



Clinical trial results:

A Phase I/II study of LDE225 in pediatric patients with recurrent or refractory medulloblastoma or other tumors potentially dependent on the Hedgehog-signaling pathway and adult patients with recurrent or refractory medulloblastoma

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2010-019348-37 |
| Trial protocol | FR GB IT |
| Global end of trial date | 03 October 2014 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 (current) |
| This version publication date | 13 July 2016 |
| First version publication date | 06 August 2015 |

Trial information

Trial identification

| | |
|-----------------------|--------------|
| Sponsor protocol code | CLDE225X2104 |
|-----------------------|--------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01125800 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Novartis Pharma AG |
| Sponsor organisation address | CH-4002, Basel, Switzerland, |
| Public contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |
| Scientific contact | Clinical Disclosure Office, Novartis Pharma AG, +41 613241111, |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000880-PIP02-11 |
| 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 | 03 October 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 October 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Determine the maximum tolerated dose (MTD) and/or recommended Phase II dose (RP2D) of sonidegib in children with advanced solid tumors (recurrent or refractory medulloblastoma, rhabdomyosarcoma, neuroblastoma, hepatoblastoma, high-grade glioma, or osteosarcoma) when administered on a continuous daily dosing schedule. (Phase I)
Assess preliminary efficacy of sonidegib, as determined by objective response rate (ORR) in recurrent or refractory medulloblastoma (MB) patients (adult and pediatric combined) regardless of Hedgehog (Hh) pathway status (activated or non-activated) (Phase II)

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. Rescue medication was not allowed during the course of the study. The investigator provided follow-up medical care for all subjects who were prematurely withdrawn from the study, or referred them for appropriate ongoing care.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 09 February 2011 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Country: Number of subjects enrolled | France: 16 |
| Country: Number of subjects enrolled | Italy: 17 |
| Country: Number of subjects enrolled | Australia: 4 |
| Country: Number of subjects enrolled | Canada: 6 |
| Country: Number of subjects enrolled | United States: 22 |
| Worldwide total number of subjects | 76 |
| EEA total number of subjects | 44 |

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) | 29 |
| Adolescents (12-17 years) | 31 |
| Adults (18-64 years) | 15 |
| From 65 to 84 years | 1 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 14 centres in 6 countries.

Pre-assignment

Screening details:

A total of 60 pediatric subjects and 16 adult subjects were enrolled in this study, of which 59 pediatric subjects received sonidegib during the dose-escalation and expansion part (Phase I); 17 subjects (1 child and 16 adults) received sonidegib in the Phase II.

Period 1

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

Blinding implementation details:

As the study was an open-label study, this section was not applicable.

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|--|
| Arm title | Pediatric subjects, LDE225 233 mg/m ² |
|------------------|--|

Arm description:

Pediatric subjects received LDE225 233 mg/m² once daily through oral route.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sonidegib |
| Investigational medicinal product code | LDE225 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

LDE225 capsules were administered once daily through oral route in pediatric subjects to provide a dose of 233 mg/m².

| | |
|------------------|--|
| Arm title | Pediatric subjects, LDE225 372 mg/m ² |
|------------------|--|

Arm description:

Pediatric subjects received LDE225 372 mg/m² once daily through oral route.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sonidegib |
| Investigational medicinal product code | LDE225 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

LDE225 capsules were administered once daily through oral route in pediatric subjects to provide a dose of 372 mg/m².

| | |
|------------------|--|
| Arm title | Pediatric subjects, LDE225 425 mg/m ² |
|------------------|--|

Arm description:

Pediatric subjects received LDE225 425 mg/m² once daily through oral route.

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

| | |
|--|-----------|
| Investigational medicinal product name | Sonidegib |
| Investigational medicinal product code | LDE225 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

LDE225 capsules were administered once daily through oral route in pediatric subjects to provide a dose of 425 mg/m².

| | |
|------------------|--|
| Arm title | Pediatric subjects, LDE225 680 mg/m ² |
|------------------|--|

Arm description:

Pediatric subjects received LDE225 680 mg/m² once daily through oral route.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sonidegib |
| Investigational medicinal product code | LDE225 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

LDE225 capsules were administered once daily through oral route in pediatric subjects to provide a dose of 680 mg/m².

| | |
|------------------|-------------------------------|
| Arm title | Adult subjects, LDE225 800 mg |
|------------------|-------------------------------|

Arm description:

Adult subjects were treated with LDE225 800 mg capsule once daily.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Sonidegib |
| Investigational medicinal product code | LDE225 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

LDE225 capsules of 800 mg strength was administered once daily.

| Number of subjects in period 1 | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² |
|---------------------------------------|--|--|--|
| Started | 11 | 16 | 11 |
| Completed | 0 | 0 | 0 |
| Not completed | 11 | 16 | 11 |
| Adverse event, non-fatal | 1 | 1 | 1 |
| Death | - | - | - |
| Disease Progression | 10 | 15 | 10 |

| Number of subjects in period 1 | Pediatric subjects, LDE225 680 mg/m ² | Adult subjects, LDE225 800 mg |
|---------------------------------------|--|----------------------------------|
| Started | 22 | 16 |
| Completed | 0 | 0 |
| Not completed | 22 | 16 |
| Adverse event, non-fatal | 1 | 2 |

| | | |
|---------------------|----|----|
| Death | - | 2 |
| Disease Progression | 21 | 12 |

Baseline characteristics

Reporting groups

| | |
|---|--|
| Reporting group title | Pediatric subjects, LDE225 233 mg/m ² |
| Reporting group description: | |
| Pediatric subjects received LDE225 233 mg/m ² once daily through oral route. | |
| Reporting group title | Pediatric subjects, LDE225 372 mg/m ² |
| Reporting group description: | |
| Pediatric subjects received LDE225 372 mg/m ² once daily through oral route. | |
| Reporting group title | Pediatric subjects, LDE225 425 mg/m ² |
| Reporting group description: | |
| Pediatric subjects received LDE225 425 mg/m ² once daily through oral route. | |
| Reporting group title | Pediatric subjects, LDE225 680 mg/m ² |
| Reporting group description: | |
| Pediatric subjects received LDE225 680 mg/m ² once daily through oral route. | |
| Reporting group title | Adult subjects, LDE225 800 mg |
| Reporting group description: | |
| Adult subjects were treated with LDE225 800 mg capsule once daily. | |

| Reporting group values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² |
|------------------------|--|--|--|
| Number of subjects | 11 | 16 | 11 |
| Age categorical | | | |
| Units: Subjects | | | |
| ≤ 10 years | 4 | 3 | 5 |
| >10 years to 17 years | 7 | 13 | 6 |
| 18-65 years | 0 | 0 | 0 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 12.36 | 12.88 | 10.27 |
| standard deviation | ± 3.202 | ± 3.519 | ± 4.88 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 4 | 6 | 3 |
| Male | 7 | 10 | 8 |

| Reporting group values | Pediatric subjects, LDE225 680 mg/m ² | Adult subjects, LDE225 800 mg | Total |
|------------------------|--|----------------------------------|-------|
| Number of subjects | 22 | 16 | 76 |
| Age categorical | | | |
| Units: Subjects | | | |
| ≤ 10 years | 11 | 0 | 23 |
| >10 years to 17 years | 11 | 0 | 37 |
| 18-65 years | 0 | 16 | 16 |
| Age continuous | | | |
| Units: years | | | |
| arithmetic mean | 9.68 | 35.13 | - |
| standard deviation | ± 4.932 | ± 14.118 | - |

| | | | |
|--------------------|----|---|----|
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 10 | 7 | 30 |
| Male | 12 | 9 | 46 |

End points

End points reporting groups

| | |
|---|--|
| Reporting group title | Pediatric subjects, LDE225 233 mg/m ² |
| Reporting group description: Pediatric subjects received LDE225 233 mg/m ² once daily through oral route. | |
| Reporting group title | Pediatric subjects, LDE225 372 mg/m ² |
| Reporting group description: Pediatric subjects received LDE225 372 mg/m ² once daily through oral route. | |
| Reporting group title | Pediatric subjects, LDE225 425 mg/m ² |
| Reporting group description: Pediatric subjects received LDE225 425 mg/m ² once daily through oral route. | |
| Reporting group title | Pediatric subjects, LDE225 680 mg/m ² |
| Reporting group description: Pediatric subjects received LDE225 680 mg/m ² once daily through oral route. | |
| Reporting group title | Adult subjects, LDE225 800 mg |
| Reporting group description: Adult subjects were treated with LDE225 800 mg capsule once daily. | |
| Subject analysis set title | Pediatric subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All the pediatric subjects were treated with LDE225 dose determined in the Phase I (233, 372, 425 and 680 mg/m ²). | |
| Subject analysis set title | Adult subjects |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: All adult subjects were treated with sonidegib 800 mg once daily in phase II portion of the study. Pediatric patients were also enrolled in phase II portion of the study at the recommended phase II pediatric dose - 680 mg/m ² | |

Primary: Maximum tolerated dose (MTD) of sonidegib in Phase 1

| | |
|---|--|
| End point title | Maximum tolerated dose (MTD) of sonidegib in Phase 1 ^{[1][2]} |
| End point description: MTD was defined as highest dose level for which for is unlikely to have more than 33% of patients experienced dose-limiting toxicity (DLT) during the first 6 weeks of treatment, no more than 1 subject in a dose cohort experienced dose-limiting toxicity (DLT), based on a Bayesian logistic regression model (BLRM) employing the escalation with overdose control (EWOC) principle. DLT was defined as an adverse event (AE) or abnormal laboratory value assessed as unrelated to disease, disease progression, intercurrent illness, or concomitant medications. MTD was not achieved since no more than 1 DLT was observed in any cohort. One DLT was observed at 372 mg/m ² dose. The posterior probability of true DLT rate lies in excessive toxicity interval [0.33, 1] even at 680 mg/m ² was still very small (0.7%); The RP2D was established using the BLRM and joint clinical review of the safety data by the Investigators and Novartis personnel, including the Novartis medical monitor, at a dose escalation meeting | |
| End point type | Primary |
| End point timeframe: Baseline, End of dose escalation part | |
| 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 summary statistics was planned for this primary outcome measure. [2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: The end point summary statistics was planned only for treatment arms in Part 1 of the study. | |

| End point values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² | Pediatric subjects, LDE225 680 mg/m ² |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 ^[3] | 16 ^[4] | 11 ^[5] | 22 ^[6] |
| Units: mg/m ² | | | | |
| arithmetic mean (standard deviation) | 0 (± 0) | 0 (± 0) | 0 (± 0) | 0 (± 0) |

Notes:

[3] - The MTD for the pediatric population was not established in this study.

[4] - The MTD for the pediatric population was not established in this study.

[5] - The MTD for the pediatric population was not established in this study.

[6] - The MTD for the pediatric population was not established in this study.

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of subjects with objective response rate (ORR) by treatment

| | |
|-----------------|---|
| End point title | Percentage of subjects with objective response rate (ORR) by treatment ^[7] |
|-----------------|---|

End point description:

The tumour response to the sonidegib treatment was measured by ORR. The ORR was defined as the proportion of subjects with partial response or complete response as their best overall response. Subjects with stable disease, progressive disease tumour assessment were considered as non-responders. The analysis was performed in full analysis set (FAS), defined as all the subjects who received at least one dose of sonidegib.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline to End of treatment

Notes:

[7] - 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 summary statistics was planned for this primary outcome measure.

| End point values | Pediatric subjects | Adult subjects | | |
|-------------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 60 | 16 | | |
| Units: percentage of tumor response | | | | |
| number (not applicable) | | | | |
| Complete response | 3.3 | 13.5 | | |
| Partial response | 0 | 6.3 | | |
| Stable disease | 8.3 | 37.5 | | |
| Progressive disease | 76.7 | 37.5 | | |
| Objective response rate | 3.3 | 18.3 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events (AEs), serious adverse events

(SAEs), treatment related AEs and death during the study

| | |
|---|---|
| End point title | Number of subjects with adverse events (AEs), serious adverse events (SAEs), treatment related AEs and death during the study |
| End point description: An AE was defined as any unfavorable and unintended sign, symptom, or disease temporally associated with the use of study drug, whether or not related to study drug. A SAE was defined as an event which was fatal or life threatening, required or prolonged hospitalization, was significantly or permanently disabling or incapacitating, constituted a congenital anomaly or a birth defect, or encompassed any other clinically significant event that could jeopardize the subject or require medical or surgical intervention to prevent one of the aforementioned outcomes. Treatment related AEs were defined as AEs that were suspected to be related to study treatment as per investigator. On-treatment deaths were deaths which occurred up to 30 days after last date of study treatment. The analysis was performed in safety set (SS), defined as all the subjects who received at least 1 dose of sonidegib. | |
| End point type | Secondary |
| End point timeframe: Baseline (start of study treatment) up to End of treatment + 30 days | |

| End point values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² | Pediatric subjects, LDE225 680 mg/m ² |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 16 | 11 | 22 |
| Units: Number of subjects | | | | |
| AEs | 11 | 16 | 11 | 22 |
| AEs suspected to be drug related | 8 | 13 | 9 | 14 |
| AEs leading to discontinuation | 1 | 1 | 1 | 1 |
| On-treatment deaths | 2 | 2 | 1 | 8 |
| SAEs | 5 | 8 | 4 | 14 |

| End point values | Adult subjects, LDE225 800 mg | | | |
|----------------------------------|-------------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 16 | | | |
| Units: Number of subjects | | | | |
| AEs | 16 | | | |
| AEs suspected to be drug related | 13 | | | |
| AEs leading to discontinuation | 3 | | | |
| On-treatment deaths | 2 | | | |
| SAEs | 5 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Area under the drug concentration time curve from time zero to 24

hours after dosing (AUC0-24h) of sonidegib in Phase 1

| | |
|-----------------|--|
| End point title | Area under the drug concentration time curve from time zero to 24 hours after dosing (AUC0-24h) of sonidegib in Phase 1 ^[8] |
|-----------------|--|

End point description:

AUC(0-24h) was defined as the area under the drug concentration time curve calculated using linear trapezoidal summation from time zero to 24 hours after dosing. The analysis was performed in pharmacokinetic analysis set (PAS), defined as all the subjects who received at least one (full or partial) dose of sonidegib and provided at least one evaluable pharmacokinetic (PK) blood sample. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

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

End point timeframe:

Day 1 and Day 22 of Cycle 1

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point summary statistics was planned only for treatment arms in Part 1 of the study.

| End point values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² | Pediatric subjects, LDE225 680 mg/m ² |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 16 | 11 | 22 |
| Units: nanograms*hours/millilitres (ng*hr/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1/Day 1 (n=11, 15, 11, 19) | 1981.56 (± 736.928) | 2194.29 (± 1592.396) | 5309.44 (± 3247.088) | 5117.61 (± 2658.133) |
| Cycle 1/Day 22 (n=9, 14, 9, 15) | 10589.53 (± 4163.192) | 15431.43 (± 10433.35) | 17753.32 (± 11551.57) | 32622.67 (± 11670.63) |

Statistical analyses

No statistical analyses for this end point

Secondary: Time to reach maximum observed plasma concentration (Tmax) of sonidegib in Phase 1

| | |
|-----------------|---|
| End point title | Time to reach maximum observed plasma concentration (Tmax) of sonidegib in Phase 1 ^[9] |
|-----------------|---|

End point description:

Tmax was defined as the time required to reach maximum observed plasma concentration. Tmax was directly determined from the raw plasma concentration time data. The analysis was performed in PAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

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

End point timeframe:

Day 1 and Day 22 of Cycle 1

Notes:

[9] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point summary statistics was planned only for treatment arms in Part 1 of the study.

| End point values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² | Pediatric subjects, LDE225 680 mg/m ² |
|----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 16 | 11 | 22 |
| Units: Hours | | | | |
| median (full range (min-max)) | | | | |
| Cycle 1/Day 1 (n=11, 15, 10, 17) | 3.98 (1.07 to 6.75) | 2.03 (1 to 7) | 2.92 (0.5 to 7) | 2.08 (1 to 4.08) |
| Cycle 1/Day 22 (n=9, 12, 9, 15) | 1.98 (1 to 7) | 2.06 (0.95 to 4.25) | 2 (0.67 to 7) | 2 (0 to 7.05) |

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum observed plasma concentration (Cmax) of sonidegib in Phase 1

| | |
|-----------------|--|
| End point title | Maximum observed plasma concentration (Cmax) of sonidegib in Phase 1 ^[10] |
|-----------------|--|

End point description:

Maximum observed plasma concentration following drug administration was calculated from the raw plasma concentration time data. The analysis was performed in PAS population. The 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively.

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

End point timeframe:

Day 1 and Day 22 of Cycle 1

Notes:

[10] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: The end point summary statistics was planned only for treatment arms in Part 1 of the study.

| End point values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² | Pediatric subjects, LDE225 680 mg/m ² |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 11 | 16 | 11 | 22 |
| Units: nanograms/millilitres(ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 1/Day 1 (n=11, 15, 10, 17) | 191.18 (± 82.464) | 246.39 (± 211.034) | 642.5 (± 486.709) | 618.88 (± 403.466) |
| Cycle 1/Day 22 (n=9, 12, 9, 15) | 769.22 (± 496.021) | 944.17 (± 553.395) | 1122 (± 736.862) | 1930 (± 677.949) |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of pediatric subjects with objective response rate (ORR) by Hedgehog (Hh) signaling pathway status

| | |
|-----------------|---|
| End point title | Percentage of pediatric subjects with objective response rate (ORR) by Hedgehog (Hh) signaling pathway status |
|-----------------|---|

End point description:

ORR was determined in the subjects with mutations on Hh gene (Hh positive) and the subjects without mutations on Hh gene (Hh negative). The analysis was performed in full analysis set (FAS). 'n' signifies those subjects evaluable for this measure at specified time points for each group, respectively. 60 patients were screened, 10 were Hh positive, of the 10, 3 were pediatric.

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

End point timeframe:

Baseline to End of treatment

| | | | | |
|-------------------------------|----------------------|--|--|--|
| End point values | Pediatric subjects | | | |
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 3 ^[11] | | | |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Objective response rate | 66.7 | | | |

Notes:

[11] - Number Hh positive pediatric subjects

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of response by treatment

| | |
|-----------------|-----------------------------------|
| End point title | Duration of response by treatment |
|-----------------|-----------------------------------|

End point description:

Duration of overall response (complete response (CR) or partial response (PR)) was calculated for those subjects whose best overall response was CR or PR. The start date was the date of the first documented tumor response (CR or PR) and the end date was the date of the event defined as the first documented progression or death due to underlying cancer or after the same treatment line. If a subject did not have a progression or death, the duration of response was censored at the date of last adequate tumor assessment in that treatment line. The analysis was performed in FAS population.

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

End point timeframe:

Baseline to End of treatment

| | | | | |
|-------------------------------|--|--|--|--|
| End point values | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² | Pediatric subjects, LDE225 680 mg/m ² |
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 0 ^[12] | 1 ^[13] | 1 ^[14] | 0 ^[15] |
| Units: Months | | | | |
| median (full range (min-max)) | (to) | 7.03 (7 to 7.03) | 8.08 (8 to 8.1) | (to) |

Notes:

[12] - none of the subjects in this group achieved the endpoint

[13] - only one responder in this group

[14] - only one responder in this group

[15] - none of the subjects in this group achieved the endpoint

| | | | | |
|-------------------------------|-------------------------------------|--|--|--|
| End point values | Adult subjects, LDE225 800 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 ^[16] | | | |
| Units: Months | | | | |
| median (full range (min-max)) | 4.86 (1.6 to 8.7) | | | |

Notes:

[16] - 3 responders in this group

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Serious Adverse Events are monitored from date of First Subject First Visit (FSFV) until Last Subject Last Visit (LSLV). All other adverse events are monitored from First Subject First Treatment (FSFT) until Last Subject Last Visit (LSLV).

Adverse event reporting additional description:

Consistent with EudraCT disclosure specifications, Novartis has reported under the Serious adverse events field "number of deaths resulting from adverse events" all those deaths, resulting from serious adverse events that are deemed to be causally related to treatment by the investigator.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 17.0 |

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Pediatric subjects, LDE225 233 mg/m ² |
|-----------------------|--|

Reporting group description:

Pediatric subjects received LDE225 233 mg/m² once daily through oral route.

| | |
|-----------------------|--|
| Reporting group title | Pediatric subjects, LDE225 372 mg/m ² |
|-----------------------|--|

Reporting group description:

Pediatric subjects received LDE225 372 mg/m² once daily through oral route.

| | |
|-----------------------|--|
| Reporting group title | Pediatric subjects, LDE225 425 mg/m ² |
|-----------------------|--|

Reporting group description:

Pediatric subjects received LDE225 425 mg/m² once daily through oral route.

| | |
|-----------------------|--|
| Reporting group title | Pediatric subjects, LDE225 680 mg/m ² |
|-----------------------|--|

Reporting group description:

Pediatric subjects received LDE225 680 mg/m² once daily through oral route.

| | |
|-----------------------|-------------------------------|
| Reporting group title | Adult subjects, LDE225 800 mg |
|-----------------------|-------------------------------|

Reporting group description:

Adult subjects were treated with LDE225 800 mg capsule once daily.

| Serious adverse events | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 8 / 16 (50.00%) | 4 / 11 (36.36%) |
| number of deaths (all causes) | 2 | 2 | 1 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour Haemorrhage | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Vascular disorders | | | |

| | | | |
|--|----------------|-----------------|----------------|
| Venous Insufficiency | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| General disorders and administration site conditions | | | |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (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 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Pleural Effusion | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Pneumonia Aspiration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Respiratory Distress | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Confusional State | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Disorientation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Suicidal Ideation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Aspartate Aminotransferase | | | |

| | | | | |
|---|----------------|----------------|----------------|--|
| Increased | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 | |
| Blood Creatine Phosphokinase Increased | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 | |
| Myoglobin Blood Increased | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 | |
| Injury, poisoning and procedural complications | | | | |
| Femur Fracture | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 | |
| Procedural Complication | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | | |
| Altered State Of Consciousness | | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 | |
| Amnesia | | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (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 | |
| Aphasia | | | | |

| | | | |
|---|----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Coma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Depressed Level Of Consciousness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Dysaesthesia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Dystonia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (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 |
| Headache | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hydrocephalus | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Intracranial Pressure Increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Neurological Decompensation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Quadripareisis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Tremor | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Vision Blurred | | | |

| | | | |
|--|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Urinary Incontinence | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular Weakness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| 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 In Extremity | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (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 |
| Cystitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Mucosal Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (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 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (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 |

| Serious adverse events | Pediatric subjects, LDE225 680 mg/m ² | Adult subjects, LDE225 800 mg | |
|---|--|----------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 14 / 22 (63.64%) | 5 / 16 (31.25%) | |
| number of deaths (all causes) | 8 | 2 | |
| number of deaths resulting from adverse events | 0 | 0 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Tumour Haemorrhage | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Venous Insufficiency | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |

| | | | |
|---|----------------|----------------|--|
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural Effusion | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Aspiration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Distress | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional State | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|----------------|-----------------|--|
| Suicidal Ideation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood Creatine Phosphokinase Increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 16 (12.50%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myoglobin Blood Increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Procedural Complication | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Altered State Of Consciousness | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amnesia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed Level Of Consciousness | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dystonia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Encephalopathy | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Headache | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hydrocephalus | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intracranial Pressure Increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neurological Decompensation | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Quadriparesis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Somnolence | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Vision Blurred | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Urinary Incontinence | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Muscular Weakness | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain In Extremity | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cystitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mucosal Infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Wound Infection | | | |

| | | | |
|---|----------------|----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (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 | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Pediatric subjects, LDE225 233 mg/m ² | Pediatric subjects, LDE225 372 mg/m ² | Pediatric subjects, LDE225 425 mg/m ² |
|---|--|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 11 / 11 (100.00%) | 16 / 16 (100.00%) | 11 / 11 (100.00%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Skin Papilloma | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hypotension | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| Pallor | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| General disorders and administration site conditions | | | |

| | | | |
|---------------------------------------|-----------------|-----------------|-----------------|
| Asthenia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 4 / 16 (25.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 5 | 2 |
| Chest Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Chills | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Face Oedema | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Facial Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Fatigue | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 7 / 16 (43.75%) | 3 / 11 (27.27%) |
| occurrences (all) | 7 | 10 | 3 |
| Gait Disturbance | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza Like Illness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Oedema Peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |

| | | | |
|---|----------------------|----------------------|----------------------|
| Performance Status Decreased subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Reproductive system and breast disorders Penile Pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Vaginal Discharge subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Apnoea subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Cough subjects affected / exposed occurrences (all) | 3 / 11 (27.27%) 3 | 1 / 16 (6.25%) 1 | 5 / 11 (45.45%) 5 |
| Dyspnoea subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 3 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Epistaxis subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 2 / 16 (12.50%) 2 | 0 / 11 (0.00%) 0 |
| Hiccups subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Laryngeal Inflammation subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |

| | | | |
|-----------------------------|-----------------|-----------------|----------------|
| Nasal Congestion | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Pleural Effusion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stridor | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Anxiety | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |
| Bruxism | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Confusional State | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 3 | 1 |
| Disorientation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Euphoric Mood | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Insomnia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 2 / 16 (12.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 2 | 1 |
| Irritability | | | |

| | | | |
|---|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Mood Altered | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Paranoia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Investigations | | | |
| Activated Partial Thromboplastin Time Prolonged | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 2 | 0 |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 2 | 2 |
| Blood Alkaline Phosphatase Increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 1 |
| Blood Bilirubin Increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Blood Creatine Phosphokinase Increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 3 | 4 |
| Blood Creatinine Increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Blood Fibrinogen Decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood Lactate Dehydrogenase Increased | | | |

| | | | |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Blood Magnesium Decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Blood Urea Increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Cardiac Murmur | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Haemoglobin Decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Lymphocyte Count Decreased | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 16 (6.25%) | 3 / 11 (27.27%) |
| occurrences (all) | 2 | 2 | 4 |
| Neutrophil Count Decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 2 | 2 |
| Platelet Count Decreased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 2 |
| Weight Decreased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 2 | 0 |
| White Blood Cell Count Decreased | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 2 / 16 (12.50%) | 3 / 11 (27.27%) |
| occurrences (all) | 3 | 4 | 4 |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Femur Fracture | | | |

| | | | |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Procedural Pain subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Thermal Burn subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Vascular Procedure Complication subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Cardiac disorders Left Ventricular Hypertrophy subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Sinus Bradycardia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Nervous system disorders Amnesia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 2 / 16 (12.50%) 3 | 0 / 11 (0.00%) 0 |
| Aphasia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Ataxia subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 2 / 16 (12.50%) 2 | 2 / 11 (18.18%) 2 |
| Balance Disorder subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 2 |
| Brain Oedema subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Cerebellar Syndrome | | | |

| | | | |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Coma | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Convulsion | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 1 | 7 |
| Coordination Abnormal | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Depressed Level Of Consciousness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 2 | 1 |
| Dysaesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Dysarthria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Dysgeusia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Facial Nerve Disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Facial Paresis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Headache | | | |
| subjects affected / exposed | 6 / 11 (54.55%) | 7 / 16 (43.75%) | 4 / 11 (36.36%) |
| occurrences (all) | 7 | 17 | 13 |
| Hemiparesis | | | |

| | | | |
|---------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hemiplegia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperaesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Hypoaesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| IIIrd nerve paresis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intracranial Pressure Increased | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Lethargy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 3 / 11 (27.27%) |
| occurrences (all) | 1 | 0 | 3 |
| Meningism | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Neuralgia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Neurological Decompensation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Neuropathy Peripheral | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paraesthesia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Paraparesis | | | |

| | | | |
|--------------------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Peripheral Sensory Neuropathy | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Peroneal Nerve Palsy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Pyramidal Tract Syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Somnolence | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 16 (18.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 3 | 3 |
| Speech Disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Tremor | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| VIIth nerve paralysis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| VIth nerve disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 4 / 11 (36.36%) |
| occurrences (all) | 0 | 2 | 4 |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |

| | | | |
|---|----------------------|---------------------|---------------------|
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Lymphopenia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Ear and labyrinth disorders | | | |
| Cerumen Impaction subjects affected / exposed occurrences (all) | 2 / 11 (18.18%) 2 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Deafness subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Ear Canal Stenosis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 2 | 0 / 11 (0.00%) 0 |
| Ear Pain subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Hypoacusis subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 1 / 16 (6.25%) 1 | 0 / 11 (0.00%) 0 |
| Vertigo subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Eye disorders | | | |
| Blindness Unilateral subjects affected / exposed occurrences (all) | 1 / 11 (9.09%) 1 | 0 / 16 (0.00%) 0 | 0 / 11 (0.00%) 0 |
| Conjunctivitis Allergic subjects affected / exposed occurrences (all) | 0 / 11 (0.00%) 0 | 0 / 16 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Diplopia | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dry Eye | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Eyelid Ptosis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Eye Irritation | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Lacrimation Increased | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Ocular Hyperaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Strabismus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Vision Blurred | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 1 | 2 |
| Visual Acuity Reduced | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Visual Impairment | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 3 / 16 (18.75%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 4 | 4 |
| Abdominal Pain Lower | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| Anal Pruritus | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 6 / 16 (37.50%) | 4 / 11 (36.36%) |
| occurrences (all) | 1 | 10 | 5 |
| Dental Caries | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 5 / 16 (31.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 2 | 7 | 2 |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |
| Faecal Incontinence | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Faeces Hard | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastritis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Gastrointestinal Pain | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gingival Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Mouth Ulceration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Nausea | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 4 / 16 (25.00%) | 3 / 11 (27.27%) |
| occurrences (all) | 5 | 5 | 8 |

| | | | |
|--|-----------------|-----------------|-----------------|
| Odynophagia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral Dysaesthesia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Oral Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 1 | 2 |
| Tooth Disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Toothache | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 2 | 1 | 0 |
| Vomiting | | | |
| subjects affected / exposed | 5 / 11 (45.45%) | 9 / 16 (56.25%) | 7 / 11 (63.64%) |
| occurrences (all) | 5 | 12 | 13 |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 3 / 11 (27.27%) |
| occurrences (all) | 0 | 1 | 3 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis Acneiform | | | |

| | | | |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dry Skin | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 3 / 11 (27.27%) |
| occurrences (all) | 0 | 2 | 3 |
| Erythema | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungating Wound | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Madarosis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 5 | 3 | 2 |
| Nail Disorder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Pain Of Skin | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Pruritus | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 3 / 16 (18.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 4 | 1 |
| Rash | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash Maculo-Papular | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Rash Papular | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin Exfoliation | | | |

| | | | |
|-----------------------------|----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Solar Dermatitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 2 / 16 (12.50%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Micturition Disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Micturition Urgency | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Neurogenic Bladder | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Pollakiuria | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Polyuria | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Urinary Incontinence | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 2 |
| Urinary Retention | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Urinary Tract Disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Endocrine disorders | | | |
| Cushingoid | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 3 / 16 (18.75%) | 3 / 11 (27.27%) |
| occurrences (all) | 3 | 5 | 5 |
| Back Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 4 / 16 (25.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 4 | 0 |
| Chondropathy | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Epiphyseal Disorder | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Muscle Spasms | | | |
| subjects affected / exposed | 2 / 11 (18.18%) | 4 / 16 (25.00%) | 5 / 11 (45.45%) |
| occurrences (all) | 5 | 9 | 9 |
| Muscular Weakness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 2 | 1 |
| Musculoskeletal Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 1 | 2 |
| Musculoskeletal Stiffness | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 2 / 16 (12.50%) | 4 / 11 (36.36%) |
| occurrences (all) | 2 | 2 | 10 |
| Neck Pain | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 3 / 16 (18.75%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 5 | 2 |
| Pain In Extremity | | | |

| | | | |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 2 / 11 (18.18%) | 6 / 16 (37.50%) | 4 / 11 (36.36%) |
| occurrences (all) | 2 | 11 | 6 |
| Pain In Jaw | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 1 | 0 | 3 |
| Posture Abnormal | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Sensation Of Heaviness | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Temporomandibular Joint Syndrome | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Infections and infestations | | | |
| Catheter Site Cellulitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Ear Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Influenza | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |

| | | | |
|------------------------------------|----------------|----------------|-----------------|
| Pharyngitis | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin Infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tooth Abscess | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Vulvovaginal Mycotic Infection | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 3 / 11 (27.27%) |
| occurrences (all) | 1 | 1 | 5 |
| Dehydration | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 0 | 0 | 4 |
| Hypermagnesaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hypernatraemia | | | |

| | | | |
|-----------------------------|----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hyperphagia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Hyperphosphataemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypocalcaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 0 / 16 (0.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Hyponatraemia | | | |
| subjects affected / exposed | 1 / 11 (9.09%) | 3 / 16 (18.75%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 4 | 4 |
| Hypophosphataemia | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 1 / 16 (6.25%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Vitamin D Deficiency | | | |
| subjects affected / exposed | 0 / 11 (0.00%) | 0 / 16 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |

| Non-serious adverse events | Pediatric subjects, LDE225 680 mg/m ² | Adult subjects, LDE225 800 mg | |
|---|--|----------------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 21 / 22 (95.45%) | 16 / 16 (100.00%) | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |

| | | | |
|--|----------------------|----------------------|--|
| Skin Papilloma subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Vascular disorders | | | |
| Haematoma subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Hypotension subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 1 / 16 (6.25%) 1 | |
| Pallor subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 3 / 16 (18.75%) 3 | |
| Chest Pain subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 0 / 16 (0.00%) 0 | |
| Chills subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Face Oedema subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Facial Pain subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 16 (6.25%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 6 / 22 (27.27%) 6 | 1 / 16 (6.25%) 1 | |
| Gait Disturbance subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 2 / 16 (12.50%) 2 | |
| General Physical Health Deterioration | | | |

| | | | |
|---|-----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Influenza Like Illness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Non-Cardiac Chest Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Oedema Peripheral | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Performance Status Decreased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 16 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Reproductive system and breast disorders | | | |
| Penile Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vaginal Discharge | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cough | | | |

| | | | |
|-----------------------------|----------------|-----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 3 / 16 (18.75%) | |
| occurrences (all) | 1 | 3 | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Hiccups | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 3 / 16 (18.75%) | |
| occurrences (all) | 0 | 3 | |
| Laryngeal Inflammation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nasal Congestion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pleural Effusion | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Stridor | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Bruxism | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|---|----------------|-----------------|--|
| Confusional State | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Disorientation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Euphoric Mood | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Insomnia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Irritability | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Mood Altered | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Paranoia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Investigations | | | |
| Activated Partial Thromboplastin Time Prolonged | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Alanine Aminotransferase Increased | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 4 / 16 (25.00%) | |
| occurrences (all) | 2 | 4 | |
| Aspartate Aminotransferase Increased | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 16 (6.25%) | |
| occurrences (all) | 3 | 1 | |
| Blood Alkaline Phosphatase Increased | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Blood Bilirubin Increased | | | |

| | | |
|--|-----------------|-----------------|
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 1 |
| Blood Creatine Phosphokinase Increased | | |
| subjects affected / exposed | 6 / 22 (27.27%) | 8 / 16 (50.00%) |
| occurrences (all) | 6 | 15 |
| Blood Creatinine Increased | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 |
| Blood Fibrinogen Decreased | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Blood Lactate Dehydrogenase Increased | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Blood Magnesium Decreased | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Blood Urea Increased | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Cardiac Murmur | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Haemoglobin Decreased | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Lymphocyte Count Decreased | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 1 / 16 (6.25%) |
| occurrences (all) | 3 | 1 |
| Neutrophil Count Decreased | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 16 (0.00%) |
| occurrences (all) | 5 | 0 |
| Platelet Count Decreased | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Weight Decreased | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 3 / 16 (18.75%) | |
| occurrences (all) | 2 | 3 | |
| White Blood Cell Count Decreased | | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 1 / 16 (6.25%) | |
| occurrences (all) | 5 | 3 | |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Femur Fracture | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Procedural Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Thermal Burn | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vascular Procedure Complication | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cardiac disorders | | | |
| Left Ventricular Hypertrophy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sinus Bradycardia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Nervous system disorders | | | |
| Amnesia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Aphasia | | | |

| | | |
|----------------------------------|-----------------|----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Ataxia | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 |
| Balance Disorder | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 |
| Brain Oedema | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Cerebellar Syndrome | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 16 (6.25%) |
| occurrences (all) | 1 | 1 |
| Coma | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Convulsion | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 1 |
| Coordination Abnormal | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Depressed Level Of Consciousness | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Dizziness | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Dysaesthesia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 2 |
| Dysarthria | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 |
| Dysgeusia | | |

| | | |
|---------------------------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 |
| Facial Nerve Disorder | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Facial Paresis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Headache | | |
| subjects affected / exposed | 9 / 22 (40.91%) | 2 / 16 (12.50%) |
| occurrences (all) | 10 | 2 |
| Hemiparesis | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 0 |
| Hemiplegia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hyperaesthesia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hypoaesthesia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| IIIrd nerve paresis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Intracranial Pressure Increased | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Lethargy | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Meningism | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Neuralgia | | |

| | | |
|-------------------------------|----------------|-----------------|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 |
| Neurological Decompensation | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Neuropathy Peripheral | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 |
| Paraesthesia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 16 (12.50%) |
| occurrences (all) | 0 | 3 |
| Paraparesis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Peripheral Sensory Neuropathy | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Peroneal Nerve Palsy | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 |
| Presyncope | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Pyramidal Tract Syndrome | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Somnolence | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 |
| Speech Disorder | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Tremor | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 |
| VIIth nerve paralysis | | |

| | | | |
|---|---------------------|---------------------|--|
| subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| VIth nerve disorder subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 0 / 16 (0.00%) 0 | |
| Leukopenia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 16 (6.25%) 1 | |
| Lymphadenopathy subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Lymphopenia subjects affected / exposed occurrences (all) | 2 / 22 (9.09%) 2 | 1 / 16 (6.25%) 2 | |
| Thrombocytopenia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Ear and labyrinth disorders | | | |
| Cerumen Impaction subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Deafness subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Ear Canal Stenosis subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Ear Pain subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Hypoacusis | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Eye disorders | | | |
| Blindness Unilateral | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Conjunctivitis Allergic | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Diplopia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry Eye | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Eyelid Ptosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Eye Irritation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Lacrimation Increased | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Ocular Hyperaemia | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Strabismus | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Vision Blurred | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |

| | | | |
|---|----------------------|----------------------|--|
| Visual Acuity Reduced subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Visual Impairment subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain subjects affected / exposed occurrences (all) | 5 / 22 (22.73%) 5 | 1 / 16 (6.25%) 1 | |
| Abdominal Pain Lower subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Anal Pruritus subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Constipation subjects affected / exposed occurrences (all) | 3 / 22 (13.64%) 5 | 2 / 16 (12.50%) 3 | |
| Dental Caries subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 22 (4.55%) 1 | 4 / 16 (25.00%) 5 | |
| Dysphagia subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 1 / 16 (6.25%) 1 | |
| Faecal Incontinence subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Faeces Hard subjects affected / exposed occurrences (all) | 0 / 22 (0.00%) 0 | 0 / 16 (0.00%) 0 | |
| Gastritis | | | |

| | | |
|-----------------------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 |
| Gastrointestinal Pain | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Gingival Pain | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Mouth Ulceration | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Nausea | | |
| subjects affected / exposed | 8 / 22 (36.36%) | 4 / 16 (25.00%) |
| occurrences (all) | 10 | 5 |
| Odynophagia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oesophagitis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oral Dysaesthesia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Oral Pain | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Stomatitis | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 3 / 16 (18.75%) |
| occurrences (all) | 0 | 3 |
| Tooth Disorder | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Toothache | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Vomiting | | |

| | | | |
|--|------------------------|----------------------|--|
| subjects affected / exposed occurrences (all) | 15 / 22 (68.18%) 21 | 2 / 16 (12.50%) 3 | |
| Hepatobiliary disorders | | | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Dermatitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dermatitis Acneiform | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Dry Skin | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Erythema | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Fungating Wound | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Madarosis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Nail Disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain Of Skin | | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Pruritus | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 16 (0.00%) | |
| occurrences (all) | 3 | 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Rash Maculo-Papular | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rash Papular | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin Exfoliation | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Solar Dermatitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Renal and urinary disorders | | | |
| Dysuria | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Micturition Disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Micturition Urgency | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Neurogenic Bladder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pollakiuria | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |

| | | | |
|---|----------------|-----------------|--|
| Polyuria | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Urinary Incontinence | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Urinary Retention | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 1 | 0 | |
| Urinary Tract Disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Endocrine disorders | | | |
| Cushingoid | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Back Pain | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Chondropathy | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Epiphyseal Disorder | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Muscle Spasms | | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 4 / 16 (25.00%) | |
| occurrences (all) | 2 | 5 | |
| Muscular Weakness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal Pain | | | |

| | | | |
|----------------------------------|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Musculoskeletal Stiffness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Myalgia | | | |
| subjects affected / exposed | 5 / 22 (22.73%) | 5 / 16 (31.25%) | |
| occurrences (all) | 5 | 5 | |
| Neck Pain | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 2 / 16 (12.50%) | |
| occurrences (all) | 1 | 2 | |
| Pain In Extremity | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pain In Jaw | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Posture Abnormal | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Rhabdomyolysis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Sensation Of Heaviness | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Temporomandibular Joint Syndrome | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Infections and infestations | | | |
| Catheter Site Cellulitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |

| | | | |
|------------------------------------|-----------------|-----------------|--|
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Ear Infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 2 | |
| Influenza | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Skin Infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) | |
| occurrences (all) | 0 | 1 | |
| Tooth Abscess | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 2 / 16 (12.50%) | |
| occurrences (all) | 0 | 2 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 1 / 16 (6.25%) | |
| occurrences (all) | 1 | 1 | |
| Vulvovaginal Mycotic Infection | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased Appetite | | | |
| subjects affected / exposed | 4 / 22 (18.18%) | 3 / 16 (18.75%) | |
| occurrences (all) | 4 | 3 | |
| Dehydration | | | |

| | | |
|-----------------------------|-----------------|----------------|
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 16 (0.00%) |
| occurrences (all) | 3 | 0 |
| Hyperglycaemia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 2 |
| Hyperkalaemia | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 1 / 16 (6.25%) |
| occurrences (all) | 2 | 1 |
| Hypermagnesaemia | | |
| subjects affected / exposed | 2 / 22 (9.09%) | 0 / 16 (0.00%) |
| occurrences (all) | 2 | 0 |
| Hypernatraemia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 |
| Hyperphagia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hyperphosphataemia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hypocalcaemia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hypoglycaemia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 1 / 16 (6.25%) |
| occurrences (all) | 0 | 1 |
| Hypokalaemia | | |
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) |
| occurrences (all) | 1 | 0 |
| Hypomagnesaemia | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) |
| occurrences (all) | 0 | 0 |
| Hyponatraemia | | |
| subjects affected / exposed | 3 / 22 (13.64%) | 0 / 16 (0.00%) |
| occurrences (all) | 4 | 0 |
| Hypophosphataemia | | |

| | | | |
|-----------------------------|----------------|----------------|--|
| subjects affected / exposed | 1 / 22 (4.55%) | 0 / 16 (0.00%) | |
| occurrences (all) | 2 | 0 | |
| Vitamin D Deficiency | | | |
| subjects affected / exposed | 0 / 22 (0.00%) | 0 / 16 (0.00%) | |
| occurrences (all) | 0 | 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 11 July 2011 | List of breast cancer resistance protein (BCRP) substrates was added as non-authorized drugs in the study to avoid potential adverse drug-drug interactions. |
| 11 November 2011 | <ol style="list-style-type: none">1. The second part of the study (Phase II) was incorporated to enroll approximately 55 adults and children with recurrent or refractory MB.2. The plasma PK parameters to be analyzed was updated based on the emerging PK data.3. The definition of MTD and RP2D was added and, clarified the BLRM considerations for specific DLTs with potentially more serious medical implications.4. Hypersensitivity or signs of allergic reaction were not considered a DLT. |
| 23 July 2014 | Inclusion criteria for female subjects was modified. The language states that woman of child bearing potential must not become pregnant during the study and for 20 months after taking the last dose of study drug. This was changed from 6 to 20 months. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported