Clinical trial results:
A Phase II Randomised, Double-Blind, Parallel Cohort Study of Neoadjuvant Letrozole + GDC-0032 versus Letrozole + Placebo in Post-Menopausal Women with ER+/HER2-Primary Breast Cancer

Summary

EudraCT number	2013-000568-28
Trial protocol	BE DE AT CZ PT HU IT GB ES PL
Global end of trial date	13 March 2017

Results information

Result version number	v1 (current)
This version publication date	22 March 2018
First version publication date	22 March 2018

Trial information

Trial identification

Sponsor protocol code	GO28888

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02273973
WHO universal trial number (UTN)	-
Other trial identifiers	Acroynm: LORELEI

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	Final
Date of interim/final analysis	13 March 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 March 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy of taselisib plus letrozole (taselisib+L) versus placebo plus letrozole (placebo+L) in women with ER + /HER2- early stage breast cancer.

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	12 November 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Austria: 33
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Brazil: 9
Country: Number of subjects enrolled	Chile: 3
Country: Number of subjects enrolled	Czech Republic: 8
Country: Number of subjects enrolled	El Salvador: 6
Country: Number of subjects enrolled	France: 9
Country: Number of subjects enrolled	Germany: 23
Country: Number of subjects enrolled	Guatemala: 6
Country: Number of subjects enrolled	Hungary: 29
Country: Number of subjects enrolled	Italy: 21
Country: Number of subjects enrolled	Mexico: 6
Country: Number of subjects enrolled	Panama: 3
Country: Number of subjects enrolled	Peru: 4
Country: Number of subjects enrolled	Poland: 5
Country: Number of subjects enrolled	Portugal: 10
Country: Number of subjects enrolled	Korea, Republic of: 8
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Switzerland: 2

Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	United States: 35
Worldwide total number of subjects	334
EEA total number of subjects	239

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)	176
From 65 to 84 years	158
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study recruited post-menopausal subjects with breast cancer in 22 countries from November 2014 to March 2017.

Pre-assignment

Screening details:

A total of 334 subjects were randomised: 166 subjects to the taselisib+L arm and 168 subjects to the placebo+L arm. One subject was randomised to the placebo+L arm but received taselisib+L in safety population.

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	Experimental: Taselisib + Letrozole

Arm description:

Subjects received 2.5 milligrams (mg) letrozole tablets orally once daily (QD) along with taselisib tablets at 4 mg (two 2 mg tablets) orally on a 5 days-on/2 days-off schedule for a total of 16 weeks.

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

Dosage and administration details:

Subjects received 2.5 milligrams (mg) letrozole tablets orally once daily (QD) along with taselisib tablets at 4 mg (two 2 mg tablets) orally on a 5 days-on/2 days-off schedule for a total of 16 weeks.

Arm title	Placebo Comparator: Placebo + Letrozole

Arm description:

Subjects received 2.5 mg letrozole tablets orally QD along with placebo on a 5-days-on/2-days-off schedule for a total of 16 weeks.

Arm type	Placebo
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 2.5 mg letrozole tablets orally QD along with placebo on a 5-days-on/2-days-off schedule for a total of 16 weeks.

Number of subjects in period 1	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole
Started	166	168
Completed	157	160
Not completed	9	8
Adverse event, serious fatal	1	-
Consent withdrawn by subject	2	3
Physician decision	-	1
Adverse event, non-fatal	4	-
Non-compliance	1	-
Progression of disease	-	2
Lost to follow-up	-	1
Reason not specified	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Taselisib + Letrozole
Reporting group description:	
Subjects received 2.5 milligrams (mg) letrozole tablets orally once daily (QD) along with taselisib tablets at 4 mg (two 2 mg tablets) orally on a 5 days-on/2 days-off schedule for a total of 16 weeks.	
Reporting group title	Placebo Comparator: Placebo + Letrozole
Reporting group description:	
Subjects received 2.5 mg letrozole tablets orally QD along with placebo on a 5-days-on/2-days-off schedule for a total of 16 weeks.	

Reporting group values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole	Total
Number of subjects	166	168	334
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	64.6	64.7	
standard deviation	± 8.5	± 8.7	-
Sex: Female, Male			
Units: Subjects			
Female	166	168	334
Male	0	0	0
Race/Ethnicity, Customized			
Units: Subjects			
White|	143	140	283
American Indian or Alaskan Native|	11	11	22
Asian|	6	6	12
Black or African American|	1	5	6
Multiple|	1	0	1
Other|	3	6	9
Missing|	1	0	1
Race/Ethnicity, Customized			
Units: Subjects			
Hispanic or Latino|	36	48	84
Not Hispanic or Latino|	114	109	223
Not Reported|	13	10	23
Unknown|	3	1	4

End points

End points reporting groups

Reporting group title	Experimental: Taselisib + Letrozole
Reporting group description:	
Subjects received 2.5 milligrams (mg) letrozole tablets orally once daily (QD) along with taselisib tablets at 4 mg (two 2 mg tablets) orally on a 5 days-on/2 days-off schedule for a total of 16 weeks.	
Reporting group title	Placebo Comparator: Placebo + Letrozole
Reporting group description:	
Subjects received 2.5 mg letrozole tablets orally QD along with placebo on a 5-days-on/2-days-off schedule for a total of 16 weeks.	
Subject analysis set title	Taselisib + Letrozole
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received 2.5 milligrams (mg) letrozole tablets orally once daily (QD) along with taselisib tablets at 4 mg (two 2 mg tablets) orally on a 5 days-on/2 days-off schedule for a total of 16 weeks.	
Subject analysis set title	Placebo + Letrozole
Subject analysis set type	Safety analysis
Subject analysis set description:	
Subjects received 2.5 mg letrozole tablets orally QD along with placebo on a 5-days-on/2-days-off schedule for a total of 16 weeks.	

Primary: Percentage of Subjects With Objective Response (OR) by Centrally Assessed Breast Magnetic Resonance Imaging (MRI) via Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Version 1.1

End point title	Percentage of Subjects With Objective Response (OR) by Centrally Assessed Breast Magnetic Resonance Imaging (MRI) via Modified Response Evaluation Criteria in Solid Tumors (mRECIST) Version 1.1
End point description:	
Objective response rate (ORR) was defined as proportion of subjects achieving complete response (CR) or partial response (PR). As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).	
End point type	Primary
End point timeframe:	
From Baseline to 16 weeks	

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	168		
Units: percentage of subjects				
number (not applicable)	50.0	39.3		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.049
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	10.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.11
upper limit	21.32

Primary: Percentage of Subjects with Total Pathologic Complete Response (total pCR), Defined as Having pCR in Both Breast and Axilla, Using American Joint Committee on Cancer (AJCC) Staging System

End point title	Percentage of Subjects with Total Pathologic Complete Response (total pCR), Defined as Having pCR in Both Breast and Axilla, Using American Joint Committee on Cancer (AJCC) Staging System

End point description:

Total pCR was assessed by local pathology review on samples taken at surgery following completion of neoadjuvant therapy. tpCR was defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes (i.e., ypT0/Tis, ypN0 in the AJCC staging system, 7th edition). ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Primary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	168		
Units: percentage of subjects				
number (not applicable)	1.8	0.6		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3698
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	1.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.12
upper limit	3.55

Primary: Percentage of Subjects With OR by Centrally Assessed Breast MRI via mRECIST Version 1.1 in Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (PIK3CA) Mutant (MT) Subjects

End point title	Percentage of Subjects With OR by Centrally Assessed Breast MRI via mRECIST Version 1.1 in Phosphatidylinositol-4,5-Bisphosphate 3-Kinase, Catalytic Subunit Alpha (PIK3CA) Mutant (MT) Subjects

End point description:

ORR was defined as proportion of participants achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Primary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	79		
Units: percentage of subjects				
number (not applicable)	56.2	38.0		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0332
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	18.19
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.57
upper limit	33.81

Primary: Percentage of Subjects With Total pCR , Defined as Having pCR in Both Breast and Axilla, Using AJCC Staging System in PIK3CA MT Subjects

End point title	Percentage of Subjects With Total pCR , Defined as Having pCR in Both Breast and Axilla, Using AJCC Staging System in PIK3CA MT Subjects

End point description:

Total pCR was assessed by local pathology review on samples taken at surgery following completion of neoadjuvant therapy. tpCR was defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes (i.e., ypT0/Tis, ypN0 in the AJCC staging system, 7th edition). ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Primary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	79		
Units: percentage of subjects				
number (not applicable)	1.4	0		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.4803
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	1.37
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	4.04

Secondary: Percentage of Subjects With OR by Centrally Assessed Breast MRI via mRECIST Version 1.1 in PIK3CA Wildtype (WT) Subjects

End point title	Percentage of Subjects With OR by Centrally Assessed Breast MRI via mRECIST Version 1.1 in PIK3CA Wildtype (WT) Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	89		
Units: percentage of subjects				
number (not applicable)	45.7	40.4		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.5017
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	5.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.2
upper limit	19.61

Secondary: Percentage of Subjects With Total pCR Defined as Having pCR in Both Breast and Axilla, Using AJCC Staging System in PIK3CA WT Subjects

End point title	Percentage of Subjects With Total pCR Defined as Having pCR in Both Breast and Axilla, Using AJCC Staging System in PIK3CA WT Subjects

End point description:

Total pCR was assessed by local pathology review on samples taken at surgery following completion of neoadjuvant therapy. tpCR was defined as the absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes (i.e., ypT0/Tis, ypN0 in the AJCC staging system, 7th edition). ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	89		
Units: percentage of subjects				
number (not applicable)	2.2	1.1		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
P-value	= 1
Method	Fisher exact
Parameter estimate	Difference in Response Rates
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.65
upper limit	4.75

Secondary: Percentage of Subjects With OR by Breast Ultrasound via mRECIST Version 1.1 in PIK3CA MT Subjects

End point title	Percentage of Subjects With OR by Breast Ultrasound via mRECIST Version 1.1 in PIK3CA MT Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	79		
Units: percentage of subjects				
number (not applicable)	61.6	40.5		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0115
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	21.14
Confidence interval	
level	95 %
sides	2-sided
lower limit	5.59
upper limit	36.68

Secondary: Percentage of Subjects With OR by Breast Ultrasound via mRECIST Version 1.1 in PIK3CA WT Subjects

End point title	Percentage of Subjects With OR by Breast Ultrasound via mRECIST Version 1.1 in PIK3CA WT Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	89		
Units: percentage of subjects				
number (not applicable)	54.3	51.7		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.7928
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	2.66
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.88
upper limit	17.2

Secondary: Percentage of Subjects With OR by Mammography via mRECIST Version 1.1 in PIK3CA MT Subjects

End point title	Percentage of Subjects With OR by Mammography via mRECIST Version 1.1 in PIK3CA MT Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	79		
Units: percentage of subjects				
number (not applicable)	41.1	31.6		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.2659
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	9.45
Confidence interval	
level	95 %
sides	2-sided
lower limit	-5.8
upper limit	24.7

Secondary: Percentage of Subjects With OR by Mammography via mRECIST Version 1.1 in PIK3CA WT Subjects

End point title	Percentage of Subjects With OR by Mammography via mRECIST Version 1.1 in PIK3CA WT Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	89		
Units: percentage of subjects				
number (not applicable)	40.2	32.6		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.3299
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	7.63
Confidence interval	
level	95 %
sides	2-sided
lower limit	-6.34
upper limit	21.6

Secondary: Percentage of Subjects With OR by Clinical Breast Exam (Palpation) via mRECIST Version 1.1 in PIK3CA MT Subjects

End point title	Percentage of Subjects With OR by Clinical Breast Exam (Palpation) via mRECIST Version 1.1 in PIK3CA MT Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	73	79		
Units: percentage of subjects				
number (not applicable)	74.0	63.3		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.1554
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	10.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	-3.96
upper limit	25.32

Secondary: Percentage of Subjects With OR by Clinical Breast Exam (Palpation) via mRECIST Version 1.1 in PIK3CA WT Subjects

End point title	Percentage of Subjects With OR by Clinical Breast Exam (Palpation) via mRECIST Version 1.1 in PIK3CA WT Subjects

End point description:

ORR was defined as proportion of subjects achieving CR or PR. As per modified RECIST v1.1, CR: disappearance of all target lesions, PR: at least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to 16 weeks

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	92	89		
Units: percentage of subjects				
number (not applicable)	62.0	59.6		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	181
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.787
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Response Rates
Point estimate	2.41
Confidence interval	
level	95 %
sides	2-sided
lower limit	-11.82
upper limit	16.63

Secondary: Central Assessments of Changes in Ki67 levels

End point title	Central Assessments of Changes in Ki67 levels

End point description:

Ki67 is a prognostic marker and is used to evaluate the proliferative activity of breast cancer. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to Week 3 and Surgery (Weeks 17-18); and Week 3 to Surgery (Weeks 17-18)

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	168		
Units: percentage				
number (confidence interval 95%)				
From Baseline to Week 3	-83.81 (-86.73 to -80.23)	-80.44 (-83.93 to -76.19)		
From Baseline to Surgery	-75.58 (-80.45 to -69.49)	-80.51 (-84.41 to -75.64)		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole

Statistical analysis description:

Statistical analysis for changes in Ki67 levels from Baseline to Week 3.

Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.117
Method	Regression, Linear
Parameter estimate	Ratio of Least square mean
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	1.05

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Statistical analysis description:	
Statistical analysis for changes in Ki67 levels from Baseline to Surgery.	
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole
Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.105
Method	Regression, Linear
Parameter estimate	Ratio of Least square mean
Point estimate	1.25
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.95
upper limit	1.65

Secondary: Preoperative Endocrine Prognostic Index (PEPI) Score

End point title	Preoperative Endocrine Prognostic Index (PEPI) Score

End point description:

To obtain the PEPI score, risk points for relapse-free survival (RFS) and breast cancer-specific survival (BCSS) are assigned depending on the hazard ratio (HR) from the multivariable analysis. The total PEPI score assigned to each subject is the sum of the risk points derived from the primary tumor (pT) stage, regional lymph nodes (pN) stage, Ki67 level, and estrogen receptor status of the surgical specimen. A HR in the range of 1 to 2 receives one risk point; a HR in the 2 to 2.5 range, two risk points; a HR greater than 2.5, three risk points. The total risk point score for each participant is the sum of all the risk points accumulated from the four factors in the model, ranges from 0 (best possible outcome) to 12 (worst possible outcome). ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo). Here, 99999 indicates that the centrally derived PEPI score was not interpretable; therefore, analysis was not performed.

End point type	Secondary

End point timeframe:

Week 16

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	149	155		
Units: score on a scale				
number (not applicable)	99999	99999		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Surgery in Enhancing Tumor Volume as Measured by Breast MRI

End point title	Percent Change from Baseline to Surgery in Enhancing Tumor Volume as Measured by Breast MRI

End point description:

ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

From Baseline to Surgery (Weeks 17-18)

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	168		
Units: percent change				
number (confidence interval 95%)	-70.60 (-77.53 to -63.66)	-57.28 (-64.21 to -50.35)		

Statistical analyses

Statistical analysis title	Taselisib + Letrozole vs Placebo + Letrozole
Comparison groups	Experimental: Taselisib + Letrozole v Placebo Comparator: Placebo + Letrozole

Number of subjects included in analysis	334
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Regression, Linear
Parameter estimate	Least squares mean difference
Point estimate	-13.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	-21.67
upper limit	-4.96

Secondary: Mean Score for Health-Related Quality of Life Measured by the European Organization for Research C30 (EORTC QLQ-C30)

End point title	Mean Score for Health-Related Quality of Life Measured by the European Organization for Research C30 (EORTC QLQ-C30)

End point description:

EORTC QLQ-C30 includes 30 questions used to assess overall quality of life(QOL)in cancer subjects. The first 28 questions used a 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much) for evaluating 5 functional scales (physical, role, social, cognitive, emotional), 8 symptom scales/items (diarrhea, fatigue, dyspnea, appetite loss, insomnia, nausea and vomiting, constipation and pain) and a single item (financial [fin.] difficulties). The last 2 questions, the subject's assessment of overall health and quality of life, used a 7-point scale (1=very poor to 7=excellent). EORTC QLQ-C30 global scores were linearly transformed on scale of 0 to 100, with high score indicating better QOL. Negative change from Baseline values indicated deterioration in QOL or functioning and positive values indicated improvement. Here, Post surgery= PS. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

Weeks 1, 5, 9, 13, 16, 4-week Post-Surgery

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	168		
Units: score on a scale				
arithmetic mean (standard deviation)				
Appetite Loss: Baseline (n=157,165)	6.2 (± 16.4)	5.9 (± 14.2)		
Appetite Loss: Change at Week 5 (n=155,160)	3.0 (± 18.4)	1.9 (± 18.8)		
Appetite Loss: Change at Week 9 (n=152,158)	5.3 (± 21.4)	3.0 (± 17.8)		
Appetite Loss: Change at Week 13 (n=152,157)	5.5 (± 23.8)	2.1 (± 16.3)		
Appetite Loss: Change at Week 16 (n=146,151)	6.8 (± 24.1)	0.9 (± 16.3)		
Appetite Loss: Change at PS Visit (n=140,146)	5.0 (± 24.9)	5.0 (± 23.3)		

Cognitive function: Baseline (n=158,163)	90.8 (± 15.8)	90.9 (± 16.6)		
Cognitive function: Change at Week 5 (n=154,157)	0.4 (± 12.8)	-2.5 (± 12.3)		
Cognitive function: Change at Week 9 (n=151,157)	-1.1 (± 14.4)	-4.2 (± 14.7)		
Cognitive function: Change at Week 13 (n=153,156)	-3.4 (± 15.8)	-5.1 (± 15.7)		
Cognitive function: Change at Week 16 (n=147,147)	-4.2 (± 15.2)	-4.1 (± 17.5)		
Cognitive function: Change at PS Visit (n=140,144)	-3.1 (± 18.9)	-5.4 (± 16.8)		
Constipation: Baseline (n=158,164)	6.8 (± 15.9)	8.3 (± 18.2)		
Constipation: Change at Week 5 (n=155,159)	0.0 (± 16.1)	3.1 (± 22.1)		
Constipation: Change at Week 9 (n=151,158)	0.2 (± 17.0)	0.2 (± 18.6)		
Constipation: Change at Week 13 (n=151,156)	-0.4 (± 18.5)	-0.6 (± 19.5)		
Constipation: Change at Week 16 (n=146,148)	-1.1 (± 17.2)	1.6 (± 20.3)		
Constipation: Change at PS Visit (n=140,145)	4.8 (± 23.2)	1.1 (± 16.9)		
Diarrhoea: Baseline (n=157,163)	5.9 (± 14.9)	4.3 (± 11.8)		
Diarrhoea: Change at Week 5 (n=154,155)	6.7 (± 21.7)	-0.2 (± 13.4)		
Diarrhoea: Change at Week 9 (n=150,157)	6.4 (± 24.3)	0.8 (± 15.1)		
Diarrhoea: Change at Week 13 (n=152,155)	7.9 (± 22.3)	-0.4 (± 14.7)		
Diarrhoea: Change at Week 16 (n=146,146)	8.4 (± 23.1)	0.2 (± 16.4)		
Diarrhoea: Change at PS Visit (n=140,144)	0.2 (± 17.7)	-0.9 (± 15.7)		
Dyspnoea: Baseline (n=157,165)	7.4 (± 15.8)	8.5 (± 17.5)		
Dyspnoea: Change at Week 5 (n=154,160)	-0.2 (± 14.0)	0.6 (± 18.1)		
Dyspnoea: Change at Week 9 (n=150,159)	2.0 (± 17.4)	1.9 (± 19.9)		
Dyspnoea: Change at Week 13 (n=151,157)	3.5 (± 21.1)	1.7 (± 22.3)		
Dyspnoea: Change at Week 16 (n=146,151)	3.4 (± 20.2)	2.6 (± 22.6)		
Dyspnoea: Change at PS Visit (n=138,146)	3.1 (± 24.8)	2.1 (± 21.5)		
Emotional function: Baseline (n=158,163)	77.0 (± 20.4)	78.2 (± 19.9)		
Emotional function: Change at Week 5 (n=154,157)	4.2 (± 15.2)	2.4 (± 17.0)		
Emotional function: Change at Week 9 (n=151,157)	3.8 (± 14.7)	1.3 (± 20.7)		
Emotional function: Change at Week 13 (n=153,156)	2.5 (± 15.2)	-1.4 (± 18.6)		
Emotional function: Change at Week 16 (n=147,147)	1.0 (± 17.0)	-3.5 (± 20.2)		
Emotional function: Change at PS Visit (n=140,144)	-0.8 (± 19.0)	-3.6 (± 20.9)		
Fatigue: Baseline (n=158,165)	14.8 (± 18.7)	15.6 (± 18.5)		
Fatigue: Change at Week 5 (n=155,161)	4.7 (± 13.9)	4.9 (± 17.9)		

Fatigue: Change at Week 9 (n=152,159)	5.0 (± 15.9)	7.5 (± 20.3)		
Fatigue: Change at Week 13 (n=151,158)	7.9 (± 18.1)	8.8 (± 21.4)		
Fatigue: Change at Week 16 (n=146,151)	6.8 (± 17.5)	8.0 (± 20.4)		
Fatigue: Change at PS Visit (n=140,146)	12.3 (± 19.5)	12.4 (± 22.6)		
Fin. difficulties: Baseline (n=156,160)	9.0 (± 20.9)	10.0 (± 20.4)		
Fin. difficulties: Change at Week 5 (n=152,154)	-2.6 (± 14.6)	-0.4 (± 20.2)		
Fin. difficulties: Change at Week 9 (n=151,153)	-2.6 (± 17.9)	0.7 (± 20.4)		
Fin. difficulties: Change at Week 13 (n=150,152)	-1.1 (± 17.9)	0.0 (± 19.9)		
Fin. difficulties: Change at Week 16 (n=145,144)	-1.1 (± 15.9)	2.1 (± 24.4)		
Fin. difficulties: Change at PS Visit (n=138,141)	1.9 (± 20.0)	3.8 (± 23.6)		
Global health status:Baseline(n=158,162)	75.3 (± 19.7)	74.6 (± 21.2)		
Global health status:Change at Week 5(n=153,156)	1.5 (± 15.2)	-1.1 (± 18.5)		
Global health status:Change at Week 9(n=150,155)	-1.1 (± 15.9)	-3.2 (± 22.7)		
Global health status:Change at Week 13(n=152,155)	-2.4 (± 19.5)	-3.7 (± 20.7)		
Global health status:Change at Week 16(n=147,146)	-2.2 (± 18.4)	-2.9 (± 22.6)		
Global health status:Change at PS Visit(n=139,143)	-5.9 (± 19.7)	-7.0 (± 22.2)		
Insomnia: Baseline (n=158,165)	23.0 (± 27.1)	22.4 (± 28.1)		
Insomnia: Change at Week 5 (n=155,161)	-2.4 (± 24.1)	-0.4 (± 27.6)		
Insomnia: Change at Week 9 (n=151,159)	-1.8 (± 24.9)	-0.6 (± 26.9)		
Insomnia: Change at Week 13 (n=153,158)	-1.1 (± 27.7)	2.1 (± 29.5)		
Insomnia: Change at Week 16 (n=146,149)	-0.7 (± 26.1)	-2.2 (± 27.6)		
Insomnia: Change at PS Visit (n=140,146)	-1.4 (± 26.8)	3.2 (± 34.4)		
Nausea / vomiting: Baseline (n=158,165)	1.9 (± 7.5)	1.6 (± 6.2)		
Nausea / vomiting: Change at Week 5 (n=155,161)	3.7 (± 11.3)	1.9 (± 9.9)		
Nausea / vomiting: Change at Week 9 (n=152,159)	3.4 (± 10.9)	1.7 (± 10.3)		
Nausea / vomiting: Change at Week 13 (n=153,158)	3.7 (± 12.9)	0.7 (± 8.5)		
Nausea / vomiting: Change at Week 16 (n=146,151)	2.5 (± 14.0)	0.6 (± 8.0)		
Nausea / vomiting: Change at PS Visit (n=140,146)	2.1 (± 14.8)	1.0 (± 8.6)		
Pain: Baseline (n=157,165)	13.1 (± 20.4)	12.3 (± 19.6)		
Pain: Change at Week 5 (n=155,161)	-0.6 (± 18.8)	2.6 (± 17.5)		
Pain: Change at Week 9 (n=152,159)	-1.8 (± 16.5)	3.8 (± 22.9)		
Pain: Change at Week 13 (n=152,158)	-1.4 (± 18.4)	4.7 (± 23.4)		
Pain: Change at Week 16 (n=147,151)	-0.9 (± 19.1)	1.8 (± 22.0)		
Pain: Change at PS Visit (n=140,146)	11.1 (± 26.0)	13.8 (± 26.6)		

Physical function: Baseline (n=158,165)	89.6 (± 13.7)	90.8 (± 13.4)		
Physical function: Change at Week 5 (n=155,161)	0.5 (± 9.6)	-1.2 (± 11.5)		
Physical function: Change at Week 9 (n=152,157)	0.2 (± 10.1)	-2.0 (± 13.1)		
Physical function: Change at Week 13 (n=152,158)	-0.3 (± 12.4)	-1.9 (± 14.0)		
Physical function: Change at Week 16 (n=146,150)	-0.5 (± 10.9)	-3.4 (± 15.1)		
Physical function: Change at PS Visit (n=140,146)	-5.2 (± 16.0)	-7.5 (± 15.7)		
Role function: Baseline (n=157,165)	90.7 (± 20.1)	93.1 (± 16.5)		
Role function: Change at Week 5 (n=155,160)	1.3 (± 14.3)	-2.5 (± 17.1)		
Role function: Change at Week 9 (n=150,159)	-0.2 (± 12.8)	-4.9 (± 18.9)		
Role function: Change at Week 13 (n=152,157)	-2.3 (± 17.4)	-5.6 (± 19.8)		
Role function: Change at Week 16 (n=146,151)	-4.6 (± 16.3)	-4.4 (± 18.9)		
Role function: Change at PS Visit (n=140,146)	-15.1 (± 24.7)	-20.1 (± 28.1)		
Social function: Baseline (n=155,161)	91.2 (± 17.6)	94.9 (± 14.3)		
Social function: Change at Week 5 (n=151,155)	3.1 (± 12.8)	-2.0 (± 15.7)		
Social function: Change at Week 9 (n=150,155)	2.0 (± 13.4)	-4.0 (± 18.1)		
Social function: Change at Week 13 (n=150,154)	0.0 (± 13.7)	-4.0 (± 19.0)		
Social function: Change at Week 16 (n=146,145)	-0.5 (± 13.7)	-3.1 (± 19.3)		
Social function: Change at PS Visit (n=139,142)	-6.4 (± 20.3)	-10.1 (± 24.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Score for Treatment of Cancer Quality of Life Questionnaire BR23 (QLQ-BR23)

End point title	Mean Score for Treatment of Cancer Quality of Life Questionnaire BR23 (QLQ-BR23)

End point description:

EORTC-QLQ-BR23 is a 23-item breast cancer-specific companion module to the EORTC-QLQ-C30 and consists of four functional scales (body image, sexual enjoyment, sexual functioning, future perspective [FP]) and four symptom scales (systematic therapy side effects [SE], upset by hair loss, arm symptoms, breast symptoms). Questions used 4-point scale (1=not at all, 2=a little, 3=quite a bit, 4=very much). Scores were averaged and transformed to 0-100 scale. High score for functional scale indicated high/better level of functioning/healthy functioning. Negative change from Baseline indicated deterioration in QOL and positive change from Baseline indicated an improvement in QOL. Here, Post surgery= PS. ITT population includes all randomised subjects regardless of whether they received any study drug (taselisib or placebo).

End point type	Secondary

End point timeframe:

Weeks 1, 5, 9, 13, 16, 4-week Post-Surgery

End point values	Experimental: Taselisib + Letrozole	Placebo Comparator: Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	166	168		
Units: score on a scale				
arithmetic mean (standard deviation)				
Body image: Baseline (n=155,160)	91.8 (± 15.7)	94.0 (± 14.6)		
Body image: Change at Week 5 (n=152,151)	2.8 (± 8.8)	0.6 (± 11.4)		
Body image: Change at Week 9 (n=149,150)	1.2 (± 9.8)	-0.2 (± 10.3)		
Body image: Change at Week 13 (n=150,149)	1.2 (± 11.6)	-1.6 (± 13.8)		
Body image: Change at Week 16 (n=145,143)	0.1 (± 10.8)	-1.2 (± 12.8)		
Body image: Change at PS Visit (n=138,140)	-6.5 (± 22.3)	-8.3 (± 19.2)		
Breast symptoms: Baseline (n=154,160)	5.3 (± 9.8)	6.9 (± 12.7)		
Breast symptoms: Change at Week 5 (n=148,150)	2.3 (± 14.6)	1.0 (± 13.0)		
Breast symptoms: Change at Week 9 (n=148,151)	4.5 (± 15.1)	1.8 (± 11.7)		
Breast symptoms: Change at Week 13 (n=149,151)	5.8 (± 16.0)	2.3 (± 13.3)		
Breast symptoms: Change at Week 16 (n=146,146)	7.9 (± 18.6)	3.9 (± 14.9)		
Breast symptoms: Change at PS Visit (n=136,140)	6.6 (± 17.9)	4.3 (± 14.2)		
Future perspective: Baseline (n=157,159)	57.7 (± 31.0)	58.7 (± 29.9)		
Future perspective: Change at Week 5 (n=154,151)	6.5 (± 26.7)	9.3 (± 28.1)		
Future perspective: Change at Week 9 (n=150,151)	10.2 (± 25.0)	9.7 (± 26.6)		
Future perspective: Change at Week 13 (n=151,152)	7.7 (± 28.4)	4.4 (± 29.1)		
Future perspective: Change at Week 16 (n=147,145)	10.2 (± 26.1)	5.1 (± 29.2)		
Future perspective: Change at PS Visit (n=139,139)	6.5 (± 29.7)	3.4 (± 34.8)		
Sexual enjoyment: Baseline (n=48,29)	41.7 (± 22.3)	47.1 (± 28.9)		
Sexual enjoyment: Change at Week 5 (n=40,24)	3.3 (± 18.2)	11.1 (± 23.4)		
Sexual enjoyment: Change at Week 9 (n=40,22)	8.3 (± 23.6)	10.6 (± 23.9)		
Sexual enjoyment: Change at Week 13 (n=33,21)	6.1 (± 19.5)	1.6 (± 22.3)		
Sexual enjoyment: Change at Week 16 (n=34,22)	9.8 (± 19.3)	7.6 (± 22.8)		
Sexual enjoyment: Change at PS Visit (n=21,15)	14.3 (± 27.0)	2.2 (± 23.5)		
Sexual functioning: Baseline (n=149,147)	81.2 (± 23.4)	85.1 (± 20.2)		

Sexual functioning: Change at Week 5 (n=144,133)	1.2 (± 13.6)	1.0 (± 15.0)		
Sexual functioning: Change at Week 9 (n=136,131)	1.3 (± 14.5)	0.3 (± 16.5)		
Sexual functioning: Change at Week 13 (n=129,126)	4.1 (± 16.1)	1.6 (± 17.7)		
Sexual functioning: Change at Week 16 (n=128,124)	4.8 (± 15.9)	1.1 (± 18.1)		
Sexual functioning: Change at PS Visit (n=120,121)	9.6 (± 19.2)	4.1 (± 21.8)		
SE: Baseline (n=159,162)	8.7 (± 10.8)	9.5 (± 11.5)		
SE: Change at Week 5 (n=156,153)	4.3 (± 10.0)	3.9 (± 10.5)		
SE: Change at Week 9 (n=153,154)	6.7 (± 10.8)	5.9 (± 12.1)		
SE: Change at Week 13 (n=154,155)	7.3 (± 11.0)	6.2 (± 13.1)		
SE: Change at Week 16 (n=149,149)	7.5 (± 12.9)	7.1 (± 12.6)		
SE: Change at PS Visit (n=141,142)	7.0 (± 12.0)	5.9 (± 12.1)		
Upset by hair loss: Baseline (n=19,18)	24.6 (± 26.9)	35.2 (± 31.3)		
Upset by hair loss: Change at Week 5 (n=12,10)	11.1 (± 32.8)	-3.3 (± 18.9)		
Upset by hair loss: Change at Week 9 (n=11,11)	9.1 (± 44.9)	-9.1 (± 26.2)		
Upset by hair loss: Change at Week 13 (n=10,11)	16.7 (± 36.0)	-3.0 (± 34.8)		
Upset by hair loss: Change at Week 16 (n=11,14)	21.2 (± 34.2)	-7.1 (± 23.3)		
Upset by hair loss: Change at PS Visit (n=13,13)	30.8 (± 37.2)	-2.6 (± 34.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Adverse Events

End point title	Percentage of Subjects With Adverse Events

End point description:

An adverse event (AE) is any untoward medical occurrence in a subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The safety population includes all randomised subjects who received at least one dose of taselisib or placebo.

End point type	Secondary

End point timeframe:

Baseline up to 22 weeks

End point values	Taselisib + Letrozole	Placebo + Letrozole		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	167	167		
Units: percentage of subjects				
number (not applicable)	91.0	83.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up to 22 weeks

Adverse event reporting additional description:

The safety population includes all randomised subjects who received at least one dose of taselisib or placebo.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	19, 19.1

Reporting groups

Reporting group title	Placebo Comparator: Placebo + Letrozole

Reporting group description:

Subjects received 2.5 mg letrozole tablets orally QD along with placebo on a 5-days-on/2-days-off schedule for a total of 16 weeks.

Reporting group title	Experimental: Taselisib + Letrozole

Reporting group description:

Subjects received 2.5 milligrams (mg) letrozole tablets orally once daily (QD) along with taselisib tablets at 4 mg (two 2 mg tablets) orally on a 5 days-on/2 days-off schedule for a total of 16 weeks.

Serious adverse events	Placebo Comparator: Placebo + Letrozole	Experimental: Taselisib + Letrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 167 (2.40%)	20 / 167 (11.98%)	
number of deaths (all causes)	0	1	
number of deaths resulting from adverse events			
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hypertensive encephalopathy			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory impairment			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
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			
Impaired healing			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sudden death			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	0 / 167 (0.00%)	5 / 167 (2.99%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis haemorrhagic			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
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 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (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	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Erythema multiforme			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Postoperative wound infection			
subjects affected / exposed	1 / 167 (0.60%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 167 (0.00%)	2 / 167 (1.20%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial diarrhoea			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea infectious			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
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 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	1 / 167 (0.60%)	0 / 167 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 167 (0.00%)	1 / 167 (0.60%)	
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 / 167 (0.00%)	1 / 167 (0.60%)	
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	0 / 167 (0.00%)	1 / 167 (0.60%)	
occurrences causally related to treatment / all	0 / 0	0 / 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 Comparator: Placebo + Letrozole	Experimental: Taselisib + Letrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 167 (75.45%)	130 / 167 (77.84%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 167 (2.40%)	9 / 167 (5.39%)	
occurrences (all)	4	9	
Vascular disorders			
Hot flush			
subjects affected / exposed	33 / 167 (19.76%)	25 / 167 (14.97%)	
occurrences (all)	33	25	
Hypertension			
subjects affected / exposed	11 / 167 (6.59%)	10 / 167 (5.99%)	
occurrences (all)	13	10	
Nervous system disorders			
Headache			
subjects affected / exposed	18 / 167 (10.78%)	16 / 167 (9.58%)	
occurrences (all)	19	18	
Dizziness			
subjects affected / exposed	9 / 167 (5.39%)	9 / 167 (5.39%)	
occurrences (all)	9	9	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	40 / 167 (23.95%)	33 / 167 (19.76%)	
occurrences (all)	43	34	
Asthenia			
subjects affected / exposed	16 / 167 (9.58%)	17 / 167 (10.18%)	
occurrences (all)	18	20	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	20 / 167 (11.98%)	49 / 167 (29.34%)	
occurrences (all)	25	68	
Nausea			
subjects affected / exposed	19 / 167 (11.38%)	35 / 167 (20.96%)	
occurrences (all)	21	40	
Stomatitis			

subjects affected / exposed	5 / 167 (2.99%)	22 / 167 (13.17%)	
occurrences (all)	6	26	
Dry mouth			
subjects affected / exposed	14 / 167 (8.38%)	6 / 167 (3.59%)	
occurrences (all)	14	6	
Constipation			
subjects affected / exposed	7 / 167 (4.19%)	10 / 167 (5.99%)	
occurrences (all)	7	10	
Vomiting			
subjects affected / exposed	6 / 167 (3.59%)	10 / 167 (5.99%)	
occurrences (all)	6	10	
Dyspepsia			
subjects affected / exposed	1 / 167 (0.60%)	9 / 167 (5.39%)	
occurrences (all)	1	9	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 167 (4.79%)	9 / 167 (5.39%)	
occurrences (all)	8	11	
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	8 / 167 (4.79%)	14 / 167 (8.38%)	
occurrences (all)	8	14	
Rash			
subjects affected / exposed	5 / 167 (2.99%)	15 / 167 (8.98%)	
occurrences (all)	6	16	
Pruritus			
subjects affected / exposed	9 / 167 (5.39%)	6 / 167 (3.59%)	
occurrences (all)	10	6	
Dry skin			
subjects affected / exposed	3 / 167 (1.80%)	10 / 167 (5.99%)	
occurrences (all)	3	10	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	11 / 167 (6.59%)	6 / 167 (3.59%)	
occurrences (all)	11	7	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	36 / 167 (21.56%)	19 / 167 (11.38%)	
occurrences (all)	39	20	
Back pain			
subjects affected / exposed	10 / 167 (5.99%)	6 / 167 (3.59%)	
occurrences (all)	10	6	
Infections and infestations			
Viral upper respiratory tract infection			
subjects affected / exposed	13 / 167 (7.78%)	6 / 167 (3.59%)	
occurrences (all)	13	7	
Urinary tract infection			
subjects affected / exposed	9 / 167 (5.39%)	7 / 167 (4.19%)	
occurrences (all)	9	7	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	12 / 167 (7.19%)	26 / 167 (15.57%)	
occurrences (all)	12	27	
Decreased appetite			
subjects affected / exposed	6 / 167 (3.59%)	11 / 167 (6.59%)	
occurrences (all)	6	12	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 April 2014	• To improve clarity: Language was added that the investigator had the sole responsibility to break the treatment code in emergency situations • To improve safety of subjects in respect to pneumonitis as a known taselisib toxicity: Additional screening and management of pulmonary function was added • To ensure enrollment of appropriate subjects: Exclusion criteria were added for subjects with immediate surgery indicated and chemotherapy judged to be the optimal neoadjuvant treatment • To improve safety of subjects in respect to letrozole being an estrogen-lowering agent: Additional assessments and adequate monitoring were added • Bisphosphonates were added as permitted concomitant therapy for osteoporosis • Potent CYP3A4 inducers were added as prohibited therapy
22 May 2014	• Taselisib 2 mg tablet formulation information and information on relative bioavailability of taselisib capsules and tablets were added • Requirement for taking taselisib on an empty stomach was removed • Adverse event of special interest (AESI) management guidelines were updated
27 July 2015	• To increase monitoring of diarrhea: AESI Grade ≥3 diarrhea was changed to Grade ≥2 diarrhea; Grade ≥1 diarrhea that persisted for more than 2 weeks despite antidiarrheals (e.g., loperamide) was added as an AESI; recommendation for management of Gastrointestinal (GI) toxicities that subjects experiencing Grade ≥1 diarrhea be contacted at least weekly was added; AE assessments at Weeks 7 and 11 by telephone were added • To enable correlation of response with biomarker analysis: Collection was added of an additional blood sample at 4-week post-surgical follow-up visit for Circulating Tumor Deoxyribonucleic Acid (ctDNA) and plasma protein biomarkers analysis
27 July 2015	• To prevent subjects with potential predisposition to gastrointestinal side effects from being enrolled: Additional restriction was added to the following exclusion criterion: "History of prior or currently active small or large intestine inflammation (such as Crohn's disease or ulcerative colitis). Any subject with a baseline medical condition involving the GI tract or who may have a predisposition for GI toxicity requires prior approval from the Medical Monitor" • To improve clarity: Requirement was added for Target Lesion #2, if selected, to be ≥10 mm; "Investigational Agents" was added amongst prohibited concomitant therapies; specification that there was a 4-week "wash-out" period for any other investigational agent prior to initiation of taselisib treatment was added

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported