



Clinical trial results:

A Phase 2 clinical study of pomalidomide (CC-4047) monotherapy for children and young adults with recurrent or progressive primary brain tumors.

Summary

| | |
|--------------------------|-------------------|
| EudraCT number | 2016-002903-25 |
| Trial protocol | ES FR GB IT |
| Global end of trial date | 14 September 2023 |

Results information

| | |
|--------------------------------|---------------|
| Result version number | v1 (current) |
| This version publication date | 24 March 2024 |
| First version publication date | 24 March 2024 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | CC-4047-BRN-001 |
|-----------------------|-----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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 | 19 October 2023 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 14 September 2023 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Establish the preliminary efficacy of pomalidomide in children and young adults with recurrent or progressive primary brain tumors within four distinct tumor types.

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 Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial participants were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 18 September 2017 |
| 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 | Italy: 20 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | United Kingdom: 9 |
| Country: Number of subjects enrolled | United States: 12 |
| Worldwide total number of subjects | 53 |
| EEA total number of subjects | 32 |

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) | 26 |
| Adolescents (12-17 years) | 27 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study consisted of 4 groups, for each of the following primary brain tumor types: diffuse intrinsic pontine glioma (DIPG), ependymoma, high-grade glioma, and medulloblastoma.

Pre-assignment

Screening details:

In stage 1 approximately 9 participants were to be enrolled in parallel to each group. If two or more participants in a group achieved an objective response or long-term stable disease within the first 6 cycles of treatment (within the first 3 cycles for DIPG) an additional 11 participants were to be enrolled in that group.

Period 1

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

Arms

| | |
|------------------------------|----------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Diffuse Intrinsic Pontine Glioma |

Arm description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | pomalidomide |
| Investigational medicinal product code | CC-4047 |
| Other name | |
| Pharmaceutical forms | Capsule, Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

2.6 mg/m²/day

| | |
|------------------|------------|
| Arm title | Ependymoma |
|------------------|------------|

Arm description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | pomalidomide |
| Investigational medicinal product code | CC-4047 |
| Other name | |
| Pharmaceutical forms | Capsule, Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

2.6 mg/m²/day

| | |
|------------------|-------------------|
| Arm title | High-grade Glioma |
|------------------|-------------------|

Arm description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|----------|--------------|
| Arm type | Experimental |
|----------|--------------|

| | |
|--|--------------------------|
| Investigational medicinal product name | pomalidomide |
| Investigational medicinal product code | CC-4047 |
| Other name | |
| Pharmaceutical forms | Capsule, Oral suspension |
| Routes of administration | Oral use |
| Dosage and administration details: | |
| 2.6 mg/m ² /day | |
| Arm title | Medulloblastoma |

Arm description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|--|--------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | pomalidomide |
| Investigational medicinal product code | CC-4047 |
| Other name | |
| Pharmaceutical forms | Capsule, Oral suspension |
| Routes of administration | Oral use |

Dosage and administration details:

2.6 mg/m²/day

| Number of subjects in period 1 | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma |
|---------------------------------------|----------------------------------|------------|-------------------|
| Started | 11 | 9 | 23 |
| Received Study Drug | 11 | 9 | 22 |
| Completed | 0 | 0 | 1 |
| Not completed | 11 | 9 | 22 |
| Adverse event, serious fatal | 1 | - | 1 |
| Adverse event, non-fatal | - | - | 2 |
| Progressive Disease | 10 | 9 | 17 |
| Withdrawal by Parent/Guardian | - | - | 2 |

| Number of subjects in period 1 | Medulloblastoma |
|---------------------------------------|-----------------|
| Started | 10 |
| Received Study Drug | 10 |
| Completed | 0 |
| Not completed | 10 |
| Adverse event, serious fatal | 1 |
| Adverse event, non-fatal | - |
| Progressive Disease | 8 |
| Withdrawal by Parent/Guardian | 1 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Diffuse Intrinsic Pontine Glioma |
|-----------------------|----------------------------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|-----------------------|------------|
| Reporting group title | Ependymoma |
|-----------------------|------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|-----------------------|-------------------|
| Reporting group title | High-grade Glioma |
|-----------------------|-------------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|-----------------------|-----------------|
| Reporting group title | Medulloblastoma |
|-----------------------|-----------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| Reporting group values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma |
|---|----------------------------------|------------|-------------------|
| Number of subjects | 11 | 9 | 23 |
| Age Categorical Units: participants | | | |
| ≥ 1 to < 6 years | 1 | 2 | 1 |
| ≥ 6 to < 12 years | 9 | 1 | 5 |
| ≥ 12 years | 1 | 6 | 17 |
| Age Continuous Units: years | | | |
| median | 7.0 | 12.0 | 14.0 |
| full range (min-max) | 4 to 12 | 4 to 15 | 5 to 18 |
| Sex: Female, Male Units: participants | | | |
| Female | 4 | 4 | 8 |
| Male | 7 | 5 | 15 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 4 | 0 | 6 |
| Not Hispanic or Latino | 7 | 9 | 13 |
| Unknown or Not Reported | 0 | 0 | 4 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 |
| Asian | 1 | 0 | 2 |
| Black or African American | 0 | 0 | 2 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |

| | | | |
|---------------------------|----|---|----|
| White | 10 | 9 | 11 |
| Not Collected or Reported | 0 | 0 | 5 |
| Other | 0 | 0 | 3 |

| Reporting group values | Medulloblastoma | Total | |
|---|-----------------|-------|--|
| Number of subjects | 10 | 53 | |
| Age Categorical | | | |
| Units: participants | | | |
| ≥ 1 to < 6 years | 1 | 5 | |
| ≥ 6 to < 12 years | 6 | 21 | |
| ≥ 12 years | 3 | 27 | |
| Age Continuous | | | |
| Units: years | | | |
| median | 10.0 | | |
| full range (min-max) | 4 to 17 | - | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 3 | 19 | |
| Male | 7 | 34 | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 1 | 11 | |
| Not Hispanic or Latino | 8 | 37 | |
| Unknown or Not Reported | 1 | 5 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaskan Native | 0 | 0 | |
| Asian | 0 | 3 | |
| Black or African American | 0 | 2 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| White | 8 | 38 | |
| Not Collected or Reported | 2 | 7 | |
| Other | 0 | 3 | |

End points

End points reporting groups

| | |
|---|----------------------------------|
| Reporting group title | Diffuse Intrinsic Pontine Glioma |
| Reporting group description: Participants received 2.6 mg/m ² /day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first. | |
| Reporting group title | Ependymoma |
| Reporting group description: Participants received 2.6 mg/m ² /day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first. | |
| Reporting group title | High-grade Glioma |
| Reporting group description: Participants received 2.6 mg/m ² /day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first. | |
| Reporting group title | Medulloblastoma |
| Reporting group description: Participants received 2.6 mg/m ² /day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first. | |

Primary: Percentage of Participants with an Objective Response and Long-term Stable Disease

| | |
|---|---|
| End point title | Percentage of Participants with an Objective Response and Long-term Stable Disease ^[1] |
| End point description: The percentage of participants who achieved either an objective response, defined as a complete response (CR) or partial response (PR) in the first 6 cycles of treatment (or within 3 cycles for DIPG), or long-term stable disease (SD) defined as SD maintained for ≥ 6 cycles (≥ 3 cycles for DIPG), measured from first dose date. CR: Disappearance of all lesions and no new lesions. PR: A reduction of $\geq 50\%$ in the size of measurable lesions, and/or persistence of non-target lesions with no progression or decrease in size. SD: A decrease of $< 50\%$ or an increase of $< 25\%$ in the size of measurable lesions and no evidence of new lesions, response does not meet the criteria for CR, PR, or progressive disease, and/or the persistence of non-target lesions with no progression or decrease in size. Progressive Disease (PD): $\geq 25\%$ increase in the size of the measurable lesions, or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions. | |
| End point type | Primary |
| End point timeframe: 6 months (first 6 cycles) or 3 months (first 3 cycles) for participants in the DIPG group | |

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 summary statistics planned for this endpoint.

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|-----------------------------------|----------------------------------|--------------------|--------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 9 | 9 | 19 | 9 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0.0 to 33.6) | 11.1 (0.3 to 48.2) | 10.5 (1.3 to 33.1) | 0 (0.0 to 33.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Achieved an Objective Response (ORR)

| | |
|-----------------|---|
| End point title | Percentage of Participants who Achieved an Objective Response (ORR) |
|-----------------|---|

End point description:

Objective response rate was defined as the percentage of participants who achieved a complete response (CR) or partial response (PR) within the first 6 cycles of treatment (or within 3 cycles for participants in the DIPG group). Disease assessments were based on MRI and assessed by an independent central review. CR: Disappearance of all lesions and no new lesions. PR: A reduction of $\geq 50\%$ in the size of measurable lesions compared to baseline, and/or the persistence of non-target lesions with no progression or decrease in size. Progressive Disease (PD): $\geq 25\%$ increase in the size of the measurable lesions, or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

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

End point timeframe:

6 months (first 6 cycles) or 3 months (first 3 cycles) for participants in the DIPG group

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|-----------------------------------|----------------------------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 9 | 9 | 19 | 9 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0.0 to 33.6) | 0 (0.0 to 33.6) | 5.3 (0.1 to 26.0) | 0 (0.0 to 33.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Long-term Stable Disease

| | |
|-----------------|--|
| End point title | Percentage of Participants with Long-term Stable Disease |
|-----------------|--|

End point description:

Long-term stable disease (SD) rate was defined as the percentage of participants who achieved SD maintained for ≥ 6 cycles (or > 3 cycles for DIPG), measured from the date of first dose of treatment. Disease assessments were based on MRI and assessed by an independent central review. SD: A decrease of $< 50\%$ or an increase of $< 25\%$ in the size of measurable lesions and no evidence of new lesions, response does not meet the criteria for CR, PR, or progressive disease, and/or the persistence of non-target lesions with no progression or decrease in size. CR: Disappearance of all lesions and no new lesions. PR: A reduction of $\geq 50\%$ in the size of measurable lesions compared to baseline, and/or the persistence of non-target lesions with no progression or decrease in size. Progressive Disease (PD): $\geq 25\%$ increase in the size of the measurable lesions, or the appearance of one or more new lesions

and/or unequivocal progression of existing non-target lesions.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 6 months (first 6 cycles) or 3 months (first 3 cycles) for participants in the DIPG group | |

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|-----------------------------------|----------------------------------|--------------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 9 | 9 | 19 | 9 |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0 (0.0 to 33.6) | 11.1 (0.3 to 48.2) | 5.3 (0.1 to 26.0) | 0 (0.0 to 33.6) |

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Duration of Response (DoR)

| | |
|-----------------|---|
| End point title | Kaplan-Meier Estimate of Duration of Response (DoR) |
|-----------------|---|

End point description:

DoR is defined as the time from the date of the first objective response (complete response [CR] or partial response [PR]) to disease progression. Participants who did not have disease progression or had not died were censored at the time of their last disease assessment or at the time of start of new anticancer therapy, whichever occurred first. Progressive disease (PD): $\geq 25\%$ increase in the size of the measurable lesions taking as a reference the smallest disease measurement recorded since the start of protocol therapy (nadir), or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions, or if spine MRI and/or lumbar cerebrospinal fluid (CSF) cytology were previously negative and became positive. CR: Disappearance of all lesions and no new lesions. PR: A reduction of $\geq 50\%$ in the size of measurable lesions compared to baseline, and/or the persistence of non-target lesions with no progression or decrease in size.
-99999, 99999 = NA

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

End point timeframe:

From the first dose of pomalidomide to the date of the first documented tumor progression or death due to any cause, whichever occurs first (Up to 71 months)

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|----------------------------------|----------------------------------|------------------|------------------------|------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 1 | 0 ^[2] | 1 | 0 ^[3] |
| Units: weeks | | | | |
| median (confidence interval 95%) | 12.29 (-99999 to 99999) | (to) | 99999 (99999 to 99999) | (to) |

Notes:

[2] - 0 participants with CR or PR

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Progression-Free Survival (PFS)

| | |
|-----------------|--|
| End point title | Kaplan-Meier Estimate of Progression-Free Survival (PFS) |
|-----------------|--|

End point description:

Progression-free survival was defined as the time from the date of first dose of pomalidomide until the date progressive disease (PD) was first observed or until the date of death due to any cause, whichever occurred first. Participants who did not have PD or had not died at the time of analysis were censored at the time of their last disease assessment or at the start of new anticancer therapy, whichever occurred first. Progressive Disease (PD): $\geq 25\%$ increase in the size of the measurable lesions taking as a reference the smallest disease measurement recorded since the start of protocol therapy (nadir), or the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions, or if spine MRI and/or lumbar CSF cytology were previously negative and became positive.

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

End point timeframe:

From the first dose of pomalidomide to the date of the first documented tumor progression or death due to any cause, whichever occurs first (Up to 71 months)

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|----------------------------------|----------------------------------|----------------------|---------------------|----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 9 | 23 | 10 |
| Units: weeks | | | | |
| median (confidence interval 95%) | 11.43 (4.43 to 12.57) | 8.43 (5.57 to 16.14) | 7.86 (5.43 to 8.29) | 8.29 (7.29 to 18.00) |

Statistical analyses

No statistical analyses for this end point

Secondary: Kaplan-Meier Estimate of Overall Survival (OS)

| | |
|-----------------|--|
| End point title | Kaplan-Meier Estimate of Overall Survival (OS) |
|-----------------|--|

End point description:

Overall survival was defined as the time from the date of the first dose to the date of death (any cause). Participants who were alive were censored at the last known time that the participant was alive.

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

End point timeframe:

From the first dose of pomalidomide to the date of death due to any cause (Up to 71 months)

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|----------------------------------|----------------------------------|-----------------------|----------------------|-----------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 9 | 23 | 10 |
| Units: months | | | | |
| median (confidence interval 95%) | 4.86 (1.02 to 10.91) | 12.02 (2.86 to 20.90) | 5.06 (2.04 to 16.66) | 11.60 (1.74 to 35.32) |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-Emergent Adverse Events (TEAEs)

| | |
|-----------------|---|
| End point title | Number of Participants with Treatment-Emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

Treatment-emergent adverse events were defined as any adverse events (AE) occurring from the first dose of pomalidomide until 28 days after the last dose. The severity of each AE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03 and according to the following scale: Grade 1: Mild (transient or mild discomfort; no limitation in activity or medical intervention required); Grade 2: Moderate (mild to moderate limitation in activity, assistance may be needed; minimal medical intervention required); Grade 3: Severe (marked limitation in activity, assistance and medical intervention required, hospitalization possible); Grade 4: Life-threatening (extreme limitation in activity, significant assistance or medical intervention required, hospitalization or hospice care probable); Grade 5: Death. Drug-related AEs are those suspected by the Investigator as being related to administration of study drug.

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

End point timeframe:

From the first dose of pomalidomide until 28 days after the last dose (Up to approximately 72 months)

| End point values | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma | Medulloblastoma |
|---|----------------------------------|-----------------|-------------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 9 | 22 | 10 |
| Units: participants | | | | |
| Any treatment-emergent adverse event (TEAE) | 11 | 8 | 21 | 9 |
| TEAE related to study drug | 5 | 7 | 14 | 8 |
| Serious TEAE | 9 | 4 | 14 | 4 |
| Serious TEAE related to study drug | 1 | 0 | 6 | 0 |
| Grade 3/4 TEAE | 8 | 6 | 14 | 6 |
| Grade 3/4 TEAE related to study drug | 3 | 2 | 10 | 4 |
| TEAE leading to death | 5 | 1 | 3 | 1 |
| TEAE leading to dose reduction | 1 | 0 | 3 | 0 |

| | | | | |
|--|---|---|---|---|
| TEAE leading to dose interruption | 4 | 3 | 5 | 2 |
| TEAE leading to study drug discontinuation | 2 | 1 | 2 | 0 |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Participants were assessed for all-cause mortality from their first dose until their study completion (up to approximately 72 months). SAEs and other AEs were assessed from first dose until 28 days after last dose (up to approximately 72 months).

Adverse event reporting additional description:

The number at Risk for All-cause mortality represents all enrolled participants, regardless of whether the participant received study treatment or not. The number at Risk for Serious Adverse Events and Other (Not Including Serious) Adverse Events represents all participants who received at least 1 dose of pomalidomide.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 26.0 |

Reporting groups

| | |
|-----------------------|----------------------------------|
| Reporting group title | Diffuse Intrinsic Pontine Glioma |
|-----------------------|----------------------------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|-----------------------|------------|
| Reporting group title | Ependymoma |
|-----------------------|------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|-----------------------|-------------------|
| Reporting group title | High-grade Glioma |
|-----------------------|-------------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| | |
|-----------------------|-----------------|
| Reporting group title | Medulloblastoma |
|-----------------------|-----------------|

Reporting group description:

Participants received 2.6 mg/m²/day oral pomalidomide on days 1 to 21 of each 28-day treatment cycle for up to 24 cycles or until disease progression, withdrawal of consent/assent, treatment became intolerable, or death, whichever occurred first.

| Serious adverse events | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma |
|---|----------------------------------|----------------|-------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 9 / 11 (81.82%) | 4 / 9 (44.44%) | 14 / 22 (63.64%) |
| number of deaths (all causes) | 11 | 6 | 15 |
| number of deaths resulting from adverse events | 5 | 1 | 3 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |

| | | | |
|---|----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 9 (22.22%) | 2 / 22 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 3 / 22 (13.64%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 9 (22.22%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyskinesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ataxia | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intracranial pressure increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Monoplegia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Dysmetria | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 2 / 22 (9.09%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 2 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|---------------|----------------|
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Respiratory syncytial virus bronchitis | | | |

| | | | |
|---|----------------|---------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 2 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mastoiditis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|-------------------------------|-----------------|--|--|
| Serious adverse events | Medulloblastoma | | |
|-------------------------------|-----------------|--|--|

| | | | |
|---|-----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | | |
| number of deaths (all causes) | 9 | | |
| number of deaths resulting from adverse events | 1 | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour haemorrhage | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Headache | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dyskinesia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | | |
|---|-----------------|--|--|--|
| Depressed level of consciousness subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ataxia subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Intracranial pressure increased subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Monoplegia subjects affected / exposed | 1 / 10 (10.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Transient ischaemic attack subjects affected / exposed | 1 / 10 (10.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Seizure subjects affected / exposed | 1 / 10 (10.00%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Presyncope subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Paraesthesia subjects affected / exposed | 0 / 10 (0.00%) | | | |
| occurrences causally related to treatment / all | 0 / 0 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Neurological decompensation | | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Dysmetria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |

| | | | |
|--|----------------------------------|--|--|
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Eye disorders Vision blurred subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Gastrointestinal disorders Nausea subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Constipation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Abdominal pain subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders Respiratory failure subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Pneumonitis subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all | 0 / 10 (0.00%) 0 / 0 0 / 0 | | |
| Dyspnoea | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Respiratory syncytial virus bronchitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mastoiditis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Encephalitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Anorectal infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Sepsis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |

| | | | |
|---|-----------------|--|--|
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Diffuse Intrinsic Pontine Glioma | Ependymoma | High-grade Glioma |
|---|----------------------------------|----------------|-------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | 8 / 9 (88.89%) | 20 / 22 (90.91%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Haemangioma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Flushing | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pallor | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Gait disturbance | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 4 / 22 (18.18%) |
| occurrences (all) | 2 | 1 | 4 |
| Asthenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 3 / 22 (13.64%) |
| occurrences (all) | 0 | 0 | 3 |
| General physical health deterioration | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyrexia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 2 / 22 (9.09%) |
| occurrences (all) | 2 | 1 | 2 |
| Oedema peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Bronchostenosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 3 / 22 (13.64%) |
| occurrences (all) | 1 | 0 | 5 |
| Tonsillar inflammation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 0 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 0 | 1 |
| Hiccups | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypoxia | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Pharyngeal erythema subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Respiratory failure subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Psychiatric disorders | | | |
| Personality change subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Insomnia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Confusional state subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 2 | 1 / 22 (4.55%) 1 |
| Investigations | | | |
| Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 2 | 0 / 22 (0.00%) 0 |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 1 / 9 (11.11%) 2 | 4 / 22 (18.18%) 4 |
| Urine output decreased | | | |

| | | | |
|---|----------------------|---------------------|-----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Weight decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 22 (9.09%) 2 |
| Injury, poisoning and procedural complications | | | |
| Upper limb fracture subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Ligament sprain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 22 (9.09%) 2 |
| Fall subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 22 (9.09%) 2 |
| Contusion subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 22 (9.09%) 2 |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 11 (27.27%) 5 | 4 / 9 (44.44%) 7 | 5 / 22 (22.73%) 14 |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Depressed level of consciousness | | | |

| | | | |
|-----------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Ataxia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 2 | 0 | 1 |
| Aphasia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 | 1 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Hydrocephalus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 1 | 1 |
| Muscle spasticity | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 0 | 2 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 3 / 22 (13.64%) |
| occurrences (all) | 0 | 0 | 6 |
| Vlth nerve disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Tremor | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 0 | 1 |
| Seizure | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pyramidal tract syndrome | | | |

| | | | |
|--|---------------------|--------------------|---------------------|
| subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 6 / 9 (66.67%) | 8 / 22 (36.36%) |
| occurrences (all) | 11 | 10 | 14 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Anaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 3 / 9 (33.33%) | 7 / 22 (31.82%) |
| occurrences (all) | 1 | 4 | 10 |
| Lymphopenia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 6 / 9 (66.67%) | 6 / 22 (27.27%) |
| occurrences (all) | 1 | 10 | 9 |
| Neutropenia | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 7 / 9 (77.78%) | 9 / 22 (40.91%) |
| occurrences (all) | 15 | 18 | 29 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 9 (33.33%) | 8 / 22 (36.36%) |
| occurrences (all) | 0 | 6 | 12 |
| Eye disorders | | | |
| Blindness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Conjunctival hyperaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Mydriasis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Gastrointestinal disorders | | | |
| Salivary hypersecretion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 0 | 1 |
| Odynophagia | | | |

| | | | |
|---|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 4 / 22 (18.18%) |
| occurrences (all) | 4 | 1 | 7 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysphagia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 1 | 0 | 2 |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 5 / 22 (22.73%) |
| occurrences (all) | 0 | 1 | 9 |
| Constipation | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 9 (11.11%) | 5 / 22 (22.73%) |
| occurrences (all) | 2 | 1 | 5 |
| Abdominal pain | | | |
| subjects affected / exposed | 3 / 11 (27.27%) | 1 / 9 (11.11%) | 1 / 22 (4.55%) |
| occurrences (all) | 3 | 1 | 6 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 4 / 9 (44.44%) | 5 / 22 (22.73%) |
| occurrences (all) | 3 | 5 | 6 |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysaesthesia syndrome | | | |

| | | | |
|-----------------------------|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Eczema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry skin | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 9 (22.22%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 1 | 0 | 2 |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rash maculo-papular | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 9 (33.33%) | 2 / 22 (9.09%) |
| occurrences (all) | 0 | 3 | 2 |
| Rash | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 9 (0.00%) | 1 / 22 (4.55%) |
| occurrences (all) | 2 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 3 / 9 (33.33%) | 1 / 22 (4.55%) |
| occurrences (all) | 2 | 3 | 1 |
| Urticaria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary hesitation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|--|---------------------|---------------------|---------------------|
| Urinary retention subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Urinary incontinence subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 1 / 22 (4.55%) 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Temporomandibular joint syndrome subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Muscular weakness subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Muscle spasms subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Neck pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 22 (9.09%) 2 |
| Infections and infestations | | | |
| Molluscum contagiosum subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Laryngitis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Fungal infection subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Eye infection | | | |

| | | | |
|------------------------------------|-----------------|----------------|-----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Device related infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 2 / 22 (9.09%) |
| occurrences (all) | 0 | 0 | 3 |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Parotitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 1 | 1 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 9 (11.11%) | 1 / 22 (4.55%) |
| occurrences (all) | 1 | 1 | 1 |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 9 (11.11%) | 0 / 22 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 9 (33.33%) | 1 / 22 (4.55%) |
| occurrences (all) | 0 | 3 | 1 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 9 (0.00%) | 0 / 22 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 9 (0.00%) | 3 / 22 (13.64%) |
| occurrences (all) | 3 | 0 | 3 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Hypercalcaemia subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 0 / 22 (0.00%) 0 |
| Hypernatraemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 1 / 22 (4.55%) 2 |
| Hypoalbuminaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 1 / 22 (4.55%) 1 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 9 (11.11%) 1 | 2 / 22 (9.09%) 2 |
| Hypokalaemia subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 1 / 9 (11.11%) 1 | 2 / 22 (9.09%) 2 |
| Hypomagnesaemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |
| Hyponatraemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 2 / 22 (9.09%) 2 |
| Hypophosphataemia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 9 (0.00%) 0 | 0 / 22 (0.00%) 0 |

| | | | |
|--|---------------------|--|--|
| Non-serious adverse events | Medulloblastoma | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 9 / 10 (90.00%) | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) Haemangioma subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Vascular disorders | | | |

| | | | |
|--|----------------------|--|--|
| Hypertension subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Flushing subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Pallor subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| General disorders and administration site conditions Gait disturbance subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Fatigue subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 2 | | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| General physical health deterioration subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Non-cardiac chest pain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders Bronchostenosis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Cough | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Tonsillar inflammation | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Sleep apnoea syndrome | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Pharyngeal erythema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Respiratory failure | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Psychiatric disorders | | | |
| Personality change | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Confusional state | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |

| | | | |
|---|----------------------|--|--|
| Anxiety subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Investigations Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Blood alkaline phosphatase increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Aspartate aminotransferase increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Alanine aminotransferase increased subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 4 | | |
| Urine output decreased subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Weight decreased subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Weight increased subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Injury, poisoning and procedural complications Upper limb fracture subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Ligament sprain subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Fall subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |

| | | | |
|--|----------------------|--|--|
| Contusion subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Cardiac disorders | | | |
| Bradycardia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Sinus tachycardia subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 3 / 10 (30.00%) 7 | | |
| Peripheral sensory neuropathy subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Depressed level of consciousness subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Ataxia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Aphasia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Hemiparesis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Hydrocephalus subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Muscle spasticity subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Paraesthesia | | | |

| | | | |
|--------------------------------------|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dizziness | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vith nerve disorder | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Tremor | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Seizure | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Pyramidal tract syndrome | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 3 / 10 (30.00%) | | |
| occurrences (all) | 3 | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | | |
| occurrences (all) | 7 | | |

| | | | |
|---|----------------------|--|--|
| Thrombocytopenia subjects affected / exposed occurrences (all) | 3 / 10 (30.00%) 3 | | |
| Eye disorders | | | |
| Blindness subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Conjunctival hyperaemia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Mydriasis subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Gastrointestinal disorders | | | |
| Salivary hypersecretion subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Odynophagia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Nausea subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Enteritis subjects affected / exposed occurrences (all) | 1 / 10 (10.00%) 1 | | |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Dyspepsia subjects affected / exposed occurrences (all) | 0 / 10 (0.00%) 0 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 2 / 10 (20.00%) 3 | | |
| Constipation | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 3 / 10 (30.00%) | | |
| occurrences (all) | 3 | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 10 (40.00%) | | |
| occurrences (all) | 5 | | |
| Hepatobiliary disorders | | | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Skin and subcutaneous tissue disorders | | | |
| Palmar-plantar erythrodysesthesia syndrome | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eczema | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dry skin | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Dermatitis acneiform | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rash maculo-papular | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Rash | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pruritus | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Urticaria | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Rash pruritic | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Renal and urinary disorders | | | |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Urinary hesitation | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Urinary retention | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Urinary incontinence | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Temporomandibular joint syndrome | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Muscular weakness | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Muscle spasms | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Neck pain | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Infections and infestations | | | |
| Molluscum contagiosum | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Laryngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Fungal infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Eye infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Device related infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Otitis externa | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Parotitis | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |

| | | | |
|------------------------------------|-----------------|--|--|
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Rhinitis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Oral candidiasis | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 2 | | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypernatraemia | | | |
| subjects affected / exposed | 0 / 10 (0.00%) | | |
| occurrences (all) | 0 | | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 2 / 10 (20.00%) | | |
| occurrences (all) | 4 | | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 2 | | |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 1 | | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 1 / 10 (10.00%) | | |
| occurrences (all) | 2 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 16 June 2017 | Updated exploratory endpoints |
| 18 August 2017 | Updated inclusion and exclusion criteria |
| 20 December 2017 | Updated exclusion criteria |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported