



Clinical trial results:

A Randomized, Multicenter, Open-Label, Two-Arm, Phase II, Neoadjuvant Study Evaluating the Efficacy, Safety, and Pharmacokinetics of GDC-9545 Plus Palbociclib Compared With Anastrozole Plus Palbociclib for Postmenopausal Women With Estrogen Receptor-Positive and HER2-Negative Untreated Early Breast Cancer Summary

EudraCT number	2020-001007-16
Trial protocol	HU PL DE
Global end of trial date	24 November 2021

Results information

Result version number	v1 (current)
This version publication date	15 December 2022
First version publication date	15 December 2022

Trial information

Trial identification

Sponsor protocol code	WO42133
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04436744
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	F. Hoffmann-La Roche AG
Sponsor organisation address	Grenzacherstrasse 124, Basel, Switzerland, CH-4070
Public contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.com
Scientific contact	F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, +41 616878333, global.trial_information@roche.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	24 November 2021
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 November 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to evaluate the efficacy, safety, and pharmacokinetics of giredestrant versus anastrozole (in the window-of-opportunity phase) and giredestrant plus palbociclib compared with anastrozole plus palbociclib (in the neoadjuvant phase) in postmenopausal women with untreated, estrogen receptor (ER)-positive, human epidermal growth factor receptor-2 (HER2)-negative, early breast cancer.

Protection of trial subjects:

All participants were required to sign the informed consent form (ICF).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	04 September 2020
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	Australia: 3
Country: Number of subjects enrolled	Brazil: 18
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Spain: 78
Country: Number of subjects enrolled	Hungary: 4
Country: Number of subjects enrolled	Korea, Republic of: 7
Country: Number of subjects enrolled	Poland: 8
Country: Number of subjects enrolled	Russian Federation: 21
Country: Number of subjects enrolled	Taiwan: 4
Country: Number of subjects enrolled	Ukraine: 36
Country: Number of subjects enrolled	United States: 34
Worldwide total number of subjects	221
EEA total number of subjects	98

Notes:

Subjects enrolled per age group

In utero	0
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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)	135
From 65 to 84 years	86
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in this study at 64 investigative sites in Australia, Brazil, Germany, Hungary, Korea, Poland, Russia, Spain, Taiwan, the United States, and Ukraine, from 4 September 2020 to 24 November 2021.

Pre-assignment

Screening details:

A total of 264 participants were screened.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Giredestrant + Palbociclib

Arm description:

Participants received giredestrant, 30 milligrams (mg), orally, once per day (QD), during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received giredestrant, 30 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Arm type	Experimental
Investigational medicinal product name	Giredestrant
Investigational medicinal product code	
Other name	GDC-9545, RO7197597
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Window-of-opportunity phase: Giredestrant 30 mg, administered orally, QD, for two weeks. Neoadjuvant treatment phase: Giredestrant, 30 mg, administered orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles.

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

Dosage and administration details:

Palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Arm title	Anastrozole + Palbociclib
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Arm description:

Participants received anastrozole, 1 mg, orally, QD, during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received anastrozole, 1 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Arm type	Active comparator
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Investigational medicinal product name	Palbociclib
Investigational medicinal product code	
Other name	Ibrance
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

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

Dosage and administration details:

Window-of-opportunity phase: Anastrozole, 1 mg, administered orally, QD, for two weeks. Neoadjuvant treatment phase: Anastrozole, 1 mg, administered orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles.

Number of subjects in period 1	Giredestrant + Palbociclib	Anastrozole + Palbociclib
Started	112	109
Completed	108	98
Not completed	4	11
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	2
Physician decision	-	1
Adverse event, non-fatal	1	1
Protocol Deviation	1	1
Progressive Disease	-	4
Lost to follow-up	-	2

Baseline characteristics

Reporting groups

Reporting group title	Giredestrant + Palbociclib
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Reporting group description:

Participants received giredestrant, 30 milligrams (mg), orally, once per day (QD), during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received giredestrant, 30 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Reporting group title	Anastrozole + Palbociclib
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Reporting group description:

Participants received anastrozole, 1 mg, orally, QD, during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received anastrozole, 1 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Reporting group values	Giredestrant + Palbociclib	Anastrozole + Palbociclib	Total
Number of subjects	112	109	221
Age categorical Units:			

Age Continuous Units: years			
arithmetic mean	63.1	62.4	
standard deviation	± 7.9	± 9.3	-

Sex: Female, Male Units: participants			
Female	112	109	221
Male	0	0	0

Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	16	11	27
Not Hispanic or Latino	95	98	193
Unknown or Not Reported	1	0	1

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	9	15
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	1	3
White	100	94	194
More than one race	0	0	0
Unknown or Not Reported	4	5	9

Ki67 Scores			
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The Ki67 is a proliferation biomarker with prognostic value in estrogen receptor (ER)-positive breast cancer. Ki67 score was centrally assessed.

Units: percent Ki67 scores			
arithmetic mean	37.92	41.66	
full range (min-max)	6.6 to 96.3	7.8 to 98.9	-

End points

End points reporting groups

Reporting group title	Giredestrant + Palbociclib
Reporting group description:	
Participants received giredestrant, 30 milligrams (mg), orally, once per day (QD), during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received giredestrant, 30 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.	
Reporting group title	Anastrozole + Palbociclib
Reporting group description:	
Participants received anastrozole, 1 mg, orally, QD, during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received anastrozole, 1 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.	

Primary: Percent Reduction from Baseline in Ki67 Scores at Week 2

End point title	Percent Reduction from Baseline in Ki67 Scores at Week 2
End point description:	
The Ki67 is a proliferation biomarker with prognostic value in estrogen receptor (ER)-positive breast cancer. Change in Ki67 score during the window-of-opportunity phase was defined as the mean change of Ki67 score from baseline to Week 2. Ki67 score was centrally assessed. Efficacy-evaluable population included participants with Ki67-evaluable tumor specimens at baseline and Week 2. Participants with missing central Ki67 scores at baseline and/or Week 2 were excluded from the analysis.	
End point type	Primary
End point timeframe:	
Baseline, Week 2	

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	94		
Units: percent reduction in Ki67 scores				
geometric mean (confidence interval 95%)	75 (70 to 80)	67 (59 to 73)		

Statistical analyses

Statistical analysis title	GDC-9545+Palbociclib vs Anastrozole+Palbociclib
Comparison groups	Giredestrant + Palbociclib v Anastrozole + Palbociclib

Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.0433
Method	t-test, 2-sided

Secondary: Overall Response Rate (ORR) by Ultrasound as Determined by the Investigator

End point title	Overall Response Rate (ORR) by Ultrasound as Determined by the Investigator
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End point description:

ORR was defined as the percentage of participants with a complete response (CR) or partial response (PR), as determined by the investigator according to Modified Response Evaluation Criteria in Solid Tumors (mRECIST). Ultrasound and clinical exam were used to assess response. CR per mRECIST was defined as the disappearance of all target lesions. PR per mRECIST was defined as at least 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters. An estimate of ORR and its 95% confidence interval (CI) was calculated using the Clopper-Pearson method. ORR-evaluable population included all randomised participants with measurable disease at baseline. Participants not meeting the criteria for ORR, including participants without any post-baseline tumor assessment, were considered as non-responders.

End point type	Secondary
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End point timeframe:

Baseline up to Cycle 4 Day 1 (each cycle is 28 days)

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	108		
Units: percentage of participants				
number (confidence interval 95%)	50.0 (40.40 to 59.60)	49.1 (39.33 to 58.87)		

Statistical analyses

Statistical analysis title	GDC-9545+Palbociclib vs Anastrozole+Palbociclib
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Statistical analysis description:

ORR was calculated using the stratified Cochran-Mantel-Haenszel test.

Comparison groups	Giredestrant + Palbociclib v Anastrozole + Palbociclib
Number of subjects included in analysis	220
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.8272
Method	Cochran-Mantel-Haenszel
Parameter estimate	Difference in Overall Response Rates
Point estimate	-0.93

Confidence interval	
level	95 %
sides	2-sided
lower limit	-14.66
upper limit	12.81

Secondary: Complete Cell Cycle Arrest (CCCA) Rate at Week 2

End point title	Complete Cell Cycle Arrest (CCCA) Rate at Week 2
End point description:	
CCCA was defined as the percentage of participants with centrally assessed Ki67 scores $\leq 2.7\%$. The CCCA rate at Week 2 was summarized. Efficacy-evaluable population included participants with Ki67-evaluable tumor specimens at baseline and Week 2. Participants with missing central Ki67 scores at baseline and/or Week 2 were excluded from the analysis.	
End point type	Secondary
End point timeframe:	
Week 2	

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	107	94		
Units: percentage of participants				
number (not applicable)	19.6	12.8		

Statistical analyses

Statistical analysis title	GDC-9545+Palbociclib vs Anastrozole+Palbociclib
Comparison groups	Giredestrant + Palbociclib v Anastrozole + Palbociclib
Number of subjects included in analysis	201
Analysis specification	Pre-specified
Analysis type	
Parameter estimate	Difference in Rate
Point estimate	6.86
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.25
upper limit	17.97

Secondary: Number of Participants with Adverse Events (AEs) with Severity Determined in Accordance With National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 (NCI CTCAE v5.0)

End point title	Number of Participants with Adverse Events (AEs) with Severity
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End point description:

AE is any untoward medical occurrence in clinical investigation participant administered a pharmaceutical product regardless of causal attribution. An AE can be any unfavorable & unintended sign, symptom/disease temporally related to use of medicinal product, whether/not related to medicinal product. Severity of AEs was determined per NCI CTCAE v5.0. Grade 1: Mild; asymptomatic/mild symptoms; clinical/diagnostic observations only; or intervention not indicated; Grade 2: Moderate; minimal, local/non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living; Grade 3: Severe/medically significant, but not immediately life-threatening: hospitalization/prolongation of hospitalization indicated; disabling/limiting self-care activities of daily living; Grade 4: Life-threatening consequences/urgent intervention indicated; Grade 5: Death related to AE. Safety-evaluable population included all participants who received any amount of study treatment.

End point type Secondary

End point timeframe:

From baseline up to 28 days after the last dose (up to approximately 24 weeks)

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: participants				
AEs	104	98		
Grade 1	19	20		
Grade 2	35	31		
Grade 3	45	45		
Grade 4	4	2		
Grade 5	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Respiratory Rate Over Time

End point title Change from Baseline in Respiratory Rate Over Time

End point description:

Respiratory rate was measured while the participant was in a seated position. Safety-evaluable population included all participants who received any amount of study treatment. Overall number analysed is the number of participants with data available for analysis. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type Secondary

End point timeframe:

Baseline; Cycles 1-2: Day 1 and Day 15; Cycles 3-4: Day 1; day of surgery and end of study (up to approximately 24 weeks)

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: breath/minute (min)				
arithmetic mean (standard deviation)				
Baseline (n=98,102)	17.16 (± 2.27)	17.10 (± 2.05)		
Change from Baseline at Cycle 1 Day 1 (n=91,91)	0.30 (± 2.12)	0.26 (± 1.50)		
Change from Baseline at Cycle 1 Day 15 (n=90,88)	-0.01 (± 1.49)	-0.06 (± 1.36)		
Change from Baseline at Cycle 2 Day 1 (n=89,92)	-0.10 (± 1.83)	0.16 (± 1.34)		
Change from Baseline at Cycle 2 Day 15 (n=89,91)	-0.24 (± 1.71)	-0.03 (± 1.64)		
Change from Baseline at Cycle 3 Day 1 (n=87,89)	0.07 (± 1.58)	0.01 (± 1.61)		
Change from Baseline at Cycle 4 Day 1 (n=91,83)	-0.04 (± 1.71)	0.01 (± 1.53)		
Change from Baseline at Day of Surgery (n=72,62)	0.04 (± 1.72)	-0.02 (± 1.69)		
Change from Baseline at End of Study (n=88,81)	-0.26 (± 1.65)	0.01 (± 1.42)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pulse Rate Over Time

End point title	Change from Baseline in Pulse Rate Over Time
End point description:	
Pulse rate was measured while the participant was in a seated position. Safety-evaluable population included all participants who received any amount of study treatment. Overall number analysed is the number of participants with data available for analysis. Number analysed is the number of participants with data available for analysis at the specified time point.	
End point type	Secondary
End point timeframe:	
Baseline; Cycles 1-2: Day 1 and Day 15; Cycles 3-4: Day 1; day of surgery and end of study (up to approximately 24 weeks)	

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: beats/min				
arithmetic mean (standard deviation)				
Baseline (n=98, 102)	75.86 (± 10.67)	76.73 (± 9.85)		
Change from Baseline at Cycle 1 Day 1 (n=90,92)	-4.74 (± 9.07)	-1.96 (± 9.43)		
Change from Baseline at Cycle 1 Day 15 (n=91,90)	-6.02 (± 12.02)	-1.47 (± 8.15)		

Change from Baseline at Cycle 2 Day 1 (n=90,92)	-5.20 (± 10.26)	-1.11 (± 10.79)		
Change from Baseline at Cycle 2 Day 15 (n=92,91)	-7.68 (± 11.03)	-1.95 (± 8.64)		
Change from Baseline at Cycle 3 Day 1 (n=88,90)	-5.47 (± 11.61)	-0.81 (± 10.83)		
Change from Baseline at Cycle 4 Day 1 (n=91,83)	-5.67 (± 9.79)	-1.11 (± 10.62)		
Change from Baseline at Day of Surgery (n=73,65)	-4.14 (± 11.25)	-1.26 (± 10.46)		
Change from Baseline at End of Study (n=88,81)	-0.61 (± 10.74)	1.59 (± 10.44)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Systolic Blood Pressure Over Time

End point title	Change from Baseline in Systolic Blood Pressure Over Time
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End point description:

Systolic blood pressure was measured while the participant was in a seated position. Safety-evaluable population included all participants who received any amount of study treatment. Overall number analysed is the number of participants with data available for analysis. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-2: Day 1 and Day 15; Cycles 3-4: Day 1; day of surgery and end of study (up to approximately 24 weeks)

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Baseline (n=98,102)	135.63 (± 14.13)	130.03 (± 16.43)		
Change from Baseline at Cycle 1 Day 1 (n=91,92)	-0.82 (± 11.11)	1.12 (± 13.65)		
Change from Baseline at Cycle 1 Day 15 (n=91,90)	-2.55 (± 14.01)	0.23 (± 15.85)		
Change from Baseline at Cycle 2 Day 1 (n=90,92)	-2.08 (± 14.13)	0.28 (± 14.43)		
Change from Baseline at Cycle 2 Day 15 (n=92,90)	-4.25 (± 15.37)	0.16 (± 16.49)		
Change from Baseline at Cycle 3 Day 1 (n=88,90)	-2.66 (± 16.95)	0.33 (± 15.81)		
Change from Baseline at Cycle 4 Day 1 (n=91,83)	-1.29 (± 15.30)	-0.25 (± 14.17)		
Change from Baseline at Day of Surgery (n=74,65)	-2.35 (± 13.79)	1.51 (± 15.24)		
Change from Baseline at End of Study (n=88,81)	-5.38 (± 13.98)	-1.67 (± 16.20)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Diastolic Blood Pressure Over Time

End point title	Change from Baseline in Diastolic Blood Pressure Over Time
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End point description:

Diastolic blood pressure was measured while the participant was in a seated position. Safety-evaluable population included all participants who received any amount of study treatment. Overall number analysed is the number of participants with data available for analysis. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-2: Day 1 and Day 15; Cycles 3-4: Day 1; day of surgery and end of study (up to approximately 24 weeks)

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	102		
Units: mmHg				
arithmetic mean (standard deviation)				
Baseline (n=98, 102)	80.40 (± 8.84)	78.49 (± 9.55)		
Change from Baseline at Cycle 1 Day 1 (n=91,92)	-2.42 (± 7.77)	0.39 (± 8.13)		
Change from Baseline at Cycle 1 Day 15 (n=91,90)	-4.80 (± 8.58)	-2.42 (± 8.71)		
Change from Baseline at Cycle 2 Day 1 (n=90,92)	-4.79 (± 10.08)	-0.76 (± 8.80)		
Change from Baseline at Cycle 2 Day 15 (n=92,90)	-5.64 (± 9.24)	-1.32 (± 9.64)		
Change from Baseline at Cycle 3 Day 1 (n=88,90)	-5.25 (± 8.51)	-0.16 (± 9.52)		
Change from Baseline at Cycle 4 Day 1 (n=91,83)	-4.35 (± 9.31)	-2.57 (± 9.50)		
Change from Baseline at Day of Surgery (n=74,65)	-4.93 (± 8.72)	-2.15 (± 9.58)		
Change from Baseline at End of Study (n=88,81)	-2.73 (± 8.37)	-2.52 (± 12.11)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Body Temperature Over Time

End point title	Change from Baseline in Body Temperature Over Time
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End point description:

Safety-evaluable population included all participants who received any amount of study treatment. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Baseline; Cycles 1-2: Day 1 and Day 15; Cycles 3-4: Day 1; day of surgery and end of study (up to approximately 24 weeks)

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	109		
Units: Celsius (C)				
arithmetic mean (standard deviation)				
Baseline (n=112,109)	36.35 (± 0.41)	36.45 (± 0.38)		
Change from Baseline at Cycle 1 Day 1 (n=110,105)	0.07 (± 0.39)	0.04 (± 0.36)		
Change from Baseline at Cycle 1 Day 15 (n=107,103)	0.01 (± 0.41)	-0.01 (± 0.43)		
Change from Baseline at Cycle 2 Day 1 (n=108,105)	0.03 (± 0.40)	-0.04 (± 0.52)		
Change from Baseline at Cycle 2 Day 15 (n=110,102)	-0.03 (± 0.37)	-0.12 (± 0.47)		
Change from Baseline at Cycle 3 Day 1 (n=109,102)	-0.04 (± 0.42)	0.01 (± 0.39)		
Change from Baseline at Cycle 4 Day 1 (n=109,103)	-0.03 (± 0.37)	-0.08 (± 0.38)		
Change from Baseline at Day of Surgery (n=97,85)	0.06 (± 0.39)	-0.01 (± 0.38)		
Change from Baseline at End of Study (n=107,102)	0.05 (± 0.39)	-0.04 (± 0.48)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts in Hematology Test Parameters from NCI-CTCAE Grade 0-2 at Baseline to Grade 3-4 at Post-baseline

End point title	Number of Participants With Shifts in Hematology Test Parameters from NCI-CTCAE Grade 0-2 at Baseline to Grade 3-4 at Post-baseline
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End point description:

Haematology test parameters like hemoglobin, lymphocytes absolute (Abs), neutrophils, total, Abs, platelet, total leukocyte count were measured per NCI CTCAE v5.0. Number of participants with shift in the laboratory values from grade 0-2 at baseline to grade 3-4 at post-baseline were reported. Safety-evaluable population included all participants who received any amount of study treatment. Participants with at least 1 post-baseline assessment were included in the analysis. Overall number analysed is the number of participants with data available for analysis. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary
End point timeframe:	
From baseline up to 28 days after the last dose (up to approximately 24 weeks)	

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	108		
Units: participants				
Hemoglobin: Low (n=101,103)	3	1		
Hemoglobin: High (n=111,105)	0	1		
Lymphocytes Abs: Low (n=95,91)	9	2		
Lymphocytes Abs: High (n=90,88)	1	2		
Neutrophils, Total, Abs: Low (n=98,96)	43	38		
Platelet: Low (n=112,108)	0	0		
Total Leukocyte Count: Low (n=112,108)	15	11		
Total Leukocyte Count: High (n=104,105)	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Shifts in Blood Chemistry Parameters from NCI-CTCAE Grade 0-2 at Baseline to Grade 3-4 at Post-baseline

End point title	Number of Participants With Shifts in Blood Chemistry Parameters from NCI-CTCAE Grade 0-2 at Baseline to Grade 3-4 at Post-baseline
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End point description:

Blood chemistry parameters albumin, alkaline phosphatase, serum glutamic pyruvic transaminase (SGPT)/alanine transaminase (ALT), serum glutamic oxaloacetic transaminase (SGOT)/aspartate transaminase (AST), calcium, cholesterol, creatinine, glucose, potassium, sodium, bilirubin, triglycerides and uric acid were measured per NCI CTCAE v5.0. Number of participants with shift in the laboratory values from grade 0-2 at baseline to grade 3-4 at post-baseline were reported. Safety-evaluable population included all participants who received any amount of study treatment. Participants with at least 1 post-baseline assessment were included in the analysis. Overall number analysed is the number of participants with data available for analysis. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary
End point timeframe:	
From baseline up to 28 days after the last dose (up to approximately 24 weeks)	

End point values	Giredestrant + Palbociclib	Anastrozole + Palbociclib		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	112	108		
Units: participants				
Albumin: low (n=111,108)	1	0		
Alkaline Phosphatase: High (n=112,108)	0	0		
SGPT/ALT: High (n=112,108)	1	5		
SGOT/AST: High (n=112,108)	1	3		
Calcium: Low (n=102,101)	0	3		
Calcium: High (n=109,103)	0	0		
Cholesterol: High (n=93,89)	0	0		
Creatinine: High (n=112,108)	0	1		
Glucose: Low (n=112,108)	0	0		
Potassium: Low (n=106,101)	0	0		
Potassium: High (n=112,107)	0	0		
Sodium: Low (n=111,107)	0	0		
Sodium: High (n=111,106)	0	0		
Bilirubin: High (n=112,108)	0	0		
Triglycerides: High (n=93,88)	1	0		
Uric Acid: High (n=87,86)	21	22		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Giredestrant at Specified Timepoints

End point title	Plasma Concentration of Giredestrant at Specified Timepoints ^[1]
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End point description:

Pharmacokinetics (PK) evaluable population included all participants who received giredestrant and had at least one evaluable post-dose giredestrant plasma concentration. Number analysed is the number of participants with data available for analysis at the specified time point.

End point type	Secondary
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End point timeframe:

Cycle 0 Day 1, 3 hours Postdose; Cycle 0 Day 15, Predose; Cycle 2 Day 1, Predose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only descriptive analysis was planned to be reported for this endpoint.

End point values	Giredestrant + Palbociclib			
Subject group type	Reporting group			
Number of subjects analysed	108			
Units: nanograms per milliliters (ng/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 0 Day 1, 3-h Postdose (n=108)	81.8 (± 284)			
Cycle 0 Day 15, Predose (n=104)	137 (± 61.1)			
Cycle 2 Day 1, Predose (n=99)	130 (± 122)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to 28 days after the last dose (up to approximately 24 weeks)

Adverse event reporting additional description:

AEs are reported for the safety-evaluable population that was defined as all participants who received any amount of study treatment, grouped according to treatment received. All-cause mortality was also reported for the safety-evaluable population.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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Reporting groups

Reporting group title	Giredestrant + Palbociclib
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Reporting group description:

Participants received giredestrant, 30 mg, orally, QD, during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received giredestrant, 30 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Reporting group title	Giredestrant + Palbociclib
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Reporting group description:

Participants received anastrozole, 1 mg, orally, QD, during the window-of-opportunity phase of two weeks. During the neoadjuvant treatment phase, participants received anastrozole, 1 mg, orally, QD on Days 1-28 of each 28-day cycle for a total of 4 cycles in combination with palbociclib, 125 mg, administered orally, QD on Days 1-21 of each 28-day cycle for a total of 4 cycles.

Serious adverse events	Giredestrant + Palbociclib	Giredestrant + Palbociclib	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 112 (4.46%)	2 / 109 (1.83%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 112 (0.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural pain			
subjects affected / exposed	0 / 112 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine perforation			

subjects affected / exposed	1 / 112 (0.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 112 (0.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	1 / 112 (0.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	0 / 112 (0.00%)	1 / 109 (0.92%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 112 (0.89%)	0 / 109 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Giredestrant + Palbociclib	Giredestrant + Palbociclib	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	99 / 112 (88.39%)	93 / 109 (85.32%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 112 (0.89%)	9 / 109 (8.26%)	
occurrences (all)	1	9	
Aspartate aminotransferase increased			

subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1	6 / 109 (5.50%) 6	
Neutrophil count decreased subjects affected / exposed occurrences (all)	26 / 112 (23.21%) 39	24 / 109 (22.02%) 32	
White blood cell count decreased subjects affected / exposed occurrences (all)	14 / 112 (12.50%) 19	10 / 109 (9.17%) 12	
Injury, poisoning and procedural complications Procedural pain subjects affected / exposed occurrences (all)	2 / 112 (1.79%) 2	6 / 109 (5.50%) 6	
Vascular disorders Hot flush subjects affected / exposed occurrences (all)	16 / 112 (14.29%) 16	16 / 109 (14.68%) 17	
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 112 (4.46%) 5	9 / 109 (8.26%) 9	
Blood and lymphatic system disorders Leukopenia subjects affected / exposed occurrences (all)	14 / 112 (12.50%) 20	16 / 109 (14.68%) 29	
Anaemia subjects affected / exposed occurrences (all)	12 / 112 (10.71%) 13	6 / 109 (5.50%) 7	
Neutropenia subjects affected / exposed occurrences (all)	46 / 112 (41.07%) 77	44 / 109 (40.37%) 79	
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	25 / 112 (22.32%) 28	27 / 109 (24.77%) 31	
Fatigue			

subjects affected / exposed occurrences (all)	10 / 112 (8.93%) 10	18 / 109 (16.51%) 19	
Mucosal inflammation subjects affected / exposed occurrences (all)	9 / 112 (8.04%) 9	3 / 109 (2.75%) 3	
Pyrexia subjects affected / exposed occurrences (all)	1 / 112 (0.89%) 1	6 / 109 (5.50%) 6	
Gastrointestinal disorders			
Constipation subjects affected / exposed occurrences (all)	3 / 112 (2.68%) 3	6 / 109 (5.50%) 6	
Diarrhoea subjects affected / exposed occurrences (all)	8 / 112 (7.14%) 11	18 / 109 (16.51%) 25	
Nausea subjects affected / exposed occurrences (all)	16 / 112 (14.29%) 19	13 / 109 (11.93%) 15	
Vomiting subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6	1 / 109 (0.92%) 1	
Skin and subcutaneous tissue disorders			
Alopecia subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 6	5 / 109 (4.59%) 5	
Rash subjects affected / exposed occurrences (all)	6 / 112 (5.36%) 7	2 / 109 (1.83%) 2	
Musculoskeletal and connective tissue disorders			
Arthralgia subjects affected / exposed occurrences (all)	12 / 112 (10.71%) 13	21 / 109 (19.27%) 22	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported