Clinical trial results:
A Phase III, Double-Blind, Placebo-Controlled, Randomized Study of Taselisib Plus Fulvestrant Versus Placebo Plus Fulvestrant in Postmenopausal Women With Estrogen Receptor-Positive And Her2-Negative Locally Advanced or Metastatic Breast Cancer Who Have Disease Recurrence or Progression During or After Aromatases Inhibitor Therapy

Summary

EudraCT number	2014-003185-25
Trial protocol	IT PT ES CZ DE AT NL PL BG FR SE GR RO FI
Global end of trial date	

Results information

Result version number	v1
This version publication date	19 June 2019
First version publication date	19 June 2019

Trial information

Trial identification

Sponsor protocol code	GO29058

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02340221
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	15 October 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 October 2017
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to compare the efficacy between taselisib + fulvestrant (Tas + Ful) versus placebo + fulvestrant (Pbo + Ful) as measured by investigator-assessed progression-free Survival (PFS) in subjects with phosphatidylinositol-4,5-bisphosphate 3-kinase (PIK3CA)-mutant tumors.

Protection of trial subjects:

All study subjects were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 April 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	3 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 35
Country: Number of subjects enrolled	Austria: 9
Country: Number of subjects enrolled	Bulgaria: 22
Country: Number of subjects enrolled	Bosnia and Herzegovina: 1
Country: Number of subjects enrolled	Canada: 64
Country: Number of subjects enrolled	China: 21
Country: Number of subjects enrolled	Colombia: 4
Country: Number of subjects enrolled	Czech Republic: 4
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 49
Country: Number of subjects enrolled	Finland: 2
Country: Number of subjects enrolled	France: 32
Country: Number of subjects enrolled	Greece: 12
Country: Number of subjects enrolled	Italy: 40
Country: Number of subjects enrolled	Korea, Republic of: 60
Country: Number of subjects enrolled	Mexico: 32
Country: Number of subjects enrolled	Netherlands: 4
Country: Number of subjects enrolled	Peru: 20
Country: Number of subjects enrolled	Poland: 44
Country: Number of subjects enrolled	Portugal: 23
Country: Number of subjects enrolled	Romania: 30

Country: Number of subjects enrolled	Russian Federation: 23
Country: Number of subjects enrolled	Serbia: 10
Country: Number of subjects enrolled	Sweden: 3
Country: Number of subjects enrolled	Thailand: 5
Country: Number of subjects enrolled	Turkey: 20
Country: Number of subjects enrolled	Taiwan: 10
Country: Number of subjects enrolled	United States: 43
Worldwide total number of subjects	631
EEA total number of subjects	283

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)	430
From 65 to 84 years	198
85 years and over	3

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 2127 subjects were screened and out of them, 631 subjects were randomised into the study. Of the 631 subjects, 214 and 417 were randomised to Placebo+Fulvestrant and Taselisib+Fulvestrant arms, respectively.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo+Fulvestrant

Arm description:

Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

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

Dosage and administration details:

Subjects received fulvestrant 500 mg IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

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

Dosage and administration details:

Subjects received taselisib-matching placebo orally QD beginning at Cycle 1, Day 1 until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Arm title	Taselisib+Fulvestrant

Arm description:

Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Arm type	Experimental

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

Dosage and administration details:

Subjects received fulvestrant 500 mg IM injection on Days 1 and 15 of Cycle 1 and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Investigational medicinal product name	Taselisib
Investigational medicinal product code	RO5537381
Other name	GDC-0032
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received taselisib 4 mg orally QD beginning at Cycle 1, Day 1 until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Number of subjects in period 1	Placebo+Fulvestrant	Taselisib+Fulvestrant
Started	214	417
Completed	0	0
Not completed	214	417
Death	58	101
Reason Not Specified	-	1
Withdrawal by Subject	14	22
Continued on Study	140	290
Lost to follow-up	2	3

Baseline characteristics

Reporting groups	
Reporting group title	Placebo+Fulvestrant
Reporting group description:	
Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.	
Reporting group title	Taselisib+Fulvestrant
Reporting group description:	
Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.	

Reporting group values	Placebo+Fulvestrant	Taselisib+Fulvestrant	Total
Number of subjects	214	417	631
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	60.7	60.1	
standard deviation	± 10.0	± 9.9	-
Sex: Female, Male			
Units: Subjects			
Female	214	417	631
Male	0	0	0

End points

End points reporting groups

Reporting group title	Placebo+Fulvestrant

Reporting group description:

Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Reporting group title	Taselisib+Fulvestrant

Reporting group description:

Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Primary: Progression-Free Survival (PFS) in Subjects with PIK3CA-mutant Tumours as Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1)

End point title	Progression-Free Survival (PFS) in Subjects with PIK3CA-mutant Tumours as Assessed by Investigator Using Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1 (v1.1)

End point description:

PFS was defined as the time from randomisation to disease progression as determined by the investigator with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 millimetres (mm). For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

End point type	Primary

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	340		
Units: months				
median (confidence interval 95%)	5.39 (3.68 to 7.29)	7.43 (7.26 to 9.07)		

Statistical analyses

Statistical analysis title	Taselisib+Fulvestrant vs Placebo+Fulvestrant
Comparison groups	Taselisib+Fulvestrant v Placebo+Fulvestrant

Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.56
upper limit	0.89

Secondary: Percentage of Subjects with Objective Response (Partial Response [PR] plus Complete Response [CR]), as Assessed Using RECIST v.1.1

End point title	Percentage of Subjects with Objective Response (Partial Response [PR] plus Complete Response [CR]), as Assessed Using RECIST v.1.1

End point description:

PR was defined as at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. CR was defined as disappearance of all target and non-target lesions and normalisation of tumor marker levels (as applicable to non-target lesions). Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

End point type	Secondary

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	264		
Units: percentage of subjects				
number (confidence interval 95%)	11.9 (7.1 to 18.3)	28.0 (22.7 to 33.8)		

Statistical analyses

Statistical analysis title	Taselisib+Fulvestrant vs Placebo+Fulvestrant
Comparison groups	Placebo+Fulvestrant v Taselisib+Fulvestrant

Number of subjects included in analysis	398
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Cochran-Mantel-Haenszel

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)

End point description:

OS was defined as the time from the date of randomisation to the date of death due to any cause. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point. 99999 represents that the upper limit of confidence interval was not estimable due to the low number of subjects with events.

End point type	Secondary

End point timeframe:

From randomisation up to death from any cause (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	340		
Units: months				
median (confidence interval 95%)	23.56 (18.00 to 99999)	26.81 (21.29 to 99999)		

Statistical analyses

Statistical analysis title	Taselisib+Fulvestrant vs Placebo+Fulvestrant
Comparison groups	Placebo+Fulvestrant v Taselisib+Fulvestrant
Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.58
upper limit	1.25

Secondary: Percentage of Subjects with Clinical Benefit, as Assessed According to

RECIST v1.1

End point title	Percentage of Subjects with Clinical Benefit, as Assessed According to RECIST v1.1

End point description:

Clinical benefit:objective response (PR+CR),or no disease progression lasting for more than or equal to (>/=) 24 weeks since randomisation.PR:at least a 30% decrease in sum of diameters of target lesions,taking as reference baseline sum of diameters.CR:disappearance of all target and non-target lesions and normalisation of tumor marker levels.Disease progression:at least a 20% increase in sum of diameters of target lesions,taking as reference smallest sum on study,including baseline.In addition to relative increase of 20%,sum must also demonstrate absolute increase of at least 5 mm.For non-target lesions,disease progression:unequivocal progression of existing lesions.Appearance of one or more new lesions was also considered progression.Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline,regardless of whether they received any amount of study treatment.Number of subjects analysed is number of subjects with data available at given time point.

End point type	Secondary

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	134	264		
Units: percentage of subjects				
number (confidence interval 95%)	37.3 (29.1 to 45.7)	51.5 (45.3 to 57.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Objective Response (DOR), as Assessed by Investigator Using RECIST v1.1

End point title	Duration of Objective Response (DOR), as Assessed by Investigator Using RECIST v1.1

End point description:

DOR:time from first tumor assessment for objective response to first documented disease progression or death due to any cause, whichever occurred first. CR:disappearance of all target and non-target lesions and normalisation of tumor marker levels.PR:at least a 30% decrease in the sum of diameters of target lesions,taking as reference baseline sum of diameters. Disease progression:at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline.For non-target lesions, disease progression:unequivocal progression of existing lesions.Appearance of one or more new lesions was also considered progression.Randomised subjects with PIK3CA-mutant tumors and measurable disease at baseline, regardless of whether they received any amount of study treatment. Number analysed:number of subjects with data available for analysis at given timepoint. 99999=upper limit of CI was not estimable due to low number of subjects with events.

End point type	Secondary

End point timeframe:

Time from the first occurrence of a documented objective response to the time of the first documented disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	74		
Units: months				
median (confidence interval 95%)	7.23 (6.51 to 99999)	8.74 (5.72 to 11.24)		

Statistical analyses

Statistical analysis title	Taselisib+Fulvestrant vs Placebo+Fulvestrant
Comparison groups	Placebo+Fulvestrant v Taselisib+Fulvestrant
Number of subjects included in analysis	90
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.23
upper limit	2.59

Secondary: PFS as Assessed by Blinded Independent Central Review (BICR) Using RECIST v1.1

End point title	PFS as Assessed by Blinded Independent Central Review (BICR) Using RECIST v1.1

End point description:

PFS was defined as the time from randomisation to disease progression as determined by BICR with the use of RECIST v1.1 or death due to any cause, whichever occurred earlier. Disease progression was defined as at least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study, including baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. For non-target lesions, disease progression was defined as unequivocal progression of existing lesions. The appearance of one or more new lesions was also considered progression. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. Number of subjects analysed is the number of subjects with data available for analysis at given time point.

End point type	Secondary

End point timeframe:

From randomisation until the first occurrence of disease progression or death from any cause, whichever occurs earlier (up to the 15 Oct 2017 data cutoff, approximately 2.5 years)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	340		
Units: months				
median (confidence interval 95%)	5.39 (3.68 to 9.23)	8.97 (7.39 to 9.49)		

Statistical analyses

Statistical analysis title	Taselisib+Fulvestrant vs Placebo+Fulvestrant
Comparison groups	Placebo+Fulvestrant v Taselisib+Fulvestrant
Number of subjects included in analysis	516
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0023
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.86

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)

End point description:

An adverse event (AE) was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product, regardless of causal attribution. The safety-evaluable population included all randomised subjects who received at least one dose of taselisib or placebo or fulvestrant.

End point type	Secondary

End point timeframe:

From randomisation up to the 15 Oct 2017 data cutoff, approximately 2.5 years

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	213	416		
Units: percentage of subjects				
number (not applicable)	89.7	95.4		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Plasma Concentration (Cmax) of Taselisib

End point title	Maximum Observed Plasma Concentration (Cmax) of

End point description:

The Pharmacokinetic (PK) population included all subjects who received at least one dose of taselisib and provided valid (adequately documented dose time and PK sample time) PK assessments. "n" is the number of subjects with data available for analysis at given time point.

End point type	Secondary

End point timeframe:

1 to 4 hours (hrs) post-dose on Cycle (C) 1, Day (D) 1; 0 to 3 hrs pre-dose and 2 to 6 hrs post dose on Cycle 2, Day 1 (each cycle=28 days)

Notes:

[1] - 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 Cmax of taselisib is only reported for the arm, which received taselisib.

End point values	Taselisib+Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	417			
Units: ng/mL				
arithmetic mean (standard deviation)				
C1D1 (n= 391) C2D1 (n=359)	18.2 (± 14.6) 66.6 (± 35.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: Minimum Observed Plasma Concentration (Cmin) of Taselisib

End point title	Minimum Observed Plasma Concentration (Cmin) of Taselisib[2]

End point description:

The PK population included all subjects who received at least one dose of taselisib and provided valid (adequately documented dose time and PK sample time) PK assessments. "n" is the number of subjects with data available for analysis at given time point.

End point type	Secondary

End point timeframe:

1 to 4 hrs post-dose on Cycle 1, Day 1; 0 to 3 hrs pre-dose and 2 to 6 hrs post dose on Cycle 2, Day 1; 0 to 3 hrs pre-dose on Cycle 6, Day 1 (each cycle=28 days)

Notes:

[2] - 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 Cmin of taselisib is only reported for the arm, which received taselisib.

End point values	Taselisib+Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	417			
Units: ng/mL				
arithmetic mean (standard deviation)				
C2D1 (n=377)	42.8 (± 26.6)			
C6D1 (n=213)	35.3 (± 31.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Score

End point title	Change From Baseline in European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire Core 30 (QLQ-C30) Score

End point description:

The EORTC QLQ-C30 consists of 30 questions that comprise aspects of subject's functioning assessment (physical, emotional, role, cognitive, and social); symptom scales (fatigue; nausea, vomiting, and pain; the global health/quality of life [QoL]); and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, and financial difficulties), within a recall period of "the past week." Most questions used a 4-point scale (1=Not at all to 4=Very much; two questions used a 7-point scale (1=Very poor to 7=Excellent). Scores were averaged and transformed to a 0-100 scale; a higher score for Global Qol/functional scales=better level of functioning; a higher score for symptom scale=greater degree of symptoms. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. "n" is the number of subjects with data available for analysis at given time point.

End point type	Secondary

End point timeframe:

Baseline, C2D1 up to C7D1 (each cycle=28 days)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	340		
Units: score on a scale				
arithmetic mean (standard deviation)				
Appetite Loss:Baseline (n=159, 312)	15.9 (± 25.9)	15.3 (± 23.3)		
Appetite Loss: Change at C2D1 (n=147, 292)	-0.2 (± 25.7)	6.2 (± 26.2)		
Appetite Loss: Change at C3D1 (n=117, 260)	-4.3 (± 27.2)	8.7 (± 28.1)		
Appetite Loss: Change at C4D1 (n=100, 231)	-1.7 (± 26.1)	8.4 (± 28.1)		
Appetite Loss: Change at C5D1 (n=75, 206)	-0.4 (± 26.6)	6.0 (± 27.2)		
Appetite Loss: Change at C6D1 (n=66, 171)	-0.5 (± 22.3)	6.6 (± 27.2)		
Appetite Loss: Change at C7D1 (n=58, 145)	-5.7 (± 28.7)	4.6 (± 26.5)		

Cognitive Functioning: Baseline (n=160, 312)	85.3 (± 18.1)	85.9 (± 18.7)		
Cognitive Functioning: Change at C2D1 (n=147, 292)	0.7 (± 16.5)	-1.1 (± 16.8)		
Cognitive Functioning: Change at C3D1 (n=117, 260)	0.9 (± 17.9)	-2.9 (± 19.1)		
Cognitive Functioning: Change at C4D1 (n=100, 231)	1.8 (± 18.9)	-1.7 (± 18.4)		
Cognitive Functioning: Change at C5D1 (n=76, 207)	-1.5 (± 17.7)	-3.2 (± 17.7)		
Cognitive Functioning: Change at C6D1 (n=66, 171)	-0.5 (± 18.5)	-2.8 (± 17.6)		
Cognitive Functioning: Change at C7D1 (n=58, 145)	-2.3 (± 18.1)	-0.8 (± 18.8)		
Constipation: Baseline (n=160, 312)	15.8 (± 23.9)	14.5 (± 23.7)		
Constipation: Change at C2D1 (n=147, 291)	0.0 (± 24.0)	-6.0 (± 21.1)		
Constipation: Change at C3D1 (n=117, 260)	-2.3 (± 25.0)	-4.9 (± 20.8)		
Constipation: Change at C4D1 (n=99, 231)	-2.7 (± 24.6)	-5.5 (± 22.0)		
Constipation: Change at C5D1 (n=76, 207)	-1.3 (± 22.7)	-4.0 (± 21.0)		
Constipation: Change at C6D1 (n=66, 170)	-3.0 (± 27.3)	-3.5 (± 21.8)		
Constipation: Change at C7D1 (n=58, 145)	-4.6 (± 24.5)	-6.9 (± 22.5)		
Diarrhoea: Baseline (n=159, 311)	6.3 (± 15.1)	5.0 (± 14.4)		
Diarrhoea: Change at C2D1 (n=147, 292)	-0.5 (± 17.9)	10.2 (± 22.4)		
Diarrhoea: Change at C3D1 (n=117, 260)	-0.9 (± 16.6)	13.7 (± 26.3)		
Diarrhoea: Change at C4D1 (n=100, 231)	-2.7 (± 21.0)	13.1 (± 28.9)		
Diarrhoea: Change at C5D1 (n=76, 207)	-2.6 (± 19.4)	11.1 (± 27.7)		
Diarrhoea: Change at C6D1 (n=66, 171)	-2.0 (± 17.4)	14.0 (± 29.1)		
Diarrhoea: Change at C7D1 (n=58, 145)	1.1 (± 20.7)	15.6 (± 30.9)		
Dyspnoea: Baseline (n=160, 311)	15.0 (± 23.0)	15.4 (± 22.2)		
Dyspnoea: Change at C2D1 (n=146, 291)	4.1 (± 23.5)	-2.1 (± 19.5)		
Dyspnoea: Change at C3D1 (n=117, 260)	2.8 (± 20.3)	0.0 (± 20.9)		
Dyspnoea: Change at C4D1 (n=100, 231)	0.7 (± 23.2)	0.0 (± 23.3)		
Dyspnoea: Change at C5D1 (n=76, 207)	2.6 (± 26.5)	1.6 (± 23.2)		
Dyspnoea: Change at C6D1 (n=66, 170)	3.0 (± 26.6)	0.2 (± 23.4)		
Dyspnoea: Change at C7D1 (n=58, 145)	1.7 (± 24.5)	-2.1 (± 21.2)		
Emotional Functioning: Baseline (n=160, 312)	73.1 (± 22.1)	71.9 (± 22.1)		
Emotional Functioning: Change at C2D1 (n=147, 292)	4.0 (± 17.9)	5.1 (± 18.5)		
Emotional Functioning: Change at C3D1 (n=117, 260)	4.5 (± 19.1)	2.3 (± 21.6)		
Emotional Functioning: Change at C4D1 (n=100, 231)	4.5 (± 18.5)	2.6 (± 19.7)		

Emotional Functioning: Change at C5D1 (n=76, 207)	5.2 (± 20.1)	-0.4 (± 21.8)		
Emotional Functioning: Change at C6D1 (n=66, 171)	2.1 (± 20.5)	2.4 (± 21.6)		
Emotional Functioning: Change at C7D1 (n=58, 145)	5.3 (± 20.7)	2.8 (± 19.7)		
Fatigue: Baseline (n=160, 312)	30.8 (± 22.5)	30.8 (± 22.0)		
Fatigue: Change at C2D1 (n=147, 292)	2.0 (± 19.2)	-0.5 (± 18.8)		
Fatigue: Change at C3D1 (n=117, 260)	-1.5 (± 19.5)	1.8 (± 21.5)		
Fatigue: Change at C4D1 (n=100, 231)	-0.2 (± 19.1)	2.4 (± 21.9)		
Fatigue: Change at C5D1 (n=76, 207)	-0.1 (± 20.8)	2.8 (± 20.4)		
Fatigue: Change at C6D1 (n=66, 171)	3.3 (± 20.0)	2.4 (± 20.5)		
Fatigue: Change at C7D1 (n=58, 145)	1.0 (± 20.0)	1.8 (± 20.5)		
Financial Difficulties: Baseline(n=160,310)	18.5 (± 25.8)	19.2 (± 27.1)		
Financial Difficulties:Change at C2D1(n=147,287)	-1.1 (± 20.4)	-2.8 (± 21.4)		
Financial Difficulties:Change at C3D1(n=117,258)	-0.9 (± 24.9)	-1.6 (± 24.4)		
Financial Difficulties:Change at C4D1(n=100,230)	0.7 (± 25.1)	-0.3 (± 23.7)		
Financial Difficulties:Change at C5D1(n=76,205)	-0.4 (± 28.0)	0.3 (± 24.9)		
Financial Difficulties:Change at C6D1(n=66,169)	5.6 (± 30.1)	0.4 (± 23.6)		
Financial Difficulties:Change at C7D1(n=58,143)	-0.6 (± 26.1)	2.1 (± 23.1)		
Global Health Status/QoL:Baseline(n=160,311)	65.2 (± 18.4)	67.4 (± 20.3)		
Global Health Status/QoL:Change at C2D1(n=147,291)	-0.1 (± 16.7)	1.0 (± 19.9)		
Global Health Status/QoL:Change at C3D1(n=117,259)	-1.0 (± 18.5)	-1.5 (± 20.9)		
Global Health Status/QoL:Change at C4D1(n=100,230)	-1.5 (± 18.6)	-1.6 (± 20.3)		
Global Health Status/QoL:Change at C5D1(n=76,207)	0.3 (± 19.9)	-2.8 (± 20.3)		
Global Health Status/QoL:Change at C6D1(n=66,171)	-1.6 (± 18.6)	-3.4 (± 19.5)		
Global Health Status/QoL: Change at C7D1(n=58,145)	-1.1 (± 18.9)	-1.0 (± 18.9)		
Insomnia: Baseline (n=160, 311)	26.0 (± 27.6)	26.5 (± 27.7)		
Insomnia: Change at C2D1 (n=146, 289)	-0.9 (± 24.4)	-3.8 (± 23.7)		
Insomnia: Change at C3D1 (n=117, 260)	-3.4 (± 30.1)	-4.1 (± 26.4)		
Insomnia: Change at C4D1 (n=100, 231)	-4.0 (± 28.9)	-1.0 (± 26.8)		
Insomnia: Change at C5D1 (n=76, 206)	-0.4 (± 29.1)	-3.9 (± 25.6)		
Insomnia: Change at C6D1 (n=66, 170)	-2.0 (± 30.3)	-2.4 (± 28.2)		
Insomnia: Change at C7D1 (n=57, 145)	-4.1 (± 28.2)	-1.8 (± 27.2)		
Nausea/Vomiting: Baseline (n=160, 312)	5.9 (± 13.4)	6.7 (± 13.7)		
Nausea/Vomiting: Change at C2D1 (n=147, 292)	0.1 (± 11.9)	1.6 (± 18.1)		
Nausea/Vomiting: Change at C3D1 (n=117, 260)	0.7 (± 15.2)	2.2 (± 17.6)		
Nausea/Vomiting: Change at C4D1 (n=100, 231)	0.3 (± 17.9)	2.3 (± 18.6)		

Nausea/Vomiting: Change at C5D1 (n=76, 207)	-1.1 (± 18.3)	0.5 (± 15.4)		
Nausea/Vomiting: Change at C6D1 (n=66, 171)	1.5 (± 18.0)	-0.6 (± 15.9)		
Nausea/Vomiting: Change at C7D1 (n=58, 145)	2.6 (± 15.5)	2.2 (± 18.8)		
Pain: Baseline (n=160, 312)	28.0 (± 25.4)	27.1 (± 24.9)		
Pain: Change at C2D1 (n=147, 292)	-0.2 (± 24.0)	-5.0 (± 20.8)		
Pain: Change at C3D1 (n=117, 260)	-3.7 (± 23.3)	-3.5 (± 22.6)		
Pain: Change at C4D1 (n=100, 231)	-3.2 (± 24.7)	-1.7 (± 24.2)		
Pain: Change at C5D1 (n=76, 207)	-3.3 (± 24.2)	-4.3 (± 22.9)		
Pain: Change at C6D1 (n=66, 171)	-1.0 (± 23.0)	-2.2 (± 22.5)		
Pain: Change at C7D1 (n=58, 145)	0.3 (± 23.5)	-4.4 (± 19.8)		
Physical Functioning: Baseline (n=160, 311)	76.7 (± 19.9)	78.4 (± 18.8)		
Physical Functioning: Change at C2D1 (n=147, 292)	-1.1 (± 13.4)	1.6 (± 12.7)		
Physical Functioning: Change at C3D1 (n=117, 260)	2.0 (± 14.1)	0.8 (± 15.7)		
Physical Functioning: Change at C4D1 (n=100, 231)	1.5 (± 16.1)	0.3 (± 15.7)		
Physical Functioning: Change at C5D1 (n=76, 207)	2.0 (± 17.7)	1.0 (± 13.5)		
Physical Functioning: Change at C6D1 (n=66, 171)	0.9 (± 18.4)	1.1 (± 14.9)		
Physical Functioning: Change at C7D1 (n=58, 145)	1.6 (± 16.2)	0.6 (± 14.2)		
Role Functioning: Baseline (n=160, 312)	79.1 (± 24.6)	78.7 (± 24.0)		
Role Functioning: Change at C2D1 (n=147, 292)	-2.0 (± 19.3)	1.7 (± 21.5)		
Role Functioning: Change at C3D1 (n=117, 260)	-0.4 (± 23.4)	-1.0 (± 23.9)		
Role Functioning: Change at C4D1 (n=100, 231)	0.3 (± 23.0)	0.4 (± 24.2)		
Role Functioning: Change at C5D1 (n=76, 207)	1.8 (± 22.5)	-1.6 (± 21.6)		
Role Functioning: Change at C6D1 (n=66, 171)	-1.3 (± 23.8)	-1.6 (± 23.4)		
Role Functioning: Change at C7D1 (n=58, 145)	-0.3 (± 22.6)	0.0 (± 22.9)		
Social Functioning: Baseline (n=160, 312)	83.2 (± 21.8)	81.2 (± 23.1)		
Social Functioning: Change at C2D1 (n=147, 292)	-0.8 (± 19.9)	2.7 (± 20.0)		
Social Functioning: Change at C3D1 (n=117, 259)	1.3 (± 21.9)	-0.8 (± 23.2)		
Social Functioning: Change at C4D1 (n=100, 231)	1.8 (± 18.2)	-0.5 (± 21.3)		
Social Functioning: Change at C5D1 (n=76, 207)	0.9 (± 19.4)	-1.0 (± 23.3)		
Social Functioning: Change at C6D1 (n=66, 170)	-0.8 (± 20.1)	-1.6 (± 23.4)		
Social Functioning: Change at C7D1 (n=58, 145)	0.6 (± 21.2)	0.1 (± 19.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Modified EORTC Quality of Life Questionnaire Breast Cancer Module 23 (QLQ-BR23) Score

End point title	Change From Baseline in Modified EORTC Quality of Life Questionnaire Breast Cancer Module 23 (QLQ-BR23) Score

End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and symptom scales (systemic side effects [SE], upset by hair loss, arm symptoms, breast symptoms). Questions used a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to a 0-100 scale. Higher scores for the functional scales indicated a higher/better level of functioning/healthy functioning. Higher scores for the symptom scales indicated worse symptoms. Randomised subjects with PIK3CA-mutant tumors, regardless of whether they received any amount of study treatment. "n" is the number of subjects with data available for analysis at given time point.

End point type	Secondary

End point timeframe:

Baseline, C2D1 up to C7D1 (each cycle=28 days)

End point values	Placebo+Fulvestrant	Taselisib+Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	176	340		
Units: score on a scale				
arithmetic mean (standard deviation)				
Arm Symptoms: Baseline (n=152, 304)	15.5 (± 18.8)	19.3 (± 21.1)		
Arm Symptoms: Change at C2D1 (n=140, 282)	0.1 (± 17.4)	-5.4 (± 15.6)		
Arm Symptoms: Change at C3D1 (n=111, 250)	-0.7 (± 19.5)	-6.1 (± 17.4)		
Arm Symptoms: Change at C4D1 (n=95, 219)	-1.4 (± 21.9)	-5.8 (± 15.8)		
Arm Symptoms: Change at C5D1 (n=72, 203)	0.8 (± 17.0)	-6.6 (± 15.7)		
Arm Symptoms: Change at C6D1 (n=63, 167)	1.1 (± 20.8)	-5.0 (± 18.5)		
Arm Symptoms: Change at C7D1 (n=57, 140)	-1.2 (± 19.7)	-6.0 (± 15.2)		
Body Image: Baseline (n=149, 300)	82.0 (± 21.7)	80.8 (± 22.5)		
Body Image: Change at C2D1 (n=135, 276)	1.8 (± 14.9)	1.5 (± 16.5)		
Body Image: Change at C3D1 (n=106, 242)	1.6 (± 18.0)	1.1 (± 20.6)		
Body Image: Change at C4D1 (n=92, 214)	1.1 (± 17.8)	1.8 (± 20.6)		
Body Image: Change at C5D1 (n=68, 198)	0.2 (± 19.5)	0.0 (± 17.5)		
Body Image: Change at C6D1 (n=60, 164)	1.1 (± 21.0)	0.4 (± 18.2)		
Body Image: Change at C7D1 (n=54, 137)	5.6 (± 18.8)	-0.3 (± 18.2)		
Breast Symptoms: Baseline (n=151, 304)	8.7 (± 14.6)	11.0 (± 14.1)		
Breast Symptoms: Change at C2D1 (n=139, 282)	0.0 (± 13.7)	-3.0 (± 11.8)		

Breast Symptoms: Change at C3D1 (n=112, 250)	-0.8 (± 13.3)	-3.5 (± 11.6)		
Breast Symptoms: Change at C4D1 (n=95, 220)	0.1 (± 14.2)	-3.0 (± 11.8)		
Breast Symptoms: Change at C5D1 (n=72, 203)	-0.9 (± 14.5)	-2.0 (± 11.7)		
Breast Symptoms: Change at C6D1 (n=63, 167)	1.7 (± 16.0)	-2.0 (± 12.9)		
Breast Symptoms: Change at C7D1 (n=57, 140)	0.3 (± 12.6)	-3.2 (± 13.1)		
Future Perspective: Baseline (n=152, 303)	47.4 (± 31.5)	47.3 (± 29.6)		
Future Perspective: Change at C2D1 (n=139, 281)	3.4 (± 30.1)	6.8 (± 27.4)		
Future Perspective: Change at C3D1 (n=111, 247)	5.1 (± 29.5)	4.3 (± 30.5)		
Future Perspective: Change at C4D1 (n=95, 220)	6.0 (± 30.7)	7.0 (± 29.2)		
Future Perspective: Change at C5D1 (n=72, 202)	6.0 (± 30.3)	5.0 (± 26.8)		
Future Perspective: Change at C6D1 (n=63, 167)	6.9 (± 28.8)	9.0 (± 31.4)		
Future Perspective: Change at C7D1 (n=57, 139)	12.9 (± 29.4)	7.0 (± 30.2)		
Sexual Enjoyment: Baseline (n=27, 61)	51.9 (± 26.7)	62.8 (± 26.6)		
Sexual Enjoyment: Change at C2D1 (n=17, 35)	5.9 (± 21.2)	0.0 (± 18.1)		
Sexual Enjoyment: Change at C3D1 (n=14, 26)	4.8 (± 22.1)	1.3 (± 24.0)		
Sexual Enjoyment: Change at C4D1 (n=8, 24)	-8.3 (± 15.4)	4.2 (± 24.7)		
Sexual Enjoyment: Change at C5D1 (n=7, 26)	-4.8 (± 23.0)	2.6 (± 29.7)		
Sexual Enjoyment: Change at C6D1 (n=5, 17)	-6.7 (± 14.9)	-5.9 (± 24.3)		
Sexual Enjoyment: Change at C7D1 (n=5, 14)	-13.3 (± 29.8)	9.5 (± 20.4)		
Sexual Functioning: Baseline (n=142, 291)	89.6 (± 17.9)	89.9 (± 17.3)		
Sexual Functioning: Change at C2D1 (n=126, 267)	1.6 (± 11.0)	1.5 (± 14.2)		
Sexual Functioning: Change at C3D1 (n=98, 235)	1.4 (± 10.6)	1.8 (± 15.6)		
Sexual Functioning: Change at C4D1 (n=86, 203)	1.9 (± 15.4)	1.6 (± 13.9)		
Sexual Functioning: Change at C5D1 (n=63, 186)	-0.8 (± 20.6)	2.6 (± 15.1)		
Sexual Functioning: Change at C6D1 (n=55, 156)	2.4 (± 18.8)	2.7 (± 15.0)		
Sexual Functioning: Change at C7D1 (n=49, 132)	2.7 (± 18.1)	2.3 (± 15.7)		
Systematic Therapy SEs: Baseline (n=152, 304)	15.7 (± 14.2)	14.7 (± 12.0)		
Systematic Therapy SEs:Change at C2D1 (n=140, 282)	0.2 (± 11.4)	2.5 (± 11.0)		
Systematic Therapy SEs:Change at C3D1 (n=112, 250)	1.2 (± 14.4)	4.0 (± 13.6)		
Systematic Therapy SEs:Change at C4D1 (n=95, 220)	1.5 (± 13.2)	4.0 (± 13.3)		
Systematic Therapy SEs:Change at C5D1 (n=72, 203)	2.4 (± 13.8)	5.5 (± 14.1)		

Systematic Therapy SEs:Change at C6D1 (n=63, 167)	2.9 (± 15.2)	5.7 (± 15.6)		
Systematic Therapy SEs:Change at C7D1 (n=57, 140)	3.5 (± 16.7)	4.8 (± 15.0)		
Upset by Hair Loss: Baseline (n=33, 63)	23.2 (± 28.2)	27.0 (± 29.2)		
Upset by Hair Loss: Change at C2D1 (n=14, 31)	-11.9 (± 28.1)	-4.3 (± 22.3)		
Upset by Hair Loss: Change at C3D1 (n=13, 29)	-7.7 (± 30.9)	0.0 (± 26.7)		
Upset by Hair Loss: Change at C4D1 (n=13, 27)	2.6 (± 16.5)	0.0 (± 29.2)		
Upset by Hair Loss: Change at C5D1 (n=8, 28)	0.0 (± 25.2)	10.7 (± 27.3)		
Upset by Hair Loss: Change at C6D1 (n=6, 26)	11.1 (± 27.2)	16.7 (± 30.2)		
Upset by Hair Loss: Change at C7D1 (n=8, 26)	4.2 (± 11.8)	14.1 (± 32.9)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomisation up to the 15 Oct 2017 data cutoff, approximately 2.5 years

Adverse event reporting additional description:

Safety-evaluable population:all randomised subjects who received at least one dose of taselisib/placebo/fulvestrant regardless of PIK3CA-mutation status of their tumors and separately for subgroups of subjects with and without detectable PIK3CA-mutant tumors, with subjects allocated to treatment arm associated with the regimen actually received.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

Reporting groups

Reporting group title	Placebo+Fulvestrant

Reporting group description:

Subjects received taselisib-matching placebo taken orally once daily (QD) beginning at Cycle 1, Day 1, and fulvestrant 500 mg administered by intramuscular (IM) injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Reporting group title	Taselisib+Fulvestrant

Reporting group description:

Subjects received taselisib 4 milligrams (mg) taken orally QD beginning at Cycle 1, Day 1 and fulvestrant 500 mg by IM injection at Cycle 1, Days 1 and 15, and then on Day 1 of each subsequent 28-day cycle until disease progression, unacceptable toxicity, or study termination by the Sponsor.

Serious adverse events	Placebo+Fulvestrant	Taselisib+Fulvestrant	
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 213 (8.92%)	133 / 416 (31.97%)	
number of deaths (all causes)	57	101	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Intracranial tumour haemorrhage			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Embolism			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism venous			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 213 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Asthenia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 213 (0.47%)	9 / 416 (2.16%)	
occurrences causally related to treatment / all	1 / 1	9 / 9	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cough			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 213 (0.47%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			

subjects affected / exposed	2 / 213 (0.94%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleuritic pain			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Mental status changes			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 213 (0.47%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspartate aminotransferase			

increased			
subjects affected / exposed	1 / 213 (0.47%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Clavicle fracture			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femur fracture			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure congestive			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Supraventricular tachycardia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 213 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral haematoma			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	2 / 213 (0.94%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoaesthesia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial paralysis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Pancytopenia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 213 (0.00%)	32 / 416 (7.69%)	
occurrences causally related to treatment / all	0 / 0	33 / 34	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 213 (0.00%)	14 / 416 (3.37%)	
occurrences causally related to treatment / all	0 / 0	15 / 15	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	1 / 213 (0.47%)	4 / 416 (0.96%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			

subjects affected / exposed	1 / 213 (0.47%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 1	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis acute			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcoholic pancreatitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspepsia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dysphagia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroduodenitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophageal ulcer			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash generalised			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxic skin eruption			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Swelling face			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haematuria			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coccydynia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscle spasms			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			

subjects affected / exposed	1 / 213 (0.47%)	0 / 416 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 213 (0.47%)	9 / 416 (2.16%)	
occurrences causally related to treatment / all	0 / 1	4 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 213 (0.47%)	5 / 416 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Diarrhoea infectious			
subjects affected / exposed	0 / 213 (0.00%)	3 / 416 (0.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis infectious			
subjects affected / exposed	0 / 213 (0.00%)	2 / 416 (0.48%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atypical mycobacterial pneumonia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile colitis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis escherichia			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Skin infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			

subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 213 (0.47%)	6 / 416 (1.44%)	
occurrences causally related to treatment / all	0 / 1	5 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 213 (0.00%)	6 / 416 (1.44%)	
occurrences causally related to treatment / all	0 / 0	6 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 213 (0.00%)	1 / 416 (0.24%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo+Fulvestrant	Taselisib+Fulvestrant	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	190 / 213 (89.20%)	396 / 416 (95.19%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	13 / 213 (6.10%)	30 / 416 (7.21%)	
occurrences (all)	16	38	
Weight decreased			
subjects affected / exposed	4 / 213 (1.88%)	34 / 416 (8.17%)	
occurrences (all)	4	38	
Alanine aminotransferase increased			
subjects affected / exposed	9 / 213 (4.23%)	31 / 416 (7.45%)	
occurrences (all)	12	37	
Blood alkaline phosphatase increased			

subjects affected / exposed	12 / 213 (5.63%)	10 / 416 (2.40%)	
occurrences (all)	12	11	
Vascular disorders			
Hot flush			
subjects affected / exposed	26 / 213 (12.21%)	22 / 416 (5.29%)	
occurrences (all)	26	24	
Hypertension			
subjects affected / exposed	11 / 213 (5.16%)	28 / 416 (6.73%)	
occurrences (all)	15	37	
Nervous system disorders			
Headache			
subjects affected / exposed	25 / 213 (11.74%)	83 / 416 (19.95%)	
occurrences (all)	34	108	
Dizziness			
subjects affected / exposed	18 / 213 (8.45%)	41 / 416 (9.86%)	
occurrences (all)	23	51	
Dysgeusia			
subjects affected / exposed	6 / 213 (2.82%)	40 / 416 (9.62%)	
occurrences (all)	6	44	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	18 / 213 (8.45%)	34 / 416 (8.17%)	
occurrences (all)	20	47	
Neutropenia			
subjects affected / exposed	8 / 213 (3.76%)	27 / 416 (6.49%)	
occurrences (all)	11	33	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	38 / 213 (17.84%)	100 / 416 (24.04%)	
occurrences (all)	45	123	
Asthenia			
subjects affected / exposed	39 / 213 (18.31%)	76 / 416 (18.27%)	
occurrences (all)	62	102	
Mucosal inflammation			
subjects affected / exposed	11 / 213 (5.16%)	43 / 416 (10.34%)	
occurrences (all)	15	64	

Pyrexia			
subjects affected / exposed	7 / 213 (3.29%)	41 / 416 (9.86%)	
occurrences (all)	8	52	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	42 / 213 (19.72%)	235 / 416 (56.49%)	
occurrences (all)	70	520	
Nausea			
subjects affected / exposed	52 / 213 (24.41%)	140 / 416 (33.65%)	
occurrences (all)	68	208	
Vomiting			
subjects affected / exposed	23 / 213 (10.80%)	76 / 416 (18.27%)	
occurrences (all)	38	98	
Stomatitis			
subjects affected / exposed	7 / 213 (3.29%)	82 / 416 (19.71%)	
occurrences (all)	10	121	
Abdominal pain			
subjects affected / exposed	19 / 213 (8.92%)	51 / 416 (12.26%)	
occurrences (all)	23	60	
Dry mouth			
subjects affected / exposed	16 / 213 (7.51%)	51 / 416 (12.26%)	
occurrences (all)	17	57	
Constipation			
subjects affected / exposed	31 / 213 (14.55%)	28 / 416 (6.73%)	
occurrences (all)	35	30	
Dyspepsia			
subjects affected / exposed	4 / 213 (1.88%)	31 / 416 (7.45%)	
occurrences (all)	4	42	
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 213 (1.41%)	21 / 416 (5.05%)	
occurrences (all)	3	23	
Abdominal pain upper			
subjects affected / exposed	6 / 213 (2.82%)	23 / 416 (5.53%)	
occurrences (all)	6	25	
Respiratory, thoracic and mediastinal disorders			

Cough			
subjects affected / exposed	28 / 213 (13.15%)	53 / 416 (12.74%)	
occurrences (all)	30	63	
Dyspnoea			
subjects affected / exposed	16 / 213 (7.51%)	42 / 416 (10.10%)	
occurrences (all)	16	44	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	16 / 213 (7.51%)	74 / 416 (17.79%)	
occurrences (all)	22	107	
Pruritus			
subjects affected / exposed	16 / 213 (7.51%)	45 / 416 (10.82%)	
occurrences (all)	25	58	
Alopecia			
subjects affected / exposed	6 / 213 (2.82%)	47 / 416 (11.30%)	
occurrences (all)	6	50	
Dry skin			
subjects affected / exposed	10 / 213 (4.69%)	32 / 416 (7.69%)	
occurrences (all)	10	34	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	16 / 213 (7.51%)	33 / 416 (7.93%)	
occurrences (all)	17	36	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	24 / 213 (11.27%)	53 / 416 (12.74%)	
occurrences (all)	26	65	
Arthralgia			
subjects affected / exposed	27 / 213 (12.68%)	47 / 416 (11.30%)	
occurrences (all)	37	58	
Musculoskeletal pain			
subjects affected / exposed	14 / 213 (6.57%)	34 / 416 (8.17%)	
occurrences (all)	17	35	
Myalgia			
subjects affected / exposed	13 / 213 (6.10%)	33 / 416 (7.93%)	
occurrences (all)	13	39	

Pain in extremity			
subjects affected / exposed	18 / 213 (8.45%)	25 / 416 (6.01%)	
occurrences (all)	25	29	
Muscle spasms			
subjects affected / exposed	6 / 213 (2.82%)	30 / 416 (7.21%)	
occurrences (all)	7	32	
Bone pain			
subjects affected / exposed	17 / 213 (7.98%)	19 / 416 (4.57%)	
occurrences (all)	18	21	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	8 / 213 (3.76%)	34 / 416 (8.17%)	
occurrences (all)	8	39	
Upper respiratory tract infection			
subjects affected / exposed	10 / 213 (4.69%)	23 / 416 (5.53%)	
occurrences (all)	13	27	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	18 / 213 (8.45%)	157 / 416 (37.74%)	
occurrences (all)	21	207	
Decreased appetite			
subjects affected / exposed	22 / 213 (10.33%)	109 / 416 (26.20%)	
occurrences (all)	24	120	
Hypokalaemia			
subjects affected / exposed	2 / 213 (0.94%)	24 / 416 (5.77%)	
occurrences (all)	2	28	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2015	The changes in protocol were as follows:•Section 3.1 was updated for clarification and consistency with other sections of protocol. For example, now all subjects who discontinued study treatment were followed for OS and subsequent anti-cancer therapies, not only those who discontinued study treatment due to disease progression. The text was also updated to clarify that only subjects who discontinued taselisib/placebo for toxicity could continue single agent fulvestrant at the discretion of the investigator while those who discontinued fulvestrant for an AE, albeit rare, should discuss continuation of single agent taselisib/placebo with the Medical Monitor •Figure 1 was reformatted and key enrollment criteria were updated for consistency with text in section 4.1 •Section 3.3.8.9 was updated to clarify the analysis of optional post-progression biopsies and sharing of the resulting molecular report with investigator who may then share the data with the subject (if the subject agreed) •Sections 4.3.2.1 and 4.3.2.2 were updated to align better with information outlined in Appendix 1 •Section 4.4.2 was clarified relative to specific washouts required in the exclusion criteria in Section 4.1.2 •Section 4.5.5 was updated to be consistent with requirements outlined in Appendix 1 and for clarification. For example, the tumor assessment requirements were clarified based on additional details provided in the Appendix 1 footnotes and inconsistencies were removed regarding the window of the screening tumor assessments. For consistency with Section 3.1, the text was updated to reflect the original intent of the protocol that subjects who discontinue study treatment for reasons other than disease progression will continue to undergo tumor assessments until progressive disease (PD), even if a subject initiates anti-cancer therapy subsequent to study drug discontinuation. The same update was made in Appendix 1 footnote l.
10 December 2015	The changes in protocol were as follows:Section 4.5.6 was updated for consistency and to clarify the analysis of post-progression biopsies •Section 4.5.11 was updated for consistency with the relevant changes made in Section 3.1, for example that all subjects who discontinued study treatment were followed for OS and subsequent anti-cancer therapies, not only those who discontinued study treatment due to disease progression •Table 3 was updated to clarify corticosteroid treatment for Grade 3 diarrhoea or colitis •Table 5 was updated for clarification of the pneumonitis guidelines related to local clinical practice •Table 7 was updated with a footnote to clarify for Grade 1 or 2 hyperglycemia that increases in anti-hyperglycemic medications only applied to subjects who initiated these after randomization since subjects with diabetes requiring anti-hyperglycemic medications were not eligible •Section 5.1.1.1.7 was updated for clarification referring to Table 8 for specific management guidelines for subjects who experienced changes in blood counts or showed signs of infections if deemed clinically appropriate by the investigator •Section 5.2.4 was updated for clarification regarding additional supporting data sponsor may request for certain AEs •Section 7.1 was updated for clarification as the study used electronic patient-reported outcome (ePRO) devices but no paper questionnaires •Appendix 1 was updated for consistency with the remainder of the Protocol footnotes n through p were revised so that Cycle 1 Day 1 safety laboratory samples did not need to be redrawn if the corresponding screening samples were taken within 2 days prior to Cycle 1 Day 1. Footnote z was added to the ECG assessments for clarification consistent with the text in Section 4.5.8.

15 January 2017	The changes in protocol were as follows:•In Sections 2.1, 6.4.2.1, and 6.4.2.2, the secondary efficacy objectives were reordered to emphasize the change in the hierarchical testing. The testing hierarchy of the secondary endpoints was changed to objective response rate (ORR) first followed by OS after a statistically significant investigator-assessed PFS compared with OS first in the original protocol. Anti-tumor responses have been seen in subjects with estrogen receptor (ER)+breast cancer who have been treated with taselisib. The goal was to now test formally if there was a statistically significant difference in ORR between the treatment arms. OS was still formally tested if both investigator-assessed PFS and ORR reached their significance level •In Sections 2.1, 3.4.1, and 6.4.2.5, a secondary efficacy objective and outcome measure was added: BICR-assessed PFS was intended to show that there was no potential bias in the primary efficacy objective investigator-assessed PFS •In Section 2.5, clinical benefit rate (CBR) was added to the exploratory objectives for consistency with the secondary efficacy objectives •In Sections 3.1, 3.3.2, 6.10, and 9.4, the possible addition of a China extension cohort was introduced. In order to characterize the efficacy and safety profile of taselisib in combination with fulvestrant in Chinese subjects and to potentially support a regulatory submission in China, a China extension cohort was planned in the study. After the global enrollment closes, additional Chinese subjects may continue to be recruited into the China extension cohort. A total of up to 150 Chinese subjects with detectable PIK3CA-mutant tumors may be enrolled as part of the global study population and extension cohort combined •In Section 4.1.1, an additional inclusion criterion was added to define the subject population in the China extension cohort to be from the People's Republic of China.
15 January 2017	The changes in protocol were as follows:•In Section 4.2, further description of blinding criteria for study personnel on the basis of the results of the interim and final analyses for investigator-assessed PFS was added •In Section 4.5.6, a change with regard to timing of optional post-progression biopsies was introduced relative to the start of new anti-cancer treatment. The post-progression biopsy could still be obtained within approximately 14 days of the start of the new anti-cancer treatment as long as it was deemed safe by the investigator •In Section 4.5.10 and Appendix 1, there was an explanation of study drug discontinuation visit (SDDVs) occurring if study treatment was interrupted to allow for a SDDV more than 28 days after the decision to permanently discontinue study treatment •In Section 5.1.1.1.1, there was a clarification of AE management guidelines For diarrhoea, dose resumption was distinguished for certain cases of infectious diarrhoea •In Section 5.1.1.1.2, there was a clarification of AE management guidelines. For pneumonitis, infectious work-up was listed as a relevant investigation•In Section 5.7, the reference document for fulvestrant was added, in Sections 6.1, 6.4.1, and 6.9.1, and Table 11, there was the addition of an interim efficacy analysis of investigator-assessed PFS. This interim efficacy analysis was added to enable an earlier assessment of efficacy that could provide subjects with PIK3CA-mutant tumors with earlier access to a potentially effective targeted therapy should the iDMC recommended stopping the study early on the basis of results from the interim analysis for investigator-assessed PFS and should the Sponsor decided to accept the recommendation and obtained regulatory approval.
15 January 2017	The changes in protocol were as follows:•In Section 6.4.2.3, the analysis of CBR was clarified to be performed for subjects with PIK3CA-mutant tumors with measurable disease at baseline and also to be repeated for the group of subjects with PIK3CA-mutant tumors regardless of measurable disease at baseline •In Section 6.7, a time-to-deterioration analysis was included as one of the PRO analyses in order to assess if there was a difference between the treatment arms •In Appendix 2, the table has been updated such that predose blood samples could be drawn within 2 days prior to the cycle visit.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported