Clinical trial results:
A randomized double-blind, placebo-controlled study of ribociclib in combination with fulvestrant for the treatment of men and postmenopausal women with hormone receptor positive, HER2-negative, advanced breast cancer who have received no or only one line of prior endocrine treatment

Summary

EudraCT number	2015-000617-43
Trial protocol	SE DE AT ES CZ DK NL HU BE BG FR PT IT
Global end of trial date	11 January 2023

Results information

Result version number	v1 (current)
This version publication date	18 November 2023
First version publication date	18 November 2023

Trial information

Trial identification

Sponsor protocol code	CLEE011F2301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02422615
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	11 January 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	11 January 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to compare progression free survival (PFS) between ribociclib in combination with fulvestrant to placebo in combination with fulvestrant among men and postmenopausal women with HR+, HER2-negative advanced breast cancer who received no or only one prior endocrine treatment for advanced disease.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from theDeclaration of Helsinki and the International Conference onHarmonization (ICH) Good Clinical Practice (GCP) guidelines. All the localregulatory requirements pertinent to safety of trial subjects were alsofollowed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	09 June 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	Austria: 7
Country: Number of subjects enrolled	Belgium: 56
Country: Number of subjects enrolled	Bulgaria: 20
Country: Number of subjects enrolled	Canada: 41
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	Australia: 28
Country: Number of subjects enrolled	Czechia: 21
Country: Number of subjects enrolled	Denmark: 32
Country: Number of subjects enrolled	France: 43
Country: Number of subjects enrolled	Germany: 108
Country: Number of subjects enrolled	Hungary: 24
Country: Number of subjects enrolled	Italy: 39
Country: Number of subjects enrolled	Jordan: 5
Country: Number of subjects enrolled	Korea, Republic of: 36
Country: Number of subjects enrolled	Lebanon: 6
Country: Number of subjects enrolled	Malaysia: 6
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	Netherlands: 56

Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Portugal: 3
Country: Number of subjects enrolled	Russian Federation: 7
Country: Number of subjects enrolled	Singapore: 8
Country: Number of subjects enrolled	Spain: 56
Country: Number of subjects enrolled	Sweden: 4
Country: Number of subjects enrolled	Switzerland: 7
Country: Number of subjects enrolled	Thailand: 6
Country: Number of subjects enrolled	Turkey: 11
Country: Number of subjects enrolled	United Kingdom: 9
Country: Number of subjects enrolled	United States: 71
Country: Number of subjects enrolled	Norway: 5
Worldwide total number of subjects	726
EEA total number of subjects	476

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)	387
From 65 to 84 years	335
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

174 sites across 30 countries enrolled participants

Pre-assignment

Screening details:

Screening assessments were conducted up to 28 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

Blinding implementation details:

A protocol amendment 4 (dated 29-Jan-2020) allowed for unblinding of study participants, and those still receiving placebo had the option to switch to the ribociclib arm. The decision for crossover was made at the investigator’s discretion and required patient consent.

Arms

Are arms mutually exclusive?	Yes
Arm title	Ribociclib + fulvestrant

Arm description:

Ribociclib was administered orally at a daily dose of 600mg for 21 consecutive days within a 28-day cycle. This treatment was combined with fulvestrant, which was administered via intramuscular injections of 500mg every 28 days starting on Day 1 of each cycle. Additionally, an extra dose of fulvestrant was given on Day 15 of Cycle 1.

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

Dosage and administration details:

Ribociclib capsules were administered orally at a daily dose of 600mg for 21 consecutive days within a 28-day cycle.

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

Dosage and administration details:

Placebo capsules were administered orally for 21 consecutive days within a 28-day cycle.

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

Dosage and administration details:

Fulvestrant was administered via intramuscular injections at a dose of 500mg every 28 days, starting on Day 1 of each cycle. In Cycle 1, an additional dose of Fulvestrant was given on Day 15

Arm title	Placebo + fulvestrant

Arm description:

Placebo was administered orally for 21 consecutive days within a 28-day cycle. This treatment was combined with fulvestrant, which was administered via intramuscular injections of 500mg every 28 days starting on Day 1 of each cycle. Additionally, an extra dose of fulvestrant was given on Day 15 of Cycle 1. Participants were unblinded after the implementation of protocol amendment 4 (29-Jan-20) and were given the option to crossover to treatment with ribociclib and fulvestrant.

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:

Fulvestrant was administered via intramuscular injections at a dose of 500mg every 28 days, starting on Day 1 of each cycle. In Cycle 1, an additional dose of Fulvestrant was given on Day 15

Number of subjects in period 1	Ribociclib + fulvestrant	Placebo + fulvestrant
Started	484	242
Untreated	1	1
Crossover cohort	0	3
Completed	0	0
Not completed	484	242
Adverse event, serious fatal	2	1
Physician decision	32	8
Adverse event, non-fatal	51	9
Technical problems	-	1
Protocol deviation	1	1
Study terminated per protocol	46	14
Progressive disease	314	200
Subject/guardian decision	38	8

Baseline characteristics

Reporting groups	
Reporting group title	Ribociclib + fulvestrant
Reporting group description:	
Ribociclib was administered orally at a daily dose of 600mg for 21 consecutive days within a 28-day cycle. This treatment was combined with fulvestrant, which was administered via intramuscular injections of 500mg every 28 days starting on Day 1 of each cycle. Additionally, an extra dose of fulvestrant was given on Day 15 of Cycle 1.	
Reporting group title	Placebo + fulvestrant
Reporting group description:	
Placebo was administered orally for 21 consecutive days within a 28-day cycle. This treatment was combined with fulvestrant, which was administered via intramuscular injections of 500mg every 28 days starting on Day 1 of each cycle. Additionally, an extra dose of fulvestrant was given on Day 15 of Cycle 1. Participants were unblinded after the implementation of protocol amendment 4 (29-Jan-20) and were given the option to crossover to treatment with ribociclib and fulvestrant.	

Reporting group values	Ribociclib + fulvestrant	Placebo + fulvestrant	Total
Number of subjects	484	242	726
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)	258	129	387
From 65-84 years	223	112	335
85 years and over	3	1	4
Age Continuous Units: Years			
arithmetic mean	63.4	62.8	
standard deviation	± 9.78	± 10.59	-
Sex: Female, Male Units: Participants			
Female	484	242	726
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	406	213	619
Asian	45	18	63
Native American	5	1	6
Black	3	2	5
Other	10	3	13
Unkown	15	5	20

End points

End points reporting groups

Reporting group title	Ribociclib + fulvestrant

Reporting group description:

Ribociclib was administered orally at a daily dose of 600mg for 21 consecutive days within a 28-day cycle. This treatment was combined with fulvestrant, which was administered via intramuscular injections of 500mg every 28 days starting on Day 1 of each cycle. Additionally, an extra dose of fulvestrant was given on Day 15 of Cycle 1.

Reporting group title	Placebo + fulvestrant

Reporting group description:

Placebo was administered orally for 21 consecutive days within a 28-day cycle. This treatment was combined with fulvestrant, which was administered via intramuscular injections of 500mg every 28 days starting on Day 1 of each cycle. Additionally, an extra dose of fulvestrant was given on Day 15 of Cycle 1. Participants were unblinded after the implementation of protocol amendment 4 (29-Jan-20) and were given the option to crossover to treatment with ribociclib and fulvestrant.

Primary: Progression Free Survival (PFS) per Investigator assessment

End point title	Progression Free Survival (PFS) per 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 via local radiology 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.
The distribution of PFS between the two arms was compared using a stratified log-rank test at a one-sided 2.5% level of significance. The PFS hazard ratio with two-sided 95% confidence interval was derived from the stratified Cox proportional hazards model.

End point type	Primary

End point timeframe:

From randomization to first documented progression or death, assessed up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Months				
median (confidence interval 95%)	20.5 (18.5 to 23.5)	12.8 (10.9 to 16.3)		

Statistical analyses

Statistical analysis title	PFS: Ribociclib vs placebo
Comparison groups	Ribociclib + fulvestrant v Placebo + fulvestrant

Number of subjects included in analysis	726
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0 [1]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.593
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.732

Notes:

[1] - P-value= 0.00000041

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. The median OS, along with 95% confidence intervals (CIs), 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From randomization to death, assessed up to approximately 46 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Months				
median (confidence interval 95%)	9999 (42.5 to 9999)	40.0 (37.0 to 9999)		

Statistical analyses

Statistical analysis title	OS: Ribociclib vs Placebo
Comparison groups	Ribociclib + fulvestrant v Placebo + fulvestrant

Number of subjects included in analysis	726
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.00455
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.724
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.568
upper limit	0.924

Secondary: Clinical benefit rate (CBR) per investigator assessment

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

End point description:

CBR was defined as the percentage of participants with a best overall response of CR or PR or stable disease (SD) lasting 24 weeks or longer as defined in RECIST 1.1 as per investigator assessment.
CR: Disappearance of all lesions with lymph nodes measuring < 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 approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Percentage of participants				
number (confidence interval 95%)	70.2 (66.2 to 74.3)	62.8 (56.7 to 68.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression Free Survival (PFS) per Blinded Independent Review Committee (BIRC)

End point title	Progression Free Survival (PFS) per Blinded Independent Review Committee (BIRC)

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 via BIRC 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From randomization to first documented progression or death, assessed up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Months				
median (confidence interval 95%)	9999 (18.2 to 9999)	10.9 (3.8 to 17.2)		

Statistical analyses

Statistical analysis title	PFS: Ribociclib vs Placebo
Comparison groups	Ribociclib + fulvestrant v Placebo + fulvestrant
Number of subjects included in analysis	726
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Cox proportional hazard
Point estimate	0.492
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.345
upper limit	0.703

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 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 lesions with lymph nodes measuring < 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 approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Percentage of participants				
number (confidence interval 95%)	32.4 (28.3 to 36.6)	21.5 (16.3 to 26.7)		

Statistical analyses

No statistical analyses for this end point

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, a GHS/QoL scale, and 6 single items. GHS/QoL scale scores range 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Months				
median (confidence interval 95%)	9999 (22.1 to 9999)	19.4 (16.6 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR) per investigator assessment

End point title	Duration of response (DOR) per investigator assessment

End point description:

DOR was defined as the time from the first documented response (CR or PR) to the first documented progression or death due to underlying cancer as defined in RECIST 1.1 per investigator assessment. The Kaplan-Meier method was used to estimate DOR, and the median DOR, along with 95% confidence intervals, was reported for each treatment group. If a participant had not had an event, duration was censored at the date of last adequate tumor assessment.
CR: Disappearance of all lesions with lymph nodes measuring < 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From first documented response to progression or death, assessed up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	157	52		
Units: Months				
median (confidence interval 95%)	9999 (16.1 to 9999)	9999 (13.8 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR) per investigator assessment

End point title	Time to response (TTR) per investigator assessment

End point description:

TTR was defined as the time from randomization to the first documented and confirmed response (CR or PR) as defined by RECIST 1.1 per investigator assessment. The Kaplan-Meier method was used to estimate TTR, and the median TTR, along with 95% confidence intervals, was reported for each treatment group. Participants who did not achieve a confirmed response were censored at the maximum follow-up time for patients who had a PFS event (i.e. either progressed or died due to any cause) or at the date of last adequate tumor assessment otherwise.
CR: Disappearance of all lesions with lymph nodes measuring < 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

From randomization to first response, assessed up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Months				
median (confidence interval 95%)	9999 (-9999 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, a GHS/QoL scale, and 6 single items. GHS/QoL scale scores range 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 indicates 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Baseline, every 8 weeks after randomization during 18 months, then every 12 weeks up to end of treatment; end of treatment; and every 8 or 12 weeks post-treatment until progression (post-treatment efficacy visits), assessed up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	361	169		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1 (n=361/169)	4.5 (± 18.53)	2.7 (± 17.50)		
Cycle 5 Day 1 (n=316/149)	4.2 (± 19.97)	3.2 (± 18.09)		
Cycle 7 Day 1 (n=300/133)	4.9 (± 19.47)	4.3 (± 17.30)		
Cycle 9 Day 1 (n=283/133)	4.1 (± 19.36)	3.3 (± 17.61)		
Cycle 11 Day 1 (n=251/116)	4.9 (± 17.57)	2.3 (± 18.21)		
Cycle 13 Day 1 (n=240/105)	4.4 (± 18.53)	1.3 (± 19.48)		
Cycle 15 Day 1 (n=218/96)	3.6 (± 18.34)	3.6 (± 19.86)		
Cycle 17 Day 1 (n=216/84)	3.9 (± 20.31)	3.4 (± 21.61)		
Cycle 19 Day 1 (n=185/82)	3.8 (± 17.57)	3.7 (± 18.52)		
Cycle 22 Day 1 (n=118/46)	6.6 (± 20.78)	4.7 (± 17.00)		
Cycle 25 Day 1 (n=54/19)	5.7 (± 16.81)	8.3 (± 18.22)		
Cycle 28 Day 1 (n=12/3)	12.5 (± 16.48)	19.4 (± 12.73)		
End of treatment (EOT) (n=184/113)	-5.2 (± 25.84)	-5.5 (± 24.54)		

Post EOT1 (n=11/2)	4.5 (± 21.20)	-33.3 (± 23.57)		
Post EOT2 (n=7/2)	-4.8 (± 19.75)	-16.7 (± 23.57)		
Post EOT3 (n=4/2)	14.6 (± 24.88)	-16.7 (± 0.00)		
Post EOT4 (n=5/1)	10.0 (± 20.75)	-25.0 (± 9999)		
Post EOT5 (n=3/0)	13.9 (± 20.97)	9999 (± 9999)		
Post EOT6 (n=3/0)	22.2 (± 12.73)	9999 (± 9999)		
Post EOT7 (n=3/0)	19.4 (± 20.97)	9999 (± 9999)		
Post EOT8 (n=2/0)	37.5 (± 17.68)	9999 (± 9999)		
Post EOT9 (n=3/0)	8.3 (± 46.40)	9999 (± 9999)		
Post EOT10 (n=1/0)	-8.3 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

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

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

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 the time from randomization to the date of the event, defined as experiencing an increase in ECOG PS by at least one category from baseline or death. A deterioration was considered definitive if no improvements were observed at a subsequent time. The KM method was used to estimate the distribution, and the median time to definitive deterioration, along with 95% confidence intervals, was reported for each treatment group. 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.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Up to approximately 26 months

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Months				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Ribociclib plasma concentrations

End point title	Ribociclib plasma concentrations[2]

End point description:

Blood samples were collected to assess the concentration by time point for ribociclib. Participants were classified into the following dose groups at each timepoint: 1) ribociclib 600 mg: consisted of all participants who provided evaluable concentrations after receiving at least 10 consecutive daily ribociclib doses of 600 mg immediately prior to the blood collection without a dose change or interruption. 2) ribociclib 400 mg: consisted of all participants who provided evaluable concentrations after receiving at least 10 consecutive daily ribociclib doses of 400 mg immediately prior to the blood collection without a dose change or interruption. 3) ribociclib 200 mg: consisted of all participants who provided evaluable concentrations after receiving at least 10 consecutive daily ribociclib doses of 200 mg immediately prior to the blood collection without a dose change or interruption.
Note: 9999 indicates that the value was not estimable

End point type	Secondary

End point timeframe:

Cycle (C) 1 and Cycle 2 at Day (D) 15 pre-dose and at 2, 4, and 6 hours (h) post-dose. 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: This endpoint reports results for the arm that received ribociclib

End point values	Ribociclib + fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	253			
Units: nanogram (ng) / miliLiter (mL)				
geometric mean (geometric coefficient of variation)				
C1D15 predose (ribociclib 600 mg) n=253	627 (± 67.6)			
C1D15 predose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 predose (ribociclib 200 mg) n=0	9999 (± 9999)			
C1D15 2 hours post-dose (ribociclib 600 mg) n=102	1670 (± 52.0)			
C1D15 2 hours post-dose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 2 hours post-dose (ribociclib 200 mg) n=0	9999 (± 9999)			
C1D15 4 hours post-dose (ribociclib 600 mg) n=107	1690 (± 46.2)			
C1D15 4 hours post-dose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 4 hours post-dose (ribociclib 200 mg) n=0	9999 (± 9999)			
C1D15 6 hours post-dose (ribociclib 600 mg) n=107	1420 (± 50.9)			
C1D15 6 hours post-dose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 6 hours post-dose (ribociclib 200 mg) n=0	9999 (± 9999)			
C2D15 predose (ribociclib 600 mg) n=177	553 (± 80.7)			
C2D15 predose (ribociclib 400 mg) n=7	220 (± 81.6)			
C2D15 predose (ribociclib 200 mg) n=0	9999 (± 9999)			
C2D15 2 hours post-dose (ribociclib 600 mg) n=75	1470 (± 80.7)			

C2D15 2 hours post-dose (ribociclib 400 mg) n=7	794 (± 85.0)			
C2D15 2 hours post-dose (ribociclib 200 mg) n=1	104 (± 9999)			
C2D15 4 hours post-dose (ribociclib 600 mg) n=79	1610 (± 53.6)			
C2D15 4 hours post-dose (ribociclib 400 mg) n=7	913 (± 69.4)			
C2D15 4 hours post-dose (ribociclib 200 mg) n=1	112 (± 9999)			
C2D15 6 hours post-dose (ribociclib 600 mg) n=69	1280 (± 89.6)			
C2D15 6 hours post-dose (ribociclib 400 mg) n=5	710 (± 47.4)			
C2D15 6 hours post-dose (ribociclib 200 mg) n=1	104 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: LEQ803 plasma concentrations

End point title	LEQ803 plasma concentrations[3]

End point description:

Blood samples were collected to assess the concentration by time point for LEQ803, a metabolite of ribociclib. Participants were classified into the following dose groups at each timepoint: 1) ribociclib 600 mg: consisted of all participants who provided evaluable concentrations after receiving at least 10 consecutive daily ribociclib doses of 600 mg immediately prior to the blood collection without a dose change or interruption. 2) ribociclib 400 mg: consisted of all participants who provided evaluable concentrations after receiving at least 10 consecutive daily ribociclib doses of 400 mg immediately prior to the blood collection without a dose change or interruption. 3) ribociclib 200 mg: consisted of all participants who provided evaluable concentrations after receiving at least 10 consecutive daily ribociclib doses of 200 mg immediately prior to the blood collection without a dose change or interruption.

End point type	Secondary

End point timeframe:

Cycle (C) 1 and Cycle 2 at Day (D) 15 pre-dose and at 2, 4, and 6 hours (h) post-dose. Cycle = 28 days

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: This endpoint reports results for the arm that received ribociclib

End point values	Ribociclib + fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	253			
Units: ng/mL				
geometric mean (geometric coefficient of variation)				
C1D15 predose (ribociclib 600 mg) n=253	75.6 (± 50.4)			
C1D15 predose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 predose (ribociclib 200 mg) n=0	9999 (± 9999)			
C1D15 2 hours post-dose (ribociclib 600 mg) n=102	134 (± 44.5)			
C1D15 2 hours post-dose (ribociclib 400 mg) n=0	9999 (± 9999)			

C1D15 2 hours post-dose (ribociclib 200 mg) n=0	9999 (± 9999)			
C1D15 4 hours post-dose (ribociclib 600 mg) n=107	137 (± 42.0)			
C1D15 4 hours post-dose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 4 hours post-dose (ribociclib 200 mg) n=0	9999 (± 9999)			
C1D15 6 hours post-dose (ribociclib 600 mg) n=92	128 (± 42.4)			
C1D15 6 hours post-dose (ribociclib 400 mg) n=0	9999 (± 9999)			
C1D15 6 hours post-dose (ribociclib 200 mg) n=0	9999 (± 9999)			
C2D15 predose (ribociclib 600 mg) n=177	72.7 (± 62.9)			
C2D15 predose (ribociclib 400 mg) n=7	46.2 (± 52.3)			
C2D15 predose (ribociclib 200 mg) n=0	9999 (± 9999)			
C2D15 2 hours post-dose (ribociclib 600 mg) n=75	126 (± 56.4)			
C2D15 2 hours post-dose (ribociclib 400 mg) n=7	70.8 (± 68.5)			
C2D15 2 hours post-dose (ribociclib 200 mg) n=1	36.0 (± 9999)			
C2D15 4 hours post-dose (ribociclib 600 mg) n=79	134 (± 44.9)			
C2D15 4 hours post-dose (ribociclib 400 mg) n=7	79.3 (± 67.2)			
C2D15 4 hours post-dose (ribociclib 200 mg) n=1	41.9 (± 9999)			
C2D15 6 hours post-dose (ribociclib 600 mg) n=69	122 (± 60.1)			
C2D15 6 hours post-dose (ribociclib 400 mg) n=5	72.3 (± 75.4)			
C2D15 6 hours post-dose (ribociclib 200 mg) n=1	38.3 (± 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 efficacy/survival follow-up deaths were collected from day 31 after last dose of study treatment to end of study.
Crossover post-treatment efficacy/survival follow-up 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 28 days. On-treatment: Up to 82 months. Crossover on-treatment: Up to 3.5 months. Post-treatment efficacy/survival follow-up: Up to 82 months. Crossover post-treatment efficacy/survival follow-up: Up to 1 year

End point values	Ribociclib + fulvestrant	Placebo + fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	484	242		
Units: Participants				
Pre-treatment deaths	0	0		
On-treatment deaths	13	8		
Crossover on-treatment deaths	0	0		
Post-treatment efficacy/survival deaths	264	153		
Crossover post-treatment efficacy/survival deaths	0	1		
All deaths	277	162		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	25.1

Reporting groups	
Reporting group title	Ribociclib + Fulvestrant
Reporting group description:	
Ribociclib + Fulvestrant	
Reporting group title	Placebo+Fulvestrant crossover to Ribociclib+Fulvestrant
Reporting group description:	
Placebo+Fulvestrant crossover to Ribociclib+Fulvestrant	
Reporting group title	Placebo + Fulvestrant
Reporting group description:	
Placebo + Fulvestrant	

Serious adverse events	Ribociclib + Fulvestrant	Placebo+Fulvestrant crossover to Ribociclib+Fulvestrant	Placebo + Fulvestrant
Total subjects affected by serious adverse events			
subjects affected / exposed	179 / 483 (37.06%)	1 / 3 (33.33%)	51 / 241 (21.16%)
number of deaths (all causes)	13	0	8
number of deaths resulting from adverse events	2	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cancer pain			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Endometrial adenocarcinoma			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endometrial cancer			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lung neoplasm malignant			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tumour pain			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 central nervous system			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to lung			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to peritoneum			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Squamous cell carcinoma of skin			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Thyroid neoplasm			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Transitional cell carcinoma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 pleural effusion			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arteriosclerosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Deep vein thrombosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Embolism			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Hypertension			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Ischaemia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Superior vena cava syndrome			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Shock haemorrhagic			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Lymphoedema			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Terminal state			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Systemic inflammatory response syndrome			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Swelling face			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			

subjects affected / exposed	6 / 483 (1.24%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	4 / 7	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malaise			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General physical health deterioration			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Fatigue			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Asthenia			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Non-cardiac chest pain			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Reproductive system and breast disorders			
Uterine prolapse			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vaginal haematoma			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
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			
Cough			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Acute pulmonary oedema			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Asthma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	9 / 483 (1.86%)	0 / 3 (0.00%)	5 / 241 (2.07%)
occurrences causally related to treatment / all	1 / 10	0 / 0	0 / 6
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Dyspnoea exertional			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	7 / 483 (1.45%)	0 / 3 (0.00%)	3 / 241 (1.24%)
occurrences causally related to treatment / all	0 / 8	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1

Pneumonitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Pneumothorax			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	5 / 483 (1.04%)	0 / 3 (0.00%)	3 / 241 (1.24%)
occurrences causally related to treatment / all	2 / 5	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 1	0 / 0	1 / 1
Respiratory failure			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Sleep disorder			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Anxiety			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	1 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Delirium			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Disorientation			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Blood creatinine increased			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Alanine aminotransferase increased			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	4 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (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 alkaline phosphatase increased			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood phosphorus decreased			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	2 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Liver function test abnormal			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Liver function test increased			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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			
Contusion			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Ankle fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Cervical vertebral fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Facial bones fracture			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Fall			
subjects affected / exposed	5 / 483 (1.04%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Femur fracture			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Foot fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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	5 / 483 (1.04%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Incisional hernia			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Infusion related reaction			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Multiple fractures			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Overdose			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Procedural pain			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Radius fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Rib fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 fracture			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Subdural haematoma			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Toxicity to various agents			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Wound dehiscence			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Wrist fracture			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Upper limb fracture			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Cardiac disorders			
Atrioventricular block second degree			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Bradycardia			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	2 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Cardiomyopathy			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiopulmonary failure			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Ischaemic cardiomyopathy			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Acute coronary syndrome			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Acute myocardial infarction			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Angina pectoris			

subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Myocardial infarction			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Atrial fibrillation			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Aortic valve sclerosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Ventricular arrhythmia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Tachycardia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachyarrhythmia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Supraventricular tachycardia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Carotid artery stenosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Cerebral haemorrhage			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebral infarction			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Cerebral ischaemia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Cerebrovascular accident			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
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	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysarthria			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Headache			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hemiparesis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Intercostal neuralgia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Paraesthesia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Dizziness			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Somnolence			

subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Spinal cord compression			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Syncope			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Transient ischaemic attack			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Trigeminal neuralgia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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			
Neutropenia			
subjects affected / exposed	7 / 483 (1.45%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	7 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancytopenia			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Anaemia			
subjects affected / exposed	7 / 483 (1.45%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	7 / 8	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			

subjects affected / exposed	6 / 483 (1.24%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	6 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune thrombocytopenia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Thrombocytopenia			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	4 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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			
Myopia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Diplopia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 disorders			
Abdominal distension			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (1.24%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Anal incontinence			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 upper			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aphthous ulcer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Ascites			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Intestinal obstruction			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Ileus			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Gingival disorder			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 perforation			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
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 ulcer			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Faecaloma			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Dysphagia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Diarrhoea			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Constipation			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Nausea			

subjects affected / exposed	10 / 483 (2.07%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	7 / 11	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	8 / 483 (1.66%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	4 / 8	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Hepatobiliary disorders			
Acute hepatic failure			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 2
Biliary colic			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic cytolysis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 failure			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Hepatotoxicity			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Cholangitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Cholecystitis acute			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Rash macular			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 ulcer			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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	6 / 483 (1.24%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	2 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bladder hypertrophy			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Prerenal failure			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Ureteric obstruction			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Ureterolithiasis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Urinary tract obstruction			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Adrenal insufficiency			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone pain			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint effusion			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Lumbar spinal stenosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 pain			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Osteonecrosis of jaw			

subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pain in extremity			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pathological fracture			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Muscle twitching			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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			
Anal abscess			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Appendicitis			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Breast cellulitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
COVID-19			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
COVID-19 pneumonia			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Cellulitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Clostridium difficile infection			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	13 / 483 (2.69%)	0 / 3 (0.00%)	3 / 241 (1.24%)
occurrences causally related to treatment / all	2 / 13	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Gangrene			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Gastroenteritis			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (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
Infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Influenza			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenic sepsis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Escherichia pyelonephritis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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 influenzal			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Postoperative wound infection			

subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Pyelonephritis			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Respiratory tract infection			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (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
Sepsis			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Urosepsis			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Wound infection			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Urinary tract infection			

subjects affected / exposed	4 / 483 (0.83%)	1 / 3 (33.33%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyponatraemia			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	0 / 241 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Dehydration			
subjects affected / exposed	4 / 483 (0.83%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	4 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypercalcaemia			
subjects affected / exposed	2 / 483 (0.41%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypervolaemia			
subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypocalcaemia			
subjects affected / exposed	3 / 483 (0.62%)	0 / 3 (0.00%)	0 / 241 (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
Hypokalaemia			
subjects affected / exposed	1 / 483 (0.21%)	0 / 3 (0.00%)	0 / 241 (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
Hypophagia			

subjects affected / exposed	0 / 483 (0.00%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
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 + Fulvestrant	Placebo+Fulvestrant crossover to Ribociclib+Fulvestrant	Placebo + Fulvestrant
Total subjects affected by non-serious adverse events			
subjects affected / exposed	475 / 483 (98.34%)	3 / 3 (100.00%)	225 / 241 (93.36%)
Vascular disorders			
Hypertension			
subjects affected / exposed	66 / 483 (13.66%)	0 / 3 (0.00%)	26 / 241 (10.79%)
occurrences (all)	88	0	29
Hypotension			
subjects affected / exposed	18 / 483 (3.73%)	1 / 3 (33.33%)	6 / 241 (2.49%)
occurrences (all)	22	1	6
Hot flush			
subjects affected / exposed	69 / 483 (14.29%)	0 / 3 (0.00%)	40 / 241 (16.60%)
occurrences (all)	77	0	47
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	74 / 483 (15.32%)	0 / 3 (0.00%)	31 / 241 (12.86%)
occurrences (all)	114	0	38
Fatigue			
subjects affected / exposed	164 / 483 (33.95%)	0 / 3 (0.00%)	82 / 241 (34.02%)
occurrences (all)	218	0	102
Influenza like illness			
subjects affected / exposed	38 / 483 (7.87%)	0 / 3 (0.00%)	17 / 241 (7.05%)
occurrences (all)	49	0	18
Injection site pain			
subjects affected / exposed	25 / 483 (5.18%)	0 / 3 (0.00%)	14 / 241 (5.81%)
occurrences (all)	30	0	16
Non-cardiac chest pain			

subjects affected / exposed	25 / 483 (5.18%)	0 / 3 (0.00%)	13 / 241 (5.39%)
occurrences (all)	31	0	13
Oedema peripheral			
subjects affected / exposed	70 / 483 (14.49%)	0 / 3 (0.00%)	16 / 241 (6.64%)
occurrences (all)	95	0	20
Pyrexia			
subjects affected / exposed	70 / 483 (14.49%)	0 / 3 (0.00%)	17 / 241 (7.05%)
occurrences (all)	102	0	22
Reproductive system and breast disorders			
Breast pain			
subjects affected / exposed	7 / 483 (1.45%)	0 / 3 (0.00%)	14 / 241 (5.81%)
occurrences (all)	7	0	15
Respiratory, thoracic and mediastinal disorders			
Oropharyngeal pain			
subjects affected / exposed	39 / 483 (8.07%)	0 / 3 (0.00%)	17 / 241 (7.05%)
occurrences (all)	48	0	20
Dyspnoea			
subjects affected / exposed	85 / 483 (17.60%)	0 / 3 (0.00%)	32 / 241 (13.28%)
occurrences (all)	118	0	42
Cough			
subjects affected / exposed	126 / 483 (26.09%)	0 / 3 (0.00%)	42 / 241 (17.43%)
occurrences (all)	188	0	51
Psychiatric disorders			
Insomnia			
subjects affected / exposed	63 / 483 (13.04%)	1 / 3 (33.33%)	30 / 241 (12.45%)
occurrences (all)	70	1	34
Depression			
subjects affected / exposed	38 / 483 (7.87%)	0 / 3 (0.00%)	13 / 241 (5.39%)
occurrences (all)	40	0	14
Anxiety			
subjects affected / exposed	34 / 483 (7.04%)	0 / 3 (0.00%)	15 / 241 (6.22%)
occurrences (all)	36	0	16
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	77 / 483 (15.94%)	0 / 3 (0.00%)	16 / 241 (6.64%)
occurrences (all)	94	0	26

Amylase increased			
subjects affected / exposed	13 / 483 (2.69%)	1 / 3 (33.33%)	3 / 241 (1.24%)
occurrences (all)	27	1	3
Aspartate aminotransferase increased			
subjects affected / exposed	70 / 483 (14.49%)	0 / 3 (0.00%)	17 / 241 (7.05%)
occurrences (all)	91	0	26
Blood cholesterol increased			
subjects affected / exposed	21 / 483 (4.35%)	0 / 3 (0.00%)	14 / 241 (5.81%)
occurrences (all)	22	0	17
Blood creatinine increased			
subjects affected / exposed	44 / 483 (9.11%)	1 / 3 (33.33%)	10 / 241 (4.15%)
occurrences (all)	75	1	20
Electrocardiogram QT prolonged			
subjects affected / exposed	30 / 483 (6.21%)	0 / 3 (0.00%)	3 / 241 (1.24%)
occurrences (all)	72	0	19
Gamma-glutamyltransferase increased			
subjects affected / exposed	39 / 483 (8.07%)	0 / 3 (0.00%)	19 / 241 (7.88%)
occurrences (all)	48	0	28
Lipase increased			
subjects affected / exposed	24 / 483 (4.97%)	0 / 3 (0.00%)	14 / 241 (5.81%)
occurrences (all)	51	0	28
Neutrophil count decreased			
subjects affected / exposed	105 / 483 (21.74%)	0 / 3 (0.00%)	4 / 241 (1.66%)
occurrences (all)	458	0	21
Weight decreased			
subjects affected / exposed	27 / 483 (5.59%)	0 / 3 (0.00%)	12 / 241 (4.98%)
occurrences (all)	30	0	12
White blood cell count decreased			
subjects affected / exposed	66 / 483 (13.66%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences (all)	148	0	12
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	19 / 483 (3.93%)	0 / 3 (0.00%)	16 / 241 (6.64%)
occurrences (all)	21	0	19
Headache			

subjects affected / exposed	120 / 483 (24.84%)	0 / 3 (0.00%)	51 / 241 (21.16%)
occurrences (all)	184	0	87
Dizziness			
subjects affected / exposed	71 / 483 (14.70%)	1 / 3 (33.33%)	22 / 241 (9.13%)
occurrences (all)	99	1	26
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	92 / 483 (19.05%)	2 / 3 (66.67%)	21 / 241 (8.71%)
occurrences (all)	188	2	31
Lymphopenia			
subjects affected / exposed	31 / 483 (6.42%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences (all)	46	0	2
Neutropenia			
subjects affected / exposed	279 / 483 (57.76%)	1 / 3 (33.33%)	6 / 241 (2.49%)
occurrences (all)	1240	1	10
Thrombocytopenia			
subjects affected / exposed	30 / 483 (6.21%)	0 / 3 (0.00%)	5 / 241 (2.07%)
occurrences (all)	63	0	8
Leukopenia			
subjects affected / exposed	93 / 483 (19.25%)	0 / 3 (0.00%)	1 / 241 (0.41%)
occurrences (all)	200	0	3
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	35 / 483 (7.25%)	0 / 3 (0.00%)	4 / 241 (1.66%)
occurrences (all)	39	0	4
Eye disorders			
Dry eye			
subjects affected / exposed	28 / 483 (5.80%)	0 / 3 (0.00%)	8 / 241 (3.32%)
occurrences (all)	30	0	8
Lacrimation increased			
subjects affected / exposed	27 / 483 (5.59%)	0 / 3 (0.00%)	2 / 241 (0.83%)
occurrences (all)	31	0	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	46 / 483 (9.52%)	0 / 3 (0.00%)	18 / 241 (7.47%)
occurrences (all)	56	0	23
Abdominal pain upper			

subjects affected / exposed	59 / 483 (12.22%)	0 / 3 (0.00%)	19 / 241 (7.88%)
occurrences (all)	73	0	20
Colitis			
subjects affected / exposed	3 / 483 (0.62%)	1 / 3 (33.33%)	1 / 241 (0.41%)
occurrences (all)	3	1	1
Constipation			
subjects affected / exposed	123 / 483 (25.47%)	0 / 3 (0.00%)	33 / 241 (13.69%)
occurrences (all)	161	0	42
Diarrhoea			
subjects affected / exposed	164 / 483 (33.95%)	1 / 3 (33.33%)	54 / 241 (22.41%)
occurrences (all)	300	3	85
Dry mouth			
subjects affected / exposed	27 / 483 (5.59%)	0 / 3 (0.00%)	5 / 241 (2.07%)
occurrences (all)	28	0	5
Dyspepsia			
subjects affected / exposed	56 / 483 (11.59%)	0 / 3 (0.00%)	15 / 241 (6.22%)
occurrences (all)	70	0	18
Dysphagia			
subjects affected / exposed	12 / 483 (2.48%)	1 / 3 (33.33%)	3 / 241 (1.24%)
occurrences (all)	13	1	3
Gastrooesophageal reflux disease			
subjects affected / exposed	25 / 483 (5.18%)	0 / 3 (0.00%)	5 / 241 (2.07%)
occurrences (all)	27	0	6
Nausea			
subjects affected / exposed	226 / 483 (46.79%)	1 / 3 (33.33%)	75 / 241 (31.12%)
occurrences (all)	377	1	104
Stomatitis			
subjects affected / exposed	63 / 483 (13.04%)	0 / 3 (0.00%)	13 / 241 (5.39%)
occurrences (all)	84	0	15
Toothache			
subjects affected / exposed	33 / 483 (6.83%)	0 / 3 (0.00%)	5 / 241 (2.07%)
occurrences (all)	44	0	5
Vomiting			
subjects affected / exposed	135 / 483 (27.95%)	1 / 3 (33.33%)	34 / 241 (14.11%)
occurrences (all)	208	1	49
Skin and subcutaneous tissue disorders			

Rash			
subjects affected / exposed	106 / 483 (21.95%)	0 / 3 (0.00%)	19 / 241 (7.88%)
occurrences (all)	155	0	25
Pruritus			
subjects affected / exposed	107 / 483 (22.15%)	0 / 3 (0.00%)	18 / 241 (7.47%)
occurrences (all)	150	0	23
Erythema			
subjects affected / exposed	26 / 483 (5.38%)	0 / 3 (0.00%)	3 / 241 (1.24%)
occurrences (all)	32	0	3
Dry skin			
subjects affected / exposed	40 / 483 (8.28%)	0 / 3 (0.00%)	8 / 241 (3.32%)
occurrences (all)	44	0	8
Alopecia			
subjects affected / exposed	100 / 483 (20.70%)	0 / 3 (0.00%)	12 / 241 (4.98%)
occurrences (all)	107	0	13
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	4 / 483 (0.83%)	2 / 3 (66.67%)	1 / 241 (0.41%)
occurrences (all)	4	2	1
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	86 / 483 (17.81%)	0 / 3 (0.00%)	48 / 241 (19.92%)
occurrences (all)	115	0	69
Neck pain			
subjects affected / exposed	41 / 483 (8.49%)	0 / 3 (0.00%)	14 / 241 (5.81%)
occurrences (all)	47	0	14
Myalgia			
subjects affected / exposed	49 / 483 (10.14%)	0 / 3 (0.00%)	27 / 241 (11.20%)
occurrences (all)	64	0	30
Musculoskeletal pain			
subjects affected / exposed	27 / 483 (5.59%)	0 / 3 (0.00%)	16 / 241 (6.64%)
occurrences (all)	35	0	19
Musculoskeletal chest pain			
subjects affected / exposed	21 / 483 (4.35%)	0 / 3 (0.00%)	23 / 241 (9.54%)
occurrences (all)	29	0	25
Muscle spasms			

subjects affected / exposed	37 / 483 (7.66%)	0 / 3 (0.00%)	14 / 241 (5.81%)
occurrences (all)	43	0	18
Arthralgia			
subjects affected / exposed	155 / 483 (32.09%)	0 / 3 (0.00%)	91 / 241 (37.76%)
occurrences (all)	295	0	153
Back pain			
subjects affected / exposed	108 / 483 (22.36%)	0 / 3 (0.00%)	46 / 241 (19.09%)
occurrences (all)	154	0	64
Bone pain			
subjects affected / exposed	49 / 483 (10.14%)	0 / 3 (0.00%)	24 / 241 (9.96%)
occurrences (all)	71	0	25
Infections and infestations			
Bronchitis			
subjects affected / exposed	34 / 483 (7.04%)	0 / 3 (0.00%)	12 / 241 (4.98%)
occurrences (all)	45	0	14
Cystitis			
subjects affected / exposed	26 / 483 (5.38%)	0 / 3 (0.00%)	9 / 241 (3.73%)
occurrences (all)	36	0	9
Influenza			
subjects affected / exposed	31 / 483 (6.42%)	0 / 3 (0.00%)	12 / 241 (4.98%)
occurrences (all)	32	0	13
Nasopharyngitis			
subjects affected / exposed	70 / 483 (14.49%)	0 / 3 (0.00%)	34 / 241 (14.11%)
occurrences (all)	109	0	53
Oral candidiasis			
subjects affected / exposed	0 / 483 (0.00%)	1 / 3 (33.33%)	0 / 241 (0.00%)
occurrences (all)	0	1	0
Oral herpes			
subjects affected / exposed	11 / 483 (2.28%)	1 / 3 (33.33%)	4 / 241 (1.66%)
occurrences (all)	22	1	4
Pharyngitis			
subjects affected / exposed	10 / 483 (2.07%)	1 / 3 (33.33%)	5 / 241 (2.07%)
occurrences (all)	13	1	5
Upper respiratory tract infection			
subjects affected / exposed	60 / 483 (12.42%)	0 / 3 (0.00%)	19 / 241 (7.88%)
occurrences (all)	88	0	25

Urinary tract infection			
subjects affected / exposed	62 / 483 (12.84%)	1 / 3 (33.33%)	29 / 241 (12.03%)
occurrences (all)	137	1	41
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	93 / 483 (19.25%)	0 / 3 (0.00%)	32 / 241 (13.28%)
occurrences (all)	112	0	36
Hyperglycaemia			
subjects affected / exposed	27 / 483 (5.59%)	0 / 3 (0.00%)	11 / 241 (4.56%)
occurrences (all)	37	0	11

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2016	Guidance for management of QTcF prolongation and hepatic toxicities. As QT prolongation is an important identified risk identified risk in patients treated with ribociclib, ECG monitoring was updated from single ECG monitoring to triplicate ECG monitoring. As hepatic toxicity is an important identified risk in patients treated with ribociclib, liver function monitoring and dose adjustment guidance were updated. Additional blood collections for laboratory assessments to further characterize potential drug-induced liver injury, including immunologic markers (e.g. immunoglobulins, C-reactive protein, autoimmune hepatitis markers) and total bile acids as part of clinical safety assessments, as well as blood collections for retrospective analysis of exploratory liver biomarkers (e.g. micro-RNA 122) and genome wide association studies (GWAS/HLA) were added. Management of dose modifications based on local laboratory results. Modification of the study population and eligibility criteria to include men (based on Health Authority interactions)
28 July 2016	Originally planned futility interim analysis (IA) was eliminated. Originally planned efficacy IA was eliminated and a requirement for a minimum amount of events coming from 1st line patients in the final analysis was added. PFS based on BIRC assessments was not a secondary endpoint but was added as a supportive analysis for the primary analysis. Progression on next-line therapy was added as an exploratory objective.
06 August 2018	Updated the dose adjustment and management recommendations for QTcF prolongation. Updated the prohibited concomitant medications based on drug-drug interaction and comedication considerations. PRO assessment schedule updated to follow the efficacy assessment schedule. As the radiology review from the blinded independent review is completed, note added on stopping the transmission of images to Contract Research organization (CRO). Updated the withdrawal of consent language to align with the new Global Data Protection Requirements.
29 January 2020	Allowed unblinding of all patients and investigators to allow for knowledge of patient's current treatment allocation and allow for patients currently receiving placebo the opportunity to transition to ribociclib treatment per investigator discretion. Also, visit evaluation schedule was updated for patients on placebo transitioning to ribociclib. Allowed for central safety electrocardiogram (ECG) assessments to cease and ECG assessments to be performed locally. Added guidance that patient reported outcome (PRO) measures should no longer be collected. Updated the biomarker collection schedule. The blood for circulating tumor DNA will be collected from all patients only at end of trial (EOT) and an additional collection on the first day of LEE011 treatment for patients who elect to cross-over from placebo

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported