Clinical trial results:
A Phase II randomized, double-blind placebo controlled, study of letrozole with or without alpelisib (BYL719) or buparlisib (BKM120), for the neo-adjuvant treatment of postmenopausal women with hormone receptor-positive HER2-negative breast cancer

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Summary

EudraCT number	2013-001862-41
Trial protocol	ES IT AT BE DE NL CZ BG
Global end of trial date	08 July 2017

Results information

Result version number	v1 (current)
This version publication date	21 July 2018
First version publication date	21 July 2018

Trial information

Trial identification

Sponsor protocol code	CBYL719A2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01923168
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma, AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.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	08 July 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 July 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the anti-tumor activity of alpelisib once daily plus letrozole versus letrozole alone in increasing the pathologic complete response (pCR) rate during neo-adjuvant treatment among postmenopausal subjects with hormone receptor-positive (HR-positive), human epidermal growth factor receptor-2 negative (HER2-negative) breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild type tumors based on tumor tissue.

To assess the anti-tumor activity of alpelisib once daily plus letrozole versus letrozole alone in increasing the Objective Response Rate (ORR) during neo-adjuvant treatment among postmenopausal subjects with HR-positive, HER2-negative breast cancer for each of the two cohorts: i) PIK3CA mutated and ii) PIK3CA wild type tumors based on tumor tissue. The primary objective of the study was considered met if either one or both of these two objectives

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 March 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	Austria: 49
Country: Number of subjects enrolled	Belgium: 13
Country: Number of subjects enrolled	Brazil: 15
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	Germany: 26
Country: Number of subjects enrolled	Hong Kong: 8

Country: Number of subjects enrolled	Israel: 9
Country: Number of subjects enrolled	Japan: 11
Country: Number of subjects enrolled	Lebanon: 8
Country: Number of subjects enrolled	Netherlands: 10
Country: Number of subjects enrolled	Spain: 63
Country: Number of subjects enrolled	United States: 100
Worldwide total number of subjects	340
EEA total number of subjects	168

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)	187
From 65 to 84 years	152
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of approximately 320 patients were planned to be randomized: this was based on 60 patients per arm in each cohort (PIK3CA mutant and PIK3CA wild-type) for the alpelisib+letrozole and placebo+letrozole arms, plus the estimated number of patients randomized to buparlisib+letrozole arm at the time this arm was discontinued.

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, Carer

Arms

Are arms mutually exclusive?	Yes
Arm title	Alpelisib + Letrozole

Arm description:

Participants took alpelisib 300 mg once daily plus letrozole 2.5 mg once daily.

Arm type	Experimental
Investigational medicinal product name	Alpelisib
Investigational medicinal product code	BYL719
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Alpelisib came in 50 mg and 200 mg tablets and was administered at a dose of 300 mg orally daily .

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

Dosage and administration details:

Letrozole was administered at a dose of 2.5 mg orally daily

Arm title	Buparlisib + Letrozole

Arm description:

Participants took buparlisib 100 mg once daily or 5 days on/2 days off plus letrozole 2.5 mg once daily.

Arm type	Active comparator
Investigational medicinal product name	Buparlisib
Investigational medicinal product code	BKM120
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Buparlisib was administered at a dose of 100 mg orally daily in combination with Letrozole 2.5 mg orally daily.

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

Dosage and administration details:

Letrozole was administered at a dose of 2.5 mg orally daily

Arm title	Placebo + Letrozole

Arm description:

Participants took matching Placebo (of alpelisib 300 mg once daily/buparlisib 100 mg once daily or 5 days on/2 days off) plus Letrozole 2.5 mg once daily.

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:

came in 50 mg and 200 mg tablets.

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

Dosage and administration details:

Letrozole was dosed at 2.5 mg orally daily.

Number of subjects in period 1	Alpelisib + Letrozole	Buparlisib + Letrozole	Placebo + Letrozole
Started	131	83	126
Completed	94	44	109
Not completed	37	39	17
Adverse event, serious fatal	-	-	1
Physician decision	6	9	5
Adverse event, non-fatal	12	12	-
Progressive disease	4	3	7
Subject/guardian decision	14	14	4
Protocol deviation	1	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Alpelisib + Letrozole
Reporting group description:	
Participants took alpelisib 300 mg once daily plus letrozole 2.5 mg once daily.	
Reporting group title	Buparlisib + Letrozole
Reporting group description:	
Participants took buparlisib 100 mg once daily or 5 days on/2 days off plus letrozole 2.5 mg once daily.	
Reporting group title	Placebo + Letrozole
Reporting group description:	
Participants took matching Placebo (of alpelisib 300 mg once daily/buparlisib 100 mg once daily or 5 days on/2 days off) plus Letrozole 2.5 mg once daily.	

Reporting group values	Alpelisib + Letrozole	Buparlisib + Letrozole	Placebo + Letrozole
Number of subjects	131	83	126
Age categorical Units: Subjects			
Adults (18-64 years)	69	40	78
From 65-84 years	61	43	48
85 years and over	1	0	0
Age Continuous Units: Years			
arithmetic mean	64.3	65.2	63.1
standard deviation	± 8.53	± 8.61	± 8.31
Sex: Female, Male Units: Subjects			
Female	131	83	126
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
White	117	68	105
Asian	7	4	10
Black or African American	3	3	5
Other	3	6	3
Unknown	1	2	3

Reporting group values	Total		
Number of subjects	340		
Age categorical Units: Subjects			
Adults (18-64 years)	187		
From 65-84 years	152		
85 years and over	1		
Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		

Sex: Female, Male Units: Subjects			
Female	340		
Male	0		
Race/Ethnicity, Customized Units: Subjects			
White	290		
Asian	21		
Black or African American	11		
Other	12		
Unknown	6		

End points

End points reporting groups

Reporting group title	Alpelisib + Letrozole
Reporting group description:	
Participants took alpelisib 300 mg once daily plus letrozole 2.5 mg once daily.	
Reporting group title	Buparlisib + Letrozole
Reporting group description:	
Participants took buparlisib 100 mg once daily or 5 days on/2 days off plus letrozole 2.5 mg once daily.	
Reporting group title	Placebo + Letrozole
Reporting group description:	
Participants took matching Placebo (of alpelisib 300 mg once daily/buparlisib 100 mg once daily or 5 days on/2 days off) plus Letrozole 2.5 mg once daily.	

Primary: Pathological Complete Response (pCR) per Investigator assessment for alpelisib vs. Placebo for PIK3CA mutant cohort

End point title	Pathological Complete Response (pCR) per Investigator assessment for alpelisib vs. Placebo for PIK3CA mutant cohort[1]
End point description:	
Pathologic complete response (pCR) defined as absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of 24 weeks of treatment by local assessment (ypT0/Tis ypN0). Patients who experienced progression of disease while undergoing neoadjuvant therapy, or who did not receive surgery for any reason, or received antineoplastic treatment other than study drug(s) before surgery were considered as non-responders for the calculation of pCR rate.	
End point type	Primary
End point timeframe:	
After 24 weeks of treatment	

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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: Percentage of Participants				
number (confidence interval 80%)	1.7 (0.2 to 6.3)	3.0 (0.8 to 7.7)		

Statistical analyses

Statistical analysis title	pCR: Alpelisib vs Placebo - mutant cohort
Comparison groups	Alpelisib + Letrozole v Placebo + Letrozole

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other[2]
P-value	= 0.282
Method	Posterior mean diff. & credible interval
Parameter estimate	Mean difference (final values)
Point estimate	-1.3
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.5
upper limit	1.7

Notes:

[2] - Bayesian double criteria

Primary: Pathological Complete Response (pCR) per Investigator assessment for alpelisib vs. Placebo for PIK3CA wild-type cohort

End point title	Pathological Complete Response (pCR) per Investigator assessment for alpelisib vs. Placebo for PIK3CA wild-type cohort[3]

End point description:

Pathologic complete response (pCR) defined as absence of any residual invasive cancer on hematoxylin and eosin evaluation of the resected breast specimen and all sampled ipsilateral lymph nodes following completion of 24 weeks of treatment by local assessment (ypT0/Tis ypN0). Patients who experienced progression of disease while undergoing neoadjuvant therapy, or who did not receive surgery for any reason, or received antineoplastic treatment other than study drug(s) before surgery were considered as non-responders for the calculation of pCR rate.

End point type	Primary

End point timeframe:

After 24 weeks of treatment

Notes:

[3] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	59		
Units: Percentage of Participants				
number (confidence interval 80%)	2.8 (0.8 to 7.3)	1.7 (0.2 to 6.4)		

Statistical analyses

Statistical analysis title	pCR: Alpelisib vs Placebo - wild-type cohort
Comparison groups	Alpelisib + Letrozole v Placebo + Letrozole

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[4]
P-value	= 0.697
Method	Posterior mean difference
Parameter estimate	Mean difference (final values)
Point estimate	1.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.9
upper limit	4.2

Notes:

[4] - Bayesian double criteria

Primary: Objective Response Rate per Investigator assessment according to RECIST 1.1 for alpelisib vs. placebo - PIK3CA mutant cohort

End point title	Objective Response Rate per Investigator assessment according to RECIST 1.1 for alpelisib vs. placebo - PIK3CA mutant cohort[5]

End point description:

Objective Response Rate (ORR) defined as the proportion of patients with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) based on local investigator's assessment according to RECIST 1.1.

End point type	Primary

End point timeframe:

After 24 weeks of treatment

Notes:

[5] - 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: At protocol amendment 5 enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: Percentage of Participants				
number (confidence interval 80%)	43.3 (34.6 to 52.4)	44.8 (36.5 to 53.3)		

Statistical analyses

Statistical analysis title	ORR: Alpelisib vs Placebo - mutant cohort
Comparison groups	Alpelisib + Letrozole v Placebo + Letrozole

Number of subjects included in analysis	127
Analysis specification	Pre-specified
Analysis type	other[6]
P-value	= 0.435
Method	Posterior mean diff. & credible interval
Parameter estimate	Mean difference (final values)
Point estimate	-1.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-12.5
upper limit	9.7

Notes:

[6] - Bayesian double criteria

Primary: Objective Response Rate according to RECIST 1.1 per Investigator assessment for alpelisib vs. placebo - PIK3CA wild-type cohort

End point title	Objective Response Rate according to RECIST 1.1 per Investigator assessment for alpelisib vs. placebo - PIK3CA wild-type cohort[7]

End point description:

Objective Response Rate (ORR) defined as the proportion of patients with a Best Overall Response (BOR) of Complete Response (CR) or Partial Response (PR) based on local investigator's assessment according to RECIST 1.1.

End point type	Primary

End point timeframe:

After 24 weeks of treatment

Notes:

[7] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	59		
Units: Percentage of Participants				
number (confidence interval 80%)	63.4 (55.1 to 71.0)	61.0 (51.8 to 69.6)		

Statistical analyses

Statistical analysis title	ORR: Alpelisib vs Placebo - wild-type cohort
Comparison groups	Alpelisib + Letrozole v Placebo + Letrozole

Number of subjects included in analysis	130
Analysis specification	Pre-specified
Analysis type	other[8]
P-value	= 0.611
Method	Posterior mean diff. & credible interval
Parameter estimate	Mean difference (final values)
Point estimate	2.4
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-8.4
upper limit	13.2

Notes:

[8] - Bayesian double criteria

Secondary: pCR and Objective response rate according to RECIST 1.1 criteria per Investigator assessment for alpelisib vs. placebo in PIK3CA mutant cohort based on ctDNA

End point title	pCR and Objective response rate according to RECIST 1.1 criteria per Investigator assessment for alpelisib vs. placebo in PIK3CA mutant cohort based on ctDNA[9]

End point description:

pCR and Objective response rate according to RECIST 1.1 per investigator assessment after 24 weeks of treatment

End point type	Secondary

End point timeframe:

After 24 weeks of treatment

Notes:

[9] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[10]	0[11]		
Units: Participants				

Notes:

[10] - No patients were analyzed for this endpoint

[11] - No patients were analyzed for this endpoint

Statistical analyses

No statistical analyses for this end point

Secondary: pCR and Objective response rate according to RECIST 1.1 criteria per Investigator assessment for alpelisib vs. placebo in PIK3CA wild-type cohort based on ctDNA

End point title	pCR and Objective response rate according to RECIST 1.1 criteria per Investigator assessment for alpelisib vs. placebo in PIK3CA wild-type cohort based on ctDNA[12]

End point description:

pCR and Objective response rate according to RECIST 1.1 per investigator assessment after 24 weeks of

treatment

End point type	Secondary

End point timeframe:

After 24 weeks of treatment

Notes:

[12] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[13]	0[14]		
Units: Participants				

Notes:

[13] - No patients were analyzed for this endpoint

[14] - No patients were analyzed for this endpoint

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of breast conserving surgery for alpelisib vs. placebo - PIK3CA mutant cohort

End point title	Rate of breast conserving surgery for alpelisib vs. placebo - PIK3CA mutant cohort[15]

End point description:

Breast conserving surgery is defined as the percentage of participants with no mastectomy following completion of 24 weeks of treatment

End point type	Secondary

End point timeframe:

After 24 weeks of treatment

Notes:

[15] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: Percentage of participants				
number (confidence interval 80%)				
Breast conserving surgery	56.7 (47.6 to 65.4)	50.7 (42.2 to 59.2)		
No Surgery	15.0 (9.3 to 22.6)	9.0 (4.8 to 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Rate of breast conserving surgery for alpelisib vs. placebo - PIK3CA wild-type cohort

End point title	Rate of breast conserving surgery for alpelisib vs. placebo - PIK3CA wild-type cohort[16]

End point description:

Breast conserving surgery is defined as the percentage of participants with no mastectomy following completion of 24 weeks of treatment

End point type	Secondary

End point timeframe:

After 24 weeks of treatment

Notes:

[16] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	59		
Units: Percentage of participants				
number (confidence interval 80%)				
Breast conserving surgery	50.7 (42.5 to 58.9)	62.7 (53.6 to 71.2)		
No Surgery	18.3 (12.5 to 25.6)	8.5 (4.5 to 15.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA mutant cohort: responders as per pCR

End point title	Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA mutant cohort: responders as per pCR[17]

End point description:

Association between pCR and change in Ki67 from baseline to day 15 and baseline to surgery

End point type	Secondary

End point timeframe:

Baseline, Day 15 and surgery (End of Treatment (EOT))

Notes:

[17] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	2		
Units: Percentage of positive cells				
median (full range (min-max))				
Baseline|	5.0 (5 to 5)	11.0 (5 to 17)		
C1D15: % change from Baseline (n=1,1)|	-80.0 (-80 to -80)	80.0 (80 to 80)		
EOT % change from Baseline (n= 0,0)|	99.9 (99.9 to 99.9)	99.9 (99.9 to 99.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA mutant cohort: non-responders as per pCR

End point title	Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA mutant cohort: non-responders as per pCR[18]

End point description:

Association between pCR and change in Ki67 from baseline to day 15 and baseline to surgery

End point type	Secondary

End point timeframe:

Baseline, Day 15, Surgery (End of Treatment (EOT))

Notes:

[18] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	59	65		
Units: Percentage of positive cells				
median (full range (min-max))				
Baseline|	14.0 (0 to 82)	13.0 (3 to 89)		
C1D15 % change from Baseline (n=45,52)|	-62.5 (-97 to 467)	-60.0 (-96 to 733)		
EOT % change from Baseline (n= 34,49)|	-51.2 (-94 to 400)	-60.0 (-97 to 223)		

Statistical analyses

No statistical analyses for this end point

Secondary: Association between pCR and changes in Ki67 from baseline for alpelisib

vs. placebo - PIK3CA wild-type cohort: responders as per pCR

End point title	Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA wild-type cohort: responders as per pCR[19]

End point description:

Association between pCR and changes in Ki67 from baseline to day 15 and baseline to surgery

End point type	Secondary

End point timeframe:

Baseline, Day 15 and surgery (End of Treatment (EOT))

Notes:

[19] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2	1		
Units: Percentage of positive cells				
median (full range (min-max))				
Baseline|	16.5 (3 to 30)	20.0 (20 to 20)		
C1D15: % change from Baseline (n =1,0)|	-80.0 (-80 to -80)	0 (0 to 0)		
EOT % change from Baseline (n= 2,0)|	-45.0 (-90 to 0)	0 (0 to 0)		

Statistical analyses

No statistical analyses for this end point

Secondary: Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA wild-type cohort: non-responders as per pCR

End point title	Association between pCR and changes in Ki67 from baseline for alpelisib vs. placebo - PIK3CA wild-type cohort: non-responders as per pCR[20]

End point description:

Association between pCR and changes in Ki67 from baseline to day 15 and baseline to surgery

End point type	Secondary

End point timeframe:

Baseline, Day 15, Surgery (End of Treatment (EOT))

Notes:

[20] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	58		
Units: Percentage of positive cells				
median (full range (min-max))				
Baseline|	16.0 (3 to 60)	18.0 (4 to 85)		
C1D15 % change from Baseline (n =51,47)|	-60.0 (-97 to 220)	-52.0 (-93 to 50)		
EOT % change from Baseline (n= 37,41)|	-60.0 (-90 to 190)	-71.1 (-100 to 250)		

Statistical analyses

No statistical analyses for this end point

Secondary: Preoperative endocrine prognostic index (PEPI) as per central assessment for alpelisib vs. placebo - PIK3CA mutant cohort

End point title	Preoperative endocrine prognostic index (PEPI) as per central assessment for alpelisib vs. placebo - PIK3CA mutant cohort[21]

End point description:

PEPI response is defined as central PEPI score of 0 at surgery

End point type	Secondary

End point timeframe:

After 24 weeks of treatment

Notes:

[21] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	60	67		
Units: Number of participants	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Preoperative endocrine prognostic index (PEPI) as per central assessment for alpelisib vs. placebo - PIK3CA wild-type cohort

End point title	Preoperative endocrine prognostic index (PEPI) as per central assessment for alpelisib vs. placebo - PIK3CA wild-type cohort[22]

End point description:

PEPI response is defined as central PEPI score of 0 at surgery

End point type	Secondary

End point timeframe:

After 24 weeks of treatment

Notes:

[22] - 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: At protocol amendment 5, enrollment to the buparlisib plus letrozole arm was discontinued and the assessment of the anti-tumor activity of buparlisib plus letrozole became an exploratory objective, hence the efficacy results are not reported for this arm.

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	59		
Units: Number of participants	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Alpelisib PK parameters: AUC0-24, AUClast at cycle 1 day 1

End point title	Alpelisib PK parameters: AUC0-24, AUClast at cycle 1 day 1[23]

End point description:

Summary of primary PK parameters for alpelisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[23] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0-24 (n = 3) AUClast	30800 (± 20.6) 27300 (± 68.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alpelisib PK parameter: Cmax at cycle 1 day 1

End point title	Alpelisib PK parameter: Cmax at cycle 1 day 1[24]

End point description:

Summary of primary PK parameters for alpelisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[24] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3160 (± 25.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alpelisib and PK parameter: Tmax at cycle 1 day 1

End point title	Alpelisib and PK parameter: Tmax at cycle 1 day 1[25]

End point description:

Summary of primary PK parameters for alpelisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[25] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: HR				
median (full range (min-max))	2.93 (1 to 6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alpelisib PK parameters: AUC0-24, AUClast at cycle 4 day 1

End point title	Alpelisib PK parameters: AUC0-24, AUClast at cycle 4 day 1[26]

End point description:

Summary of primary PK parameters for alpelisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[26] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	5			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0-24 (n = 2) AUClast (n = 2)	38000 (± 13.2) 38000 (± 13.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Alpelisib PK parameter: Cmax at cycle 4 day 1

End point title	Alpelisib PK parameter: Cmax at cycle 4 day 1[27]

End point description:

Summary of primary PK parameters for alpelisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[27] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	5[28]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	3260 (± 26.7)			

Notes:

[28] - n = 2

Statistical analyses

No statistical analyses for this end point

Secondary: Alpelisib PK parameter: Tmax at cycle 4 day 1

End point title	Alpelisib PK parameter: Tmax at cycle 4 day 1[29]

End point description:

Summary of primary PK parameters for alpelisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[29] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	5[30]			
Units: hr				
median (full range (min-max))	2.99 (2.98 to 3)			

Notes:

[30] - n = 2

Statistical analyses

No statistical analyses for this end point

Secondary: Letrozole and PK parameters: AUC0-24, AUClast at cycle 1 day 1

End point title	Letrozole and PK parameters: AUC0-24, AUClast at cycle 1 day 1[31]

End point description:

Summary of primary PK parameters for Letrozole plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[31] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	15		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0 - 24 (n = 3, 10)	433 (± 36.3)	427 (± 28.8)		
AUClast (n= 5, 14)	314 (± 96.9)	347 (± 49.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Letrozole PK parameter: Cmax at cycle 1 day 1

End point title	Letrozole PK parameter: Cmax at cycle 1 day 1[32]

End point description:

Summary of primary PK parameters for letrozole plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[32] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	15[33]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	30.2 (± 33.2)	28 (± 42.3)		

Notes:

[33] - n =14

Statistical analyses

No statistical analyses for this end point

Secondary: Letrozole PK parameter: Tmax at cycle 1 day 1

End point title	Letrozole PK parameter: Tmax at cycle 1 day 1[34]

End point description:

Summary of primary PK parameters for letrozole plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[34] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	15		
Units: hr				
median (full range (min-max))	1.03 (1 to 3)	2.25 (1 to 24.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Letrozole PK parameters: AUC0-24, AUClast at cycle 4 day 1

End point title	Letrozole PK parameters: AUC0-24, AUClast at cycle 4 day 1[35]
End point description:	
Summary of primary PK parameters for Letrozole plasma concentration	
End point type	Secondary
End point timeframe:	
Cycle 4 Day 1	

Notes:

[35] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	15		
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0-24 (n = 2, 8)	1280 (± 18)	1810 (± 33.1)		
AUClast (n = 2, 13)	1280 (± 17.9)	1440 (± 66.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Letrozole PK parameter: Cmax at cycle 4 day 1

End point title	Letrozole PK parameter: Cmax at cycle 4 day 1[36]
End point description:	
Summary of primary PK parameters for letrozole plasma concentration	
End point type	Secondary
End point timeframe:	
Cycle 4 Day 1	

Notes:

[36] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[37]	15[38]		
Units: ng/mL				
geometric mean (geometric coefficient of variation)	75.6 (± 6.84)	103 (± 30)		

Notes:

[37] - n = 2

[38] - n = 13

Statistical analyses

No statistical analyses for this end point

Secondary: Letrozole PK parameter: Tmax at cycle 4 day 1

End point title	Letrozole PK parameter: Tmax at cycle 4 day 1[39]

End point description:

Summary of primary PK parameters for letrozole plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[39] - 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: No statistical analysis was planned for this endpoint

End point values	Alpelisib + Letrozole	Placebo + Letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5[40]	15[41]		
Units: hr				
median (full range (min-max))	2 (1 to 3)	1.17 (1 to 6)		

Notes:

[40] - n = 2

[41] - n = 13

Statistical analyses

No statistical analyses for this end point

Secondary: Buparlisib PK parameters: AUC0-24, AUClast at cycle 1 day 1

End point title	Buparlisib PK parameters: AUC0-24, AUClast at cycle 1 day

End point description:

Summary of primary PK parameters for Buparlisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[42] - 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: No statistical analysis was planned for this endpoint

End point values	Buparlisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: ng*hr/mL				
geometric mean (geometric coefficient of variation)				
AUC0-24 (n = 8)| AUClast (n = 9)|	6420 (± 60) 4820 (± 123)			

Statistical analyses

No statistical analyses for this end point

Secondary: Buparlisib PK parameter: Cmax at cycle 1 day 1

End point title	Buparlisib PK parameter: Cmax at cycle 1 day 1[43]

End point description:

Summary of primary PK parameters for buparlisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[43] - 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: No statistical analysis was planned for this endpoint

End point values	Buparlisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	10[44]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	760 (± 86.7)			

Notes:

[44] - n = 9

Statistical analyses

No statistical analyses for this end point

Secondary: Buparlisib PK parameter: Tmax at cycle 1 day 1

End point title	Buparlisib PK parameter: Tmax at cycle 1 day 1[45]

End point description:

Summary of primary PK parameters for buparlisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 1 Day 1

Notes:

[45] - 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: No statistical analysis was planned for this endpoint

End point values	Buparlisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	10[46]			
Units: hr				
median (full range (min-max))	1.03 (0.5 to 3.5)			

Notes:

[46] - n = 9

Statistical analyses

No statistical analyses for this end point

Secondary: Buparlisib PK parameter: AUClast at cycle 4 day 1

End point title	Buparlisib PK parameter: AUClast at cycle 4 day 1[47]

End point description:

Summary of primary PK parameters for Buparlisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[47] - 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: No statistical analysis was planned for this endpoint

End point values	Buparlisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	10[48]			
Units: ng*hr/mL				
median (full range (min-max))	10400 (10400 to 10400)			

Notes:

[48] - n = 1

Statistical analyses

No statistical analyses for this end point

Secondary: Buparlisb PK parameter: Cmax at cycle 4 day 1

End point title	Buparlisb PK parameter: Cmax at cycle 4 day 1[49]

End point description:

Summary of primary PK parameters for buparlisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[49] - 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: No statistical analysis was planned for this endpoint

End point values	Buparlisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	10[50]			
Units: ng/mL				
median (full range (min-max))	610 (610 to 610)			

Notes:

[50] - n = 1

Statistical analyses

No statistical analyses for this end point

Secondary: Buparlisib PK parameter: Tmax at cycle 4 day 1

End point title	Buparlisib PK parameter: Tmax at cycle 4 day 1[51]

End point description:

Summary of primary PK parameters for buparlisib plasma concentration

End point type	Secondary

End point timeframe:

Cycle 4 Day 1

Notes:

[51] - 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: No statistical analysis was planned for this endpoint

End point values	Buparlisib + Letrozole			
Subject group type	Reporting group			
Number of subjects analysed	10[52]			
Units: hr				
median (full range (min-max))	3 (3 to 3)			

Notes:

[52] - n = 1

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse Events reported in this record are on-treatment events (from first dose of study treatment to last dose of study treatment + 30 days).

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups

Reporting group title	Alpelisib + Letrozole
Reporting group description:	
Alpelisib + Letrozole	
Reporting group title	Buparlisib + Letrozole
Reporting group description:	
Buparlisib + Letrozole	
Reporting group title	Placebo + Letrozole
Reporting group description:	
Placebo + Letrozole	

Serious adverse events	Alpelisib + Letrozole	Buparlisib + Letrozole	Placebo + Letrozole
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 130 (16.15%)	22 / 81 (27.16%)	6 / 125 (4.80%)
number of deaths (all causes)	1	0	1
number of deaths resulting from adverse events	0	0	0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			

subjects affected / exposed	2 / 130 (1.54%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 2	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised oedema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 130 (1.54%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sudden death			
subjects affected / exposed	0 / 130 (0.00%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 130 (1.54%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Epistaxis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	0 / 130 (0.00%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	2 / 130 (1.54%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 130 (0.00%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 130 (0.00%)	7 / 81 (8.64%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	7 / 7	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 130 (0.00%)	6 / 81 (7.41%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	6 / 6	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ejection fraction decreased			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Contusion			
subjects affected / exposed	0 / 130 (0.00%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post procedural haematoma			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 130 (0.00%)	2 / 81 (2.47%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorder			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stress cardiomyopathy			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			

subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	0 / 130 (0.00%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Iritis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 130 (0.77%)	2 / 81 (2.47%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	1 / 130 (0.77%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Stomatitis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Hepatotoxicity			
subjects affected / exposed	0 / 130 (0.00%)	3 / 81 (3.70%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertransaminasaemia			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pruritus			
subjects affected / exposed	2 / 130 (1.54%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash			
subjects affected / exposed	3 / 130 (2.31%)	2 / 81 (2.47%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	3 / 3	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rash maculo-papular			
subjects affected / exposed	2 / 130 (1.54%)	2 / 81 (2.47%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin necrosis			
subjects affected / exposed	0 / 130 (0.00%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Ureterolithiasis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Appendicitis			
subjects affected / exposed	0 / 130 (0.00%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	1 / 125 (0.80%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 130 (0.77%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	2 / 130 (1.54%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	7 / 130 (5.38%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	7 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperuricaemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Hyponatraemia			
subjects affected / exposed	1 / 130 (0.77%)	0 / 81 (0.00%)	0 / 125 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Alpelisib + Letrozole	Buparlisib + Letrozole	Placebo + Letrozole
Total subjects affected by non-serious adverse events			
subjects affected / exposed	126 / 130 (96.92%)	80 / 81 (98.77%)	106 / 125 (84.80%)
Vascular disorders			
Hot flush			
subjects affected / exposed	8 / 130 (6.15%)	12 / 81 (14.81%)	31 / 125 (24.80%)
occurrences (all)	8	12	32
Hypertension			
subjects affected / exposed	16 / 130 (12.31%)	10 / 81 (12.35%)	8 / 125 (6.40%)
occurrences (all)	24	13	16
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	21 / 130 (16.15%)	16 / 81 (19.75%)	17 / 125 (13.60%)
occurrences (all)	23	18	20
Chills			
subjects affected / exposed	7 / 130 (5.38%)	8 / 81 (9.88%)	5 / 125 (4.00%)
occurrences (all)	8	9	6
Fatigue			
subjects affected / exposed	53 / 130 (40.77%)	30 / 81 (37.04%)	42 / 125 (33.60%)
occurrences (all)	60	35	46
Mucosal dryness			
subjects affected / exposed	7 / 130 (5.38%)	2 / 81 (2.47%)	0 / 125 (0.00%)
occurrences (all)	7	2	0
Oedema peripheral			
subjects affected / exposed	9 / 130 (6.92%)	4 / 81 (4.94%)	4 / 125 (3.20%)
occurrences (all)	10	4	4
Pyrexia			

subjects affected / exposed	12 / 130 (9.23%)	1 / 81 (1.23%)	3 / 125 (2.40%)
occurrences (all)	14	1	3
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	4 / 130 (3.08%)	8 / 81 (9.88%)	10 / 125 (8.00%)
occurrences (all)	4	9	11
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	9 / 130 (6.92%)	8 / 81 (9.88%)	9 / 125 (7.20%)
occurrences (all)	9	8	9
Psychiatric disorders			
Anxiety			
subjects affected / exposed	10 / 130 (7.69%)	16 / 81 (19.75%)	10 / 125 (8.00%)
occurrences (all)	12	18	11
Depression			
subjects affected / exposed	5 / 130 (3.85%)	12 / 81 (14.81%)	3 / 125 (2.40%)
occurrences (all)	5	14	4
Insomnia			
subjects affected / exposed	15 / 130 (11.54%)	8 / 81 (9.88%)	17 / 125 (13.60%)
occurrences (all)	16	8	17
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	14 / 130 (10.77%)	49 / 81 (60.49%)	3 / 125 (2.40%)
occurrences (all)	17	52	4
Aspartate aminotransferase increased			
subjects affected / exposed	11 / 130 (8.46%)	44 / 81 (54.32%)	2 / 125 (1.60%)
occurrences (all)	12	54	3
Blood bilirubin increased			
subjects affected / exposed	2 / 130 (1.54%)	6 / 81 (7.41%)	1 / 125 (0.80%)
occurrences (all)	3	6	1
Blood creatinine increased			
subjects affected / exposed	12 / 130 (9.23%)	1 / 81 (1.23%)	4 / 125 (3.20%)
occurrences (all)	12	1	6
Blood glucose increased			

subjects affected / exposed	12 / 130 (9.23%)	3 / 81 (3.70%)	2 / 125 (1.60%)
occurrences (all)	17	3	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	5 / 130 (3.85%)	6 / 81 (7.41%)	1 / 125 (0.80%)
occurrences (all)	5	6	1
Weight decreased			
subjects affected / exposed	16 / 130 (12.31%)	10 / 81 (12.35%)	3 / 125 (2.40%)
occurrences (all)	18	10	4
Injury, poisoning and procedural complications			
Procedural pain			
subjects affected / exposed	2 / 130 (1.54%)	5 / 81 (6.17%)	9 / 125 (7.20%)
occurrences (all)	2	5	10
Cardiac disorders			
Tachycardia			
subjects affected / exposed	3 / 130 (2.31%)	5 / 81 (6.17%)	1 / 125 (0.80%)
occurrences (all)	3	5	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 130 (5.38%)	22 / 81 (27.16%)	19 / 125 (15.20%)
occurrences (all)	8	25	22
Dysgeusia			
subjects affected / exposed	24 / 130 (18.46%)	11 / 81 (13.58%)	7 / 125 (5.60%)
occurrences (all)	27	12	7
Headache			
subjects affected / exposed	26 / 130 (20.00%)	10 / 81 (12.35%)	16 / 125 (12.80%)
occurrences (all)	31	14	19
Memory impairment			
subjects affected / exposed	2 / 130 (1.54%)	5 / 81 (6.17%)	2 / 125 (1.60%)
occurrences (all)	2	5	2
Paraesthesia			
subjects affected / exposed	8 / 130 (6.15%)	2 / 81 (2.47%)	4 / 125 (3.20%)
occurrences (all)	8	2	4
Tremor			
subjects affected / exposed	0 / 130 (0.00%)	8 / 81 (9.88%)	1 / 125 (0.80%)
occurrences (all)	0	10	1
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	5 / 130 (3.85%)	5 / 81 (6.17%)	6 / 125 (4.80%)
occurrences (all)	5	6	7
Eye disorders			
Vision blurred			
subjects affected / exposed	9 / 130 (6.92%)	3 / 81 (3.70%)	0 / 125 (0.00%)
occurrences (all)	9	3	0
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	3 / 130 (2.31%)	6 / 81 (7.41%)	4 / 125 (3.20%)
occurrences (all)	3	6	4
Abdominal pain			
subjects affected / exposed	7 / 130 (5.38%)	5 / 81 (6.17%)	4 / 125 (3.20%)
occurrences (all)	9	6	4
Abdominal pain upper			
subjects affected / exposed	5 / 130 (3.85%)	7 / 81 (8.64%)	4 / 125 (3.20%)
occurrences (all)	5	7	6
Constipation			
subjects affected / exposed	5 / 130 (3.85%)	7 / 81 (8.64%)	13 / 125 (10.40%)
occurrences (all)	5	11	14
Diarrhoea			
subjects affected / exposed	66 / 130 (50.77%)	29 / 81 (35.80%)	19 / 125 (15.20%)
occurrences (all)	106	44	26
Dry mouth			
subjects affected / exposed	14 / 130 (10.77%)	5 / 81 (6.17%)	4 / 125 (3.20%)
occurrences (all)	15	5	4
Dyspepsia			
subjects affected / exposed	11 / 130 (8.46%)	11 / 81 (13.58%)	6 / 125 (4.80%)
occurrences (all)	13	12	6
Nausea			
subjects affected / exposed	57 / 130 (43.85%)	37 / 81 (45.68%)	23 / 125 (18.40%)
occurrences (all)	73	43	25
Stomatitis			
subjects affected / exposed	42 / 130 (32.31%)	18 / 81 (22.22%)	5 / 125 (4.00%)
occurrences (all)	50	19	6
Vomiting			

subjects affected / exposed	23 / 130 (17.69%)	6 / 81 (7.41%)	6 / 125 (4.80%)
occurrences (all)	30	9	6
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	28 / 130 (21.54%)	3 / 81 (3.70%)	7 / 125 (5.60%)
occurrences (all)	28	3	7
Dry skin			
subjects affected / exposed	19 / 130 (14.62%)	14 / 81 (17.28%)	4 / 125 (3.20%)
occurrences (all)	21	15	4
Pruritus			
subjects affected / exposed	22 / 130 (16.92%)	18 / 81 (22.22%)	9 / 125 (7.20%)
occurrences (all)	23	18	10
Rash			
subjects affected / exposed	58 / 130 (44.62%)	31 / 81 (38.27%)	10 / 125 (8.00%)
occurrences (all)	82	45	11
Rash maculo-papular			
subjects affected / exposed	22 / 130 (16.92%)	9 / 81 (11.11%)	3 / 125 (2.40%)
occurrences (all)	26	12	3
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 130 (8.46%)	13 / 81 (16.05%)	34 / 125 (27.20%)
occurrences (all)	12	13	41
Back pain			
subjects affected / exposed	1 / 130 (0.77%)	7 / 81 (8.64%)	11 / 125 (8.80%)
occurrences (all)	2	8	13
Muscle spasms			
subjects affected / exposed	13 / 130 (10.00%)	5 / 81 (6.17%)	5 / 125 (4.00%)
occurrences (all)	16	5	5
Musculoskeletal pain			
subjects affected / exposed	2 / 130 (1.54%)	4 / 81 (4.94%)	7 / 125 (5.60%)
occurrences (all)	2	4	8
Myalgia			
subjects affected / exposed	6 / 130 (4.62%)	4 / 81 (4.94%)	13 / 125 (10.40%)
occurrences (all)	6	4	13
Infections and infestations			

Urinary tract infection			
subjects affected / exposed	15 / 130 (11.54%)	7 / 81 (8.64%)	7 / 125 (5.60%)
occurrences (all)	19	9	8
Viral upper respiratory tract infection			
subjects affected / exposed	5 / 130 (3.85%)	5 / 81 (6.17%)	13 / 125 (10.40%)
occurrences (all)	5	5	14
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	40 / 130 (30.77%)	25 / 81 (30.86%)	10 / 125 (8.00%)
occurrences (all)	41	28	10
Hyperglycaemia			
subjects affected / exposed	69 / 130 (53.08%)	38 / 81 (46.91%)	8 / 125 (6.40%)
occurrences (all)	116	51	17
Hypokalaemia			
subjects affected / exposed	9 / 130 (6.92%)	1 / 81 (1.23%)	0 / 125 (0.00%)
occurrences (all)	9	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
06 December 2013	This protocol amendment was implemented before the inclusion of the first subject. • Revised the starting dose of alpelisib from 350 mg QD to 300 mg QD and corresponding dose reduction guidelines. • Changed study inclusion/exclusion criteria, concomitant medications, dose adjustments and follow up of toxicities. • Included additional analyses for safety. Administrative changes are made for clarification and typographical errors had been corrected.
29 January 2015	Amendment 2, issued when 76 subjects had been randomized in the study. •Revised the dosing schedule of buparlisib, from 100 mg QD to 100 mg QD 5 days on/2 days off. •Modified the guidelines for pneumonitis management that had been revised based on the Urgent Safety Measure released on 19-Dec-2014 following accumulation of pneumonitis cases up to nine (including three with fatal outcome) within the alpelisib development program. The most recent fatal case was reported from the CLJM716X2103 trial (alpelisib in combination with the anti-HER-3 monoclonal antibody LJM716).” •Modified and clarified some of the inclusion/exclusion criteria. •Updated clinical efficacy and safety data of both buparlisib and alpelisib as a result of new available data and in alignment with the latest Buparlisib and alpelisib Investigators’ Brochure updates. •Made administrative changes for clarification and typographical errors have been corrected.
09 February 2015	The main purpose of this protocol amendment was to correct a typo identified in Inclusion criteria #4 (“T1c-Tc” to “T1c-T3”) and #13 (formatting issues).
20 July 2015	This amendment was issued when 146 subjects had been randomized in the study. The main purpose of this amendment was to provide additional guidance to Investigators around management of liver toxicities.

12 February 2016	This amendment was issued when 241 subjects had been randomized in the study. Of these, 121 subjects had been randomized to buparlisib/buparlisib-placebo arms, and 120 subjects had been randomized to alpelisib/ alpelisib-placebo. The main purpose of this amendment was to introduce the following key changes: •Updated the clinical study protocol according to the decision made by the Sponsor on 22-Dec-2015 to stop permanently the accrual in the buparlisib/buparlisib-placebo treatment arms. •Changed the assessment of the anti-tumor activity of buparlisib/buparlisib-placebo plus letrozole into an exploratory objective. •Changed the ORR from being secondary to primary endpoint. •Changed the assessment of the anti-tumor activity of alpelisib plus letrozole versus letrozole alone on pCR and ORR by PIK3CA status based on circulating tumor DNA (ctDNA), from exploratory to secondary objective. •Stopped the conduct of the central review for pathological response. •Implemented regular safety review of unblinded data performed by a DMC •Updated the inclusion criteria with regards to baseline glucose metabolism parameters, potassium, and values of amylase and lipase. •Retired the exclusion criteria related to psychiatric disorders and viral hepatitis, and update the exclusion criterion on uncontrolled medical conditions. •Updated the safety monitoring and guidance for the management of hyperglycemia, skin toxicity, and pancreatitis •Revised and updated the Appendix 14-1 "List of concomitant medications" due to a recent re-classification of drugs with QT prolongation •Updated the language of some protocol sections as part of a general update implemented across the program (e.g. safety monitoring for liver toxicity; language for Adverse Eventsreporting)
04 May 2016	This protocol amendment was classified as non-substantial. The purpose of this protocol amendment was to correct formatting error of "Table 6-4: Cardiac QTC prolongation
18 October 2016	This amendment was issued when 325 subjects have been randomized in study. Of these, 204 subjects have been randomized to alpelisib/alpelisib-placebo. All 121 subjects randomized to buparlisib/buparlisib-placebo arm had discontinued study treatment. PIK3CA wild-type cohort enrollment was completed and 7 subjects remained to be enrolled in the PIK3CA mutant cohort. The main purpose of this amendment was to introduce the following key changes: - Provided more detailed treatment guidance for AE of hyperglycemia and update on AE management for skin toxicity following an advisory-board meeting recommendation - Updated the general administration guidelines for alpelisib/placebo based on a food effect and acid reducing agents (ARA) drug-drug interaction (DDI) study: alpelisib must be taken with a meal regardless of composition or overall calorie intake. A staggered approach for co-administration of alpelisib with acid reducing agents is no longer required

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/CtrdWeb/home.novfor complete trial results.

Notes: