



## Clinical trial results:

### A phase III trial of marizomib in combination with standard temozolomide-based radiochemotherapy versus standard temozolomide-based radiochemotherapy alone in patients with newly diagnosed glioblastoma - MIRAGE

#### Summary

EudraCT number	2017-003908-50
Trial protocol	BE GB DK DE NL ES AT NO
Global end of trial date	22 August 2022

#### Results information

Result version number	v1 (current)
This version publication date	22 February 2023
First version publication date	22 February 2023

#### Trial information

##### Trial identification

Sponsor protocol code	EORTC-1709-BTG
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03345095
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	83 Avenue Mounier, Brussels, Belgium, 1200
Public contact	Regulatory Affairs Department, European Organisation for the Research and Treatment of Cancer (EORTC), +32 27741013, thierry.gorlia@eortc.org
Scientific contact	Regulatory Affairs Department, European Organisation for the Research and Treatment of Cancer (EORTC), 027741652 27741013, thierry.gorlia@eortc.org

Notes:

#### Paediatric regulatory details

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

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 February 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	09 February 2022
Global end of trial reached?	Yes
Global end of trial date	22 August 2022
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to compare overall survival in patients receiving Marizomib in combination with standard treatment with patients receiving standard treatment only.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol was written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice . The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy:

Standard arm(TMZ/RT): Standard radiotherapy (RT) (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m<sup>2</sup>p.o. daily for 6 weeks (during RT) then (after 4-week break) up to 6 cycles of maintenance TMZ 150-200 mg/m<sup>2</sup>p.o. on days 1-5 of a 28-day cycle. All patients will have regular follow-up by MRI, 4 weeks after the end of RT, then every 8 weeks thereafter until progression. Once patients stop study treatment, they will be followed as per institution's standard.

Evidence for comparator:

Experimental arm(TMZ/RT+MRZ): Standard radiotherapy ( RT)(60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m<sup>2</sup>p.o. daily for 6 weeks (during RT) and marizomib (MRZ) dose 0.8 mg/m<sup>2</sup>IV at days 1, 8, 15, 29 and 36. This is followed, after 4-week break, by up to 6 cycles of maintenance TMZ 150-200 mg/m<sup>2</sup>p.o. on days 1-5 of a 28-day cycle and up to 18 cycles of maintenance MRZ treatment (0.8mg/m<sup>2</sup>IV) at days 1, 8, 15 of a 28-day cycle until disease progression, unacceptable toxicity or withdrawal of consent.

Actual start date of recruitment	18 June 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	22 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 190
Country: Number of subjects enrolled	Switzerland: 43
Country: Number of subjects enrolled	United States: 15
Country: Number of subjects enrolled	Netherlands: 71
Country: Number of subjects enrolled	Norway: 8
Country: Number of subjects enrolled	Spain: 47
Country: Number of subjects enrolled	United Kingdom: 15

Country: Number of subjects enrolled	Austria: 8
Country: Number of subjects enrolled	Belgium: 51
Country: Number of subjects enrolled	Denmark: 12
Country: Number of subjects enrolled	France: 101
Country: Number of subjects enrolled	Germany: 55
Worldwide total number of subjects	616
EEA total number of subjects	353

Notes:

<b>Subjects enrolled per age group</b>	
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)	466
From 65 to 84 years	150
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Patient registration was only be accepted from authorized investigators. Patients were registered directly on the Medidata Rave EDC system, accessible 24 hours a day, 7 days a week. As soon as the registration process was started, a Subject ID was allocated to the patient. This number allowed the identification of the patients in Medidata Rave.

### Period 1

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

### Arms

Are arms mutually exclusive?	Yes
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<b>Arm title</b>	TMZ/RT
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Arm description:

Standard arm

Arm type	Active comparator
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Standard radiotherapy (RT) (60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m<sup>2</sup> p.o. daily for 6 weeks (during RT) then (after 4-week break) up to 6 cycles of maintenance TMZ 150-200 mg/m<sup>2</sup> p.o. on days 1-5 of a 28-day cycle.

<b>Arm title</b>	TMZ/RT+MRZ
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Arm description:

Experimental arm

Arm type	Experimental
Investigational medicinal product name	Marizomib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Standard radiotherapy (RT)(60 Gy in 30 fractions over 6 weeks) + TMZ 75 mg/m<sup>2</sup> p.o. daily for 6 weeks (during RT) and marizomib (MRZ) dose 0.8 mg/m<sup>2</sup> IV at days 1, 8, 15, 29 and 36. This is followed, after 4-week break, by up to 6 cycles of maintenance TMZ 150-200 mg/m<sup>2</sup> p.o. on days 1-5 of a 28-day cycle and up to 18 cycles of maintenance MRZ treatment (0.8 mg/m<sup>2</sup> IV) at days 1, 8, 15 of a 28-day cycle until disease progression, unacceptable toxicity or withdrawal of consent.

<b>Number of subjects in period 1</b>	TMZ/RT	TMZ/RT+MRZ
Started	307	309
Completed	64	0
Not completed	243	309
Adverse event, serious fatal	1	4
Consent withdrawn by subject	13	21
Physician decision	4	3
Adverse event, non-fatal	27	76
MRZ ongoing	-	104
Other reasons	1	3
TMZ treatment ongoing	82	-
Lack of efficacy	113	96
Missing reason	2	1
Protocol deviation	-	1

## Baseline characteristics

### Reporting groups

Reporting group title	TMZ/RT
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Reporting group description:

Standard arm

Reporting group title	TMZ/RT+MRZ
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Reporting group description:

Experimental arm

Reporting group values	TMZ/RT	TMZ/RT+MRZ	Total
Number of subjects	307	309	616
Age categorical			
Units: Subjects			
Adults (18-64 years)	237	229	466
From 65-84 years	70	80	150
Gender categorical			
Units: Subjects			
Female	103	113	216
Male	204	196	400

## End points

### End points reporting groups

Reporting group title	TMZ/RT
Reporting group description:	
Standard arm	
Reporting group title	TMZ/RT+MRZ
Reporting group description:	
Experimental arm	

### Primary: Overall Survival in the ITT population

End point title	Overall Survival in the ITT population
End point description:	
ITT population is defined as: All randomized patients will be analyzed in the arm they were allocated by randomization.	
End point type	Primary
End point timeframe:	
Overall Survival (OS): OS is defined as the number of days from date of randomization to the date of death due to any cause. If a patient has not died, the data will be censored at the last date documented to be alive.	

End point values	TMZ/RT	TMZ/RT+MRZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	309		
Units: Months				
median (confidence interval 95%)	15.08 (13.73 to 16.99)	16.13 (14.92 to 17.77)		

### Statistical analyses

Statistical analysis title	OS between TMZ/RT+MRZ and TMZ/RT in ITT
Comparison groups	TMZ/RT v TMZ/RT+MRZ
Number of subjects included in analysis	616
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.04
Confidence interval	
level	Other: 97 %
sides	2-sided
lower limit	0.86
upper limit	1.27

### Primary: Overall Survival in the uMGMT population

End point title	Overall Survival in the uMGMT population
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End point description:

uMGMT population : all randomized patients will be analyzed in the arm they were allocated by randomization (ITT) with unmethylated MGMT gene promoter.

End point type	Primary
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End point timeframe:

Overall Survival (OS): OS is defined as the number of days from date of randomization to the date of death due to any cause. If a patient has not died, the data will be censored at the last date documented to be alive.

End point values	TMZ/RT	TMZ/RT+MRZ		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	184	179		
Units: Months				
median (confidence interval 95%)	13.77 (13.08 to 15.7)	14.92 (11.50 to 15.7)		

### Statistical analyses

<b>Statistical analysis title</b>	OS between TMZ/RT+MRZ and TMZ/RT in uMGMT
Comparison groups	TMZ/RT v TMZ/RT+MRZ
Number of subjects included in analysis	363
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.27
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.9
Confidence interval	
level	Other: 98 %
sides	2-sided
lower limit	0.52
upper limit	1.55



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AEs were collected on a CRF to be submitted at pre-specified timepoint: Within 7 days of randomization, During the 6 weeks of RT and TMZ ± MRZ, during TMZ maintenance ± MRZ and uring Marizomib maintenance, before every cycle start, after the end of treatment

Adverse event reporting additional description:

AEs are evaluated using CTCAE v5 grading, SAEs using MedDra. Non-SAEs has not been collected specifically, all AEs will be reported in non-SAE section.

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.1
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### Reporting groups

Reporting group title	TMZ/RT+MRZ
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Reporting group description:

Experimental group : TMZ/RT+MRZ

Reporting group title	TMZ/RT
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Reporting group description:

Control group : TMZ/RT

Serious adverse events	TMZ/RT+MRZ	TMZ/RT	
Total subjects affected by serious adverse events			
subjects affected / exposed	115 / 305 (37.70%)	87 / 297 (29.29%)	
number of deaths (all causes)	53	54	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BRAIN NEOPLASM			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLIOBLASTOMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 1	
GLIOBLASTOMA MULTIFORME			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
MALIGNANT NEOPLASM PROGRESSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	8 / 305 (2.62%)	5 / 297 (1.68%)	
occurrences causally related to treatment / all	0 / 8	0 / 5	
deaths causally related to treatment / all	0 / 1	0 / 0	
METASTASES TO MENINGES			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOPLASM PROGRESSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (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			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERITUMOURAL OEDEMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
DEEP VEIN THROMBOSIS			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
JUGULAR VEIN THROMBOSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
FATIGUE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 305 (1.31%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	3 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CATHETER SITE THROMBOSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GAIT DISTURBANCE			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPAIRED HEALING			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 305 (1.31%)	6 / 297 (2.02%)	
occurrences causally related to treatment / all	2 / 4	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 1	
INFLUENZA LIKE ILLNESS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SWELLING			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASCULAR DEVICE OCCLUSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
ACUTE RESPIRATORY FAILURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOTHORAX			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)	
occurrences causally related to treatment / all	1 / 2	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
AGITATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	3 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANXIETY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELIRIUM			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 305 (1.31%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	3 / 4	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	7 / 305 (2.30%)	3 / 297 (1.01%)	
occurrences causally related to treatment / all	6 / 7	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	7 / 305 (2.30%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	7 / 7	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DELUSION			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION, VISUAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
IMPULSIVE BEHAVIOUR			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
IRRITABILITY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INSOMNIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MANIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOMOTOR RETARDATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

PARANOIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOTIC DISORDER			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
ALANINE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD CREATININE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASPARTATE AMINOTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (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			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
alternative dictionary used:			



MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	8 / 297 (2.69%)	
occurrences causally related to treatment / all	2 / 2	8 / 8	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTE COUNT DECREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WEIGHT DECREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WHITE BLOOD CELL COUNT DECREASED			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
HEAD INJURY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEMORAL NECK FRACTURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FALL			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	5 / 305 (1.64%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	2 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMOCEPHALUS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION NECROSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSEUDOMENINGOCELE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPINAL FRACTURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TENDON RUPTURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SUBDURAL HAEMATOMA alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 305 (0.00%) 0 / 0 0 / 0	1 / 297 (0.34%) 0 / 1 0 / 0	
Cardiac disorders ANGINA PECTORIS alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 305 (0.33%) 0 / 1 0 / 0	0 / 297 (0.00%) 0 / 0 0 / 0	
ATRIAL FLUTTER alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 305 (0.33%) 0 / 1 0 / 0	0 / 297 (0.00%) 0 / 0 0 / 0	
Nervous system disorders APHASIA alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	2 / 305 (0.66%) 2 / 2 0 / 0	1 / 297 (0.34%) 1 / 1 0 / 0	
AKATHISIA alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 305 (0.33%) 1 / 1 0 / 0	0 / 297 (0.00%) 0 / 0 0 / 0	
BRAIN STEM HAEMATOMA alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 305 (0.33%) 0 / 1 0 / 1	0 / 297 (0.00%) 0 / 0 0 / 0	
BRAIN OEDEMA alternative dictionary used: MedDRA 19			

subjects affected / exposed	8 / 305 (2.62%)	8 / 297 (2.69%)	
occurrences causally related to treatment / all	6 / 8	6 / 8	
deaths causally related to treatment / all	0 / 0	0 / 1	
BALANCE DISORDER			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	1 / 2	0 / 0	
ATAXIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 305 (1.31%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CLONUS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL VENOUS THROMBOSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

COGNITIVE DISORDER alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	   1 / 305 (0.33%) 0 / 1 0 / 0	   0 / 297 (0.00%) 0 / 0 0 / 0		
DEPRESSED LEVEL OF CONSCIOUSNESS alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	   3 / 305 (0.98%) 3 / 3 0 / 0	   0 / 297 (0.00%) 0 / 0 0 / 0		
COORDINATION ABNORMAL alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	   1 / 305 (0.33%) 1 / 1 0 / 0	   0 / 297 (0.00%) 0 / 0 0 / 0		
DIZZINESS alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	   1 / 305 (0.33%) 1 / 1 0 / 0	   1 / 297 (0.34%) 0 / 1 0 / 0		
DYSARTHRIA alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	   1 / 305 (0.33%) 1 / 1 0 / 0	   0 / 297 (0.00%) 0 / 0 0 / 0		
EPILEPSY alternative dictionary used: MedDRA 19 subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	   4 / 305 (1.31%) 1 / 4 0 / 0	   4 / 297 (1.35%) 1 / 4 0 / 0		
ENCEPHALOPATHY alternative dictionary used: MedDRA 19				

subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)		
occurrences causally related to treatment / all	1 / 1	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
GENERALISED TONIC-CLONIC SEIZURE				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
HEADACHE				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	6 / 305 (1.97%)	2 / 297 (0.67%)		
occurrences causally related to treatment / all	6 / 6	2 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
HEMIPARESIS				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	3 / 305 (0.98%)	3 / 297 (1.01%)		
occurrences causally related to treatment / all	0 / 3	2 / 3		
deaths causally related to treatment / all	0 / 0	0 / 0		
HYDROCEPHALUS				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	2 / 305 (0.66%)	2 / 297 (0.67%)		
occurrences causally related to treatment / all	0 / 2	0 / 2		
deaths causally related to treatment / all	0 / 0	0 / 0		
INTRACRANIAL PRESSURE INCREASED				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)		
occurrences causally related to treatment / all	0 / 2	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
ISCHAEMIC STROKE				
alternative dictionary used: MedDRA 19				

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LETHARGY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NERVOUS SYSTEM DISORDER			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MOTOR DYSFUNCTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOENCEPHALOPATHY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
NEUROLOGICAL DECOMPENSATION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	3 / 4	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
NEUROMYELITIS OPTICA SPECTRUM DISORDER			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROLOGICAL SYMPTOM			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NYSTAGMUS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYRAMIDAL TRACT SYNDROME			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST HERPETIC NEURALGIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADICULAR PAIN			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	



SEIZURE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	15 / 305 (4.92%)	16 / 297 (5.39%)	
occurrences causally related to treatment / all	7 / 15	5 / 16	
deaths causally related to treatment / all	1 / 1	0 / 0	
SOMNOLENCE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
STATUS EPILEPTICUS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL EFFUSION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	3 / 297 (1.01%)	
occurrences causally related to treatment / all	0 / 0	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
VASOGENIC CEREBRAL OEDEMA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	3 / 305 (0.98%)	3 / 297 (1.01%)	
occurrences causally related to treatment / all	2 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
LEUKOPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	3 / 3	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	7 / 305 (2.30%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	7 / 7	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
VERTIGO			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
DIPLOPIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
COLITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIARRHOEA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	2 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DIVERTICULUM INTESTINAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRITIS			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
GASTROOESOPHAGEAL REFLUX DISEASE				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)		
occurrences causally related to treatment / all	0 / 0	1 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
GASTROINTESTINAL INFLAMMATION				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)		
occurrences causally related to treatment / all	0 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
ILEUS				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	0 / 0	0 / 0		
NAUSEA				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	7 / 305 (2.30%)	1 / 297 (0.34%)		
occurrences causally related to treatment / all	6 / 7	0 / 1		
deaths causally related to treatment / all	0 / 0	0 / 0		
INTESTINAL PERFORATION				
alternative dictionary used: MedDRA 19				
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)		
occurrences causally related to treatment / all	1 / 1	0 / 0		
deaths causally related to treatment / all	1 / 1	0 / 0		
UPPER GASTROINTESTINAL HAEMORRHAGE				
alternative dictionary used: MedDRA 19				

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)	
occurrences causally related to treatment / all	5 / 5	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
DRUG-INDUCED LIVER INJURY			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
RASH MACULO-PAPULAR			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STEVENS-JOHNSON SYNDROME			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (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			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Musculoskeletal and connective tissue disorders</b>			
<b>BACK PAIN</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>MUSCULAR WEAKNESS</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	3 / 297 (1.01%)	
occurrences causally related to treatment / all	0 / 1	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>MYALGIA</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Infections and infestations</b>			
<b>BACTERIAL INFECTION</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>ANAL ABSCESS</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>BRAIN ABSCESS</b>			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYSTITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CYTOMEGALOVIRUS INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED SEPSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTEROCOLITIS INFECTIOUS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

HERPES ZOSTER INFECTION NEUROLOGICAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS VIRAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LABYRINTHITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LOWER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS BACTERIAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 1	
PNEUMOCYSTIS JIROVECI PNEUMONIA			
alternative dictionary used: MedDRA 19			



subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RETINITIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE ABSCESS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA CHLAMYDIAL			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	5 / 305 (1.64%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	3 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBDURAL ABSCESS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SEPSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

SEPTIC SHOCK			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STAPHYLOCOCCAL BACTERAEMIA			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIRAL RASH			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
UROSEPSIS			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 19			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>Metabolism and nutrition disorders</b>			
<b>DEHYDRATION</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>HYPOKALAEMIA</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
<b>STEROID DIABETES</b>			
alternative dictionary used: MedDRA 19			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	TMZ/RT+MRZ	TMZ/RT	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	300 / 305 (98.36%)	283 / 297 (95.29%)	
<b>Neoplasms benign, malignant and unspecified (incl cysts and polyps)</b>			
<b>Brain neoplasm</b>			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
<b>Glioblastoma</b>			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	2	1	

Glioblastoma multiforme		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Lipoma		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Malignant neoplasm progression		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	5 / 297 (1.68%)
occurrences (all)	8	5
Melanocytic naevus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Metastases to meninges		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Neoplasm progression		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Peritumoural oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Squamous cell carcinoma		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Squamous cell carcinoma of skin		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Deep vein thrombosis			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	8 / 305 (2.62%)	3 / 297 (1.01%)	
occurrences (all)	8	3	
Embolism			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Flushing			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)	
occurrences (all)	4	1	
Haematoma			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	2 / 297 (0.67%)	
occurrences (all)	2	2	
Hot flush			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)	
occurrences (all)	5	2	
Orthostatic hypotension			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Lymphoedema			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Jugular vein thrombosis			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hypotension		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)
occurrences (all)	5	2
Hypertension		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	14 / 305 (4.59%)	9 / 297 (3.03%)
occurrences (all)	18	19
Phlebitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	0 / 297 (0.00%)
occurrences (all)	10	0
Peripheral ischaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Raynaud's phenomenon		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Subclavian vein thrombosis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Thrombophlebitis superficial		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	0 / 297 (0.00%)
occurrences (all)	7	0
Thrombophlebitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	0 / 297 (0.00%)
occurrences (all)	6	0

<p>Varicose ulceration</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 305 (0.33%)</p> <p>1</p>	<p>0 / 297 (0.00%)</p> <p>0</p>	
<p>Thrombosis</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 305 (0.00%)</p> <p>0</p>	<p>2 / 297 (0.67%)</p> <p>2</p>	
<p>Vascular pain</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 305 (0.66%)</p> <p>3</p>	<p>0 / 297 (0.00%)</p> <p>0</p>	
<p>Venous thrombosis</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 305 (0.33%)</p> <p>1</p>	<p>0 / 297 (0.00%)</p> <p>0</p>	
<p>General disorders and administration site conditions</p> <p>Catheter site thrombosis</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Catheter site pain</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Asthenia</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Administration site dysaesthesia</p> <p>alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Disease progression</p> <p>alternative dictionary used: CTCAE</p>	<p>3 / 305 (0.98%)</p> <p>5</p> <p>4 / 305 (1.31%)</p> <p>5</p> <p>33 / 305 (10.82%)</p> <p>70</p> <p>0 / 305 (0.00%)</p> <p>0</p>	<p>0 / 297 (0.00%)</p> <p>0</p> <p>0 / 297 (0.00%)</p> <p>0</p> <p>28 / 297 (9.43%)</p> <p>39</p> <p>1 / 297 (0.34%)</p> <p>1</p>	

5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Face oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	5 / 297 (1.68%)
occurrences (all)	8	5
Chills		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	4 / 297 (1.35%)
occurrences (all)	7	4
Discomfort		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Chest pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	3	2
Chest discomfort		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Fatigue		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	188 / 305 (61.64%)	170 / 297 (57.24%)
occurrences (all)	413	261
Feeling abnormal		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Feeling cold		
alternative dictionary used: CTCAE 5		



subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Feeling drunk		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	4	0
Gait disturbance		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	72 / 305 (23.61%)	15 / 297 (5.05%)
occurrences (all)	155	17
General physical health deterioration		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	11 / 297 (3.70%)
occurrences (all)	9	13
Generalised oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Granuloma		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Impaired healing		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	2
Induration		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Influenza like illness		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	5 / 297 (1.68%)
occurrences (all)	22	5

Infusion site discomfort alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Infusion site extravasation alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Infusion site irritation alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Infusion site pain alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	0 / 297 (0.00%)
occurrences (all)	9	0
Infusion site phlebitis alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Injection site bruising alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Injection site discomfort alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Injection site pain alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	0 / 297 (0.00%)
occurrences (all)	16	0
Injection site reaction alternative dictionary used: CTCAE 5		

subjects affected / exposed	9 / 305 (2.95%)	0 / 297 (0.00%)
occurrences (all)	20	0
Localised oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Malaise		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	5 / 297 (1.68%)
occurrences (all)	5	5
Mucosal inflammation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	3	0
Non-cardiac chest pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	3	0
Oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	2 / 297 (0.67%)
occurrences (all)	2	2
Oedema peripheral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	18 / 305 (5.90%)	8 / 297 (2.69%)
occurrences (all)	22	8
Pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	3 / 297 (1.01%)
occurrences (all)	5	3
Peripheral swelling		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0

Pyrexia alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	34 / 305 (11.15%) 46	11 / 297 (3.70%) 15	
Scar inflammation alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	2 / 297 (0.67%) 2	
Temperature regulation disorder alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Thirst alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Vascular device occlusion alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Vessel puncture site pain alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Xerosis alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Immune system disorders Allergic oedema alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Drug hypersensitivity alternative dictionary used: CTCAE 5			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Hypersensitivity			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Seasonal allergy			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Amenorrhoea			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Balanoposthitis			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Benign prostatic hyperplasia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Breast inflammation			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Erectile dysfunction			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Heavy menstrual bleeding			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Pelvic pain			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Prostatic pain			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Pruritus genital			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Vaginal discharge			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Asthma			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Bronchospasm			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Cough			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	29 / 305 (9.51%)	15 / 297 (5.05%)
occurrences (all)	31	16
Dry throat		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Dysphonia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	2 / 297 (0.67%)
occurrences (all)	9	2
Dyspnoea		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	9 / 305 (2.95%)	15 / 297 (5.05%)
occurrences (all)	13	15
Dyspnoea exertional		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Epistaxis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	4 / 297 (1.35%)
occurrences (all)	3	6
Haemoptysis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hiccups		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Nasal congestion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	3	2

Oropharyngeal pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	4 / 297 (1.35%)
occurrences (all)	7	4
Pleural effusion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Pneumonia aspiration		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Pneumonitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
occurrences (all)	3	2
Pneumothorax		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Productive cough		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)
occurrences (all)	5	1
Pulmonary embolism		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	4 / 297 (1.35%)
occurrences (all)	6	4
Respiratory tract congestion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Rhinitis allergic		
alternative dictionary used: CTCAE 5		



subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)	
occurrences (all)	3	1	
Sinus congestion			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)	
occurrences (all)	0	2	
Sleep apnoea syndrome			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Upper-airway cough syndrome			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Wheezing			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Psychiatric disorders			
Abnormal dreams			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	7 / 305 (2.30%)	0 / 297 (0.00%)	
occurrences (all)	12	0	
Abulia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Adjustment disorder			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Affect lability		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	3	1
Affective disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Agitation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	17 / 305 (5.57%)	4 / 297 (1.35%)
occurrences (all)	23	4
Alcohol abuse		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Anhedonia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Anxiety		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	33 / 305 (10.82%)	18 / 297 (6.06%)
occurrences (all)	40	20
Apathy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Attention deficit hyperactivity disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1

Bradyphrenia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	3	2
Confusional state		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	62 / 305 (20.33%)	24 / 297 (8.08%)
occurrences (all)	99	39
Deja vu		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Delirium		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	11 / 305 (3.61%)	2 / 297 (0.67%)
occurrences (all)	13	4
Delusion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	3	0
Depressed mood		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	1 / 297 (0.34%)
occurrences (all)	9	2
Depression		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	19 / 305 (6.23%)	14 / 297 (4.71%)
occurrences (all)	21	14
Depressive symptom		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Derealisation		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Discouragement		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Disorientation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	3	2
Euphoric mood		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Hallucination		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	115 / 305 (37.70%)	1 / 297 (0.34%)
occurrences (all)	189	1
Hallucination, auditory		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	0 / 297 (0.00%)
occurrences (all)	5	0
Hallucination, visual		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	20 / 305 (6.56%)	1 / 297 (0.34%)
occurrences (all)	30	2
Hallucinations, mixed		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	4	0
Illusion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0

Impulsive behaviour		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	3	0
Insomnia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	87 / 305 (28.52%)	36 / 297 (12.12%)
occurrences (all)	112	37
Irritability		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)
occurrences (all)	10	2
Libido decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Logorrhoea		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Mania		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	0 / 297 (0.00%)
occurrences (all)	4	0
Mental fatigue		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Mental status changes		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Nervousness		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)
occurrences (all)	10	1
Nightmare		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	14 / 305 (4.59%)	1 / 297 (0.34%)
occurrences (all)	19	1
Obsessive thoughts		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Panic attack		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Paranoia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	4	0
Perseveration		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Personality change		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	1 / 297 (0.34%)
occurrences (all)	6	1
Phobia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Procedural anxiety		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1

Psychomotor retardation alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	3 / 305 (0.98%) 3	0 / 297 (0.00%) 0	
Psychotic disorder alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Reading disorder alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 3	0 / 297 (0.00%) 0	
Restlessness alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	2 / 297 (0.67%) 2	
Sleep disorder alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	8 / 305 (2.62%) 12	0 / 297 (0.00%) 0	
Investigations Alanine aminotransferase increased alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	18 / 305 (5.90%) 29	12 / 297 (4.04%) 16	
Amylase increased alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Aspartate aminotransferase increased alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	8 / 305 (2.62%) 15	4 / 297 (1.35%) 8	
Blood alkaline phosphatase increased alternative dictionary used: CTCAE			

5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Blood bilirubin increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	0 / 297 (0.00%)
occurrences (all)	11	0
Blood calcium decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Blood cholesterol increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Blood creatinine		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Blood creatinine increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	9 / 305 (2.95%)	5 / 297 (1.68%)
occurrences (all)	11	6
Blood folate decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Blood glucose increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Blood lactate dehydrogenase increased		
alternative dictionary used: CTCAE 5		



subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Blood potassium decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Blood sodium decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Blood testosterone decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Blood uric acid increased alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Cardiac murmur alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Computerised tomogram head alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
C-reactive protein increased alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	0 / 297 (0.00%)
occurrences (all)	5	0
Electrocardiogram QT prolonged alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	7	0

Gamma-glutamyltransferase increased alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	4 / 297 (1.35%)
occurrences (all)	16	4
International normalised ratio increased alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	3
Lymphocyte count decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	15 / 305 (4.92%)	17 / 297 (5.72%)
occurrences (all)	29	48
Neutrophil count decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	11 / 305 (3.61%)	15 / 297 (5.05%)
occurrences (all)	20	29
Neutrophil count increased alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	2
OTHER INVESTIGATIONS alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Oxygen saturation decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Platelet count decreased alternative dictionary used: CTCAE 5		
subjects affected / exposed	25 / 305 (8.20%)	37 / 297 (12.46%)
occurrences (all)	64	99
Propionibacterium test positive alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Serum ferritin decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Transaminases increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	4	0
Urine output increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Vitamin B12 decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Vitamin D decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Weight decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	48 / 305 (15.74%)	23 / 297 (7.74%)
occurrences (all)	75	29
Weight increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	13 / 297 (4.38%)
occurrences (all)	21	20
White blood cell count		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1

<p>White blood cell count decreased alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>7 / 305 (2.30%)</p> <p>7</p>	<p>11 / 297 (3.70%)</p> <p>31</p>	
<p>White blood cell count increased alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>2 / 305 (0.66%)</p> <p>2</p>	<p>0 / 297 (0.00%)</p> <p>0</p>	
<p>Injury, poisoning and procedural complications</p> <p>Animal bite alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Brain herniation alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Chemical phlebitis alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Contusion alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Eye contusion alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Fall alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Femoral neck fracture alternative dictionary used: CTCAE</p>	<p>1 / 305 (0.33%)</p> <p>1</p> <p>0 / 305 (0.00%)</p> <p>0</p> <p>1 / 305 (0.33%)</p> <p>1</p> <p>2 / 305 (0.66%)</p> <p>2</p> <p>0 / 305 (0.00%)</p> <p>0</p> <p>35 / 305 (11.48%)</p> <p>41</p>	<p>0 / 297 (0.00%)</p> <p>0</p> <p>1 / 297 (0.34%)</p> <p>1</p> <p>0 / 297 (0.00%)</p> <p>0</p> <p>3 / 297 (1.01%)</p> <p>3</p> <p>1 / 297 (0.34%)</p> <p>1</p> <p>15 / 297 (5.05%)</p> <p>19</p>	

5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Foot fracture		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Foreign body in eye		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Head injury		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Incision site dermatitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Incision site swelling		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Infusion related reaction		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	0 / 297 (0.00%)
occurrences (all)	23	0
Joint injury		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	2
Ligament sprain		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Limb injury		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Lumbar vertebral fracture		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Pneumocephalus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	2
Post procedural discomfort		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Procedural pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Pseudomeningocele		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	11	2
Radiation alopecia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	3 / 297 (1.01%)
occurrences (all)	1	4
Radiation necrosis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0

Radiation skin injury		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	17 / 305 (5.57%)	31 / 297 (10.44%)
occurrences (all)	17	31
Radius fracture		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Scar		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Skin abrasion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Skin laceration		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Skin wound		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Spinal fracture		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Subdural haematoma		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	2
Tendon rupture		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Thermal burn			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Toxicity to various agents			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Vascular access site haematoma			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Wound			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Wound dehiscence			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Cardiac disorders			
Angina pectoris			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Atrial fibrillation			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Atrial flutter			
alternative dictionary used: CTCAE 5			



subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Cardiac failure			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Palpitations			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)	
occurrences (all)	5	2	
Sinus bradycardia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Sinus tachycardia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	2 / 297 (0.67%)	
occurrences (all)	2	2	
Supraventricular tachycardia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Tachycardia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	2	1	
Nervous system disorders			
Ageusia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Agraphia			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Akathisia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	3	1
Alexia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Amnesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	9 / 305 (2.95%)	4 / 297 (1.35%)
occurrences (all)	9	4
Anosmia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)
occurrences (all)	2	3
Aphasia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	48 / 305 (15.74%)	22 / 297 (7.41%)
occurrences (all)	68	32
Apraxia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	5 / 297 (1.68%)
occurrences (all)	1	5
Ataxia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	70 / 305 (22.95%)	2 / 297 (0.67%)
occurrences (all)	109	2
Balance disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	42 / 305 (13.77%)	9 / 297 (3.03%)
occurrences (all)	65	10

Brain oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	14 / 305 (4.59%)	11 / 297 (3.70%)
occurrences (all)	19	13
Brain stem haematoma		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Cerebellar syndrome		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Cerebral cyst		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Cerebral haemorrhage		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	4	0
Cerebral ischaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Cerebral venous thrombosis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Clonus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Cognitive disorder		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	19 / 305 (6.23%)	12 / 297 (4.04%)
occurrences (all)	27	17
Complex regional pain syndrome alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	5
Coordination abnormal alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)
occurrences (all)	5	1
Depressed level of consciousness alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	2 / 297 (0.67%)
occurrences (all)	6	2
Disturbance in attention alternative dictionary used: CTCAE 5		
subjects affected / exposed	19 / 305 (6.23%)	7 / 297 (2.36%)
occurrences (all)	20	7
Dizziness alternative dictionary used: CTCAE 5		
subjects affected / exposed	71 / 305 (23.28%)	31 / 297 (10.44%)
occurrences (all)	116	36
Dizziness postural alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Dysaesthesia alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	3	1
Dysarthria alternative dictionary used: CTCAE 5		
subjects affected / exposed	45 / 305 (14.75%)	12 / 297 (4.04%)
occurrences (all)	61	12

Dysgeusia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	16 / 305 (5.25%)	26 / 297 (8.75%)
occurrences (all)	16	27
Dysgraphia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Dyskinesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Dyslexia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Dyspraxia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	5	1
Encephalopathy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	6	2
Epilepsy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	6 / 297 (2.02%)
occurrences (all)	6	10
Extensor plantar response		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Facial paralysis		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Facial paresis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	3 / 297 (1.01%)
occurrences (all)	1	3
Fine motor skill dysfunction		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Frontotemporal dementia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Generalised tonic-clonic seizure		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	2 / 297 (0.67%)
occurrences (all)	2	3
Gerstmann's syndrome		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Head discomfort		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Head titubation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Headache		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	163 / 305 (53.44%)	92 / 297 (30.98%)
occurrences (all)	342	121

Hemianopia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	3 / 297 (1.01%)
occurrences (all)	0	3
Hemianopia heteronymous		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Hemianopia homonymous		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Hemiparaesthesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hemiparesis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	23 / 305 (7.54%)	17 / 297 (5.72%)
occurrences (all)	32	20
Hydrocephalus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)
occurrences (all)	3	4
Hypersomnia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	10 / 305 (3.28%)	1 / 297 (0.34%)
occurrences (all)	13	2
Hypertonia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hypoaesthesia		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	10 / 305 (3.28%)	5 / 297 (1.68%)
occurrences (all)	13	5
Intracranial pressure increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	2 / 297 (0.67%)
occurrences (all)	4	4
Ischaemic stroke		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Lethargy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	9 / 305 (2.95%)	2 / 297 (0.67%)
occurrences (all)	12	3
Leukoencephalopathy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Loss of consciousness		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Memory impairment		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	19 / 305 (6.23%)	19 / 297 (6.40%)
occurrences (all)	19	23
Monoparesis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	0 / 297 (0.00%)
occurrences (all)	4	0
Monoplegia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0



Motor dysfunction		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)
occurrences (all)	6	2
Movement disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Myoclonus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Nervous system disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)
occurrences (all)	5	2
Neuralgia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Neurologic neglect syndrome		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Neurological decompensation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)
occurrences (all)	7	3
Neurological symptom		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Neuromyelitis optica spectrum disorder		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Neuropathy peripheral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Nystagmus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	0 / 297 (0.00%)
occurrences (all)	8	0
Optic neuritis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Paraesthesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	6 / 297 (2.02%)
occurrences (all)	17	7
Partial seizures		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	5 / 297 (1.68%)
occurrences (all)	4	7
Peripheral sensory neuropathy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	3 / 297 (1.01%)
occurrences (all)	5	5
Polyneuropathy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Post herpetic neuralgia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	4	1

Postural tremor		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Presyncope		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Psychomotor hyperactivity		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Pyramidal tract syndrome		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	2
Quadrantanopia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Radicular pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Resting tremor		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Restless legs syndrome		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Sciatic nerve neuropathy		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Seizure		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	35 / 305 (11.48%)	38 / 297 (12.79%)
occurrences (all)	52	56
Sensory disturbance		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Slow speech		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	3	0
Somnolence		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	17 / 305 (5.57%)	3 / 297 (1.01%)
occurrences (all)	25	4
Speech disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	10 / 305 (3.28%)	2 / 297 (0.67%)
occurrences (all)	13	2
Spinal cord oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Status epilepticus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Subdural effusion		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0

Syncope		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	5 / 297 (1.68%)
occurrences (all)	3	5
Taste disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	3	2
Temporal lobe epilepsy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Tension headache		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	2	1
Tongue biting		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Tonic clonic movements		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Tremor		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	19 / 305 (6.23%)	13 / 297 (4.38%)
occurrences (all)	24	13
Trigeminal neuralgia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Tunnel vision		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Upper motor neurone lesion			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Vasogenic cerebral oedema			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	3 / 305 (0.98%)	4 / 297 (1.35%)	
occurrences (all)	7	5	
Visual field defect			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)	
occurrences (all)	4	0	
Blood and lymphatic system disorders			
Anaemia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	16 / 305 (5.25%)	18 / 297 (6.06%)	
occurrences (all)	28	41	
Leukopenia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	8 / 305 (2.62%)	6 / 297 (2.02%)	
occurrences (all)	14	9	
Febrile neutropenia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	2	
Lymphopenia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	18 / 305 (5.90%)	18 / 297 (6.06%)	
occurrences (all)	35	29	
Neutropenia			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	13 / 305 (4.26%)	11 / 297 (3.70%)	
occurrences (all)	25	27	
Thrombocytopenia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	27 / 305 (8.85%)	29 / 297 (9.76%)	
occurrences (all)	58	65	
Pancytopenia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)	
occurrences (all)	3	1	
Ear and labyrinth disorders			
Deafness			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	3 / 297 (1.01%)	
occurrences (all)	0	3	
Ear congestion			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Ear discomfort			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)	
occurrences (all)	4	1	
Presbycusis			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Hypoacusis			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	7 / 305 (2.30%)	0 / 297 (0.00%)	
occurrences (all)	7	0	
Hyperacusis			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Ear pain			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	5 / 305 (1.64%)	3 / 297 (1.01%)	
occurrences (all)	5	3	
Vestibular disorder			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	3	0	
Vertigo			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	25 / 305 (8.20%)	3 / 297 (1.01%)	
occurrences (all)	35	3	
Tinnitus			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	11 / 305 (3.61%)	5 / 297 (1.68%)	
occurrences (all)	12	5	
Eye disorders			
Asthenopia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Blindness			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Cataract			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Diplopia			
alternative dictionary used: CTCAE 5			



subjects affected / exposed	22 / 305 (7.21%)	2 / 297 (0.67%)
occurrences (all)	36	2
Dry eye		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)
occurrences (all)	4	1
Altered visual depth perception		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Dyschromatopsia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Eye pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)
occurrences (all)	2	3
Eye irritation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Eye inflammation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Eye discharge		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Eyelid oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0

Eyelid function disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Eye paraesthesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Eyelid ptosis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Glare		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hypermetropia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Lacrimation increased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	4 / 297 (1.35%)
occurrences (all)	8	4
Ocular hyperaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
occurrences (all)	1	2
Optic atrophy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Papilloedema		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Photophobia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	2 / 297 (0.67%)
occurrences (all)	6	2
Periorbital swelling		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Periorbital oedema		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Photopsia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	0 / 297 (0.00%)
occurrences (all)	7	0
Visual field defect		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Vision blurred		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	17 / 305 (5.57%)	12 / 297 (4.04%)
occurrences (all)	21	12
Xerophthalmia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Vitreous floaters		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	3 / 297 (1.01%)
occurrences (all)	1	3

Visual impairment alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	7 / 305 (2.30%) 14	4 / 297 (1.35%) 4	
Gastrointestinal disorders			
Abdominal pain alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	10 / 305 (3.28%) 11	7 / 297 (2.36%) 7	
Abdominal distension alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	2 / 305 (0.66%) 2	3 / 297 (1.01%) 4	
Aphthous ulcer alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Anal incontinence alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Colitis alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Constipation alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	126 / 305 (41.31%) 168	97 / 297 (32.66%) 120	
Dental caries alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	1 / 297 (0.34%) 1	
Abdominal pain upper alternative dictionary used: CTCAE 5			

subjects affected / exposed	11 / 305 (3.61%)	7 / 297 (2.36%)
occurrences (all)	11	7
Diarrhoea		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	47 / 305 (15.41%)	31 / 297 (10.44%)
occurrences (all)	66	38
Dry mouth		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	2 / 297 (0.67%)
occurrences (all)	13	2
Dyspepsia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	14 / 305 (4.59%)	10 / 297 (3.37%)
occurrences (all)	15	10
Dysphagia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	2 / 297 (0.67%)
occurrences (all)	5	2
Dental paraesthesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Enterocolitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Eructation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Flatulence		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	4	2

Gastritis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Gastrointestinal inflammation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Gastrointestinal pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Gingival pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
occurrences (all)	2	2
Gastroesophageal reflux disease		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	5 / 305 (1.64%)	5 / 297 (1.68%)
occurrences (all)	6	5
Gingival bleeding		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Haematemesis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Haematochezia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Hypoaesthesia oral		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	3	0
Large intestinal stenosis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Impaired gastric emptying		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Haemorrhoids		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	4 / 297 (1.35%)
occurrences (all)	3	4
Hyperaesthesia teeth		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Odynophagia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Lip swelling		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Mouth haemorrhage		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Mouth ulceration		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0

Nausea		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	205 / 305 (67.21%)	122 / 297 (41.08%)
occurrences (all)	434	179
Oral dysaesthesia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Proctalgia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Rectal haemorrhage		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Oral pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Paraesthesia oral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Toothache		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)
occurrences (all)	8	3
Stomatitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	3 / 297 (1.01%)
occurrences (all)	4	3
Salivary hypersecretion		
alternative dictionary used: CTCAE 5		



<p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Upper gastrointestinal haemorrhage alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Vomiting alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 305 (0.33%)</p> <p>2</p> <p>1 / 305 (0.33%)</p> <p>1</p> <p>158 / 305 (51.80%)</p> <p>289</p>	<p>0 / 297 (0.00%)</p> <p>0</p> <p>0 / 297 (0.00%)</p> <p>0</p> <p>53 / 297 (17.85%)</p> <p>74</p>	
<p>Hepatobiliary disorders</p> <p>Cholestasis alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Drug-induced liver injury alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hepatic enzyme increased alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Hepatitis A alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 305 (0.00%)</p> <p>0</p> <p>1 / 305 (0.33%)</p> <p>1</p> <p>1 / 305 (0.33%)</p> <p>1</p> <p>0 / 305 (0.00%)</p> <p>0</p>	<p>1 / 297 (0.34%)</p> <p>1</p> <p>0 / 297 (0.00%)</p> <p>0</p> <p>0 / 297 (0.00%)</p> <p>1</p> <p>1 / 297 (0.34%)</p> <p>1</p>	
<p>Skin and subcutaneous tissue disorders</p> <p>Acne alternative dictionary used: CTCAE 5</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>Alopecia alternative dictionary used: CTCAE 5</p>	<p>0 / 305 (0.00%)</p> <p>0</p>	<p>2 / 297 (0.67%)</p> <p>2</p>	

subjects affected / exposed	73 / 305 (23.93%)	99 / 297 (33.33%)
occurrences (all)	74	108
Cold sweat		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Decubitus ulcer		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Dermatitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	8 / 305 (2.62%)	10 / 297 (3.37%)
occurrences (all)	9	10
Dermatitis acneiform		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)
occurrences (all)	3	3
Dermatitis allergic		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Dermatitis bullous		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Dermatitis contact		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Drug eruption		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	4

Dry skin			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	8 / 305 (2.62%)	8 / 297 (2.69%)	
occurrences (all)	8	9	
Ecchymosis			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)	
occurrences (all)	1	1	
Eczema			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)	
occurrences (all)	3	1	
Erythema			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	9 / 305 (2.95%)	7 / 297 (2.36%)	
occurrences (all)	9	7	
Erythema multiforme			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Hirsutism			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Hyperhidrosis			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Intertrigo			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Miliaria			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Nail bed inflammation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Night sweats		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Onycholysis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Pain of skin		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	4 / 297 (1.35%)
occurrences (all)	1	5
Petechiae		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	4 / 297 (1.35%)
occurrences (all)	1	5
Photosensitivity reaction		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Pruritus		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	18 / 305 (5.90%)	13 / 297 (4.38%)
occurrences (all)	23	13
Psoriasis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	3

Purpura		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Rash		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	18 / 305 (5.90%)	4 / 297 (1.35%)
occurrences (all)	21	4
Rash erythematous		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Rash maculo-papular		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	4 / 297 (1.35%)
occurrences (all)	7	5
Rash pruritic		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Scar pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	3	2
Sensitive skin		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Skin disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Skin exfoliation		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Skin irritation			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Skin lesion			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Skin striae			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Skin toxicity			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Skin ulcer			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Stevens-Johnson syndrome			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Urticaria			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	4 / 305 (1.31%)	1 / 297 (0.34%)	
occurrences (all)	4	1	
Renal and urinary disorders			
Acute kidney injury			
alternative dictionary used: CTCAE 5			

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Azotaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Chromaturia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Cystitis noninfective		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Dysuria		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Haematuria		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	3 / 297 (1.01%)
occurrences (all)	2	3
Incontinence		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Micturition urgency		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Nephrolithiasis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
occurrences (all)	1	2

Nocturia			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Pollakiuria			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	4 / 297 (1.35%)	
occurrences (all)	2	6	
Polyuria			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)	
occurrences (all)	1	2	
Proteinuria			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Renal failure			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Urethral intrinsic sphincter deficiency			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	
Urge incontinence			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Urinary incontinence			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	8 / 305 (2.62%)	3 / 297 (1.01%)	
occurrences (all)	8	4	
Endocrine disorders			



Cushing's syndrome alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Cushingoid alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	7 / 305 (2.30%) 8	5 / 297 (1.68%) 5	
Musculoskeletal and connective tissue disorders Arthralgia alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	19 / 305 (6.23%) 21	9 / 297 (3.03%) 10	
Back pain alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	18 / 305 (5.90%) 21	13 / 297 (4.38%) 16	
Bone pain alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Extremity contracture alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Facial asymmetry alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	3 / 305 (0.98%) 3	1 / 297 (0.34%) 1	
Flank pain alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	3 / 297 (1.01%) 3	
Joint stiffness alternative dictionary used: CTCAE			

5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Joint swelling		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Limb discomfort		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Mastication disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Mobility decreased		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Muscle spasms		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	4 / 297 (1.35%)
occurrences (all)	7	4
Muscle tightness		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	2
Muscle twitching		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Muscular weakness		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	31 / 305 (10.16%)	21 / 297 (7.07%)
occurrences (all)	49	25
Musculoskeletal chest pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	3	1
Musculoskeletal disorder		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Musculoskeletal pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
occurrences (all)	1	2
Musculoskeletal stiffness		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Myalgia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	11 / 305 (3.61%)	8 / 297 (2.69%)
occurrences (all)	27	9
Myokymia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Myopathy		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	2 / 297 (0.67%)
occurrences (all)	4	3
Neck pain		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	11 / 305 (3.61%)	1 / 297 (0.34%)
occurrences (all)	14	1

Osteoarthritis alternative dictionary used: CTCAE 5			
	subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
	occurrences (all)	1	2
Pain in extremity alternative dictionary used: CTCAE 5			
	subjects affected / exposed	7 / 305 (2.30%)	5 / 297 (1.68%)
	occurrences (all)	7	7
Pain in jaw alternative dictionary used: CTCAE 5			
	subjects affected / exposed	7 / 305 (2.30%)	1 / 297 (0.34%)
	occurrences (all)	15	1
Sjogren's syndrome alternative dictionary used: CTCAE 5			
	subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
	occurrences (all)	1	0
Tendon discomfort alternative dictionary used: CTCAE 5			
	subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
	occurrences (all)	0	1
Tendon disorder alternative dictionary used: CTCAE 5			
	subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
	occurrences (all)	1	0
Tendonitis alternative dictionary used: CTCAE 5			
	subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
	occurrences (all)	1	0
Trismus alternative dictionary used: CTCAE 5			
	subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
	occurrences (all)	1	0
Infections and infestations			

Anal abscess		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Bacterial infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	4
Brain abscess		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Bronchitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	9 / 305 (2.95%)	2 / 297 (0.67%)
occurrences (all)	12	2
Bronchitis viral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Candida infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	3 / 297 (1.01%)
occurrences (all)	7	3
Catheter site infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Cellulitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	2 / 297 (0.67%)
occurrences (all)	1	2
Conjunctivitis		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	4 / 297 (1.35%)
occurrences (all)	1	4
Conjunctivitis viral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
COVID-19		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	2
Cystitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	2 / 297 (0.67%)
occurrences (all)	4	2
Cytomegalovirus infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Device related infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	3	0
Device related sepsis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Ear infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Encephalomyelitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0

Enterocolitis infectious		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Escherichia urinary tract infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Folliculitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Fungal infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Gastroenteritis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	4 / 305 (1.31%)	3 / 297 (1.01%)
occurrences (all)	4	3
Gastroenteritis viral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Gingivitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Herpes dermatitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Herpes simplex		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Herpes simplex reactivation		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	2 / 297 (0.67%)
occurrences (all)	0	2
Herpes virus infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Herpes zoster		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	10 / 305 (3.28%)	7 / 297 (2.36%)
occurrences (all)	10	7
Herpes zoster infection neurological		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Influenza		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	4 / 297 (1.35%)
occurrences (all)	2	5
Kidney infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Lower respiratory tract infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0



Meningitis bacterial		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	2
Mucosal infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Nail infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Nasopharyngitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	3 / 297 (1.01%)
occurrences (all)	7	3
Oral candidiasis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	6 / 297 (2.02%)
occurrences (all)	7	6
Oral fungal infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Oral herpes		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	3	2
Oropharyngeal candidiasis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Otitis externa		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Pharyngitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	2	1
Pneumocystis jirovecii pneumonia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Pneumonia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	4 / 297 (1.35%)
occurrences (all)	8	4
Pneumonia chlamydial		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	3	0
Postoperative wound infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Rash pustular		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	1 / 297 (0.34%)
occurrences (all)	1	1
Respiratory tract infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	1 / 297 (0.34%)
occurrences (all)	3	1
Respiratory tract infection viral		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0

Retinitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Rhinitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Sepsis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Septic shock		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Sinusitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	3	1
Skin infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Staphylococcal bacteraemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Subcutaneous abscess		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Subdural abscess		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Tooth abscess		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Tooth infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Tracheitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Upper respiratory tract infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	7 / 305 (2.30%)	7 / 297 (2.36%)
occurrences (all)	7	7
Urinary tract infection		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	13 / 305 (4.26%)	10 / 297 (3.37%)
occurrences (all)	15	11
Urosepsis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Vestibular neuronitis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Viral rash		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1

Wound infection alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Metabolism and nutrition disorders Decreased appetite alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	64 / 305 (20.98%) 90	52 / 297 (17.51%) 59	
Dehydration alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	10 / 305 (3.28%) 15	0 / 297 (0.00%) 0	
Diabetes mellitus alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Dyslipidaemia alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	1 / 297 (0.34%) 1	
Glucose tolerance impaired alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	0 / 305 (0.00%) 0	2 / 297 (0.67%) 2	
Gout alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 1	0 / 297 (0.00%) 0	
Hypercreatininaemia alternative dictionary used: CTCAE 5 subjects affected / exposed occurrences (all)	1 / 305 (0.33%) 4	0 / 297 (0.00%) 0	
Hyperglycaemia alternative dictionary used: CTCAE 5			

subjects affected / exposed	12 / 305 (3.93%)	7 / 297 (2.36%)
occurrences (all)	16	8
Hyperkalaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	0 / 297 (0.00%)
occurrences (all)	3	0
Hypernatraemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	4	0
Hypertriglyceridaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Hyperuricaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hypoalbuminaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	2	0
Hypocalcaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hypoglycaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Hypokalaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	6 / 305 (1.97%)	5 / 297 (1.68%)
occurrences (all)	11	5

Hypomagnesaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	2 / 297 (0.67%)
occurrences (all)	5	3
Hyponatraemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	3 / 305 (0.98%)	1 / 297 (0.34%)
occurrences (all)	4	6
Hypophosphataemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)
occurrences (all)	2	0
Hypoproteinaemia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Increased appetite		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Lipomatosis		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)
occurrences (all)	1	0
Obesity		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Polydipsia		
alternative dictionary used: CTCAE 5		
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)
occurrences (all)	0	1
Steroid diabetes		
alternative dictionary used: CTCAE 5		

subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	3	
Type 2 diabetes mellitus			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	0 / 305 (0.00%)	1 / 297 (0.34%)	
occurrences (all)	0	1	
Vitamin B12 deficiency			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	2 / 305 (0.66%)	0 / 297 (0.00%)	
occurrences (all)	2	0	
Vitamin D deficiency			
alternative dictionary used: CTCAE 5			
subjects affected / exposed	1 / 305 (0.33%)	0 / 297 (0.00%)	
occurrences (all)	1	0	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2018	The rationale of the amendment is to extend the guidelines for the management of marizomib toxicities. Additionally this amendment also gives clarifications in the eligibility criteria and adaptations in various chapters as well as updates on timelines. Protocol/Summary: Inclusion criteria: Correction to: ability to provide written informed consent. Exclusion criteria: Clarification on prior and second invasive malignancy. Radiotherapy chapter adapted. Chapter 6.1: timelines for serology changed. Summary table adapted in sync with protocol. Chapter 11.2 : TR clarifications given. Appendix J: updated timelines Neurocognitive Testing Battery, MOS scale implemented. PISIC: Purpose of study: Clarification. Birth control: list expanded as per CTF guidelines + expanded Side effects: list updated according to the latest Marizomib IB. This amendment has been discussed and agreed by: EORTC HQ study team, Study Coordinators, CCTG study team and Celgene Study team
22 January 2019	Rationale for the scientific amendment is based on a comment of the FDA concerning the effect of marizomib on the ECG To date, there has been no signal of a safety issue with ECG abnormalities including prolonged QTc with marizomib. There has been no signal of ECG abnormalities in patient treated with marizomib. However, a thorough analysis of the QT/QTc data has not yet been submitted to the US FDA. Thus additional ECGs will be collected in the marizomib arm of the study. Protocol: - A new paragraph 5.6.4 added about ECG and marizomib - Chapter 6: sections 6.2.1, section 6.2.2 and summary table have been completed for marizomib patients. Baseline lab assessment timepoint has been aligned with the eligibility criteria. PISIC:- addendum 1, tests and procedures during the trial, has been adapted. This amendment has been discussed and agreed by the EORTC HQ study team, the Study-Coordinators, CCTG and the company Celgene.
05 February 2019	Rationale for the amendment and its classification: A change has been made in the time points of ECG in the marizomib only arm. Every 8 weeks has been changed to "as clinically indicated". PISIC has been adapted to the GDPR guidelines. Protocol: - Paragraph 5.6.4: adapted.- Chapter 6 assessments: text adapted.- Chapter 6 summary table : adapted. PISIC: - Appendix A: adapted.- Adaptation to GDPR guidelines. This amendment has been discussed and agreed by EORTC HQ 1709-team, Study-coordinators, CCTG and the company Celgene.

12 September 2019	<p>Important changes were made to the statistical section:</p> <ul style="list-style-type: none"> <li>• IDH1 mutation testing was clarified: "Patients with known IDH mutation (IDH mutation testing should be conducted for younger patients (&lt;55years old), patients with tumors with atypical features, or with history or present concurrent lower Gr gliomas".</li> <li>• Best overall response, objective response rate i.e. partial response (PR) plus complete response (CR) rate, CR rate and their duration based on investigator assessment were added to the list of secondary endpoints.</li> <li>• It was also decided that a re-randomization-test analysis will be performed to support the primary analysis in the ITT population and in uMGMT.</li> <li>• A pharmacokinetics analysis was added.</li> <li>• Further to company's discussions with the Food and Drug Administration (FDA) the following change to the initial interim analysis plan was strongly suggested: "A small alpha penalty should be paid for the futility analysis, as it will entail a review of the efficacy data." A small alpha penalty was therefore implemented although data was initially planned for futility purpose only. A small alpha spending of 0.00001 will be allocated to this interim analysis. The primary efficacy endpoint (OS) will be tested at a nominal 1-sided alpha level of 0.01499 in the overall population on the ITT set and unchanged level of 0.01 in the uMGMT group as no interim analysis will be performed in this subgroup. The alpha spending function used is of the Rho family. The Rho spending function was first published by Kim and DeMets (1987) and was generalized by Jennison and Turnbull (2000). It has following functional form: <math>\alpha(t) = \alpha t^p</math>, <math>p &gt; 0</math>. When <math>p = 1</math>, the corresponding stopping boundaries resemble the Pocock stopping boundaries. When <math>p = 3</math>, the boundaries resemble the O'Brien-Fleming boundaries. Larger value of <math>p</math> yield increasingly conservative boundaries. In this study, the small alpha spending of 0.00001 corresponds to <math>\rho = 4.26</math>. The a</li> </ul>
22 October 2019	<p>Section 1.1 of the protocol on proteasome inhibitor – Marizomib was amended with new pharmacovigilance data, described as follows:</p> <p>In this study, 3 serious adverse events (SAEs) of encephalopathy have been reported, 2 on the MRZ arm and 1 on the standard TMZ-based radiochemotherapy arm. One case of encephalopathy on the MRZ arm was fatal with the final autopsy reported as leukoencephalopathy. This subject presented with ataxia and hallucinations but rapidly became unconscious 95 days after start of MRZ/TMZ treatment and 45 days after completing radiotherapy. The investigator considered this event to be related to MRZ. The 2 other cases of encephalopathy (1 related to para-influenza virus Type 3 and 1 related to radiation treatment) were recovered and resolving, respectively.</p>

20 August 2020	Current information suggests that cancer patients have a higher risk of infection and serious complications from infections including COVID-19, than other patients. It is strongly recommended that investigators exercise medical/clinical judgement, and decisions regarding each patient should be individualized after considering the overall goals of treatment, the patient's current oncologic status and treatment tolerance as well as their general medical condition. In addition, investigators should adhere to local and institutional guidelines for SARS-CoV-2 infection and suspected COVID-19 infection. A COVID-19 appendix requested by German Regulatory Bodies was added to protocol.
30 September 2020	Sections 8.3 and 8.4 of the protocol were amended to implement the recommendations of the IDMC. IDMC v1.0 released after the recommendations of the IDMC was used to present the study results at ASCO 2021. Between September 2020 and May 2021, the database was further cleaned, and the complete medical review of eligibility, compliance, safety and efficacy was performed for the final analysis report planned to be released on early August 2021.
20 June 2022	Updates regarding the risk/benefit ratio following the IDMC review. <ul style="list-style-type: none"> <li>• Updates regarding COVID-19 pandemic (risk/benefit and vaccination) by inclusion of a specific guidelines during COVID-19 pandemic.</li> <li>• Updates related to Pharmacokinetics and translational research in order to reflect adaptation in the PK/PD project, with now a limitation to PD only to assess target engagement and to reflect new development of translational research projects and sample preparation (for example TMA for multiplex ImmunoFluorescence analysis). Addition of Zurich as a central lab.</li> <li>• Updates related to radiotherapy by the addition of a description of ancillary radiotherapy research projects using the collected RT plans and MRI imaging and by added description of how the radiotherapy quality assurance of the trial will be reported and by whom.</li> <li>• Administrative change for medical contact person at EORTC and name of new Group's Chair.</li> </ul>

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
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22 September 2020	The third IDMC review of the safety of the study and the first interim efficacy analysis (futility) took place in September 2020. Although the trial results did not cross the pre-specified futility boundary, the IDMC observed that there was as yet no evidence that this treatment provided a benefit in survival. The statistical data presented also suggested that it was extremely unlikely that a difference would emerge with additional patients or further follow-up. The IDMC observed that marizomib in this combination induced severe neurological and neuropsychiatric disorders, as well as other treatment-related grade 3-4 side effects, in a substantial proportion of the patients. The IDMC therefore recommended that the study be discontinued from further recruitment and that results be disclosed to medical community as soon as possible. However, if patients still on treatment were tolerating marizomib, they might be allowed to continue if so wished by the patient and treating physician	-
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Notes:

## Limitations and caveats

None reported