



Clinical trial results:

A Phase II, Multicenter, Randomized Study To Compare The Efficacy Of Venetoclax

Plus Fulvestrant Versus Fulvestrant In Women With Estrogen Receptor-Positive, HER2-Negative Locally Advanced Or Metastatic Breast Cancer Who Experienced Disease Recurrence Or Progression During Or After CDK4/6 Inhibitor Therapy

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-005118-74 |
| Trial protocol | GB DE |
| Global end of trial date | |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v2 |
| This version publication date | 14 October 2021 |
| First version publication date | 05 August 2021 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | WO40181 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT03584009 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124, Basel, Switzerland, CH4070 |
| 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 | Interim |
| Date of interim/final analysis | 05 August 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 05 August 2020 |
| Global end of trial reached? | No |

Notes:

General information about the trial

Main objective of the trial:

To evaluate and compare the efficacy of Venetoclax in combination with Fulvestrant versus Fulvestrant in Women with Estrogen Receptor-Positive, HER2-Negative locally advanced or Metastatic Breast Cancer

Protection of trial subjects:

All study subjects were required to sign an Informed Consent Form

Background therapy:

Subjects must not have received more than two prior lines of hormonal therapy in the locally advanced or metastatic setting. In addition, at least one line of treatment must be a CDK4/6i AND subjects must have experienced disease recurrence or progression during or after CDK4/6i therapy, which must have been administered for a minimum of 8 weeks prior to progression.

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 06 September 2018 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy |
| Long term follow-up duration | 2 Years |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Australia: 23 |
| Country: Number of subjects enrolled | Canada: 24 |
| Country: Number of subjects enrolled | Germany: 14 |
| Country: Number of subjects enrolled | United Kingdom: 13 |
| Country: Number of subjects enrolled | United States: 29 |
| Worldwide total number of subjects | 103 |
| EEA total number of subjects | 14 |

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) | 72 |
| From 65 to 84 years | 30 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 38 centers in 5 countries.

Pre-assignment

Screening details:

A total of 103 subjects were randomized in this study. Of these, 101 subjects received at least one dose of any study drug.

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 | Venetoclax + Fulvestrant |

Arm description:

Subjects were administered Venetoclax 800mg orally once daily (QD) and Fulvestrant 500mg intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).

| | |
|--|--|
| Arm type | Experimental |
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Fulvestrant was administered intramuscularly (IM) at a dose of 500mg (on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).

| | |
|--|------------|
| Investigational medicinal product name | Venetoclax |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Venetoclax was administered orally once daily (QD) at a dose of 800mg.

| | |
|------------------|-------------|
| Arm title | Fulvestrant |
|------------------|-------------|

Arm description:

Subjects were administered Fulvestrant 500mg only intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | Fulvestrant |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Concentrate for solution for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

Fulvestrant was administered intramuscularly (IM) at a dose of 500mg (on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).

| Number of subjects in period 1 | Venetoclax + Fulvestrant | Fulvestrant |
|---------------------------------------|-----------------------------|-------------|
| Started | 51 | 52 |
| Completed | 0 | 0 |
| Not completed | 51 | 52 |
| Physician decision | 1 | 1 |
| Consent withdrawn by subject | 3 | 1 |
| Ongoing in study | 29 | 40 |
| Death | 18 | 9 |
| Lost to follow-up | - | 1 |

Baseline characteristics

Reporting groups

| | |
|---|--------------------------|
| Reporting group title | Venetoclax + Fulvestrant |
| Reporting group description: | |
| Subjects were administered Venetoclax 800mg orally once daily (QD) and Fulvestrant 500mg intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days). | |
| Reporting group title | Fulvestrant |
| Reporting group description: | |
| Subjects were administered Fulvestrant 500mg only intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days). | |

| Reporting group values | Venetoclax + Fulvestrant | Fulvestrant | Total |
|--|--------------------------|-------------|-------|
| Number of subjects | 51 | 52 | 103 |
| 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) | 38 | 34 | 72 |
| From 65-84 years | 12 | 18 | 30 |
| 85 years and over | 1 | 0 | 1 |
| Age Continuous Units: years | | | |
| arithmetic mean | 57.4 | 58.8 | - |
| standard deviation | ± 10.6 | ± 11.7 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 51 | 52 | 103 |
| Male | 0 | 0 | 0 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 1 | 3 | 4 |
| Not Hispanic or Latino | 47 | 46 | 93 |
| Not Reported | 3 | 3 | 6 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 6 | 3 | 9 |
| Black or African American | 3 | 2 | 5 |
| White | 40 | 46 | 86 |
| Multiple | 1 | 0 | 1 |
| Unknown | 1 | 1 | 2 |

End points

End points reporting groups

| | |
|---|--------------------------|
| Reporting group title | Venetoclax + Fulvestrant |
| Reporting group description: Subjects were administered Venetoclax 800mg orally once daily (QD) and Fulvestrant 500mg intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days). | |
| Reporting group title | Fulvestrant |
| Reporting group description: Subjects were administered Fulvestrant 500mg only intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days). | |

Primary: Clinical benefit defined as Complete Response (CR), Partial Response (PR) or Stable Disease (SD) lasting ≥ 24 weeks, as determined by the Investigator according to RECIST v1.1

| | |
|--|--|
| End point title | Clinical benefit defined as Complete Response (CR), Partial Response (PR) or Stable Disease (SD) lasting ≥ 24 weeks, as determined by the Investigator according to RECIST v1.1 |
| End point description: Clinical Benefit was defined as Complete Response, Partial Response, or Stable Disease lasting more than equal to 24 weeks from randomization in subjects with measurable disease at baseline, as determined by the investigator according to Response Evaluation Criteria In Solid Tumors Criteria (RECIST) v1.1. Per RECIST v1.1 for target lesions assessed by CT or MRI: Complete Response (CR), Disappearance of all target lesions; Partial Response (PR), $\geq 30\%$ decrease in the sum of the diameters of target lesions; Stable Disease (SD), neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Disease Progression (PD), taking as reference the smallest sum on study. | |
| End point type | Primary |
| End point timeframe: Randomization through till 6 months after the last subject is enrolled into the study (up to approximately 23 months). | |

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|----------------------------------|--------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 51 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 11.8 (4.44 to 23.87) | 13.7 (5.70 to 26.26) | | |

Statistical analyses

| | |
|----------------------------|---|
| Statistical analysis title | (Venetoclax + Fulvestrant) vs Fulvestrant |
| Comparison groups | Fulvestrant v Venetoclax + Fulvestrant |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7286 ^[1] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -16.86 |
| upper limit | 12.94 |

Notes:

[1] - P-value is based on Stratified Analysis (Stratified by BCL2 status (High vs Low) and Lines of Therapy (2 vs 1)).

Secondary: Progression Free Survival (PFS)

| | |
|---|---------------------------------|
| End point title | Progression Free Survival (PFS) |
| End point description: | |
| PFS was defined as the time from randomization to the first occurrence of disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first. | |
| End point type | Secondary |
| End point timeframe: | |
| Randomization through till 6 months after the last subject is enrolled into the study (up to approximately 23 months). | |

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|----------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 52 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 2.69 (1.94 to 3.71) | 1.94 (1.84 to 3.55) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | (Venetoclax + Fulvestrant) vs Fulvestrant |
| Comparison groups | Venetoclax + Fulvestrant v Fulvestrant |
| Number of subjects included in analysis | 103 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.7853 ^[2] |
| Method | Regression, Cox |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.61 |
| upper limit | 1.45 |

Notes:

[2] - P-value is based on Stratified Analysis (Stratified by BCL2 status (High vs Low) and Lines of Therapy (2 vs 1)).

Secondary: Objective Response (OR)

| | |
|-----------------|-------------------------|
| End point title | Objective Response (OR) |
|-----------------|-------------------------|

End point description:

OR was defined as Complete Response (CR) or Partial response (PR), in subjects with measurable disease at baseline as determined by the investigator according to RECIST v1.1.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Randomization through till 6 months after the last subject is enrolled into the study (up to approximately 23 months).

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|----------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 51 | 51 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 3.9 (0.48 to 13.46) | 5.9 (1.23 to 16.24) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | (Venetoclax + Fulvestrant) vs Fulvestrant |
| Comparison groups | Venetoclax + Fulvestrant v Fulvestrant |
| Number of subjects included in analysis | 102 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.5978 ^[3] |
| Method | Cochran-Mantel-Haenszel |
| Parameter estimate | Risk difference (RD) |
| Point estimate | -1.96 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.29 |
| upper limit | 8.37 |

Notes:

[3] - P-value is based on Stratified Analysis (Stratified by BCL2 status (High vs Low) and Lines of Therapy (2 vs 1)).

Secondary: Duration of Response (DOR)

| | |
|--|----------------------------|
| End point title | Duration of Response (DOR) |
| End point description: DOR was defined as the time from the first occurrence of a documented objective response to the time of the first documented disease progression (as determined by the investigator according to RECIST v1.1) or death from any cause, whichever occurs first. 9999 = Not Estimable. | |
| End point type | Secondary |
| End point timeframe: Time from first occurrence of a documented objective response to the first documented disease progression or death from any cause, whichever occurs first, until 6 months after the last subject is enrolled in the study (up to approximately 23 months). | |

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|----------------------------------|--------------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 2 | 3 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 9999 (9999 to 9999) | 3.61 (1.94 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: Overall Survival (OS) is defined as the time from randomization to death due to any cause. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date. | |
| End point type | Secondary |
| End point timeframe: Randomization to death from any cause, through till the end of the study (2 years after the last subject is enrolled) | |

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|----------------------------------|--------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[4] | 0 ^[5] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | (to) | (to) | | |

Notes:

[4] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

[5] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Adverse Events (AEs)

| | |
|---|--|
| End point title | Percentage of Subjects with Adverse Events (AEs) |
| End point description: An Adverse Event (AE) is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An Adverse Event can therefore be any unfavorable and unintended sign (including abnormal laboratory values or abnormal clinical test results), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as Adverse Events. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date. | |
| End point type | Secondary |
| End point timeframe: Baseline up until 28 days after the last dose of study drug (venetoclax or fulvestrant, whichever is later) (up to approximately 23 months). | |

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|-------------------------------|--------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[6] | 0 ^[7] | | |
| Units: Percentage of Subjects | | | | |

Notes:

[6] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

[7] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Venetoclax at specified timepoints

| | |
|--|---|
| End point title | Plasma Concentrations of Venetoclax at specified timepoints |
| End point description: The PK analyses includes tabulation of plasma concentration data and summarisation of plasma concentrations by visits with subjects grouped according to treatment received. Descriptive summary statistics for the Arithmetic Mean and Standard Deviation are presented below. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date. | |
| End point type | Secondary |
| End point timeframe: At pre-defined intervals from Cycle 1, Day 1, through till the end of treatment (2 years after the last subject is enrolled). | |

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|--------------------------------------|--------------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[8] | 0 ^[9] | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[8] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

[9] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Fulvestrant at specified timepoints

| | |
|-----------------|--|
| End point title | Plasma Concentrations of Fulvestrant at specified timepoints |
|-----------------|--|

End point description:

The PK analyses includes tabulation of plasma concentration data and summarisation of plasma concentrations by visits with subjects grouped according to treatment received. Descriptive summary statistics for the Arithmetic Mean and Standard Deviation are presented below. Data collection is still ongoing and the results will be disclosed within 1 year from the Study Completion Date.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At pre-defined intervals from Cycle 1, Day 1, through till the end of treatment (2 years after the last subject is enrolled).

| End point values | Venetoclax + Fulvestrant | Fulvestrant | | |
|--------------------------------------|--------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[10] | 0 ^[11] | | |
| Units: µg/mL | | | | |
| arithmetic mean (standard deviation) | () | () | | |

Notes:

[10] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

[11] - Data for this Endpoint will only be reported within 1 year from the Final Study Completion Date.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Baseline up until 28 days after the last dose of study drug (venetoclax or fulvestrant, whichever is later) (up to approximately 23 months).

Adverse event reporting additional description:

The 1 additional death in the Ven + Fulv arm compared to in the Subject Disposition section, relates to a subject who had withdrawn consent from the study and later died. Their death was reported in public records.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 23.0 |

Reporting groups

| | |
|-----------------------|--------------------------|
| Reporting group title | Venetoclax + Fulvestrant |
|-----------------------|--------------------------|

Reporting group description:

Subjects were administered Venetoclax 800mg orally once daily (QD) and Fulvestrant 500mg intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).

| | |
|-----------------------|-------------|
| Reporting group title | Fulvestrant |
|-----------------------|-------------|

Reporting group description:

Subjects were administered Fulvestrant 500mg only intramuscularly (IM) on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).

| Serious adverse events | Venetoclax + Fulvestrant | Fulvestrant | |
|--|--------------------------|----------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 1 / 51 (1.96%) | |
| number of deaths (all causes) | 19 | 9 | |
| number of deaths resulting from adverse events | | | |
| Investigations | | | |
| Ejection fraction decreased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 51 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 51 (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 | | | |

| | | | |
|---|----------------|----------------|--|
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 51 (1.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Flank pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 51 (1.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 51 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 51 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |

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

| Non-serious adverse events | Venetoclax + Fulvestrant | Fulvestrant | |
|---|--------------------------|------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 50 (90.00%) | 34 / 51 (66.67%) | |
| Vascular disorders | | | |
| Hot flush | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 9 / 51 (17.65%) | |
| occurrences (all) | 1 | 9 | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 0 / 51 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 18 / 50 (36.00%) | 8 / 51 (15.69%) | |
| occurrences (all) | 20 | 8 | |

| | | | |
|--|----------------------|-----------------------|--|
| Injection site pain subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 9 / 51 (17.65%) 12 | |
| Injection site reaction subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 7 | 6 / 51 (11.76%) 7 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 6 | 1 / 51 (1.96%) 1 | |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 8 / 50 (16.00%) 9 | 4 / 51 (7.84%) 4 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 5 | 3 / 51 (5.88%) 3 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 8 / 50 (16.00%) 8 | 4 / 51 (7.84%) 4 | |
| Investigations Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 4 / 51 (7.84%) 4 | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 4 | 3 / 51 (5.88%) 3 | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 4 / 51 (7.84%) 4 | |
| Blood creatine phosphokinase increased subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 4 | 2 / 51 (3.92%) 2 | |
| Weight decreased | | | |

| | | | |
|---|---|--|--|
| subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 0 / 51 (0.00%) 0 | |
| Injury, poisoning and procedural complications Injection related reaction subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 9 | 4 / 51 (7.84%) 4 | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 5 7 / 50 (14.00%) 8 | 2 / 51 (3.92%) 2 8 / 51 (15.69%) 8 | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Leukopenia subjects affected / exposed occurrences (all) Lymphopenia subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 3 / 50 (6.00%) 3 7 / 50 (14.00%) 7 8 / 50 (16.00%) 11 | 3 / 51 (5.88%) 3 1 / 51 (1.96%) 1 0 / 51 (0.00%) 0 0 / 51 (0.00%) 0 | |
| Gastrointestinal disorders Abdominal distension subjects affected / exposed occurrences (all) Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 5 4 / 50 (8.00%) 4 4 / 50 (8.00%) 4 | 1 / 51 (1.96%) 1 0 / 51 (0.00%) 0 1 / 51 (1.96%) 1 | |

| | | | |
|---|------------------|-----------------|--|
| Constipation | | | |
| subjects affected / exposed | 8 / 50 (16.00%) | 2 / 51 (3.92%) | |
| occurrences (all) | 8 | 2 | |
| Diarrhoea | | | |
| subjects affected / exposed | 27 / 50 (54.00%) | 5 / 51 (9.80%) | |
| occurrences (all) | 37 | 6 | |
| Dry mouth | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 0 / 51 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Nausea | | | |
| subjects affected / exposed | 32 / 50 (64.00%) | 9 / 51 (17.65%) | |
| occurrences (all) | 40 | 10 | |
| Vomiting | | | |
| subjects affected / exposed | 15 / 50 (30.00%) | 1 / 51 (1.96%) | |
| occurrences (all) | 23 | 1 | |
| Hepatobiliary disorders | | | |
| Hepatic pain | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 0 / 51 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Pruritus | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 1 / 51 (1.96%) | |
| occurrences (all) | 5 | 1 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 6 / 51 (11.76%) | |
| occurrences (all) | 5 | 8 | |
| Back pain | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 5 / 51 (9.80%) | |
| occurrences (all) | 3 | 6 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 8 / 51 (15.69%) | |
| occurrences (all) | 2 | 9 | |
| Pain in extremity | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 1 / 51 (1.96%) | |
| occurrences (all) | 4 | 2 | |

| | | | |
|--|----------------------|---------------------|--|
| Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 1 / 51 (1.96%) 1 | |
| Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all) | 9 / 50 (18.00%) 9 | 2 / 51 (3.92%) 2 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 19 September 2018 | Primarily to provide clarifications and to ensure consistency across sections. |

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.

| |
|---|
| Primary and secondary efficacy endpoints have been updated to report 95% confidence interval (CI) for Clinical Benefit estimate and 95% CI for the Cox proportional hazards model for PFS, following reporting conventions. |
|---|

Notes: