



Clinical trial results:

Evaluation of predictive Factors for the Effectivity of Aromatase Inhibitor Therapy -

Offene, prospektive, multizentrische Phase IV-Studie zur Untersuchung des Einflusses von pharmakogenetischen Markern auf die Wirksamkeit und Nebenwirkungsrate bei postmenopausalen, steroidhormonrezeptorpositiven Mammakarzinomspatientinnen, die mit Letrozol behandelt werden.

Summary

EudraCT number	2008-004874-42
Trial protocol	DE
Global end of trial date	04 January 2016

Results information

Result version number	v1 (current)
This version publication date	09 February 2025
First version publication date	09 February 2025
Summary attachment (see zip file)	PreFace_CSR_Summary_2024-12-18 (PreFace_CSR_Summary_2024-12-18.pdf)

Trial information

Trial identification

Sponsor protocol code	TRAFO001
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01908556
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Institut für Frauengesundheit GmbH
Sponsor organisation address	Universitätsstraße 21-23, Erlangen, Germany, 91054
Public contact	Clinical Trials Information, Institut für Frauengesundheit GmbH, +49 091318536167, preface@ifg-erlangen.de
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 December 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 January 2016
Global end of trial reached?	Yes
Global end of trial date	04 January 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

- Disease free survival in association with tested genotypes (whole genome scan)

Protection of trial subjects:

The clinical trial was conducted in accordance with current ethical standards, the Declaration of Helsinki from 1996 and the Guidelines of the International Conference on Harmonization Good Clinical Practice (GCP).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 February 2009
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 3297
Worldwide total number of subjects	3297
EEA total number of subjects	3297

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)	1812
From 65 to 84 years	1472

85 years and over	13
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Subject disposition

Recruitment

Recruitment details:

Start of recruitment was on 06-Feb-2009. The clinical trial was conducted in 220 trial sites in Germany. The first patient was enrolled, the last patient was enrolled on 04-Jan-2011. The end of trial was reached 60 months after enrollment of the last patient on 04-Jan-2016. Date of database lock was 08-Feb-2022.

Pre-assignment

Screening details:

A total of 3529 patients were registered in the trial and were evaluated for eligibility. 46 patients were identified as screening failures. 102 patients were excluded as they had not started study intervention and 84 patients were excluded as lost to follow-up after screening. Therefore, 3297 patients were assessed.

Period 1

Period 1 title	Overall period (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The trial was open-label

Arms

Arm title	Letrozole
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Arm description:

Patients received regular letrozole 2.5 mg per day, p.o. for a maximum observation period of five years according to SmPC of letrozole.

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

Dosage and administration details:

Patients received a daily dose of 2.5mg letrozol film-coated tablets, oral use.

Number of subjects in period 1	Letrozole
Started	3297
Completed	1318
Not completed	1979
unknown	605
Irregular end of treatment	1374

Baseline characteristics

Reporting groups

Reporting group title	Overall period
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Reporting group description: -

Reporting group values	Overall period	Total	
Number of subjects	3297	3297	
Age categorical			
Units: Subjects			
< 65	1812	1812	
≥ 65	1472	1472	
missing	13	13	
Age continuous			
Units: years			
arithmetic mean	63.9		
standard deviation	± 7.6	-	
Gender categorical			
All patients enrolled were female			
Units: Subjects			
Female	3297	3297	
Male	0	0	
BMI			
Units: Subjects			
< 20	124	124	
20-25	1097	1097	
25-30	1246	1246	
≥ 30	790	790	
missing	40	40	
pN			
Pathological lymph node status			
Units: Subjects			
pN0	2312	2312	
pN+	949	949	
missing	36	36	
pT			
pathological tumor stage			
Units: Subjects			
pT0	45	45	
pT1	2081	2081	
pT2	991	991	
pT3	120	120	
pT4	42	42	
missing	18	18	
Grading			
Tumor grading			
Units: Subjects			
G1	603	603	
G2	2123	2123	

G3	556	556	
missing	15	15	
ER status			
estrogen receptor status			
Units: Subjects			
ER-	41	41	
ER+	3241	3241	
missing	15	15	
PgR			
progesterone receptor status			
Units: Subjects			
PgR-	456	456	
PgR+	2828	2828	
missing	13	13	
HR			
Combined hormone receptor status			
Units: Subjects			
ER-/PgR-	7	7	
ER-/PgR+	34	34	
ER+/PgR-	448	448	
ER+/PgR+	2792	2792	
missing	16	16	
HER2			
HER2 status			
Units: Subjects			
HER2-	2897	2897	
HER2+	353	353	
missing	47	47	
Histological Subtype			
Units: Subjects			
ductal invasive	2422	2422	
ductal lobular	564	564	
missing	311	311	
Previous chemotherapy			
Units: Subjects			
neoadjuvant	241	241	
adjuvant	1086	1086	
neoadjuvant and adjuvant	9	9	
naive	1917	1917	
missing	44	44	
BMI			
Units: kg/m ²			
arithmetic mean	27.2		
standard deviation	± 5.1	-	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

The full analysis set comprises of patients included in the clinical trial who have started trial treatment

and for whom at least one follow-up visit is available after therapy start.

Reporting group values	Full Analysis Set		
Number of subjects	3297		
Age categorical			
Units: Subjects			
< 65	1812		
≥ 65	1472		
missing	13		
Age continuous			
Units: years			
arithmetic mean	63.9		
standard deviation	± 7.6		
Gender categorical			
All patients enrolled were female			
Units: Subjects			
Female	3297		
Male	0		
BMI			
Units: Subjects			
< 20	124		
20-25	1097		
25-30	1246		
≥ 30	790		
missing	40		
pN			
Pathological lymph node status			
Units: Subjects			
pN0	2312		
pN+	949		
missing	36		
pT			
pathological tumor stage			
Units: Subjects			
pT0	45		
pT1	2081		
pT2	991		
pT3	120		
pT4	42		
missing	18		
Grading			
Tumor grading			
Units: Subjects			
G1	603		
G2	2123		
G3	556		
missing	15		
ER status			
estrogen receptor status			
Units: Subjects			

ER-	41		
ER+	3241		
missing	15		
PgR			
progesterone receptor status			
Units: Subjects			
PgR-	456		
PgR+	2828		
missing	13		
HR			
Combined hormone receptor status			
Units: Subjects			
ER-/PgR-	7		
ER-/PgR+	34		
ER+/PgR-	448		
ER+/PgR+	2792		
missing	16		
HER2			
HER2 status			
Units: Subjects			
HER2-	2897		
HER2+	353		
missing	47		
Histological Subtype			
Units: Subjects			
ductal invasive	2422		
ductal lobular	564		
missing	311		
Previous chemotherapy			
Units: Subjects			
neoadjuvant	241		
adjuvant	1086		
neoadjuvant and adjuvant	9		
naive	1917		
missing	44		
BMI			
Units: kg/m ²			
arithmetic mean	27.2		
standard deviation	± 5.1		

End points

End points reporting groups

Reporting group title	Letrozole
Reporting group description: Patients received regular letrozole 2.5 mg per day, p.o. for a maximum observation period of five years according to SmPC of letrozole.	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description: The full analysis set comprises of patients included in the clinical trial who have started trial treatment and for whom at least one follow-up visit is available after therapy start.	

Primary: 2-year DFS rate

End point title	2-year DFS rate ^[1]
End point description: Disease-free survival is defined as time between first dose of trial treatment and one of the following end-points, whichever occurred first: death, occurrence of distant metastases, secondary carcinoma, breast cancer recurrence (locally or axillary).	
End point type	Primary
End point timeframe: Disease-free survival after 2 years	
Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: No statistical tests were performed for non-genetic analyses.	

End point values	Letrozole	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3297	3297		
Units: percent				
number (confidence interval 95%)	96 (95 to 97)	96 (95 to 97)		

Statistical analyses

No statistical analyses for this end point

Primary: 3-year DFS rate

End point title	3-year DFS rate ^[2]
End point description: Disease-free survival is defined as time between first dose of trial treatment and one of the following end-points, whichever occurred first: death, occurrence of distant metastases, secondary carcinoma, breast cancer recurrence (locally or axillary).	
End point type	Primary
End point timeframe: Disease-free survival after 3 years	

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical tests were performed for non-genetic analyses.

End point values	Letrozole	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3297	3297		
Units: percent				
number (confidence interval 95%)	94 (93 to 95)	94 (93 to 95)		

Statistical analyses

No statistical analyses for this end point

Primary: 5-year DFS rate

End point title	5-year DFS rate ^[3]
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End point description:

Disease-free survival is defined as time between first dose of trial treatment and one of the following end-points, whichever occurred first: death, occurrence of distant metastases, secondary carcinoma, breast cancer recurrence (locally or axillary).

End point type	Primary
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End point timeframe:

Disease-free survival after 5 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: No statistical tests were performed for non-genetic analyses.

End point values	Letrozole	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3297	3297		
Units: percent				
number (confidence interval 95%)	89 (88 to 90)	89 (88 to 90)		

Statistical analyses

No statistical analyses for this end point

Secondary: 2-year OS rate

End point title	2-year OS rate
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End point description:

Overall survival is defined as time between first dose of trial treatment and patient's death regardless of reason.

End point type	Secondary
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End point timeframe:

Overall survival after 2 years

End point values	Letrozole	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3297	3297		
Units: percent				
number (confidence interval 95%)	99 (98 to 99)	99 (98 to 99)		

Statistical analyses

No statistical analyses for this end point

Secondary: 3-year OS rate

End point title	3-year OS rate
End point description:	
Overall survival is defined as time between first dose of trial treatment and patient's death regardless of reason.	
End point type	Secondary
End point timeframe:	
Overall survival after 3 years	

End point values	Letrozole	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3297	3297		
Units: percent				
number (confidence interval 95%)	98 (97 to 98)	98 (97 to 98)		

Statistical analyses

No statistical analyses for this end point

Secondary: 5-year OS rate

End point title	5-year OS rate
End point description:	
Overall survival is defined as time between first dose of trial treatment and patient's death regardless of reason.	
End point type	Secondary
End point timeframe:	
Overall survival after 5 years	

End point values	Letrozole	Full Analysis Set		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	3297	3297		
Units: percent				
number (confidence interval 95%)	95 (94 to 96)	95 (94 to 96)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time of treatment start until 14 days after last dose of trial treatment

Adverse event reporting additional description:

Adverse events are reported for letrozole

Assessment type	Systematic
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Dictionary used

Dictionary name	CTCAE
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Dictionary version	3.0
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Reporting groups

Reporting group title	Full Analysis Set
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Reporting group description:

Safety analysis was performed in the full analysis set, including all patients exposed to ribociclib for whom at least one follow-up visit was available. This is justified as no safety data is available for patient for whom only baseline data is available.

Serious adverse events	Full Analysis Set		
Total subjects affected by serious adverse events			
subjects affected / exposed	398 / 3297 (12.07%)		
number of deaths (all causes)	141		
number of deaths resulting from adverse events	28		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy	Additional description: Development of a new cancer resulting from treatment from an earlier cancer diagnosis		
alternative assessment type: Non-systematic			
subjects affected / exposed	95 / 3297 (2.88%)		
occurrences causally related to treatment / all	1 / 101		
deaths causally related to treatment / all	0 / 5		
Vascular disorders			
Peripheral arterial ischemia	Additional description: Disorder of arteries causing inadequate blood supply to extremities.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Thrombosis/thrombus/embolism	Additional description: Formation or presence of a blood clot inside a blood vessel.		
alternative assessment type: Non-systematic			

subjects affected / exposed	14 / 3297 (0.42%)		
occurrences causally related to treatment / all	4 / 14		
deaths causally related to treatment / all	1 / 1		
Vascular - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue	Additional description: Fatigue, tiredness, asthenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 2		
Death	Additional description: Death not associated with CTCAE term		
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 3297 (0.42%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 14		
Chest pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Head pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pain - Other			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergic reaction/hypersensitivity	Additional description: Allergic reaction/hypersensitivity (including drug fever)		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			
Hemorrhage, GU	Additional description: Bleeding of the vagina		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Breast pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	1 / 4		
deaths causally related to treatment / all	0 / 0		
Breast function/lactation	Additional description: Change in ability to produce milk from breasts		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 3297 (0.33%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Breast volume/hypoplasia	Additional description: Decreased size of breast tissue		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 3297 (0.27%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Sexual/Reproductive Function - Other			
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm, wheezing	Additional description: Irritation of the small airways or wheezing		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cough			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnea	Additional description: Shortness of breath		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Obstruction/stenosis of airway	Additional description: Blockage of an air tube from the windpipe to the lungs		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Pleural effusion (non-malignant)	Additional description: Collection of fluid between the thin layers of tissue (pleura) lining the lung and the wall of the chest cavity		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonitis/pulmonary infiltrates	Additional description: Inflammation of the lungs		
alternative assessment type: Non-systematic			

subjects affected / exposed	11 / 3297 (0.33%)		
occurrences causally related to treatment / all	0 / 13		
deaths causally related to treatment / all	0 / 0		
Pulmonary/Upper Respiratory - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Voice changes/dysarthria	Additional description: Voice changes, laryngitis, hoarseness (e.g., hoarseness, loss or alteration in voice, laryngitis)		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Cognitive disturbance	Additional description: Disturbances in thinking patterns		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Memory impairment	Additional description: Memory impairment		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental status	Additional description: Changes in mental status		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Mood alteration	Additional description: Depression		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Personality/behavioral	Additional description: Personality changes		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Weight gain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Weight loss			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
ALT, SGPT (serum glutamic pyruvic transaminase)	Additional description: Abnormal liver enzyme level		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bilirubin (hyperbilirubinemia)	Additional description: Abnormal level of bilirubin in the blood. Bilirubin is a bile pigment found in the liver.		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Intra-operative injury; Arm	Additional description: Damage to a part of the body during an operation: Arm		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-operative injury; nose	Additional description: Damage to a part of the body during an operation: Nose		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intra-operative injury; pelvis	Additional description: Damage to a part of the body during an operation: Pelvis		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intra-operative injury; uterus	Additional description: Damage to a part of the body during an operation: Uterus		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Intra-operative injury; vagina	Additional description: Damage to a part of the body during an operation: Vagina		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Cardiac Arrhythmia - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Conduction abnormality/atrioventricular heart block	Additional description: Irregular heart beat		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Palpitations	Additional description: Feeling the heart racing 'skipping a beat' pounding		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Supraventricular and nodal arrhythmia	Additional description: Irregular heart beat		
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 3297 (0.33%)		
occurrences causally related to treatment / all	1 / 12		
deaths causally related to treatment / all	0 / 0		
Cardiac ischemia/infarction	Additional description: Decreased blood supply to the heart/ heart attack		
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences causally related to treatment / all	4 / 17		
deaths causally related to treatment / all	0 / 0		
Cardiac General - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiopulmonary arrest, cause unknown (non-fatal)	Additional description: Heart and lungs stop working		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 2		
Hypertension	Additional description: High blood pressure		
alternative assessment type: Non-systematic			

subjects affected / exposed	9 / 3297 (0.27%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Left ventricular systolic dysfunction	Additional description: Decrease in heart's ability to pump blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Restrictive cardiomyopathy	Additional description: Decrease in heart's ability to pump blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right ventricular dysfunction (cor pulmonale)	Additional description: Decrease in heart's ability to pump blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Valvular heart disease	Additional description: Abnormal heart valves		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Hemorrhage, CNS	Additional description: Bleeding into the brain or spinal cord		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ataxia (incoordination)	Additional description: Loss of muscle coordination awkward, uncoordinated walking unsteadiness when walking		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
CNS cerebrovascular ischemia	Additional description: Decrease in blood flow to the brain		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences causally related to treatment / all	0 / 10		
deaths causally related to treatment / all	0 / 0		
Dizziness	Additional description: Dizziness		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Neurology - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 1		
Neuropathy: cranial	Additional description: Abnormal function of the nerve responsible for feeling in the face and control of the muscles for chewing		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Neuropathy: sensory	Additional description: Condition of the nervous system that causes numbness, tingling, burning.		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Syncope (fainting)	Additional description: Fainting		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nerve pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Blood/Bone Marrow - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hemoglobin	Additional description: Decrease in a part of red blood cells that carries oxygen in the body		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coagulation - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombotic microangiopathy	Additional description: Thrombotic microangiopathy (e.g., thrombotic thrombocytopenic purpura [TTP] or hemolytic uremic syndrome [HUS]). Abnormal clotting of blood in small blood vessels		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Edema: limb	Additional description: Swelling of the arms and legs		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ear and labyrinth disorders			
Auditory/Ear - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Tinnitus	Additional description: Ringing in the ears		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Ocular/Visual - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retinal detachment	Additional description: Separation of the retina from its connection at the back of the eye		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Ascites (non-malignant) Fluid collection	Additional description: Fluid collection in the abdomen		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Colitis	Additional description: Inflammation of the colon		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis (including bile reflux gastritis)	Additional description: Inflammation of the lining of the stomach		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences causally related to treatment / all	0 / 7		
deaths causally related to treatment / all	0 / 0		
Heartburn/dyspepsia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ileus, GI (functional obstruction of bowel, i.e., neuroconstipation)	Additional description: Abnormally slow bowel contraction		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Mucositis/stomatitis (functional/symptomatic)	Additional description: Irritation or sores in the lining of the small intestine		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ulcer, GI	Additional description: Ulcer of small intestine		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Hemorrhage, GI	Additional description: Bleeding of the lower digestive tract		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Belly pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Stomach pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis	Additional description: Inflammation of the gallbladder		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	1 / 3		
deaths causally related to treatment / all	0 / 1		
Hepatobiliary/Pancreas - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Liver dysfunction/failure (clinical)	Additional description: Liver problems/liver failure		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Pancreatitis	Additional description: Inflammation of the pancreas		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Atrophy, subcutaneous fat	Additional description: Loss of fat under the skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Dermatology/Skin - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Flushing	Additional description: Sudden reddening of the face and/or neck		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Induration/fibrosis (skin and subcutaneous tissue)	Additional description: Hardening of the skin and connective tissues		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash/desquamation	Additional description: Rash flaking or sloughing of skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rash: dermatitis associated with radiation	Additional description: Redness, flaking or sloughing of skin in the radiation treatment area		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Skin breakdown/decubitus ulcer	Additional description: Skin sores		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound complication, non-infectious	Additional description: Wound complication		
alternative assessment type: Non-systematic			
subjects affected / exposed	22 / 3297 (0.67%)		
occurrences causally related to treatment / all	0 / 23		
deaths causally related to treatment / all	0 / 0		
Scalp pain			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Cystitis	Additional description: Inflammation or infection of the bladder		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Incontinence, urinary	Additional description: Inability to hold urine in the bladder		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Obstruction, GU	Additional description: Blockage of tube between kidney and bladder		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal failure	Additional description: Kidney failure		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal/Genitourinary - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 3297 (0.27%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Urinary retention (including neurogenic bladder)	Additional description: Difficulty emptying the bladder		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Endocrine - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences causally related to treatment / all	0 / 5		
deaths causally related to treatment / all	0 / 0		
Thyroid function, high	Additional description: Abnormally high thyroid function (hyperthyroidism, thyrotoxicosis)		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Cervical spine-range of motion	Additional description: Stiff neck		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Extremity-lower (gait/walking)	Additional description: Limp		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibrosis-cosmesis	Additional description: Scar or thickening		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fibrosis-deep connective tissue	Additional description: Scar or thickening		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fracture	Additional description: A broken bone		
alternative assessment type: Non-systematic			
subjects affected / exposed	37 / 3297 (1.12%)		
occurrences causally related to treatment / all	1 / 40		
deaths causally related to treatment / all	0 / 0		
Joint-function	Additional description: Joint stiffness		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 0		
Local complication - device/prosthesis-related	Additional description: Local complication of an artificial body part or device		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal/Soft Tissue - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	12 / 3297 (0.36%)		
occurrences causally related to treatment / all	2 / 12		
deaths causally related to treatment / all	0 / 0		
Osteoporosis	Additional description: Bone thinning		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Seroma	Additional description: Abnormal fluid collection in a tissue or organ		
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 3297 (0.06%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Soft tissue necrosis	Additional description: Death of tissue of the belly			
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 3297 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Back pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	6 / 3297 (0.18%)			
occurrences causally related to treatment / all	1 / 6			
deaths causally related to treatment / all	0 / 0			
Bone pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	4 / 3297 (0.12%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Chest wall pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	2 / 3297 (0.06%)			
occurrences causally related to treatment / all	1 / 2			
deaths causally related to treatment / all	0 / 0			
Joint pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	14 / 3297 (0.42%)			
occurrences causally related to treatment / all	0 / 15			
deaths causally related to treatment / all	0 / 0			
Leg pain				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 3297 (0.03%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Muscle pain			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Infection - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection of body tissue	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection of the lung (pneumonia)	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection of the skin	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 3297 (0.42%)		
occurrences causally related to treatment / all	0 / 14		
deaths causally related to treatment / all	0 / 0		
Infection of the stomach	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Infection of the upper respiratory tract	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infection of the urinary tract	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Large intestine infection	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Wound infection	Additional description: Infection with unknown ANC		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Full Analysis Set		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1946 / 3297 (59.02%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Secondary Malignancy - possibly related to cancer treatment	Additional description: Development of a new cancer resulting from treatment from an earlier cancer diagnosis		
subjects affected / exposed	33 / 3297 (1.00%)		
occurrences (all)	39		
Vascular disorders			
Hematoma	Additional description: Blood clot in tissue		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Hemorrhage, CNS	Additional description: Bleeding into the brain or spinal cord		

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Bleeding of the bladder			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Bleeding of the uterus			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Bleeding of the vagina			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
hemorrhage, pulmonary/upper respiratory			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Dermal change lymphedema, phlebolymphe ^d ema			
subjects affected / exposed	94 / 3297 (2.85%)		
occurrences (all)	97		
Edema: head and neck	Additional description: Swelling of the head and neck area		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Edema: limb	Additional description: Swelling of the arms and legs		
subjects affected / exposed	146 / 3297 (4.43%)		
occurrences (all)	156		
Edema: trunk/genital	Additional description: Swelling of the trunk of the body or genitals		
subjects affected / exposed	26 / 3297 (0.79%)		
occurrences (all)	30		
Lymphatics - Other			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Peripheral arterial ischemia	Additional description: Disorder of arteries causing inadequate blood supply to extremities.		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Phlebitis (including superficial thrombosis)	Additional description: Inflammation of a vein blood clot		

subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Thrombosis/thrombus/embolism	Additional description: Formation or presence of a blood clot inside a blood vessel.		
subjects affected / exposed	11 / 3297 (0.33%)		
occurrences (all)	16		
Vascular - Other			
subjects affected / exposed	12 / 3297 (0.36%)		
occurrences (all)	13		
Vessel injury-artery	Additional description: Damage to a blood vessel in the neck		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Vessel injury-vein	Additional description: Damage to a blood vessel that carries blood back from legs		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Surgical and medical procedures			
Arm intra-operative injury	Additional description: Damage to a part of the body during an operation: Arm		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Constitutional Symptoms - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 3297 (0.42%)		
occurrences (all)	14		
Fatigue	Additional description: asthenia, lethargy, malaise/ fatigue, tiredness, asthenia		
alternative assessment type: Non-systematic			
subjects affected / exposed	340 / 3297 (10.31%)		
occurrences (all)	351		
Fever	Additional description: Fever (in the absence of neutropenia, where neutropenia is defined as ANC <1.0 x 10e9/L)		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Rigors/chills	Additional description: Chills, shivering		
alternative assessment type: Non-systematic			

subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Sweating (diaphoresis)	Additional description: Abnormal sweating		
alternative assessment type: Non-systematic			
subjects affected / exposed	76 / 3297 (2.31%)		
occurrences (all)	78		
Head pain			
subjects affected / exposed	100 / 3297 (3.03%)		
occurrences (all)	102		
Pain			
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	11		
Scalp pain			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Pain - Other			
subjects affected / exposed	9 / 3297 (0.27%)		
occurrences (all)	9		
Immune system disorders			
Allergic reaction	Additional description: Allergic reaction/hypersensitivity (including drug fever)		
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 3297 (0.52%)		
occurrences (all)	17		
Allergic rhinitis	Additional description: Allergic rhinitis (including sneezing, nasal stuffiness, postnasal drip); Stuffy or runny nose, sneezing		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Allergy/Immunology - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	7		
Reproductive system and breast disorders			
Breast pain			

subjects affected / exposed	67 / 3297 (2.03%)		
occurrences (all)	70		
Vagina pain			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Breast function/lactation	Additional description: Change in ability to produce milk from breasts		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Breast volume/hypoplasia	Additional description: Decreased size of breast tissue		
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Irregular menses (change from baseline)	Additional description: Irregular menstrual periods		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Libido	Additional description: Decrease in sexual desire		
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	10		
Orgasmic dysfunction			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Sexual/Reproductive Function - Other			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Vaginal discharge (non-infectious)			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Vaginal dryness			
subjects affected / exposed	45 / 3297 (1.36%)		
occurrences (all)	46		
Vaginal mucositis	Additional description: Irritation or sores of the lining of the vagina		
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	7		
Respiratory, thoracic and mediastinal disorders			

Pain in the membranes that line the chest cavity and cover the lungs subjects affected / exposed occurrences (all)	1 / 3297 (0.03%) 1		
Adult Respiratory Distress Syndrome	Additional description: Severe life- threatening damage to the lungs which can lead to fluid in the lungs		
subjects affected / exposed occurrences (all)	1 / 3297 (0.03%) 1		
Cough subjects affected / exposed occurrences (all)	43 / 3297 (1.30%) 43		
Dyspnea	Additional description: Shortness of breath		
subjects affected / exposed occurrences (all)	82 / 3297 (2.49%) 84		
Hypoxia	Additional description: Condition in which there is a decrease in the oxygen supply to a tissue		
subjects affected / exposed occurrences (all)	1 / 3297 (0.03%) 1		
Blockage of an air tube from the windpipe to the lungs subjects affected / exposed occurrences (all)	8 / 3297 (0.24%) 9		
Blockage or narrowing in the throat subjects affected / exposed occurrences (all)	1 / 3297 (0.03%) 1		
Blockage or narrowing of the windpipe subjects affected / exposed occurrences (all)	1 / 3297 (0.03%) 1		
Pleural effusion (non-malignant)	Additional description: Collection of fluid between the thin layers of tissue (pleura) lining the lung and the wall of the chest cavity		
subjects affected / exposed occurrences (all)	2 / 3297 (0.06%) 2		
Pneumonitis/pulmonary infiltrates	Additional description: Inflammation of the lungs		
subjects affected / exposed occurrences (all)	14 / 3297 (0.42%) 16		
Pulmonary fibrosis (radiographic changes)	Additional description: Scarring of the lungs that can affect your ability to breathe and may make you short of breath		
subjects affected / exposed occurrences (all)	2 / 3297 (0.06%) 2		

Pulmonary/Upper Respiratory - Other			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Voice changes/dysarthria	Additional description: e.g., hoarseness, loss or alteration in voice, laryngitis		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Psychiatric disorders			
Insomnia	Additional description: Difficulty sleeping or falling asleep		
alternative assessment type: Non-systematic			
subjects affected / exposed	251 / 3297 (7.61%)		
occurrences (all)	259		
Memory impairment			
subjects affected / exposed	21 / 3297 (0.64%)		
occurrences (all)	21		
Mental status	Additional description: Changes in mental status		
subjects affected / exposed	21 / 3297 (0.64%)		
occurrences (all)	21		
Agitation			
subjects affected / exposed	11 / 3297 (0.33%)		
occurrences (all)	11		
Anxiety			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences (all)	17		
Depression			
subjects affected / exposed	135 / 3297 (4.09%)		
occurrences (all)	140		
Personality/behavioral	Additional description: Personality changes		
subjects affected / exposed	25 / 3297 (0.76%)		
occurrences (all)	25		
Investigations			
ALT, SGPT (serum glutamic pyruvic transaminase)	Additional description: Abnormal liver enzyme level		
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	10		
Bilirubin (hyperbilirubinemia)	Additional description: Abnormal level of bilirubin in the blood. Bilirubin is a bile pigment found in the liver.		

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Calcium, serum-low (hypocalcemia)	Additional description: Decreased blood calcium level		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Cholesterol, serum-high (hypercholesteremia)	Additional description: Increased blood cholesterol level		
subjects affected / exposed	27 / 3297 (0.82%)		
occurrences (all)	27		
Creatinine	Additional description: Increased blood level of creatinine, a substance normally eliminated by the kidneys into the urine		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
GGT (gamma-Glutamyl transpeptidase)	Additional description: Abnormal blood level of liver enzyme		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Glucose, serum-high (hyperglycemia)	Additional description: High blood sugar level		
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Potassium, serum-low (hypokalemia)	Additional description: Decreased blood potassium level		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Uric acid, serum-high (hyperuricemia)	Additional description: Increased blood level of uric acid, a waste material from food digestion		
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Cardiac disorders			
Cardiac Arrhythmia - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	8 / 3297 (0.24%)		
occurrences (all)	8		
Conduction	Additional description: regular heart beat		
abnormality/atrioventricular heart block			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Palpitations	Additional description: Feeling the heart racing 'skipping a beat' pounding		

alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences (all)	15		
Supraventricular and nodal arrhythmia, Fast heart beat			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Supraventricular and nodal arrhythmia; Irregular heart beat			
alternative assessment type: Non-systematic			
subjects affected / exposed	7 / 3297 (0.21%)		
occurrences (all)	7		
Vasovagal episode	Additional description: Sudden drop in blood pressure that may cause fainting		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Ventricular arrhythmia	Additional description: Irregular heart beat		
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences (all)	15		
Cardiac General - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Cardiac ischemia/infarction			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	7		
Hypertension	Additional description: High blood pressure		
alternative assessment type: Non-systematic			
subjects affected / exposed	79 / 3297 (2.40%)		
occurrences (all)	85		
Hypotension	Additional description: Low blood pressure		
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Left ventricular systolic dysfunction	Additional description: Decrease in heart's ability to pump blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	7		
Restrictive cardiomyopathy	Additional description: Decrease in heart's ability to pump blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Right ventricular dysfunction (cor pulmonale)	Additional description: Decrease in heart's ability to pump blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Valvular heart disease	Additional description: Abnormal heart valves		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	6		
Chest pain			
subjects affected / exposed	19 / 3297 (0.58%)		
occurrences (all)	19		
Chest wall pain			
subjects affected / exposed	16 / 3297 (0.49%)		
occurrences (all)	16		
Nervous system disorders			
Apnea	Additional description: Sudden stopping of breathing		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Arachnoiditis/meningismus/radiculitis	Additional description: Inflammation of the linings of the brain		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
CNS cerebrovascular ischemia	Additional description: Decrease in blood flow to the brain		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Cognitive disturbance	Additional description: Disturbances in thinking patterns		

subjects affected / exposed	26 / 3297 (0.79%)		
occurrences (all)	27		
Confusion			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	3		
Dizziness			
subjects affected / exposed	113 / 3297 (3.43%)		
occurrences (all)	123		
Extrapyramidal/involuntary movement/restlessness	Additional description: Restless movements caused by abnormalities in the part of the brain that coordinates movement		
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Neurology - Other			
subjects affected / exposed	30 / 3297 (0.91%)		
occurrences (all)	30		
Neuropathy: cranial, olfactory	Additional description: Abnormal function of the nerve responsible for the sense of smell		
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Neuropathy: cranial, motory	Additional description: Abnormal function of the nerve that controls facial expression		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Neuropathy: motor	Additional description: Weakness or loss of function caused by damage to nerves		
subjects affected / exposed	7 / 3297 (0.21%)		
occurrences (all)	7		
Neuropathy: sensory	Additional description: Condition of the nervous system that causes numbness, tingling, burning.		
subjects affected / exposed	183 / 3297 (5.55%)		
occurrences (all)	198		
Speech impairment (e.g., dysphasia or aphasia)	Additional description: Speech problems		
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Syncope (fainting)			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Tremor			

subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Nerve pain			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Blood and lymphatic system disorders			
Hemoglobin	Additional description: Decrease in a part of red blood cells that carries oxygen in the body		
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Leukocytes (total WBC)	Additional description: Decreased total number of white blood cells		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 3297 (0.27%)		
occurrences (all)	10		
Platelets	Additional description: Decreased number of blood cells that help to clot blood		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	6		
Ear and labyrinth disorders			
Auditory/Ear - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	3		
Tinnitus			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Outer ear pain			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Eye disorders			
Cataract	Additional description: Condition in which the lens of the eye becomes cloudy		
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	7		
Dry eye syndrome			

subjects affected / exposed	14 / 3297 (0.42%)		
occurrences (all)	14		
Glaucoma	Additional description: High pressure within the eyeball		
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	6		
Ocular surface disease	Additional description: Damage to the surface of the eye		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Ocular/Visual - Other			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	6		
Optic disc edema	Additional description: Swelling of the nerve in the back of the eye which is responsible for vision		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Proptosis/enophthalmos	Additional description: When the eye sticks out further than normal position sunken eyeball		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Retinal detachment	Additional description: Separation of the retina from its connection at the back of the eye		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Retinopathy	Additional description: Damage to the eye that decreases vision		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Blurred Vision			
subjects affected / exposed	25 / 3297 (0.76%)		
occurrences (all)	26		
Vision-flashing lights/floaters	Additional description: Seeing flashing lights or floaters		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Vitreous hemorrhage			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Watery eye (epiphora, tearing)			

subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Eye pain			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Gastrointestinal disorders			
Anorexia	Additional description: Loss of appetite		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 3297 (0.27%)		
occurrences (all)	9		
Ascites (non-malignant)	Additional description: Fluid collection in the abdomen		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Colitis	Additional description: Inflammation of the colon		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	27 / 3297 (0.82%)		
occurrences (all)	28		
Dehydration			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Dental: periodontal disease	Additional description: Gum disease		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Dental: teeth	Additional description: Abnormal teeth		
subjects affected / exposed	7 / 3297 (0.21%)		
occurrences (all)	7		
Diarrhoea			

subjects affected / exposed	33 / 3297 (1.00%)		
occurrences (all)	33		
Distension/bloating, Abdominal	Additional description: Feeling of fullness and tightness in the belly		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Dry mouth	Additional description: Dry mouth/salivary gland (xerostomia)		
subjects affected / exposed	32 / 3297 (0.97%)		
occurrences (all)	32		
Dysphagia (difficulty swallowing)			
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	10		
Esophagitis	Additional description: Inflammation of the esophagus (the tube that carries food from the mouth to the stomach).		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Fistula, GI	Additional description: An abnormal connection between large intestine and another organ		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Flatulence	Additional description: Too much gas passed from the rectum		
subjects affected / exposed	8 / 3297 (0.24%)		
occurrences (all)	8		
Gastritis (including bile reflux gastritis)	Additional description: Inflammation of the lining of the stomach		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Gastrointestinal - Other			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences (all)	20		
Heartburn/dyspepsia			
subjects affected / exposed	22 / 3297 (0.67%)		
occurrences (all)	23		
Hemorrhoids			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Mucositis/stomatitis, oral	Additional description: Irritation or sores in the lining of the mouth		

subjects affected / exposed	17 / 3297 (0.52%)		
occurrences (all)	17		
Mucositis/stomatitis, gastric	Additional description: Irritation or sores in the lining of the stomach		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	87 / 3297 (2.64%)		
occurrences (all)	89		
Salivary gland changes/saliva	Additional description: Changes in saliva		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Taste alteration			
subjects affected / exposed	14 / 3297 (0.42%)		
occurrences (all)	14		
Ulcer, intestinal	Additional description: Ulcer of small intestine		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Ulcer, gastric	Additional description: Ulcer of the stomach		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	13 / 3297 (0.39%)		
occurrences (all)	14		
Bleeding of the mouth			
subjects affected / exposed	8 / 3297 (0.24%)		
occurrences (all)	8		
Belly pain			
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	10		
Mouth pain			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Pelvis pain			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences (all)	15		
Stomach pain			

subjects affected / exposed	32 / 3297 (0.97%)		
occurrences (all)	34		
Tooth or gum pain			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Hepatobiliary disorders			
Cholecystitis	Additional description: Inflammation of the gallbladder		
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Hepatobiliary/Pancreas - Other			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Pancreas, exocrine enzyme deficiency	Additional description: Decrease in enzymes from the pancreas that help digest food		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Pancreatitis	Additional description: Inflammation of the pancreas		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Gallbladder pain			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Skin and subcutaneous tissue disorders			
Atrophy, skin	Additional description: Thinning of skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Atrophy, subcutaneous fat	Additional description: Loss of fat under the skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Bruising	Additional description: Bruising (in absence of Grade 3 or 4 thrombocytopenia)		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Burn			

alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Dermatology/Skin - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	90 / 3297 (2.73%)		
occurrences (all)	91		
Dry skin			
alternative assessment type: Non-systematic			
subjects affected / exposed	44 / 3297 (1.33%)		
occurrences (all)	45		
Flushing	Additional description: Sudden reddening of the face and/or neck		
alternative assessment type: Non-systematic			
subjects affected / exposed	14 / 3297 (0.42%)		
occurrences (all)	14		
Hair loss	Additional description: Hair loss/alopecia (scalp or body)		
alternative assessment type: Non-systematic			
subjects affected / exposed	191 / 3297 (5.79%)		
occurrences (all)	193		
Hyperpigmentation			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Induration/fibrosis	Additional description: skin and subcutaneous tissue; hardening of the skin and connective tissues		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Nail changes			
alternative assessment type: Non-systematic			
subjects affected / exposed	32 / 3297 (0.97%)		
occurrences (all)	33		
Pruritus/itching			
alternative assessment type: Non-systematic			

subjects affected / exposed	37 / 3297 (1.12%)		
occurrences (all)	37		
Rash/desquamation	Additional description: Rash flaking or sloughing of skin		
alternative assessment type: Non-systematic			
subjects affected / exposed	51 / 3297 (1.55%)		
occurrences (all)	49		
Rash: acne/acneiform	Additional description: Acne pimples		
alternative assessment type: Non-systematic			
subjects affected / exposed	9 / 3297 (0.27%)		
occurrences (all)	9		
Rash: dermatitis associated with radiation	Additional description: Redness, flaking or sloughing of skin in the radiation treatment area		
alternative assessment type: Non-systematic			
subjects affected / exposed	60 / 3297 (1.82%)		
occurrences (all)	62		
Rash: hand-foot skin reaction	Additional description: Inflammation of the skin on the palms of the hands and soles of the feet		
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Skin breakdown/decubitus ulcer			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Telangiectasia	Additional description: Enlargement of small blood vessels near the surface of the skin, causing redness of the skin or lining of the nose or mouth		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Ulceration	Additional description: Irritation or destruction of skin or other body tissues.		
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Urticaria (hives, welts, wheals)			
alternative assessment type: Non-systematic			

subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Wound complication, non-infectious alternative assessment type: Non-systematic			
subjects affected / exposed	13 / 3297 (0.39%)		
occurrences (all)	15		
Skin pain			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Renal and urinary disorders			
Pain of tube draining bladder			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Cystitis	Additional description: Inflammation or infection of the bladder		
subjects affected / exposed	46 / 3297 (1.40%)		
occurrences (all)	51		
Incontinence, urinary	Additional description: Inability to hold urine in the bladder		
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Obstruction, GU	Additional description: Blockage of tube between kidney and bladder		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Renal failure	Additional description: Kidney failure		
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	4		
Renal/Genitourinary - Other			
subjects affected / exposed	8 / 3297 (0.24%)		
occurrences (all)	18		
Urinary frequency/urgency	Additional description: Increased need to urinate		
subjects affected / exposed	18 / 3297 (0.55%)		
occurrences (all)	18		
Urine color change			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Endocrine disorders			

Endocrine - Other			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Feminization of male	Additional description: The development of female physical characteristics in males		
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Hot flashes			
alternative assessment type: Non-systematic			
subjects affected / exposed	602 / 3297 (18.26%)		
occurrences (all)	623		
Masculinization of female	Additional description: The development of male physical characteristics in females		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Pancreatic endocrine: glucose intolerance	Additional description: Abnormal control of blood sugar level		
alternative assessment type: Non-systematic			
subjects affected / exposed	15 / 3297 (0.45%)		
occurrences (all)	15		
Thyroid function, high (hyperthyroidism, thyrotoxicosis)	Additional description: Abnormally high thyroid function		
alternative assessment type: Non-systematic			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Thyroid function, low (hypothyroidism)	Additional description: Abnormally low thyroid function		
alternative assessment type: Non-systematic			
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	10		
Musculoskeletal and connective tissue disorders			
Arthritis (non-septic)	Additional description: Arthritis		
subjects affected / exposed	28 / 3297 (0.85%)		
occurrences (all)	29		
Bone: spine-scoliosi	Additional description: Abnormal curvature of the spine		

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Cervical spine-range of motion	Additional description: Stiff neck		
subjects affected / exposed	7 / 3297 (0.21%)		
occurrences (all)	7		
Extremity-lower (gait/walking)	Additional description: Limp		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Fracture	Additional description: A broken bone		
subjects affected / exposed	37 / 3297 (1.12%)		
occurrences (all)	39		
Joint-function	Additional description: Joint stiffness		
subjects affected / exposed	125 / 3297 (3.79%)		
occurrences (all)	133		
Lumbar spine-range of motion	Additional description: Stiff lower back		
subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Muscle weakness, generalized or specific area	Additional description: Muscle weakness, generalized or specific area (not due to neuropathy); Muscle weakness of arms		
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Muscle weakness of legs	Additional description: Muscle weakness, generalized or specific area (not due to neuropathy)		
subjects affected / exposed	13 / 3297 (0.39%)		
occurrences (all)	13		
Muscle weakness of the whole body	Additional description: Muscle weakness, generalized or specific area (not due to neuropathy)		
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Musculoskeletal/Soft Tissue - Other			
subjects affected / exposed	97 / 3297 (2.94%)		
occurrences (all)	104		
Osteoporosis	Additional description: Bone thinning		
subjects affected / exposed	140 / 3297 (4.25%)		
occurrences (all)	142		
Seroma	Additional description: Abnormal fluid collection in a tissue or organ		

subjects affected / exposed	16 / 3297 (0.49%)		
occurrences (all)	17		
Death of tissue of the arms			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Death of tissue of the chest			
subjects affected / exposed	5 / 3297 (0.15%)		
occurrences (all)	5		
Death of tissue of the pelvis	Additional description: Soft tissue necrosis		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	111 / 3297 (3.37%)		
occurrences (all)	120		
Bone pain			
subjects affected / exposed	388 / 3297 (11.77%)		
occurrences (all)	401		
Buttock pain			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Joint pain			
subjects affected / exposed	942 / 3297 (28.57%)		
occurrences (all)	1051		
Leg pain			
subjects affected / exposed	192 / 3297 (5.82%)		
occurrences (all)	208		
Muscle pain			
subjects affected / exposed	211 / 3297 (6.40%)		
occurrences (all)	219		
Neck pain			
subjects affected / exposed	7 / 3297 (0.21%)		
occurrences (all)	7		
Infections and infestations			
Colitis, infectious	Additional description: e.g., Clostridium difficile		

subjects affected / exposed	4 / 3297 (0.12%)		
occurrences (all)	4		
Infection - Other			
subjects affected / exposed	10 / 3297 (0.30%)		
occurrences (all)	10		
Infection of the uterus	Additional description: Infection with normal ANC or Grade 1 or 2 neutrophils		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Bladder infection	Additional description: Infection with unknown ANC		
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Bone infection			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Catheter infection			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection in the throat			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of an air tube from the windpipe to the lungs			
subjects affected / exposed	16 / 3297 (0.49%)		
occurrences (all)	17		
Infection of body tissue			
subjects affected / exposed	8 / 3297 (0.24%)		
occurrences (all)	8		
Infection of clear front part of the eyeball			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of lining of the inner surface of the eyelid and the eyeball			
subjects affected / exposed	2 / 3297 (0.06%)		
occurrences (all)	2		
Infection of lymph node			

subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the belly			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Infection of the eye			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the joint			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Infection of the kidney			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the lung (pneumonia)			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the muscle			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	2		
Infection of the nails			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the outer ear			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the skin			
subjects affected / exposed	47 / 3297 (1.43%)		
occurrences (all)	52		
Infection of the small intestine			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the stomach			
subjects affected / exposed	7 / 3297 (0.21%)		
occurrences (all)	8		
Infection of the tissue that lines body			

parts			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Infection of the upper respiratory tract			
subjects affected / exposed	16 / 3297 (0.49%)		
occurrences (all)	17		
Infection of the voice box			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Large intestine infection			
subjects affected / exposed	6 / 3297 (0.18%)		
occurrences (all)	6		
Tooth infection			
subjects affected / exposed	1 / 3297 (0.03%)		
occurrences (all)	1		
Flu-like syndrome	Additional description: Flu-type symptoms		
subjects affected / exposed	27 / 3297 (0.82%)		
occurrences (all)	28		
Metabolism and nutrition disorders			
Obesity	Additional description: More body fat than normal		
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 3297 (0.09%)		
occurrences (all)	3		
Weight gain			
alternative assessment type: Non-systematic			
subjects affected / exposed	124 / 3297 (3.76%)		
occurrences (all)	125		
Weight loss			
alternative assessment type: Non-systematic			
subjects affected / exposed	17 / 3297 (0.52%)		
occurrences (all)	18		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 October 2009	Protocol Version 3. Planned number of patients was increased from 1000 to 3500. The recruitment period was prolonged until June 2010. The number of trial sites was increased to 220.
20 April 2010	Recruitment period was prolonged until September 2010. The protocol was amended to reflect the current SmPC of letrozole. The protocol was further amended to allow for enrollment of patients who had completed surgery irrespective of previous adjuvant chemotherapy.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported