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	06 May 2021

Results information

Result version number	v3
This version publication date	13 May 2022
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	Final
Date of interim/final analysis	06 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	06 May 2021
Was the trial ended prematurely?	Yes

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	0

months)	
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	Venetoclax
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Venetoclax was administered orally QD at a dose of 800mg.

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

Arm title	Fulvestrant

Arm description:

Subjects were administered Fulvestrant 500mg only 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 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
Death	25	18
Withdrawal by Subject	3	2
Study Terminated by Sponsor	22	30
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 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			
Age Continuous Units: years			
arithmetic mean	57.4	58.8	
standard deviation	± 10.6	± 11.7	-
Sex: Female, Male Units: Subjects			
Female	51	52	103
Male	0	0	0
Ethnicity Units: Subjects			
Hispanic or Latino	1	3	4
Not Hispanic or Latino	47	46	93
Not Reported	3	3	6
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	3	9
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	2	5
White	40	46	86
More than one race	1	0	1
Unknown or Not Reported	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 IM on Day 1 and 15 of Cycle 1 and Day 1 of subsequent cycles (Cycle length = 28 days).	
Subject analysis set title	Fulvestrant in Presence of Venetoclax
Subject analysis set type	Sub-group analysis
Subject analysis set 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).	

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 CR, PR, or SD lasting more than equal to 24 weeks from randomisation in participants 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: CR, Disappearance of all target lesions; PR, PR >= 30% decrease in the sum of diameters of target lesions (TL) taking as reference the baseline sum of diameters; SD, neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for Disease Progression (PD), PD>= 20% increase in the sum of diameters of TL taking as reference the smallest sum on study (Nadir). In addition to the relative increase of 20% sum must have demonstrate an absolute increase of at least 5mm.	
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	Venetoclax + Fulvestrant v 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 CR or 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. Here, 9999 = Insufficient number of subjects meant that Median, Lower Limit and Upper Limit values could not be estimated.

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:

OS was defined as the time from randomization to death due to any cause. ITT population included all randomized subjects whether or not they were assigned to the arm where the study treatment was administered. Here, 9999 signifies median and upper limit of confidence interval (CI) were not estimable due to fewer number of subjects with events.

End point type	Secondary

End point timeframe:

Randomization to death from any cause, through till the end of the study (Up to approximately 32 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%)	19.71 (13.73 to 9999)	9999 (20.93 to 9999)		

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	= 0.0403 [4]
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.02
upper limit	3.43

Notes:

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

Secondary: Percentage of Subjects with Adverse Events (AEs)

End point title	Percentage of Subjects with Adverse Events (AEs)

End point description:

An 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 AE 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 were also considered as AEs. Safety-evaluable population which included all subjects who received any amount of any component of the investigational or non-investigational study treatments.

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 32 months

End point values	Venetoclax + Fulvestrant	Fulvestrant		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	50	51		
Units: Percentage of Subjects				
number (not applicable)	94.0	76.5		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Venetoclax (in Presence of Fulvestrant)

End point title	Plasma Concentrations of Venetoclax (in Presence of Fulvestrant)[5]

End point description:

Pharmacokinetic (PK) evaluable population included all subjects who received at least one dose of the study drugs (either venetoclax or fulvestrant) and had evaluable PK data. "n" = number analyzed is the number of subjects with data available for analyses at the given time-point. 9999 indicates not reportable for Geometric Coefficient of Variation for that timepoint where more than one-third values are lower than reportable.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1: 4 hours (hrs) post-dose; Cycle 2 Day 1: pre-dose (within 1 hr) and 2, 4, 6, 8 hrs post-dose; any time during visits up to study drug discontinuation/Early Termination (up to approximately 32 months)

Notes:

[5] - 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: The data was reported for Venetoclax + Fulvestrant reporting arm only.

End point values	Venetoclax + Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: Micrograms per Millilitres (µg/mL)				
geometric mean (geometric coefficient of variation)				
Cycle 1 Day 1: 4 hrs post-dose (n=47)	1.78 (± 61.8)			
Cycle 2 Day 1: pre-dose (n=40)	1.04 (± 85.4)			
Cycle 2 Day 1: 2 hrs post-dose (n=39)	1.45 (± 74.1)			
Cycle 2 Day 1: 4 hrs post-dose (n=40)	2.51 (± 57.2)			
Cycle 2 Day 1: 6 hrs post-dose (n=35)	3.32 (± 56.4)			
Cycle 2 Day 1: 8 hrs post-dose (n=28)	3.55 (± 57.8)			
Treatment discontinuation visit (n=21)	0.0112 (± 9999)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Fulvestrant (in Presence of Venetoclax)

End point title	Plasma Concentrations of Fulvestrant (in Presence of Venetoclax)

End point description:

PK evaluable population included all subjects who received at least one dose of the study drugs (either venetoclax or fulvestrant) and had evaluable PK data. "n" = number analyzed is the number of subjects with data available for analyses at the given time-point.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1 and Cycle 6 Day 1: pre-dose (within 1 hr); any time during visits up to study drug discontinuation/Early Termination (up to approximately 32 months)

End point values	Fulvestrant in Presence of Venetoclax			
Subject group type	Subject analysis set			
Number of subjects analysed	42			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1: pre-dose (n=42)	0.0129 (± 37.1)			
Cycle 6 Day 1: pre-dose (n=7)	0.0145 (± 31.8)			
Treatment discontinuation visit (n=28)	0.00985 (± 29.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentrations of Fulvestrant (in Absence of Venetoclax)

End point title	Plasma Concentrations of Fulvestrant (in Absence of Venetoclax)[6]

End point description:

PK evaluable population included all participants who received at least one dose of the study drugs (either venetoclax or fulvestrant) and had evaluable PK data. "n" = number analyzed is the number of subjects with data available for analyses at the given time-point. 9999 indicates that the data for Geometric Coefficient of Variation was not estimable due to lower number of participants at given timepoint.

End point type	Secondary

End point timeframe:

Cycle 2 Day 1: pre-dose (within 1 hr); any time during visits up to study drug discontinuation/Early Termination (up to approximately 32 months)

Notes:

[6] - 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: The data was reported for Fulvestrant reporting arm only.

End point values	Fulvestrant			
Subject group type	Reporting group			
Number of subjects analysed	5[7]			
Units: µg/mL				
geometric mean (geometric coefficient of variation)				
Cycle 2 Day 1: pre-dose (n=5)	0.0103 (± 29.4)			
Treatment discontinuation visit (n=1)	0.0139 (± 9999)			

Notes:

[7] - Number of subject analysed are the subjects who were evaluated for the endpoint.

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 32 months.

Adverse event reporting additional description:

The 1 additional death in the Venetoclax + Fulvestrant arm compared to in the Subject Disposition section, relates to a participant who had withdrawn consent from the study and later died. Their death was reported in public records (reported as a post study reporting death).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	VENETOCLAX + FULVESTRANT

Reporting group description:

Subjects were administered Venetoclax 800mg orally QD and Fulvestrant 500mg 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 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%)	2 / 51 (3.92%)	
number of deaths (all causes)	26	18	
number of deaths resulting from adverse events	0	0	
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	
Bone 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%)	9 / 51 (17.65%)	
occurrences (all)	20	9	
Injection site reaction			
subjects affected / exposed	11 / 50 (22.00%)	15 / 51 (29.41%)	
occurrences (all)	15	21	
Oedema peripheral			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	
occurrences (all)	6	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	8 / 50 (16.00%)	4 / 51 (7.84%)	
occurrences (all)	9	4	
Dyspnoea			
subjects affected / exposed	5 / 50 (10.00%)	3 / 51 (5.88%)	
occurrences (all)	5	3	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	8 / 50 (16.00%)	4 / 51 (7.84%)	
occurrences (all)	8	4	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 50 (4.00%)	4 / 51 (7.84%)	
occurrences (all)	2	4	
Aspartate aminotransferase increased			
subjects affected / exposed	4 / 50 (8.00%)	3 / 51 (5.88%)	
occurrences (all)	4	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	2 / 50 (4.00%)	4 / 51 (7.84%)	
occurrences (all)	2	4	
Weight decreased			
subjects affected / exposed	3 / 50 (6.00%)	0 / 51 (0.00%)	
occurrences (all)	3	0	
Blood creatine phosphokinase			

increased			
subjects affected / exposed	4 / 50 (8.00%)	2 / 51 (3.92%)	
occurrences (all)	4	2	
Injury, poisoning and procedural complications			
Injection related reaction			
subjects affected / exposed	4 / 50 (8.00%)	5 / 51 (9.80%)	
occurrences (all)	6	5	
Nervous system disorders			
Headache			
subjects affected / exposed	7 / 50 (14.00%)	8 / 51 (15.69%)	
occurrences (all)	8	8	
Dizziness			
subjects affected / exposed	5 / 50 (10.00%)	2 / 51 (3.92%)	
occurrences (all)	5	2	
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	3 / 50 (6.00%)	1 / 51 (1.96%)	
occurrences (all)	3	1	
Anaemia			
subjects affected / exposed	2 / 50 (4.00%)	3 / 51 (5.88%)	
occurrences (all)	2	3	
Lymphopenia			
subjects affected / exposed	7 / 50 (14.00%)	0 / 51 (0.00%)	
occurrences (all)	7	0	
Neutropenia			
subjects affected / exposed	8 / 50 (16.00%)	0 / 51 (0.00%)	
occurrences (all)	11	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	5 / 50 (10.00%)	1 / 51 (1.96%)	
occurrences (all)	5	1	
Abdominal pain			
subjects affected / exposed	4 / 50 (8.00%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
Constipation			

subjects affected / exposed	8 / 50 (16.00%)	2 / 51 (3.92%)	
occurrences (all)	8	2	
Abdominal pain upper			
subjects affected / exposed	4 / 50 (8.00%)	1 / 51 (1.96%)	
occurrences (all)	4	1	
Diarrhoea			
subjects affected / exposed	28 / 50 (56.00%)	5 / 51 (9.80%)	
occurrences (all)	39	6	
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	
Dry mouth			
subjects affected / exposed	4 / 50 (8.00%)	0 / 51 (0.00%)	
occurrences (all)	4	0	
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			
Musculoskeletal chest pain			
subjects affected / exposed	1 / 50 (2.00%)	8 / 51 (15.69%)	
occurrences (all)	2	9	
Back pain			
subjects affected / exposed	3 / 50 (6.00%)	5 / 51 (9.80%)	
occurrences (all)	3	6	
Arthralgia			
subjects affected / exposed	5 / 50 (10.00%)	6 / 51 (11.76%)	
occurrences (all)	6	10	
Pain in extremity			

subjects affected / exposed occurrences (all)	4 / 50 (8.00%) 4	1 / 51 (1.96%) 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.
16 October 2020	1. The protocol was amended to update study rationale and benefit-risk assessment, based on the results of the primary analysis, it was no longer considered appropriate for subjects in this study to receive venetoclax. As of 8 October 2020, all active subjects in the venetoclax plus fulvestrant arm of the study were requested to discontinue the venetoclax treatment immediately and were given the option to continue fulvestrant treatment alone. 2. Study design, study treatment, and treatment interruption were updated to reflect the immediate discontinuation of venetoclax treatment. 3. The frequency of survival follow-up was increased from approximately every 6 months to approximately every 3 months or more frequently after treatment discontinuation, to enhance safety data collection. 4. Update was made in use of contraception to indicate that contraception should be used for up to 2 years after the last dose of study drug or based on local prescribing information for fulvestrant. 5. Adverse events of special interest for the study were modified to remove hepatitis B reactivation. 6. Statistical considerations for primary and secondary efficacy endpoints were amended to specify the calculation of the 95% CI for CBR estimate, and 95% CI for the Cox proportional hazards model for PFS, following reporting conventions.

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.

Study terminated due to Sponsor’s decision with no safety concerns. Primary/secondary efficacy endpoints- updated to report 95% CI for Clinical Benefit estimate and 95% CI for Cox proportional hazards model for PFS, following reporting conventions.

Notes: