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)	EMEA-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/m^2 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/m^2.

Arm title	Pediatric subjects, LDE225 372 mg/m^2

Arm description:

Pediatric subjects received LDE225 372 mg/m^2 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/m^2.

Arm title	Pediatric subjects, LDE225 425 mg/m^2

Arm description:

Pediatric subjects received LDE225 425 mg/m^2 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/m^2.

Arm title	Pediatric subjects, LDE225 680 mg/m^2

Arm description:

Pediatric subjects received LDE225 680 mg/m^2 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/m^2.

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/m2 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/millitres(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 acheived 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/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.

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
Quadriparesis			
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	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Pyrexia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Penile Pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Vaginal Discharge			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 11 (0.00%)	0 / 16 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Cough			
subjects affected / exposed	3 / 11 (27.27%)	1 / 16 (6.25%)	5 / 11 (45.45%)
occurrences (all)	3	1	5
Dyspnoea			
subjects affected / exposed	2 / 11 (18.18%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	3	0	0
Epistaxis			
subjects affected / exposed	1 / 11 (9.09%)	2 / 16 (12.50%)	0 / 11 (0.00%)
occurrences (all)	1	2	0
Hiccups			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Laryngeal Inflammation			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	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	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Procedural Pain			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Thermal Burn			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Vascular Procedure Complication			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Cardiac disorders			
Left Ventricular Hypertrophy			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Sinus Bradycardia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Amnesia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 16 (12.50%)	0 / 11 (0.00%)
occurrences (all)	0	3	0
Aphasia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 16 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ataxia			
subjects affected / exposed	2 / 11 (18.18%)	2 / 16 (12.50%)	2 / 11 (18.18%)
occurrences (all)	2	2	2
Balance Disorder			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	1 / 11 (9.09%)
occurrences (all)	1	0	2
Brain Oedema			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	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	0 / 11 (0.00%)	0 / 16 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Lymphopenia			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Thrombocytopenia			
subjects affected / exposed	0 / 11 (0.00%)	0 / 16 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Cerumen Impaction			
subjects affected / exposed	2 / 11 (18.18%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	2	0	0
Deafness			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Ear Canal Stenosis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	2	0
Ear Pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Hypoacusis			
subjects affected / exposed	0 / 11 (0.00%)	1 / 16 (6.25%)	0 / 11 (0.00%)
occurrences (all)	0	1	0
Vertigo			
subjects affected / exposed	0 / 11 (0.00%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Blindness Unilateral			
subjects affected / exposed	1 / 11 (9.09%)	0 / 16 (0.00%)	0 / 11 (0.00%)
occurrences (all)	1	0	0
Conjunctivitis Allergic			
subjects affected / exposed	0 / 11 (0.00%)	0 / 16 (0.00%)	1 / 11 (9.09%)
occurrences (all)	0	0	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	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Hypotension			
subjects affected / exposed	1 / 22 (4.55%)	1 / 16 (6.25%)	
occurrences (all)	1	1	
Pallor			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 22 (4.55%)	3 / 16 (18.75%)	
occurrences (all)	1	3	
Chest Pain			
subjects affected / exposed	1 / 22 (4.55%)	0 / 16 (0.00%)	
occurrences (all)	1	0	
Chills			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Face Oedema			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Facial Pain			
subjects affected / exposed	0 / 22 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	6 / 22 (27.27%)	1 / 16 (6.25%)	
occurrences (all)	6	1	
Gait Disturbance			
subjects affected / exposed	1 / 22 (4.55%)	2 / 16 (12.50%)	
occurrences (all)	1	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	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
VIth nerve disorder			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 22 (9.09%)	0 / 16 (0.00%)	
occurrences (all)	2	0	
Leukopenia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Lymphadenopathy			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Lymphopenia			
subjects affected / exposed	2 / 22 (9.09%)	1 / 16 (6.25%)	
occurrences (all)	2	2	
Thrombocytopenia			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Ear and labyrinth disorders			
Cerumen Impaction			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Deafness			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Ear Canal Stenosis			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Ear Pain			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	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	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Visual Impairment			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Gastrointestinal disorders			
Abdominal Pain			
subjects affected / exposed	5 / 22 (22.73%)	1 / 16 (6.25%)	
occurrences (all)	5	1	
Abdominal Pain Lower			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Anal Pruritus			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Constipation			
subjects affected / exposed	3 / 22 (13.64%)	2 / 16 (12.50%)	
occurrences (all)	5	3	
Dental Caries			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	1 / 22 (4.55%)	4 / 16 (25.00%)	
occurrences (all)	1	5	
Dysphagia			
subjects affected / exposed	0 / 22 (0.00%)	1 / 16 (6.25%)	
occurrences (all)	0	1	
Faecal Incontinence			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	0	
Faeces Hard			
subjects affected / exposed	0 / 22 (0.00%)	0 / 16 (0.00%)	
occurrences (all)	0	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	15 / 22 (68.18%)	2 / 16 (12.50%)	
occurrences (all)	21	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	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