



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 |
|-----------------------|---------|

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 |
|----------|---|

| | |
|---|-----|
| 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 |
|------------------|---------------------------|

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 |
|----------|-------------------|

| | |
|--|-------------|
| 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 |
|-----------------------|----------------------------|

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.

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

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

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 full range (min-max) | 37.92 6.6 to 96.3 | 41.66 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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|----------------------------|---|

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 |
|-----------------|--|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|-----------------|---|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 24.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------------|
| Reporting group title | Giredestrant + Palbociclib |
|-----------------------|----------------------------|

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 |
|-----------------------|----------------------------|

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