Clinical trial results:
A phase III trial evaluating the role of continuous letrozole versus intermittent letrozole following 4 to 6 years of prior adjuvant endocrine therapy for postmenopausal women with hormone-receptor positive, node-positive early stage breast cancer.

Summary

EudraCT number	2007-001370-88
Trial protocol	SE BE HU IT DE DK GB ES SI GR AT IE
Global end of trial date	15 May 2019

Results information

Result version number	v1 (current)
This version publication date	23 December 2020
First version publication date	23 December 2020

Trial information

Trial identification

Sponsor protocol code	IBCSG35-07/BIG1-07

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00553410
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBCSG
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 313899391, regulatoryoffice@ibcsg.org
Scientific contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 313899391, regulatoryoffice@ibcsg.org

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	15 May 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 May 2019
Global end of trial reached?	Yes
Global end of trial date	15 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare continuous letrozole for five years with intermittent letrozole over a five year period for postmenopausal women who are disease-free following 4-6 years of prior adjuvant endocrine therapy with SERM(s) and/or AI(s) for endocrine-responsive, node-positive, operable breast cancer.

Protection of trial subjects:

In compliance with GDPR.
Adverse events were reported and in case of adverse events and treatment-related toxicities, management guidance was provided in the study protocol to treat trial subjects in adequately manner. The safety of the trial treatment was regularly reviewed by the IBCSG Data Safety Monitoring Committee (DSMC).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 November 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	United States: 40
Country: Number of subjects enrolled	United Kingdom: 322
Country: Number of subjects enrolled	Slovenia: 24
Country: Number of subjects enrolled	Spain: 271
Country: Number of subjects enrolled	Sweden: 209
Country: Number of subjects enrolled	Austria: 180
Country: Number of subjects enrolled	Belgium: 1029
Country: Number of subjects enrolled	Denmark: 441
Country: Number of subjects enrolled	France: 30
Country: Number of subjects enrolled	Germany: 291
Country: Number of subjects enrolled	Hungary: 155
Country: Number of subjects enrolled	Ireland: 111
Country: Number of subjects enrolled	Italy: 578
Country: Number of subjects enrolled	Japan: 192
Country: Number of subjects enrolled	Australia: 365
Country: Number of subjects enrolled	New Zealand: 7
Country: Number of subjects enrolled	Chile: 140

Country: Number of subjects enrolled	India: 16
Country: Number of subjects enrolled	Peru: 66
Country: Number of subjects enrolled	Russian Federation: 43
Country: Number of subjects enrolled	South Africa: 56
Country: Number of subjects enrolled	Switzerland: 318
Worldwide total number of subjects	4884
EEA total number of subjects	3641

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)	3303
From 65 to 84 years	1572
85 years and over	9

Subject disposition

Recruitment

Recruitment details:

The study was activated 8 November 2007. The first patient was enrolled on 5 December 2007 and the trial closed to accrual on 8 October 2012 with 4884 patients enrolled.

Pre-assignment

Screening details:

This trial used a web-based randomization system. Each Participating Group determined how its Participating Centers will access the randomization system, either through a Group Randomization Center, or directly from the Participating Center.

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	Continuous letrozole

Arm description:

Continuous letrozole: 5 years continuously (2.5 mg Letrozole daily)

Arm type	Active comparator
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated tablet, oral use, 2.5 mg Letrozole daily for 5 years continuously

Arm title	Intermittent letrozole

Arm description:

Intermittent letrozole: 48 months over 5 yrs: 4 x 9 months (9 mo followed by 3 mo treatment-free interval in yrs 1-4, -> 36 mo) plus 1 x 12 mo in yr 5 -> 48 months

Arm type	Experimental
Investigational medicinal product name	Letrozole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Film-coated tablet, oral use, 2.5 mg daily, 48 months over 5 yrs: 4 x 9 months (9 months followed by 3 months treatment-free interval in years 1-4, -> 36 months) plus 1 x 12 months in year 5 -> 48 months

Number of subjects in period 1[1]	Continuous letrozole	Intermittent letrozole
Started	2426	2425
Completed	2426	2425

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline analysis was conducted only for ITT population. The primary ITT analysis population was 4851 of 4884 enrolled patients, 33 patients were excluded from the ITT population. Those were patients who immediately withdrew consent prior to treatment initiation and declined all participation, patients determined to be without adequate documentation of informed consent, and/or patients at a participating centre determined not to be compliant with protocol procedures.

Baseline characteristics

Reporting groups	
Reporting group title	Continuous letrozole
Reporting group description:	
Continuous letrozole: 5 years continuously (2.5 mg Letrozole daily)	
Reporting group title	Intermittent letrozole
Reporting group description:	
Intermittent letrozole: 48 months over 5 yrs: 4 x 9 months (9 mo followed by 3 mo treatment-free interval in yrs 1-4, -> 36 mo) plus 1 x 12 mo in yr 5 -> 48 months	

Reporting group values	Continuous letrozole	Intermittent letrozole	Total
Number of subjects	2426	2425	4851
Age categorical Units: Subjects			
<55	688	671	1359
55-59	504	496	1000
60-64	451	471	922
65-69	400	375	775
70+	383	412	795
Gender categorical Units: Subjects			
Female	2426	2425	4851
Male	0	0	0
Race/Ethnicity Units: Subjects			
White/Caucasian	2199	2210	4409
Black	10	9	19
Asian	119	122	241
Other	97	83	180
Unknown	1	1	2
Region of Enrollment Units: Subjects			
Hungary	78	76	154
United States	21	19	40
Japan	93	98	191
United Kingdom	160	162	322
Switzerland	159	158	317
India	8	8	16
Russia	21	21	42
Spain	133	133	266
New Zealand	10	9	19
Austria	88	92	180
Sweden	104	105	209
Belgium	501	510	1011
Denmark	222	218	440
Italy	287	291	578
South Africa	28	28	56
Australia	182	171	353

Chile	70	70	140
France	14	16	30
Peru	33	31	64
Germany	146	143	289
Slovenja	12	12	24
Ireland	56	54	110

End points

End points reporting groups

Reporting group title	Continuous letrozole
Reporting group description:	
Continuous letrozole: 5 years continuously (2.5 mg Letrozole daily)	
Reporting group title	Intermittent letrozole
Reporting group description:	
Intermittent letrozole: 48 months over 5 yrs: 4 x 9 months (9 mo followed by 3 mo treatment-free interval in yrs 1-4, -> 36 mo) plus 1 x 12 mo in yr 5 -> 48 months	

Primary: Disease-free Survival (DFS)

End point title	Disease-free Survival (DFS)
End point description:	
Duration of time from randomization to the first indication of the following events: invasive recurrence at local (including recurrence restricted to the breast after breast conserving treatment), regional or distant sites; a new invasive cancer in the contralateral breast; any second (non-breast) invasive malignancy; or a death without prior cancer event. Appearance of DCIS or LCIS either in the ipsilateral or in the contralateral breast was not be considered as an event for DFS. In the absence of an event, DFS was censored at the date of last follow-up visit.	
End point type	Primary
End point timeframe:	
5-year estimates, reported at a median follow-up of 60 months	

End point values	Continuous letrozole	Intermittent letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2426	2425		
Units: Percentage of patients				
number (confidence interval 95%)	87.5 (86.0 to 88.8)	85.8 (84.2 to 87.2)		

Statistical analyses

Statistical analysis title	Statistical analysis primary endpoint
Statistical analysis description:	
The primary endpoint is disease-free survival (DFS) and will be compared between treatment arms using a two-sided stratified logrank test with an overall experiment-wise alpha level equal to at most 0.05. Kaplan-Meier estimates of the DFS distributions will be calculated for each of the two treatment arms.	
Comparison groups	Continuous letrozole v Intermittent letrozole

Number of subjects included in analysis	4851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.31
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.93
upper limit	1.26

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Duration of time from randomization to death from any cause, or was censored at the date last known alive. (Note, for patients who withdrew consent or were lost to follow-up but follow-up for survival was possible through hospital or registry records, OS was censored at the date last known alive rather than date of last follow-up/withdrawn consent).

End point type	Secondary

End point timeframe:

5-year estimates, reported at a median follow-up of 60 months

End point values	Continuous letrozole	Intermittent letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2426	2425		
Units: Percentage of patients				
number (confidence interval 95%)	93.7 (92.6 to 94.7)	94.3 (93.2 to 95.2)		

Statistical analyses

Statistical analysis title	Statistical analysis Overall Survival
Comparison groups	Continuous letrozole v Intermittent letrozole
Number of subjects included in analysis	4851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.16
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	1.06

Secondary: Distant Recurrence-free Interval (DRFI)

End point title	Distant Recurrence-free Interval (DRFI)

End point description:

Duration of time from randomization to the first indication of invasive breast recurrence at a distant site. In the absence of an event, DRFI was censored at the date of last follow-up visit or date or death without distant recurrence.*

*This endpoint replaced DDFS, which was specified in the protocol

End point type	Secondary

End point timeframe:

5-year estimates, reported at a median follow-up of 60 months

End point values	Continuous letrozole	Intermittent letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2426	2425		
Units: Percentage of patients				
number (confidence interval 95%)	92.5 (91.3 to 93.5)	93.2 (92.0 to 94.2)		

Statistical analyses

Statistical analysis title	Statistical Analysis (DRFI)
Comparison groups	Continuous letrozole v Intermittent letrozole
Number of subjects included in analysis	4851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.25
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.09

Secondary: Breast Cancer-free Interval

End point title	Breast Cancer-free Interval

End point description:

Duration of time from randomization to the first indication of the following events: invasive breast recurrence at local, regional or distant sites; a new invasive cancer in the contralateral breast (second non-breast malignancies are ignored). In the absence of an event, BCFI was censored at the date of last follow-up visit or date of death without prior breast cancer event.

End point type	Secondary

End point timeframe:

5-year estimates, reported at a median follow-up of 60 months

End point values	Continuous letrozole	Intermittent letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2426	2425		
Units: Percentage of patients				
number (confidence interval 95%)	91.2 (89.9 to 92.3)	90.9 (89.6 to 92.1)		

Statistical analyses

Statistical analysis title	Statistical analysis BCFI
Comparison groups	Continuous letrozole v Intermittent letrozole
Number of subjects included in analysis	4851
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.84
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.18

Secondary: Adverse events

End point title	Adverse events

End point description:

AEs graded according to NCI CTCAE V.3

End point type	Secondary

End point timeframe:

Adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after final dose, regardless of whether it is considered related to a medication.

End point values	Continuous letrozole	Intermittent letrozole		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2411[1]	2417[2]		
Units: Number of patients	2411	2417		

Notes:

[1] - 15 patients never started treatment

[2] - 8 patients never started treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

During or within 30 days after stopping study treatment

Adverse event reporting additional description:

Adverse event is defined as any untoward medical occurrence that occurs from the first dose of study medication until 30 days after final dose, regardless of whether it is considered related to a medication. Any known untoward event that occurs subsequent to the adverse event reporting period that the investigator assesses as possibly related to t

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	V.3

Reporting groups

Reporting group title	Continuous Letrozole

Reporting group description:

15 pts never started treatment

Reporting group title	Intermittent Letrozole

Reporting group description:

8 patients never started treatment

Serious adverse events	Continuous Letrozole	Intermittent Letrozole	
Total subjects affected by serious adverse events			
subjects affected / exposed	121 / 2411 (5.02%)	116 / 2417 (4.80%)	
number of deaths (all causes)	38	44	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Mixed Mullerian tumor			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Carotid Stenosis			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis (R Calf)			

subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep Vein Thrombosis and Pulmonary Embolism			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 2411 (0.08%)	2 / 2417 (0.08%)	
occurrences causally related to treatment / all	2 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis (Arteria Poplitea)			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Angioedema			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Bilateral Ovarian Cysts			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst (Left)			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Bleeding			
subjects affected / exposed	2 / 2411 (0.08%)	4 / 2417 (0.17%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Vaginal Dryness			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Bleeding (Restored Ovarian Function)			
subjects affected / exposed	5 / 2411 (0.21%)	13 / 2417 (0.54%)	
occurrences causally related to treatment / all	5 / 5	13 / 13	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary Edema			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicide			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial Flutter			
subjects affected / exposed	2 / 2411 (0.08%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bradycardia (Pacemaker Implantation)			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asymptomatic Subepicardial Ischemia and LVEF Reduction			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac Ischemia			
subjects affected / exposed	2 / 2411 (0.08%)	3 / 2417 (0.12%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart Failure			
subjects affected / exposed	2 / 2411 (0.08%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			

subjects affected / exposed	1 / 2411 (0.04%)	3 / 2417 (0.12%)	
occurrences causally related to treatment / all	1 / 1	3 / 3	
deaths causally related to treatment / all	0 / 0	1 / 1	
Cardio respiratory arrest			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
Nervous system disorders			
Anxiety			
subjects affected / exposed	1 / 2411 (0.04%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome requiring surgery			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	10 / 2411 (0.41%)	8 / 2417 (0.33%)	
occurrences causally related to treatment / all	12 / 12	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusion			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	7 / 2411 (0.29%)	5 / 2417 (0.21%)	
occurrences causally related to treatment / all	10 / 10	5 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			

subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Memory Impairment			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood alteration			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosis			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Severe depression with suicidal ideation			
subjects affected / exposed	1 / 2411 (0.04%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide Attempt			
subjects affected / exposed	1 / 2411 (0.04%)	2 / 2417 (0.08%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischemic Attack			
subjects affected / exposed	3 / 2411 (0.12%)	3 / 2417 (0.12%)	
occurrences causally related to treatment / all	3 / 3	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	1 / 2411 (0.04%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Sudden deafness			

subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract			
subjects affected / exposed	2 / 2411 (0.08%)	2 / 2417 (0.08%)	
occurrences causally related to treatment / all	2 / 2	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Esophagitis			
subjects affected / exposed	1 / 2411 (0.04%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhagic gastritis			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Urticaria with itching			
subjects affected / exposed	2 / 2411 (0.08%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urosepsis			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 2411 (0.00%)	3 / 2417 (0.12%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fracture			

subjects affected / exposed	56 / 2411 (2.32%)	46 / 2417 (1.90%)	
occurrences causally related to treatment / all	58 / 58	48 / 48	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and head pain			
subjects affected / exposed	0 / 2411 (0.00%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	2 / 2411 (0.08%)	1 / 2417 (0.04%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polytrauma			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudoarthrosis (L Humerus)			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	1 / 2411 (0.04%)	0 / 2417 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Continuous Letrozole	Intermittent Letrozole	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2340 / 2411 (97.06%)	2282 / 2417 (94.41%)	
Injury, poisoning and procedural complications			
Fracture			

subjects affected / exposed	228 / 2411 (9.46%)	207 / 2417 (8.56%)	
occurrences (all)	228	207	
Thrombosis/embolism (vascular access-related)			
subjects affected / exposed	29 / 2411 (1.20%)	31 / 2417 (1.28%)	
occurrences (all)	29	31	
Vascular disorders			
Hot flashes/flushes			
subjects affected / exposed	1313 / 2411 (54.46%)	1281 / 2417 (53.00%)	
occurrences (all)	1313	1281	
Hypertension			
subjects affected / exposed	1068 / 2411 (44.30%)	1090 / 2417 (45.10%)	
occurrences (all)	1068	1090	
Cardiac disorders			
Cardiac-ischemia/infarction			
subjects affected / exposed	37 / 2411 (1.53%)	48 / 2417 (1.99%)	
occurrences (all)	37	48	
Nervous system disorders			
Hemorrhage, CNS			
subjects affected / exposed	11 / 2411 (0.46%)	13 / 2417 (0.54%)	
occurrences (all)	11	13	
CNS cerebrovascular ischemia			
subjects affected / exposed	42 / 2411 (1.74%)	36 / 2417 (1.49%)	
occurrences (all)	42	36	
General disorders and administration site conditions			
Fatigue (asthenia, lethargy, malaise)			
subjects affected / exposed	1091 / 2411 (45.25%)	1013 / 2417 (41.91%)	
occurrences (all)	1091	1013	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	1053 / 2411 (43.67%)	1017 / 2417 (42.08%)	
occurrences (all)	1053	1017	
Mood alteration - depression			
subjects affected / exposed	833 / 2411 (34.55%)	832 / 2417 (34.42%)	
occurrences (all)	833	832	
Musculoskeletal and connective tissue disorders			

Osteoporosis			
subjects affected / exposed	1150 / 2411 (47.70%)	1153 / 2417 (47.70%)	
occurrences (all)	1150	1153	
Pain - Bone			
subjects affected / exposed	702 / 2411 (29.12%)	671 / 2417 (27.76%)	
occurrences (all)	702	671	
Pain - Joint			
subjects affected / exposed	1664 / 2411 (69.02%)	1599 / 2417 (66.16%)	
occurrences (all)	1664	1599	
Pain - Muscle			
subjects affected / exposed	906 / 2411 (37.58%)	882 / 2417 (36.49%)	
occurrences (all)	906	882	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30967649

http://www.ncbi.nlm.nih.gov/pubmed/29158011