



Clinical trial results:

A Phase III randomized, double-blind, placebo-controlled study of LEE011 or placebo in combination with tamoxifen and goserelin, or a non-steroidal aromatase inhibitor (NSAI) and goserelin for the treatment of premenopausal women with hormone receptor positive (HR+), HER2-negative (HER2-), advanced breast cancer.

Summary

EudraCT number	2014-001931-36
Trial protocol	HU DE BE IT PT PL BG ES GR
Global end of trial date	20 April 2023

Results information

Result version number	v1 (current)
This version publication date	06 March 2024
First version publication date	06 March 2024

Trial information

Trial identification

Sponsor protocol code	NCT02278120
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Additional study identifiers

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

Global end of trial reached?	Yes
Global end of trial date	20 April 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine whether treatment with tamoxifen or a NSAI + goserelin + ribociclib prolongs progression-free survival compared to treatment with tamoxifen or a NSAI + goserelin + placebo in premenopausal women with HR+, HER2-negative advanced breast cancer.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	17 December 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 6
Country: Number of subjects enrolled	Australia: 20
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Brazil: 24
Country: Number of subjects enrolled	Bulgaria: 6
Country: Number of subjects enrolled	Canada: 24
Country: Number of subjects enrolled	Colombia: 8
Country: Number of subjects enrolled	France: 29
Country: Number of subjects enrolled	Germany: 34
Country: Number of subjects enrolled	Greece: 6
Country: Number of subjects enrolled	Hong Kong: 6
Country: Number of subjects enrolled	Hungary: 16
Country: Number of subjects enrolled	India: 21
Country: Number of subjects enrolled	Italy: 65
Country: Number of subjects enrolled	Korea, Republic of: 82
Country: Number of subjects enrolled	Lebanon: 28
Country: Number of subjects enrolled	Malaysia: 7
Country: Number of subjects enrolled	Mexico: 18
Country: Number of subjects enrolled	Poland: 9

Country: Number of subjects enrolled	Portugal: 20
Country: Number of subjects enrolled	Russian Federation: 9
Country: Number of subjects enrolled	Saudi Arabia: 1
Country: Number of subjects enrolled	Singapore: 11
Country: Number of subjects enrolled	Spain: 51
Country: Number of subjects enrolled	Switzerland: 1
Country: Number of subjects enrolled	Taiwan: 42
Country: Number of subjects enrolled	Thailand: 11
Country: Number of subjects enrolled	Türkiye: 23
Country: Number of subjects enrolled	United Arab Emirates: 3
Country: Number of subjects enrolled	United States: 73
Worldwide total number of subjects	672
EEA total number of subjects	254

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)	672
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 185 sites across 30 countries.

Pre-assignment

Screening details:

Screening assessments were conducted up to 28 days prior to the randomization

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Ribociclib + NSAI/tamoxifen + goserelin

Arm description:

Ribociclib 600 mg daily oral (3 weeks on/ 1 week off) in combination with NSAI or tamoxifen (tamoxifen 20 mg daily oral or letrozole 2.5 mg daily oral or anastrozole 1 mg daily oral) and goserelin 3.6 mg subcutaneous injection (once every 28 days)

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

Dosage and administration details:

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

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

Dosage and administration details:

Tamoxifen (20 mg, tablets) was administered orally on a continuous daily schedule (days 1-28 of each 28-day cycle)

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

Dosage and administration details:

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

Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use
Dosage and administration details:	
Anastrozole (1 mg, tablets) was administered orally once daily on a continuous daily schedule (days 1-28 of each 28-day cycle)	
Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant
Routes of administration	Subcutaneous use
Dosage and administration details:	
Goserelin (3.6 mg, subcutaneous implant) was administered on day 1 of every 28-day cycle	
Arm title	Placebo + NSAID/tamoxifen+ goserelin
Arm description:	
Placebo daily oral (3 weeks on/ 1 week off) in combination with NSAID or tamoxifen (tamoxifen 20 mg daily oral or letrozole 2.5 mg daily oral or anastrozole 1 mg daily oral) and goserelin 3.6 mg subcutaneous injection (once every 28 days). Participants were unblinded once the final OS analysis was conducted and after the implementation of protocol amendment 6 (16-Jul-2019) and were given the option to crossover to treatment with ribociclib +NSAID/tamoxifen + goserelin	
Arm type	Placebo
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Letrozole (2.5 mg, tablets) was administered orally once daily on a continuous daily schedule (days 1-28 of each 28-day cycle)	
Investigational medicinal product name	Anastrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Anastrozole (1 mg, tablets) was administered orally once daily on a continuous daily schedule (days 1-28 of each 28-day cycle)	
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Tamoxifen (20 mg, tablets) was administered orally on a continuous daily schedule (days 1-28 of each 28-day cycle)	
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
Placebo (hard gelatin capsules) was administered orally once daily on Days 1-21 of each 28-day cycle.	
Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant

Routes of administration	Subcutaneous use
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Dosage and administration details:

Goserelin (3.6 mg, subcutaneous implant) was administered on day 1 of every 28-day cycle

Number of subjects in period 1	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen+ goserelin
Started	335	337
Crossover cohort	0	17
Completed	0	0
Not completed	335	337
Adverse event, serious fatal	3	3
Physician decision	14	27
Adverse event, non-fatal	16	14
Protocol deviation	-	2
Study terminated as per protocol	43	11
Progressive disease	234	260
Lost to follow-up	2	-
Subject/guardian decision	23	20

Baseline characteristics

Reporting groups

Reporting group title	Ribociclib + NSAI/tamoxifen + goserelin
Reporting group description: Ribociclib 600 mg daily oral (3 weeks on/ 1 week off) in combination with NSAI or tamoxifen (tamoxifen 20 mg daily oral or letrozole 2.5 mg daily oral or anastrozole 1 mg daily oral) and goserelin 3.6 mg subcutaneous injection (once every 28 days)	
Reporting group title	Placebo + NSAI/tamoxifen+ goserelin
Reporting group description: Placebo daily oral (3 weeks on/ 1 week off) in combination with NSAI or tamoxifen (tamoxifen 20 mg daily oral or letrozole 2.5 mg daily oral or anastrozole 1 mg daily oral) and goserelin 3.6 mg subcutaneous injection (once every 28 days). Participants were unblinded once the final OS analysis was conducted and after the implementation of protocol amendment 6 (16-Jul-2019) and were given the option to crossover to treatment with ribociclib +NSAI/tamoxifen + goserelin	

Reporting group values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen+ goserelin	Total
Number of subjects	335	337	672
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)	335	337	672
From 65-84 years	0	0	0
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	42.6	43.7	
standard deviation	± 6.6	± 6.17	-
Sex: Female, Male Units: Participants			
Female	335	337	672
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	187	201	388
Asian	99	99	198
Black	10	9	19
Native American	3	3	6
Other	16	7	23
Unknown	20	18	38

End points

End points reporting groups

Reporting group title	Ribociclib + NSAI/tamoxifen + goserelin
Reporting group description: Ribociclib 600 mg daily oral (3 weeks on/ 1 week off) in combination with NSAI or tamoxifen (tamoxifen 20 mg daily oral or letrozole 2.5 mg daily oral or anastrozole 1 mg daily oral) and goserelin 3.6 mg subcutaneous injection (once every 28 days)	
Reporting group title	Placebo + NSAI/tamoxifen+ goserelin
Reporting group description: Placebo daily oral (3 weeks on/ 1 week off) in combination with NSAI or tamoxifen (tamoxifen 20 mg daily oral or letrozole 2.5 mg daily oral or anastrozole 1 mg daily oral) and goserelin 3.6 mg subcutaneous injection (once every 28 days). Participants were unblinded once the final OS analysis was conducted and after the implementation of protocol amendment 6 (16-Jul-2019) and were given the option to crossover to treatment with ribociclib +NSAI/tamoxifen + goserelin	

Primary: Progression Free Survival (PFS) by investigator assessment

End point title	Progression Free Survival (PFS) by investigator assessment
End point description: PFS was defined as the period starting from the date of randomization to the date of the first documented progression or death caused by any reason. In cases where patients did not experience an event, the PFS was censored at the date of the last adequate tumor assessment. Clinical deterioration without objective radiological evidence was not considered as documented disease progression. PFS was assessed via local radiology assessment according to RECIST 1.1. As per protocol, the final PFS analysis was conducted after approximately 392 PFS events were documented. The Kaplan-Meier method was used to estimate PFS, and the median PFS, along with 95% confidence intervals, was reported for each treatment group. A stratified Cox regression model was used to estimate the hazard ratio of PFS, along with 95% confidence interval 9999 indicates that the value was not estimable	
End point type	Primary
End point timeframe: From randomization to first documented progression or death, assessed up to approximately 29 months	

End point values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Months				
median (confidence interval 95%)	23.8 (19.2 to 9999)	13.0 (11.0 to 16.4)		

Statistical analyses

Statistical analysis title	Statistical analysis of PFS
Comparison groups	Ribociclib + NSAI/tamoxifen + goserelin v Placebo + NSAI/tamoxifen+ goserelin

Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.0001
Method	Logrank
Parameter estimate	Log hazard ratio
Point estimate	0.553
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.441
upper limit	0.694

Secondary: Overall survival (OS)

End point title	Overall survival (OS)
End point description:	
<p>OS was defined as the time from the date of randomization to the date of death from any cause. In cases where the patient's death was not recorded, the OS value was censored at the date of the last known patient's survival status. OS was estimated using the Kaplan-Meier method. As per protocol, the final OS analysis was conducted after approximately 189 deaths were documented.</p> <p>The median OS, along with 95% confidence intervals, was reported for each treatment group. The distribution of OS between the two treatment arms was compared using a log-rank test at one-sided cumulative 2.5% level of significance. A stratified Cox regression was used to estimate the OS hazard ratio and the associated 95% CI.</p> <p>9999 indicates that the value was not estimable</p>	
End point type	Secondary
End point timeframe:	
From randomization to death, assessed up to approximately 45 months	

End point values	Ribociclib + NSAID/tamoxifen + goserelin	Placebo + NSAID/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Months				
median (confidence interval 95%)	9999 (-9999 to 9999)	40.9 (37.8 to 9999)		

Statistical analyses

Statistical analysis title	Statistical analysis of OS
Comparison groups	Ribociclib + NSAID/tamoxifen + goserelin v Placebo + NSAID/tamoxifen+ goserelin

Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00973 ^[1]
Method	Logrank
Parameter estimate	Cox proportional hazard
Point estimate	0.712
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.535
upper limit	0.948

Notes:

[1] - One-sided stratified log-rank test

Secondary: Clinical Benefit Rate (CBR) by investigator assessment

End point title	Clinical Benefit Rate (CBR) by investigator assessment
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End point description:

Percentage of participants with complete response (CR) or partial response (PR) or stable disease (SD) lasting 24 weeks or longer as defined in RECIST 1.1 and local assessment. CR = Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR = At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters; SD = Neither sufficient shrinkage to qualify for PR or CR nor an increase in lesions which would qualify for progressive disease: PD = At least a 20% increase in the sum of diameter of all measured target lesions, taking as reference the smallest sum of diameter of all target lesions recorded at or after baseline. In addition to the relative increase of 20% the sum must also demonstrate an absolute increase of at least 5 mm.

End point type	Secondary
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End point timeframe:

Up to approximately 29 months

End point values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Percentage of participants				
number (confidence interval 95%)	79.1 (74.8 to 83.5)	69.7 (64.8 to 74.6)		

Statistical analyses

Statistical analysis title	Statistical analysis of CBR
Comparison groups	Ribociclib + NSAI/tamoxifen + goserelin v Placebo + NSAI/tamoxifen+ goserelin

Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.002
Method	Cochran-Mantel-Haenszel

Secondary: Overall Response Rate (ORR) by investigator assessment

End point title	Overall Response Rate (ORR) by investigator assessment
End point description:	
ORR is the percentage of participants with the best overall response of complete response (CR) or partial response (PR) according to RECIST 1.1 as per local assessment. CR = Disappearance of all non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR = At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.	
End point type	Secondary
End point timeframe:	
Up to approximately 29 months	

End point values	Ribociclib + NSAID/tamoxifen + goserelin	Placebo + NSAID/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Percentage of participants				
number (confidence interval 95%)	40.9 (35.6 to 46.2)	29.7 (24.8 to 34.6)		

Statistical analyses

Statistical analysis title	Statistical analysis of ORR
Comparison groups	Ribociclib + NSAID/tamoxifen + goserelin v Placebo + NSAID/tamoxifen + goserelin
Number of subjects included in analysis	672
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.00098
Method	Cochran-Mantel-Haenszel

Secondary: Time to Response (TTR) by investigator assessment

End point title	Time to Response (TTR) by investigator assessment
End point description:	
Time to response is the time from the date of randomization to the first documented response (CR or PR, which must be confirmed subsequently) according to RECIST 1.1 as per local 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 non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR = At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

9999 indicates that the value was not estimable

End point type	Secondary
End point timeframe:	
Up to approximately 29 months	

End point values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: months				
median (confidence interval 95%)	9999 (9999 to 9999)	9999 (9999 to 9999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR) by investigator assessment

End point title	Duration of Response (DOR) by investigator assessment
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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 non-nodal target lesions. In addition, any pathological lymph nodes assigned as target lesions must have a reduction in short axis to < 10 mm; PR = At least a 30% decrease in the sum of diameter of all target lesions, taking as reference the baseline sum of diameters.

9999 indicates that the value was not estimable

End point type	Secondary
End point timeframe:	
Up to approximately 29 months	

End point values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	137	100		
Units: Months				
median (confidence interval 95%)	21.3 (18.3 to 9999)	17.5 (12.0 to 9999)		

Statistical analyses

No statistical analyses for this end point

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

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

ECOG PS categorized patients based on their ability to perform daily activities and self-care. Scores ranged from 0 to 5, with 0 = no restrictions, and higher scores indicating increasing limitations. Time to definitive deterioration was defined as the time from the date of randomization to the date of the event, defined as experiencing an increase in ECOG PS by at least one category from the baseline or death. A deterioration was considered definitive if no improvements in the ECOG PS were observed at a subsequent time. The Kaplan-Meier method was used to estimate the distribution, and the median time to definitive deterioration, along with 95% confidence intervals, was reported. Patients receiving any further therapy prior to definitive worsening were censored at their date of last assessment prior to start of therapy. Patients that had not worsened at the data cutoff point were censored at the date of last assessment.

9999 indicates that the value was not estimable

End point type	Secondary
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End point timeframe:

Baseline, up to approximately 29 months

End point values	Ribociclib + NSAI/tamoxifen n + goserelin	Placebo + NSAI/tamoxifen n + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Months				
median (confidence interval 95%)	9999 (-9999 to 9999)	9999 (-9999 to 9999)		

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)
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End point description:

The EORTC QLQ-C30 is a questionnaire that includes 5 functional scales, 3 symptom scales, 1 GHS/QoL scale, and 6 single items. GHS/QoL scale score ranges between 0 and 100. A high score for GHS/QoL represents better functioning or QoL. The time to definitive 10% deterioration is defined as the time from the date of randomization to the date of event, which is defined as at least 10% relative to baseline worsening of the QoL score (without further improvement above the threshold) or death due to any cause. The Kaplan-Meier method was used to estimate the distribution, and the median time to definitive 10% deterioration, along with 95% confidence intervals, was reported for each treatment group. If a patient had not had an event, time to deterioration was censored at the date of the last adequate QoL evaluation.

9999 indicates that the value was not estimable

End point type	Secondary
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End point timeframe:

Up to approximately 29 months

End point values	Ribociclib + NSAI/tamoxife n + goserelin	Placebo + NSAI/tamoxife n+ goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Months				
median (confidence interval 95%)	9999 (22.2 to 9999)	21.2 (15.4 to 23.0)		

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
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End point description:

The EORTC QLQ-C30 is a questionnaire that includes 5 functional scales, 3 symptom scales, 1 GHS/QoL scale, and 6 single items. GHS/QoL scale score ranges between 0 and 100. A high score for GHS/QoL represents better functioning or QoL. The change from baseline in the GHS/QoL score was assessed. A positive change from baseline indicated improvement. For subjects who discontinued treatment without disease progression, post-treatment efficacy visits occurred every 8 weeks during the initial 18 months since start of treatment, followed by visits every 12 weeks until disease progression.

9999 indicates that the value was not estimable

End point type	Secondary
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End point timeframe:

Baseline, every 2 cycles after randomization during 18 months, then every 3 cycles up to end of treatment (EOT); EOT; and every 8 or 12 weeks post-treatment until progression, assessed up to approximately 29 months. Cycle=28 days

End point values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	300	280		
Units: Score on a Scale				
arithmetic mean (standard deviation)				
Cycle 3 Day 1 (n= 300 / 280)	4.6 (± 21.64)	5.0 (± 22.10)		
Cycle 5 Day 1 (n= 277 / 246)	5.1 (± 21.81)	5.1 (± 20.60)		
Cycle 7 Day 1 (n= 263 / 231)	5.0 (± 21.67)	4.0 (± 22.57)		
Cycle 9 Day 1 (n= 250 / 207)	4.8 (± 22.37)	3.7 (± 23.76)		
Cycle 11 Day 1 (n= 236 / 185)	4.3 (± 22.17)	4.4 (± 24.53)		
Cycle 13 Day 1 (n= 213 / 166)	4.7 (± 21.14)	3.9 (± 25.19)		
Cycle 15 Day 1 (n= 204 / 150)	4.8 (± 22.44)	3.2 (± 24.91)		
Cycle 17 Day 1 (n= 170 / 117)	4.0 (± 20.60)	2.7 (± 25.68)		
Cycle 19 Day 1 (n= 128 / 85)	5.5 (± 22.12)	-1.2 (± 24.10)		
Cycle 22 Day 1 (n= 79 / 46)	7.6 (± 25.43)	-3.4 (± 25.43)		
Cycle 25 Day 1 (n= 50 / 25)	5.2 (± 19.41)	-0.3 (± 25.51)		
Cycle 28 Day 1 (n= 19 / 11)	7.9 (± 19.54)	-8.3 (± 30.28)		
Cycle 31 Day 1 (n= 2 / 1)	8.3 (± 11.79)	-8.3 (± 9999)		
End of treatment (n= 129 / 179)	-4.4 (± 27.78)	-3.0 (± 23.41)		
Post-end of treatment 1 (n= 9 / 11)	3.7 (± 25.38)	6.8 (± 32.02)		
Post-end of treatment 2 (n= 3 / 2)	5.6 (± 12.73)	0.0 (± 11.79)		
Post-end of treatment 3 (n= 3 / 2)	8.3 (± 14.43)	-4.2 (± 5.89)		
Post-end of treatment 4 (n= 3 / 1)	11.1 (± 17.35)	-8.3 (± 9999)		
Post-end of treatment 5 (n= 1 / 0)	16.7 (± 9999)	9999 (± 9999)		

Statistical analyses

No statistical analyses for this end point

Post-hoc: All collected deaths

End point title	All collected deaths
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End point description:

On-treatment deaths were collected from start of treatment to 30 days after last dose of treatment or one day before first administration of crossover treatment (for crossover participants), whichever came first.

Crossover on-treatment deaths were collected from start of crossover treatment up to 30 days after last dose of crossover treatment.

Post-treatment survival follow-up deaths were collected from day 31 after last dose of study treatment to end of study or one day before first administration of crossover treatment

Crossover post-treatment survival follow-up deaths were collected from day 31 after last dose of crossover treatment to end of study

End point type	Post-hoc
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End point timeframe:

On-treatment: Up to 90 months. Crossover on-treatment: Up to approximately 33 months after crossing-over. Post-treatment survival follow-up: Up to 90 months. Crossover post-treatment survival follow-up: Up to approximately 33 months after crossing-over

End point values	Ribociclib + NSAI/tamoxifen + goserelin	Placebo + NSAI/tamoxifen + goserelin		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	335	337		
Units: Participants				
On-treatment deaths	5	6		
Crossover on-treatment deaths	0	0		
Post-treatment survival follow-up deaths	168	202		
Crossover post-treatment survival deaths	0	1		
All deaths	173	209		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

On-treatment AEs: from first dose to 30 days post-treatment or start of crossover treatment, up to 90 months

Crossover on-treatment AEs: from first dose of crossover treatment to 30 days post-crossover treatment, up to approximately 33 months.

Adverse event reporting additional description:

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

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	Ribociclib + NSAI/tamoxifen + goserelin (On-treatment)
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Reporting group description:

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

Reporting group title	Placebo crossover to Ribociclib (On-Treatment)
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Reporting group description:

AEs collected during crossover on-treatment period with ribociclib for participants randomized to placebo arm who crossed-over to ribociclib (up to 30 days post- crossover treatment)

Reporting group title	Placebo + NSAI/tamoxifen+ goserelin (On-treatment)
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Reporting group description:

AEs collected during on-treatment period (up to 30 days post-treatment or start of crossover treatment)

Serious adverse events	Ribociclib + NSAI/tamoxifen + goserelin (On- treatment)	Placebo crossover to Ribociclib (On- Treatment)	Placebo + NSAI/tamoxifen+ goserelin (On- treatment)
Total subjects affected by serious adverse events			
subjects affected / exposed	81 / 335 (24.18%)	1 / 17 (5.88%)	49 / 337 (14.54%)
number of deaths (all causes)	5	0	6
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign soft tissue neoplasm			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Cancer pain			

subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic myeloid leukaemia			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
HER2 positive breast cancer			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Intracranial tumour haemorrhage			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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 cell carcinoma			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to meninges			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metastases to central nervous system			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Malignant pleural effusion			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Lipoma			

subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leiomyoma			
subjects affected / exposed	0 / 335 (0.00%)	1 / 17 (5.88%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Superior vena cava syndrome			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hypovolaemic shock			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Aortic thrombosis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
General disorders and administration site conditions			
Axillary pain			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Fatigue			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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	4 / 335 (1.19%)	0 / 17 (0.00%)	4 / 337 (1.19%)
occurrences causally related to treatment / all	0 / 4	0 / 0	1 / 4
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pelvic pain			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	5 / 335 (1.49%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 5	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 1
Acute respiratory failure			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hydrothorax			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Nasal polyps			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Paranasal sinus inflammation			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pleural effusion			
subjects affected / exposed	6 / 335 (1.79%)	0 / 17 (0.00%)	5 / 337 (1.48%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 5
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Pulmonary embolism			
subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	1 / 2	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Psychiatric disorders			
Obsessive-compulsive disorder			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Confusional state			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Alcohol abuse			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic enzyme increased			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
SARS-CoV-2 antibody test positive			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Post lumbar puncture syndrome			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Alcohol poisoning			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Femur fracture			
subjects affected / exposed	3 / 335 (0.90%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hand fracture			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	0 / 337 (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
Wound haemorrhage			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Arrhythmia			

subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pericardial effusion			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus tachycardia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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 infarction			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Dizziness			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Haemorrhage intracranial			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Headache			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Superior sagittal sinus thrombosis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hypoaesthesia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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			
Anaemia			
subjects affected / exposed	4 / 335 (1.19%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	3 / 5	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	5 / 335 (1.49%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	5 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Enterocolitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Ascites			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Diarrhoea			

subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dysphagia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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	5 / 335 (1.49%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 6	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Epigastric discomfort			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Ileus			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Nausea			
subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 2	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Small intestinal obstruction			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Stomatitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			

subjects affected / exposed	3 / 335 (0.90%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Subileus			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug-induced liver injury			
subjects affected / exposed	4 / 335 (1.19%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	4 / 4	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatic haemorrhage			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatotoxicity			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Liver disorder			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hyperbilirubinaemia			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Skin and subcutaneous tissue disorders			
Skin ulcer			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erythema			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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	0 / 335 (0.00%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Myositis			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Back pain			
subjects affected / exposed	4 / 335 (1.19%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bone pain			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Arthralgia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Osteonecrosis of jaw			
subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	0 / 337 (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
Pathological fracture			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rhabdomyolysis			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal pain			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Neck pain			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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			
Bacteraemia			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Abdominal wall abscess			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute sinusitis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atypical pneumonia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cellulitis			

subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	2 / 335 (0.60%)	0 / 17 (0.00%)	0 / 337 (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
Gastroenteritis viral			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Herpes zoster			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Otitis media			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	5 / 335 (1.49%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	1 / 5	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Postoperative wound infection			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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	2 / 335 (0.60%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sepsis			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Upper respiratory tract infection			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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 device infection			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Viral infection			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hypercalcaemia			

subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Decreased appetite			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Electrolyte imbalance			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperglycaemia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hypoalbuminaemia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hypocalcaemia			
subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (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
Hypokalaemia			
subjects affected / exposed	0 / 335 (0.00%)	0 / 17 (0.00%)	1 / 337 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lactic acidosis			

subjects affected / exposed	1 / 335 (0.30%)	0 / 17 (0.00%)	0 / 337 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Ribociclib + NSAI/tamoxifen + goserelin (On- treatment)	Placebo crossover to Ribociclib (On- Treatment)	Placebo + NSAI/tamoxifen+ goserelin (On- treatment)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	326 / 335 (97.31%)	14 / 17 (82.35%)	312 / 337 (92.58%)
Vascular disorders			
Hot flush			
subjects affected / exposed	118 / 335 (35.22%)	0 / 17 (0.00%)	117 / 337 (34.72%)
occurrences (all)	139	0	143
Hypertension			
subjects affected / exposed	42 / 335 (12.54%)	0 / 17 (0.00%)	28 / 337 (8.31%)
occurrences (all)	61	0	47
Lymphoedema			
subjects affected / exposed	8 / 335 (2.39%)	1 / 17 (5.88%)	11 / 337 (3.26%)
occurrences (all)	8	1	13
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	54 / 335 (16.12%)	1 / 17 (5.88%)	43 / 337 (12.76%)
occurrences (all)	101	1	54
Chills			
subjects affected / exposed	6 / 335 (1.79%)	1 / 17 (5.88%)	4 / 337 (1.19%)
occurrences (all)	7	1	8
Fatigue			
subjects affected / exposed	89 / 335 (26.57%)	2 / 17 (11.76%)	86 / 337 (25.52%)
occurrences (all)	116	2	113
Influenza like illness			
subjects affected / exposed	23 / 335 (6.87%)	0 / 17 (0.00%)	13 / 337 (3.86%)
occurrences (all)	35	0	25
Mucosal haemorrhage			

subjects affected / exposed occurrences (all)	0 / 335 (0.00%) 0	1 / 17 (5.88%) 3	0 / 337 (0.00%) 0
Non-cardiac chest pain subjects affected / exposed occurrences (all)	26 / 335 (7.76%) 31	0 / 17 (0.00%) 0	15 / 337 (4.45%) 18
Oedema peripheral subjects affected / exposed occurrences (all)	25 / 335 (7.46%) 33	1 / 17 (5.88%) 2	18 / 337 (5.34%) 23
Pyrexia subjects affected / exposed occurrences (all)	60 / 335 (17.91%) 93	3 / 17 (17.65%) 3	29 / 337 (8.61%) 41
Localised oedema subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	1 / 17 (5.88%) 1	5 / 337 (1.48%) 5
Immune system disorders Contrast media reaction subjects affected / exposed occurrences (all)	0 / 335 (0.00%) 0	1 / 17 (5.88%) 1	0 / 337 (0.00%) 0
Reproductive system and breast disorders Breast pain subjects affected / exposed occurrences (all)	24 / 335 (7.16%) 29	0 / 17 (0.00%) 0	23 / 337 (6.82%) 26
Respiratory, thoracic and mediastinal disorders Oropharyngeal pain subjects affected / exposed occurrences (all)	33 / 335 (9.85%) 48	0 / 17 (0.00%) 0	18 / 337 (5.34%) 25
Dyspnoea subjects affected / exposed occurrences (all)	26 / 335 (7.76%) 30	1 / 17 (5.88%) 1	21 / 337 (6.23%) 28
Cough subjects affected / exposed occurrences (all)	73 / 335 (21.79%) 92	3 / 17 (17.65%) 3	42 / 337 (12.46%) 60
Productive cough subjects affected / exposed occurrences (all)	18 / 335 (5.37%) 21	0 / 17 (0.00%) 0	13 / 337 (3.86%) 14
Psychiatric disorders			

Insomnia			
subjects affected / exposed	51 / 335 (15.22%)	0 / 17 (0.00%)	55 / 337 (16.32%)
occurrences (all)	62	0	66
Depression			
subjects affected / exposed	22 / 335 (6.57%)	0 / 17 (0.00%)	23 / 337 (6.82%)
occurrences (all)	22	0	26
Anxiety			
subjects affected / exposed	22 / 335 (6.57%)	0 / 17 (0.00%)	17 / 337 (5.04%)
occurrences (all)	24	0	18
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	58 / 335 (17.31%)	2 / 17 (11.76%)	34 / 337 (10.09%)
occurrences (all)	97	2	48
Aspartate aminotransferase increased			
subjects affected / exposed	55 / 335 (16.42%)	4 / 17 (23.53%)	36 / 337 (10.68%)
occurrences (all)	91	4	48
Blood cholesterol increased			
subjects affected / exposed	12 / 335 (3.58%)	1 / 17 (5.88%)	9 / 337 (2.67%)
occurrences (all)	14	1	9
Electrocardiogram QT prolonged			
subjects affected / exposed	42 / 335 (12.54%)	1 / 17 (5.88%)	16 / 337 (4.75%)
occurrences (all)	64	1	24
Gamma-glutamyltransferase increased			
subjects affected / exposed	22 / 335 (6.57%)	0 / 17 (0.00%)	32 / 337 (9.50%)
occurrences (all)	26	0	47
Neutrophil count decreased			
subjects affected / exposed	119 / 335 (35.52%)	4 / 17 (23.53%)	5 / 337 (1.48%)
occurrences (all)	665	12	7
SARS-CoV-2 test negative			
subjects affected / exposed	2 / 335 (0.60%)	1 / 17 (5.88%)	0 / 337 (0.00%)
occurrences (all)	2	1	0
SARS-CoV-2 test positive			
subjects affected / exposed	5 / 335 (1.49%)	1 / 17 (5.88%)	1 / 337 (0.30%)
occurrences (all)	5	1	1
Weight increased			

subjects affected / exposed occurrences (all)	9 / 335 (2.69%) 10	1 / 17 (5.88%) 1	10 / 337 (2.97%) 10
White blood cell count decreased subjects affected / exposed occurrences (all)	55 / 335 (16.42%) 146	1 / 17 (5.88%) 2	4 / 337 (1.19%) 8
Injury, poisoning and procedural complications			
Post procedural erythema subjects affected / exposed occurrences (all)	0 / 335 (0.00%) 0	1 / 17 (5.88%) 1	0 / 337 (0.00%) 0
Wound subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	1 / 17 (5.88%) 1	1 / 337 (0.30%) 1
Nervous system disorders			
Syncope subjects affected / exposed occurrences (all)	2 / 335 (0.60%) 2	1 / 17 (5.88%) 1	4 / 337 (1.19%) 4
Paraesthesia subjects affected / exposed occurrences (all)	18 / 335 (5.37%) 22	0 / 17 (0.00%) 0	18 / 337 (5.34%) 26
Loss of consciousness subjects affected / exposed occurrences (all)	1 / 335 (0.30%) 1	1 / 17 (5.88%) 1	2 / 337 (0.59%) 2
Headache subjects affected / exposed occurrences (all)	96 / 335 (28.66%) 175	1 / 17 (5.88%) 1	89 / 337 (26.41%) 169
Dizziness subjects affected / exposed occurrences (all)	27 / 335 (8.06%) 34	0 / 17 (0.00%) 0	25 / 337 (7.42%) 33
Ageusia subjects affected / exposed occurrences (all)	3 / 335 (0.90%) 3	1 / 17 (5.88%) 1	0 / 337 (0.00%) 0
Blood and lymphatic system disorders			
Anaemia subjects affected / exposed occurrences (all)	73 / 335 (21.79%) 119	2 / 17 (11.76%) 4	37 / 337 (10.98%) 50
Leukopenia			

subjects affected / exposed	66 / 335 (19.70%)	1 / 17 (5.88%)	13 / 337 (3.86%)
occurrences (all)	193	1	26
Thrombocytopenia			
subjects affected / exposed	24 / 335 (7.16%)	0 / 17 (0.00%)	6 / 337 (1.78%)
occurrences (all)	41	0	9
Neutropenia			
subjects affected / exposed	194 / 335 (57.91%)	5 / 17 (29.41%)	22 / 337 (6.53%)
occurrences (all)	876	10	62
Lymphopenia			
subjects affected / exposed	29 / 335 (8.66%)	0 / 17 (0.00%)	5 / 337 (1.48%)
occurrences (all)	58	0	13
Eye disorders			
Lacrimation increased			
subjects affected / exposed	17 / 335 (5.07%)	0 / 17 (0.00%)	2 / 337 (0.59%)
occurrences (all)	22	0	2
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	62 / 335 (18.51%)	0 / 17 (0.00%)	48 / 337 (14.24%)
occurrences (all)	86	0	61
Abdominal pain upper			
subjects affected / exposed	27 / 335 (8.06%)	0 / 17 (0.00%)	24 / 337 (7.12%)
occurrences (all)	35	0	28
Abdominal pain			
subjects affected / exposed	39 / 335 (11.64%)	0 / 17 (0.00%)	27 / 337 (8.01%)
occurrences (all)	59	0	35
Vomiting			
subjects affected / exposed	76 / 335 (22.69%)	0 / 17 (0.00%)	61 / 337 (18.10%)
occurrences (all)	120	0	84
Toothache			
subjects affected / exposed	15 / 335 (4.48%)	1 / 17 (5.88%)	11 / 337 (3.26%)
occurrences (all)	18	1	11
Stomatitis			
subjects affected / exposed	48 / 335 (14.33%)	0 / 17 (0.00%)	30 / 337 (8.90%)
occurrences (all)	87	0	44
Nausea			

subjects affected / exposed	113 / 335 (33.73%)	4 / 17 (23.53%)	78 / 337 (23.15%)
occurrences (all)	197	4	113
Mouth haemorrhage			
subjects affected / exposed	0 / 335 (0.00%)	1 / 17 (5.88%)	0 / 337 (0.00%)
occurrences (all)	0	1	0
Gingival swelling			
subjects affected / exposed	0 / 335 (0.00%)	1 / 17 (5.88%)	0 / 337 (0.00%)
occurrences (all)	0	1	0
Dyspepsia			
subjects affected / exposed	20 / 335 (5.97%)	0 / 17 (0.00%)	14 / 337 (4.15%)
occurrences (all)	25	0	19
Dry mouth			
subjects affected / exposed	16 / 335 (4.78%)	0 / 17 (0.00%)	18 / 337 (5.34%)
occurrences (all)	16	0	18
Diarrhoea			
subjects affected / exposed	82 / 335 (24.48%)	1 / 17 (5.88%)	67 / 337 (19.88%)
occurrences (all)	150	1	113
Hepatobiliary disorders			
Hepatic pain			
subjects affected / exposed	1 / 335 (0.30%)	1 / 17 (5.88%)	1 / 337 (0.30%)
occurrences (all)	1	1	1
Skin and subcutaneous tissue disorders			
Rash maculo-papular			
subjects affected / exposed	13 / 335 (3.88%)	1 / 17 (5.88%)	1 / 337 (0.30%)
occurrences (all)	16	1	1
Pruritus			
subjects affected / exposed	39 / 335 (11.64%)	0 / 17 (0.00%)	18 / 337 (5.34%)
occurrences (all)	58	0	19
Dry skin			
subjects affected / exposed	28 / 335 (8.36%)	0 / 17 (0.00%)	8 / 337 (2.37%)
occurrences (all)	40	0	22
Alopecia			
subjects affected / exposed	64 / 335 (19.10%)	2 / 17 (11.76%)	41 / 337 (12.17%)
occurrences (all)	71	3	48
Rash			

subjects affected / exposed	53 / 335 (15.82%)	0 / 17 (0.00%)	32 / 337 (9.50%)
occurrences (all)	69	0	39
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	130 / 335 (38.81%)	1 / 17 (5.88%)	122 / 337 (36.20%)
occurrences (all)	213	1	193
Back pain			
subjects affected / exposed	76 / 335 (22.69%)	0 / 17 (0.00%)	72 / 337 (21.36%)
occurrences (all)	103	0	94
Bone pain			
subjects affected / exposed	34 / 335 (10.15%)	0 / 17 (0.00%)	32 / 337 (9.50%)
occurrences (all)	40	0	42
Pain in extremity			
subjects affected / exposed	53 / 335 (15.82%)	0 / 17 (0.00%)	44 / 337 (13.06%)
occurrences (all)	66	0	52
Joint stiffness			
subjects affected / exposed	11 / 335 (3.28%)	1 / 17 (5.88%)	12 / 337 (3.56%)
occurrences (all)	12	1	15
Muscle spasms			
subjects affected / exposed	19 / 335 (5.67%)	0 / 17 (0.00%)	10 / 337 (2.97%)
occurrences (all)	39	0	12
Musculoskeletal chest pain			
subjects affected / exposed	16 / 335 (4.78%)	0 / 17 (0.00%)	20 / 337 (5.93%)
occurrences (all)	23	0	24
Musculoskeletal pain			
subjects affected / exposed	14 / 335 (4.18%)	0 / 17 (0.00%)	17 / 337 (5.04%)
occurrences (all)	17	0	18
Myalgia			
subjects affected / exposed	47 / 335 (14.03%)	0 / 17 (0.00%)	42 / 337 (12.46%)
occurrences (all)	61	0	46
Neck pain			
subjects affected / exposed	19 / 335 (5.67%)	0 / 17 (0.00%)	19 / 337 (5.64%)
occurrences (all)	27	0	21
Infections and infestations			

COVID-19			
subjects affected / exposed	10 / 335 (2.99%)	2 / 17 (11.76%)	1 / 337 (0.30%)
occurrences (all)	12	2	1
Herpes zoster			
subjects affected / exposed	7 / 335 (2.09%)	1 / 17 (5.88%)	6 / 337 (1.78%)
occurrences (all)	7	1	6
Influenza			
subjects affected / exposed	29 / 335 (8.66%)	1 / 17 (5.88%)	24 / 337 (7.12%)
occurrences (all)	46	1	32
Nasopharyngitis			
subjects affected / exposed	34 / 335 (10.15%)	0 / 17 (0.00%)	23 / 337 (6.82%)
occurrences (all)	50	0	27
Suspected COVID-19			
subjects affected / exposed	1 / 335 (0.30%)	1 / 17 (5.88%)	0 / 337 (0.00%)
occurrences (all)	1	1	0
Upper respiratory tract infection			
subjects affected / exposed	53 / 335 (15.82%)	2 / 17 (11.76%)	40 / 337 (11.87%)
occurrences (all)	92	2	63
Urinary tract infection			
subjects affected / exposed	38 / 335 (11.34%)	0 / 17 (0.00%)	31 / 337 (9.20%)
occurrences (all)	46	0	47
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	34 / 335 (10.15%)	1 / 17 (5.88%)	27 / 337 (8.01%)
occurrences (all)	50	1	30
Hypercholesterolaemia			
subjects affected / exposed	15 / 335 (4.48%)	1 / 17 (5.88%)	13 / 337 (3.86%)
occurrences (all)	16	1	15
Hyperglycaemia			
subjects affected / exposed	16 / 335 (4.78%)	0 / 17 (0.00%)	18 / 337 (5.34%)
occurrences (all)	25	0	42
Hypermagnesaemia			
subjects affected / exposed	0 / 335 (0.00%)	1 / 17 (5.88%)	0 / 337 (0.00%)
occurrences (all)	0	1	0
Hypertriglyceridaemia			

subjects affected / exposed	16 / 335 (4.78%)	2 / 17 (11.76%)	17 / 337 (5.04%)
occurrences (all)	23	3	25

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 April 2015	This amendment introduced the following key changes: - Further enhance and clarify safety monitoring of patients including: 1) Management of QTc prolongation. 2) Dose modification guidance for management of cases of hepatic toxicities. 3) Changes to management of grade 3. - Update the protocol for consistency with the most recent nonclinical information. - Based on updated preclinical data and since no clinically significant thyroid events were reported in clinical studies the risk to the thyroid gland was removed from the reference safety information based on updated data and thyroid laboratory monitoring in clinical protocols was no longer mandated. - Revise the treatment allocation in case of prior use of fulvestrant - Patients who had prior dose of (neo) adjuvant fulvestrant (last dose given <12 months prior to randomization) were eligible to receive tamoxifen plus goserelin on study. However, because fulvestrant is an ER antagonist with a mechanism of action more similar to tamoxifen than to NSAIs, patients having received (neo) adjuvant fulvestrant (last dose was given <12 months prior to randomization) received a NSAID plus goserelin on study instead of tamoxifen plus goserelin. - PFS assessment as per BIRC was changed from supportive analysis of the primary endpoint to a secondary endpoint.
17 February 2016	This amendment introduced the following key changes: - Management of QTcF prolongation- Management of hepatic toxicities- Management of dose modifications based on local laboratory results. - List of prohibited concomitant medications was updated. - New information was provided on the safety pharmacology and toxicology. - Central radiology assessment by medical oncologist review was replaced by a standard BIRC assessment. - Baseline tumor collection was made mandatory.
24 June 2016	The purpose of this amendment was to: <ul style="list-style-type: none">- Eliminate the planned futility analysis since additional clinical data had been generated with ribociclib and other CDK 4/6 inhibitors compared to the start of the study providing additional assurance of the activity in patients with breast cancer.- Include the change of approach for BIRC assessment of PFS from a full read to an audit (sample) based approach.- Add an exploratory endpoint (PFS2) defined as the time from randomization to progression on next-line therapy or death, whichever occurred first, in order to make an exploratory assessment of longer-term benefit intermediate to PFS and OS.- Reflect the new Novartis guidance on the implementation of RECIST v1.1. The updates to the RECIST v1.1 guidelines were minor clarifications to existing situations and the addition of PFS2 as a substitute endpoint for OS, in alignment the EMA guidance. These changes had no impact in the efficacy evaluation of the study.- Additional changes included updates to clinical pharmacokinetic section to reflect available new data.- Palliative radiotherapy, previously only allowed for bone pain relief, was permitted following this amendment provided it was not delivered to a target lesion.- A sensitivity analysis was included for ORR based on patients with measurable disease at baseline.

24 February 2017	<p>The purpose of this amendment was:</p> <ul style="list-style-type: none"> - To remove the planned efficacy interim analysis: Interim analysis that allowed the study to stop for superior efficacy was planned after all patients had been randomized and approximately 80% PFS events (263 events) had been documented, as per local assessments. The elimination allowed additional PFS events and longer follow-up for a more robust treatment effect and PFS estimates, while not unduly delaying the readout of the study. - To update the safety set definition was updated to remove the requirement of a post-baseline safety assessment for inclusion in the Safety Set to align with the current standard Novartis definition and a widely used definition in the industry. - To include the usage conditions of interim summary PK data from anastrozole-treated patients to ensure study integrity.
06 August 2018	<p>The purpose of this amendment was:</p> <ul style="list-style-type: none"> - To update the dose adjustment and management recommendations for QTcF prolongation. - To update the list of prohibited concomitant medications based on compilation of drug-drug interaction and co-medication considerations. - To clarify on tumor and other efficacy assessments to be performed as clinically indicated after all patients had gone through 36 months of follow-up. - To update the withdrawal of consent language to align with the new Global Data Protection Requirements
18 July 2019	<p>The purpose of this amendment was:</p> <ul style="list-style-type: none"> - To unblind patients and investigators to allow for knowledge of patient's current treatment allocation and allow for patients receiving placebo the opportunity to cross over to treatment with ribociclib per Investigator discretion. - To add guidance for patients receiving placebo + tamoxifen to switch to an NSAI if they were to cross over to treatment with ribociclib and if they cross over, to complete a wash out period of 5 half-lives. - To clarify End of study (EOS), information on post-study drug access was included. - To make changes regarding the collection of PRO measures, biomarker data, and laboratory and ECG assessments.
24 January 2020	<p>The purpose of this amendment was:</p> <ul style="list-style-type: none"> - To add a ribociclib dose adjustment and management recommendation for interstitial lung disease (ILD)/pneumonitis to the protocol and to list it in the informed consent form (ICF) as a risk. - To update The 'guidance for all other adverse reactions', including a specific guidance to discontinue ribociclib if Toxic Epidermal Necrolysis (TEN) is diagnosed, and to make informed consent language updates with relevant information on TEN

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 9999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: