all)	3	0	0
iron deficiency			
alternative dictionary used: MedDRA 27.0			
subjects affected / exposed	0 / 78 (0.00%)	0 / 72 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
vitamin b12 deficiency			
alternative dictionary used: MedDRA 27.0			

subjects affected / exposed occurrences (all)	2 / 78 (2.56%) 2	0 / 72 (0.00%) 0	0 / 77 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 December 2015	- Added the safety lead-in portion for Arm A due to no data around the triplet combination
23 January 2019	- Updated the safety language regarding hepatic monitoring, assessment of renal function, and venous thromboembolic events (VTEs) for ongoing patients and align with the updated label of abemaciclib.
10 February 2020	- Added dose modification table for interstitial lung disease (ILD)/pneumonitis and updated guidance for management of ILD/pneumonitis.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported