Clinical trial results:
A randomized double-blind, placebo-controlled study of LEE011 in combination with letrozole for the treatment of postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who received no prior therapy for advanced disease

Summary

EudraCT number	2013-003084-61
Trial protocol	AT DE CZ ES SE NL HU FI IE BE DK IT
Global end of trial date	16 March 2023

Results information

Result version number	v1 (current)
This version publication date	23 March 2024
First version publication date	23 March 2024

Trial information

Trial identification

Sponsor protocol code	CLEE011A2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01958021
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	16 March 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 March 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to compare progression-free survival between ribociclib in combination with letrozole to placebo plus letrozole among postmenopausal women with hormone receptor positive, HER2- negative, advanced breast cancer who received no prior therapy for advanced disease.

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	17 December 2013
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: 6
Country: Number of subjects enrolled	Australia: 16
Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Brazil: 8
Country: Number of subjects enrolled	Canada: 16
Country: Number of subjects enrolled	Czechia: 19
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	Finland: 3
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 55
Country: Number of subjects enrolled	Hungary: 12
Country: Number of subjects enrolled	Ireland: 4
Country: Number of subjects enrolled	Israel: 32
Country: Number of subjects enrolled	Italy: 32
Country: Number of subjects enrolled	Korea, Republic of: 9
Country: Number of subjects enrolled	Lebanon: 15
Country: Number of subjects enrolled	Netherlands: 24

Country: Number of subjects enrolled	Norway: 9
Country: Number of subjects enrolled	Russian Federation: 11
Country: Number of subjects enrolled	Singapore: 9
Country: Number of subjects enrolled	South Africa: 2
Country: Number of subjects enrolled	Spain: 44
Country: Number of subjects enrolled	Sweden: 9
Country: Number of subjects enrolled	Taiwan: 19
Country: Number of subjects enrolled	Thailand: 4
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	United States: 213
Country: Number of subjects enrolled	Türkiye: 12
Worldwide total number of subjects	668
EEA total number of subjects	292

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)	373
From 65 to 84 years	290
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 223 sites across 29 countries.

Pre-assignment

Screening details:

Screening assessments were conducted up to 21 days prior to the randomization

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	Ribociclib+ letrozole

Arm description:

Ribociclib 600 mg daily oral (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg daily oral

Arm type	Experimental
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule, Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib (600 mg, in three 200 mg hard gelatin capsules or tablets) was administered orally once daily on Days 1-21 of each 28-day cycle.

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

Dosage and administration details:

Letrozole (2.5 mg, tablets) was administered orally once daily on a continuous daily schedule (days 1-28 of each 28-day cycle)

Arm title	Placebo + letrozole

Arm description:

Placebo daily oral (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg daily oral. Participants were unblinded once the final OS analysis was completed and after the implementation of protocol amendment 10 (30-Apr-21) and were given the option to crossover to treatment with ribociclib + letrozole

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

Dosage and administration details:

Letrozole (2.5 mg, tablets) was administered orally once daily on a continuous daily schedule (days 1-28

of each 28-day cycle

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

Dosage and administration details:

Placebo (hard gelatin capsules or tablets) was administered orally once daily.

Number of subjects in period 1	Ribociclib+ letrozole	Placebo + letrozole
Started	334	334
Treated	334	330
Crossover cohort	0	4
Completed	0	0
Not completed	334	334
Adverse event, serious fatal	6	1
Physician decision	28	21
Adverse event, non-fatal	38	10
Protocol deviation	3	1
Study terminated as per protocol	24	11
Progressive disease	206	265
Subject/guardian decision	29	25

Baseline characteristics

Reporting groups	
Reporting group title	Ribociclib+ letrozole
Reporting group description:	
Ribociclib 600 mg daily oral (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg daily oral	
Reporting group title	Placebo + letrozole
Reporting group description:	
Placebo daily oral (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg daily oral. Participants were unblinded once the final OS analysis was completed and after the implementation of protocol amendment 10 (30-Apr-21) and were given the option to crossover to treatment with ribociclib + letrozole	

Reporting group values	Ribociclib+ letrozole	Placebo + letrozole	Total
Number of subjects	334	334	668
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)	184	189	373
From 65-84 years	147	143	290
85 years and over	3	2	5
Age Continuous Units: Years			
arithmetic mean	61.4	61.9	
standard deviation	± 10.98	± 10.52	-
Sex: Female, Male Units:			
Female	334	334	668
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	269	280	549
Asian	28	23	51
Black	10	7	17
Native American	1	0	1
Pacific Islander	1	0	1
Other	12	8	20
Unknown	13	16	29

End points

End points reporting groups

Reporting group title	Ribociclib+ letrozole
Reporting group description:	
Ribociclib 600 mg daily oral (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg daily oral	
Reporting group title	Placebo + letrozole
Reporting group description:	
Placebo daily oral (3 weeks on/ 1 week off) in combination with letrozole 2.5 mg daily oral. Participants were unblinded once the final OS analysis was completed and after the implementation of protocol amendment 10 (30-Apr-21) and were given the option to crossover to treatment with ribociclib + letrozole	

Primary: Progression Free Survival (PFS) by investigator assessment

End point title	Progression Free Survival (PFS) by investigator assessment
End point description:	
PFS was defined as the period starting from the date of randomization to the date of the first documented progression or death caused by any reason. In cases where patients did not experience an event, the PFS was censored at the date of the last adequate tumor assessment. Clinical deterioration without objective radiological evidence was not considered as documented disease progression.PFS was assessed by investigator assessment according to RECIST 1.1. The Kaplan-Meier method was used to estimate PFS, and the median PFS, along with 95% confidence intervals, was reported for each treatment group. A stratified Cox regression model was used to estimate the hazard ratio of PFS, along with 95% confidence interval. 9999 indicates that the value was not estimable	
End point type	Primary
End point timeframe:	
Up to 23 months	

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: months				
median (confidence interval 95%)	9999 (19.3 to 9999)	14.7 (13.0 to 16.5)		

Statistical analyses

Statistical analysis title	Analysis of PFS
Comparison groups	Ribociclib+ letrozole v Placebo + letrozole

Number of subjects included in analysis	668
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.556
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.429
upper limit	0.72

Secondary: Overall survival (OS)

End point title	Overall survival (OS)

End point description:

OS was defined as the time from the date of randomization to the date of death from any cause. In cases where the patient's death was not recorded, the OS value was censored at the date of the last known patient's survival status.OS was estimated using the Kaplan-Meier method. As per protocol, the final OS analysis was conducted after approximately 400 deaths were documented.
The median OS, along with 95% confidence intervals, was reported for each treatment group.The distribution of OS between the two treatment arms was compared using a log-rank test at one-sided cumulative 2.5% level of significance. A stratified Cox regression was used to estimate the OS hazard ratio and the associated 95% CI.

End point type	Secondary

End point timeframe:

Up to approximately 87 months

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Months				
median (confidence interval 95%)	63.9 (52.4 to 71.0)	51.4 (47.2 to 59.7)		

Statistical analyses

Statistical analysis title	Analysis of OS
Comparison groups	Ribociclib+ letrozole v Placebo + letrozole

Number of subjects included in analysis	668
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.004
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.765
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.628
upper limit	0.932

Secondary: Overall response rate (ORR) by investigator assessment

End point title	Overall response rate (ORR) by investigator assessment

End point description:

ORR is the percentage of participants with the best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 as per investigator assessment. . CR = Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as 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 23 months

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Percentage of participants				
number (confidence interval 95%)	40.7 (35.4 to 46.0)	27.5 (22.8 to 32.3)		

Statistical analyses

Statistical analysis title	Analysis of ORR
Comparison groups	Ribociclib+ letrozole v Placebo + letrozole
Number of subjects included in analysis	668
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.000155
Method	Cochran-Mantel-Haenszel

Secondary: Clinical benefit rate (CBR) by investigator assessment

End point title	Clinical benefit rate (CBR) by investigator assessment

End point description:

Percentage of participants with complete response (CR) or partial response (PR) or stable disease (SD) lasting 24 weeks or longer as defined in RECIST 1.1 as per investigator assessment. CR = Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as 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: PD = 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 23 months

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Percentage of participants				
number (confidence interval 95%)	79.6 (75.3 to 84.0)	72.8 (68.0 to 77.5)		

Statistical analyses

Statistical analysis title	Analysis of CBR
Comparison groups	Ribociclib+ letrozole v Placebo + letrozole
Number of subjects included in analysis	668
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.018
Method	Cochran-Mantel-Haenszel

Secondary: Time to definitive 10% deterioration in the global health status/quality of life (GHS/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 definitive 10% deterioration in the global health status/quality of life (GHS/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 is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the QoL score (without further improvement above the threshold) or death due to any cause. The Kaplan-Meier method was used to estimate the distribution, and the median time to definitive 10% deterioration, along with 95% confidence intervals, was reported for each treatment

group. If a patient had not had an event, time to deterioration was censored at the date of the last adequate QoL evaluation.
9999 indicated that the value was not estimable.

End point type	Secondary

End point timeframe:

From baseline up to 23 months

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Months				
median (confidence interval 95%)	19.3 (16.6 to 22.1)	9999 (14.8 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to definitive deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) by at least one category of the score

End point title	Time to definitive deterioration of Eastern Cooperative Oncology Group Performance Status (ECOG PS) by at least one category of the score

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 was defined as the time from the date of randomization to the date of the event, defined as experiencing an increase in ECOG PS by at least one category from the baseline or death. 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 indicated that the value was not estimable.

End point type	Secondary

End point timeframe:

From baseline up to 23 months

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Months				
median (confidence interval 95%)	22.6 (22.6 to 9999)	9999 (-9999 to 9999)		

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 assesed. A positive change from baseline indicated improvement. For subjects who discontinued treatment without disease progression, post-treatment efficacy visits occurred every 8 weeks during the initial 18 months since start of treatment, followed by visits every 12 weeks until disease progression.
9999 indicated that the value was not estimable.

End point type	Secondary

End point timeframe:

Baseline, every 2 cycles after randomization during 18 months, then every 3 cycles up to end of treatment (EOT); EOT; and every 8 or 12 weeks post-treatment until progression (post-treatment efficacy visits), assessed up to 23 months. Cycle = 28 days

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	285	285		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1 (n=285 / 285)	2.9 (± 18.68)	4.9 (± 19.14)		
Cycle 5 Day 1 (n=262 / 254)	4.6 (± 19.86)	6.8 (± 19.64)		
Cycle 7 Day 1 (n=249 / 248)	4.6 (± 20.96)	6.0 (± 20.19)		
Cycle 9 Day 1 (n=232 / 219)	5.1 (± 21.95)	8.0 (± 20.49)		
Cycle 11 Day 1 (n=223 / 193)	4.9 (± 21.11)	7.0 (± 20.45)		
Cycle 13 Day 1 (n=203 / 177)	5.3 (± 22.37)	6.5 (± 20.40)		
Cycle 15 Day 1 (n=152 / 129)	5.5 (± 21.43)	8.7 (± 21.23)		
Cycle 17 Day 1 (n=108 / 80)	4.6 (± 22.85)	7.4 (± 21.75)		
Cycle 19 Day 1 (n=60 / 40)	5.0 (± 23.08)	7.7 (± 18.81)		
Cycle 22 Day 1 (n=19 / 14)	4.8 (± 20.09)	12.5 (± 14.15)		
Cycle 25 Day 1 (n=3 / 0)	-8.3 (± 8.33)	9999 (± 9999)		
EOT (n=97 / 142)	-1.2 (± 20.97)	-1.2 (± 15.30)		
Post EOT1 (n=4 / 3)	8.3 (± 28.87)	-16.7 (± 16.67)		
Post EOT2 (n=7 / 2)	3.6 (± 17.25)	-20.8 (± 17.68)		
Post EOT3 (n=5 / 2)	5.0 (± 21.73)	-12.5 (± 5.89)		
Post EOT4 (n=4 / 2)	6.3 (± 28.36)	8.3 (± 0.00)		
Post EOT5 (n=3 / 2)	0.0 (± 28.87)	-4.2 (± 5.89)		

Post EOT6 (n=2 / 0)	20.8 (± 41.25)	9999 (± 9999)		
Post EOT7 (n=1 / 0)	50.0 (± 9999)	9999 (± 9999)		

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 treatment or one day before first administration of crossover treatment (for crossover participants), whichever came first
Crossover on-treatment deaths were collected from start of crossover treatment up to 30 days after last dose of crossover treatment.
Post-treatment survival follow-up (FU) deaths were collected from day 31 after last dose of study treatment to end of study.
Crossover post-treatment survival FU deaths were collected from day 31 after last dose of crossover treatment to end of study

End point type	Post-hoc

End point timeframe:

Pre-treatment: Up to 21 days before treatment. On-treatment: Up to 99 months. Crossover on-treatment: Up to 12 months after crossing-over.Post-treatment survival FU: Up to 99 months.Crossover post-treatment survival FU: Up to 12 months after crossing-over

End point values	Ribociclib+ letrozole	Placebo + letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	334	334		
Units: Participants				
Pre-treatment	0	0		
On-treatment	8	3		
Crossover On-treatment	0	0		
Post-treatment survival follow-up	178	218		
Crossover post-treatment survival follow-up	0	0		
All deaths	186	221		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment: From first dose to 30 days post-treatment (or start of crossover treatment), up to 99
Cross-over on-treatment: from first crossover dose to 30 days post-crossover treatment, up to 12 months.

Adverse event reporting additional description:

Consistent with EudraCTdisclosure 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	25.1

Reporting groups

Reporting group title	Ribociclib + letrozole (on-treatment)

Reporting group description:

AEs during on-treatment period (up to 30 days after last dose of treatment

Reporting group title	Crossover to ribociclib + letrozole (crossover on-treatment)

Reporting group description:

AEs during crossover on-treatment period (from start of crossover treatment up to 30 days after last dose of crossover treatment)

Reporting group title	Placebo + letrozole (on-treatment)

Reporting group description:

AEs during on-treatment period (up to 30 days after last dose of treatment or one day before first dose of crossover treatment for crossover participants)

Serious adverse events	Ribociclib + letrozole (on-treatment)	Crossover to ribociclib + letrozole (crossover on-treatment)	Placebo + letrozole (on-treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	108 / 334 (32.34%)	1 / 4 (25.00%)	62 / 330 (18.79%)
number of deaths (all causes)	8	0	3
number of deaths resulting from adverse events	2	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder cancer			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Bowen's disease			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Colon cancer			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Laryngeal squamous cell carcinoma			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Malignant melanoma in situ			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Meningioma			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-small cell lung cancer			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Oncocytoma			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Tumour pain			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine leiomyoma			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Metastases to meninges			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Vascular disorders			
Embolism			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Hypertension			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Superior vena cava syndrome			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Orthostatic hypotension			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Peripheral arterial occlusive disease			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Peripheral artery thrombosis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Subclavian vein thrombosis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oedema peripheral			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Non-cardiac chest pain			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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	5 / 334 (1.50%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Chest discomfort			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Asthenia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute respiratory failure			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 2	0 / 0	0 / 0
Asthma			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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

Bronchial haemorrhage			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	7 / 334 (2.10%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	2 / 7	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Haemoptysis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoxia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pleural effusion			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	4 / 330 (1.21%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumothorax			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pulmonary haemorrhage			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pulmonary oedema			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Wheezing			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pulmonary embolism			
subjects affected / exposed	4 / 334 (1.20%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	1 / 1	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 334 (0.00%)	1 / 4 (25.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Major depression			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Mental status changes			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	4 / 334 (1.20%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	3 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase			

increased			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood bilirubin increased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood creatinine increased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Blood thyroid stimulating hormone decreased			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
C-reactive protein increased			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
International normalised ratio increased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Lymphocyte count decreased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Neutrophil count decreased			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Waist circumference increased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Weight decreased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
White blood cell count decreased			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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			
Inflammation of wound			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femur fracture			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fracture			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Gastrointestinal procedural complication			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Hip fracture			

subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Femoral neck fracture			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Overdose			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal compression fracture			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sternal fracture			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subdural haematoma			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Thoracic vertebral fracture			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cardiac disorders			
Cardiomyopathy			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cor pulmonale			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial infarction			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cardiac failure congestive			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cardiac arrest			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Myocardial ischaemia			

subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute myocardial infarction			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Arrhythmia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Sinus bradycardia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	5 / 334 (1.50%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Encephalopathy			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epilepsy			

subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemorrhage intracranial			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	3 / 330 (0.91%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxic encephalopathy			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Paraesthesia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			

subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal cord compression			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	4 / 334 (1.20%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Leukocytosis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Febrile neutropenia			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	4 / 334 (1.20%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Neutropenia			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cataract			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Ascites			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0

Abdominal pain upper			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal pain lower			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal incarcerated hernia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Abdominal distension			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Abdominal pain			
subjects affected / exposed	6 / 334 (1.80%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	2 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intestinal haemorrhage			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Inguinal hernia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Impaired gastric emptying			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Haematemesis			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal wall thickening			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric antral vascular ectasia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Flatulence			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Dyspepsia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenal perforation			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Duodenal obstruction			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			

subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Constipation			
subjects affected / exposed	4 / 334 (1.20%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	5 / 334 (1.50%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Obstruction gastric			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pancreatitis			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Vomiting			
subjects affected / exposed	5 / 334 (1.50%)	0 / 4 (0.00%)	3 / 330 (0.91%)
occurrences causally related to treatment / all	2 / 5	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rectal haemorrhage			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cholecystitis			

subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Hypertransaminasaemia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Hepatotoxicity			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic failure			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Hepatic cytolysis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Drug-induced liver injury			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cholelithiasis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholecystitis acute			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Hepatic function abnormal			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Skin and subcutaneous tissue disorders			
Hyperkeratosis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Actinic keratosis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Erythema			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	0 / 330 (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
Rash maculo-papular			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Skin lesion			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Skin ulcer			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal failure			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary retention			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal colic			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Back pain			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	3 / 330 (0.91%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Haemarthrosis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Osteolysis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis of jaw			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pathological fracture			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Osteoarthritis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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			
Abscess jaw			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Abdominal infection			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Atypical pneumonia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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 bacterial			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Bronchitis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bronchitis viral			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Cellulitis			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Clostridium difficile infection			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Diverticulitis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Encephalitis			

subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Erysipelas			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Herpes zoster			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteomyelitis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Pneumonia			
subjects affected / exposed	8 / 334 (2.40%)	0 / 4 (0.00%)	3 / 330 (0.91%)
occurrences causally related to treatment / all	1 / 9	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Retroperitoneal abscess			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			

subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	2 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin infection			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	3 / 334 (0.90%)	0 / 4 (0.00%)	0 / 330 (0.00%)
occurrences causally related to treatment / all	1 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Wound infection			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	2 / 334 (0.60%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	4 / 334 (1.20%)	0 / 4 (0.00%)	2 / 330 (0.61%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Hypercalcaemia			

subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	0 / 334 (0.00%)	0 / 4 (0.00%)	1 / 330 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypoglycaemia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Decreased appetite			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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
Hypophosphataemia			
subjects affected / exposed	1 / 334 (0.30%)	0 / 4 (0.00%)	0 / 330 (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

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

Non-serious adverse events	Ribociclib + letrozole (on-treatment)	Crossover to ribociclib + letrozole (crossover on-treatment)	Placebo + letrozole (on-treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	331 / 334 (99.10%)	4 / 4 (100.00%)	317 / 330 (96.06%)
Vascular disorders			
Hot flush			
subjects affected / exposed	84 / 334 (25.15%)	0 / 4 (0.00%)	88 / 330 (26.67%)
occurrences (all)	94	0	101
Hypertension			
subjects affected / exposed	71 / 334 (21.26%)	0 / 4 (0.00%)	69 / 330 (20.91%)
occurrences (all)	129	0	98
General disorders and administration site conditions			

Asthenia			
subjects affected / exposed	49 / 334 (14.67%)	1 / 4 (25.00%)	49 / 330 (14.85%)
occurrences (all)	87	1	72
Chest discomfort			
subjects affected / exposed	1 / 334 (0.30%)	1 / 4 (25.00%)	4 / 330 (1.21%)
occurrences (all)	1	1	4
Chills			
subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	11 / 330 (3.33%)
occurrences (all)	19	0	11
Influenza like illness			
subjects affected / exposed	23 / 334 (6.89%)	1 / 4 (25.00%)	23 / 330 (6.97%)
occurrences (all)	45	1	29
Non-cardiac chest pain			
subjects affected / exposed	18 / 334 (5.39%)	0 / 4 (0.00%)	29 / 330 (8.79%)
occurrences (all)	24	0	41
Oedema peripheral			
subjects affected / exposed	49 / 334 (14.67%)	0 / 4 (0.00%)	41 / 330 (12.42%)
occurrences (all)	73	0	52
Pyrexia			
subjects affected / exposed	49 / 334 (14.67%)	0 / 4 (0.00%)	24 / 330 (7.27%)
occurrences (all)	66	0	37
Fatigue			
subjects affected / exposed	145 / 334 (43.41%)	1 / 4 (25.00%)	119 / 330 (36.06%)
occurrences (all)	202	1	150
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	21 / 334 (6.29%)	0 / 4 (0.00%)	23 / 330 (6.97%)
occurrences (all)	24	0	30
Pelvic pain			
subjects affected / exposed	8 / 334 (2.40%)	1 / 4 (25.00%)	16 / 330 (4.85%)
occurrences (all)	9	1	16
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	24 / 334 (7.19%)	0 / 4 (0.00%)	21 / 330 (6.36%)
occurrences (all)	31	0	26
Epistaxis			

subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	10 / 330 (3.03%)
occurrences (all)	19	0	17
Dyspnoea			
subjects affected / exposed	48 / 334 (14.37%)	0 / 4 (0.00%)	44 / 330 (13.33%)
occurrences (all)	61	0	59
Cough			
subjects affected / exposed	89 / 334 (26.65%)	0 / 4 (0.00%)	83 / 330 (25.15%)
occurrences (all)	137	0	118
Psychiatric disorders			
Anxiety			
subjects affected / exposed	41 / 334 (12.28%)	0 / 4 (0.00%)	29 / 330 (8.79%)
occurrences (all)	47	0	33
Depression			
subjects affected / exposed	33 / 334 (9.88%)	0 / 4 (0.00%)	29 / 330 (8.79%)
occurrences (all)	36	0	37
Insomnia			
subjects affected / exposed	55 / 334 (16.47%)	0 / 4 (0.00%)	49 / 330 (14.85%)
occurrences (all)	64	0	57
Investigations			
Blood creatinine increased			
subjects affected / exposed	37 / 334 (11.08%)	1 / 4 (25.00%)	9 / 330 (2.73%)
occurrences (all)	70	1	11
Alanine aminotransferase increased			
subjects affected / exposed	66 / 334 (19.76%)	1 / 4 (25.00%)	21 / 330 (6.36%)
occurrences (all)	99	1	29
Aspartate aminotransferase increased			
subjects affected / exposed	66 / 334 (19.76%)	1 / 4 (25.00%)	23 / 330 (6.97%)
occurrences (all)	97	1	35
Blood alkaline phosphatase increased			
subjects affected / exposed	22 / 334 (6.59%)	0 / 4 (0.00%)	21 / 330 (6.36%)
occurrences (all)	27	0	23
Electrocardiogram QT prolonged			
subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	5 / 330 (1.52%)
occurrences (all)	17	0	5
Lymphocyte count decreased			

subjects affected / exposed	26 / 334 (7.78%)	1 / 4 (25.00%)	3 / 330 (0.91%)
occurrences (all)	51	2	5
Neutrophil count decreased			
subjects affected / exposed	78 / 334 (23.35%)	2 / 4 (50.00%)	5 / 330 (1.52%)
occurrences (all)	265	4	6
Platelet count decreased			
subjects affected / exposed	11 / 334 (3.29%)	1 / 4 (25.00%)	0 / 330 (0.00%)
occurrences (all)	29	1	0
Weight decreased			
subjects affected / exposed	29 / 334 (8.68%)	1 / 4 (25.00%)	16 / 330 (4.85%)
occurrences (all)	34	2	18
White blood cell count decreased			
subjects affected / exposed	70 / 334 (20.96%)	1 / 4 (25.00%)	8 / 330 (2.42%)
occurrences (all)	161	4	16
Injury, poisoning and procedural complications			
Scar			
subjects affected / exposed	0 / 334 (0.00%)	1 / 4 (25.00%)	0 / 330 (0.00%)
occurrences (all)	0	1	0
Nervous system disorders			
Dizziness			
subjects affected / exposed	54 / 334 (16.17%)	1 / 4 (25.00%)	53 / 330 (16.06%)
occurrences (all)	79	1	63
Dysgeusia			
subjects affected / exposed	20 / 334 (5.99%)	0 / 4 (0.00%)	14 / 330 (4.24%)
occurrences (all)	21	0	15
Headache			
subjects affected / exposed	98 / 334 (29.34%)	1 / 4 (25.00%)	76 / 330 (23.03%)
occurrences (all)	138	1	111
Paraesthesia			
subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	13 / 330 (3.94%)
occurrences (all)	22	0	16
Taste disorder			
subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	8 / 330 (2.42%)
occurrences (all)	19	0	8
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	77 / 334 (23.05%)	2 / 4 (50.00%)	24 / 330 (7.27%)
occurrences (all)	164	4	29
Thrombocytopenia			
subjects affected / exposed	24 / 334 (7.19%)	0 / 4 (0.00%)	3 / 330 (0.91%)
occurrences (all)	35	0	3
Neutropenia			
subjects affected / exposed	218 / 334 (65.27%)	2 / 4 (50.00%)	18 / 330 (5.45%)
occurrences (all)	899	5	37
Lymphopenia			
subjects affected / exposed	19 / 334 (5.69%)	1 / 4 (25.00%)	7 / 330 (2.12%)
occurrences (all)	30	1	7
Leukopenia			
subjects affected / exposed	56 / 334 (16.77%)	2 / 4 (50.00%)	10 / 330 (3.03%)
occurrences (all)	136	5	18
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	27 / 334 (8.08%)	0 / 4 (0.00%)	7 / 330 (2.12%)
occurrences (all)	47	0	8
Eye disorders			
Vision blurred			
subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	9 / 330 (2.73%)
occurrences (all)	18	0	9
Lacrimation increased			
subjects affected / exposed	39 / 334 (11.68%)	0 / 4 (0.00%)	7 / 330 (2.12%)
occurrences (all)	53	0	7
Dry eye			
subjects affected / exposed	27 / 334 (8.08%)	0 / 4 (0.00%)	13 / 330 (3.94%)
occurrences (all)	32	0	16
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	137 / 334 (41.02%)	2 / 4 (50.00%)	88 / 330 (26.67%)
occurrences (all)	285	3	153
Dry mouth			
subjects affected / exposed	48 / 334 (14.37%)	0 / 4 (0.00%)	37 / 330 (11.21%)
occurrences (all)	59	0	42
Dyspepsia			

subjects affected / exposed	37 / 334 (11.08%)	0 / 4 (0.00%)	25 / 330 (7.58%)
occurrences (all)	43	0	29
Nausea			
subjects affected / exposed	183 / 334 (54.79%)	3 / 4 (75.00%)	106 / 330 (32.12%)
occurrences (all)	296	3	172
Stomatitis			
subjects affected / exposed	53 / 334 (15.87%)	1 / 4 (25.00%)	24 / 330 (7.27%)
occurrences (all)	78	1	28
Toothache			
subjects affected / exposed	18 / 334 (5.39%)	0 / 4 (0.00%)	14 / 330 (4.24%)
occurrences (all)	26	0	17
Vomiting			
subjects affected / exposed	115 / 334 (34.43%)	0 / 4 (0.00%)	62 / 330 (18.79%)
occurrences (all)	196	0	105
Constipation			
subjects affected / exposed	99 / 334 (29.64%)	0 / 4 (0.00%)	75 / 330 (22.73%)
occurrences (all)	137	0	101
Abdominal pain upper			
subjects affected / exposed	31 / 334 (9.28%)	0 / 4 (0.00%)	21 / 330 (6.36%)
occurrences (all)	37	0	26
Abdominal pain			
subjects affected / exposed	41 / 334 (12.28%)	0 / 4 (0.00%)	33 / 330 (10.00%)
occurrences (all)	51	0	38
Skin and subcutaneous tissue disorders			
Dry skin			
subjects affected / exposed	34 / 334 (10.18%)	0 / 4 (0.00%)	12 / 330 (3.64%)
occurrences (all)	44	0	13
Alopecia			
subjects affected / exposed	119 / 334 (35.63%)	0 / 4 (0.00%)	55 / 330 (16.67%)
occurrences (all)	129	0	58
Erythema			
subjects affected / exposed	23 / 334 (6.89%)	0 / 4 (0.00%)	6 / 330 (1.82%)
occurrences (all)	27	0	6
Vitiligo			
subjects affected / exposed	6 / 334 (1.80%)	1 / 4 (25.00%)	0 / 330 (0.00%)
occurrences (all)	8	1	0

Urticaria			
subjects affected / exposed	5 / 334 (1.50%)	1 / 4 (25.00%)	1 / 330 (0.30%)
occurrences (all)	6	1	1
Rash			
subjects affected / exposed	68 / 334 (20.36%)	0 / 4 (0.00%)	33 / 330 (10.00%)
occurrences (all)	101	0	36
Pruritus			
subjects affected / exposed	61 / 334 (18.26%)	0 / 4 (0.00%)	27 / 330 (8.18%)
occurrences (all)	109	0	31
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	135 / 334 (40.42%)	0 / 4 (0.00%)	136 / 330 (41.21%)
occurrences (all)	222	0	229
Back pain			
subjects affected / exposed	91 / 334 (27.25%)	0 / 4 (0.00%)	76 / 330 (23.03%)
occurrences (all)	123	0	100
Bone pain			
subjects affected / exposed	44 / 334 (13.17%)	0 / 4 (0.00%)	47 / 330 (14.24%)
occurrences (all)	53	0	60
Muscle spasms			
subjects affected / exposed	26 / 334 (7.78%)	0 / 4 (0.00%)	28 / 330 (8.48%)
occurrences (all)	29	0	32
Musculoskeletal chest pain			
subjects affected / exposed	21 / 334 (6.29%)	0 / 4 (0.00%)	27 / 330 (8.18%)
occurrences (all)	25	0	37
Musculoskeletal pain			
subjects affected / exposed	15 / 334 (4.49%)	0 / 4 (0.00%)	17 / 330 (5.15%)
occurrences (all)	17	0	24
Myalgia			
subjects affected / exposed	35 / 334 (10.48%)	0 / 4 (0.00%)	30 / 330 (9.09%)
occurrences (all)	39	0	38
Neck pain			
subjects affected / exposed	20 / 334 (5.99%)	0 / 4 (0.00%)	21 / 330 (6.36%)
occurrences (all)	21	0	25
Pain in extremity			

subjects affected / exposed	62 / 334 (18.56%)	0 / 4 (0.00%)	63 / 330 (19.09%)
occurrences (all)	92	0	88
Infections and infestations			
Acarodermatitis			
subjects affected / exposed	0 / 334 (0.00%)	1 / 4 (25.00%)	0 / 330 (0.00%)
occurrences (all)	0	1	0
Bronchitis			
subjects affected / exposed	25 / 334 (7.49%)	0 / 4 (0.00%)	18 / 330 (5.45%)
occurrences (all)	35	0	21
Conjunctivitis			
subjects affected / exposed	18 / 334 (5.39%)	0 / 4 (0.00%)	5 / 330 (1.52%)
occurrences (all)	21	0	5
Influenza			
subjects affected / exposed	26 / 334 (7.78%)	0 / 4 (0.00%)	18 / 330 (5.45%)
occurrences (all)	32	0	20
Nasopharyngitis			
subjects affected / exposed	37 / 334 (11.08%)	0 / 4 (0.00%)	29 / 330 (8.79%)
occurrences (all)	59	0	46
Sinusitis			
subjects affected / exposed	22 / 334 (6.59%)	0 / 4 (0.00%)	16 / 330 (4.85%)
occurrences (all)	30	0	25
Upper respiratory tract infection			
subjects affected / exposed	51 / 334 (15.27%)	0 / 4 (0.00%)	43 / 330 (13.03%)
occurrences (all)	82	0	65
Urinary tract infection			
subjects affected / exposed	53 / 334 (15.87%)	0 / 4 (0.00%)	37 / 330 (11.21%)
occurrences (all)	81	0	59
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	74 / 334 (22.16%)	1 / 4 (25.00%)	61 / 330 (18.48%)
occurrences (all)	92	1	65
Hypercholesterolaemia			
subjects affected / exposed	12 / 334 (3.59%)	1 / 4 (25.00%)	10 / 330 (3.03%)
occurrences (all)	18	1	10
Hyperglycaemia			

subjects affected / exposed	29 / 334 (8.68%)	0 / 4 (0.00%)	25 / 330 (7.58%)
occurrences (all)	49	0	35
Hypertriglyceridaemia			
subjects affected / exposed	17 / 334 (5.09%)	0 / 4 (0.00%)	17 / 330 (5.15%)
occurrences (all)	40	0	24
Hypocalcaemia			
subjects affected / exposed	21 / 334 (6.29%)	0 / 4 (0.00%)	6 / 330 (1.82%)
occurrences (all)	37	0	6
Hypokalaemia			
subjects affected / exposed	25 / 334 (7.49%)	0 / 4 (0.00%)	11 / 330 (3.33%)
occurrences (all)	44	0	20
Hypomagnesaemia			
subjects affected / exposed	10 / 334 (2.99%)	1 / 4 (25.00%)	7 / 330 (2.12%)
occurrences (all)	14	1	11
Hyponatraemia			
subjects affected / exposed	9 / 334 (2.69%)	1 / 4 (25.00%)	3 / 330 (0.91%)
occurrences (all)	11	1	3

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 April 2014	The purpose of this amendment was to clarify some of the inclusion/exclusion criteria in the protocol, as well as some study assessments based on feedback received from participating centers' IRBs/IECs and Health Authorities. The amendment also included an update of nonclinical and clinical data for the ribociclib alone and in combination with letrozole
25 November 2014	The main purpose of this amendment was to: Include specific dose modification guidance for hepatic toxicity to better manage patient safety: dose adjustments as well as additional follow up for bilirubin and/or transaminases increases have been detailed and separated from the dose modification guidance for other AEs. Guidance for management of QTcF prolongation was extended to all AEs regardless of the grades to better manage patient safety. To better characterize the effect of the combination of ribociclib and letrozole on OS, the sample size of the trial was increased from 500 to 650. The final OS analysis was planned to be performed after observing 400 deaths instead of 300 deaths. Highlighted the need for consulting the letrozole SmPC when appropriate guidance for the management of letrozole related AEs was required as requested by Health Authorities. Update the protocol requirements for consistency with the most recent preclinical information.
09 April 2015	The purpose of this amendment was to: (i) further enhance and clarify safety monitoring for the ribociclib, ii) provide clear management guidelines for grade 3 neutropenia, iii) eliminate the planned futility assessment, (iv) revise the interim analysis for efficacy after observing 70%, instead of 80%, of targeted local PFS events, and change the statistical interim monitoring plan from the α-spending function of Lan-Demets (1983) with O'Brien-Fleming type stopping boundary to a Haybittle-Peto boundary, and (v) implementation of editorial changes to be aligned with Novartis internal protocol template language.
08 February 2016	The purpose of this amendment was to: Update and clarify the safety monitoring of patients including: Management of hepatic toxicities: Updates to monitoring and dose adjustment guidelines for hepatobiliary toxicities including ALT, AST and total bilirubin were added and separated from the dose modification guidance for other AEs. Additional blood collections for laboratory assessments to further characterize potential drug-induced liver injury were added. Management of QTc prolongation Management of dose modification based on local laboratory results: clarification was provided that, in case of safety emergency, local laboratory results could be used to evaluate the need for potential study treatment dose modifications. Remove the requirement for a central radiology assessment by medical oncologist: Less than 1% of patients met the criteria for oncologist review in CLEE011A2301 study. Therefore, medical oncologist review was replaced by a standard BIRC review assessment. Update the protocol requirements for consistency with IB version 8.
21 December 2016	To provide the updated PFS and OS analyses to global health authorities during the on-going review of the submission/registration, the second OS IA were to be performed with approximately 100 deaths (25% information fraction) documented in the database instead of 120 deaths (30% information fraction) that was planned. After interim analysis (cut-off date 29-Jan-2016) PK sample collection and analysis has been completed for the PK subgroup; as a consequence, unscheduled PK sample collection has been discontinued.

01 November 2017	The protocol and the analysis plan for OS was modified to add another IA after observing approximately 200 deaths. The study met its primary endpoint, hence 36 months after randomization, the visit schedule for efficacy and PRO assessments were clinically indicated to more closely reflect clinical practice.
06 August 2018	The purpose of this amendment is to: Update the dose adjustment and management recommendations for QTcF based on the analyses from preclinical and clinical data. Updated the prohibited concomitant medications based on drug-drug interaction and co-medication considerations Updated the withdrawal of consent language aligning with the new Global Data Protection Requirements.
19 June 2019	The purpose of this amendment was to provide a minor clarification to the protocol section related to the follow up period. During both the efficacy and the safety follow-up periods, all new anticancer therapies were to be recorded in the eCRF after the last dose of the study treatment and until death, lost to follow-up, or withdrawal of consent to efficacy or survival follow-up. In addition, patients in efficacy follow-up with tumor and PRO assessments performed as clinically indicated were also to be followed for survival every 12 weeks or earlier based on the survival update required to meet safety or regulatory needs.
27 January 2020	The main purpose of this amendment was to update protocol requirements for consistency with new safety information in the IB version 14: Interstitial Lung Disease (ILD)/pneumonitis has been observed with CDK4/6 inhibitor treatment. A new Table 6-6, ribociclib/placebo dose adjustment and management recommendation for ILD/pneumonitis, has been added to the protocol section. Toxic Epidermal Necrolysis – has been reported in the post-marketing setting in a well-documented literature case report. No case was observed in the clinical trials. Updated the protocol section 6.3.1.4, Guidance for all other adverse reactions, with clear guidance to discontinue ribociclib/placebo if toxic epidermal necrolysis is diagnosed.
30 April 2021	The purpose of this amendment was to implement the change of ribociclib/ matching placebo formulation from capsules to tablets, to update the visit evaluation schedule for patients on treatment to have safety assessments every third cycle with the exception of future cross-over patients, and to provide guidance on related COVID-19 pandemic disruption. As well as to clarify the study next steps post final OS analysis: Allow unblinding of all patients for investigators to know patients current treatment allocation Allow patients currently receiving placebo transition to investigational treatment (ribociclib, LEE011) per investigator discretion. Specify that central safety assessments can cease and all laboratory and ECG assessments should be performed locally and outline the frequency of assessments. Update the visit evaluation schedule for patients on placebo transitioning to investigational treatment (ribociclib, LEE011) Clarified about the post-trial access for the ongoing patients Clarified that patient reported outcomes measures and biomarker samples are no longer collected.

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: