



Clinical trial results:

PHASE 2 SINGLE-ARM, OPEN LABEL STUDY OF IRINOTECAN IN COMBINATION WITH TEMOZOLOMIDE IN CHILDREN WITH RECURRENT OR REFRACTORY MEDULLOBLASTOMA AND IN CHILDREN WITH NEWLY DIAGNOSED HIGH-GRADE GLIOMA

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2006-005476-40 |
| Trial protocol | GB FR DK IT PL ES |
| Global end of trial date | 15 December 2011 |

Results information

| | |
|--------------------------------|--|
| Result version number | v2 (current) |
| This version publication date | 26 March 2016 |
| First version publication date | 30 July 2015 |
| Version creation reason | <ul style="list-style-type: none">• Correction of full data setCorrection of identified Timestamp error . |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | A5961166 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00404495 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Pfizer Inc |
| Sponsor organisation address | 235 E 42nd Street, New York, United States, NY 10017 |
| Public contact | Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001800 7181021, ClinicalTrials.gov_Inquiries@pfizer.com |
| Scientific contact | Pfizer Clinical Trials.gov Call Centre, Pfizer Inc, 001800 7181021, ClinicalTrials.gov_Inquiries@pfizer.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? | Yes |

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 02 May 2012 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 December 2011 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To assess the rate of objective confirmed tumor response of irinotecan in combination with temozolomide in children with recurrent or refractory medulloblastoma and in children with newly diagnosed high-grade glioma.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|---------------|
| Actual start date of recruitment | 30 April 2007 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Poland: 9 |
| Country: Number of subjects enrolled | Spain: 13 |
| Country: Number of subjects enrolled | United Kingdom: 20 |
| Country: Number of subjects enrolled | Belgium: 4 |
| Country: Number of subjects enrolled | Denmark: 2 |
| Country: Number of subjects enrolled | France: 30 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Australia: 4 |
| Worldwide total number of subjects | 83 |
| EEA total number of subjects | 79 |

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) | 61 |
| Adolescents (12-17 years) | 22 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

83 subjects were enrolled; 66 subjects were treated with Temozolomide + Irinotecan for medulloblastoma and 17 subjects were treated with Temozolomide + Irinotecan for high-grade glioma.

Period 1

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

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Temozolomide + Irinotecan for Medulloblastoma |

Arm description:

For subjects with medulloblastoma: Irinotecan 10 mg/m²/Day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.

| | |
|--|-----------------|
| Arm type | Experimental |
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Irinotecan 10 milligram per square meter (mg/m²) per Day on Days 1-5 and Days 8-12 in repeated 3 week cycles.

| | |
|--|--------------|
| Investigational medicinal product name | Temozolomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3 week cycles.

| | |
|------------------|---|
| Arm title | Temozolomide + Irinotecan for High-Grade Glioma |
|------------------|---|

Arm description:

For subjects with high-grade glioma: Irinotecan 10 mg/m²/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.

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

Dosage and administration details:

Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3 week cycles.

| | |
|--|-----------------|
| Investigational medicinal product name | Irinotecan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Irinotecan 10 mg/m² per Day on Days 1-5 and Days 8-12 in repeated 3 week cycles.

| Number of subjects in period 1 | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High- Grade Glioma |
|---------------------------------------|---|--|
| Started | 66 | 17 |
| Completed | 22 | 6 |
| Not completed | 44 | 11 |
| Consent withdrawn by subject | 1 | - |
| Death | 37 | 11 |
| Not specified | 1 | - |
| Lost to follow-up | 5 | - |

Baseline characteristics

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Temozolomide + Irinotecan for Medulloblastoma |
|-----------------------|---|

Reporting group description:

For subjects with medulloblastoma: Irinotecan 10 mg/m²/Day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.

| | |
|-----------------------|---|
| Reporting group title | Temozolomide + Irinotecan for High-Grade Glioma |
|-----------------------|---|

Reporting group description:

For subjects with high-grade glioma: Irinotecan 10 mg/m²/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.

| Reporting group values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | Total |
|---------------------------------------|---|---|-------|
| Number of subjects | 66 | 17 | 83 |
| Age categorical Units: Subjects | | | |
| 2 years to 12 years | 49 | 12 | 61 |
| Greater than (>) 12 years to 18 years | 17 | 5 | 22 |
| Gender categorical Units: Subjects | | | |
| Female | 21 | 3 | 24 |
| Male | 45 | 14 | 59 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Temozolomide + Irinotecan for Medulloblastoma |
| Reporting group description: For subjects with medulloblastoma: Irinotecan 10 mg/m ² /Day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m ² daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression. | |
| Reporting group title | Temozolomide + Irinotecan for High-Grade Glioma |
| Reporting group description: For subjects with high-grade glioma: Irinotecan 10 mg/m ² /day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m ² daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy. | |

Primary: Percentage of Subjects With Objective Response of Complete Response or Partial Response

| | |
|--|--|
| End point title | Percentage of Subjects With Objective Response of Complete Response or Partial Response ^[1] |
| End point description: Percentage of subjects with objective response based assessment of confirmed complete response (CR) or confirmed partial response (PR). CR persisted on repeat imaging study at least (\geq) 4 weeks after initial documentation of response. PR, for bidimensionally measurable disease, was a decrease by $\geq 50\%$ of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. Best overall response recorded any time while the subject was receiving treatment. External Response Review Committee (ERRC) assessment. Primary Evaluable Population: subset of evaluable population predetermined by 2-stage Optimum Simon design. Medulloblastoma cohort: n=consecutive evaluable subjects up to 46 if 6 responses obtained in first 15 evaluable subjects. Glioma cohort: n=consecutive evaluable subjects up to 29 if 1 response in first 10 evaluable subjects. | |
| End point type | Primary |
| End point timeframe: Baseline to 1 Year (medulloblastoma), Baseline to 6 Weeks (high-grade glioma) | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification:

Only descriptive data was planned to be collected for this endpoint. No statistical analysis was performed as per planned analysis.

| End point values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 46 | 10 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 32.6 (19.5 to 48) | 0 (0 to 30.8) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Objective Response of Complete Response or Partial Response, Investigator's Assessment

| | |
|-----------------|--|
| End point title | Percentage of Subjects With Objective Response of Complete Response or Partial Response, Investigator's Assessment |
|-----------------|--|

End point description:

Percentage of subjects with objective response based assessment of confirmed CR or confirmed PR. CR persisted on repeat imaging study ≥ 4 weeks after initial documentation of response. PR, in case of bidimensionally measurable disease, was a decrease by $\geq 50\%$ of the sum of the products of the largest perpendicular diameters of all measurable lesions as determined by 2 observations not less than 4 weeks apart. Best overall response could be recorded any time while the subject was receiving treatment. Investigator's assessment. Evaluable local population: Subjects received at least 1 dose of study medication, had measurable disease under study, at least 1 on-study objective tumor assessment, completed at least 2 cycles of study treatment or progressed. Based on investigator's assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to 1 Year (medulloblastoma), Baseline to 6 Weeks (high-grade glioma)

| End point values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 63 | 17 | | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | 34.9 (23.3 to 48) | 11.8 (1.5 to 36.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

| | |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Median duration (50%) of tumor response for subjects with objective disease response: who have not progressed or died due to any cause; with a response and subsequent progression or death due to any cause for duration of response (DR). DR was defined as time from start of first documented objective tumor response (CR or PR) to first documented objective tumor progression or death due to any cause, whichever occurred first. DR (calculated in Weeks) = (the end date for DR minus first subsequent confirmed CR or PR plus 1) divided by 7. Investigator's assessment. Evaluable local population.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Date of Tumor Response (Up to 1 Year)

| End point values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | | |
|-------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 22 ^[2] | 2 ^[3] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 22.4 (6.9 to 46.6) | 36.3 (4 to 68.6) | | |

Notes:

[2] - Number of subjects analyzed=number of subjects who responded.

[3] - Number of subjects analyzed=number of subjects who responded.

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Treatment Failure (TTF)

| | |
|-----------------|---------------------------------|
| End point title | Time to Treatment Failure (TTF) |
|-----------------|---------------------------------|

End point description:

TTF was defined as the time from the date of first dose of study treatment to the date of the first documentation of progressive disease (PD), the date of treatment discontinuation except completion of treatment, or date of death due to cancer. Investigator's assessment. Evaluable local population was assessed.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline to Date of Treatment Failure (Up to 1 Year)

| End point values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 63 | 17 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.8 (2.9 to 5.4) | 1.6 (1.3 to 2.4) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Tumor Progression (TTP)

| | |
|-----------------|---------------------------------|
| End point title | Time to Tumor Progression (TTP) |
|-----------------|---------------------------------|

End point description:

TTP was defined as the time in months from start of study treatment to first documentation of objective tumor progression or death due to cancer, whichever came first. TTP was calculated as (first event date minus the date of first dose of study medication plus 1) divided by 7 multiplied by 4.33. Tumor progression was determined from oncologic assessment data (where data met the criteria for PD). Investigator's assessment. Evaluable local population was analyzed.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Date of Progression (Up to 1 Year) | |

| End point values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 63 | 17 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 5.6 (3.8 to 7.4) | 1.6 (1.3 to 7.5) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS)

| | |
|---|-----------------------|
| End point title | Overall Survival (OS) |
| End point description: | |
| Time in months from the start of study treatment to date of death due to any cause. OS was calculated as (the death date minus the date of first dose of study medication plus 1) divided by 7 multiplied by 4.33. Death was determined from adverse event data (where outcome was death) or from follow-up contact data (where the subject current status was death). Investigator's assessment. All subjects were analyzed. One subject in the Temozolomide + Irinotecan for Medulloblastoma cohort did not have recurrent or refractory medulloblastoma and 3 subjects in the Temozolomide + Irinotecan for High-Grade Glioma cohort did not have high-grade glioma, and were not considered evaluable for survival. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline to Date of Death (Up to 1 Year After Treatment) | |

| End point values | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High-Grade Glioma | | |
|----------------------------------|---|---|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 65 | 14 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 16.7 (13.3 to 19.8) | 9.4 (5.8 to 20.2) | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events are reported from time of first dose of study treatment up to 30 days after last dose of study treatment .

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 17.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Temozolomide + Irinotecan for Medulloblastoma |
|-----------------------|---|

Reporting group description:

For subjects with medulloblastoma: Irinotecan 10 mg/m²/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3-week cycles; treatment duration: up to 1 year or until progression.

| | |
|-----------------------|---|
| Reporting group title | Temozolomide + Irinotecan for High-Grade Glioma |
|-----------------------|---|

Reporting group description:

For subjects with high-grade glioma: Irinotecan 10 mg/m²/day on Days 1-5 and Days 8-12 in repeated 3-week cycles. Temozolomide 100-125 mg/m² daily on Days 1-5 in repeated 3-week cycles; treatment duration: 2 cycles as a window phase before starting standard therapy.

| Serious adverse events | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High- Grade Glioma | |
|---|---|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 31 / 66 (46.97%) | 5 / 17 (29.41%) | |
| number of deaths (all causes) | 7 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Investigations | | | |
| Blood culture positive | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (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) | | | |
| Medulloblastoma | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angiopathy | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (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 | | | |
| Complex partial seizures | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotonia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial pressure increased | | | |

| | | | |
|--|----------------|----------------|--|
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (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 | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chills | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (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 | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 66 (6.06%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 6 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|--|----------------|-----------------|--|
| Disease progression subjects affected / exposed | 4 / 66 (6.06%) | 2 / 17 (11.76%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 2 | |
| Immune system disorders | | | |
| Drug hypersensitivity subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed | 6 / 66 (9.09%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 8 / 8 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Proctalgia subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory disorder | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Depression | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile infection | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Dehydration | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Temozolomide + Irinotecan for Medulloblastoma | Temozolomide + Irinotecan for High- Grade Glioma | |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 64 / 66 (96.97%) | 17 / 17 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour associated fever | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Melanocytic naevus | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin papilloma | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Haematoma | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hot flush | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hypotension | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 4 / 66 (6.06%) | 1 / 17 (5.88%) | |
| occurrences (all) | 7 | 1 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pallor | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Asthenia | | | |
| subjects affected / exposed | 6 / 66 (9.09%) | 2 / 17 (11.76%) | |
| occurrences (all) | 6 | 2 | |
| Catheter site rash | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Catheter site pain | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Catheter site swelling | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Device occlusion | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Fatigue | | | |
| subjects affected / exposed | 15 / 66 (22.73%) | 4 / 17 (23.53%) | |
| occurrences (all) | 18 | 4 | |
| Chest pain | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Feeling abnormal | | | |

| | | | |
|--|------------------|-----------------|--|
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Feeling hot | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Inflammation | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Mucosal inflammation | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 2 / 17 (11.76%) | |
| occurrences (all) | 1 | 2 | |
| Pain | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Peripheral swelling | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 14 / 66 (21.21%) | 2 / 17 (11.76%) | |
| occurrences (all) | 15 | 2 | |
| Xerosis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Immune system disorders | | | |
| Drug hypersensitivity | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Reproductive system and breast disorders | | | |

| | | | |
|---|------------------|----------------|--|
| Genital lesion | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Penis disorder | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vulvovaginal discomfort | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchospasm | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cough | | | |
| subjects affected / exposed | 13 / 66 (19.70%) | 0 / 17 (0.00%) | |
| occurrences (all) | 21 | 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hiccups | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Nasal congestion | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oropharyngeal pain | | | |

| | | | |
|--|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 6 / 66 (9.09%) 7 | 0 / 17 (0.00%) 0 | |
| Rhinalgia subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 3 | 0 / 17 (0.00%) 0 | |
| Respiratory disorder subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 5 / 66 (7.58%) 6 | 0 / 17 (0.00%) 0 | |
| Psychiatric disorders Agitation subjects affected / exposed occurrences (all) | 0 / 66 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Confusional state subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Anxiety subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 1 / 17 (5.88%) 1 | |
| Depression subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Disorientation subjects affected / exposed occurrences (all) | 0 / 66 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Insomnia subjects affected / exposed occurrences (all) | 4 / 66 (6.06%) 5 | 0 / 17 (0.00%) 0 | |
| Nightmare subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 5 | 0 / 17 (0.00%) 0 | |
| Investigations Alanine aminotransferase increased | | | |

| | | |
|--------------------------------------|----------------|----------------|
| subjects affected / exposed | 5 / 66 (7.58%) | 1 / 17 (5.88%) |
| occurrences (all) | 22 | 1 |
| Alanine aminotransferase | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Blood bicarbonate decreased | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Aspartate aminotransferase | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Aspartate aminotransferase increased | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) |
| occurrences (all) | 5 | 0 |
| Blood bicarbonate increased | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 6 | 0 |
| Blood creatinine increased | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood culture positive | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Blood magnesium decreased | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood phosphorus decreased | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood urea decreased | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 4 | 0 |
| Blood potassium decreased | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 12 | 0 |

| | | | |
|--|----------------------|----------------------|--|
| C-reactive protein increased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 2 | 0 / 17 (0.00%) 0 | |
| Haemoglobin decreased subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | 0 / 17 (0.00%) 0 | |
| Heart rate subjects affected / exposed occurrences (all) | 0 / 66 (0.00%) 0 | 1 / 17 (5.88%) 1 | |
| Haemoglobin subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Monocyte count decreased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Protein total increased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Platelet count subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Platelet count decreased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 1 / 17 (5.88%) 1 | |
| Weight increased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 2 / 17 (11.76%) 2 | |
| Weight decreased subjects affected / exposed occurrences (all) | 6 / 66 (9.09%) 12 | 0 / 17 (0.00%) 0 | |
| Injury, poisoning and procedural complications | | | |

| | | | |
|--|----------------|----------------|--|
| Animal bite | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Contusion | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Fall | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Stoma site pain | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Post procedural discharge | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Skin abrasion | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Wound | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Congenital, familial and genetic disorders | | | |
| Aplasia | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Cardiac disorders | | | |
| Bradycardia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Sinus tachycardia | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Aphasia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Balance disorder | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 0 / 17 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Cerebellar syndrome | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Cholinergic syndrome | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) | |
| occurrences (all) | 2 | 1 | |
| Cranial nerve disorder | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Convulsion | | | |
| subjects affected / exposed | 4 / 66 (6.06%) | 0 / 17 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Cranial nerve paralysis | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Dysarthria | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dizziness | | | |
| subjects affected / exposed | 6 / 66 (9.09%) | 1 / 17 (5.88%) | |
| occurrences (all) | 6 | 1 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 4 | 0 | |

| | | |
|---------------------------------|------------------|-----------------|
| Hemiparesis | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Headache | | |
| subjects affected / exposed | 20 / 66 (30.30%) | 5 / 17 (29.41%) |
| occurrences (all) | 35 | 7 |
| IIIrd nerve paralysis | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Hyperreflexia | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypoaesthesia | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Intracranial pressure increased | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Lethargy | | |
| subjects affected / exposed | 4 / 66 (6.06%) | 0 / 17 (0.00%) |
| occurrences (all) | 4 | 0 |
| Meningeal disorder | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Monoparesis | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Muscle spasticity | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 2 |
| Migraine | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Neuralgia | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |

| | | |
|-------------------------------|----------------|----------------|
| Neurological symptom | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Neuropathy peripheral | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |
| Nystagmus | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Paraesthesia | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Partial seizures | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Peripheral sensory neuropathy | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Peripheral motor neuropathy | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Presyncope | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Pyramidal tract syndrome | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Reflexes abnormal | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Slow speech | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Sensory disturbance | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) |
| occurrences (all) | 0 | 1 |

| | | | |
|--------------------------------------|------------------|----------------|--|
| Tardive dyskinesia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Syncope | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Somnolence | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 1 / 17 (5.88%) | |
| occurrences (all) | 6 | 1 | |
| Visual field defect | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Tonic convulsion | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Tremor | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 1 / 17 (5.88%) | |
| occurrences (all) | 2 | 1 | |
| Blood and lymphatic system disorders | | | |
| Eosinopenia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 66 (15.15%) | 1 / 17 (5.88%) | |
| occurrences (all) | 40 | 1 | |
| Leukopenia | | | |
| subjects affected / exposed | 6 / 66 (9.09%) | 0 / 17 (0.00%) | |
| occurrences (all) | 39 | 0 | |
| Lymphadenopathy | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lymphopenia | | | |

| | | | |
|---|------------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 10 / 66 (15.15%) 62 | 0 / 17 (0.00%) 0 | |
| Neutropenia subjects affected / exposed occurrences (all) | 15 / 66 (22.73%) 41 | 1 / 17 (5.88%) 6 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 17 / 66 (25.76%) 54 | 1 / 17 (5.88%) 2 | |
| Ear and labyrinth disorders Ear canal erythema subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Deafness subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Ear pain subjects affected / exposed occurrences (all) | 3 / 66 (4.55%) 3 | 0 / 17 (0.00%) 0 | |
| Tinnitus subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 2 | 0 / 17 (0.00%) 0 | |
| Hypoacusis subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 2 | 0 / 17 (0.00%) 0 | |
| Vertigo subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Eye disorders Diplopia subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Conjunctival hyperaemia subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Eye pain | | | |

| | | | |
|-----------------------------|------------------|-----------------|--|
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Eye movement disorder | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Eyelid ptosis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Strabismus | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Keratitis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Lacrimation increased | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Visual acuity reduced | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Gastrointestinal disorders | | | |
| Abdominal discomfort | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 22 / 66 (33.33%) | 4 / 17 (23.53%) | |
| occurrences (all) | 50 | 4 | |
| Anal erosion | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 66 (12.12%) | 1 / 17 (5.88%) | |
| occurrences (all) | 9 | 1 | |
| Anal haemorrhage | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |

| | | |
|-----------------------------|------------------|------------------|
| Anal fissure | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Aphthous stomatitis | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Breath odour | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Constipation | | |
| subjects affected / exposed | 22 / 66 (33.33%) | 4 / 17 (23.53%) |
| occurrences (all) | 32 | 5 |
| Faecal incontinence | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Diarrhoea | | |
| subjects affected / exposed | 38 / 66 (57.58%) | 10 / 17 (58.82%) |
| occurrences (all) | 136 | 12 |
| Dyspepsia | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Gastrointestinal ulcer | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Gingival bleeding | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Gastritis | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nausea | | |
| subjects affected / exposed | 20 / 66 (30.30%) | 7 / 17 (41.18%) |
| occurrences (all) | 45 | 12 |
| Mouth ulceration | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |

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|--|------------------|------------------|--|
| Lip oedema | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Oral mucosal eruption | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Oral pain | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Odynophagia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Proctalgia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Retching | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Stomatitis | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 6 | 0 | |
| Toothache | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Vomiting | | | |
| subjects affected / exposed | 42 / 66 (63.64%) | 13 / 17 (76.47%) | |
| occurrences (all) | 106 | 36 | |
| Skin and subcutaneous tissue disorders | | | |
| Acne | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Alopecia | | | |

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| subjects affected / exposed | 2 / 66 (3.03%) | 1 / 17 (5.88%) |
| occurrences (all) | 2 | 1 |
| Dry skin | | |
| subjects affected / exposed | 4 / 66 (6.06%) | 1 / 17 (5.88%) |
| occurrences (all) | 5 | 1 |
| Decubitus ulcer | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Dermatitis | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Ecchymosis | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Erythema | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) |
| occurrences (all) | 1 | 1 |
| Hyperhidrosis | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 2 / 17 (11.76%) |
| occurrences (all) | 1 | 2 |
| Petechiae | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Nail disorder | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Ingrowing nail | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pruritus generalised | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Pruritus | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Rash macular | | |

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| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash pruritic | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Rash | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 1 / 17 (5.88%) | |
| occurrences (all) | 6 | 1 | |
| Skin hyperpigmentation | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin striae | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Skin fissures | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 4 / 66 (6.06%) | 0 / 17 (0.00%) | |
| occurrences (all) | 4 | 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary incontinence | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Urine flow decreased | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |

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| Urogenital haemorrhage subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthropathy subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Arthralgia subjects affected / exposed occurrences (all) | 2 / 66 (3.03%) 3 | 1 / 17 (5.88%) 1 | |
| Back pain subjects affected / exposed occurrences (all) | 7 / 66 (10.61%) 9 | 0 / 17 (0.00%) 0 | |
| Bone pain subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Joint range of motion decreased subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Limb discomfort subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Muscle spasms subjects affected / exposed occurrences (all) | 4 / 66 (6.06%) 4 | 0 / 17 (0.00%) 0 | |
| Joint swelling subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Muscular weakness subjects affected / exposed occurrences (all) | 3 / 66 (4.55%) 3 | 1 / 17 (5.88%) 1 | |
| Musculoskeletal chest pain subjects affected / exposed occurrences (all) | 1 / 66 (1.52%) 1 | 0 / 17 (0.00%) 0 | |
| Myalgia | | | |

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| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Musculoskeletal stiffness | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in jaw | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 9 / 66 (13.64%) | 1 / 17 (5.88%) | |
| occurrences (all) | 14 | 1 | |
| Neck pain | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 0 / 17 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Infections and infestations | | | |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 66 (0.00%) | 1 / 17 (5.88%) | |
| occurrences (all) | 0 | 1 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 1 / 17 (5.88%) | |
| occurrences (all) | 5 | 1 | |
| Ear infection | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Device related infection | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Gastroenteritis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |

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|-----------------------------------|-----------------|-----------------|
| Herpes zoster | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hordeolum | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Infection | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Nasopharyngitis | | |
| subjects affected / exposed | 8 / 66 (12.12%) | 3 / 17 (17.65%) |
| occurrences (all) | 14 | 3 |
| Oral herpes | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Oral candidiasis | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Pharyngitis | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) |
| occurrences (all) | 3 | 0 |
| Respiratory tract infection | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) |
| occurrences (all) | 1 | 0 |
| Rhinitis | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 1 / 17 (5.88%) |
| occurrences (all) | 2 | 1 |
| Sinusitis | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) |
| occurrences (all) | 2 | 0 |
| Upper respiratory tract infection | | |
| subjects affected / exposed | 7 / 66 (10.61%) | 0 / 17 (0.00%) |
| occurrences (all) | 10 | 0 |
| Urinary tract infection | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 2 / 17 (11.76%) |
| occurrences (all) | 9 | 2 |

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| Tonsillitis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 1 / 17 (5.88%) | |
| occurrences (all) | 1 | 1 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Viral rhinitis | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 11 / 66 (16.67%) | 2 / 17 (11.76%) | |
| occurrences (all) | 17 | 2 | |
| Hyperalbuminaemia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 5 | 0 | |
| Hypochloraemia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypokalaemia | | | |

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|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 4 / 66 (6.06%) | 0 / 17 (0.00%) | |
| occurrences (all) | 16 | 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 2 / 66 (3.03%) | 0 / 17 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 5 / 66 (7.58%) | 0 / 17 (0.00%) | |
| occurrences (all) | 9 | 0 | |
| Hypophagia | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 3 / 66 (4.55%) | 0 / 17 (0.00%) | |
| occurrences (all) | 7 | 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 66 (1.52%) | 0 / 17 (0.00%) | |
| occurrences (all) | 1 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---------------|--|
| 06 March 2007 | <p>1) Subjects who had response or achieved SD with temozolomide were eligible to receive irinotecan added to this temozolomide treatment (from first cycle of adjuvant chemotherapy) for maximum period of 1 year until disease progression, unacceptable toxicity, or subject's desire to discontinue therapy, following radiotherapy and/or surgery, or other supportive care.</p> <p>2) Inclusion criterion modified such that investigators could allow for effect of motor paresis due to disease in assessment in children with relatively stable neurological deficits.</p> <p>3) Additional exclusion criteria on hypersensitivity/intolerance added.</p> <p>5) Pathological Assessment section was added: For all high-grade glioma (HGG) subjects, pathological samples used for diagnosis were to be reviewed by a central pathologist. For recurrent medulloblastoma subjects in Cohort 1, pathological samples from initial diagnosis and/or a subsequent biopsy or resection were also reviewed if available. Rebiopsy at relapse not mandated. Central pathologist diagnosis used to determine evaluability.</p> <p>6) For HGG subjects following 2 cycles of treatment, nonresponders were to discontinue study treatment and be treated with standard therapy.</p> <p>7) HGG subjects with measurable residual disease were to have this confirmed by a post operative magnetic resonance imaging (MRI) performed within 72 hours of surgery. Subjects were to have a screening scan dated no more than 14 days prior treatment.</p> |
| 25 April 2007 | <p>1) Under Exclusion Criteria, chronic inflammatory bowel disease and/or bowel obstruction was added.</p> |
| 24 April 2009 | <p>1) This protocol was amended to clarify the maximum time any subject was permitted on treatment and to clarify the duration of post-treatment follow-up.</p> <p>2) For subjects with recurrent or refractory medulloblastoma, treatment continued (for a maximum of 1 year) until disease progression, unacceptable toxicity, or the subject's desire to discontinue therapy.</p> <p>3) Subjects were followed up every 3 months for 1 year or until death or lost to follow-up.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This study had one treatment arm but two distinct cohorts with different diagnostics and treatment durations.

Notes: