Clinical trial results:
A phase III trial evaluating the role of ovarian function suppression and the role of exemestane as adjuvant therapies for premenopausal women with endocrine responsive breast cancer.

Summary

EudraCT number	2004-000166-13
Trial protocol	DK SE DE ES IE HU
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021

Trial information

Trial identification

Sponsor protocol code	IBCSG 24-02 BIG 2-02 SOFT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00066690
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 31 511 94 00, regulatoryoffice@ibcsg.org
Scientific contact	IBCSG Coordinating Center, International Breast Cancer Study Group (IBCSG), +41 31 511 94 00, 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	Interim
Date of interim/final analysis	31 March 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 March 2014
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

This trial will evaluate the worth of ovarian function suppression (achieved by either long-term use of GnRH analogue or surgical oophorectomy or ovarian irradiation) plus tamoxifen compared with tamoxifen alone for premenopausal women with steroid hormone receptor positive early invasive breast cancer who either receive no adjuvant chemotherapy or remain premenopausal following adjuvant and/or neoadjuvant chemotherapy. In addition, the worth of exemestane will be evaluated for this premenopausal patient population by comparing ovarian function suppression plus exemestane with tamoxifen alone and by comparing ovarian function suppression plus exemestane with ovarian function suppression plus tamoxifen.

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	04 August 2003
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	11 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 74
Country: Number of subjects enrolled	Australia: 182
Country: Number of subjects enrolled	New Zealand: 58
Country: Number of subjects enrolled	Brazil: 6
Country: Number of subjects enrolled	Chile: 72
Country: Number of subjects enrolled	India: 52
Country: Number of subjects enrolled	Italy: 288
Country: Number of subjects enrolled	Peru: 53
Country: Number of subjects enrolled	Switzerland: 114
Country: Number of subjects enrolled	South Africa: 13
Country: Number of subjects enrolled	Belgium: 122
Country: Number of subjects enrolled	Israel: 8
Country: Number of subjects enrolled	Netherlands: 11

Country: Number of subjects enrolled	Turkey: 17
Country: Number of subjects enrolled	Poland: 2
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	United States: 1030
Country: Number of subjects enrolled	Portugal: 31
Country: Number of subjects enrolled	Spain: 451
Country: Number of subjects enrolled	Sweden: 62
Country: Number of subjects enrolled	France: 194
Country: Number of subjects enrolled	Germany: 54
Country: Number of subjects enrolled	Hungary: 150
Country: Number of subjects enrolled	Ireland: 13
Worldwide total number of subjects	3066
EEA total number of subjects	1452

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)	3066
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

3066 patients were randomized between 17Dec03 and 27Jan11 at 426 centers in 25 countries.

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
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Tamoxifen

Arm description:

Tamoxifen 20mg orally daily for 5 years

Arm type	Active comparator
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tamoxifen 20mg orally daily for 5 years

Arm title	T+OFS

Arm description:

Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)

Arm type	Experimental
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Tamoxifen 20mg orally daily for 5 years

Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl, Detryptoreline, GnRH analogue, Trelstar Depot, Decape
Pharmaceutical forms	Injection

Routes of administration	Intravenous use

Dosage and administration details:

3.75 mg by im injection q28 days for 5 years

Arm title	E + OFS

Arm description:

Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)

Arm type	Experimental
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	Aromasin, FCE-24304
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

25mg orally daily for 5 years

Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl, Detryptoreline, GnRH analogue, Trelstar Depot, Decape
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

3.75 mg by im injection q28 days for 5 years

Number of subjects in period 1	Tamoxifen	T+OFS	E + OFS
Started	1021	1024	1021
Completed	1018	1015	1014
Not completed	3	9	7
Consent withdrawn by subject	3	9	7

Period 2

Period 2 title	ITT analysis
Is this the baseline period?	Yes[1]
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes

Arm title	Tamoxifen
Arm description:	
Tamoxifen 20mg orally daily for 5 years	
Arm type	Active comparator
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Tamoxifen 20mg orally daily for 5 years	
Arm title	T+OFS
Arm description:	
Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	
Arm type	Experimental
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Apo-Tamox, Clonoxifen, Dignotamoxi, Ebefen, Emblon, Estroxyn, Fentamox, Gen-Tamoxifen, Genox, ICI 46.474, ICI-46474, Jenoxifen, Kessar, Ledertam, Lesporene
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Tamoxifen 20mg orally daily for 5 years	
Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl, Detryptoreline, GnRH analogue, Trelstar Depot, Decape
Pharmaceutical forms	Injection
Routes of administration	Intravenous use
Dosage and administration details:	
3.75 mg by im injection q28 days for 5 years	
Arm title	E + OFS
Arm description:	
Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	
Arm type	Experimental
Investigational medicinal product name	Exemestane
Investigational medicinal product code	
Other name	Aromasin, FCE-24304
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
25mg orally daily for 5 years	
Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	6-D-Tryptophan-LH-RH, 6-D-Tryptophanluteinizing Hormone-releasing Factor, AY-25650, CL-118532, Decapeptyl,

	Detryptoreline, GnRH analogue, Trelstar Depot, Decape
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

3.75 mg by im injection q28 days for 5 years

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: Baseline characteristics were only reported for Intention-to-treat population

Number of subjects in period 2[2]	Tamoxifen	T+OFS	E + OFS
Started	1018	1015	1014
Completed	1018	1015	1014

Notes:

[2] - 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: Intention-to-treat population, excludes 19 patients who immediately withdrew consent.

Baseline characteristics

Reporting groups	
Reporting group title	Tamoxifen
Reporting group description:	
Tamoxifen 20mg orally daily for 5 years	
Reporting group title	T+OFS
Reporting group description:	
Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	
Reporting group title	E + OFS
Reporting group description:	
Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	

Reporting group values	Tamoxifen	T+OFS	E + OFS
Number of subjects	1018	1015	1014
Age categorical Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous Units: years			
median	43	43	43
inter-quartile range (Q1-Q3)	38 to 46	38 to 47	38 to 47
Gender categorical Units: Subjects			
Female	1018	1015	1014
Male	0	0	0
Race/Ethnicity Units: Subjects			
American Indian/Alaskan native	1	5	3
Asian	36	34	33
Black/African American	32	27	34
Hawaiian/Pacific Islander	5	4	3
White/Caucasian	877	873	866
Other	4	2	3
Unknown	19	22	22
Hispanic/Latino/South American native	44	48	50

Reporting group values	Total		
Number of subjects	3047		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		
Age continuous Units: years			
median			
inter-quartile range (Q1-Q3)	-		
Gender categorical Units: Subjects			
Female	3047		
Male	0		
Race/Ethnicity Units: Subjects			
American Indian/Alaskan native	9		
Asian	103		
Black/African American	93		
Hawaiian/Pacific Islander	12		
White/Caucasian	2616		
Other	9		
Unknown	63		
Hispanic/Latino/South American native	142		

End points

End points reporting groups

Reporting group title	Tamoxifen
Reporting group description:	
Tamoxifen 20mg orally daily for 5 years	
Reporting group title	T+OFS
Reporting group description:	
Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	
Reporting group title	E + OFS
Reporting group description:	
Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	
Reporting group title	Tamoxifen
Reporting group description:	
Tamoxifen 20mg orally daily for 5 years	
Reporting group title	T+OFS
Reporting group description:	
Tamoxifen 20mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	
Reporting group title	E + OFS
Reporting group description:	
Exemestane 25mg orally daily for 5 years plus ovarian function suppression (OFS; triptorelin (GnRH analogue) 3.75 mg by im injection q28 days for 5 years; or surgical oophorectomy; or ovarian irradiation)	

Primary: Disease-free Survival

End point title	Disease-free Survival
End point description:	
Estimated percentage of patients alive and disease-free at 5 years from randomization, where disease-free survival is defined as the time from randomization to the first appearance of one of the following: invasive breast cancer recurrence at local, regional, or distant site, invasive contralateral breast cancer, second (non-breast) invasive cancer, or death without cancer event; or censored at date of last follow-up.	
End point type	Primary
End point timeframe:	
5-year estimates, reported at a median follow-up of 67 months.	

End point values	Tamoxifen	T+OFS	E + OFS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1018	1015	1014	
Units: Percentage of participants				
number (confidence interval 95%)	84.7 (82.2 to 86.9)	86.6 (84.2 to 88.7)	89 (86.8 to 90.9)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Tamoxifen, T+OFS	
Comparison groups	Tamoxifen v T+OFS
Number of subjects included in analysis	2033
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.04

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Tamoxifen, E+OFS	
Comparison groups	Tamoxifen v E + OFS
Number of subjects included in analysis	2032
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.68
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	0.86

Secondary: Breast Cancer-free Interval

End point title	Breast Cancer-free Interval

End point description:

Estimated percentage of patients alive and disease-free at 5 years from randomization, where breast cancer-free interval is defined as the time from randomization to invasive breast cancer recurrence at local, regional, or distant site, or invasive contralateral breast cancer; or censored at date of last follow up.

End point type	Secondary

End point timeframe:

5-year estimates, reported at a median follow-up of 67 months.

End point values	Tamoxifen	T+OFS	E + OFS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1018	1015	1014	
Units: Percentage of participants				
number (confidence interval 85%)	86.4 (84.0 to 88.5)	88.4 (86.1 to 90.3)	90.9 (88.9 to 92.6)	

Statistical analyses

Statistical analysis title	Statistical analysis 1
Statistical analysis description: Tamoxifen, T+OFS	
Comparison groups	Tamoxifen v T+OFS
Number of subjects included in analysis	2033
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.09
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.3
upper limit	1.03

Statistical analysis title	Statistical analysis 2
Statistical analysis description: Tamoxifen, E+OFS	
Comparison groups	Tamoxifen v E + OFS
Number of subjects included in analysis	2032
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	0.83

Secondary: Distant Recurrence-free Interval

End point title	Distant Recurrence-free Interval

End point description:

Estimated percentage of patients alive and disease-free at 5 years from randomization, where distant recurrence-free Interval is defined as the time from randomization to invasive breast cancer recurrence at distant site, or invasive contralateral breast cancer; or censored at date of last follow up.

End point type	Secondary

End point timeframe:

5-year estimates, reported at a median follow-up of 67 months.

End point values	Tamoxifen	T+OFS	E + OFS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1018	1015	1014	
Units: Percentage of participants				
number (confidence interval 95%)	90.7 (88.6 to 92.4)	91.3 (89.2 to 92.9)	93.0 (91.2 to 94.5)	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Tamoxifen, T+OFS

Comparison groups	Tamoxifen v T+OFS
Number of subjects included in analysis	2033
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.18

Statistical analysis title	Statistical analysis 2

Statistical analysis description:

Tamoxifen, E+OFS

Comparison groups	Tamoxifen v E + OFS

Number of subjects included in analysis	2032
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	0.96

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Estimated percentage of patients alive at 8 years from randomization, where overall survival is defined as the time from randomization to death from any cause; or censored at date last known alive.

End point type	Secondary

End point timeframe:

8-year estimates, reported at a median follow-up of 8 years

End point values	Tamoxifen	T+OFS	E + OFS	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	1018	1015	1014	
Units: Percentage of participants				
number (confidence interval 95%)	91.5 (89.4 to 93.2)	93.3 (91.4 to 94.8)	92.1 (90.0 to 93.7)	

Statistical analyses

Statistical analysis title	Statistical analysis 1

Statistical analysis description:

Tamoxifen, T+OFS

Comparison groups	Tamoxifen v T+OFS
Number of subjects included in analysis	2033
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.01
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.67

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	0.92

Statistical analysis title	Statistical analysis 2
Comparison groups	Tamoxifen v E + OFS
Number of subjects included in analysis	2032
Analysis specification	Pre-specified
Analysis type	superiority
Parameter estimate	Hazard ratio (HR)
Point estimate	0.85
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.15

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed every 3 months for the first year, then every 6 month until year 6. Reported at a median follow-up of 67 months.

Adverse event reporting additional description:

Targeted AEs and other grade 3 or higher AEs were collected on CRFs, regardless of attribution. The safety population EXCLUDES patients who never started protocol-assigned therapy.

Assessment type	Systematic

Dictionary used

Dictionary name	NCI CTCAE
Dictionary version	3.0

Reporting groups

Reporting group title	Tamoxifen

Reporting group description:

The safety population EXCLUDES patients who never started protocol-assigned therapy.

Reporting group title	T+OFS

Reporting group description:

The safety population EXCLUDES patients who never started protocol-assigned therapy.

Reporting group title	E+OFS

Reporting group description: -

Serious adverse events	Tamoxifen	T+OFS	E+OFS
Total subjects affected by serious adverse events			
subjects affected / exposed	315 / 1007 (31.28%)	375 / 1007 (37.24%)	375 / 1001 (37.46%)
number of deaths (all causes)	3	0	3
number of deaths resulting from adverse events			
Vascular disorders			
Postoperative bleeding (breast reconstruction) leading to severe anemia			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Subarachnoidale hemorrhage			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Central vein thrombosis (L eye)			

subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Deep Vein Thrombosis			
subjects affected / exposed	10 / 1007 (0.99%)	6 / 1007 (0.60%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	10 / 10	6 / 6	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Ischemic Necrosis of Ileum and Jejunum			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Peripheral arterial ischemia			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pulmonary Embolism			
subjects affected / exposed	1 / 1007 (0.10%)	3 / 1007 (0.30%)	3 / 1001 (0.30%)
occurrences causally related to treatment / all	1 / 1	3 / 3	2 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Superficial Vein Thrombosis			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Thrombosis			
subjects affected / exposed	2 / 1007 (0.20%)	2 / 1007 (0.20%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	1 / 2	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Surgical and medical procedures			
Induced/elective abortion 8 weeks in to pregnancy			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pregnancy, puerperium and perinatal			

conditions			
Pregnancy			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
General disorders and administration site conditions			
Fatigue (asthenia, lethargy, malaise)			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Insomnia			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Obesity			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Postoperative fever (in the abscence of neutropenia)			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Immune system disorders			
Allergic reaction			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	3 / 1001 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Reproductive system and breast disorders			
Pain Left Breast			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Adnexal and Ovarian Lesion			

subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cervical Polyp			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cervical Dysplasia			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Endometrial Hyperplasia			
subjects affected / exposed	15 / 1007 (1.49%)	6 / 1007 (0.60%)	5 / 1001 (0.50%)
occurrences causally related to treatment / all	15 / 15	5 / 6	4 / 5
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Endometrial Polyp			
subjects affected / exposed	8 / 1007 (0.79%)	3 / 1007 (0.30%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	9 / 9	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
High grade squamous intraepithelial lesion			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Intramural leiomyoma leading to hemorrhage			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Irregular Menses			
subjects affected / exposed	1 / 1007 (0.10%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	1 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Ovarian Cyst			

subjects affected / exposed	24 / 1007 (2.38%)	2 / 1007 (0.20%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	26 / 26	2 / 2	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Uterine Adenomyosis			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Uterine Fibroma			
subjects affected / exposed	5 / 1007 (0.50%)	3 / 1007 (0.30%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	3 / 5	3 / 3	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Uterine Myoma			
subjects affected / exposed	2 / 1007 (0.20%)	2 / 1007 (0.20%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	2 / 2	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Uterine Polyp			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Uterine prolapse			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Vaginal Bleeding			
subjects affected / exposed	8 / 1007 (0.79%)	2 / 1007 (0.20%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	6 / 8	2 / 2	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Atypical Ductal Hyperplasia and Fibroadenoma (R Breast)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Benign fibroadenoma R breast			

subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Respiratory, thoracic and mediastinal disorders			
Atypical pleuritic pain			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Chest Pain			
subjects affected / exposed	3 / 1007 (0.30%)	4 / 1007 (0.40%)	6 / 1001 (0.60%)
occurrences causally related to treatment / all	0 / 3	1 / 4	1 / 6
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pain Chest wall			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Acute respiratory insufficiency			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Dyspnea due to Enlarged Uvula			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Exacerbation of COPD			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pleural Effusion (Left)			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pulmonary Xanthofibroma			

subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Respiratory Failure			
subjects affected / exposed	1 / 1007 (0.10%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Endometriosis			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Injury, poisoning and procedural complications			
Death (cause unknown)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	1 / 3
Death (mixed drug intoxication)			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 3
Dural leak after lumbar fusion surgery			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Post-operative hematoma after oophorectomy			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cardiac disorders			
Anemia post surgery			

subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
AV-Block Grade III			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Palpitations			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Prolonged QT and sinus bradycardia			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Sinus Carotis Syndrome requiring pacemaker implantation			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cardiac Failure			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 3
Cardiac ischemia			
subjects affected / exposed	1 / 1007 (0.10%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Congestive Heart Failure			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Dilated cardiomyopathy in context of congenital abnormality			

subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hypertension			
subjects affected / exposed	0 / 1007 (0.00%)	2 / 1007 (0.20%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Left ventricular systolic dysfunction			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Myocardial Infarction			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Severe Mitral Insufficiency			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Nervous system disorders			
Anxiety			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Carpal Tunnel Syndrome			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	3 / 1001 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	3 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cerebrovascular Accident			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cerebrovascular Ischemia			

subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
CNS Cerebrovascular ischemia			
subjects affected / exposed	3 / 1007 (0.30%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	3 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Concussion cerebri			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Depression			
subjects affected / exposed	5 / 1007 (0.50%)	5 / 1007 (0.50%)	3 / 1001 (0.30%)
occurrences causally related to treatment / all	3 / 6	3 / 5	2 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Dizziness			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	3 / 1001 (0.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	2 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hot flushes leading to syncope			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Multiple Sclerosis			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	1 / 3	0 / 0	0 / 3
Neuromyelitis optica			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Neuropathy: sensory			

subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Partial Amnesia			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Personality/Behavioral			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Suicide attempt			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Syncope			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Trigeminal neuralgia			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Vestibular neuropathy			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Eye disorders			
Cataract and Retinal Detachment (R Eye)			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Intermittent blurred vision L eye			

subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Papilledema bilateral			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Retinal Detachment			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Acute Appendicitis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Anal Fissure			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Colitis			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Dehydration due to vomiting and diarrhea			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Gastrointestinal Obstruction (small bowel)			

subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Inguinal Hernia			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pyloric Ulcer			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Gastric ulcer			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Gastrointestinal Bleeding			
subjects affected / exposed	2 / 1007 (0.20%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pain Abdomen NOS			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Gastroenteritis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Ischemic Colitis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hepatobiliary disorders			
Cholecystitis			

subjects affected / exposed	2 / 1007 (0.20%)	4 / 1007 (0.40%)	4 / 1001 (0.40%)
occurrences causally related to treatment / all	0 / 2	0 / 4	0 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	1 / 3
Cholecystolithiasis			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cholecystolithiasis requiring surgery			
subjects affected / exposed	3 / 1007 (0.30%)	1 / 1007 (0.10%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 3	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Choledocholithiasis			
subjects affected / exposed	2 / 1007 (0.20%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cholelithiasis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hepatic Adenoma			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hepatic steatosis			
subjects affected / exposed	1 / 1007 (0.10%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Liver dysfunction (ethylic hepatitis)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	1 / 3
Pancreatitis			

subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	4 / 1001 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Cellulitis			
subjects affected / exposed	4 / 1007 (0.40%)	10 / 1007 (0.99%)	7 / 1001 (0.70%)
occurrences causally related to treatment / all	0 / 4	0 / 11	0 / 7
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Skin and subcutaneous tissue disorders			
Acute generalized pustular dermatosis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Rash pustular			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Renal and urinary disorders			
Hydronephrosis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Nephrolithiasis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Renal failure			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Ureteral Obstruction			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3

Ureteral stenosis (L)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Urinary Incontinence			
subjects affected / exposed	2 / 1007 (0.20%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Endocrine disorders			
Bilateral hyperplasia of adrenal glands			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Diabetes mellitus Type 1			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Diabetes mellitus type 2			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Follicular hyperplasia of thyroid gland			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hyperparathyroidism			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pheochromocytoma			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3

Schwannoma L benign requiring parotidectomy			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Struma nodosa			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Thyroid Nodule (R Thyroid)			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Bone Fracture			
subjects affected / exposed	16 / 1007 (1.59%)	10 / 1007 (0.99%)	24 / 1001 (2.40%)
occurrences causally related to treatment / all	2 / 16	4 / 10	20 / 28
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Diaphragmatic lesions (benign)			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Discus Hernia			
subjects affected / exposed	1 / 1007 (0.10%)	1 / 1007 (0.10%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Dislocation of hip prosthesis R			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3

Meniscus Lesion			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Osteoarthritis			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Rheumatoid arthritis leading to R knee replacement			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Spondylolisthesis requiring surgery (lumbal fusion L4-5)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Wound dehiscence			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Back pain			
subjects affected / exposed	2 / 1007 (0.20%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Joint pain			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Polytrauma			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Infections and infestations			

Appendicitis			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Breast implant infection			
subjects affected / exposed	1 / 1007 (0.10%)	1 / 1007 (0.10%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Breast Infection			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Bursitis and cellulitis (L Elbow)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Chest Wall Infection			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
CMV Colitis, UTI and Pneumonia			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Colitis and Urinary Infection			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Erysipelas (R Arm)			
subjects affected / exposed	0 / 1007 (0.00%)	2 / 1007 (0.20%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Infected ingrown toe nail			

subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Infection (MRSA)			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Infective endocarditis after mitral valve replacement			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Influenza A			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
L breast abscess			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Meningitis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Peri-rectal abscess			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pneumonia			
subjects affected / exposed	2 / 1007 (0.20%)	4 / 1007 (0.40%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 2	0 / 8	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pneumonia/Pleuritis			

subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Postoperative infection			
subjects affected / exposed	0 / 1007 (0.00%)	3 / 1007 (0.30%)	4 / 1001 (0.40%)
occurrences causally related to treatment / all	0 / 0	0 / 3	0 / 4
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Pyelonephritis			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Recurrent urinary tract infections			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Sepsis			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Septic Shock			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Skin infection			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Superinfection of Posttraumatic Hematoma (R Shank)			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Urinary tract infection			

subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Urosepsis			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Ventriculoperitoneal shunt infection			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Wound Infection			
subjects affected / exposed	3 / 1007 (0.30%)	2 / 1007 (0.20%)	2 / 1001 (0.20%)
occurrences causally related to treatment / all	0 / 3	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Metabolism and nutrition disorders			
Dyspnea and Fatigue			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hypoglycemia			
subjects affected / exposed	0 / 1007 (0.00%)	0 / 1007 (0.00%)	1 / 1001 (0.10%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Hypokalemia			
subjects affected / exposed	0 / 1007 (0.00%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3
Increased GGT Levels			
subjects affected / exposed	1 / 1007 (0.10%)	0 / 1007 (0.00%)	0 / 1001 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 3	0 / 0	0 / 3

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

Non-serious adverse events	Tamoxifen	T+OFS	E+OFS
Total subjects affected by non-serious adverse events			
subjects affected / exposed	951 / 1007 (94.44%)	982 / 1007 (97.52%)	980 / 1001 (97.90%)
Vascular disorders			
Hot flashes/flushes			
subjects affected / exposed	727 / 1007 (72.19%)	806 / 1007 (80.04%)	820 / 1001 (81.92%)
occurrences (all)	727	806	820
Hypertension			
subjects affected / exposed	119 / 1007 (11.82%)	158 / 1007 (15.69%)	165 / 1001 (16.48%)
occurrences (all)	119	158	165
General disorders and administration site conditions			
Fatigue (asthenia, lethargy, malaise)			
subjects affected / exposed	571 / 1007 (56.70%)	595 / 1007 (59.09%)	591 / 1001 (59.04%)
occurrences (all)	571	595	591
Injection site reaction/extravasation changes			
subjects affected / exposed	4 / 1007 (0.40%)	88 / 1007 (8.74%)	84 / 1001 (8.39%)
occurrences (all)	4	88	84
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	31 / 1007 (3.08%)	42 / 1007 (4.17%)	46 / 1001 (4.60%)
occurrences (all)	31	42	46
Reproductive system and breast disorders			
Pain - Vagina			
subjects affected / exposed	224 / 1007 (22.24%)	240 / 1007 (23.83%)	290 / 1001 (28.97%)
occurrences (all)	224	240	290
Vaginal dryness			
subjects affected / exposed	421 / 1007 (41.81%)	500 / 1007 (49.65%)	541 / 1001 (54.05%)
occurrences (all)	421	500	541
Psychiatric disorders			
Insomnia			

subjects affected / exposed	437 / 1007 (43.40%)	529 / 1007 (52.53%)	549 / 1001 (54.85%)
occurrences (all)	437	529	549
Libido			
subjects affected / exposed	427 / 1007 (42.40%)	477 / 1007 (47.37%)	492 / 1001 (49.15%)
occurrences (all)	427	477	492
Mood alteration - depression			
subjects affected / exposed	431 / 1007 (42.80%)	478 / 1007 (47.47%)	476 / 1001 (47.55%)
occurrences (all)	431	478	476
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	41 / 1007 (4.07%)	46 / 1007 (4.57%)	51 / 1001 (5.09%)
occurrences (all)	41	46	51
Thrombosis/embolism (vascular access-related)			
subjects affected / exposed	5 / 1007 (0.50%)	3 / 1007 (0.30%)	2 / 1001 (0.20%)
occurrences (all)	5	3	2
Cardiac disorders			
Cardiac-ischemia/infarction			
subjects affected / exposed	1 / 1007 (0.10%)	2 / 1007 (0.20%)	5 / 1001 (0.50%)
occurrences (all)	1	2	5
Nervous system disorders			
Hemorrhage, CNS			
subjects affected / exposed	14 / 1007 (1.39%)	9 / 1007 (0.89%)	8 / 1001 (0.80%)
occurrences (all)	14	9	8
CNS cerebrovascular ischemia			
subjects affected / exposed	2 / 1007 (0.20%)	1 / 1007 (0.10%)	0 / 1001 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	239 / 1007 (23.73%)	215 / 1007 (21.35%)	228 / 1001 (22.78%)
occurrences (all)	239	215	228
Skin and subcutaneous tissue disorders			
Sweating (diaphoresis)			
subjects affected / exposed	486 / 1007 (48.26%)	621 / 1007 (61.67%)	566 / 1001 (56.54%)
occurrences (all)	486	621	566
Renal and urinary disorders			

Incontinence, urinary			
subjects affected / exposed	156 / 1007 (15.49%)	180 / 1007 (17.87%)	120 / 1001 (11.99%)
occurrences (all)	156	180	120
Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	123 / 1007 (12.21%)	198 / 1007 (19.66%)	316 / 1001 (31.57%)
occurrences (all)	123	198	316
Pain - Joint			
subjects affected / exposed	631 / 1007 (62.66%)	700 / 1007 (69.51%)	778 / 1001 (77.72%)
occurrences (all)	631	700	778
Metabolism and nutrition disorders			
Glucose, serum-high (hyperglycemia)			
subjects affected / exposed	15 / 1007 (1.49%)	37 / 1007 (3.67%)	17 / 1001 (1.70%)
occurrences (all)	15	37	17
Pancreatic endocrine: glucose intolerance			
subjects affected / exposed	15 / 1007 (1.49%)	21 / 1007 (2.09%)	28 / 1001 (2.80%)
occurrences (all)	15	21	28

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2005	1.Modifiedthe eligibility and other sections to include patients with bilateral breast cancer. 2.Increasedthe eligibility timeframe after chemotherapy from 6 months to 8 months. 3.Modified/clarifiedeligibility requirements including:a. Defining a premenopausal group that does not require estradiol testing;b. Clarifying definitions of surgical margins;c. Defining eligible prior malignancies. 4.Clarifiedtiming of randomization with respect to surgery, radiotherapy, and chemotherapy. 5.Clarifiedthat trastuzumab is allowed prior to and/or concurrent with protocol treatment. 6.Includednew findings about exemestane efficacy and side effects in postmenopausal women. 7.Addeddetails of treatment administration. 8.Clarifiedpathology requirements and central review. 9.Administrative corrections and updates.
24 August 2011	1. Modifiedthe statistical analysis plan to compare: a. OFS + tamoxifen versus tamoxifen alone for a primary analysis with a data cut-off anticipated for the third quarterof 2013 at a median follow-up of at least 5 years. b. OFS + exemestane versus OFS + tamoxifen in the originally-planned combined analysis of SOFT and TEXT with a data cut-off anticipated for the fall of 2013 at a median follow-up of approximately 5 years in the SOFT population. 2. Includedbreast cancer-free interval (BCFI) and distant recurrence-free interval (DRFI) assecondary endpoints replacing systemic disease-free survival. 3. Added targeted adverse event information on diabetes and collection of anti-diabetic concomitant medications. Increased risk of diabetes has been suggested by epidemiologicstudies in men being treated with GnRH agonists for prostate cancer. Glucose intolerance (diabetes) and hyperglycemia wereadded to the case report forms as targetedadverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported