Clinical trial results:
A Phase III Trial Evaluating the Role of Exemestane Plus GnRH Analogue as Adjuvant Therapy for Premenopausal Women with Endocrine Responsive Breast Cancer.

Summary

EudraCT number	2004-000168-28
Trial protocol	SE BE DE
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	19 May 2021
First version publication date	19 May 2021

Trial information

Trial identification

Sponsor protocol code	IBCSG25-02/BIG3-02 TEXT

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00066703
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IBCSG
Sponsor organisation address	Effingerstrasse 40, Bern, Switzerland, 3008
Public contact	IBCSG Coordinating Center, IBCSG, +41 31389 93 91, regulatoryoffice@ibcsg.org
Scientific contact	IBCSG Coordinating Center, IBCSG, +41 31389 93 91, 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 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 August 2013
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

Compare the disease-free survival, breast cancer-free interval, distant recurrence-free interval and overall survival of premenopausal women with endocrine-responsive breast cancer when treated with triptorelin and exemestane vs triptorelin and tamoxifen.

Compare the quality of life, including late side effects of early menopause, of patients treated with these regimens.

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	Slovenia: 29
Country: Number of subjects enrolled	Sweden: 11
Country: Number of subjects enrolled	Belgium: 92
Country: Number of subjects enrolled	Germany: 39
Country: Number of subjects enrolled	United Kingdom: 4
Country: Number of subjects enrolled	Australia: 249
Country: Number of subjects enrolled	Egypt: 6
Country: Number of subjects enrolled	Hungary: 189
Country: Number of subjects enrolled	India: 28
Country: Number of subjects enrolled	Italy: 866
Country: Number of subjects enrolled	Peru: 121
Country: Number of subjects enrolled	Switzerland: 165
Country: Number of subjects enrolled	South Africa: 7
Country: Number of subjects enrolled	United States: 739

Country: Number of subjects enrolled	Canada: 127
Worldwide total number of subjects	2672
EEA total number of subjects	1230

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)	2672
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Final accrual for TEXT was 2672 patients (target: 2639) from 182 centers.

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	T+OFS

Arm description:

Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus tamoxifen 20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.

Arm type	Active comparator
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Nolvadex
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin.

Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	GnRH analogue, Trelstar Depot, Decapeptyl Depot
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

3.75mg by im injection q28 days for 5 years

Arm title	E+OFS

Arm description:

Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus exemestane 25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.

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

Dosage and administration details:	
25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin.	
Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	GnRH analogue, Trelstar Depot, Decapeptyl Depot
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use
Dosage and administration details:	
3.75mg by im injection q28 days for 5 years	

Number of subjects in period 1	T+OFS	E+OFS
Started	1334	1338
Completed	1328	1332
Not completed	6	6
Consent withdrawn by subject	4	3
Center not compliant with protocol procedure	2	1
Protocol deviation	-	2

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	T+OFS
Arm description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus tamoxifen 20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	
Arm type	Active comparator
Investigational medicinal product name	Tamoxifen
Investigational medicinal product code	
Other name	Nolvadex
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use
Dosage and administration details:	
20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin.	

Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	GnRH analogue, Trelstar Depot, Decapeptyl Depot
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

3.75mg by im injection q28 days for 5 years

Arm title	E+OFS

Arm description:

Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus exemestane 25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.

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

Dosage and administration details:

25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin.

Investigational medicinal product name	Triptorelin
Investigational medicinal product code	
Other name	GnRH analogue, Trelstar Depot, Decapeptyl Depot
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

3.75mg 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]	T+OFS	E+OFS
Started	1328	1332
Completed	1328	1332

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 12 patients in total - 7 patients who withdrew consent, 2 patients with protocol deviations and 3 patients from centers not compliant with protocol procedures.

Baseline characteristics

Reporting groups	
Reporting group title	T+OFS
Reporting group description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus tamoxifen 20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	
Reporting group title	E+OFS
Reporting group description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus exemestane 25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	

Reporting group values	T+OFS	E+OFS	Total
Number of subjects	1328	1332	2660
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	44	43	
inter-quartile range (Q1-Q3)	40 to 46	39 to 46	-
Gender categorical			
Units: Subjects			
Female	1328	1332	2660
Male	0	0	0

End points

End points reporting groups

Reporting group title	T+OFS
Reporting group description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus tamoxifen 20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	
Reporting group title	E+OFS
Reporting group description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus exemestane 25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	
Reporting group title	T+OFS
Reporting group description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus tamoxifen 20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	
Reporting group title	E+OFS
Reporting group description:	
Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus exemestane 25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.	

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 estimate reported at a median follow-up of 72 months	

End point values	T+OFS	E+OFS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1328	1332		
Units: Percentage of participants				
number (confidence interval 95%)	87.3 (85.7 to 88.7)	91.1 (89.7 to 92.3)		

Statistical analyses

Statistical analysis title	Statistical analysis primary endpoint
Comparison groups	T+OFS v E+OFS
Number of subjects included in analysis	2660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.717
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.602
upper limit	0.855

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 the 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 estimate reported at a median follow-up of 72 months

End point values	T+OFS	E+OFS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1328	1332		
Units: Percentage of participants				
number (confidence interval 95%)	88.8 (87.3 to 90.1)	92.8 (91.6 to 93.9)		

Statistical analyses

Statistical analysis title	Breast Cancer-free Interval
Comparison groups	T+OFS v E+OFS

Number of subjects included in analysis	2660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.664
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.548
upper limit	0.804

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 breast cancer recurrence at a distant site; 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 72 months

End point values	T+OFS	E+OFS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1328	1332		
Units: Percentage of participants				
number (confidence interval 95%)	92 (90.7 to 93.1)	93.8 (92.7 to 94.8)		

Statistical analyses

Statistical analysis title	Distant Recurrence-free Interval
Comparison groups	T+OFS v E+OFS
Number of subjects included in analysis	2660
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.624
upper limit	0.967

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 9 years

End point values	T+OFS	E+OFS		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1328	1332		
Units: Percentage of participants				
number (confidence interval 95%)	93.3 (92.1 to 94.3)	93.4 (92.2 to 94.4)		

Statistical analyses

Statistical analysis title	Overall Survival
Comparison groups	T+OFS v E+OFS
Number of subjects included in analysis	2660
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	0.79
upper limit	1.22

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed every 3 months for the first year, then every 6 months until year 6. Reported at a median follow-up of 72 months.

Adverse event reporting additional description:

Targeted adverse events and other grade 3 or higher adverse events 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	T+OFS

Reporting group description:

Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus tamoxifen 20mg orally daily for 5 years. Tamoxifen (T) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.

Reporting group title	E+OFS

Reporting group description:

Ovarian function suppression (OFS) by triptorelin (GnRH analogue) 3.75mg by im injection q28 days for 5 years plus exemestane 25mg orally daily for 5 years. Exemestane (E) begins after the completion of adjuvant chemotherapy if given, or approximately 6-8 weeks after the initiation of triptorelin. Bilateral oophorectomy or ovarian irradiation was allowed after at least 6 months of triptorelin.

Serious adverse events	T+OFS	E+OFS	
Total subjects affected by serious adverse events			
subjects affected / exposed	290 / 1328 (21.84%)	295 / 1332 (22.15%)	
number of deaths (all causes)	5	5	
number of deaths resulting from adverse events	3	1	
Vascular disorders			
Deep Vein Thrombosis			
subjects affected / exposed	12 / 1328 (0.90%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	7 / 12	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	3 / 1328 (0.23%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	1 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Pregnancy			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Allergic reaction/hypersensitivity			
subjects affected / exposed	3 / 1328 (0.23%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 3	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalized edema inclusive pleura effusion			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute sarcoidosis (Loefgren Syndrome)			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical Changes			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cervical Polyp			
subjects affected / exposed	2 / 1328 (0.15%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Hyperplasia			
subjects affected / exposed	5 / 1328 (0.38%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial Polyp			

subjects affected / exposed	6 / 1328 (0.45%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	6 / 6	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian Cyst			
subjects affected / exposed	3 / 1328 (0.23%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	3 / 3	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine adenomyosis and chronic cervicitis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Hemorrhage			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Leiomyoma			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Myoma			
subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine Prolapse			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Bleeding			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal Prolapse			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Benign Lesion-Fibrosis (L Breast)			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibrocystic Breast			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mammary Duct Ectasia			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sclerosing adenosis (R breast)			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic Pansinusitis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroglossal duct cyst			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary Embolism			
subjects affected / exposed	2 / 1328 (0.15%)	4 / 1332 (0.30%)	
occurrences causally related to treatment / all	2 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma exacerbation			

subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 1328 (0.08%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation Pneumonitis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Larynx Stricture requiring surgery			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Sudden death due to lethal dose of diphenhydramine			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Ureter and vaginal cuff injury after hysterectomy and BSO			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Atrial Fibrillation			
subjects affected / exposed	2 / 1328 (0.15%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			

subjects affected / exposed	0 / 1328 (0.00%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular arrhythmia			
subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular Tachycardia			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular fibrilation in context of allergic reaction			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac ischemia/infarction			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest Pain			
subjects affected / exposed	4 / 1328 (0.30%)	5 / 1332 (0.38%)	
occurrences causally related to treatment / all	0 / 6	2 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congestive Heart Failure and Asthma Exacerbation			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Heart Failure			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischemic Heart Disease			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral and tricuspid valve disease requiring surgery			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mitral valve stenosis requiring surgery			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial Infarction			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular Insufficiency			
subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression			
subjects affected / exposed	8 / 1328 (0.60%)	6 / 1332 (0.45%)	
occurrences causally related to treatment / all	9 / 9	7 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness			

subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Facial spasms R			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 1328 (0.08%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mood Alteration			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuronitis Vestibularis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neuropathy			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attacks with dyspnoea and chest pain			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychogenic seizure			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychosis			

subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)		
occurrences causally related to treatment / all	0 / 0	3 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
Seizure				
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Ethylic intoxication with depressive syndrome				
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Lumboischialgia				
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Sensory neuropathy				
subjects affected / exposed	0 / 1328 (0.00%)	2 / 1332 (0.15%)		
occurrences causally related to treatment / all	0 / 0	1 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
Spinal Meningioma and Primary Lateral Sclerosis				
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)		
occurrences causally related to treatment / all	0 / 0	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Subarachnoidal bleeding				
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
Suicidal Ideation				
subjects affected / exposed	2 / 1328 (0.15%)	1 / 1332 (0.08%)		
occurrences causally related to treatment / all	2 / 2	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
Suicide Attempt				

subjects affected / exposed	4 / 1328 (0.30%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	1 / 4	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 1328 (0.00%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient Ischemic Attack			
subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trigeminal neuralgia			
subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety and depression			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral contusion			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal Tunnel Syndrome			

subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bipolar disorder			
subjects affected / exposed	2 / 1328 (0.15%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular Accident			
subjects affected / exposed	2 / 1328 (0.15%)	4 / 1332 (0.30%)	
occurrences causally related to treatment / all	1 / 2	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Neutropenia			
subjects affected / exposed	6 / 1328 (0.45%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polycythemia Vera			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral Hemorrhage			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gum bleeding under anticoagulation			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemoptoe			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Edema			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anemia			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Cataract and Retinal Detachment			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Central vein occlusion (L eye)			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinal Detachment			
subjects affected / exposed	0 / 1328 (0.00%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Retinopathy			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Thyroid Nodules			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon polyps			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhea			
subjects affected / exposed	3 / 1328 (0.23%)	5 / 1332 (0.38%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 1328 (0.00%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Esophageal Achalasia			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Faecaloma			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric Ulcer			

subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastritis			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastro-eosphageal reflux disease			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hemorrhoids			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea and Vomiting			
subjects affected / exposed	2 / 1328 (0.15%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small bowel obstruction			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal bleeding			

subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome leading to rectal bleeding			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Terminal Ileitisv			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	3 / 1328 (0.23%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal Perforation			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Hemorrhoidal bleeding			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute/Recurrent Pancreatitis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	6 / 1328 (0.45%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 6	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Choledocholytiasis			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	4 / 1328 (0.30%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gallbladder Sludge			
subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatopathy			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver disfunction			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Hemorrhagic cystitis due to cyclophosphamide			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hydroureteronephrosis left			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mature cystic teratoma and endometrial polyp			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	0 / 1328 (0.00%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal calculi			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic due to lithiasis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suspicion of junction syndrom (R ureter)			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Incontinence			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention due to opioids treatment			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Endocrine disorders			
Hyperparathyroidism			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotis Adenoma			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid Adenoma			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroiditis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain and arthralgia			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone fracture			
subjects affected / exposed	17 / 1328 (1.28%)	30 / 1332 (2.25%)	
occurrences causally related to treatment / all	7 / 18	17 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Discus Hernia			
subjects affected / exposed	1 / 1328 (0.08%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Exacerbation of ankylosing spondylitis			

subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint pain			
subjects affected / exposed	0 / 1328 (0.00%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 0	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myalgia			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthrosis			
subjects affected / exposed	1 / 1328 (0.08%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periarthritis humero-scapularis requiring surgery			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Polytrauma			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
R knee dislocation			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rheumatoid Arthritis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rupture of achilles tendon L			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendinitis calcarea (L Shoulder)			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Traumatic injuries on the face			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal pain			
subjects affected / exposed	4 / 1328 (0.30%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Elevated liver function tests			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abscess breast			
subjects affected / exposed	0 / 1328 (0.00%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute Appendicitis			

subjects affected / exposed	1 / 1328 (0.08%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast implant infection			
subjects affected / exposed	5 / 1328 (0.38%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	1 / 1328 (0.08%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bruise of abdominal wall with abscess			
subjects affected / exposed	5 / 1328 (0.38%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	10 / 1328 (0.75%)	9 / 1332 (0.68%)	
occurrences causally related to treatment / all	0 / 10	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile Neutropenia			
subjects affected / exposed	19 / 1328 (1.43%)	29 / 1332 (2.18%)	
occurrences causally related to treatment / all	0 / 22	0 / 30	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia during chemotherapy			
subjects affected / exposed	2 / 1328 (0.15%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	4 / 1328 (0.30%)	5 / 1332 (0.38%)	
occurrences causally related to treatment / all	0 / 5	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	2 / 1328 (0.15%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gram negative sepsis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection (L arm cellulitis) in neutropenia			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection around the port system			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with normal ANC			
subjects affected / exposed	1 / 1328 (0.08%)	5 / 1332 (0.38%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza A leading to pulmonary complications			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis			
subjects affected / exposed	1 / 1328 (0.08%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HIV infection			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pleural effusion due to infection			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	4 / 1328 (0.30%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Port-A-Cath infection			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative infection after oophorectomy			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock from infection of breast implant			

subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcus aureus infection (catheter related)			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth Abscess			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary Tract Infection			
subjects affected / exposed	1 / 1328 (0.08%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Viral upper respiratory infection			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound Infection			
subjects affected / exposed	1 / 1328 (0.08%)	2 / 1332 (0.15%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sigmoid colitis			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint Infection (Right wrist)			

subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection with neutropenia			
subjects affected / exposed	3 / 1328 (0.23%)	4 / 1332 (0.30%)	
occurrences causally related to treatment / all	0 / 3	1 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes Mellitus			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercholesterolemia G3 and Hypertrigyceridemia G4			
subjects affected / exposed	0 / 1328 (0.00%)	1 / 1332 (0.08%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperglycemia			
subjects affected / exposed	0 / 1328 (0.00%)	3 / 1332 (0.23%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fibromyalgia			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Accidental CO - intoxication			
subjects affected / exposed	1 / 1328 (0.08%)	0 / 1332 (0.00%)	
occurrences causally related to treatment / all	0 / 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	T+OFS	E+OFS	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1293 / 1328 (97.36%)	1298 / 1332 (97.45%)	
Vascular disorders			
Hot flashes/flushes			
subjects affected / exposed	1081 / 1328 (81.40%)	1076 / 1332 (80.78%)	
occurrences (all)	1081	1076	
Hypertension			
subjects affected / exposed	179 / 1328 (13.48%)	213 / 1332 (15.99%)	
occurrences (all)	179	213	
General disorders and administration site conditions			
Fatigue (asthenia, lethargy, malaise)			
subjects affected / exposed	807 / 1328 (60.77%)	760 / 1332 (57.06%)	
occurrences (all)	807	760	
Injection site reaction/extravasation changes			
subjects affected / exposed	99 / 1328 (7.45%)	86 / 1332 (6.46%)	
occurrences (all)	99	86	
Immune system disorders			
Allergic reaction/hypersensitivity (including drug fever)			
subjects affected / exposed	56 / 1328 (4.22%)	60 / 1332 (4.50%)	
occurrences (all)	56	60	
Reproductive system and breast disorders			
Pain - Vagina			
subjects affected / exposed	336 / 1328 (25.30%)	374 / 1332 (28.08%)	
occurrences (all)	336	374	
Vaginal dryness			
subjects affected / exposed	611 / 1328 (46.01%)	683 / 1332 (51.28%)	
occurrences (all)	611	683	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	738 / 1328 (55.57%)	714 / 1332 (53.60%)	
occurrences (all)	738	714	
Libido			

subjects affected / exposed	486 / 1328 (36.60%)	555 / 1332 (41.67%)	
occurrences (all)	486	555	
Mood alteration - depression			
subjects affected / exposed	592 / 1328 (44.58%)	610 / 1332 (45.80%)	
occurrences (all)	592	610	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	57 / 1328 (4.29%)	82 / 1332 (6.16%)	
occurrences (all)	57	82	
Thrombosis/embolism (vascular access-related)			
subjects affected / exposed	3 / 1328 (0.23%)	3 / 1332 (0.23%)	
occurrences (all)	3	3	
Cardiac disorders			
Cardiac-ischemia/infarction			
subjects affected / exposed	2 / 1328 (0.15%)	4 / 1332 (0.30%)	
occurrences (all)	2	4	
Nervous system disorders			
Hemorrhage, CNS			
subjects affected / exposed	12 / 1328 (0.90%)	7 / 1332 (0.53%)	
occurrences (all)	12	7	
CNS cerebrovascular ischemia			
subjects affected / exposed	2 / 1328 (0.15%)	1 / 1332 (0.08%)	
occurrences (all)	2	1	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	446 / 1328 (33.58%)	478 / 1332 (35.89%)	
occurrences (all)	446	478	
Skin and subcutaneous tissue disorders			
Sweating (diaphoresis)			
subjects affected / exposed	752 / 1328 (56.63%)	705 / 1332 (52.93%)	
occurrences (all)	752	705	
Renal and urinary disorders			
Incontinence, urinary			
subjects affected / exposed	232 / 1328 (17.47%)	182 / 1332 (13.66%)	
occurrences (all)	232	182	

Musculoskeletal and connective tissue disorders			
Osteoporosis			
subjects affected / exposed	388 / 1328 (29.22%)	588 / 1332 (44.14%)	
occurrences (all)	388	588	
Pain - Joint			
subjects affected / exposed	953 / 1328 (71.76%)	1030 / 1332 (77.33%)	
occurrences (all)	953	1030	
Metabolism and nutrition disorders			
Glucose, serum-high (hyperglycemia)			
subjects affected / exposed	30 / 1328 (2.26%)	31 / 1332 (2.33%)	
occurrences (all)	30	31	
Pancreatic endocrine: glucose intolerance			
subjects affected / exposed	16 / 1328 (1.20%)	17 / 1332 (1.28%)	
occurrences (all)	16	17	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2005	1. Modified the eligibility and other sections to include patients with bilateral breast cancer. 2. Modified/clarified eligibility requirements including: a. Defining a premenopausal group that does not require estradiol testing; b. Clarifying definitions of surgical margins; c. Defining eligible prior malignancies. 3. Clarified timing of randomization with respect to surgery, radiotherapy, and chemotherapy. 4. Clarified that trastuzumab is allowed prior to and/or concurrent with protocol treatment. 5. Included new findings about exemestane efficacy and side effects in postmenopausal women. 6. Added details of treatment administration. 7. Clarified pathology requirements and central review. 8. Administrative corrections and updates.
25 July 2008	1. Re-opened enrollment for an additional 600 patients (target accrual: 2639). 2. Added translational research investigations which involved a one-time blood sample for genotyping.
24 August 2011	1. Modified the statistical analysis plan to combine data available from SOFT and TEXT for the comparison of OFS + exemestane versus OFS + tamoxifen for a primary analysis with a data cut-off anticipated for the third quarter of 2013 at 5 years' median follow-up. 2. Included breast cancer-free interval (BCFI) and distant recurrence-free interval (DRFI) as secondary 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 epidemiologic studies in men being treated with GnRH agonists for prostate cancer. Glucose intolerance (diabetes) and hyperglycemia were added to the case report forms as targeted adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported