



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 |
|-----------------------|----------------|

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 |
|------------------|-----------------------------|

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 |
|----------|-------------------|

| | |
|--|-----------------------|
| 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 |
|-----------------------|---|

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 |
|-----------------------|-----------------------------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|---|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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] |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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

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|--|--|
| End point title | EuroQol 5-Dimensions (EQ-5D) Questionnaire Index |
| End point description: | |
| <p>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.</p> | |
| 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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|---|

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 |
|----------------|-----------|

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 |
|-----------------|--|

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 |
|----------------|-----------|

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 |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|----|
| Dictionary version | 15 |
|--------------------|----|

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/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 |
|-----------------------|-----------------------------|

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 | |
| DYSPNOEA | | | |
| 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 | <p>To adapt certain processes of study conduct based on the global practical experience. These included the following:</p> <p>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)</p> <p>The detailed time windows from screening to randomization were revised to allow more flexibility.</p> <p>The inclusion criterion "normal PTT" was revised to "below ULN PTT".</p> <p>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.</p> <p>To introduce a general description of cilengitide handling independent of dose strength by referring to the handling instructions.</p> <p>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).</p> <p>To include minor corrections and clarifications to the protocol.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported