Clinical trial results:
A phase II, multicenter, randomized, open-label study to evaluate the safety and efficacy of 400 mg of ribociclib in combination with non-steroidal aromatase inhibitors for the treatment of pre- and postmenopausal women with hormone receptor-positive, HER2-negative advanced breast cancer who received no prior therapy for advanced disease

Summary

EudraCT number	2018-004234-15
Trial protocol	BE SE CZ FR LT AT FI DE PT HU BG
Global end of trial date	30 August 2024

Results information

Result version number	v1 (current)
This version publication date	19 July 2025
First version publication date	19 July 2025

Trial information

Trial identification

Sponsor protocol code	CLEE011A2207

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03822468
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	Lichtstrasse 35, Basel, Switzerland, 4056
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	30 August 2024
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 August 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of the study was to evaluate the safety and efficacy of a reduced ribociclib starting dose of 400 mg in combination with a non-steroidal aromatase inhibitor (NSAI) (letrozole or anastrozole) for the treatment of pre- and postmenopausal women with hormone receptor-positive (HR-positive), HER2-negative advanced breast cancer (aBC) who have received no prior therapy for advanced disease. Premenopausal women were required to receive goserelin in both treatment arms.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 June 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 4
Country: Number of subjects enrolled	Austria: 14
Country: Number of subjects enrolled	Belgium: 7
Country: Number of subjects enrolled	Brazil: 35
Country: Number of subjects enrolled	Bulgaria: 16
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Colombia: 22
Country: Number of subjects enrolled	Costa Rica: 6
Country: Number of subjects enrolled	Czechia: 10
Country: Number of subjects enrolled	Finland: 13
Country: Number of subjects enrolled	France: 20
Country: Number of subjects enrolled	Germany: 22
Country: Number of subjects enrolled	Hungary: 11
Country: Number of subjects enrolled	India: 21
Country: Number of subjects enrolled	Jordan: 8
Country: Number of subjects enrolled	Lithuania: 9
Country: Number of subjects enrolled	Peru: 8

Country: Number of subjects enrolled	Portugal: 21
Country: Number of subjects enrolled	Russian Federation: 60
Country: Number of subjects enrolled	South Africa: 11
Country: Number of subjects enrolled	Sweden: 6
Country: Number of subjects enrolled	Thailand: 9
Country: Number of subjects enrolled	United States: 40
Worldwide total number of subjects	376
EEA total number of subjects	149

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)	252
From 65 to 84 years	119
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled in 90 centers across 23 countries.

Pre-assignment

Screening details:

A total of 558 subjects were screened of which 376 participants were randomized on a 1:1 basis.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Ribociclib 400 mg

Arm description:

Ribociclib 400 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+goserelin in premenopausal women)

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

Dosage and administration details:

Ribociclib (at a dosage of 400 mg or 600 mg) QD orally taken on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (days 22 to 28). Ribociclib was supplied as 200 mg tablets as individual patient supply packaged bottles.

Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin 3.6 mg subcutaneously once every 4 weeks (pre-menopausal women only)

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 for oral use QD continuously

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 for oral use QD continuously

Arm title	Ribociclib 600 mg

Arm description:

Ribociclib 600 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+ goserelin in premenopausal women)

Arm type	Active comparator
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	LEE011
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ribociclib (at a dosage of 400 mg or 600 mg) QD orally taken on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (days 22 to 28). Ribociclib was supplied as 200 mg tablets as individual patient supply packaged bottles.

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 for oral use QD continuously

Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin 3.6 mg subcutaneously once every 4 weeks (pre-menopausal women only)

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 for oral use QD continuously

Number of subjects in period 1	Ribociclib 400 mg	Ribociclib 600 mg
Started	188	188
Completed	0	0
Not completed	188	188
Adverse event, serious fatal	2	3
Consent withdrawn by subject	9	5
Physician decision	9	7
Adverse event, non-fatal	21	24
Progressive disease	98	94
Lost to follow-up	1	1

Sponsor decision	46	53
Protocol deviation	2	1

Period 2

Period 2 title	Post-treatment efficacy follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	No
Arm title	Ribociclib 400 mg

Arm description:

Ribociclib 400 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+goserelin in premenopausal women)

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

Dosage and administration details:

Ribociclib (at a dosage of 400 mg or 600 mg) QD orally taken on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (days 22 to 28). Ribociclib was supplied as 200 mg tablets as individual patient supply packaged bottles.

Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

Goserelin 3.6 mg subcutaneously once every 4 weeks (pre-menopausal women only)

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 for oral use QD continuously

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 for oral use QD continuously	

Arm title	Ribociclib 600 mg
Arm description:	
Ribociclib 600 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+ goserelin in premenopausal women)	
Arm type	Active comparator
Investigational medicinal product name	Ribociclib
Investigational medicinal product code	
Other name	LEE011
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Ribociclib (at a dosage of 400 mg or 600 mg) QD orally taken on days 1 to 21 of a 28-day cycle, followed by 7 days off ribociclib (days 22 to 28). Ribociclib was supplied as 200 mg tablets as individual patient supply packaged bottles.	
Investigational medicinal product name	Goserelin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Implant in pre-filled syringe
Routes of administration	Subcutaneous use
Dosage and administration details:	
Goserelin 3.6 mg subcutaneously once every 4 weeks (pre-menopausal women only)	
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 for oral use QD continuously	
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 for oral use QD continuously	

Number of subjects in period 2	Ribociclib 400 mg	Ribociclib 600 mg
Started	22	26
Completed	0	0
Not completed	22	26
Adverse event, serious fatal	1	-
Consent withdrawn by subject	4	3

Physician decision	1	2
Adverse event, non-fatal	1	-
Progressive disease	11	14
Lost to follow-up	1	-
Sponsor decision	3	7

Baseline characteristics

Reporting groups	
Reporting group title	Ribociclib 400 mg
Reporting group description:	
Ribociclib 400 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+goserelin in premenopausal women)	
Reporting group title	Ribociclib 600 mg
Reporting group description:	
Ribociclib 600 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+ goserelin in premenopausal women)	

Reporting group values	Ribociclib 400 mg	Ribociclib 600 mg	Total
Number of subjects	188	188	376
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)	124	128	252
From 65-84 years	59	60	119
85 years and over	5	0	5
Age Continuous Units: Years			
arithmetic mean	58.7	57.0	
standard deviation	± 12.96	± 12.37	-
Sex: Female, Male Units: Participants			
Female	188	188	376
Male	0	0	0
Race/Ethnicity, Customized Units: Subjects			
Caucasian	147	143	290
Native American or Alaska Native	14	10	24
Asian	13	9	22
Black	5	12	17
Other	1	4	5
Unknown	8	10	18

End points

End points reporting groups

Reporting group title	Ribociclib 400 mg
Reporting group description:	
Ribociclib 400 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+goserelin in premenopausal women)	
Reporting group title	Ribociclib 600 mg
Reporting group description:	
Ribociclib 600 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+ goserelin in premenopausal women)	
Reporting group title	Ribociclib 400 mg
Reporting group description:	
Ribociclib 400 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+goserelin in premenopausal women)	
Reporting group title	Ribociclib 600 mg
Reporting group description:	
Ribociclib 600 mg QD 3 weeks on/1 week off + letrozole or anastrozole (+ goserelin in premenopausal women)	

Primary: Overall Response Rate (ORR)

End point title	Overall Response Rate (ORR)[1]
End point description:	
ORR defined as the percentage of participants with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) assessed by local investigators according to RECIST 1.1. 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	Primary
End point timeframe:	
Up to 23.8 months	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Only descriptive statistics performed

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: Percentage of participants				
number (confidence interval 95%)	41.5 (34.4 to 48.7)	45.3 (38.1 to 52.6)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in QTc (with Fridericia's correction) at Cycle 1 Day

15 (at 2 hours post-dose)

End point title	Change from baseline in QTc (with Fridericia's correction) at Cycle 1 Day 15 (at 2 hours post-dose)

End point description:

Electrocardiogram (ECG) data was collected via 12-lead digital ECG machines. Change from baseline in the QT interval (a segment of the ECG that reflects the time it takes for the heart to repolarize after each heartbeat) was corrected for heart rate using Fridericia's formula (ΔQTcF).

End point type	Secondary

End point timeframe:

Baseline and Cycle 1 Day 15 at 2 hours post-dose. Cycle = 28 days

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	174	175		
Units: milliseconds				
arithmetic mean (standard deviation)	12.5 (± 12.91)	19.7 (± 18.50)		

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical benefit rate (CBR)

End point title	Clinical benefit rate (CBR)

End point description:

Clinical benefit rate (CBR) was defined as the proportion of patients with a best overall response of complete response (CR), or partial response (PR), or an overall response of stable disease (SD), lasting for at least 24 weeks. CR, PR, and SD were defined as per local review as well as Blinded Independent Review Committee (BIRC) according to RECIST 1.1. A patient was considered to have SD for 24 weeks or longer if a SD response was recorded at 24-1=23 weeks or later from randomization, allowing for the ±1 week visit window for tumor assessments.
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 60 months

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: Participants	142	133		

Statistical analyses

No statistical analyses for this end point

Secondary: Progression-free survival (PFS)

End point title	Progression-free survival (PFS)

End point description:

Progression free survival (PFS) was defined as the time from the date of randomization to the date of the first documented disease progression or death due to any cause. PFS was censored if no PFS event was observed. The censoring date was 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 a local radiology assessment as well as Blinded Independent Review Committee (BIRC) according to RECIST 1.1.

End point type	Secondary

End point timeframe:

Up to approximately 60 months

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	188	188		
Units: Months				
median (full range (min-max))	26.9 (20.3 to 30.4)	25.1 (19.4 to 33.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response (DOR)

End point title	Duration of response (DOR)

End point description:

Duration of response (DOR) only applied to patients whose best overall response was complete response (CR) or partial response (PR) according to RECIST 1.1 based on tumor response data per local review. The start date was the date of first documented response of CR or PR (i.e. the start date of response, not the date when response was confirmed), and the end date was defined as the date of the first documented progression or death due to underlying cancer. Patients continuing without progression or death due to underlying cancer were censored at the date of their 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.

End point type	Secondary

End point timeframe:

Up to approximately 60 months

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	103		
Units: Months				
median (confidence interval 95%)	26.5 (16.8 to 999)	28.8 (22.6 to 999)		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR)

End point title	Time to response (TTR)

End point description:

Time to response (TTR) was defined as the time from the date of randomization to the first documented response of either complete response (CR) or partial response (PR), which had to be subsequently confirmed (although the date of initial response was used, not the date of confirmation). CR and PR were based on tumor response data as per local review and according to RECIST 1.1.
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 60 months

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	90	103		
Units: Months				
median (confidence interval 95%)	13.1 (7.4 to 999)	9.0 (5.6 to 16.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) of ribociclib: Maximum observed plasma concentration (Cmax)

End point title	Pharmacokinetics (PK) of ribociclib: Maximum observed plasma concentration (Cmax)

End point description:

PK parameters were calculated by non-compartmental analysis. Cmax is the maximum observed plasma drug concentration after single dose administration.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15 at pre-dose, and 2, 4, 6 and 24 hours post-dose. Cycle = 28 days

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	16		
Units: nanogram / milliliter (ng / mL)				
arithmetic mean (standard deviation)	1240 (± 739)	1740 (± 918)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of ribociclib: Time to reach observed maximum concentration (Tmax)

End point title	PK of ribociclib: Time to reach observed maximum concentration (Tmax)

End point description:

PK parameters were calculated by non-compartmental analysis. Tmax is the time to reach maximum observed plasma concentration. Actual recorded sampling times were considered for the calculations.

End point type	Secondary

End point timeframe:

Cycle 1 Day 15 at pre-dose, and 2, 4, 6 and 24 hours post-dose. Cycle = 28 days

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	16		
Units: hours (h)				
median (full range (min-max))	2.08 (1.83 to 4.38)	4.00 (1.83 to 23.8)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK of ribociclib: Area under the plasma concentration-time curve from 0 to 24 hours (AUC0-24)

End point title	PK of ribociclib: Area under the plasma concentration-time

	curve from 0 to 24 hours (AUC0-24)

End point description:

PK parameters were calculated by non-compartmental analysis. AUC0-24 is the area under the plasma concentration-time curve from 0 to 24 hours

End point type	Secondary

End point timeframe:

Cycle 1 Day 15 at pre-dose, and 2, 4, 6 and 24 hours post-dose. Cycle = 28 days

End point values	Ribociclib 400 mg	Ribociclib 600 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	13		
Units: ng x h / mL				
arithmetic mean (standard deviation)	18700 (± 11600)	31600 (± 14300)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were collected from first dose of study treatment to 30 days after last dose of study medication (on-treatment), up to 23.8 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

Dictionary used

Dictionary name	MedDRA
Dictionary version	27.0

Reporting groups

Reporting group title	Ribociclib 600mg

Reporting group description:

Ribociclib 600mg

Reporting group title	Ribociclib 400mg

Reporting group description:

Ribociclib 400mg

Serious adverse events	Ribociclib 600mg	Ribociclib 400mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 188 (19.68%)	38 / 188 (20.21%)	
number of deaths (all causes)	6	5	
number of deaths resulting from adverse events	1	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			

subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Peripheral embolism			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Ill-defined disorder			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			

Haemophagocytic lymphohistiocytosis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Acute respiratory failure			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Dyspnoea			
subjects affected / exposed	4 / 188 (2.13%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Interstitial lung disease			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	2 / 188 (1.06%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary thrombosis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 188 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disorientation			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Investigations			
Blood bilirubin increased			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation injury			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal column injury			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial fibrillation			

subjects affected / exposed	2 / 188 (1.06%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Hydrocephalus			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphopenia			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukopenia			

subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 188 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterocolitis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			

subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Autoimmune hepatitis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatotoxicity			
subjects affected / exposed	0 / 188 (0.00%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury			
subjects affected / exposed	1 / 188 (0.53%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			

subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute kidney injury			
subjects affected / exposed	2 / 188 (1.06%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Fracture pain			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone pain			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	2 / 188 (1.06%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthralgia			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pain in extremity			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	3 / 188 (1.60%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 0	
Oesophageal candidiasis			
subjects affected / exposed	1 / 188 (0.53%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphangitis			
subjects affected / exposed	2 / 188 (1.06%)	0 / 188 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronavirus pneumonia			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	1 / 188 (0.53%)	3 / 188 (1.60%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			

subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	2 / 188 (1.06%)	2 / 188 (1.06%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	1 / 188 (0.53%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Hypercalcaemia			
subjects affected / exposed	0 / 188 (0.00%)	1 / 188 (0.53%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Ribociclib 600mg	Ribociclib 400mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	178 / 188 (94.68%)	175 / 188 (93.09%)	
Investigations			
Aspartate aminotransferase increased			
subjects affected / exposed	40 / 188 (21.28%)	41 / 188 (21.81%)	
occurrences (all)	52	57	
Alanine aminotransferase increased			
subjects affected / exposed	47 / 188 (25.00%)	49 / 188 (26.06%)	
occurrences (all)	55	63	
Blood alkaline phosphatase increased			

subjects affected / exposed	17 / 188 (9.04%)	11 / 188 (5.85%)	
occurrences (all)	22	17	
Blood creatinine increased			
subjects affected / exposed	15 / 188 (7.98%)	12 / 188 (6.38%)	
occurrences (all)	23	13	
White blood cell count decreased			
subjects affected / exposed	22 / 188 (11.70%)	13 / 188 (6.91%)	
occurrences (all)	31	23	
Weight decreased			
subjects affected / exposed	11 / 188 (5.85%)	11 / 188 (5.85%)	
occurrences (all)	11	11	
Neutrophil count decreased			
subjects affected / exposed	24 / 188 (12.77%)	25 / 188 (13.30%)	
occurrences (all)	69	60	
Lipase increased			
subjects affected / exposed	12 / 188 (6.38%)	9 / 188 (4.79%)	
occurrences (all)	16	12	
Gamma-glutamyltransferase increased			
subjects affected / exposed	16 / 188 (8.51%)	17 / 188 (9.04%)	
occurrences (all)	17	22	
Electrocardiogram QT prolonged			
subjects affected / exposed	26 / 188 (13.83%)	14 / 188 (7.45%)	
occurrences (all)	49	17	
Vascular disorders			
Hot flush			
subjects affected / exposed	14 / 188 (7.45%)	24 / 188 (12.77%)	
occurrences (all)	14	24	
Hypertension			
subjects affected / exposed	10 / 188 (5.32%)	6 / 188 (3.19%)	
occurrences (all)	15	8	
Nervous system disorders			
Headache			
subjects affected / exposed	31 / 188 (16.49%)	18 / 188 (9.57%)	
occurrences (all)	65	20	
Blood and lymphatic system disorders			

Lymphopenia			
subjects affected / exposed	18 / 188 (9.57%)	17 / 188 (9.04%)	
occurrences (all)	34	27	
Leukopenia			
subjects affected / exposed	52 / 188 (27.66%)	40 / 188 (21.28%)	
occurrences (all)	124	94	
Anaemia			
subjects affected / exposed	49 / 188 (26.06%)	31 / 188 (16.49%)	
occurrences (all)	67	47	
Neutropenia			
subjects affected / exposed	125 / 188 (66.49%)	100 / 188 (53.19%)	
occurrences (all)	414	255	
Thrombocytopenia			
subjects affected / exposed	19 / 188 (10.11%)	13 / 188 (6.91%)	
occurrences (all)	37	17	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	12 / 188 (6.38%)	8 / 188 (4.26%)	
occurrences (all)	13	8	
Fatigue			
subjects affected / exposed	40 / 188 (21.28%)	22 / 188 (11.70%)	
occurrences (all)	50	23	
Asthenia			
subjects affected / exposed	23 / 188 (12.23%)	24 / 188 (12.77%)	
occurrences (all)	26	26	
Pain			
subjects affected / exposed	14 / 188 (7.45%)	1 / 188 (0.53%)	
occurrences (all)	21	1	
Pyrexia			
subjects affected / exposed	12 / 188 (6.38%)	11 / 188 (5.85%)	
occurrences (all)	14	12	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 188 (6.38%)	10 / 188 (5.32%)	
occurrences (all)	15	18	
Abdominal pain upper			

subjects affected / exposed	12 / 188 (6.38%)	5 / 188 (2.66%)	
occurrences (all)	15	6	
Nausea			
subjects affected / exposed	44 / 188 (23.40%)	31 / 188 (16.49%)	
occurrences (all)	63	37	
Diarrhoea			
subjects affected / exposed	25 / 188 (13.30%)	22 / 188 (11.70%)	
occurrences (all)	35	24	
Constipation			
subjects affected / exposed	21 / 188 (11.17%)	17 / 188 (9.04%)	
occurrences (all)	22	20	
Vomiting			
subjects affected / exposed	22 / 188 (11.70%)	15 / 188 (7.98%)	
occurrences (all)	27	16	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	15 / 188 (7.98%)	8 / 188 (4.26%)	
occurrences (all)	17	10	
Cough			
subjects affected / exposed	23 / 188 (12.23%)	17 / 188 (9.04%)	
occurrences (all)	26	24	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	16 / 188 (8.51%)	7 / 188 (3.72%)	
occurrences (all)	17	9	
Pruritus			
subjects affected / exposed	17 / 188 (9.04%)	4 / 188 (2.13%)	
occurrences (all)	24	4	
Dry skin			
subjects affected / exposed	15 / 188 (7.98%)	6 / 188 (3.19%)	
occurrences (all)	17	6	
Alopecia			
subjects affected / exposed	24 / 188 (12.77%)	19 / 188 (10.11%)	
occurrences (all)	24	20	
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	28 / 188 (14.89%)	31 / 188 (16.49%)	
occurrences (all)	32	41	
Back pain			
subjects affected / exposed	23 / 188 (12.23%)	20 / 188 (10.64%)	
occurrences (all)	26	27	
Pain in extremity			
subjects affected / exposed	17 / 188 (9.04%)	12 / 188 (6.38%)	
occurrences (all)	23	13	
Infections and infestations			
COVID-19			
subjects affected / exposed	27 / 188 (14.36%)	17 / 188 (9.04%)	
occurrences (all)	27	17	
Nasopharyngitis			
subjects affected / exposed	12 / 188 (6.38%)	6 / 188 (3.19%)	
occurrences (all)	14	7	
Urinary tract infection			
subjects affected / exposed	17 / 188 (9.04%)	15 / 188 (7.98%)	
occurrences (all)	19	21	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	12 / 188 (6.38%)	9 / 188 (4.79%)	
occurrences (all)	15	12	
Decreased appetite			
subjects affected / exposed	13 / 188 (6.91%)	11 / 188 (5.85%)	
occurrences (all)	14	13	
Hypocalcaemia			
subjects affected / exposed	15 / 188 (7.98%)	12 / 188 (6.38%)	
occurrences (all)	23	17	
Hypokalaemia			
subjects affected / exposed	10 / 188 (5.32%)	9 / 188 (4.79%)	
occurrences (all)	15	10	
Hypophosphataemia			
subjects affected / exposed	10 / 188 (5.32%)	4 / 188 (2.13%)	
occurrences (all)	15	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
24 January 2020	Key changes introduced in Amendment 1 for ribociclib: 1. ILD/pneumonitis observed with all CDK4/6 inhibitors; ribociclib dose adjustment and management guidance added. 2. TEN reported post-marketing (not in trials); guidance updated to discontinue ribociclib if diagnosed. 3. For patients on tamoxifen/toremifene: a. These drugs must be stopped for a 5 half-life washout before randomization due to QT risk. b. Postmenopausal status criteria updated per NCCN v4 2018. 4. Sodium and phosphorus level checks removed from inclusion criteria; concurrent HRT use added as exclusion. 5. Patients with prior treatment toxicities (not safety risks) now allowed. 6. Uncorrected hypocalcemia added as exclusion due to QT risk. 7. Corticosteroid use guidance aligned with 'Concomitant medications' section. 8. Hormonal contraceptives prohibited due to breast cancer risk. 9. Vasectomy as contraception requires medical confirmation (per CTFG). 10. Clarified eligibility for patients in other medical research. 11. Lists of prohibited and cautionary medications during treatment added. 12. Justification for PK analysis sample size included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to EudraCT system limitations, which EMA is aware of, data using 999 as data points in this record are not an accurate representation of the clinical trial results.

Notes: