Clinical trial results:
SOLAR-1: A Phase III randomized double-blind, placebo controlled study of alpelisib in combination with fulvestrant for men and postmenopausal women with hormone receptor positive, HER2-negative advanced breast cancer which progressed on or after aromatase inhibitor treatment

Summary

EudraCT number	2015-000340-42
Trial protocol	DE SE AT NL CZ HU IT BE FR ES GR GB BG PT DK
Global end of trial date	09 June 2023

Results information

Result version number	v1 (current)
This version publication date	12 June 2024
First version publication date	12 June 2024

Trial information

Trial identification

Sponsor protocol code	CBYL719C2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02437318
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Novartis Campus,, 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	09 June 2023
Is this the analysis of the primary completion data?	No

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

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to determine whether treatment with alpelisib in combination with fulvestrant prolongs progression-free survival (PFS) based on local investigator assessment compared to treatment with placebo in combination with fulvestrant for subjects with advanced breast cancer with a PIK3CA mutation.

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	23 July 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 10
Country: Number of subjects enrolled	Australia: 7
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 21
Country: Number of subjects enrolled	Brazil: 7
Country: Number of subjects enrolled	Bulgaria: 14
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Chile: 11
Country: Number of subjects enrolled	Czechia: 6
Country: Number of subjects enrolled	France: 54
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Greece: 4
Country: Number of subjects enrolled	Hong Kong: 2
Country: Number of subjects enrolled	Hungary: 27
Country: Number of subjects enrolled	India: 6
Country: Number of subjects enrolled	Israel: 30
Country: Number of subjects enrolled	Italy: 28
Country: Number of subjects enrolled	Japan: 68

Country: Number of subjects enrolled	Korea, Republic of: 25
Country: Number of subjects enrolled	Lebanon: 8
Country: Number of subjects enrolled	Mexico: 4
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Peru: 11
Country: Number of subjects enrolled	Romania: 9
Country: Number of subjects enrolled	Russian Federation: 12
Country: Number of subjects enrolled	Spain: 65
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Taiwan: 13
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 53
Worldwide total number of subjects	572
EEA total number of subjects	280

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)	321
From 65 to 84 years	246
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 198 centers across 31 countries

Pre-assignment

Screening details:

One subject in the PIK3CA mutant cohort, who was randomized to the placebo + fulvestrant arm, did not receive study treatment due to a protocol deviation.

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, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Alpelisib + fulvestrant

Arm description:

Subjects treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Arm type	Experimental
Investigational medicinal product name	Alpelisib
Investigational medicinal product code	BYL719
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

300 mg of alpelisib tablets for oral use administered once daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Placebo tablets for oral use administered once daily

Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg of fulvestrant administered via intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle

Arm title	Placebo + fulvestrant

Arm description:

Subjects treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Arm type	Placebo
Investigational medicinal product name	Fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg of fulvestrant administered via intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle

Number of subjects in period 1	Alpelisib + fulvestrant	Placebo + fulvestrant
Started	284	288
Treated	284	287
PIK3CA mutant cohort by tumor tissue	169	172
PIK3CA non-mutant cohort by tumor tissue	115	116
PIK3CA mutant cohort by ctDNA	92	94
PIK3CA non-mutant cohort by ctDNA	181	182
Completed	0	0
Not completed	284	288
Adverse event, serious fatal	4	4
Physician decision	29	22
Adverse event, non-fatal	14	4
Protocol deviation	5	7
Study terminated by sponsor	1	-
Progressive disease	207	240
Subject/guardian decision	24	11

Baseline characteristics

Reporting groups	
Reporting group title	Alpelisib + fulvestrant
Reporting group description:	
Subjects treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Reporting group title	Placebo + fulvestrant
Reporting group description:	
Subjects treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	

Reporting group values	Alpelisib + fulvestrant	Placebo + fulvestrant	Total
Number of subjects	284	288	572
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	167	154	321
From 65-84 years	116	130	246
85 years and over	1	4	5
Age Continuous Units: Years			
arithmetic mean	62.6	63.3	
standard deviation	± 9.74	± 10.26	-
Sex: Female, Male Units: Participants			
Female	283	288	571
Male	1	0	1
Race/Ethnicity, Customized Units: Subjects			
White	199	178	377
Asian	59	66	125
Black or African American	2	6	8
American Indian or Alaska	1	4	5
Other	9	17	26
Unknown	14	17	31

Subject analysis sets	
Subject analysis set title	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer with a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer with a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA non-mutant cohort by tumor tissue:alpelisib+fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer without a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA non-mutant cohort by tumor tissue:placebo+fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer without a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA mutant determined by ctDNA: alpelisib + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer with a PIK3CA mutation (measured in ctDNA) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA mutant determined by ctDNA: placebo + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer with a PIK3CA mutation (measured in ctDNA) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA non-mutant determined by ctDNA: alpelisib + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer without a PIK3CA mutation (measured in ctDNA) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA non-mutant determined by ctDNA: placebo + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer without a PIK3CA mutation (measured in ctDNA) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Reporting group values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant	PIK3CA non-mutant cohort by tumor tissue:alpelisib+fulvestrant
Number of subjects	169	172	115

Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	11.0	5.7	7.43
standard deviation	±	±	±
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Asian Black or African American American Indian or Alaska Other Unknown			

Reporting group values	PIK3CA non-mutant cohort by tumor tissue:placebo+fulvestrant	PIK3CA mutant determined by ctDNA: alpelisib + fulvestrant	PIK3CA mutant determined by ctDNA: placebo + fulvestrant
Number of subjects	116	92	94
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	7.23	10.9	3.7
standard deviation	±	±	±

Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Asian Black or African American American Indian or Alaska Other Unknown			

Reporting group values	PIK3CA non-mutant determined by ctDNA: alpelisib + fulvestrant	PIK3CA non-mutant determined by ctDNA: placebo + fulvestrant	
Number of subjects	181	182	
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	9.0	7.4	
standard deviation	±	±	
Sex: Female, Male Units: Participants			
Female Male			
Race/Ethnicity, Customized Units: Subjects			
White Asian Black or African American American Indian or Alaska Other Unknown			

End points

End points reporting groups

Reporting group title	Alpelisib + fulvestrant
Reporting group description:	
Subjects treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Reporting group title	Placebo + fulvestrant
Reporting group description:	
Subjects treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with advanced breast cancer with a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with advanced breast cancer with a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA non-mutant cohort by tumor tissue:alpelisib+fulvestrant
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with advanced breast cancer without a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA non-mutant cohort by tumor tissue:placebo+fulvestrant
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with advanced breast cancer without a PIK3CA mutation (based on central testing of hotspot-mutations in tumor tissue) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA mutant determined by ctDNA: alpelisib + fulvestrant
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with advanced breast cancer with a PIK3CA mutation (measured in ctDNA) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA mutant determined by ctDNA: placebo + fulvestrant
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Subjects with advanced breast cancer with a PIK3CA mutation (measured in ctDNA) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)	
Subject analysis set title	PIK3CA non-mutant determined by ctDNA: alpelisib + fulvestrant

Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer without a PIK3CA mutation (measured in ctDNA) treated with alpelisib (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Subject analysis set title	PIK3CA non-mutant determined by ctDNA: placebo + fulvestrant
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Subjects with advanced breast cancer without a PIK3CA mutation (measured in ctDNA) treated with placebo (300 mg; oral; once daily) in combination with fulvestrant (500 mg; intramuscular injection on Day 1 and Day 15 of Cycle 1, and then Day 1 of each subsequent 28-day cycle)

Primary: Progression-free survival (PFS) per Investigator assessment in the PIK3CA mutant cohort

End point title	Progression-free survival (PFS) per Investigator assessment in the PIK3CA mutant cohort

End point description:

PFS was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS was assessed via a local radiology assessment according to RECIST 1.1. If a patient did not have an event, PFS was censored at the date of last adequate tumor assessment.
The PFS distribution was estimated using Kaplan-Meier methodology.
Progression was defined as at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Primary

End point timeframe:

Once approximately 243 PFS events in the PIK3CA mutant cohort had been observed, up to 33.3 months

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	169	172		
Units: Months				
median (confidence interval 95%)	11.0 (7.49 to 14.52)	5.7 (3.65 to 7.36)		

Statistical analyses

Statistical analysis title	PFS analysis
Comparison groups	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant v PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant

Number of subjects included in analysis	341
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00065 [1]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.5
upper limit	0.85

Notes:

[1] - (one-sided)

Secondary: Overall survival (OS) in the PIK3CA mutant cohort

End point title	Overall survival (OS) in the PIK3CA mutant cohort

End point description:

OS was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last known date patient alive.
The OS distribution was estimated using Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

Once approximately 178 deaths in the PIK3CA mutant cohort had been observed, up to 55.7 months

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	169	172		
Units: Months				
median (confidence interval 95%)	39.3 (34.10 to 44.85)	31.4 (26.78 to 41.30)		

Statistical analyses

No statistical analyses for this end point

Secondary: Overall response rate (ORR) per Investigator assessment

End point title	Overall response rate (ORR) per Investigator assessment

End point description:

ORR was defined as the percentage of patients with best overall response of complete response (CR) or partial response (PR) based on local investigator’s assessment according to RECIST 1.1.
CR: Disappearance of all non-nodal target and non-target lesions. In addition, any pathological lymph nodes assigned as target and non-target lesions must have a reduction in short axis to < 10 mm.
PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

End point type	Secondary
End point timeframe:	
Up to 56.4 months	

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169	172	115	116
Units: Percentage of participants				
number (confidence interval 95%)	26.6 (20.1 to 34.0)	13.4 (8.7 to 19.4)	20.9 (13.9 to 29.4)	12.9 (7.4 to 20.4)

Statistical analyses

No statistical analyses for this end point

Secondary: OS in the PIK3CA non-mutant cohort

End point title	OS in the PIK3CA non-mutant cohort
End point description:	
OS was defined as the time from date of randomization to date of death due to any cause. If a patient was not known to have died, survival was censored at the date of last known date patient alive. The OS distribution was estimated using Kaplan-Meier methodology.	
End point type	Secondary
End point timeframe:	
Up to 56.4 months	

End point values	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	115	116		
Units: Months				
median (confidence interval 95%)	37.29 (27.89 to 45.47)	34.30 (26.81 to 39.03)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per investigator assessment in the PIK3CA non-mutant cohort

End point title	PFS per investigator assessment in the PIK3CA non-mutant cohort

End point description:

PFS was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS was assessed via a local radiology assessment according to RECIST 1.1. If a patient did not have an event, PFS was censored at the date of last adequate tumor assessment.
The PFS distribution was estimated using Kaplan-Meier methodology.
Progression was defined as at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

Up to 56.4 months

End point values	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	115	116		
Units: Months				
median (confidence interval 95%)	7.43 (5.55 to 10.84)	7.23 (5.06 to 9.17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR) per Investigator assessment

End point title	Clinical benefit rate (CBR) per Investigator assessment

End point description:

Clinical benefit rate was defined as the percentage of patients with a best overall response of CR or PR or stable disease (SD) or Non-CR/Non-PD lasting more than 24 weeks based on local investigator assessment according to RECIST 1.1.
CR: Disappearance of all non-nodal target and non-target lesions. In addition, any pathological lymph nodes assigned as target and non-target lesions must have a reduction in short axis to < 10 mm.
PR: At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.
SD: Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease.

End point type	Secondary

End point timeframe:

Up to 56.4 months

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169	172	115	116
Units: Percentage of participants				
number (confidence interval 95%)	61.5 (53.8 to 68.9)	44.8 (37.2 to 52.5)	53.9 (44.4 to 63.2)	49.1 (39.7 to 58.6)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of Eastern Cooperative Oncology Group (ECOG) performance status (PS) score from baseline

End point title	Time to definitive deterioration of Eastern Cooperative Oncology Group (ECOG) performance status (PS) score from baseline

End point description:

ECOG PS categorized patients based on their ability to perform daily activities and self-care, with scores ranging from 0 to 5. A score of 0 indicated no restrictions in activity, while higher scores indicated increasing limitations. Time to definitive deterioration of ECOG PS by one score was defined as the time from the date of randomization to the date of the event, defined as experiencing at least one score lower than the baseline. A deterioration was considered definitive if no improvements in the ECOG PS were observed at a subsequent time. The Kaplan-Meier method was used to estimate the distribution. Patients receiving any further therapy prior to definitive worsening were censored at their date of last assessment prior to start of therapy. Patients that had not worsened at the data cutoff point were censored at the date of last assessment.
9999 indicates that the value was not estimable.

End point type	Secondary

End point timeframe:

From baseline up to 56.4 months

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169	172	115	116
Units: Months				
median (confidence interval 95%)	34.07 (26.32 to 9999)	9999 (22.11 to 9999)	9999 (13.83 to 9999)	40.44 (18.46 to 47.21)

Statistical analyses

No statistical analyses for this end point

Secondary: Time to 10% deterioration in the global health status (GHS) /Quality of Life (QOL) scale score of the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30)

End point title	Time to 10% deterioration in the global health status (GHS) /Quality of Life (QOL) scale score of the European Organization for Research and Treatment of Cancer's core quality of life questionnaire (EORTC QLQ-C30)

End point description:

The EORTC QLQ-C30 is a questionnaire that includes 5 functional scales, 3 symptom scales, 1 GHS/QoL scale, and 6 single items. GHS/QoL scale score ranges between 0 and 100. A high score for GHS/QoL represents better functioning or QoL.The time to definitive 10% deterioration was defined as the time from the date of randomization to the date of event, which was defined as at least 10% relative to baseline worsening of the GHS/QoL score (without further improvement above the threshold) or death due to any cause. The Kaplan-Meier method was used to estimate the distribution. If a patient had not had an event, time to deterioration was censored at the date of the last adequate QoL evaluation. 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From baseline up to 55.7 months

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	169	172	115	116
Units: Months				
median (confidence interval 95%)	18.14 (14.55 to 28.68)	19.98 (11.50 to 25.59)	7.39 (5.62 to 9999)	9.23 (3.94 to 13.17)

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the GHS/QOL scale score of the EORTC QLQ-C30

End point title	Change from baseline in the GHS/QOL scale score of the EORTC QLQ-C30

End point description:

The EORTC QLQ-C30 is a questionnaire that includes 5 functional scales, 3 symptom scales, 1 GHS/QoL

scale, and 6 single items. GHS/QoL scale score ranges between 0 and 100. A high score for GHS/QoL represents better functioning or QoL.The change from baseline in the GHS/QoL score was assessed. A positive change from baseline indicated improvement.
For each cohort, this analysis only included assessments up to the time point where there were at least 10 patients on each of the 2 treatment groups.
9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks after randomization during the first 18 months and thereafter every 12 weeks, up to 120 weeks.

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant	PIK3CA non-mutant cohort by tumor tissue:alpelisib +fulvestrant	PIK3CA non-mutant cohort by tumor tissue:placebo +fulvestrant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	142	140	98	92
Units: Score on a Scale				
least squares mean (standard error)				
Week 8 (n=142 / 140 / 98 / 92)	-2.477 (± 2.286)	-0.369 (± 2.324)	1.524 (± 2.578)	2.698 (± 2.601)
Week 16 (n=124 / 107 / 66 / 66)	-1.796 (± 2.349)	-2.685 (± 2.455)	2.866 (± 2.809)	1.700 (± 2.835)
Week 24 (n=105 / 81 / 46 / 34)	-3.010 (± 2.415)	-0.337 (± 2.587)	1.383 (± 3.087)	4.909 (± 3.385)
Week 32 (n=86 / 73 / 32 / 25)	-2.802 (± 2.519)	-0.891 (± 2.646)	1.063 (± 3.420)	4.345 (± 3.731)
Week 40 (n=75 / 62 / 12 / 20)	-2.815 (± 2.581)	-1.854 (± 2.739)	13.232 (± 4.783)	4.923 (± 4.003)
Week 48 (n=69 / 51 / 0 / 0)	-3.635 (± 2.621)	-1.460 (± 2.853)	9999 (± 9999)	9999 (± 9999)
Week 56 (n=59 / 45 / 0 / 0)	-1.617 (± 2.701)	0.248 (± 2.935)	9999 (± 9999)	9999 (± 9999)
Week 64 (n=47 / 42 / 0 / 0)	-1.937 (± 2.835)	-1.979 (± 2.984)	9999 (± 9999)	9999 (± 9999)
Week 72 (n=48 / 36 / 0 / 0)	-2.525 (± 2.823)	-1.526 (± 3.098)	9999 (± 9999)	9999 (± 9999)
Week 84 (n=40 / 34 / 0 / 0)	-1.135 (± 2.958)	-1.495 (± 3.143)	9999 (± 9999)	9999 (± 9999)
Week 96 (n=35/ 25 / 0 / 0)	-3.869 (± 3.054)	-3.581 (± 3.423)	9999 (± 9999)	9999 (± 9999)
Week 108 (n=26 / 21 / 0 / 0)	-2.158 (± 3.328)	-2.068 (± 3.609)	9999 (± 9999)	9999 (± 9999)
Week 120 (n=28 / 17 / 0 / 0)	-2.928 (± 3.251)	-2.593 (± 3.868)	9999 (± 9999)	9999 (± 9999)

Statistical analyses

No statistical analyses for this end point

Secondary: Trough plasma concentration of alpelisib

End point title	Trough plasma concentration of alpelisib[2]

End point description:

Pre-dose plasma concentrations of alpelisib were assessed. Only participants randomized to the alpelisib + fulvestrant arm were included in this analysis.

End point type	Secondary

End point timeframe:

Day 8 and Day 15 of Cycle 1, then Day 1 of Cycles 2, 4, 6 and 8. Cycle = 28 days

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: Only participants who were randomized to receive alpelisib were included in this analysis.

End point values	Alpelisib + fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	96			
Units: nanogram (ng)/ milliliter (mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 8	424 (± 41.1)			
Cycle 1 Day 15	468 (± 57.6)			
Cycle 2 Day 1	436 (± 53.4)			
Cycle 4 Day 1	458 (± 69.4)			
Cycle 6 Day 1	418 (± 57.1)			
Cycle 8 Day 1	469 (± 58.3)			

Statistical analyses

No statistical analyses for this end point

Secondary: Trough plasma concentration of fulvestrant

End point title	Trough plasma concentration of fulvestrant

End point description:

Pre-dose plasma concentrations of fulvestrant were assessed.

End point type	Secondary

End point timeframe:

Day 15 of Cycle 1, then Day 1 of Cycles 2, 4, 6 and 8. Cycle = 28 days

End point values	Alpelisib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	124	124		
Units: nanogram (ng)/ milliliter (mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 15	10.8 (± 43.5)	10.3 (± 51.0)		
Cycle 2 Day 1	14.0 (± 39.7)	14.7 (± 41.2)		
Cycle 4 Day 1	11.5 (± 32.2)	12.2 (± 29.8)		
Cycle 6 Day 1	12.6 (± 30.5)	14.0 (± 24.2)		

Cycle 8 Day 1	13.5 (± 35.2)	14.7 (± 23.2)		

Statistical analyses

No statistical analyses for this end point

Secondary: PFS per investigator criteria in subjects with PIK3CA mutation status measured in ctDNA at baseline

End point title	PFS per investigator criteria in subjects with PIK3CA mutation status measured in ctDNA at baseline

End point description:

PFS was defined as the time from the date of randomization to the date of the first documented progression or death due to any cause. PFS was assessed via a local radiology assessment according to RECIST 1.1. If a patient did not have an event, PFS was censored at the date of last adequate tumor assessment. The PFS distribution was estimated using Kaplan-Meier methodology.
Subjects were analyzed according to the PIK3CA mutation status (mutant or non-mutant) as identified using plasma ctDNA.
Progression was defined as at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Secondary

End point timeframe:

From baseline up to 56.4 months

End point values	PIK3CA mutant determined by ctDNA: alpelisib + fulvestrant	PIK3CA mutant determined by ctDNA: placebo + fulvestrant	PIK3CA non-mutant determined by ctDNA: alpelisib + fulvestrant	PIK3CA non-mutant determined by ctDNA: placebo + fulvestrant
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	92	94	181	182
Units: Months				
median (confidence interval 95%)	10.9 (7.03 to 15.28)	3.7 (2.27 to 6.11)	9.0 (7.23 to 11.01)	7.4 (5.55 to 9.20)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Updated PFS per Investigator assessment in the PIK3CA mutant cohort (longer follow-up)

End point title	Updated PFS per Investigator assessment in the PIK3CA mutant cohort (longer follow-up)

End point description:

PFS was defined as the time from the date of randomization to the date of the first documented

progression or death due to any cause. PFS was assessed via a local radiology assessment according to RECIST 1.1. If a patient did not have an event, PFS was censored at the date of last adequate tumor assessment.
The PFS distribution was estimated using Kaplan-Meier methodology.
This analysis was conducted at the time of the final OS analysis (when approximately 178 deaths in the PIK3CA mutant cohort had been achieved) and includes a longer follow-up time.
Progression was defined as at least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Other pre-specified

End point timeframe:

Up to 55.7 months

End point values	PIK3CA mutant cohort by tumor tissue: alpelisib + fulvestrant	PIK3CA mutant cohort by tumor tissue: placebo + fulvestrant		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	169	172		
Units: Months				
median (confidence interval 95%)	10.97 (7.49 to 14.52)	5.65 (3.65 to 7.36)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths

End point description:

Pre-treatment deaths were collected from day of participant’s informed consent to the day before first dose of study medication.
On-treatment deaths were collected from start of treatment to 30 days after last dose of study medication.
Post-treatment survival follow-up deaths were collected from day 31 after last dose of study treatment to end of study.

End point type	Post-hoc

End point timeframe:

Pre-treatment: Up to 35 days prior to treatment. On-treatment: Up to approx. 6.5 years. Post-treatment survival follow-up: Up to approx. 6.5 years

End point values	Alpelisib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	284	288		
Units: Participants				
Pre-treatment	0	0		
On-treatment	9	12		
Post-treatment survival follow-up	151	156		
All deaths	160	168		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study treatment to 30 days after last dose of treatment, up to approx. 6.5 years.

Adverse event reporting additional description:

Consistent with EudraCTdisclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting fromadverse 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	26.0

Reporting groups

Reporting group title	Placebo + fulvestrant (on-treatment)

Reporting group description:

AEs collected during on-treatment period (up to 30 days post-treatment)

Reporting group title	Alpelisib + fulvestrant (on-treatment)

Reporting group description:

AEs collected during on-treatment period (up to 30 days post-treatment)

Serious adverse events	Placebo + fulvestrant (on-treatment)	Alpelisib + fulvestrant (on-treatment)	
Total subjects affected by serious adverse events			
subjects affected / exposed	54 / 287 (18.82%)	110 / 284 (38.73%)	
number of deaths (all causes)	12	9	
number of deaths resulting from adverse events	0	1	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to meninges			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Tumour pain			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Thrombosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 287 (0.00%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	0 / 0	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mucosal inflammation			
subjects affected / exposed	0 / 287 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

General physical health deterioration			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adverse drug reaction			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypersensitivity			
subjects affected / exposed	0 / 287 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast			

disorders			
Pelvic pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (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			
Interstitial lung disease			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 287 (0.35%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aspiration			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchostenosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	4 / 287 (1.39%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	1 / 5	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
Haemoptysis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	5 / 287 (1.74%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	1 / 6	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	

Pulmonary embolism			
subjects affected / exposed	3 / 287 (1.05%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	1 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Bipolar disorder			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood creatinine increased			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoglobin decreased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lipase increased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Weight decreased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Jaw fracture			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation proctitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Arteriospasm coronary			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina pectoris			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sinus tachycardia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pericardial effusion			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			

subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhagic stroke			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Altered state of consciousness			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain oedema			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal cord compression			
subjects affected / exposed	2 / 287 (0.70%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Motor dysfunction			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 287 (0.00%)	6 / 284 (2.11%)	
occurrences causally related to treatment / all	0 / 0	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombotic microangiopathy			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 287 (0.70%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	2 / 287 (0.70%)	6 / 284 (2.11%)	
occurrences causally related to treatment / all	0 / 2	1 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	1 / 287 (0.35%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Constipation			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 287 (0.00%)	9 / 284 (3.17%)	
occurrences causally related to treatment / all	0 / 0	7 / 9	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallstone ileus			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ileus			

subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	2 / 287 (0.70%)	5 / 284 (1.76%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stomatitis			
subjects affected / exposed	0 / 287 (0.00%)	4 / 284 (1.41%)	
occurrences causally related to treatment / all	0 / 0	3 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	3 / 287 (1.05%)	5 / 284 (1.76%)	
occurrences causally related to treatment / all	0 / 4	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subileus			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hepatic failure			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis acute			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
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			
Dermatitis acneiform			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dermatitis allergic			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug eruption			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema			

subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erythema multiforme			
subjects affected / exposed	0 / 287 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			
subjects affected / exposed	0 / 287 (0.00%)	5 / 284 (1.76%)	
occurrences causally related to treatment / all	0 / 0	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash macular			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash maculo-papular			
subjects affected / exposed	0 / 287 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stevens-Johnson syndrome			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 287 (0.35%)	6 / 284 (2.11%)	
occurrences causally related to treatment / all	0 / 1	2 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			

subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	4 / 287 (1.39%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Muscular weakness			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal chest pain			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis of jaw			

subjects affected / exposed	2 / 287 (0.70%)	9 / 284 (3.17%)	
occurrences causally related to treatment / all	0 / 3	1 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal stenosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pulmonary tuberculosis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (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	6 / 287 (2.09%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 6	1 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
Peritonsillar abscess			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mediastinitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis intestinal haemorrhagic			

subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	2 / 287 (0.70%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess jaw			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal infection			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			

subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	1 / 287 (0.35%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin infection			
subjects affected / exposed	1 / 287 (0.35%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	3 / 287 (1.05%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 3	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	1 / 287 (0.35%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Decreased appetite			
subjects affected / exposed	0 / 287 (0.00%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			

subjects affected / exposed	3 / 287 (1.05%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetic ketoacidosis			
subjects affected / exposed	0 / 287 (0.00%)	2 / 284 (0.70%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
subjects affected / exposed	2 / 287 (0.70%)	0 / 284 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycaemia			
subjects affected / exposed	0 / 287 (0.00%)	28 / 284 (9.86%)	
occurrences causally related to treatment / all	0 / 0	30 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypochloraemia			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	1 / 287 (0.35%)	3 / 284 (1.06%)	
occurrences causally related to treatment / all	0 / 1	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ketoacidosis			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 287 (0.00%)	1 / 284 (0.35%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo + fulvestrant (on-treatment)	Alpelisib + fulvestrant (on-treatment)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	244 / 287 (85.02%)	280 / 284 (98.59%)	
Vascular disorders			
Lymphoedema			
subjects affected / exposed	6 / 287 (2.09%)	17 / 284 (5.99%)	
occurrences (all)	6	19	
Hypertension			
subjects affected / exposed	15 / 287 (5.23%)	29 / 284 (10.21%)	
occurrences (all)	18	34	
Hot flush			
subjects affected / exposed	19 / 287 (6.62%)	9 / 284 (3.17%)	
occurrences (all)	19	10	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	14 / 287 (4.88%)	46 / 284 (16.20%)	
occurrences (all)	20	60	
Mucosal inflammation			
subjects affected / exposed	4 / 287 (1.39%)	53 / 284 (18.66%)	
occurrences (all)	4	73	
Fatigue			
subjects affected / exposed	51 / 287 (17.77%)	73 / 284 (25.70%)	
occurrences (all)	58	87	
Asthenia			
subjects affected / exposed	40 / 287 (13.94%)	64 / 284 (22.54%)	
occurrences (all)	51	89	
Pyrexia			
subjects affected / exposed	16 / 287 (5.57%)	47 / 284 (16.55%)	
occurrences (all)	17	73	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	32 / 287 (11.15%)	27 / 284 (9.51%)	
occurrences (all)	36	33	

Cough			
subjects affected / exposed	28 / 287 (9.76%)	36 / 284 (12.68%)	
occurrences (all)	34	40	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	12 / 287 (4.18%)	22 / 284 (7.75%)	
occurrences (all)	12	25	
Investigations			
Lipase increased			
subjects affected / exposed	12 / 287 (4.18%)	21 / 284 (7.39%)	
occurrences (all)	21	29	
Gamma-glutamyltransferase increased			
subjects affected / exposed	23 / 287 (8.01%)	28 / 284 (9.86%)	
occurrences (all)	24	33	
Blood creatinine increased			
subjects affected / exposed	4 / 287 (1.39%)	36 / 284 (12.68%)	
occurrences (all)	4	45	
Aspartate aminotransferase increased			
subjects affected / exposed	18 / 287 (6.27%)	32 / 284 (11.27%)	
occurrences (all)	20	39	
Alanine aminotransferase increased			
subjects affected / exposed	18 / 287 (6.27%)	28 / 284 (9.86%)	
occurrences (all)	20	33	
Weight decreased			
subjects affected / exposed	7 / 287 (2.44%)	79 / 284 (27.82%)	
occurrences (all)	7	91	
Nervous system disorders			
Headache			
subjects affected / exposed	38 / 287 (13.24%)	53 / 284 (18.66%)	
occurrences (all)	57	76	
Dysgeusia			
subjects affected / exposed	8 / 287 (2.79%)	39 / 284 (13.73%)	
occurrences (all)	9	46	
Dizziness			
subjects affected / exposed	20 / 287 (6.97%)	27 / 284 (9.51%)	
occurrences (all)	21	33	

Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	20 / 287 (6.97%)	29 / 284 (10.21%)	
occurrences (all)	23	45	
Eye disorders			
Vision blurred			
subjects affected / exposed	2 / 287 (0.70%)	15 / 284 (5.28%)	
occurrences (all)	2	15	
Gastrointestinal disorders			
Dyspepsia			
subjects affected / exposed	17 / 287 (5.92%)	32 / 284 (11.27%)	
occurrences (all)	19	37	
Dry mouth			
subjects affected / exposed	13 / 287 (4.53%)	30 / 284 (10.56%)	
occurrences (all)	17	33	
Abdominal pain			
subjects affected / exposed	20 / 287 (6.97%)	33 / 284 (11.62%)	
occurrences (all)	22	49	
Abdominal pain upper			
subjects affected / exposed	13 / 287 (4.53%)	19 / 284 (6.69%)	
occurrences (all)	15	23	
Constipation			
subjects affected / exposed	37 / 287 (12.89%)	25 / 284 (8.80%)	
occurrences (all)	48	30	
Diarrhoea			
subjects affected / exposed	48 / 287 (16.72%)	167 / 284 (58.80%)	
occurrences (all)	72	376	
Nausea			
subjects affected / exposed	64 / 287 (22.30%)	133 / 284 (46.83%)	
occurrences (all)	82	203	
Vomiting			
subjects affected / exposed	27 / 287 (9.41%)	80 / 284 (28.17%)	
occurrences (all)	36	126	
Stomatitis			
subjects affected / exposed	20 / 287 (6.97%)	70 / 284 (24.65%)	
occurrences (all)	27	96	
Skin and subcutaneous tissue disorders			

Rash maculo-papular			
subjects affected / exposed	4 / 287 (1.39%)	39 / 284 (13.73%)	
occurrences (all)	5	49	
Rash			
subjects affected / exposed	20 / 287 (6.97%)	101 / 284 (35.56%)	
occurrences (all)	23	143	
Pruritus			
subjects affected / exposed	19 / 287 (6.62%)	54 / 284 (19.01%)	
occurrences (all)	22	71	
Erythema			
subjects affected / exposed	2 / 287 (0.70%)	19 / 284 (6.69%)	
occurrences (all)	2	20	
Dry skin			
subjects affected / exposed	10 / 287 (3.48%)	44 / 284 (15.49%)	
occurrences (all)	11	50	
Alopecia			
subjects affected / exposed	7 / 287 (2.44%)	58 / 284 (20.42%)	
occurrences (all)	8	60	
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	24 / 287 (8.36%)	29 / 284 (10.21%)	
occurrences (all)	25	32	
Osteonecrosis of jaw			
subjects affected / exposed	3 / 287 (1.05%)	15 / 284 (5.28%)	
occurrences (all)	4	18	
Myalgia			
subjects affected / exposed	9 / 287 (3.14%)	20 / 284 (7.04%)	
occurrences (all)	10	23	
Muscle spasms			
subjects affected / exposed	12 / 287 (4.18%)	23 / 284 (8.10%)	
occurrences (all)	12	28	
Bone pain			
subjects affected / exposed	19 / 287 (6.62%)	14 / 284 (4.93%)	
occurrences (all)	21	14	
Back pain			

subjects affected / exposed	43 / 287 (14.98%)	44 / 284 (15.49%)	
occurrences (all)	48	53	
Arthralgia			
subjects affected / exposed	56 / 287 (19.51%)	44 / 284 (15.49%)	
occurrences (all)	87	51	
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	13 / 287 (4.53%)	28 / 284 (9.86%)	
occurrences (all)	27	49	
Upper respiratory tract infection			
subjects affected / exposed	19 / 287 (6.62%)	15 / 284 (5.28%)	
occurrences (all)	22	27	
Nasopharyngitis			
subjects affected / exposed	26 / 287 (9.06%)	24 / 284 (8.45%)	
occurrences (all)	39	35	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	5 / 287 (1.74%)	25 / 284 (8.80%)	
occurrences (all)	7	31	
Decreased appetite			
subjects affected / exposed	30 / 287 (10.45%)	103 / 284 (36.27%)	
occurrences (all)	31	125	
Hyperglycaemia			
subjects affected / exposed	27 / 287 (9.41%)	182 / 284 (64.08%)	
occurrences (all)	44	429	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 February 2016	The main purpose of this protocol amendment was to modify the study design for the PIK3CA non-mutant cohort from pivotal to a proof-of-concept. The PIK3CA mutant cohort remained unchanged. Consequently the primary and key secondary objectives of the study were to compare the two treatment groups, based on PFS and OS respectively, for patients in the PIK3CA mutant cohort. Comparison of PFS and OS for patients in the PIK3CA non-mutant cohort was part of the secondary objectives
30 August 2016	The purpose of this amendment was to: - Modify the patient population to be enrolled in the study. Patients who relapsed more than 12 months from completion of (neo)adjuvant endocrine therapy with no treatment for metastatic disease will no longer be enrolled in the study - Modify the criteria to define futility at the interim analysis in the PIK3CA mutant cohort - Update inclusion criteria and provide more detailed treatment guidance for AE of hyperglycemia and update on AE management for skin toxicity following an advisory-board meeting recommendation - Update the general administration guidelines for alpelisib/placebo based on a food effect and ARA 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 - Change the approach for Blinded Independent Review Committee (BIRC) assessment of PFS from a full read to an audit (sample) based approach. As PFS in the PIK3CA nonmutant cohort is a secondary endpoint, no BIRC assessment will be made for these patients. - Add PFS2 as an exploratory endpoint, defined as the time from randomization to progression on next-line therapy or death, whichever occurs first, in order to make an exploratory assessment of long term benefit intermediate to PFS and OS - Update the estimated timing of interim and final PFS and OS analyses taking into account current and expected enrolment rates.
14 December 2016	The purpose of this amendment was to: - Modify the interim PFS analysis efficacy stopping boundary from Lan-DeMets (O'Brien- Fleming) to Haybittle-Peto boundary in the PIK3CA mutant cohort - Ensure that the Novartis clinical team will remain blinded to the treatment allocation in both cohorts until the time point when PIK3CA mutant cohort can be unblinded. The responsibility for performing the final PFS analysis (and first interim OS analysis) in the PIK3CA non-mutant cohort is modified from the Novartis Clinical Team to an independent statistical group. The results from this analysis will be provided by the independent statistical group to the DMC for decision making on the outcome of the PIK3CA non-mutant cohort
22 November 2017	The purpose of this amendment was to provide updated guidance on the management of skin and subcutaneous reactions.

11 February 2020	The purpose of this amendment was to provide a protocol update on the following based on the released IB Edition 13: -Update on permitted concomitant medications and the use of bisphosphonates/denosumab -Update on guidance of dose interruption/modifications, management of AEs associated with the use of alpelisib, and guidance for follow-up on toxicities -Add AST/ALT/Total Bilirubin dose modifications in Table 6-3 (based on a feedback from FDA to match PIQRAY USPI). Accordingly, Table 6-4 was replaced with a table on alternative causes of liver diseases; and section on follow-up of potential drug-induced liver injury (DILI) was updated -Minor update for the guidelines of skin rash (based on feedback from KOL Dermatologist) -Add DRESS as one of possible manifestations of severe cutaneous skin reactions -Update of the VES for PRO, ECG, ECHO/MUGA assessments

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 9999 as data points in this record are not an accurate representation of the clinical trial results. Please use https://www.novctrd.com/ for complete trial results

Notes: