Clinical trial results:
A Randomized, Double-Blind, Phase 2 Trial of Fulvestrant Plus Enzastaurin versus Fulvestrant Plus Placebo in Aromatase Inhibitor-Resistant Metastatic Breast Cancer

Summary

EudraCT number	2006-005305-58
Trial protocol	NL FR DE IT ES
Global end of trial date	18 October 2018

Results information

Result version number	v2 (current)
This version publication date	26 January 2020
First version publication date	13 October 2019
Version creation reason	• Correction of full data set Correction of full data set

Trial information

Trial identification

Sponsor protocol code	H6Q-MC-S023

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00451555
WHO universal trial number (UTN)	-
Other trial identifiers	Trial Number: 10736

Notes:

Sponsors

Sponsor organisation name	Eli Lilly and Company
Sponsor organisation address	Lilly Corporate Center, Indianapolis, IN, United States, 46285
Public contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 877CTLilly,
Scientific contact	Available Mon Fri 9 AM 5 PM EST, Eli Lilly and Company, 1 8772854559,

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	18 October 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary purpose of this study is to help answer the following research question: whether enzastaurin given together with fulvestrant can help participants who have breast cancer and make the tumor smaller or disappear and for how long.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonization (ICH) Good Clinical Practice, and the principles of the Declaration of Helsinki, in addition to following the laws and regulations of the country or countries in which a study is conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 April 2007
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Italy: 18
Country: Number of subjects enrolled	France: 60
Country: Number of subjects enrolled	Germany: 19
Country: Number of subjects enrolled	Spain: 35
Country: Number of subjects enrolled	Netherlands: 20
Worldwide total number of subjects	152
EEA total number of subjects	152

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)	84
From 65 to 84 years	62
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

No Text Available

Pre-assignment

Screening details:

Completers include participants who had died from any cause, who discontinued due to progressive disease or were alive and on study but off treatment at end of the study.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	No
Arm title	Enzastaurin + Fulvestrant

Arm description:

(Initial Therapy) Participants received Enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 500 mg orally (QD) once daily in a 28-day cycle.

(Amended Therapy) Participants received enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 250 mg orally (BID) twice daily in a 28-day cycle.

Enzastaurin Once Daily Dosing: Participants received Enzastaurin 500 mg QD. Enzastaurin Twice Daily Dosing: Participants received Enzastaurin 500 mg BID. Fulvestrant was given intramuscularly at a loading dose of 500 mg on Day 1 and 250 mg on Day 15 in Cycle 1. Subsequent doses of Fulvestrant 250 mg were given on Day 1 of Cycle 2 and every 28 days thereafter.

Arm type	Experimental
Investigational medicinal product name	enzastaurin
Investigational medicinal product code	
Other name	LY317615
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received Enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 500 mg orally (QD) once daily in a 28-day cycle.
Participants received enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 250 mg orally (BID) twice daily in a 28-day cycle.

Investigational medicinal product name	fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg, intramuscular (IM), day 1, 1250 mg, IM, day 15 cycle 1 then 250 mg, IM, every 28 days, until disease progression

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet

Routes of administration	Oral use

Dosage and administration details:

Participants received placebo, oral, daily.

Arm title	Fulvestrant + Placebo

Arm description:

Participants received fulvestrant: 500 mg, intramuscular (IM), day 1, 1250 mg, IM, day 15 cycle 1 then 250 mg, IM, every 28 days, until disease progression.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Participants received placebo, oral, daily.

Investigational medicinal product name	fulvestrant
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

500 mg, intramuscular (IM), day 1, 1250 mg, IM, day 15 cycle 1 then 250 mg, IM, every 28 days, until disease progression

Number of subjects in period 1	Enzastaurin + Fulvestrant	Fulvestrant + Placebo
Started	96	60
Enzastaurin Twice Daily Dosing (BID)	39 [1]	0 [2]
Enzastaurin Once Daily Dosing (QD)	55 [3]	0 [4]
Progressive Disease	75 [5]	54 [6]
Death	2 [7]	0 [8]
Received at least one dose of study drug	94	58
Completed	83	56
Not completed	13	4
Consent withdrawn by subject	6	-
Physician decision	2	1
Adverse event, non-fatal	3	1
Protocol deviation	2	2

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: The number of participants at this milestone is a subpopulation to the overall number of participants enrolled in the study.

Baseline characteristics

Reporting groups	
Reporting group title	Overall Study

Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	152	152	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	64.9		
standard deviation	± 10.0	-	
Gender categorical Units: Subjects			
Female	152	152	
Male	0	0	
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	57	57	
Not Hispanic or Latino	95	95	
Unknown or Not Reported	0	0	
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Black or African American	1	1	
White	151	151	
More than one race	0	0	
Unknown or Not Reported	0	0	
Region of Enrollment Units: Subjects			
Netherlands	20	20	
Italy	18	18	
France	60	60	
Germany	19	19	
Spain	35	35	

End points

End points reporting groups

Reporting group title	Enzastaurin + Fulvestrant

Reporting group description:

(Initial Therapy) Participants received Enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 500 mg orally (QD) once daily in a 28-day cycle.

(Amended Therapy) Participants received enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 250 mg orally (BID) twice daily in a 28-day cycle.

Enzastaurin Once Daily Dosing: Participants received Enzastaurin 500 mg QD. Enzastaurin Twice Daily Dosing: Participants received Enzastaurin 500 mg BID. Fulvestrant was given intramuscularly at a loading dose of 500 mg on Day 1 and 250 mg on Day 15 in Cycle 1. Subsequent doses of Fulvestrant 250 mg were given on Day 1 of Cycle 2 and every 28 days thereafter.

Reporting group title	Fulvestrant + Placebo

Reporting group description:

Participants received fulvestrant: 500 mg, intramuscular (IM), day 1, 1250 mg, IM, day 15 cycle 1 then 250 mg, IM, every 28 days, until disease progression.

Subject analysis set title	Enzastaurin + Fulvestrant BID
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Enzastaurin 1125 mg loading dose then 250 mg, oral, twice daily (BID) (for a total of 500 mg), until disease progression

Fulvestrant was given intramuscularly at a loading dose of 500 mg on Day 1 and 250 mg on Day 15 in Cycle 1. Subsequent doses of Fulvestrant 250 mg were given on Day 1 of Cycle 2 and every 28 days thereafter.

Subject analysis set title	Enzastaurin + Fulvestrant QD
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Enzastaurin 1125 mg loading dose then received Enzastaurin once daily (QD) regimen of enzastaurin 500 mg orally QD in a 28-day cycle until disease progression.

Fulvestrant was given intramuscularly at a loading dose of 500 mg on Day 1 and 250 mg on Day 15 in Cycle 1. Subsequent doses of Fulvestrant 250 mg were given on Day 1 of Cycle 2 and every 28 days thereafter.

Subject analysis set title	Placebo + Fulvestrant BID
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received fulvestrant: 500 mg, IM, day 1, 1250 mg, IM, day 15 cycle 1 then 250 mg, IM, every 28 days, until disease progression.

Then, participants received placebo, oral, daily.

Subject analysis set title	Enzastaurin + Fulvestrant QD + BID
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 500 mg orally (QD) once daily in a 28-day cycle.
Participants received enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 250 mg orally (BID) twice daily in a 28-day cycle.
Fulvestrant was given intramuscularly at a loading dose of 500 mg on Day 1 and 250 mg on Day 15 in Cycle 1. Subsequent doses of Fulvestrant 250 mg were given on Day 1 of Cycle 2 and every 28 days thereafter.
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Subject analysis set title	Enzastaurin + Fulvestrant BID + QD Duration Clinical Benefit
Subject analysis set type	Per protocol

Subject analysis set description:

Participants received Enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received

Enzastaurin 500 mg orally (QD) once daily in a 28-day cycle.
Participants received enzastaurin loading dose of 1125 mg, on Day 1 of Cycle 1 only then received Enzastaurin 250 mg orally (BID) twice daily in a 28-day cycle.
Fulvestrant was given intramuscularly at a loading dose of 500 mg on Day 1 and 250 mg on Day 15 in Cycle 1. Subsequent doses of Fulvestrant 250 mg were given on Day 1 of Cycle 2 and every 28 days thereafter.
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Primary: Percentage of Participants Who Achieved a Best Response of Complete Response, Partial Response, and Stable Disease (CR+PR+SD) (Clinical Benefit Rate)

End point title	Percentage of Participants Who Achieved a Best Response of Complete Response, Partial Response, and Stable Disease (CR+PR+SD) (Clinical Benefit Rate)

End point description:

Clinical benefit rate is defined as the rate of confirmed CR, confirmed PR, and SD for 24 weeks duration and is the best response CR, PR, or SD as classified by the investigators according to the RECIST v1.1. CR is a disappearance of all target and non-target lesions and normalization of tumor marker level. PR is an at least 30% decrease in the sum of the diameters of target lesions (taking as reference the baseline sum diameter) without progression of not-target lesions or appearance of new lesions. SD is neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum diameter since treatment started. Kaplan-Meier (KM) techniques were used to assess the time-to-event endpoints. Progressive Disease (PD) was defined as having at least 20% increase in sum of longest diameter of target lesions and minimum 5 mm increase above nadir.

End point type	Primary

End point timeframe:

Baseline to Measured Progressive Disease or Study Discontinuation (Up to 24 Weeks)

End point values	Enzastaurin + Fulvestrant BID	Enzastaurin + Fulvestrant QD	Placebo + Fulvestrant BID	Enzastaurin + Fulvestrant QD + BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[1]	55[2]	58[3]	94[4]
Units: percentage of participants				
number (confidence interval 95%)	43.6 (27.8 to 60.4)	43.6 (30.3 to 57.7)	44.8 (31.7 to 58.5)	43.6 (33.4 to 54.2)

Notes:

[1] - All randomized participants who received at least one dose of study drug.

[2] - All randomized participants who received at least one dose of study drug.

[3] - All randomized participants who received at least one dose of study drug.

[4] - All randomized participants who received at least one dose of study drug.

Statistical analyses

Statistical analysis title	Achieved a Best Response of CR+PR+SD (CBR)
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant BID
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6282
Method	Fisher exact

Statistical analysis title	Achieved a Best Response of CR+PR+SD (CBR)

Comparison groups	Enzastaurin + Fulvestrant QD v Placebo + Fulvestrant BID
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6242
Method	Fisher exact

Statistical analysis title	Achieved a Best Response CR+PR+SD (CBR)
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant QD + BID
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6238
Method	Fisher exact

Secondary: Percentage of Participants Achieving Overall Tumor Response Complete Response (CR) or Partial Response (PR) [Overall Response Rate (ORR])

End point title	Percentage of Participants Achieving Overall Tumor Response Complete Response (CR) or Partial Response (PR) [Overall Response Rate (ORR])

End point description:

The ORR is equal to the percentage of participants achieving a best overall response of partial response or complete response (PR + CR), according to RECIST version 1.1 criteria. CR was defined as the disappearance of all target and non-target lesions and any pathological lymph nodes must have reduction in short axis to <10 millimeter (mm) and normalization of tumor marker level of non-target lesions; PR was defined as having at least a 30% decrease in sum of longest diameter of target lesions; PD was defined as having at least 20% increase in sum of longest diameter of target lesions and minimum 5 mm increase above nadir; SD was defined as small changes that did not meet above criteria. Participants who had no post baseline tumor assessments were considered non-responders and included in the denominator when calculating response rate. The 95% confidence interval (CI) was calculated by exact method. Kaplan-Meier (KM) techniques were used to assess the time-to-event endpoints.

End point type	Secondary

End point timeframe:

Baseline to Measured Progressive Disease or Study Discontinuation (Up to 24 Weeks)

End point values	Enzastaurin + Fulvestrant BID	Enzastaurin + Fulvestrant QD	Placebo + Fulvestrant BID	Enzastaurin + Fulvestrant QD + BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[5]	55[6]	58[7]	94[8]
Units: percentage of participants				
number (confidence interval 95%)	5.1 (0.6 to 17.3)	5.5 (1.1 to 15.1)	5.2 (1.1 to 14.4)	5.3 (1.7 to 12.0)

Notes:

[5] - All randomized participants who received at least one dose of study drug.

[6] - All randomized participants who received at least one dose of study drug.
[7] - All randomized participants who received at least one dose of study drug.
[8] - All randomized participants who received at least one dose of study drug.

Statistical analyses

Statistical analysis title	Percentage of Participants Achieving Overall Tumo
Comparison groups	Enzastaurin + Fulvestrant BID v Placebo + Fulvestrant BID
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6721
Method	Fisher exact

Statistical analysis title	Percentage of Participants Achieving Overall Tumo
Comparison groups	Enzastaurin + Fulvestrant QD v Placebo + Fulvestrant BID
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6349
Method	Fisher exact

Statistical analysis title	Percentage of Participants Achieving Overall Tumo
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant QD + BID
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.639
Method	Fisher exact

Secondary: Duration of Clinical Benefit

End point title	Duration of Clinical Benefit

End point description:

The duration of clinical benefit was measured from the time of clinical benefit of CR, PR or SD to the time of progressive disease or death from any cause. PD was defined as having at least 20% increase in sum of longest diameter of target lesions and minimum 5 mm increase above nadir. Kaplan-Meier (KM) techniques were used to assess the time-to-event endpoints.

End point type	Secondary

End point timeframe:

Time of Clinical Benefit to Progressive Disease or Death (Up to 3 Years)

End point values	Enzastaurin + Fulvestrant BID	Enzastaurin + Fulvestrant QD	Placebo + Fulvestrant BID	Enzastaurin + Fulvestrant BID + QD Duration Clinical Benefit
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	17[9]	24[10]	26[11]	41[12]
Units: months				
median (confidence interval 95%)	9.4 (7.4 to 12.2)	9.6 (7.9 to 11.1)	9.7 (7.4 to 12.6)	9.6 (8.2 to 11.0)

Notes:

[9] - All randomized participants who received at least one dose of study drug and had evaluable data.

[10] - All randomized participants who received at least one dose of study drug and had evaluable data.

[11] - All randomized participants who received at least one dose of study drug and had evaluable data.

[12] - All randomized participants who received at least one dose of study drug and had evaluable data.

Statistical analyses

Statistical analysis title	Duration of Clinical Benefit
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant BID + QD Duration Clinical Benefit
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8582
Method	Logrank

Statistical analysis title	Duration of Clinical Benefit
Comparison groups	Enzastaurin + Fulvestrant BID v Placebo + Fulvestrant BID
Number of subjects included in analysis	43
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7307
Method	Logrank

Statistical analysis title	Duration of Clinical Benefit
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant QD
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9798
Method	Logrank

Secondary: Progression Free Survival (PFS)

End point title	Progression Free Survival (PFS)

End point description:

Progression-free survival (PFS) time was defined as the time from baseline to the first date of progressive disease (symptomatic or objective) or death due to any cause, whichever occurred first. PD was defined as having at least 20% increase in sum of longest diameter of target lesions and minimum 5 mm increase above nadir.For participants who were not known to have died or progressed as of the data-inclusion cutoff date, PFS time was censored at the date of the last objective progression-free disease assessment prior to the date of any subsequent systematic anticancer therapy. PFS was summarized using Kaplan-Meier estimates. Participants were censored in Fulvestrant + Enzastaurin (QD) arm = 4, the Fulvestrant + Enzastaurin (BID) arm = 6, and the Fulvestrant + Placebo arm = 6.

End point type	Secondary

End point timeframe:

Baseline to Measured Progressive Disease or Death Due to Any Cause (Up to 3 Years)

End point values	Enzastaurin + Fulvestrant BID	Enzastaurin + Fulvestrant QD	Placebo + Fulvestrant BID	Enzastaurin + Fulvestrant QD + BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[13]	55[14]	58[15]	94[16]
Units: months				
median (confidence interval 95%)	3.7 (2.8 to 7.4)	6.0 (2.8 to 7.9)	5.5 (3.8 to 7.4)	5.2 (3.5 to 7.4)

Notes:

[13] - All randomized participants who received at least one dose of study drug.

[14] - All randomized participants who received at least one dose of study drug.

[15] - All randomized participants who received at least one dose of study drug.

[16] - All randomized participants who received at least one dose of study drug.

Statistical analyses

Statistical analysis title	Progression Free Survival (PFS)
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant QD + BID
Number of subjects included in analysis	152
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5887
Method	Logrank

Statistical analysis title	Progression Free Survival (PFS)
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant BID
Number of subjects included in analysis	97
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4516
Method	Logrank

Statistical analysis title	Progression Free Survival (PFS)
Comparison groups	Placebo + Fulvestrant BID v Enzastaurin + Fulvestrant QD
Number of subjects included in analysis	113
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7965
Method	Logrank

Secondary: Number of Participants Who Discontinued with Adverse Events (AE) and Serious Adverse Events (SAEs)

End point title	Number of Participants Who Discontinued with Adverse Events (AE) and Serious Adverse Events (SAEs)

End point description:

Clinically significant events were defined as serious AEs (SAEs) and other non-serious AEs, regardless of causality. A summary of SAEs and other non-serious AEs, regardless of causality, is located in the Reported Adverse Events module. Participants who discontinued due to an AE or SAE are reported.

End point type	Secondary

End point timeframe:

From Baseline To Study Completion (Up to 3 years, 9 months)

End point values	Enzastaurin + Fulvestrant BID	Enzastaurin + Fulvestrant QD	Placebo + Fulvestrant BID	Enzastaurin + Fulvestrant QD + BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	39[17]	55[18]	58[19]	94[20]
Units: participants				
Adverse Events (AEs)	1	2	1	3
Serious Adverse Events (SAEs)	0	0	1	0

Notes:

[17] - All randomized participants who received at least one dose of study drug.

[18] - All randomized participants who received at least one dose of study drug.

[19] - All randomized participants who received at least one dose of study drug.

[20] - All randomized participants who received at least one dose of study drug.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Enzastaurin Biomarkers and Disease State

End point title	Percentage of Participants with Enzastaurin Biomarkers and Disease State

End point description:

End point type	Secondary

End point timeframe:

From Baseline, Cycle 2 to Study Completion (Up to 3 Years, 9 Months)

End point values	Enzastaurin + Fulvestrant BID	Enzastaurin + Fulvestrant QD	Placebo + Fulvestrant BID	Enzastaurin + Fulvestrant QD + BID
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	0[21]	0[22]	0[23]	0[24]
Units: participants				

Notes:

[21] - Zero participants were analyzed due to insufficient samples being collected.

[22] - Zero participants were analyzed due to insufficient samples being collected.

[23] - Zero participants were analyzed due to insufficient samples being collected.

[24] - Zero participants were analyzed due to insufficient samples being collected.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From Baseline To Study Completion (Up to 3 Years, 9 Months)	
Adverse event reporting additional description: h6q_mc_s023	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	13.1

Reporting groups	
Reporting group title	Fulvestrant Plus Enzastaurin (QD + BID)
Reporting group description: -	
Reporting group title	Fulvestrant Plus Enzastaurin (BID)
Reporting group description: -	
Reporting group title	Fulvestrant Plus Enzastaurin (QD)
Reporting group description: -	
Reporting group title	Fulvestrant Plus Placebo
Reporting group description: -	

Serious adverse events	Fulvestrant Plus Enzastaurin (QD + BID)	Fulvestrant Plus Enzastaurin (BID)	Fulvestrant Plus Enzastaurin (QD)
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 94 (18.09%)	9 / 39 (23.08%)	8 / 55 (14.55%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
leiomyoma			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
metastases to skin			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			

phlebitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	10 / 10	0 / 0	10 / 10
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
disease progression			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
oedema peripheral			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

dyspnoea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
pleural effusion			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
respiratory failure			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
blood creatinine increased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 7
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			

femoral neck fracture			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
angina pectoris			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic cardiomyopathy			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
myocardial infarction			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Nervous system disorders			
cerebrovascular accident			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ischaemic stroke			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
syncope			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	2 / 39 (5.13%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 5	0 / 5	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
lymphadenopathy			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
haemorrhoids			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ileus			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
nausea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	3 / 3	3 / 3	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
vomiting			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
hepatic function abnormal			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 1	0 / 0	1 / 1
Renal and urinary disorders			
hydronephrosis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
ureteric dilatation			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
device related infection			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
urinary tract infection			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Fulvestrant Plus Placebo		
Total subjects affected by serious adverse events			

subjects affected / exposed	11 / 58 (18.97%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
leiomyoma			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
metastases to skin			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
phlebitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
disease progression			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
oedema peripheral			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
hypersensitivity			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
chronic obstructive pulmonary disease			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
dyspnoea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
pleural effusion			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences causally related to treatment / all	0 / 8		
deaths causally related to treatment / all	0 / 0		
respiratory failure			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
depression			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Investigations				
blood creatinine increased				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
gamma-glutamyltransferase increased				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
femoral neck fracture				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
angina pectoris				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 11			
deaths causally related to treatment / all	0 / 0			
ischaemic cardiomyopathy				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 16			
deaths causally related to treatment / all	0 / 0			
myocardial infarction				
alternative dictionary used: MedDRA 13.1				

subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
cerebrovascular accident			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
ischaemic stroke			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
syncope			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
lymphadenopathy			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
haemorrhoids			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
ileus				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
nausea				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
vomiting				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
hepatic function abnormal				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
hydronephrosis				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
ureteric dilatation				
alternative dictionary used: MedDRA 13.1				

subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
device related infection			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
urinary tract infection			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Fulvestrant Plus Enzastaurin (QD + BID)	Fulvestrant Plus Enzastaurin (BID)	Fulvestrant Plus Enzastaurin (QD)
Total subjects affected by non-serious adverse events			
subjects affected / exposed	78 / 94 (82.98%)	31 / 39 (79.49%)	47 / 55 (85.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	2 / 39 (5.13%)	1 / 55 (1.82%)
occurrences (all)	6	4	2
Vascular disorders			
hot flush			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	14 / 94 (14.89%)	8 / 39 (20.51%)	6 / 55 (10.91%)
occurrences (all)	248	203	45
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	15 / 94 (15.96%)	6 / 39 (15.38%)	9 / 55 (16.36%)
occurrences (all)	169	124	45
chest pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	0 / 39 (0.00%)	3 / 55 (5.45%)
occurrences (all)	9	0	9
fatigue			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	21 / 94 (22.34%)	9 / 39 (23.08%)	12 / 55 (21.82%)
occurrences (all)	119	37	82
influenza like illness			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	2 / 39 (5.13%)	2 / 55 (3.64%)
occurrences (all)	7	4	3
malaise			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	2 / 39 (5.13%)	0 / 55 (0.00%)
occurrences (all)	5	5	0
oedema peripheral			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 94 (7.45%)	4 / 39 (10.26%)	3 / 55 (5.45%)
occurrences (all)	79	58	21
pyrexia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 94 (7.45%)	4 / 39 (10.26%)	3 / 55 (5.45%)
occurrences (all)	20	16	4
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	9 / 94 (9.57%)	2 / 39 (5.13%)	7 / 55 (12.73%)
occurrences (all)	66	46	20
dysphonia			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	4 / 94 (4.26%)	1 / 39 (2.56%)	3 / 55 (5.45%)
occurrences (all)	24	19	5
dyspnoea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	13 / 94 (13.83%)	5 / 39 (12.82%)	8 / 55 (14.55%)
occurrences (all)	123	91	32
Psychiatric disorders			
insomnia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	1 / 39 (2.56%)	1 / 55 (1.82%)
occurrences (all)	7	4	3
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	1 / 39 (2.56%)	3 / 55 (5.45%)
occurrences (all)	26	10	16
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	0 / 39 (0.00%)	3 / 55 (5.45%)
occurrences (all)	33	0	33
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	1 / 39 (2.56%)	3 / 55 (5.45%)
occurrences (all)	29	7	22
weight decreased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	2 / 39 (5.13%)	0 / 55 (0.00%)
occurrences (all)	7	7	0
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	3 / 39 (7.69%)	0 / 55 (0.00%)
occurrences (all)	8	8	0
headache			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	11 / 94 (11.70%)	4 / 39 (10.26%)	7 / 55 (12.73%)
occurrences (all)	35	9	26
paraesthesia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	2 / 39 (5.13%)	1 / 55 (1.82%)
occurrences (all)	40	16	24
sciatica			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	0 / 39 (0.00%)	3 / 55 (5.45%)
occurrences (all)	10	0	10
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	9 / 94 (9.57%)	4 / 39 (10.26%)	5 / 55 (9.09%)
occurrences (all)	49	15	34
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	0 / 39 (0.00%)	2 / 55 (3.64%)
occurrences (all)	12	0	12
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	8 / 94 (8.51%)	3 / 39 (7.69%)	5 / 55 (9.09%)
occurrences (all)	17	7	10
abdominal pain upper			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 94 (7.45%)	3 / 39 (7.69%)	4 / 55 (7.27%)
occurrences (all)	31	10	21
constipation			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	17 / 94 (18.09%)	7 / 39 (17.95%)	10 / 55 (18.18%)
occurrences (all)	50	17	33
diarrhoea			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	20 / 94 (21.28%)	6 / 39 (15.38%)	14 / 55 (25.45%)
occurrences (all)	76	20	56
dry mouth			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	2 / 39 (5.13%)	1 / 55 (1.82%)
occurrences (all)	17	13	4
dyspepsia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	3 / 39 (7.69%)	1 / 55 (1.82%)
occurrences (all)	10	6	4
faeces discoloured			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	2 / 39 (5.13%)	1 / 55 (1.82%)
occurrences (all)	15	12	3
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 94 (0.00%)	0 / 39 (0.00%)	0 / 55 (0.00%)
occurrences (all)	0	0	0
nausea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	31 / 94 (32.98%)	13 / 39 (33.33%)	18 / 55 (32.73%)
occurrences (all)	78	34	44
vomiting			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	10 / 94 (10.64%)	4 / 39 (10.26%)	6 / 55 (10.91%)
occurrences (all)	17	6	11
Skin and subcutaneous tissue disorders			
dry skin			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	0 / 39 (0.00%)	2 / 55 (3.64%)
occurrences (all)	11	0	11
pruritus			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	4 / 94 (4.26%)	3 / 39 (7.69%)	1 / 55 (1.82%)
occurrences (all)	33	31	2
rash			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	1 / 39 (2.56%)	3 / 55 (5.45%)
occurrences (all)	17	4	13
Renal and urinary disorders			
chromaturia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	9 / 94 (9.57%)	3 / 39 (7.69%)	6 / 55 (10.91%)
occurrences (all)	94	25	69
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	9 / 94 (9.57%)	7 / 39 (17.95%)	2 / 55 (3.64%)
occurrences (all)	160	138	22
back pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	8 / 94 (8.51%)	5 / 39 (12.82%)	3 / 55 (5.45%)
occurrences (all)	36	22	14
bone pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	9 / 94 (9.57%)	2 / 39 (5.13%)	7 / 55 (12.73%)
occurrences (all)	37	6	31
musculoskeletal pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 94 (1.06%)	0 / 39 (0.00%)	1 / 55 (1.82%)
occurrences (all)	2	0	2
myalgia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	0 / 39 (0.00%)	2 / 55 (3.64%)
occurrences (all)	8	0	8
osteoarthritis			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	3 / 94 (3.19%)	2 / 39 (5.13%)	1 / 55 (1.82%)
occurrences (all)	39	36	3
pain in extremity			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 94 (5.32%)	0 / 39 (0.00%)	5 / 55 (9.09%)
occurrences (all)	23	0	23
Infections and infestations			
bronchitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	2 / 39 (5.13%)	2 / 55 (3.64%)
occurrences (all)	56	51	5
cystitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 94 (5.32%)	3 / 39 (7.69%)	2 / 55 (3.64%)
occurrences (all)	8	6	2
infection			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 94 (4.26%)	2 / 39 (5.13%)	2 / 55 (3.64%)
occurrences (all)	8	5	3
nasopharyngitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 94 (5.32%)	0 / 39 (0.00%)	5 / 55 (9.09%)
occurrences (all)	9	0	9
pharyngitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 94 (2.13%)	2 / 39 (5.13%)	0 / 55 (0.00%)
occurrences (all)	4	4	0
rhinitis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	0 / 39 (0.00%)	3 / 55 (5.45%)
occurrences (all)	15	0	15
urinary tract infection			
alternative dictionary used: MedDRA 13.1			

subjects affected / exposed	1 / 94 (1.06%)	1 / 39 (2.56%)	0 / 55 (0.00%)
occurrences (all)	2	2	0
Metabolism and nutrition disorders			
decreased appetite			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 94 (5.32%)	2 / 39 (5.13%)	3 / 55 (5.45%)
occurrences (all)	25	16	9
hypercalcaemia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 94 (3.19%)	3 / 39 (7.69%)	0 / 55 (0.00%)
occurrences (all)	47	47	0

Non-serious adverse events	Fulvestrant Plus Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 58 (86.21%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
tumour pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Vascular disorders			
hot flush			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	24		
General disorders and administration site conditions			
asthenia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	54		
chest pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	9		
fatigue			

alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	11 / 58 (18.97%)		
occurrences (all)	68		
influenza like illness			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
malaise			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
oedema peripheral			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	16		
pyrexia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	3		
Respiratory, thoracic and mediastinal disorders			
cough			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	21		
dysphonia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	17		
dyspnoea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	8 / 58 (13.79%)		
occurrences (all)	18		
Psychiatric disorders			

insomnia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	30		
Investigations			
alanine aminotransferase increased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
electrocardiogram qt prolonged			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	4		
gamma-glutamyltransferase increased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	7		
weight decreased			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
Nervous system disorders			
dizziness			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	11		
headache			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	28		
paraesthesia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	6		
sciatica			

alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	10		
Blood and lymphatic system disorders			
anaemia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	27		
Ear and labyrinth disorders			
vertigo			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	5		
Gastrointestinal disorders			
abdominal pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	6		
abdominal pain upper			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	5		
constipation			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	20		
diarrhoea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	23		
dry mouth			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	11		
dyspepsia			

alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	13		
faeces discoloured			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
gastrooesophageal reflux disease			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	15		
nausea			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	18 / 58 (31.03%)		
occurrences (all)	60		
vomiting			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	6 / 58 (10.34%)		
occurrences (all)	11		
Skin and subcutaneous tissue disorders			
dry skin			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	4 / 58 (6.90%)		
occurrences (all)	33		
pruritus			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	1		
rash			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	5		
Renal and urinary disorders			

chromaturia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	1 / 58 (1.72%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
arthralgia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	36		
back pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	7 / 58 (12.07%)		
occurrences (all)	21		
bone pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	10 / 58 (17.24%)		
occurrences (all)	61		
musculoskeletal pain			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	3 / 58 (5.17%)		
occurrences (all)	10		
myalgia			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	5 / 58 (8.62%)		
occurrences (all)	18		
osteoarthritis			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	0 / 58 (0.00%)		
occurrences (all)	0		
pain in extremity			
alternative dictionary used: MedDRA 13.1			
subjects affected / exposed	2 / 58 (3.45%)		
occurrences (all)	7		
Infections and infestations			

bronchitis				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	7			
cystitis				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences (all)	2			
infection				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences (all)	4			
nasopharyngitis				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	0 / 58 (0.00%)			
occurrences (all)	0			
pharyngitis				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	2			
rhinitis				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	1 / 58 (1.72%)			
occurrences (all)	2			
urinary tract infection				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	4 / 58 (6.90%)			
occurrences (all)	8			
Metabolism and nutrition disorders				
decreased appetite				
alternative dictionary used: MedDRA 13.1				
subjects affected / exposed	2 / 58 (3.45%)			
occurrences (all)	4			
hypercalcaemia				
alternative dictionary used: MedDRA 13.1				

subjects affected / exposed occurrences (all)	1 / 58 (1.72%) 2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 April 2007	Overview of changes for protocol amendment a - modified inclusion criterion to clarify the definition of females with postmenopausal status and exclusion criterion to clarify the exclusion of participants receiving concurrent administration of any other antitumor therapy. Exclusion criterion included the following: -to clarify the evaluation methods for HR2 positive participants -to improve the safety of participants with known hypersensitivity to the drug or any of its component -to improve the safety of participants with a potential risk for osteoporosis, including those who have problems with the loss of the mineral contents of the bones Deleted blinding text Concomitant therapy section modified for clarity Serious Adverse Events deleted redundant text that will not be captured by CRF Deleted monocytes from list of required laboratory values.
29 September 2008	Protocol amendment (b): Participants received enzastaurin loading dose (1125 mg; 3 tablets, TID [9 tablets]) on Day 1 of Cycle 1 ONLY. Thereafter, enzastaurin (250 mg; 2 tablets) was administered orally BID in a 28-day cycle.

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.

The translational research component of the study was cancelled due to lack of efficacy in the experimental arm. Due to an amendment to the initial therapy, 250 mg BID dosing was added.

Notes: