



Clinical trial results:

PALbociclib CoLlaborative Adjuvant Study:

A randomized phase III trial of Palbociclib with standard adjuvant endocrine therapy versus standard adjuvant endocrine therapy alone for hormone receptor positive (HR+) / human epidermal growth factor receptor 2 (HER2)-negative early breast cancer

Summary

EudraCT number	2014-005181-30
Trial protocol	AT ES IE HU PT DE SE NL BE PL GB IT
Global end of trial date	

Results information

Result version number	v1 (current)
This version publication date	11 January 2022
First version publication date	11 January 2022

Trial information

Trial identification

Sponsor protocol code	AFT-05/ABCSG-42/BIG_14-03
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02513394
WHO universal trial number (UTN)	-
Other trial identifiers	IND number: 126003

Notes:

Sponsors

Sponsor organisation name	ABCSG GmbH
Sponsor organisation address	Nußdorfer Platz 8/12, Vienna, Austria, 1190
Public contact	Trial Office (Studienzentrale), Austrian Breast & Colorectal Cancer Study Group (ABCSG) , +43 14089230, info@abcsbg.at
Scientific contact	Prof. Michael Gnant , Austrian Breast & Colorectal Cancer Study Group (ABCSG) , +43 14089230, info@abcsbg.at

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	20 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 November 2020
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

To compare invasive disease-free survival (iDFS) for the combination of at least 5 years endocrine therapy and 2-year palbociclib treatment versus at least 5 years endocrine therapy alone in patients with histologically confirmed HR+/HER2- invasive early breast cancer (EBC).

Protection of trial subjects:

A dedicated IDMC was established to regularly review patient safety data and provide recommendations to the Steering Committee during the active treatment phase. In addition, dedicated Medical Monitors are assigned for ongoing support to safeguard patient safety and well being by providing immediate assistance on any clinical / medical questions. The study specific Informed Consent Forms include language on patient advocacy, available 24/7 contacts and patient cards were provided to participants, containing important contact details. During the COVID-19 pandemic, additional measures have been set-up to allow for high quality patient care despite fewer on-site visits or restrictions in clinic routine (e.g. direct IP shipments to patients where needed, safety assessments by the sponsors, study PIs and drug provider to provide further guidance on assessments, vaccinations etc.).

Background therapy:

Background therapy (endocrine therapy) as NIMP:

According to the EU Guidance for IMP & NIMP (Annex 2, section 2a) the agents to be used are authorized products and a particular brand is not defined in the study protocol. Locally obtained commercial supply will be administered to the patients at the discretion of the principal investigator as well as according to standard institutional or regional practice.

- Tamoxifen
- Non-steroidal aromatase-inhibitors (anastrozole, letrozole)
- Steroidal aromatase inhibitor (exemestane)
- LHRH agonists in combination with tamoxifen or AI

No additional information is required.

Evidence for comparator:

Yes

Actual start date of recruitment	01 September 2015
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	8 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 27
Country: Number of subjects enrolled	Poland: 115
Country: Number of subjects enrolled	Portugal: 84
Country: Number of subjects enrolled	Spain: 1136
Country: Number of subjects enrolled	Sweden: 43
Country: Number of subjects enrolled	United Kingdom: 213

Country: Number of subjects enrolled	Austria: 479
Country: Number of subjects enrolled	Belgium: 134
Country: Number of subjects enrolled	Germany: 138
Country: Number of subjects enrolled	Hungary: 173
Country: Number of subjects enrolled	Ireland: 148
Country: Number of subjects enrolled	Italy: 117
Country: Number of subjects enrolled	Australia: 484
Country: Number of subjects enrolled	Canada: 194
Country: Number of subjects enrolled	Israel: 51
Country: Number of subjects enrolled	Japan: 45
Country: Number of subjects enrolled	Korea, Republic of: 33
Country: Number of subjects enrolled	Mexico: 37
Country: Number of subjects enrolled	Switzerland: 150
Country: Number of subjects enrolled	Taiwan: 42
Country: Number of subjects enrolled	United States: 2845
Worldwide total number of subjects	6688
EEA total number of subjects	2594

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)	5421
From 65 to 84 years	1251
85 years and over	16

Subject disposition

Recruitment

Recruitment details:

Recruitment period started on 1-Sep-2015 and a global enrollment of 4.600 patients within 3 years was planned. Throughout the study, sample size was increased to 5.600 patients and the recruitment period concluded on 30-Nov-2018. IxRS patient management system was used and patients were randomized 1:1 into one of the two treatment arms.

Pre-assignment

Screening details:

Eligibility was carefully assessed by study sites, based on the protocol specified inclusion and exclusion criteria, local screening logs were kept at study sites. Patients were entered into the IxRS system upon screening (to allow for patient ID assignment prior to randomization, in order to label and track the mandatory biospecimen accordingly).

Pre-assignment period milestones

Number of subjects started	6688
Number of subjects completed	5761

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Consent withdrawn by subject: 35
Reason: Number of subjects	declined to participate: 259
Reason: Number of subjects	not meeting inclusion criteria: 466
Reason: Number of subjects	Other: 167

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Palbociclib plus endocrine therapy

Arm description:

palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy for a duration of at least 5 years

Arm type	Experimental
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991-00
Other name	Ibrance, PD-332,991
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

125mg orally once daily, day 1 to day 21 followed by 7 days off treatment in a 28-day cycle for a total of 2 years

Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991-00
Other name	Ibrance, PD-332,991
Pharmaceutical forms	Capsule, hard

Routes of administration	Oral use
Dosage and administration details:	
100mg orally once daily, day 1 to day 21 followed by 7 days off. Only be administered in case of first dose reduction (Level -1) from 125mg to 100mg due to toxicity, dose interruption or cycle delay when treatment is resumed.	
Investigational medicinal product name	Palbociclib
Investigational medicinal product code	PD-0332991-00
Other name	Ibrance, PD-332,991
Pharmaceutical forms	Capsule, hard
Routes of administration	Oral use
Dosage and administration details:	
75mg orally once daily, day 1 to day 21 followed by 7 days off. Only be administered in case of second dose reduction (Level -2) from initially 125mg to 100mg to final 75mg due to toxicity, dose interruption or cycle delay when treatment is resumed.	
Arm title	Endocrine therapy
Arm description:	
standard adjuvant endocrine therapy for a duration of at least 5 years	
Arm type	NIMP background treatment
No investigational medicinal product assigned in this arm	

Number of subjects in period 1^[1]	Palbociclib plus endocrine therapy	Endocrine therapy
Started	2884	2877
Completed	2475	2507
Not completed	409	370
Adverse event, serious fatal	100	76
Consent withdrawn by subject	289	285
Other	13	7
Lost to follow-up	7	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Several patients started (hence, were enrolled) but didn't complete the pre-assignment period due to reasons given in the pre-assignment section.

Baseline characteristics

Reporting groups

Reporting group title	Palbociclib plus endocrine therapy
Reporting group description: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy for a duration of at least 5 years	
Reporting group title	Endocrine therapy
Reporting group description: standard adjuvant endocrine therapy for a duration of at least 5 years	

Reporting group values	Palbociclib plus endocrine therapy	Endocrine therapy	Total
Number of subjects	2884	2877	5761
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	2397	2385	4782
From 65-84 years	482	488	970
85 years and over	5	4	9
Age continuous			
Units: years			
median	52	52	
full range (min-max)	25 to 90	22 to 85	-
Gender categorical			
Units: Subjects			
Female	2867	2858	5725
Male	17	19	36
Anatomic stage			
Units: Subjects			
I/IIA	513	519	1032
IIB/III	2370	2358	4728
Unknown	1	0	1
T-stage			
Assessed by pathological staging or by clinical staging if pre-operative therapy was given with the higher stage presented in this table			
Units: Subjects			
T0/T1/Tis/TX	558	501	1059
T2	1603	1636	3239
T3/T4	722	740	1462
Unknown	1	0	1
N-stage			
Units: Subjects			

N0	365	385	750
N1	1431	1411	2842
N2	700	709	1409
N3	386	372	758
NX	1	0	1
Unknown	1	0	1
Tumor grade			
Units: Subjects			
G1/G2	1926	1971	3897
G3	836	769	1605
GX	118	137	255
Unknown	4	0	4
Neo/adjuvant chemotherapy			
Units: Subjects			
No	499	507	1006
Yes	2384	2370	4754
Unknown	1	0	1
Menopausal status			
Units: Subjects			
Postmenopausal	1562	1534	3096
Premenopausal (including perimenopausal)	1303	1323	2626
Not applicable (male patient)	17	19	36
Unknown	2	1	3

End points

End points reporting groups

Reporting group title	Palbociclib plus endocrine therapy
Reporting group description: palbociclib at a dose of 125 mg orally once daily, Day 1 to Day 21 followed by 7 days off treatment in a 28-day cycle for a total duration of 2 years, in addition to standard adjuvant endocrine therapy for a duration of at least 5 years	
Reporting group title	Endocrine therapy
Reporting group description: standard adjuvant endocrine therapy for a duration of at least 5 years	
Subject analysis set title	ITT
Subject analysis set type	Intention-to-treat
Subject analysis set description: The ITT population was comprised of all randomized patients, including those who did not start palbociclib or endocrine treatment. This population provided the basis for the main efficacy analyses. Randomized patients consisted of all patients who have given their written informed consent and for whom there was confirmation of successful allocation of a randomization number through the IxRS. Patients who withdrew informed consent for all follow-up and for all data collected until the time of withdrawal were excluded from all analyses. Patients were analysed according to the treatment group to which they were randomized.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description: For the purposes of evaluating and monitoring AEs and patient safety, the SAF population was defined as all randomized patients, excluding those who did not start palbociclib or endocrine treatment, i.e. as-treated. Patients were analysed according to the treatment actually received. Randomized patients who wrongly received IP palbociclib at any time point were included in the SAF population as palbociclib patients (Arm A). Patients randomized to the palbociclib arm, who never received palbociclib, but received endocrine therapy, were included in the SAF population as endocrine therapy patients (Arm B). Randomized patients for whom it is unclear (due to missing or inconsistent data entry) whether they took treatment were included in the SAF population as treated according to their randomized arm.	

Primary: iDFS

End point title	iDFS
End point description: The primary endpoint was invasive disease free survival (iDFS), using STEEP criteria defined as the time from randomization to the date of first event (plus one day): local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence, second primary invasive cancer of non-breast origin or death from any cause. Surviving patients who are event-free were censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first. Survival rate estimates at 4 years with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.	
End point type	Primary
End point timeframe: Until the date of awareness of the 469th event	

End point values	Palbociclib plus endocrine therapy	Endocrine therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2884	2877		
Units: percent				
number (confidence interval 95%)	84.2 (81.0 to	84.5 (81.4 to		

Statistical analyses

Statistical analysis title	Primary endpoint analysis
Statistical analysis description:	
Results were compared between treatment arms by Log-rank tests. Hazard ratios with 2-sided 95% CIs were calculated via stratified Cox proportional hazards regression models.	
Comparison groups	Palbociclib plus endocrine therapy v Endocrine therapy
Number of subjects included in analysis	5761
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.65
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.96
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.81
upper limit	1.14

Secondary: iBCFS

End point title	iBCFS
End point description:	
Invasive breast cancer free survival (iBCFS) - hence, iDFS excluding second primary invasive cancers of non-breast origin - was defined as the time from randomization to the date of the first event (plus one day): local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer, distant recurrence or death from any cause. Patients with second primary invasive cancers of non-breast origin will continue to be followed for iDFS. Surviving patients who are event-free will be censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first. Survival rate estimates at 4 years with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.	
End point type	Secondary
End point timeframe:	
Until the date of awareness of the 469th event	

End point values	Palbociclib plus endocrine therapy	Endocrine therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2884	2877		
Units: percent				
number (confidence interval 95%)	85.4 (82.1 to 88.1)	86.0 (82.9 to 88.6)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - iBCFS
Statistical analysis description: Hazard ratios with 2-sided 95% CIs were calculated via stratified Cox proportional hazards regression models.	
Comparison groups	Palbociclib plus endocrine therapy v Endocrine therapy
Number of subjects included in analysis	5761
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.82
upper limit	1.19

Secondary: LRRFS

End point title	LRRFS
End point description: Loco-regional recurrence free survival (LRRFS), was defined as the time from randomization to the date of the first event (plus one day): local/regional invasive ipsilateral recurrence, contralateral invasive breast cancer or death from any cause. Patients with second primary invasive cancers of non-breast origin or distant recurrence were censored at the date of diagnosis. Surviving patients who were event-free were censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first. Survival rate estimates at 4 years with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.	
End point type	Secondary
End point timeframe: Until the date of awareness of the 469th event	

End point values	Palbociclib plus endocrine therapy	Endocrine therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2884	2877		
Units: percent				
number (confidence interval 95%)	96.8 (94.4 to 98.2)	95.4 (92.6 to 97.2)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - LRRFS
Statistical analysis description: Hazard ratios with 2-sided 95% CIs were calculated via stratified Cox proportional hazards regression models.	
Comparison groups	Palbociclib plus endocrine therapy v Endocrine therapy
Number of subjects included in analysis	5761
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	0.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.23

Secondary: DRFS

End point title	DRFS
End point description: Distant recurrence free survival (DRFS), was defined according to STEEP criteria as the time from randomization to the date of the first event: distant recurrence or death from any cause. Patients with a locoregional recurrence, contralateral invasive breast cancer or second primary invasive cancer of non-breast origin were continued to be followed for DRFS. Surviving patients who were event-free were censored at: the date of last disease assessment, or withdrawal of consent to be followed, whichever occurs first. Survival rate estimates at 4 years with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.	
End point type	Secondary
End point timeframe: Until the date of awareness of the 469th event	

End point values	Palbociclib plus endocrine therapy	Endocrine therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2884	2877		
Units: percent				
number (confidence interval 95%)	86.2 (82.9 to 88.8)	87.8 (84.9 to 90.2)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - DRFS
Statistical analysis description: Hazard ratios with 2-sided 95% CIs were calculated via stratified Cox proportional hazards regression models.	
Comparison groups	Palbociclib plus endocrine therapy v Endocrine therapy
Number of subjects included in analysis	5761
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.87
upper limit	1.28

Secondary: OS

End point title	OS
End point description: Overall survival (OS), was defined according to STEEP criteria as the composite of: death from any cause. The time period between randomization and death from any cause was observed. Surviving patients who were event-free were censored at: the date of last contact (including patient's status and patient's end of study information) or withdrawal of consent to be followed, whichever occurs first. Survival rate estimates at 4 years with 2-sided 95% confidence intervals were calculated by Kaplan-Meier method.	
End point type	Secondary
End point timeframe: Until the date of awareness of the 469th event	

End point values	Palbociclib plus endocrine therapy	Endocrine therapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	2884	2877		
Units: percent				
number (confidence interval 95%)	93.8 (91.9 to 95.3)	95.2 (93.2 to 96.6)		

Statistical analyses

Statistical analysis title	Secondary endpoint analysis - OS
Statistical analysis description: Hazard ratios with 2-sided 95% CIs were calculated via stratified Cox proportional hazards regression models.	
Comparison groups	Palbociclib plus endocrine therapy v Endocrine therapy
Number of subjects included in analysis	5761
Analysis specification	Pre-specified
Analysis type	other
Parameter estimate	Hazard ratio (HR)
Point estimate	1.32
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.78

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Start: date of informed consent form signature;

End: 30 to 42 days after a patients' final treatment which is defined as the end of the Treatment Phase of the study. This would be approximately 2 years post-randomization, plus an additional 30-42 days.

Adverse event reporting additional description:

Screening Phase: only AEs deemed to be serious (SAEs) and related to protocol mandated and not routinely performed procedures have to be reported;

Follow up: SAEs deemed to be related to IP treatment have to be reported

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Palbociclib plus endocrine therapy
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Reporting group description: -

Reporting group title	Endocrine therapy
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Reporting group description: -

Serious adverse events	Palbociclib plus endocrine therapy	Endocrine therapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	369 / 2841 (12.99%)	229 / 2902 (7.89%)	
number of deaths (all causes)	100	76	
number of deaths resulting from adverse events	14	10	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Acute myeloid leukaemia	Additional description: Acute myeloid leukaemia		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute promyelocytic leukaemia	Additional description: Acute promyelocytic leukaemia		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas	Additional description: Adenocarcinoma pancreas		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

B-cell small lymphocytic lymphoma subjects affected / exposed	Additional description: B-cell small lymphocytic lymphoma		
	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Basal cell carcinoma subjects affected / exposed	Additional description: Basal cell carcinoma		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Benign breast neoplasm subjects affected / exposed	Additional description: Benign breast neoplasm		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Bladder neoplasm subjects affected / exposed	Additional description: Bladder neoplasm		
	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Breast cancer metastatic subjects affected / exposed	Additional description: Breast cancer metastatic		
	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
	0 / 3	0 / 1	
	0 / 2	0 / 1	
Breast cancer recurrent subjects affected / exposed	Additional description: Breast cancer recurrent		
	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
Cervix carcinoma subjects affected / exposed	Additional description: Cervix carcinoma		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Cervix carcinoma stage 0 subjects affected / exposed	Additional description: Cervix carcinoma stage 0		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Colon cancer	Additional description: Colon cancer		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endometrial adenocarcinoma	Additional description: Endometrial adenocarcinoma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intraductal papillary-mucinous carcinoma of pancreas	Additional description: Intraductal papillary-mucinous carcinoma of pancreas		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant	Additional description: Lung neoplasm malignant		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoma	Additional description: Lymphoma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoplasmacytoid lymphoma/immunocytoma	Additional description: Lymphoplasmacytoid lymphoma/immunocytoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma	Additional description: Malignant melanoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malignant melanoma in situ	Additional description: Malignant melanoma in situ		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastatic malignant melanoma	Additional description: Metastatic malignant melanoma		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ovarian adenoma	Additional description: Ovarian adenoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma	Additional description: Renal cell carcinoma		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salivary gland adenoma	Additional description: Salivary gland adenoma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Second primary malignancy	Additional description: Second primary malignancy		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell carcinoma	Additional description: Small cell carcinoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma	Additional description: Squamous cell carcinoma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Squamous cell carcinoma of the tongue	Additional description: Squamous cell carcinoma of the tongue		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thyroid adenoma	Additional description: Thyroid adenoma		

subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyoma	Additional description: Uterine leiomyoma		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine leiomyosarcoma	Additional description: Uterine leiomyosarcoma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uveal melanoma	Additional description: Uveal melanoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis	Additional description: Deep vein thrombosis		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Axillary vein thrombosis	Additional description: Axillary vein thrombosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Embolism	Additional description: Embolism		
subjects affected / exposed	4 / 2841 (0.14%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis	Additional description: Hypertensive crisis		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension	Additional description: Hypotension		

subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphoedema	Additional description: Lymphoedema		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia	Additional description: Peripheral ischaemia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Capsular contracture associated with breast implant	Additional description: Capsular contracture associated with breast implant		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest discomfort	Additional description: Chest discomfort		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain	Additional description: Chest pain		
subjects affected / exposed	3 / 2841 (0.11%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death	Additional description: Death		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Disease progression	Additional description: Disease progression		
subjects affected / exposed	1 / 2841 (0.04%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 1	0 / 2	
Disease recurrence	Additional description: Disease recurrence		

subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Dysplasia	Additional description: Dysplasia		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothermia	Additional description: Hypothermia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired healing	Additional description: Impaired healing		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Implant site fibrosis	Additional description: Implant site fibrosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infusion site extravasation	Additional description: Infusion site extravasation		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Non-cardiac chest pain	Additional description: Non-cardiac chest pain		

subjects affected / exposed	4 / 2841 (0.14%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	3 / 2841 (0.11%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction	Additional description: Anaphylactic reaction		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
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			
Adnexa uteri cyst	Additional description: Adnexa uteri cyst		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast calcifications	Additional description: Breast calcifications		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cyst	Additional description: Breast cyst		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast haematoma	Additional description: Breast haematoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast necrosis	Additional description: Breast necrosis		
subjects affected / exposed	1 / 2841 (0.04%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Breast swelling	Additional description: Breast swelling		
	subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Cervical cyst	Additional description: Cervical cyst		
	subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Endometrial disorder	Additional description: Endometrial disorder		
	subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Endometrial hyperplasia	Additional description: Endometrial hyperplasia		
	subjects affected / exposed	1 / 2841 (0.04%)	2 / 2902 (0.07%)
	occurrences causally related to treatment / all	0 / 1	0 / 2
	deaths causally related to treatment / all	0 / 0	0 / 0
Endometrial hypertrophy	Additional description: Endometrial hypertrophy		
	subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)
	occurrences causally related to treatment / all	0 / 1	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Endometrial thickening	Additional description: Endometrial thickening		
	subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Endometriosis	Additional description: Endometriosis		
	subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)
	occurrences causally related to treatment / all	0 / 0	0 / 1
	deaths causally related to treatment / all	0 / 0	0 / 0
Ovarian cyst	Additional description: Ovarian cyst		
	subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)
	occurrences causally related to treatment / all	0 / 1	0 / 0
	deaths causally related to treatment / all	0 / 0	0 / 0
Uterine polyp	Additional description: Uterine polyp		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Uterine prolapse	Additional description: Uterine prolapse		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haematoma	Additional description: Vaginal haematoma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal prolapse	Additional description: Vaginal prolapse		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome	Additional description: Acute respiratory distress syndrome		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma	Additional description: Asthma		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure	Additional description: Acute respiratory failure		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchospasm	Additional description: Bronchospasm		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma-chronic obstructive pulmonary disease overlap syndrome	Additional description: Asthma-chronic obstructive pulmonary disease overlap syndrome		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	2 / 2841 (0.07%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic obstructive pulmonary disease	Additional description: Chronic obstructive pulmonary disease		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypoxia	Additional description: Hypoxia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngeal stenosis	Additional description: Laryngeal stenosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleurisy	Additional description: Pleurisy		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion	Additional description: Pleural effusion		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism	Additional description: Pulmonary embolism		
subjects affected / exposed	13 / 2841 (0.46%)	5 / 2902 (0.17%)	
occurrences causally related to treatment / all	3 / 13	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonitis	Additional description: Pneumonitis		

subjects affected / exposed	4 / 2841 (0.14%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary fibrosis	Additional description: Pulmonary fibrosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage	Additional description: Pulmonary haemorrhage		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema	Additional description: Pulmonary oedema		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary sarcoidosis	Additional description: Pulmonary sarcoidosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory disorder	Additional description: Respiratory disorder		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure	Additional description: Respiratory failure		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord dysfunction	Additional description: Vocal cord dysfunction		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vocal cord polyp	Additional description: Vocal cord polyp		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders	Additional description: Alcohol use disorder		
Alcohol use disorder			
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol abuse	Additional description: Alcohol abuse		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol withdrawal syndrome	Additional description: Alcohol withdrawal syndrome		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety	Additional description: Anxiety		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state	Additional description: Confusional state		
subjects affected / exposed	3 / 2841 (0.11%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Delusion	Additional description: Delusion		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Depression	Additional description: Depression		
subjects affected / exposed	3 / 2841 (0.11%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug abuse	Additional description: Drug abuse		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mania	Additional description: Mania		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental disorder	Additional description: Mental disorder		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes	Additional description: Mental status changes		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Panic attack	Additional description: Panic attack		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paranoia	Additional description: Paranoia		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychotic disorder	Additional description: Psychotic disorder		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation	Additional description: Suicidal ideation		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicide attempt	Additional description: Suicide attempt		

subjects affected / exposed	0 / 2841 (0.00%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage	Additional description: Device breakage		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation	Additional description: Device dislocation		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device leakage	Additional description: Device leakage		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood bilirubin increased	Additional description: Blood bilirubin increased		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Liver function test increased	Additional description: Liver function test increased		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Troponin increased	Additional description: Troponin increased		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Abdominal wound dehiscence	Additional description: Abdominal wound dehiscence		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Alcohol poisoning	Additional description: Alcohol poisoning		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Animal bite	Additional description: Animal bite		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ankle fracture	Additional description: Ankle fracture		
subjects affected / exposed	3 / 2841 (0.11%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain contusion	Additional description: Brain contusion		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast procedural complication	Additional description: Breast procedural complication		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clavicle fracture	Additional description: Clavicle fracture		

subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Concussion	Additional description: Concussion		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Craniocerebral injury	Additional description: Craniocerebral injury		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall	Additional description: Fall		
subjects affected / exposed	3 / 2841 (0.11%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 3	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury	Additional description: Head injury		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture	Additional description: Hip fracture		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture	Additional description: Humerus fracture		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury	Additional description: Limb injury		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture	Additional description: Lower limb fracture		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus injury	Additional description: Meniscus injury		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Open fracture	Additional description: Open fracture		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haematoma	Additional description: Post procedural haematoma		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound complication	Additional description: Postoperative wound complication		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication	Additional description: Procedural complication		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radiation pneumonitis	Additional description: Radiation pneumonitis		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture	Additional description: Radius fracture		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture	Additional description: Rib fracture		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seroma	Additional description: Seroma		
subjects affected / exposed	3 / 2841 (0.11%)	4 / 2902 (0.14%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin flap necrosis	Additional description: Skin flap necrosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture	Additional description: Spinal fracture		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sternal fracture	Additional description: Sternal fracture		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma	Additional description: Subdural haematoma		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thermal burn	Additional description: Thermal burn		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture	Additional description: Thoracic vertebral fracture		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture	Additional description: Upper limb fracture		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal cuff dehiscence	Additional description: Vaginal cuff dehiscence		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular access site thrombosis	Additional description: Vascular access site thrombosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound complication	Additional description: Wound complication		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound dehiscence	Additional description: Wound dehiscence		
subjects affected / exposed	9 / 2841 (0.32%)	5 / 2902 (0.17%)	
occurrences causally related to treatment / all	1 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wrist fracture	Additional description: Wrist fracture		
subjects affected / exposed	3 / 2841 (0.11%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect	Additional description: Atrial septal defect		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gene mutation	Additional description: Gene mutation		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute coronary syndrome subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Acute coronary syndrome		
	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
	0 / 0	0 / 2	
	0 / 0	0 / 0	
Acute myocardial infarction subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Acute myocardial infarction		
	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Angina pectoris subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Angina pectoris		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Arteriospasm coronary subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Arteriospasm coronary		
	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
	0 / 1	0 / 0	
	0 / 0	0 / 0	
Atrial fibrillation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Atrial fibrillation		
	2 / 2841 (0.07%)	4 / 2902 (0.14%)	
	0 / 2	0 / 4	
	0 / 0	0 / 0	
Atrioventricular block subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Atrioventricular block		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Atrioventricular block complete subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Atrioventricular block complete		
	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
	0 / 0	0 / 1	
	0 / 0	0 / 0	
Cardiac arrest subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Additional description: Cardiac arrest		
	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
	0 / 1	0 / 0	
	0 / 1	0 / 0	
Cardiac failure	Additional description: Cardiac failure		

subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute	Additional description: Cardiac failure acute		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive	Additional description: Cardiac failure congestive		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac ventricular thrombosis	Additional description: Cardiac ventricular thrombosis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiomyopathy	Additional description: Cardiomyopathy		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery disease	Additional description: Coronary artery disease		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Extrasystoles	Additional description: Extrasystoles		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure	Additional description: Left ventricular failure		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial ischaemia	Additional description: Myocardial ischaemia		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations	Additional description: Palpitations		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinus bradycardia	Additional description: Sinus bradycardia		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stress cardiomyopathy	Additional description: Stress cardiomyopathy		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Supraventricular tachycardia	Additional description: Supraventricular tachycardia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Ageusia	Additional description: Ageusia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aphasia	Additional description: Aphasia		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carpal tunnel syndrome	Additional description: Carpal tunnel syndrome		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Carotid artery stenosis	Additional description: Carotid artery stenosis		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral infarction	Additional description: Cerebral infarction		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebral ischaemia	Additional description: Cerebral ischaemia		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	2 / 2841 (0.07%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident	Additional description: Cerebrovascular accident		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalopathy	Additional description: Encephalopathy		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Facial paralysis	Additional description: Facial paralysis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy	Additional description: Epilepsy		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache	Additional description: Headache		

subjects affected / exposed	3 / 2841 (0.11%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial	Additional description: Haemorrhage intracranial		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
IIIrd nerve disorder	Additional description: IIIrd nerve disorder		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intercostal neuralgia	Additional description: Intercostal neuralgia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke	Additional description: Ischaemic stroke		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myasthenia gravis	Additional description: Myasthenia gravis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paraesthesia	Additional description: Paraesthesia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope	Additional description: Presyncope		
subjects affected / exposed	3 / 2841 (0.11%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ruptured cerebral aneurysm	Additional description: Ruptured cerebral aneurysm		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Subarachnoid haemorrhage	Additional description: Subarachnoid haemorrhage		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope	Additional description: Syncope		
subjects affected / exposed	2 / 2841 (0.07%)	4 / 2902 (0.14%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack	Additional description: Transient ischaemic attack		
subjects affected / exposed	2 / 2841 (0.07%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIth nerve paralysis	Additional description: VIth nerve paralysis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo CNS origin	Additional description: Vertigo CNS origin		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	3 / 2841 (0.11%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anaemia macrocytic	Additional description: Anaemia macrocytic		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia	Additional description: Febrile neutropenia		

subjects affected / exposed	13 / 2841 (0.46%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	13 / 13	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis	Additional description: Leukocytosis		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lymphadenitis	Additional description: Lymphadenitis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia	Additional description: Neutropenia		
subjects affected / exposed	4 / 2841 (0.14%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia	Additional description: Pancytopenia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction	Additional description: Splenic infarction		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Deafness unilateral	Additional description: Deafness unilateral		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo	Additional description: Vertigo		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vertigo positional	Additional description: Vertigo positional		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (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	Additional description: Cataract		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diplopia	Additional description: Diplopia		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eyelid function disorder	Additional description: Eyelid function disorder		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Maculopathy	Additional description: Maculopathy		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal hernia	Additional description: Abdominal hernia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper	Additional description: Abdominal pain upper		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic	Additional description: Colitis ischaemic		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis	Additional description: Colitis		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenal ulcer	Additional description: Duodenal ulcer		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenitis	Additional description: Duodenitis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enteritis	Additional description: Enteritis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroesophageal reflux disease	Additional description: Gastroesophageal reflux disease		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ileus	Additional description: Ileus		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal obstruction	Additional description: Intestinal obstruction		

subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intestinal perforation	Additional description: Intestinal perforation		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intussusception	Additional description: Intussusception		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine perforation	Additional description: Large intestine perforation		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Large intestine polyp	Additional description: Large intestine polyp		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea	Additional description: Nausea		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic colitis	Additional description: Neutropenic colitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedematous pancreatitis	Additional description: Oedematous pancreatitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oesophagitis	Additional description: Oesophagitis		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis	Additional description: Pancreatitis		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritoneal perforation	Additional description: Peritoneal perforation		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction	Additional description: Small intestinal obstruction		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Volvulus of small bowel	Additional description: Volvulus of small bowel		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	2 / 2841 (0.07%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure	Additional description: Acute hepatic failure		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Bile duct stone	Additional description: Bile duct stone		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangitis	Additional description: Cholangitis		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis	Additional description: Cholecystitis		
subjects affected / exposed	3 / 2841 (0.11%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute	Additional description: Cholecystitis acute		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis	Additional description: Cholelithiasis		
subjects affected / exposed	4 / 2841 (0.14%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug-induced liver injury	Additional description: Drug-induced liver injury		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure	Additional description: Hepatic failure		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatitis acute	Additional description: Hepatitis acute		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Keloid scar	Additional description: Keloid scar		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin necrosis	Additional description: Skin necrosis		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria	Additional description: Urticaria		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury	Additional description: Acute kidney injury		
subjects affected / exposed	4 / 2841 (0.14%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic kidney disease	Additional description: Chronic kidney disease		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis	Additional description: Nephrolithiasis		
subjects affected / exposed	1 / 2841 (0.04%)	4 / 2902 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal colic	Additional description: Renal colic		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subcapsular renal haematoma	Additional description: Subcapsular renal haematoma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric obstruction	Additional description: Ureteric obstruction		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureteric stenosis	Additional description: Ureteric stenosis		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ureterolithiasis	Additional description: Ureterolithiasis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
Goitre	Additional description: Goitre		
subjects affected / exposed	3 / 2841 (0.11%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperparathyroidism	Additional description: Hyperparathyroidism		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypothyroidism	Additional description: Hypothyroidism		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	1 / 2841 (0.04%)	4 / 2902 (0.14%)	
occurrences causally related to treatment / all	0 / 1	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Arthritis	Additional description: Arthritis		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Back pain	Additional description: Back pain		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Flank pain	Additional description: Flank pain		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Foot deformity	Additional description: Foot deformity		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemarthrosis	Additional description: Haemarthrosis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion	Additional description: Intervertebral disc protrusion		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint range of motion decreased	Additional description: Joint range of motion decreased		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis	Additional description: Osteoarthritis		
subjects affected / exposed	1 / 2841 (0.04%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rotator cuff syndrome	Additional description: Rotator cuff syndrome		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue necrosis	Additional description: Soft tissue necrosis		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal synovial cyst	Additional description: Spinal synovial cyst		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tendonitis	Additional description: Tendonitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess	Additional description: Anal abscess		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anorectal infection	Additional description: Anorectal infection		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendiceal abscess	Additional description: Appendiceal abscess		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis	Additional description: Appendicitis		
subjects affected / exposed	3 / 2841 (0.11%)	5 / 2902 (0.17%)	
occurrences causally related to treatment / all	1 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis perforated	Additional description: Appendicitis perforated		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacterial infection	Additional description: Bacterial infection		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast abscess	Additional description: Breast abscess		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Breast cellulitis	Additional description: Breast cellulitis		
subjects affected / exposed	16 / 2841 (0.56%)	10 / 2902 (0.34%)	
occurrences causally related to treatment / all	7 / 17	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis	Additional description: Bronchitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia	Additional description: COVID-19 pneumonia		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Campylobacter infection	Additional description: Campylobacter infection		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis	Additional description: Cellulitis		
subjects affected / exposed	24 / 2841 (0.84%)	9 / 2902 (0.31%)	
occurrences causally related to treatment / all	9 / 26	0 / 10	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cystitis	Additional description: Cystitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection	Additional description: Device related infection		

subjects affected / exposed	2 / 2841 (0.07%)	4 / 2902 (0.14%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Disseminated varicella zoster virus infection	Additional description: Disseminated varicella zoster virus infection		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis	Additional description: Diverticulitis		
subjects affected / exposed	0 / 2841 (0.00%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas	Additional description: Erysipelas		
subjects affected / exposed	5 / 2841 (0.18%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	2 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelothrix sepsis	Additional description: Erysipelothrix sepsis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia pyelonephritis	Additional description: Escherichia pyelonephritis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis	Additional description: Escherichia sepsis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis	Additional description: Gastroenteritis		
subjects affected / exposed	4 / 2841 (0.14%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 4	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus	Additional description: Gastroenteritis norovirus		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral	Additional description: Gastroenteritis viral		
subjects affected / exposed	4 / 2841 (0.14%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Herpes zoster	Additional description: Herpes zoster		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infected seroma	Additional description: Infected seroma		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infection	Additional description: Infection		
subjects affected / exposed	2 / 2841 (0.07%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza	Additional description: Influenza		
subjects affected / exposed	16 / 2841 (0.56%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	3 / 16	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laryngitis	Additional description: Laryngitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Listeria sepsis	Additional description: Listeria sepsis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Localised infection	Additional description: Localised infection		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection	Additional description: Lower respiratory tract infection		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mastitis	Additional description: Mastitis		
subjects affected / exposed	13 / 2841 (0.46%)	10 / 2902 (0.34%)	
occurrences causally related to treatment / all	5 / 14	0 / 11	
deaths causally related to treatment / all	0 / 0	0 / 0	
Paronychia	Additional description: Paronychia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease	Additional description: Pelvic inflammatory disease		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis	Additional description: Peritonitis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia	Additional description: Pneumonia		
subjects affected / exposed	16 / 2841 (0.56%)	7 / 2902 (0.24%)	
occurrences causally related to treatment / all	10 / 18	0 / 8	
deaths causally related to treatment / all	0 / 1	0 / 0	
Postoperative wound infection	Additional description: Postoperative wound infection		
subjects affected / exposed	1 / 2841 (0.04%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis	Additional description: Pyelonephritis		

subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute	Additional description: Pyelonephritis acute		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection	Additional description: Respiratory tract infection		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis	Additional description: Sepsis		
subjects affected / exposed	8 / 2841 (0.28%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	4 / 9	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock	Additional description: Septic shock		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sinusitis	Additional description: Sinusitis		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin infection	Additional description: Skin infection		
subjects affected / exposed	8 / 2841 (0.28%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	3 / 8	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Soft tissue infection	Additional description: Soft tissue infection		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal bacteraemia	Additional description: Staphylococcal bacteraemia		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Staphylococcal infection	Additional description: Staphylococcal infection		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	2 / 2841 (0.07%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	1 / 2	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	8 / 2841 (0.28%)	3 / 2902 (0.10%)	
occurrences causally related to treatment / all	2 / 8	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis	Additional description: Urosepsis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular device infection	Additional description: Vascular device infection		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular neuronitis	Additional description: Vestibular neuronitis		
subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection	Additional description: Viral infection		
subjects affected / exposed	4 / 2841 (0.14%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral labyrinthitis	Additional description: Viral labyrinthitis		

subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pericarditis			
	Additional description: Viral pericarditis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vulvovaginal candidiasis			
	Additional description: Vulvovaginal candidiasis		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound abscess			
	Additional description: Wound abscess		
subjects affected / exposed	2 / 2841 (0.07%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound infection			
	Additional description: Wound infection		
subjects affected / exposed	3 / 2841 (0.11%)	4 / 2902 (0.14%)	
occurrences causally related to treatment / all	1 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration	Additional description: Dehydration		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypercalcaemia			
	Additional description: Hypercalcaemia		
subjects affected / exposed	1 / 2841 (0.04%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hypoglycaemia			
	Additional description: Hypoglycaemia		
subjects affected / exposed	1 / 2841 (0.04%)	0 / 2902 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
	Additional description: Hypokalaemia		

subjects affected / exposed	0 / 2841 (0.00%)	1 / 2902 (0.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia	Additional description: Hyponatraemia		
subjects affected / exposed	0 / 2841 (0.00%)	2 / 2902 (0.07%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Palbociclib plus endocrine therapy	Endocrine therapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2824 / 2841 (99.40%)	2600 / 2902 (89.59%)	
Vascular disorders			
Hot flush	Additional description: Hot flush		
subjects affected / exposed	703 / 2841 (24.74%)	849 / 2902 (29.26%)	
occurrences (all)	888	1066	
Hypertension	Additional description: Hypertension		
subjects affected / exposed	205 / 2841 (7.22%)	227 / 2902 (7.82%)	
occurrences (all)	363	382	
Lymphoedema	Additional description: Lymphoedema		
subjects affected / exposed	337 / 2841 (11.86%)	268 / 2902 (9.24%)	
occurrences (all)	396	303	
General disorders and administration site conditions			
Asthenia	Additional description: Asthenia		
subjects affected / exposed	274 / 2841 (9.64%)	153 / 2902 (5.27%)	
occurrences (all)	468	193	
Fatigue	Additional description: Fatigue		
subjects affected / exposed	1163 / 2841 (40.94%)	560 / 2902 (19.30%)	
occurrences (all)	1869	714	
Influenza like illness	Additional description: Influenza like illness		
subjects affected / exposed	166 / 2841 (5.84%)	90 / 2902 (3.10%)	
occurrences (all)	205	108	
Mucosal inflammation	Additional description: Mucosal inflammation		

subjects affected / exposed	206 / 2841 (7.25%)	10 / 2902 (0.34%)	
occurrences (all)	362	10	
Oedema peripheral	Additional description: Oedema peripheral		
subjects affected / exposed	178 / 2841 (6.27%)	121 / 2902 (4.17%)	
occurrences (all)	218	137	
Pyrexia	Additional description: Pyrexia		
subjects affected / exposed	205 / 2841 (7.22%)	83 / 2902 (2.86%)	
occurrences (all)	251	92	
Reproductive system and breast disorders			
Breast pain	Additional description: Breast pain		
subjects affected / exposed	145 / 2841 (5.10%)	158 / 2902 (5.44%)	
occurrences (all)	163	186	
Vulvovaginal dryness	Additional description: Vulvovaginal dryness		
subjects affected / exposed	182 / 2841 (6.41%)	213 / 2902 (7.34%)	
occurrences (all)	211	254	
Respiratory, thoracic and mediastinal disorders			
Cough	Additional description: Cough		
subjects affected / exposed	416 / 2841 (14.64%)	222 / 2902 (7.65%)	
occurrences (all)	543	256	
Dyspnoea	Additional description: Dyspnoea		
subjects affected / exposed	197 / 2841 (6.93%)	130 / 2902 (4.48%)	
occurrences (all)	247	144	
Oropharyngeal pain	Additional description: Oropharyngeal pain		
subjects affected / exposed	155 / 2841 (5.46%)	60 / 2902 (2.07%)	
occurrences (all)	169	65	
Psychiatric disorders			
Anxiety	Additional description: Anxiety		
subjects affected / exposed	157 / 2841 (5.53%)	143 / 2902 (4.93%)	
occurrences (all)	184	168	
Depression	Additional description: Depression		
subjects affected / exposed	156 / 2841 (5.49%)	150 / 2902 (5.17%)	
occurrences (all)	191	175	
Insomnia	Additional description: Insomnia		
subjects affected / exposed	383 / 2841 (13.48%)	357 / 2902 (12.30%)	
occurrences (all)	468	418	

Investigations			
Aspartate aminotransferase increased	Additional description: Aspartate aminotransferase increased		
subjects affected / exposed	210 / 2841 (7.39%)	114 / 2902 (3.93%)	
occurrences (all)	288	151	
Alanine aminotransferase increased	Additional description: Alanine aminotransferase increased		
subjects affected / exposed	212 / 2841 (7.46%)	138 / 2902 (4.76%)	
occurrences (all)	345	175	
Lymphocyte count decreased	Additional description: Lymphocyte count decreased		
subjects affected / exposed	317 / 2841 (11.16%)	100 / 2902 (3.45%)	
occurrences (all)	926	161	
Neutrophil count decreased	Additional description: Neutrophil count decreased		
subjects affected / exposed	1344 / 2841 (47.31%)	67 / 2902 (2.31%)	
occurrences (all)	6144	109	
Platelet count decreased	Additional description: Platelet count decreased		
subjects affected / exposed	436 / 2841 (15.35%)	35 / 2902 (1.21%)	
occurrences (all)	850	50	
White blood cell count decreased	Additional description: White blood cell count decreased		
subjects affected / exposed	1187 / 2841 (41.78%)	155 / 2902 (5.34%)	
occurrences (all)	5122	242	
Nervous system disorders			
Headache	Additional description: Headache		
subjects affected / exposed	445 / 2841 (15.66%)	338 / 2902 (11.65%)	
occurrences (all)	590	405	
Dizziness	Additional description: Dizziness		
subjects affected / exposed	248 / 2841 (8.73%)	169 / 2902 (5.82%)	
occurrences (all)	306	190	
Neuropathy peripheral	Additional description: Neuropathy peripheral		
subjects affected / exposed	148 / 2841 (5.21%)	102 / 2902 (3.51%)	
occurrences (all)	186	121	
Blood and lymphatic system disorders			
Anaemia	Additional description: Anaemia		
subjects affected / exposed	634 / 2841 (22.32%)	147 / 2902 (5.07%)	
occurrences (all)	1161	211	
Neutropenia	Additional description: Neutropenia		

subjects affected / exposed	1126 / 2841 (39.63%)	76 / 2902 (2.62%)	
occurrences (all)	5383	112	
Leukopenia	Additional description: Leukopenia		
subjects affected / exposed	397 / 2841 (13.97%)	64 / 2902 (2.21%)	
occurrences (all)	1798	98	
Thrombocytopenia	Additional description: Thrombocytopenia		
subjects affected / exposed	195 / 2841 (6.86%)	15 / 2902 (0.52%)	
occurrences (all)	403	18	
Gastrointestinal disorders			
Abdominal pain	Additional description: Abdominal pain		
subjects affected / exposed	153 / 2841 (5.39%)	110 / 2902 (3.79%)	
occurrences (all)	190	134	
Constipation	Additional description: Constipation		
subjects affected / exposed	395 / 2841 (13.90%)	172 / 2902 (5.93%)	
occurrences (all)	485	190	
Nausea	Additional description: Nausea		
subjects affected / exposed	552 / 2841 (19.43%)	241 / 2902 (8.30%)	
occurrences (all)	735	294	
Diarrhoea	Additional description: Diarrhoea		
subjects affected / exposed	475 / 2841 (16.72%)	150 / 2902 (5.17%)	
occurrences (all)	682	194	
Vomiting	Additional description: Vomiting		
subjects affected / exposed	219 / 2841 (7.71%)	91 / 2902 (3.14%)	
occurrences (all)	278	120	
Stomatitis	Additional description: Stomatitis		
subjects affected / exposed	280 / 2841 (9.86%)	21 / 2902 (0.72%)	
occurrences (all)	428	23	
Skin and subcutaneous tissue disorders			
Alopecia	Additional description: Alopecia		
subjects affected / exposed	511 / 2841 (17.99%)	149 / 2902 (5.13%)	
occurrences (all)	559	163	
Dry skin	Additional description: Dry skin		
subjects affected / exposed	153 / 2841 (5.39%)	56 / 2902 (1.93%)	
occurrences (all)	178	67	
Pruritus	Additional description: Pruritus		

subjects affected / exposed	183 / 2841 (6.44%)	95 / 2902 (3.27%)	
occurrences (all)	222	105	
Rash	Additional description: Rash		
subjects affected / exposed	229 / 2841 (8.06%)	90 / 2902 (3.10%)	
occurrences (all)	288	102	
Musculoskeletal and connective tissue disorders			
Arthralgia	Additional description: Arthralgia		
subjects affected / exposed	1087 / 2841 (38.26%)	1305 / 2902 (44.97%)	
occurrences (all)	1650	2034	
Back pain	Additional description: Back pain		
subjects affected / exposed	311 / 2841 (10.95%)	287 / 2902 (9.89%)	
occurrences (all)	369	346	
Muscle spasms	Additional description: Muscle spasms		
subjects affected / exposed	193 / 2841 (6.79%)	124 / 2902 (4.27%)	
occurrences (all)	229	131	
Myalgia	Additional description: Myalgia		
subjects affected / exposed	250 / 2841 (8.80%)	235 / 2902 (8.10%)	
occurrences (all)	315	276	
Pain in extremity	Additional description: Pain in extremity		
subjects affected / exposed	265 / 2841 (9.33%)	280 / 2902 (9.65%)	
occurrences (all)	346	349	
Infections and infestations			
Nasopharyngitis	Additional description: Nasopharyngitis		
subjects affected / exposed	210 / 2841 (7.39%)	127 / 2902 (4.38%)	
occurrences (all)	275	157	
Upper respiratory tract infection	Additional description: Upper respiratory tract infection		
subjects affected / exposed	304 / 2841 (10.70%)	185 / 2902 (6.37%)	
occurrences (all)	390	229	
Urinary tract infection	Additional description: Urinary tract infection		
subjects affected / exposed	234 / 2841 (8.24%)	145 / 2902 (5.00%)	
occurrences (all)	320	204	
Metabolism and nutrition disorders			
Decreased appetite	Additional description: Decreased appetite		
subjects affected / exposed	151 / 2841 (5.32%)	73 / 2902 (2.52%)	
occurrences (all)	176	87	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 August 2015	Updates to clarify endpoints, analyses and concomitant medication. Updated description of recurrences, duration of disease monitoring and diagnosis. Administrative updates and wordsmithing.
04 April 2018	Sample size increase, updates to timepoints of sample collection and in regards to updated IB. Updates to clarify eligibility criteria, administrative updates and wordsmithing.
23 December 2020	Updates to implement results of second interim analysis, measures during COVID-19 pandemic to safeguard patient safety and data integrity and additional biosample collection 7 and 10 years post-randomization. Updates to clarify statistical endpoints, administrative changes and wordsmithing.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Limitation of an unblinded design.

Notes:

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/33460574>