Clinical trial results:
Randomized trial assessing the significance of Bevacizumab in recurrent grade II and Grade III gliomas. The TAVAREC trial.

Summary

EudraCT number	2009-017422-39
Trial protocol	NL DE BE GB IT AT
Global end of trial date	24 September 2017

Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	26091

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	EORTC
Sponsor organisation address	83 Avenue Mounier, Brussels, Belgium, 1200
Public contact	Medical Department, European Organisation for Research and Treatment of Cancer, 0032 2774 1047/, regulatory@eortc.be
Scientific contact	Medical Department, European Organisation for Research and Treatment of Cancer, 0032 2774 1047/, regulatory@eortc.be

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	26 January 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 January 2017
Global end of trial reached?	Yes
Global end of trial date	24 September 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to compare the activity of both the combination Temozolomide (TMZ) plus bevacizumab and TMZ alone in recurrent grade II or grade III glioma patients without 1p/19q co-deletion.

Protection of trial subjects:

The responsible investigator ensured that this study was conducted in agreement with either the Declaration of Helsinki (available on the World Medical Association web site (http://www.wma.net) and/or the laws and regulations of the country, whichever provides the greatest protection of the patient. The protocol had been written, and the study was conducted according to the ICH Harmonized Tripartite Guideline on Good Clinical Practice (ICH-GCP). The protocol was approved by the competent ethics committee(s) as required by the applicable national legislation.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	08 February 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 36
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Netherlands: 46
Country: Number of subjects enrolled	United Kingdom: 33
Country: Number of subjects enrolled	Austria: 4
Country: Number of subjects enrolled	Belgium: 15
Country: Number of subjects enrolled	Germany: 16
Country: Number of subjects enrolled	Italy: 3
Worldwide total number of subjects	155
EEA total number of subjects	153

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
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)	140
From 65 to 84 years	15
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Main eligibility criteria:
Histologically proven grade II or grade III astrocytoma, oligodendroglioma or oligoastrocytoma
Demonstrated absence of 1p/19q co-deletion
First recurrence after initial treatment with either radiotherapy and/or chemotherapy
Enhancing recurrence
No more than one line of chemotherapy

Period 1

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

Blinding implementation details:

No blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	Temozolomide

Arm description:

Temozolomide 150 or 200 mg/m² d1-5

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:

Temozolomide dose after prior adjuvant/concurrent chemotherapy
Temozolomide will be administered orally on day 1-5, 150 mg/m² (dose per cycle: 750 mg/m²), and will be repeated every 4 weeks. The doses may be rounded to the nearest 20 mg to accommodate tablet strengths. If no significant toxicity (CTCAE criteria<2) is observed in cycle 1 dose escalation to 200 mg/m² (dose per cycle: 1000 mg/m²) is allowed.
Temozolomide dose in chemotherapy naïve patients
Temozolomide will be administered orally on day 1-5, 200 mg/m² (dose per cycle: 1000 mg/m²), and will be repeated every 4 weeks. The doses may be rounded to the nearest 20 mg to accommodate capsule strengths.

Arm title	TMZ+Bev

Arm description:

Temozolomide 150 or 200 mg/m² d1-5 +Bevacizumab 10 mg/kg d1 every 2 weeks

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

Dosage and administration details:

Temozolomide dose after prior adjuvant/concurrent chemotherapy
Temozolomide will be administered orally on day 1-5, 150 mg/m² (dose per cycle: 750 mg/m²), and will be repeated every 4 weeks. The doses may be rounded to the nearest 20 mg to accommodate tablet

strengths. If no significant toxicity (CTCAE criteria<2) is observed in cycle 1 dose escalation to 200 mg/m² (dose per cycle: 1000 mg/m²) is allowed.
Temozolomide dose in chemotherapy naïve patients
Temozolomide will be administered orally on day 1-5, 200 mg/m² (dose per cycle: 1000 mg/m²), and will be repeated every 4 weeks. The doses may be rounded to the nearest 20 mg to accommodate capsule strengths.

Investigational medicinal product name	Bevacizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

Bevacizumab at a dose of 10 mg/kg bodyweight i.v. in 90 min on day 1 was given every 2 weeks in cycles of 4 weeks. The subject's weight at baseline was used to calculate the Bevacizumab dose. If the weight changes by > 10% during the course of the study, the Bevacizumab dose was recalculated. The calculated dose was placed in a sterile, empty, i.v. bag and filled to 100 mL with 0.9% NaCl using aseptic technique.

Number of subjects in period 1	Temozolomide	TMZ+Bev
Started	77	78
Completed	20	14
Not completed	57	64
Physician decision	1	5
Consent withdrawn by subject	1	2
Disease progression	46	43
Adverse event, non-fatal	6	12
Patient did not come to the planned visit	1	-
Treatment never started	2	2

Baseline characteristics

Reporting groups	
Reporting group title	Temozolomide
Reporting group description:	
Temozolomide 150 or 200 mg/m² d1-5	
Reporting group title	TMZ+Bev
Reporting group description:	
Temozolomide 150 or 200 mg/m² d1-5 +Bevacizumab 10 mg/kg d1 every 2 weeks	

Reporting group values	Temozolomide	TMZ+Bev	Total
Number of subjects	77	78	155
Age categorical			
Age at randomization			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	71	69	140
From 65-84 years	6	9	15
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	45	57	102
Male	32	21	53

Subject analysis sets	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who are eligible and have started their allocated treatment (at least one dose of Bevacizumab in combination arm and at least one dose of TMZ in the TMZ alone arm).	

Reporting group values	Per protocol population		
Number of subjects	141		
Age categorical			
Age at randomization			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	0		

Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	140		
From 65-84 years	15		
85 years and over	0		
Gender categorical Units: Subjects			
Female	102		
Male	53		

End points

End points reporting groups

Reporting group title	Temozolomide
Reporting group description:	
Temozolomide 150 or 200 mg/m² d1-5	
Reporting group title	TMZ+Bev
Reporting group description:	
Temozolomide 150 or 200 mg/m² d1-5 +Bevacizumab 10 mg/kg d1 every 2 weeks	
Subject analysis set title	Per protocol population
Subject analysis set type	Per protocol
Subject analysis set description:	
All patients who are eligible and have started their allocated treatment (at least one dose of Bevacizumab in combination arm and at least one dose of TMZ in the TMZ alone arm).	

Primary: Overall Survival at 12 months

End point title	Overall Survival at 12 months
End point description:	
End point type	Primary
End point timeframe:	
All patients we observed during a minimum follow-up of 1 year. The number of patients alive at 1 year were computed and the following decision rule applied. Patients lost to follow-up before 1 year were considered as failures at the time of analysis.	

End point values	Temozolomide	TMZ+Bev		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	72	69		
Units: patients	44	38		

Statistical analyses

Statistical analysis title	Non comparative phase II trial with decision rule
Statistical analysis description:	
This is a non comparative phase II trial. The following decision rule is applied in each arm independently. If ≤ 41 patients alive at 1 year out of 72 are observed, the conclusion was that Bevacizumab-TMZ and/or TMZ alone should not be further investigated. If ≥ 42 patients alive at 1 year are observed, we concluded that Bevacizumab-TMZ and/or TMZ alone should be further investigated. In this case, the two-sided 80% confidence interval (CI) excludes the null hypothesis (P0).	
Comparison groups	Temozolomide v TMZ+Bev

Number of subjects included in analysis	141
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.59 [2]
Method	Regression, Cox
Parameter estimate	Percentage

Notes:

[1] - In TMZ+Bev, 3 patients were missing to reach the 72 patients included in the per protocol population required by the statistical design. The number of patients alive at 1 year was 38 of 69. The 80% CI around OS12 included P0=50%. The conclusion is that TMZ+Bv should not be further investigated in this disease. In the TMZ arm: 44 patients in the PP population (≥42) were alive at 1 year. The 80% CI excluded P0=50%. Conclusion is that TMZ should be further investigated in this disease.

[2] - This p value results from a sensitivity analysis in the intent to treat population comparing TMZ+Bev to TMZ. The Cox model was used with adjustment for previous line of treatment (no,PCV, TMZ/RT), grade (II,III), WHO performance status (0,1 vs 2).

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Before treatment start; Every 4 weeks during treatment; After the end of treatment (Follow-up): Every 12 weeks until progression

Adverse event reporting additional description:

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

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	TMZ+Bev

Reporting group description:

Temozolomide+ Bevacizumab

Reporting group title	Temozolomide

Reporting group description:

Temozolomide

Serious adverse events	TMZ+Bev	Temozolomide	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 76 (26.32%)	8 / 75 (10.67%)	
number of deaths (all causes)	60	55	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
INTRACRANIAL TUMOUR HAEMORRHAGE			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
ASTHENIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	4 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
DYSPNOEA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
DRUG ABUSE			

alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
WOUND DEHISCENCE			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
LEFT VENTRICULAR FAILURE			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
COGNITIVE DISORDER			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (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 21.1			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STATUS EPILEPTICUS			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TONIC CONVULSION			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LEUKOPENIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	5 / 76 (6.58%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOCYTOPENIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences causally related to treatment / all	6 / 6	3 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATITIS			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TOOTHACHE			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (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			
URINARY RETENTION			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BONE PAIN			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
ABSCESS			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAL ABSCESS			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CELLULITIS			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPIDURAL EMPYEMA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFECTED DERMAL CYST			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INFLUENZA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

PHARYNGITIS			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
SKIN INFECTION			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS ABSCESS			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 21.1			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TYPE 2 DIABETES MELLITUS			
alternative dictionary used: MedDRA 21.1			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	TMZ+Bev	Temozolomide	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	75 / 76 (98.68%)	74 / 75 (98.67%)	
Vascular disorders			
EMBOLISM			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
FLUSHING			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	5	
HAEMATOMA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
HYPERTENSION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	37 / 76 (48.68%)	14 / 75 (18.67%)	
occurrences (all)	228	67	
HYPOTENSION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	2	
THROMBOPHLEBITIS SUPERFICIAL			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
General disorders and administration			

site conditions			
CATHETER SITE PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
CHILLS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	1 / 75 (1.33%)	
occurrences (all)	7	1	
FACIAL PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	6	0	
FATIGUE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	61 / 76 (80.26%)	53 / 75 (70.67%)	
occurrences (all)	552	290	
GAIT DISTURBANCE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
INFLUENZA LIKE ILLNESS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	5	1	
INJECTION SITE REACTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
MALAISE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
OEDEMA			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
OEDEMA PERIPHERAL			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences (all)	25	10	
PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
PYREXIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences (all)	5	5	
Immune system disorders			
ANAPHYLACTIC REACTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
HYPERSENSITIVITY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	3 / 75 (4.00%)	
occurrences (all)	7	13	
Reproductive system and breast disorders			
MENSTRUATION IRREGULAR			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	8	0	
VAGINAL DISCHARGE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	3	
Respiratory, thoracic and mediastinal disorders			

COUGH			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 76 (10.53%)	4 / 75 (5.33%)	
occurrences (all)	44	7	
DYSPHONIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 76 (11.84%)	1 / 75 (1.33%)	
occurrences (all)	57	3	
DYSPNOEA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	7 / 76 (9.21%)	7 / 75 (9.33%)	
occurrences (all)	29	32	
EPISTAXIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 76 (10.53%)	1 / 75 (1.33%)	
occurrences (all)	32	1	
HICCUPS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
NASAL CONGESTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
OROPHARYNGEAL PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	7	1	
RHINITIS ALLERGIC			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences (all)	17	0	
RHINORRHOEA			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
SINUS DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
AGITATION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	2 / 75 (2.67%)	
occurrences (all)	17	7	
ANXIETY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	2 / 75 (2.67%)	
occurrences (all)	18	4	
BRADYPHRENIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
CONFUSIONAL STATE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	5 / 75 (6.67%)	
occurrences (all)	42	8	
DEPRESSION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	2 / 75 (2.67%)	
occurrences (all)	40	20	
DRUG ABUSE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
INSOMNIA			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	7 / 76 (9.21%)	3 / 75 (4.00%)	
occurrences (all)	26	20	
PERSONALITY CHANGE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	7	5	
Investigations			
ACTIVATED PARTIAL THROMBOPLASTIN TIME PROLONGED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	10	0	
BLOOD CHOLESTEROL INCREASED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
ELECTROCARDIOGRAM T WAVE ABNORMAL			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	9	0	
GAMMA-GLUTAMYLTRANSFERASE INCREASED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	27	2	
NEUTROPHIL COUNT DECREASED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
WEIGHT DECREASED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	17 / 76 (22.37%)	6 / 75 (8.00%)	
occurrences (all)	89	39	
WEIGHT INCREASED			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	19 / 76 (25.00%)	16 / 75 (21.33%)	
occurrences (all)	175	79	
Injury, poisoning and procedural complications			
ANKLE FRACTURE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	3	
CONCUSSION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
FACIAL BONES FRACTURE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
FALL			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
SPINAL FRACTURE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	10	
WOUND COMPLICATION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
WOUND DEHISCENCE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	6	3	
Cardiac disorders			
ANGINA PECTORIS			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
LEFT VENTRICULAR DYSFUNCTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
PALPITATIONS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
PERICARDITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
SINUS BRADYCARDIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
AMNESIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	1 / 75 (1.33%)	
occurrences (all)	38	1	
APHASIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	6 / 76 (7.89%)	8 / 75 (10.67%)	
occurrences (all)	20	31	
ATAXIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	6 / 76 (7.89%)	4 / 75 (5.33%)	
occurrences (all)	18	17	
CEREBROSPINAL FLUID LEAKAGE			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	3	
COGNITIVE DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 76 (10.53%)	4 / 75 (5.33%)	
occurrences (all)	20	11	
DISTURBANCE IN ATTENTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	40	5	
DIZZINESS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	13 / 76 (17.11%)	8 / 75 (10.67%)	
occurrences (all)	51	35	
DYSAESTHESIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	2	5	
DYSARTHRIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	6 / 76 (7.89%)	2 / 75 (2.67%)	
occurrences (all)	12	6	
DYSGEUSIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	4 / 75 (5.33%)	
occurrences (all)	18	10	
EXTRAPYRAMIDAL DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	7	0	
FACIAL NERVE DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	1 / 75 (1.33%)	
occurrences (all)	15	12	

FACIAL PARALYSIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	8	0	
GLOSSOPHARYNGEAL NERVE DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	3	
HAEMORRHAGE INTRACRANIAL			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
HEADACHE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	40 / 76 (52.63%)	22 / 75 (29.33%)	
occurrences (all)	237	60	
HEMIPARESIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	5 / 75 (6.67%)	
occurrences (all)	19	16	
HYPERSOMNIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	6	0	
LETHARGY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	3 / 75 (4.00%)	
occurrences (all)	6	16	
MEMORY IMPAIRMENT			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	10 / 76 (13.16%)	12 / 75 (16.00%)	
occurrences (all)	95	44	
MULTIPLE SCLEROSIS			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
MUSCLE SPASTICITY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	5	5	
PARAESTHESIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	1 / 75 (1.33%)	
occurrences (all)	4	2	
PERIPHERAL MOTOR NEUROPATHY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 76 (11.84%)	6 / 75 (8.00%)	
occurrences (all)	42	24	
PERIPHERAL SENSORY NEUROPATHY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	10 / 76 (13.16%)	7 / 75 (9.33%)	
occurrences (all)	52	26	
PYRAMIDAL TRACT SYNDROME			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	11	0	
SEIZURE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	35 / 76 (46.05%)	33 / 75 (44.00%)	
occurrences (all)	183	110	
SOMNOLENCE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	3	3	
SPEECH DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	

SYNCOPE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
TREMOR			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	3 / 75 (4.00%)	
occurrences (all)	8	13	
Blood and lymphatic system disorders			
ANAEMIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	6	
BICYTOPENIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
FEBRILE NEUTROPENIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
LYMPHADENOPATHY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	4	
Ear and labyrinth disorders			
EAR PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
HYPOACUSIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
TINNITUS			

alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	20	8	
VERTIGO			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Eye disorders			
CONJUNCTIVITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
DIPLOPIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
DRY EYE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	4	1	
EXTRAOCULAR MUSCLE PARESIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	9	0	
OPTIC NERVE DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	4 / 75 (5.33%)	
occurrences (all)	15	22	
PERIORBITAL OEDEMA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	4	
PHOTOPHOBIA			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
RETINOPATHY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
VISION BLURRED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	6 / 76 (7.89%)	3 / 75 (4.00%)	
occurrences (all)	21	6	
VISUAL IMPAIRMENT			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
VITREOUS FLOATERS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	25	5	
Gastrointestinal disorders			
ABDOMINAL DISTENSION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
ABDOMINAL PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	4 / 75 (5.33%)	
occurrences (all)	2	10	
ABDOMINAL PAIN UPPER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	3 / 75 (4.00%)	
occurrences (all)	2	8	
ANAL HAEMORRHAGE			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	4	2	
ANAL INCONTINENCE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
COLITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
CONSTIPATION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	30 / 76 (39.47%)	27 / 75 (36.00%)	
occurrences (all)	95	95	
DENTAL CARIES			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
DIARRHOEA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	14 / 76 (18.42%)	6 / 75 (8.00%)	
occurrences (all)	45	13	
DRY MOUTH			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	20	2	
DYSPEPSIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	2 / 75 (2.67%)	
occurrences (all)	0	3	
DYSPHAGIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	16	12	

GASTROINTESTINAL DISORDER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
GASTROINTESTINAL PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	3	7	
GASTROOESOPHAGEAL REFLUX DISEASE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	7	4	
GINGIVAL BLEEDING			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences (all)	16	0	
GINGIVAL PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	6	
HAEMORRHOIDS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	1 / 75 (1.33%)	
occurrences (all)	10	6	
NAUSEA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	43 / 76 (56.58%)	39 / 75 (52.00%)	
occurrences (all)	167	108	
OESOPHAGEAL PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
ORAL PAIN			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
PANCREATITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
PROCTALGIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
RECTAL HAEMORRHAGE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
STOMATITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	4 / 75 (5.33%)	
occurrences (all)	15	9	
TOOTHACHE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	2 / 75 (2.67%)	
occurrences (all)	9	3	
VOMITING			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	21 / 76 (27.63%)	20 / 75 (26.67%)	
occurrences (all)	43	34	
Hepatobiliary disorders			
HEPATIC FAILURE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	6	
HEPATIC PAIN			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Skin and subcutaneous tissue disorders			
ALOPECIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	13	4	
DERMATITIS ACNEIFORM			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	4 / 75 (5.33%)	
occurrences (all)	8	16	
DRY SKIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	2 / 75 (2.67%)	
occurrences (all)	3	7	
ERYTHEMA MULTIFORME			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
HYPERHIDROSIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
NIGHT SWEATS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	4	
PAIN OF SKIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	19	0	
PRURITUS			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	4 / 76 (5.26%)	5 / 75 (6.67%)	
occurrences (all)	7	17	
PURPURA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	6	0	
RASH			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
RASH MACULO-PAPULAR			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	12 / 76 (15.79%)	6 / 75 (8.00%)	
occurrences (all)	69	13	
SCAR PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
SKIN HYPERPIGMENTATION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
SKIN ULCER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
TELANGIECTASIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
URTICARIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
CYSTITIS NONINFECTIVE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
HAEMATURIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	4	2	
PROTEINURIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 76 (10.53%)	0 / 75 (0.00%)	
occurrences (all)	27	0	
URINARY INCONTINENCE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	2 / 75 (2.67%)	
occurrences (all)	21	6	
URINARY RETENTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
CUSHINGOID			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	9	0	
HYPERTHYROIDISM			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	2 / 75 (2.67%)	
occurrences (all)	20	12	

ARTHRITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
BACK PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	6 / 76 (7.89%)	3 / 75 (4.00%)	
occurrences (all)	50	18	
BONE PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
FIBROMYALGIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
JOINT RANGE OF MOTION DECREASED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	4	0	
MUSCLE RIGIDITY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
MUSCULAR WEAKNESS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	26	3	
MUSCULOSKELETAL CHEST PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
MUSCULOSKELETAL PAIN			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	7	0	
MYALGIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	4 / 76 (5.26%)	1 / 75 (1.33%)	
occurrences (all)	18	2	
NECK PAIN			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	31	8	
PAIN IN EXTREMITY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	6 / 76 (7.89%)	2 / 75 (2.67%)	
occurrences (all)	31	6	
PAIN IN JAW			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
TEMPOROMANDIBULAR JOINT SYNDROME			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
ABSCESS JAW			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
BRONCHITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	4	
CANDIDA INFECTION			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
CYSTITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	1 / 75 (1.33%)	
occurrences (all)	1	1	
DEVICE RELATED INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
EPIDURAL EMPYEMA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
EYE INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
GINGIVAL ABSCESS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
GINGIVITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
HERPES ZOSTER			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
INFLUENZA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	

LIP INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
LUNG INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences (all)	3	0	
ORAL HERPES			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
OTITIS EXTERNA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	2	
OTITIS MEDIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	1	
PHARYNGITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	1 / 75 (1.33%)	
occurrences (all)	2	1	
RASH PUSTULAR			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	0 / 75 (0.00%)	
occurrences (all)	19	0	
RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	3	
RHINITIS			
alternative dictionary used: MedDRA 18			

subjects affected / exposed	4 / 76 (5.26%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
SINUSITIS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	3 / 75 (4.00%)	
occurrences (all)	22	11	
SKIN INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	5 / 76 (6.58%)	0 / 75 (0.00%)	
occurrences (all)	13	0	
SUBCUTANEOUS ABSCESS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
TOOTH ABSCESS			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	16	0	
TOOTH INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
UPPER RESPIRATORY TRACT INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	8 / 76 (10.53%)	9 / 75 (12.00%)	
occurrences (all)	11	14	
URINARY TRACT INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	2 / 76 (2.63%)	0 / 75 (0.00%)	
occurrences (all)	5	0	
VAGINAL INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	2 / 75 (2.67%)	
occurrences (all)	10	3	

VULVOVAGINAL MYCOTIC INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	1	0	
WOUND INFECTION			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	2	0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	9 / 76 (11.84%)	8 / 75 (10.67%)	
occurrences (all)	42	17	
GLUCOSE TOLERANCE IMPAIRED			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	0 / 76 (0.00%)	1 / 75 (1.33%)	
occurrences (all)	0	5	
HYPERGLYCAEMIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	2 / 75 (2.67%)	
occurrences (all)	3	12	
HYPERTRIGLYCERIDAEMIA			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	3 / 76 (3.95%)	1 / 75 (1.33%)	
occurrences (all)	7	5	
OBESITY			
alternative dictionary used: MedDRA 18			
subjects affected / exposed	1 / 76 (1.32%)	0 / 75 (0.00%)	
occurrences (all)	10	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported