



Clinical trial results:

Cilengitide for subjects with newly diagnosed glioblastoma multiforme and methylated MGMT gene promoter - a multicenter, open-label, controlled Phase III study, testing cilengitide in combination with standard treatment (temozolomide with concomitant radiation therapy, followed by temozolomide maintenance therapy) versus standard treatment alone (CENTRIC)

Summary

EudraCT number	2007-004344-78
Trial protocol	BE GB AT DE CZ FR ES IT SK HU NL
Global end of trial date	30 July 2013

Results information

Result version number	v2 (current)
This version publication date	30 June 2016
First version publication date	26 July 2015
Version creation reason	• Correction of full data set Correction of full data set

Trial information

Trial identification

Sponsor protocol code	EMD 121974-011
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00689221
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Merck KGaA
Sponsor organisation address	Frankfurter Str. 250, Darmstadt, Germany,
Public contact	Communication Center, Merck KGaA, 49 6151-72-5200 , service@merckgroup.com
Scientific contact	Communication Center, Merck KGaA, 49 6151-72-5200 , service@merckgroup.com

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	19 November 2012
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 November 2012
Global end of trial reached?	Yes
Global end of trial date	30 July 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess whether overall survival time in subjects receiving cilengitide (2000 mg twice weekly intravenously in combination with standard treatment is statistically significantly prolonged compared to subjects receiving standard treatment alone.

Protection of trial subjects:

In this trial highest medical and ethical standards were followed, in accordance with the principles laid down in the Declaration of Helsinki, and that are consistent with Good Clinical Practice and applicable regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Hungary: 18
Country: Number of subjects enrolled	Italy: 20
Country: Number of subjects enrolled	Serbia: 31
Country: Number of subjects enrolled	Switzerland: 16
Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	United States: 54
Country: Number of subjects enrolled	Australia: 27
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	India: 24
Country: Number of subjects enrolled	Singapore: 5
Country: Number of subjects enrolled	Korea, Republic of: 34
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Netherlands: 15
Country: Number of subjects enrolled	Poland: 46
Country: Number of subjects enrolled	Slovakia: 5
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 16

Country: Number of subjects enrolled	Austria: 11
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Czech Republic: 6
Country: Number of subjects enrolled	France: 31
Country: Number of subjects enrolled	Germany: 117
Country: Number of subjects enrolled	Israel: 10
Worldwide total number of subjects	545
EEA total number of subjects	311

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	420
From 65 to 84 years	125
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

First/last subject (informed consent): Sep 2008/Aug 2011. Clinical data cut-off: 19 Nov 2012, Study completion date: Aug 2013.

Pre-assignment

Screening details:

Enrolled: 3471 screened for eligibility; 2926 excluded (mainly due to unmethylated O6-methylguanine-DNA methyltransferase status and non-fulfillment of inclusion or exclusion criteria), 545 subjects randomized.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Cilengitide + Temozolomide + Radiotherapy

Arm description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m^2] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Arm type	Experimental
Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Temozolomide (TMZ) 75 mg/m^2 intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34

Investigational medicinal product name	Cilengitide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77

Arm title	Temozolomide + Radiotherapy
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Arm description:

TMZ 75 mg/m^2 administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m^2 for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Arm type	Active comparator
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Investigational medicinal product name	Temozolomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Temozolomide (TMZ) 75 milligram per square meter [mg/m²] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m² for consecutive 5 days every 4 weeks until Week 34

Number of subjects in period 1	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy
Started	272	273
Completed	233	237
Not completed	39	36
Ongoing at cut-off date	39	36

Baseline characteristics

Reporting groups

Reporting group title	Cilengitide + Temozolomide + Radiotherapy
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Reporting group description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m²] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m² for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.

Reporting group title	Temozolomide + Radiotherapy
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Reporting group description:

TMZ 75 mg/m² administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m² for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Reporting group values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	Total
Number of subjects	272	273	545
Age categorical Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	56.8 ± 11	56 ± 10.97	-
Gender categorical Units: Subjects			
Female	124	130	254
Male	148	143	291

End points

End points reporting groups

Reporting group title	Cilengitide + Temozolomide + Radiotherapy
Reporting group description: Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m ²] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m ² for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 Gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 was optional in subjects without disease progression, If considered beneficial in the opinion of the Investigator.	
Reporting group title	Temozolomide + Radiotherapy
Reporting group description: TMZ 75 mg/m ² administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m ² for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.	

Primary: Overall survival (OS) time

End point title	Overall survival (OS) time
End point description: The OS time was defined as the time (in months) from randomization to death or last day known to be alive. Subjects without event were censored at the last date known to be alive or at the clinical cut-off date, whatever was earlier. ITT population included all the participants who were randomized to study treatment.	
End point type	Primary
End point timeframe: Time from randomization to death or last day known to be alive, reported between day of first subject randomized, that was, Sep 2008 until cut-off date, (19 Nov 2012)	

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	273		
Units: Months				
median (confidence interval 95%)	26.3 (23.8 to 28.8)	26.3 (23.9 to 34.7)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1 for Overall Survival (OS)
Comparison groups	Cilengitide + Temozolomide + Radiotherapy v Temozolomide + Radiotherapy

Number of subjects included in analysis	545
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.8623
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	1.021
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.808
upper limit	1.291

Secondary: Progression free survival (PFS) time - investigator and independent read

End point title	Progression free survival (PFS) time - investigator and independent read
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End point description:

The PFS time was defined as the duration from randomization to either first observation of progressive disease (PD) or occurrence of death due to any cause. Investigator read was the assessment of all imaging by the treating physician at the local trial site. Independent Read was the assessment of all imaging centrally by an Independent Review Committee (IRC). ITT population included all the participants who were randomized to study treatment.

End point type	Secondary
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End point timeframe:

Time from randomization to disease progression, death or last tumor assessment, reported between day of first subject randomized, that was, Sep 2008 until cut-off date, (19 Nov 2012)

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	272	273		
Units: Months				
median (confidence interval 95%)				
PFS Time-Investigator read	13.5 (10.8 to 15.9)	10.7 (8.1 to 13.3)		
PFS Time-Independent read	10.6 (8.2 to 13.4)	7.9 (5.9 to 12.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax)

End point title	Maximum observed plasma concentration (Cmax) ^[1]
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End point description:

The Cmax for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2.1. This endpoint was assessed in all subjects of "Cilengitide + Temozolomide + Radiotherapy" group who received at least 1 cilengitide dose with plasma concentration data available on Day 1 of Week -1.

End point type	Secondary
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End point timeframe:

Day 1 of Week -1

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only "Cilengitide + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	38 ^[2]			
Units: nanogram per milliliter (ng/mL)				
arithmetic mean (standard deviation)	167363 (± 368301.1)			

Notes:

[2] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Time to maximum plasma concentration (Tmax)

End point title	Time to maximum plasma concentration (Tmax) ^[3]
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End point description:

The Tmax for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2.1. This endpoint was assessed in all subjects of "Cilengitide + Temozolomide + Radiotherapy" group who received at least 1 cilengitide dose with plasma concentration data available on Day 1 of Week -1.

End point type	Secondary
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End point timeframe:

Day 1 of Week -1

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only "Cilengitide + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	38 ^[4]			
Units: hour				
arithmetic mean (standard deviation)	1.029 (± 0.401)			

Notes:

[4] - N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the plasma concentration curve from time 0 to 6 hours (AUC [0-6]) after dose

End point title	Area under the plasma concentration curve from time 0 to 6 hours (AUC [0-6]) after dose ^[5]
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End point description:

The AUC (0-6) for cilengitide was calculated by non-compartmental analysis using the computer program WinNonlin, Version 6.2.1. This endpoint was assessed in all subjects of "Cilengitide + Temozolomide + Radiotherapy" group who received at least 1 cilengitide dose with plasma concentration data available on Day 1 of Week -1.

End point type	Secondary
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End point timeframe:

Day 1 of Week -1

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Only "Cilengitide + Temozolomide + Radiotherapy" group was analyzed for this outcome measure as per planned analysis

End point values	Cilengitide + Temozolomide + Radiotherapy			
Subject group type	Reporting group			
Number of subjects analysed	37 ^[6]			
Units: hour*ng/mL				
arithmetic mean (standard deviation)	295171.2 (± 198050.6)			

Notes:

[6] - 'N' (number of participants analyzed) signifies those participants who were evaluable for this OM

Statistical analyses

No statistical analyses for this end point

Secondary: European organization for the research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) sub-scale scores

End point title	European organization for the research and treatment of cancer quality of life questionnaire core 30 (EORTC QLQ-C30) sub-scale scores
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End point description:

The EORTC QLQ-C30 is a questionnaire including following sub-scales: global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social activity), symptom scales (fatigue, nausea and vomiting, and pain) and single items (dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties). Scores are averaged for each scale and transformed to 0-100 scale; higher score indicates better quality of life on global health status and functional scales and worse quality of life on symptom scales and financial difficulty scale. This endpoint was assessed in all subjects who were randomized to study treatment and who were evaluable for this outcome measure. 'n' signifies those subjects who were evaluable for the specified category.

End point type	Secondary
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End point timeframe:

Up to 50 months

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	71	93		
Units: units on a scale				
arithmetic mean (standard deviation)				
Global Health Status (n=71, 92)	54.34 (± 25.58)	55.43 (± 27.02)		
Physical Functioning (n=71, 92)	65.7 (± 33.01)	67.46 (± 31.19)		
Role Functioning (n=71, 92)	56.34 (± 37.31)	56.34 (± 35.19)		
Emotional Functioning (n=71, 93)	67.49 (± 30.58)	67 (± 27.29)		
Cognitive Functioning (n=70, 93)	64.05 (± 29.16)	65.41 (± 31.4)		
Social Activity (n=71, 93)	56.34 (± 36.77)	62.72 (± 35.73)		
Fatigue (n=71, 92)	44.37 (± 33.07)	39.73 (± 29.93)		
Nausea and Vomiting (n=71, 93)	10.33 (± 20.77)	7.71 (± 16.03)		
Pain (n=71, 93)	22.3 (± 29.4)	24.37 (± 28.93)		
Dyspnoea (n=71, 92)	15.96 (± 28.09)	13.04 (± 22.62)		
Insomnia (n=71, 91)	20.66 (± 30.01)	20.51 (± 26.65)		
Appetite Loss (n=71, 92)	21.13 (± 30.47)	15.94 (± 28.59)		
Constipation (n=71, 93)	18.78 (± 28.02)	13.98 (± 25.69)		
Diarrhoea (n=70, 92)	6.67 (± 18.48)	4.35 (± 13.28)		
Financial difficulties (n=71, 93)	27.23 (± 31.53)	22.94 (± 31.46)		

Statistical analyses

No statistical analyses for this end point

Secondary: European organization for the research and treatment of cancer quality of life questionnaire brain module (EORTC QLQ-BN20) sub-scale scores

End point title	European organization for the research and treatment of cancer quality of life questionnaire brain module (EORTC QLQ-BN20) sub-scale scores
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End point description:

The QLQ-BN20 is a questionnaire specifically designed as the QLQ-C30 supplement for the evaluation of quality of life in brain tumor subjects. It includes 4 multi-item sub-scales: future uncertainty, visual disorder, motor dysfunction, communication deficits, and 7 single-item scales: headaches, seizures, drowsiness, itchy skin, hair loss, weakness of legs, and bladder control. All items are rated on a 4-point Likert-type scale ('1=not at all', '2=a little', '3=quite a bit' and '4=very much'), and are linearly transformed to a 0-100 scale, with higher scores indicating more severe symptoms. This endpoint was

assessed in all the subjects who were randomized and who were evaluable for this outcome measure. 'n' signifies those subjects who were evaluable for the specified category.

End point type	Secondary
End point timeframe:	
Up to 50 months	

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	68	87		
Units: units on a scale				
arithmetic mean (standard deviation)				
Future Uncertainty (n=68, 86)	44.49 (± 29.7)	39.31 (± 30.24)		
Visual Disorder (n=68, 85)	12.99 (± 20.24)	17.78 (± 23.77)		
Motor Dysfunction (n=68, 86)	27.45 (± 30.62)	23.39 (± 25.95)		
Communication Deficit (n=68, 86)	26.14 (± 28.59)	19.96 (± 27.89)		
Headaches (n=68, 86)	25.98 (± 32.5)	21.71 (± 26.45)		
Seizures (n=68, 87)	9.31 (± 22.93)	8.05 (± 20.94)		
Drowsiness (n=66, 87)	38.38 (± 33.71)	35.25 (± 31.07)		
Itchy Skin (n=68, 86)	9.8 (± 20)	13.57 (± 24.72)		
Hair Loss (n=66, 86)	13.13 (± 22.55)	15.12 (± 26.4)		
Weakness of Legs (n=67, 85)	24.38 (± 34.12)	20.39 (± 28.68)		
Bladder Control (n=67, 85)	19.4 (± 29.67)	10.2 (± 21.22)		

Statistical analyses

No statistical analyses for this end point

Secondary: EuroQol 5-Dimensions (EQ-5D) Questionnaire Index

End point title	EuroQol 5-Dimensions (EQ-5D) Questionnaire Index
End point description:	
The EuroQol-5D (EQ-5D) questionnaire is a measure of health status that provides a simple descriptive profile and a single index value. The optional part of the questionnaire was not applied. The EQ-5D defines health in terms of mobility, self-care, usual activities, pain/discomfort and anxiety/depression. The 5 items are combined to generate health profiles. These profiles were converted to a continuous single index score using a one to one matching. The lowest possible score is -0.594 (death) and the highest is 1.00 (full health). This endpoint was assessed in all subjects who were randomized to study treatment and who were evaluable for this outcome measure.	
End point type	Secondary
End point timeframe:	
Up to 50 months	

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	90		
Units: units on a scale				
arithmetic mean (standard deviation)	0.598 (± 0.43)	0.623 (± 0.36)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with change from baseline in work status at end of study

End point title	Number of subjects with change from baseline in work status at end of study
End point description:	
Number of subjects with change from baseline in work status (working full time [FT], part-time [PT], unemployed/retired [U/R]) at end of study (EOS) (up to cut-off date, [19 Nov 2012]) was reported. For the category 'part-time', the following sub-categories were defined: part-time due to basic disease (PT1); part-time not due to basic disease (PT2); part-time reason not known (PT3). This endpoint was assessed in safety population which included subjects who received any dose of study treatment that is Cilengitide, Temozolomide or Radiotherapy. According to trial design safety data in trial arms (Cilengitide vs Control) were collected based on different visit frequency and different safety surveillance period.	
End point type	Secondary
End point timeframe:	
Baseline, End of study (up to cut-off date, [19 Nov 2012])	

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	258		
Units: Subjects				
Baseline: FT, EOS: FT	3	6		
Baseline: FT, EOS: PT1	2	1		
Baseline: FT, EOS: PT2	1	0		
Baseline: FT, EOS: PT3	0	0		
Baseline: FT, EOS: U/R	24	22		
Baseline: PT1, EOS: FT	3	2		
Baseline: PT1, EOS: PT1	3	1		
Baseline: PT1, EOS: PT2	0	0		
Baseline: PT1, EOS: PT3	0	0		
Baseline: PT1, EOS: U/R	9	12		
Baseline: PT2, EOS: FT	0	1		

Baseline: PT2, EOS: PT1	0	0		
Baseline: PT2, EOS: PT2	0	0		
Baseline: PT2, EOS: PT3	1	0		
Baseline: PT2, EOS: U/R	5	4		
Baseline: PT3, EOS: FT	0	0		
Baseline: PT3, EOS: PT1	0	0		
Baseline: PT3, EOS: PT2	0	0		
Baseline: PT3, EOS: PT3	0	0		
Baseline: PT3, EOS: U/R	0	0		
Baseline: U/R, EOS: FT	5	8		
Baseline: U/R, EOS: PT1	5	7		
Baseline: U/R, EOS: PT2	1	1		
Baseline: U/R, EOS: PT3	0	0		
Baseline: U/R, EOS: U/R	199	191		
Baseline: Missing, EOS: FT	0	0		
Baseline: Missing, EOS: PT1	0	0		
Baseline: Missing, EOS: PT2	0	0		
Baseline: Missing, EOS: PT3	0	0		
Baseline: Missing, EOS: U/R	1	1		
Baseline: Missing, EOS: Missing	1	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious AEs, treatment-related AEs, treatment-related serious AEs, AEs leading to death, treatment related AEs leading to death, AEs of Grade 3 or 4 and treatment related AEs of Grade 3 or 4

End point title	Number of subjects with adverse events (AEs), serious AEs, treatment-related AEs, treatment-related serious AEs, AEs leading to death, treatment related AEs leading to death, AEs of Grade 3 or 4 and treatment related AEs of Grade 3 or 4
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End point description:

An AE is defined as any new untoward medical occurrences/worsening of pre-existing medical condition without regard to possibility of causal relationship. Treatment-emergent AEs are the events between first dose of study drug and up to 28 days after last dose of study treatment. A Serious AE is an AE that resulted in any of the following outcomes: death; life threatening; persistent/significant disability/incapacity; initial or prolonged inpatient hospitalization; congenital anomaly/birth defect. Treatment-related AEs are the AEs which are suspected to be reasonably related to the study treatment (cilengitide, or radiotherapy, or temozolomide) as per investigator assessment. The severity of AEs was assessed according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTCAE) (version 3.0): Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life threatening or disabling. Note: Death (Grade 5) was regarded as an outcome. This endpoint was assessed in Safety population.

End point type	Secondary
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End point timeframe:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first subject randomized, that is, Sep 2008 until cut-off date (19 Nov 2012)

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	258		
Units: Subjects				
AEs	261	253		
Serious AEs	138	115		
Treatment-related AEs	229	222		
Treatment-Related Serious AEs	55	47		
AEs leading to death	11	9		
Treatment-related AEs leading to death	3	3		
AEs with NCI–CTC toxicity Grade 3 or 4	169	158		
Treatment-related AEs of Grade 3 or 4	100	101		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with AEs belonging to standardized medical dictionary for regulatory activities (MedDRA) queries (SMQs) thromboembolic events and haemorrhage with NCI–CTC toxicity Grade 3 or 4

End point title	Number of subjects with AEs belonging to standardized medical dictionary for regulatory activities (MedDRA) queries (SMQs) thromboembolic events and haemorrhage with NCI–CTC toxicity Grade 3 or 4
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End point description:

Thromboembolic events (standardized MedDRA query [SMQ]) Grade 3 or 4 AEs encompassed hemiparesis and cerebrovascular accident, pulmonary embolism, and deep vein thrombosis. Thromboembolic events (SMQ) of any grade and of Grade 3 or 4 were generally more frequent in the Cilengitide + Temozolomide/Radiotherapy group than in the Temozolomide/Radiotherapy group but were still in the expected range of this patient population. The severity of AEs was assessed according to the National Cancer Institute–Common Toxicity Criteria (NCI–CTCAE) (version 3.0): Grade 1=mild, Grade 2=moderate, Grade 3=severe, Grade 4=life threatening or disabling. Note: Death (Grade 5) was regarded as an outcome. This endpoint was assessed in safety analysis population.

End point type	Secondary
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End point timeframe:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first subject randomized, that is, Sep 2008 until cut-off date (19 Nov 2012).

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	263	258		
Units: Subjects				
SMQ:Thromboembolic events	35	23		
SMQ: Haemorrhage	4	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with clinically significant abnormal electrocardiogram (ECG) and lab parameters

End point title	Number of subjects with clinically significant abnormal electrocardiogram (ECG) and lab parameters
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End point description:

Any clinically significant abnormal ECG and lab finding was planned to be reported as AE only so they have been captured in the below mentioned adverse event section.

End point type	Secondary
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End point timeframe:

Up to 50 months

End point values	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0 ^[7]	0 ^[8]		
Units: Subjects				

Notes:

[7] - Clinically significant abnormal ECG and lab finding was planned to be reported as AE only

[8] - Clinically significant abnormal ECG and lab finding was planned to be reported as AE only

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Time from first dose up to 28 days after last dose of study treatment, reported between day of first participant randomized, that is, Sep 2008 until cut-off date (19 Nov 2012)

Assessment type	Non-systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	15

Reporting groups

Reporting group title	Cilengitide + Temozolomide + Radiotherapy
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Reporting group description:

Cilengitide 2000 milligram (mg) twice weekly over 1 hour intravenous infusion from Weeks -1 to 77, Temozolomide (TMZ) 75 milligram per square meter [mg/m²] intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m² for consecutive 5 days every 4 weeks until Week 34 and radiotherapy (RTX) at a dose of 2 gray (Gy) per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason. Continuation of cilengitide treatment after Week 77 will be optional in participants without disease progression.

Reporting group title	Temozolomide + Radiotherapy
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Reporting group description:

TMZ 75 mg/m² administered intravenously once daily from Weeks 1 to 6, from Week 11 onward, TMZ was given as maintenance treatment at a dose of 150-200 mg/m² for consecutive 5 days every 4 weeks until Week 34 and RTX at a dose of 2 Gy per fraction once daily, 5 days per week from Weeks 1 to 6 or until occurrence of progressive disease, unacceptable toxicity, or withdrawal for any other reason.

Serious adverse events	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	
Total subjects affected by serious adverse events			
subjects affected / exposed	138 / 263 (52.47%)	115 / 258 (44.57%)	
number of deaths (all causes)	139	130	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
BASAL CELL CARCINOMA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GLIOBLASTOMA			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

INTRACRANIAL TUMOUR HAEMORRHAGE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
METASTASES TO MENINGES			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEURILEMMOMA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCREATIC CARCINOMA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SMALL CELL LUNG CANCER STAGE UNSPECIFIED			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
THYROID CANCER			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TUMOUR HAEMORRHAGE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOPLASM RECURRENCE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEOPLASMS BENIGN, MALIGNANT			

AND UNSPECIFIED (INCL #CYSTS AND POLYPS)			
subjects affected / exposed	6 / 263 (2.28%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	1 / 6	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
DEEP VEIN THROMBOSIS			
subjects affected / exposed	5 / 263 (1.90%)	6 / 258 (2.33%)	
occurrences causally related to treatment / all	1 / 5	1 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
EMBOLISM VENOUS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERTENSION			
subjects affected / exposed	1 / 263 (0.38%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOTENSION			
subjects affected / exposed	3 / 263 (1.14%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	2 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PELVIC VENOUS THROMBOSIS			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCLAVIAN VEIN THROMBOSIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
THROMBOSIS			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

VENOUS THROMBOSIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
SURGERY			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PALLIATIVE CARE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLADDER CATHETERISATION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (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			
CHEST PAIN			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ASTHENIA			
subjects affected / exposed	5 / 263 (1.90%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
GENERAL PHYSICAL HEALTH DETERIORATION			
subjects affected / exposed	2 / 263 (0.76%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 2	0 / 3	
deaths causally related to treatment / all	0 / 1	0 / 0	
GAIT DISTURBANCE			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FATIGUE			
subjects affected / exposed	4 / 263 (1.52%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	4 / 4	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISEASE PROGRESSION			
subjects affected / exposed	4 / 263 (1.52%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 3	0 / 0	
DEVICE MALFUNCTION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PAIN			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYREXIA			
subjects affected / exposed	4 / 263 (1.52%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 4	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
DRUG HYPERSENSITIVITY			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERSENSITIVITY			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

CHRONIC OBSTRUCTIVE PULMONARY DISEASE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE RESPIRATORY DISTRESS SYNDROME			
subjects affected / exposed	0 / 263 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
DYSпноEA			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMOTHORAX			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOXIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLEURAL EFFUSION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA ASPIRATION			
subjects affected / exposed	4 / 263 (1.52%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	2 / 4	0 / 0	
deaths causally related to treatment / all	1 / 1	0 / 0	
VOCAL CORD POLYP			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONITIS			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PULMONARY EMBOLISM			
subjects affected / exposed	12 / 263 (4.56%)	7 / 258 (2.71%)	
occurrences causally related to treatment / all	6 / 12	0 / 7	
deaths causally related to treatment / all	2 / 2	0 / 0	
RESPIRATORY DISTRESS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RESPIRATORY FAILURE			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Psychiatric disorders			
DELIRIUM			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISORIENTATION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONFUSIONAL STATE			
subjects affected / exposed	5 / 263 (1.90%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 5	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
AGITATION			
subjects affected / exposed	0 / 263 (0.00%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSION			

subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HALLUCINATION, VISUAL			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENTAL STATUS CHANGES			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANIC ATTACK			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERSONALITY CHANGE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PSYCHOTIC DISORDER			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSTHYMIC DISORDER			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SCHIZOPHRENIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
FIBRIN D DIMER INCREASED			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ELECTROCARDIOGRAM QT PROLONGED			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BLOOD URIC ACID INCREASED			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PLATELET COUNT DECREASED			
subjects affected / exposed	2 / 263 (0.76%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOCYTE COUNT DECREASED			
subjects affected / exposed	2 / 263 (0.76%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	2 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPHIL COUNT DECREASED			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSAMINASES INCREASED			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
FALL			
subjects affected / exposed	1 / 263 (0.38%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
FRACTURE			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
LIMB INJURY			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST PROCEDURAL OEDEMA			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OVERDOSE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
OPEN WOUND			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL BONES FRACTURE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
THORACIC VERTEBRAL FRACTURE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIUS FRACTURE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION NECROSIS			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
RADIATION INJURY			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
POSTOPERATIVE WOUND COMPLICATION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
CARDIAC FAILURE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATRIAL FIBRILLATION			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CORONARY ARTERY THROMBOSIS			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ACUTE MYOCARDIAL INFARCTION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MYOCARDIAL ISCHAEMIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

APHASIA			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ATAXIA			
subjects affected / exposed	2 / 263 (0.76%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN INJURY			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BRAIN OEDEMA			
subjects affected / exposed	5 / 263 (1.90%)	5 / 258 (1.94%)	
occurrences causally related to treatment / all	0 / 5	4 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
COGNITIVE DISORDER			
subjects affected / exposed	3 / 263 (1.14%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBROVASCULAR ACCIDENT			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL VENTRICLE DILATATION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL ISCHAEMIA			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL HAEMORRHAGE			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CEREBRAL CYST			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CENTRAL NERVOUS SYSTEM NECROSIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPILEPSY			
subjects affected / exposed	6 / 263 (2.28%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	2 / 6	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONVULSION			
subjects affected / exposed	20 / 263 (7.60%)	14 / 258 (5.43%)	
occurrences causally related to treatment / all	2 / 20	1 / 14	
deaths causally related to treatment / all	0 / 0	0 / 0	
FACIAL NERVE DISORDER			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEPRESSED LEVEL OF CONSCIOUSNESS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COMA			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
DIZZINESS			

subjects affected / exposed	3 / 263 (1.14%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COORDINATION ABNORMAL			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HAEMORRHAGE INTRACRANIAL			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEADACHE			
subjects affected / exposed	5 / 263 (1.90%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 5	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEMIPARESIS			
subjects affected / exposed	12 / 263 (4.56%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 12	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYDROCEPHALUS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
INTRACRANIAL PRESSURE INCREASED			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GRAND MAL CONVULSION			
subjects affected / exposed	5 / 263 (1.90%)	3 / 258 (1.16%)	
occurrences causally related to treatment / all	0 / 5	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
NORMAL PRESSURE HYDROCEPHALUS			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUROLOGICAL DECOMPENSATION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
MIGRAINE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
MEMORY IMPAIRMENT			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LETHARGY			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PARTIAL SEIZURES			
subjects affected / exposed	4 / 263 (1.52%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL MOTOR NEUROPATHY			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PERIPHERAL SENSORY NEUROPATHY			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYRAMIDAL TRACT SYNDROME			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SOMNOLENCE			
subjects affected / exposed	3 / 263 (1.14%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 3	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SPEECH DISORDER			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
POST HERPETIC NEURALGIA			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRIGEMINAL NEURALGIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
STATUS EPILEPTICUS			
subjects affected / exposed	4 / 263 (1.52%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 4	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TRANSIENT ISCHAEMIC ATTACK			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SYNCOPE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VISUAL FIELD DEFECT			

subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
VIITH NERVE PARALYSIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
FEBRILE NEUTROPENIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ANAEMIA			
subjects affected / exposed	2 / 263 (0.76%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 2	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
DISSEMINATED INTRAVASCULAR COAGULATION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
FEBRILE BONE MARROW APLASIA			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PANCYTOPENIA			
subjects affected / exposed	1 / 263 (0.38%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 1	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
NEUTROPENIA			
subjects affected / exposed	6 / 263 (2.28%)	11 / 258 (4.26%)	
occurrences causally related to treatment / all	6 / 6	10 / 11	
deaths causally related to treatment / all	0 / 0	1 / 1	
THROMBOCYTOPENIA			

subjects affected / exposed	16 / 263 (6.08%)	24 / 258 (9.30%)	
occurrences causally related to treatment / all	16 / 16	24 / 24	
deaths causally related to treatment / all	0 / 0	1 / 1	
LEUKOPENIA			
subjects affected / exposed	4 / 263 (1.52%)	10 / 258 (3.88%)	
occurrences causally related to treatment / all	4 / 4	10 / 10	
deaths causally related to treatment / all	0 / 0	1 / 1	
HAEMATOTOXICITY			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
LYMPHOPENIA			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Ear and labyrinth disorders			
VERTIGO			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
DIARRHOEA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CONSTIPATION			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
COLITIS			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
ABDOMINAL PAIN UPPER			

subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DYSPHAGIA			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ABDOMINAL PAIN			
subjects affected / exposed	1 / 263 (0.38%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ENTERITIS			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTRIC DISORDER			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NAUSEA			
subjects affected / exposed	2 / 263 (0.76%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	1 / 2	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
UPPER GASTROINTESTINAL HAEMORRHAGE			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
VOMITING			
subjects affected / exposed	3 / 263 (1.14%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	1 / 3	2 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
CHOLECYSTITIS			

subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
DRUG-INDUCED LIVER INJURY			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC STEATOSIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HEPATIC FAILURE			
subjects affected / exposed	0 / 263 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
DRUG ERUPTION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RASH			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
EXFOLIATIVE RASH			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
BLADDER NECK OBSTRUCTION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
CALCULUS URINARY			

subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
RENAL FAILURE ACUTE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Endocrine disorders			
ADRENAL INSUFFICIENCY			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
INAPPROPRIATE ANTIDIURETIC HORMONE SECRETION			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
MUSCLE SPASMS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
BACK PAIN			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MUSCULAR WEAKNESS			
subjects affected / exposed	1 / 263 (0.38%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Infections and infestations APPENDICITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 263 (0.38%) 0 / 1 0 / 0	0 / 258 (0.00%) 0 / 0 0 / 0	
BACTERIAL INFECTION subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 263 (0.38%) 0 / 1 0 / 0	0 / 258 (0.00%) 0 / 0 0 / 0	
CELLULITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 263 (0.38%) 0 / 1 0 / 0	1 / 258 (0.39%) 0 / 1 0 / 0	
BRONCHOPNEUMONIA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 263 (0.38%) 0 / 1 0 / 0	0 / 258 (0.00%) 0 / 0 0 / 0	
BRONCHITIS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	1 / 263 (0.38%) 0 / 1 0 / 0	0 / 258 (0.00%) 0 / 0 0 / 0	
BRAIN ABSCESS subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 263 (0.00%) 0 / 0 0 / 0	1 / 258 (0.39%) 0 / 1 0 / 0	
LOWER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	3 / 263 (1.14%) 1 / 3 0 / 1	0 / 258 (0.00%) 0 / 0 0 / 0	
INFLUENZA subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	0 / 263 (0.00%) 0 / 0 0 / 0	1 / 258 (0.39%) 1 / 1 0 / 0	

HERPES ZOSTER			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
H1N1 INFLUENZA			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
GASTROENTERITIS			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
ESCHERICHIA URINARY TRACT INFECTION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEVICE RELATED SEPSIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
EPIGLOTTITIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
OSTEOMYELITIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
ORAL CANDIDIASIS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
NECROTISING FASCIITIS			

subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PNEUMONIA			
subjects affected / exposed	9 / 263 (3.42%)	7 / 258 (2.71%)	
occurrences causally related to treatment / all	3 / 9	3 / 7	
deaths causally related to treatment / all	0 / 1	2 / 2	
POSTOPERATIVE WOUND INFECTION			
subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
PYELONEPHRITIS ACUTE			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
MENINGITIS			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
URINARY TRACT INFECTION			
subjects affected / exposed	2 / 263 (0.76%)	4 / 258 (1.55%)	
occurrences causally related to treatment / all	1 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND ABSCESS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
WOUND INFECTION			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SUBCUTANEOUS ABSCESS			

subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPSIS			
subjects affected / exposed	2 / 263 (0.76%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
SEPTIC SHOCK			
subjects affected / exposed	0 / 263 (0.00%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
SKIN INFECTION			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
DEHYDRATION			
subjects affected / exposed	1 / 263 (0.38%)	2 / 258 (0.78%)	
occurrences causally related to treatment / all	0 / 1	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERGLYCAEMIA			
subjects affected / exposed	0 / 263 (0.00%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
TYPE 2 DIABETES MELLITUS			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPONATRAEMIA			

subjects affected / exposed	1 / 263 (0.38%)	1 / 258 (0.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOGLYCAEMIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPERURICAEMIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
HYPOCALCAEMIA			
subjects affected / exposed	1 / 263 (0.38%)	0 / 258 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Cilengitide + Temozolomide + Radiotherapy	Temozolomide + Radiotherapy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	252 / 263 (95.82%)	241 / 258 (93.41%)	
Vascular disorders			
HYPERTENSION			
subjects affected / exposed	17 / 263 (6.46%)	8 / 258 (3.10%)	
occurrences (all)	17	8	
General disorders and administration site conditions			
FATIGUE			
subjects affected / exposed	101 / 263 (38.40%)	84 / 258 (32.56%)	
occurrences (all)	101	84	
OEDEMA PERIPHERAL			
subjects affected / exposed	36 / 263 (13.69%)	24 / 258 (9.30%)	
occurrences (all)	36	24	
ASTHENIA			

subjects affected / exposed occurrences (all)	42 / 263 (15.97%) 42	20 / 258 (7.75%) 20	
PYREXIA subjects affected / exposed occurrences (all)	27 / 263 (10.27%) 27	16 / 258 (6.20%) 16	
Respiratory, thoracic and mediastinal disorders COUGH subjects affected / exposed occurrences (all)	51 / 263 (19.39%) 51	23 / 258 (8.91%) 23	
DYSPNOEA subjects affected / exposed occurrences (all)	21 / 263 (7.98%) 21	9 / 258 (3.49%) 9	
OROPHARYNGEAL PAIN subjects affected / exposed occurrences (all)	20 / 263 (7.60%) 20	6 / 258 (2.33%) 6	
Psychiatric disorders ANXIETY subjects affected / exposed occurrences (all)	13 / 263 (4.94%) 13	14 / 258 (5.43%) 14	
CONFUSIONAL STATE subjects affected / exposed occurrences (all)	14 / 263 (5.32%) 14	12 / 258 (4.65%) 12	
DEPRESSION subjects affected / exposed occurrences (all)	19 / 263 (7.22%) 19	14 / 258 (5.43%) 14	
INSOMNIA subjects affected / exposed occurrences (all)	35 / 263 (13.31%) 35	24 / 258 (9.30%) 24	
Investigations WEIGHT DECREASED subjects affected / exposed occurrences (all)	15 / 263 (5.70%) 15	14 / 258 (5.43%) 14	
ALANINE AMINOTRANSFERASE INCREASED subjects affected / exposed occurrences (all)	21 / 263 (7.98%) 21	17 / 258 (6.59%) 17	
Injury, poisoning and procedural			

complications			
RADIATION SKIN INJURY			
subjects affected / exposed	20 / 263 (7.60%)	22 / 258 (8.53%)	
occurrences (all)	20	22	
Nervous system disorders			
CONVULSION			
subjects affected / exposed	46 / 263 (17.49%)	19 / 258 (7.36%)	
occurrences (all)	46	19	
DIZZINESS			
subjects affected / exposed	34 / 263 (12.93%)	25 / 258 (9.69%)	
occurrences (all)	34	25	
HEADACHE			
subjects affected / exposed	118 / 263 (44.87%)	88 / 258 (34.11%)	
occurrences (all)	118	88	
HEMIPARESIS			
subjects affected / exposed	17 / 263 (6.46%)	11 / 258 (4.26%)	
occurrences (all)	17	11	
APHASIA			
subjects affected / exposed	25 / 263 (9.51%)	11 / 258 (4.26%)	
occurrences (all)	25	11	
MEMORY IMPAIRMENT			
subjects affected / exposed	27 / 263 (10.27%)	18 / 258 (6.98%)	
occurrences (all)	27	18	
PARAESTHESIA			
subjects affected / exposed	14 / 263 (5.32%)	7 / 258 (2.71%)	
occurrences (all)	14	7	
TREMOR			
subjects affected / exposed	20 / 263 (7.60%)	11 / 258 (4.26%)	
occurrences (all)	20	11	
Blood and lymphatic system disorders			
ANAEMIA			
subjects affected / exposed	16 / 263 (6.08%)	17 / 258 (6.59%)	
occurrences (all)	16	17	
NEUTROPENIA			
subjects affected / exposed	32 / 263 (12.17%)	23 / 258 (8.91%)	
occurrences (all)	32	23	
LYMPHOPENIA			

subjects affected / exposed	46 / 263 (17.49%)	35 / 258 (13.57%)	
occurrences (all)	46	35	
LEUKOPENIA			
subjects affected / exposed	30 / 263 (11.41%)	28 / 258 (10.85%)	
occurrences (all)	30	28	
THROMBOCYTOPENIA			
subjects affected / exposed	61 / 263 (23.19%)	61 / 258 (23.64%)	
occurrences (all)	61	61	
Eye disorders			
VISION BLURRED			
subjects affected / exposed	16 / 263 (6.08%)	11 / 258 (4.26%)	
occurrences (all)	16	11	
Gastrointestinal disorders			
ABDOMINAL PAIN UPPER			
subjects affected / exposed	15 / 263 (5.70%)	7 / 258 (2.71%)	
occurrences (all)	15	7	
ABDOMINAL PAIN			
subjects affected / exposed	16 / 263 (6.08%)	7 / 258 (2.71%)	
occurrences (all)	16	7	
CONSTIPATION			
subjects affected / exposed	101 / 263 (38.40%)	78 / 258 (30.23%)	
occurrences (all)	101	78	
DIARRHOEA			
subjects affected / exposed	44 / 263 (16.73%)	20 / 258 (7.75%)	
occurrences (all)	44	20	
DYSPEPSIA			
subjects affected / exposed	24 / 263 (9.13%)	8 / 258 (3.10%)	
occurrences (all)	24	8	
VOMITING			
subjects affected / exposed	79 / 263 (30.04%)	86 / 258 (33.33%)	
occurrences (all)	79	86	
NAUSEA			
subjects affected / exposed	129 / 263 (49.05%)	126 / 258 (48.84%)	
occurrences (all)	129	126	
Skin and subcutaneous tissue disorders			

ALOPECIA			
subjects affected / exposed	70 / 263 (26.62%)	70 / 258 (27.13%)	
occurrences (all)	70	70	
RASH			
subjects affected / exposed	28 / 263 (10.65%)	19 / 258 (7.36%)	
occurrences (all)	28	19	
PRURITUS			
subjects affected / exposed	32 / 263 (12.17%)	15 / 258 (5.81%)	
occurrences (all)	32	15	
DRY SKIN			
subjects affected / exposed	16 / 263 (6.08%)	12 / 258 (4.65%)	
occurrences (all)	16	12	
ERYTHEMA			
subjects affected / exposed	21 / 263 (7.98%)	10 / 258 (3.88%)	
occurrences (all)	21	10	
Renal and urinary disorders			
URINARY INCONTINENCE			
subjects affected / exposed	15 / 263 (5.70%)	4 / 258 (1.55%)	
occurrences (all)	15	4	
Musculoskeletal and connective tissue disorders			
ARTHRALGIA			
subjects affected / exposed	25 / 263 (9.51%)	6 / 258 (2.33%)	
occurrences (all)	25	6	
BACK PAIN			
subjects affected / exposed	31 / 263 (11.79%)	8 / 258 (3.10%)	
occurrences (all)	31	8	
MUSCULAR WEAKNESS			
subjects affected / exposed	22 / 263 (8.37%)	15 / 258 (5.81%)	
occurrences (all)	22	15	
PAIN IN EXTREMITY			
subjects affected / exposed	24 / 263 (9.13%)	13 / 258 (5.04%)	
occurrences (all)	24	13	
Infections and infestations			
NASOPHARYNGITIS			
subjects affected / exposed	32 / 263 (12.17%)	11 / 258 (4.26%)	
occurrences (all)	32	11	

UPPER RESPIRATORY TRACT INFECTION			
subjects affected / exposed	28 / 263 (10.65%)	16 / 258 (6.20%)	
occurrences (all)	28	16	
URINARY TRACT INFECTION			
subjects affected / exposed	16 / 263 (6.08%)	21 / 258 (8.14%)	
occurrences (all)	16	21	
Metabolism and nutrition disorders			
DECREASED APPETITE			
subjects affected / exposed	54 / 263 (20.53%)	45 / 258 (17.44%)	
occurrences (all)	54	45	
HYPOKALAEMIA			
subjects affected / exposed	14 / 263 (5.32%)	8 / 258 (3.10%)	
occurrences (all)	14	8	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 March 2010	To adapt certain processes of study conduct based on the global practical experience. These included the following: The eligibility decision could be based on local laboratory blood results if the process time for the central laboratory could result in the subject being ineligible (however the respective central laboratory tests still to be performed) The detailed time windows from screening to randomization were revised to allow more flexibility. The inclusion criterion "normal PTT" was revised to "below ULN PTT". Based on updated safety data in newly diagnosed GBM patients and in alignment with other recently initiated study protocols of cilengitide combination treatments (EMR 200052-013 and EMR 200037-014), a case-by-case decision was allowed to potentially use therapeutic doses of heparin (after initial resolution of a disease-related thromboembolic event, e.g., a DVT) with cilengitide treatment after resolution of the event. To introduce a general description of cilengitide handling independent of dose strength by referring to the handling instructions. To adapt the technical cut-off value of the applied MGMT assay to reflect the technical modalities of this assay version based on the current data set (actual nadir of the bimodal distribution). To include minor corrections and clarifications to the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported