Clinical trial results:
A phase I, multi-center, open-label study of LEE011 in patients with malignant rhabdoid tumors and neuroblastoma

Summary

EudraCT number	2012-004228-40
Trial protocol	GB FR
Global end of trial date	29 June 2017

Results information

Result version number	v1 (current)
This version publication date	23 December 2017
First version publication date	23 December 2017

Trial information

Trial identification

Sponsor protocol code	CLEE011X2102

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01747876
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, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma, AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 June 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 June 2017
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to estimate the maximum tolerated dose (MTD) and/or the recommended expansion dose (RDE) of LEE011 when administered orally as a single agent in pediatric patients.

Protection of trial subjects:

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

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2013
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	Australia: 1
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 2
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	United States: 15
Worldwide total number of subjects	32
EEA total number of subjects	16

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)	3
Children (2-11 years)	19

Adolescents (12-17 years)	7
Adults (18-64 years)	3
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Approximately 64 patients were to be treated during the entire study; however, 32 patients were enrolled and treated at the time of the enrollment halt.

Pre-assignment

Screening details:

The escalation part of the study explored the 3 doses 280, 350 & 470 mg/m2) in successive cohorts. The dose expansion phase of the study was not conducted (due to enrollment halt).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	LEE011 280 mg/m2 - Dose Escalation only

Arm description:

Patients who took 280 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.

Arm type	Experimental
Investigational medicinal product name	LEE011
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Powder for oral suspension, Capsule
Routes of administration	Oral use

Dosage and administration details:

Three formulations for oral use: Capsules (10 mg, 50 mg, and 200 mg dose strength), powder in bottle (1200 mg in 125 mL amber bottles), and liquid formulation, which was not explored due to early enrollment halt.

Arm title	LEE011 350 mg/m2 - Dose Escalation only

Arm description:

Patients who took 350 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.

Arm type	Experimental
Investigational medicinal product name	LEE011
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Three formulations for oral use: Capsules (10 mg, 50 mg, and 200 mg dose strength), powder in bottle (1200 mg in 125 mL amber bottles), and liquid formulation, which was not explored due to early enrollment halt.

Arm title	LEE011 470 mg/m2 - Dose Escalation only

Arm description:

Patients who took 470 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.

Arm type	Experimental

Investigational medicinal product name	LEE011
Investigational medicinal product code	LEE011
Other name	
Pharmaceutical forms	Capsule, Powder for oral suspension
Routes of administration	Oral use

Dosage and administration details:

Three formulations for oral use: Capsules (10 mg, 50 mg, and 200 mg dose strength), powder in bottle (1200 mg in 125 mL amber bottles), and liquid formulation, which was not explored due to early enrollment halt.

Number of subjects in period 1	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only
Started	5	15	12
Completed	0	0	0
Not completed	5	15	12
Consent withdrawn by subject	-	1	1
Disease progression	4	13	8
Adverse event, non-fatal	1	-	2
Trtment duration compl. as per protocol	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	LEE011 280 mg/m2 - Dose Escalation only
Reporting group description:	
Patients who took 280 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.	
Reporting group title	LEE011 350 mg/m2 - Dose Escalation only
Reporting group description:	
Patients who took 350 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.	
Reporting group title	LEE011 470 mg/m2 - Dose Escalation only
Reporting group description:	
Patients who took 470 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.	

Reporting group values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only
Number of subjects	5	15	12
Age Categorical Units: Subjects			
Infants and toddlers (28 days - 23 months)	2	0	1
Children (2 - 11 years)	2	10	7
Adolescents (12 - 17 years)	1	4	2
Adults (18 - 64 years)	0	1	2
Gender, Male/Female Units: Subjects			
Female	1	6	4
Male	4	9	8
Race/Ethnicity Units: Subjects			
Caucasian	1	10	9
Not available	4	5	3

Reporting group values	Total		
Number of subjects	32		
Age Categorical Units: Subjects			
Infants and toddlers (28 days - 23 months)	3		
Children (2 - 11 years)	19		
Adolescents (12 - 17 years)	7		
Adults (18 - 64 years)	3		
Gender, Male/Female Units: Subjects			
Female	11		
Male	21		

Race/Ethnicity Units: Subjects			
Caucasian	20		
Not available	12		

End points

End points reporting groups

Reporting group title	LEE011 280 mg/m2 - Dose Escalation only
Reporting group description:	
Patients who took 280 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.	
Reporting group title	LEE011 350 mg/m2 - Dose Escalation only
Reporting group description:	
Patients who took 350 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.	
Reporting group title	LEE011 470 mg/m2 - Dose Escalation only
Reporting group description:	
Patients who took 470 mg/m2 of LEE011. The dose escalation part of the study explored the 3 doses (280, 350 & 470 mg/m2) in successive cohorts.	
Subject analysis set title	MRT group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients had a confirmed diagnosis of malignant rhabdoid tumors	
Subject analysis set title	Neuroblastoma (NB)
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Patients had a confirmed diagnosis of neuroblastoma.	

Primary: Incidence rate of dose limiting toxicities (DLTs) by primary system organ class, preferred term and treatment

End point title	Incidence rate of dose limiting toxicities (DLTs) by primary system organ class, preferred term and treatment[1]
End point description:	
A DLT was defined as an AE or clinically significant abnormal laboratory value assessed as unrelated to disease, disease progression, inter-current illness, or concomitant medications that occurred within the first 28 days of treatment with LEE011 and met any of the predefined criteria. For the purpose of dose-escalation decisions, DLTs were considered and included in the Bayesian Logistic Regression Model (BLRM). Patients who did not experience DLT during the first cycle were considered to have had sufficient safety evaluations if they were observed for ≥ 28 days following the first dose and were considered to have had enough safety data to conclude that a DLT did not occur. Patients who did not meet these minimum safety evaluation requirements were regarded as ineligible for the DDS. A patient with multiple DLTs within a primary system organ class is counted only once in the total row.	
End point type	Primary
End point timeframe:	
cycle 1 = 28 days (from the time of first dose)	

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: No comparative statistical analysis was conducted for this endpoint. The relationship between dose and the probability of DLT was modelled using adaptive Bayesian logistic regression model with overdose control principle.

End point values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	15	10	
Units: Participants				
Any primary system organ class total	1	0	2	

Blood & lymphatic sys. disorders(Thrombocytopenia)	0	0	1	
Gen. disorders & admin. site conditions (fatigue)	1	0	0	
Investigations (Platelet count decreased)	0	0	1	

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response Rate

End point title	Overall Response Rate

End point description:

This analysis was not done as there were no responders.

End point type	Secondary

End point timeframe:

Every 2 cycles (cycle = 28 days) up to end of treatment, the maximum time a patient was on study was 1311 days

End point values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	15	12	
Units: months				
median (confidence interval 95%)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	0.0 (0.0 to 0.0)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to disease progression (TTP) per RECIST 1.1

End point title	Time to disease progression (TTP) per RECIST 1.1

End point description:

TTP was assessed per Investigator, for the MRT & neuroblastoma patients for the pooled MTD & RDE according to RECIST 1.1 criteria using Kaplan-Meier method. Time to progression (TTP) is the time from date of randomization/start of treatment to the date of event defined as the first documented progression or death due to underlying cancer. If a patient has not had an event, time to progression is censored at the date of last adequate tumor assessment.

End point type	Secondary

End point timeframe:

Every 2 cycles (cycle = 28 days) up to end of treatment, the maximum time a patient was on study was 1311 days

End point values	MRT group	Neuroblastoma (NB)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	11	14		
Units: months				
median (confidence interval 95%)	1.8 (1.7 to 2.0)	1.8 (1.7 to 4.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response (DOR)

End point title	Duration of Response (DOR)

End point description:

Assess the anti-tumor activity of LEE011 by RECIST 1.1. DOR was not assessed.

End point type	Secondary

End point timeframe:

Every 2 cycles (cycle = 28 days) up to end of treatment, the maximum time a patient was on study was 1311 days

End point values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[2]	0[3]	0[4]	
Units: weeks				
median (confidence interval 95%)	(to)	(to)	(to)	

Notes:

[2] - Due to halted enrollment &/lack of CR & PR, analysis wasn't performed for DOR during dose-escalation

[3] - Due to halted enrollment &/lack of CR & PR, analysis wasn't performed for DOR during dose-escalation

[4] - Due to halted enrollment &/lack of CR & PR, analysis wasn't performed for DOR during dose-escalation

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter: AUC0-24

End point title	Pharmacokinetics (PK) parameter: AUC0-24

End point description:

The AUC calculated to the end of a dosing interval (tau) following single dose or at steady-state (amount x time x volume-1). PK parameters were estimated from individual plasma concentration-time profiles using noncompartmental methods in Phoenix WinNonlin.

End point type	Secondary

End point timeframe:

Cycle 1 Day 1 (C1D1), Cycle 1 Day 15 (C1D15)

End point values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	12	7	
Units: h*ng/ml				
median (full range (min-max))				
C1D1 (n = 5, 12, 7)	9250 (4580 to 22000)	10000 (5320 to 43600)	17600 (8010 to 28500)	
C1D15 (n = 3, 7, 5)	13800 (8910 to 60100)	24500 (15100 to 60100)	29100 (13300 to 50500)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter: Cmax

End point title	Pharmacokinetics (PK) parameter: Cmax

End point description:

Cmax is the maximum (peak) observed plasma, blood, serum, or other body fluid drug concentration after single dose administration or at steady-state (mass x volume-1). PK parameters were estimated from individual plasma concentration-time profiles using noncompartmental methods in Phoenix WinNonlin

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	12	10	
Units: ng/ml				
median (full range (min-max))				
C1D1 (n = 5, 12, 7)	937 (542 to 1910)	1130 (514 to 4140)	1960 (796 to 4360)	
C1D1 (n = 4, 12,10)	1110 (860 to 5210)	2010 (633 to 4270)	2500 (562 to 5050)	

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetics (PK) parameter: Tmax

End point title	Pharmacokinetics (PK) parameter: Tmax

End point description:

Tmax is the time to reach maximum (peak) plasma, blood, serum, or other body fluid drug concentration after single dose administration or at steady-state (time). PK parameters were estimated from individual plasma concentration-time profiles using noncompartmental methods in Phoenix WinNonlin.

End point type	Secondary

End point timeframe:

C1D1, C1D15

End point values	LEE011 280 mg/m2 - Dose Escalation only	LEE011 350 mg/m2 - Dose Escalation only	LEE011 470 mg/m2 - Dose Escalation only	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	12	10	
Units: hour				
median (full range (min-max))				
C1D1 (n = 5, 12, 7)	2.03 (1.1 to 4.08)	2.02 (1 to 4.05)	4 (2 to 4.07)	
C1D15 (n = 4, 12, 10)	2.08 (1.13 to 3.83)	2.13 (1.08 to 23.8)	3.92 (1.98 to 23.6)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0

Reporting groups	
Reporting group title	LEE011@280 mg/m2
Reporting group description:	
LEE011@280 mg/m2	
Reporting group title	LEE011@350 mg/m2
Reporting group description:	
LEE011@350 mg/m2	
Reporting group title	LEE011@470 mg/m2
Reporting group description:	
LEE011@470 mg/m2	
Reporting group title	All@patients
Reporting group description:	
All@patients	

Serious adverse events	LEE011@280 mg/m2	LEE011@350 mg/m2	LEE011@470 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 5 (60.00%)	7 / 15 (46.67%)	4 / 12 (33.33%)
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)			
Central nervous system neuroblastoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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			
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (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
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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			
Irritability			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
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			
Lymphocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Nervous system disorders			
Brain oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Depressed level of consciousness			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Extrapyramidal disorder			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (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
Febrile convulsion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Headache			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydrocephalus			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intracranial pressure increased			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (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
Seizure			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Eye disorders			

Orbital oedema			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (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
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (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
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Infections and infestations			
Device related infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumococcal bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Pneumococcal infection			

subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dehydration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Hypercalcaemia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (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
Hypokalaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (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
Polydipsia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (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

Serious adverse events	All@patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	14 / 32 (43.75%)		
number of deaths (all causes)	5		
number of deaths resulting from adverse events	0		

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Central nervous system neuroblastoma			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Face oedema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyspnoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Irritability			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			

Lymphocyte count decreased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Nervous system disorders				
Brain oedema				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Depressed level of consciousness				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Extrapyramidal disorder				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Febrile convulsion				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Headache				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Hydrocephalus				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Intracranial pressure increased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Seizure				

subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Orbital oedema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Polyuria			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Device related infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Influenza			

subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumococcal bacteraemia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumococcal infection				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Metabolism and nutrition disorders				
Decreased appetite				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dehydration				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypercalcaemia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hypokalaemia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Polydipsia				

subjects affected / exposed	1 / 32 (3.13%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	LEE011@280 mg/m2	LEE011@350 mg/m2	LEE011@470 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	15 / 15 (100.00%)	12 / 12 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Tumour pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hypotension			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Raynaud's phenomenon			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 5 (0.00%)	5 / 15 (33.33%)	1 / 12 (8.33%)
occurrences (all)	0	5	1
Catheter site pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Chills			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Complication associated with device			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Drug intolerance			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Face oedema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	1 / 5 (20.00%)	5 / 15 (33.33%)	6 / 12 (50.00%)
occurrences (all)	1	6	7
Gait disturbance			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Malaise			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Pyrexia			
subjects affected / exposed	1 / 5 (20.00%)	5 / 15 (33.33%)	2 / 12 (16.67%)
occurrences (all)	2	6	3
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Oedema genital			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Bradypnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	0 / 5 (0.00%)	6 / 15 (40.00%)	3 / 12 (25.00%)
occurrences (all)	0	9	3
Dysphonia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Epistaxis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	3 / 12 (25.00%)
occurrences (all)	0	0	3
Hypoxia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Nasal congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	0	7	1
Respiratory distress			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rhinitis allergic			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Rhinorrhoea			
subjects affected / exposed	0 / 5 (0.00%)	3 / 15 (20.00%)	3 / 12 (25.00%)
occurrences (all)	0	7	3
Sneezing			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Tachypnoea			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Upper-airway cough syndrome			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Psychiatric disorders			
Aggression			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Agitation			
subjects affected / exposed	1 / 5 (20.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	1	2	2
Anxiety			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Depressed mood			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Irritability			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Mood altered			
subjects affected / exposed	2 / 5 (40.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	3 / 15 (20.00%)	2 / 12 (16.67%)
occurrences (all)	0	7	2
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	5 / 15 (33.33%)	4 / 12 (33.33%)
occurrences (all)	0	7	6
Bilirubin conjugated increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Blood bilirubin increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	2	2
Blood creatinine decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood creatinine increased			
subjects affected / exposed	0 / 5 (0.00%)	5 / 15 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	7	3
Blood lactate dehydrogenase decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood potassium decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Blood sodium decreased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Blood urea increased			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 5 (0.00%)	4 / 15 (26.67%)	3 / 12 (25.00%)
occurrences (all)	0	9	4
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Heart rate increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 5 (0.00%)	5 / 15 (33.33%)	5 / 12 (41.67%)
occurrences (all)	0	8	11
Neutrophil count decreased			
subjects affected / exposed	0 / 5 (0.00%)	10 / 15 (66.67%)	5 / 12 (41.67%)
occurrences (all)	0	35	10
Platelet count decreased			
subjects affected / exposed	0 / 5 (0.00%)	7 / 15 (46.67%)	5 / 12 (41.67%)
occurrences (all)	0	11	7
Weight decreased			
subjects affected / exposed	1 / 5 (20.00%)	4 / 15 (26.67%)	1 / 12 (8.33%)
occurrences (all)	1	4	1
Weight increased			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
White blood cell count decreased			
subjects affected / exposed	1 / 5 (20.00%)	11 / 15 (73.33%)	9 / 12 (75.00%)
occurrences (all)	2	21	12
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Contusion			

subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	4 / 12 (33.33%)
occurrences (all)	0	2	4
Fall			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Laceration			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Ligament sprain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Procedural pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Radiation skin injury			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Scratch			
subjects affected / exposed	1 / 5 (20.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	1	2	0
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Sinus tachycardia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	2	1
Nervous system disorders			
Aphasia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Brain oedema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Dizziness			

subjects affected / exposed	1 / 5 (20.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	2	2	0
Dysgeusia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Extrapyramidal disorder			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Haemorrhage intracranial			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Headache			
subjects affected / exposed	3 / 5 (60.00%)	7 / 15 (46.67%)	5 / 12 (41.67%)
occurrences (all)	3	8	6
Hydrocephalus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
IIIrd nerve disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lethargy			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Monoplegia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Paraesthesia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Somnolence			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Syncope			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Tremor			

subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 5 (20.00%)	8 / 15 (53.33%)	6 / 12 (50.00%)
occurrences (all)	1	12	11
Haemolysis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Leukopenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Lymphopenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Neutropenia			
subjects affected / exposed	2 / 5 (40.00%)	3 / 15 (20.00%)	3 / 12 (25.00%)
occurrences (all)	2	4	15
Thrombocytopenia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	3 / 12 (25.00%)
occurrences (all)	0	1	4
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Ear pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
External ear inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
External ear pain			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hypoacusis			

subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Middle ear inflammation			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Eye disorders			
Dry eye			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Eye discharge			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Eyelid haematoma			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Heterophoria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Optic atrophy			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Photophobia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Photopsia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Retinal haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Strabismus			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			
Abdominal discomfort			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	5 / 15 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	15	3
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Anorectal disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Constipation			
subjects affected / exposed	0 / 5 (0.00%)	6 / 15 (40.00%)	1 / 12 (8.33%)
occurrences (all)	0	8	1
Diarrhoea			
subjects affected / exposed	3 / 5 (60.00%)	8 / 15 (53.33%)	2 / 12 (16.67%)
occurrences (all)	3	12	2
Dyschezia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	1	0	0
Eructation			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	3
Flatulence			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 5 (20.00%)	6 / 15 (40.00%)	5 / 12 (41.67%)
occurrences (all)	1	10	6
Oral disorder			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Stomatitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	0	2	2
Vomiting			

subjects affected / exposed	2 / 5 (40.00%)	12 / 15 (80.00%)	9 / 12 (75.00%)
occurrences (all)	3	25	18
Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dermatitis atopic			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Dry skin			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Nail discolouration			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	2 / 12 (16.67%)
occurrences (all)	1	1	2
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rash maculo-papular			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	3	0
Rash morbilliform			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Urinary incontinence			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Urinary retention			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	5 / 15 (33.33%)	1 / 12 (8.33%)
occurrences (all)	1	11	2
Bone pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Bone swelling			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Flank pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Muscle fatigue			
subjects affected / exposed	2 / 5 (40.00%)	0 / 15 (0.00%)	0 / 12 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Muscular weakness			

subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	0 / 12 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	0	3	3
Musculoskeletal pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	1	1	0
Neck pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pain in extremity			
subjects affected / exposed	0 / 5 (0.00%)	5 / 15 (33.33%)	2 / 12 (16.67%)
occurrences (all)	0	9	3
Pain in jaw			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	2
Infections and infestations			
Bacteraemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	1 / 5 (20.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	1	3	2
Device related infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Foot and mouth disease			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Myringitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1

Oral herpes			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Pharyngitis streptococcal			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Rash pustular			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Rhinitis			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	2 / 12 (16.67%)
occurrences (all)	0	0	2
Skin infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract infection			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	2 / 12 (16.67%)
occurrences (all)	0	3	3
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 5 (20.00%)	5 / 15 (33.33%)	2 / 12 (16.67%)
occurrences (all)	1	5	3
Hyperglycaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hyperkalaemia			

subjects affected / exposed	1 / 5 (20.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	1	1	1
Hypermagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	0 / 15 (0.00%)	1 / 12 (8.33%)
occurrences (all)	0	0	1
Hyperphosphataemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	0 / 12 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 5 (0.00%)	2 / 15 (13.33%)	1 / 12 (8.33%)
occurrences (all)	0	4	1
Hypocalcaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	2
Hypokalaemia			
subjects affected / exposed	1 / 5 (20.00%)	3 / 15 (20.00%)	0 / 12 (0.00%)
occurrences (all)	1	3	0
Hypomagnesaemia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 15 (6.67%)	1 / 12 (8.33%)
occurrences (all)	0	1	1
Hyponatraemia			
subjects affected / exposed	1 / 5 (20.00%)	6 / 15 (40.00%)	1 / 12 (8.33%)
occurrences (all)	1	10	1
Hypophosphataemia			
subjects affected / exposed	2 / 5 (40.00%)	4 / 15 (26.67%)	0 / 12 (0.00%)
occurrences (all)	2	8	0

Non-serious adverse events	All@patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	32 / 32 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to meninges			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Tumour pain			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Hypotension			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Raynaud's phenomenon			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Catheter site pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Complication associated with device			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Drug intolerance			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Face oedema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	12 / 32 (37.50%)		
occurrences (all)	14		
Gait disturbance			

subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Malaise			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Pain			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Pyrexia			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	11		
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Reproductive system and breast disorders			
Menstruation irregular			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Oedema genital			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Apnoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Bradypnoea			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Cough			
subjects affected / exposed	9 / 32 (28.13%)		
occurrences (all)	12		
Dysphonia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dyspnoea			

subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Epistaxis			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Hypoxia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Nasal congestion			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	3		
Oropharyngeal pain			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	8		
Respiratory distress			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rhinitis allergic			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Rhinorrhoea			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	10		
Sneezing			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Tachypnoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	3		
Upper-airway cough syndrome			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Psychiatric disorders			
Aggression			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		

Agitation				
subjects affected / exposed	5 / 32 (15.63%)			
occurrences (all)	5			
Anxiety				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Depressed mood				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Insomnia				
subjects affected / exposed	4 / 32 (12.50%)			
occurrences (all)	4			
Irritability				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Mood altered				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Investigations				
Alanine aminotransferase increased				
subjects affected / exposed	5 / 32 (15.63%)			
occurrences (all)	9			
Aspartate aminotransferase increased				
subjects affected / exposed	9 / 32 (28.13%)			
occurrences (all)	13			
Bilirubin conjugated increased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Blood alkaline phosphatase increased				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Blood bilirubin increased				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	4			
Blood creatinine decreased				

subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	7 / 32 (21.88%)			
occurrences (all)	10			
Blood lactate dehydrogenase decreased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	2			
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	2			
Blood potassium decreased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	2			
Blood sodium decreased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Blood urea increased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Electrocardiogram QT prolonged				
subjects affected / exposed	7 / 32 (21.88%)			
occurrences (all)	13			
Gamma-glutamyltransferase increased				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	3			
Heart rate increased				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Lymphocyte count decreased				
subjects affected / exposed	10 / 32 (31.25%)			
occurrences (all)	19			
Neutrophil count decreased				

subjects affected / exposed	15 / 32 (46.88%)		
occurrences (all)	45		
Platelet count decreased			
subjects affected / exposed	12 / 32 (37.50%)		
occurrences (all)	18		
Weight decreased			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Weight increased			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
White blood cell count decreased			
subjects affected / exposed	21 / 32 (65.63%)		
occurrences (all)	35		
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Contusion			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	6		
Fall			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Laceration			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Ligament sprain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Procedural pain			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Radiation skin injury			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Scratch			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Brain oedema			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	4		
Dysgeusia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Extrapyramidal disorder			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Haemorrhage intracranial			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	15 / 32 (46.88%)		
occurrences (all)	17		
Hydrocephalus			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
IIIrd nerve disorder			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Lethargy			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Monoplegia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Syncope			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	15 / 32 (46.88%)		
occurrences (all)	24		
Haemolysis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Lymphopenia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		

Neutropenia			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	21		
Thrombocytopenia			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	5		
Ear and labyrinth disorders			
Deafness			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Ear pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
External ear inflammation			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
External ear pain			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hypoacusis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Middle ear inflammation			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Eye disorders			
Dry eye			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Eye discharge			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Eyelid haematoma			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Heterophoria			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Optic atrophy			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Photophobia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Photopsia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Retinal haemorrhage			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Strabismus			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Abdominal pain			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	19		
Abdominal pain upper			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Anorectal disorder			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	7 / 32 (21.88%)		
occurrences (all)	9		
Diarrhoea			
subjects affected / exposed	13 / 32 (40.63%)		
occurrences (all)	17		

Dyschezia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Eructation				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	3			
Flatulence				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Nausea				
subjects affected / exposed	12 / 32 (37.50%)			
occurrences (all)	17			
Oral disorder				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Stomatitis				
subjects affected / exposed	4 / 32 (12.50%)			
occurrences (all)	4			
Vomiting				
subjects affected / exposed	23 / 32 (71.88%)			
occurrences (all)	46			
Skin and subcutaneous tissue disorders				
Alopecia				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Dermatitis atopic				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Dermatitis contact				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Dry skin				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Erythema				

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Nail discolouration			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Rash macular			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Rash morbilliform			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Urinary incontinence			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Urinary retention			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Back pain			

subjects affected / exposed	7 / 32 (21.88%)			
occurrences (all)	14			
Bone pain				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Bone swelling				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Flank pain				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	2			
Muscle fatigue				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Muscle spasms				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Muscular weakness				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Musculoskeletal chest pain				
subjects affected / exposed	4 / 32 (12.50%)			
occurrences (all)	6			
Musculoskeletal pain				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Myalgia				
subjects affected / exposed	2 / 32 (6.25%)			
occurrences (all)	2			
Neck pain				
subjects affected / exposed	1 / 32 (3.13%)			
occurrences (all)	1			
Pain in extremity				
subjects affected / exposed	7 / 32 (21.88%)			
occurrences (all)	12			
Pain in jaw				

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	2		
Infections and infestations			
Bacteraemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Conjunctivitis			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	6		
Device related infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Foot and mouth disease			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Myringitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Oral herpes			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Otitis media			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Pharyngitis streptococcal			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rash pustular			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		

Skin infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	6		
Urinary tract infection			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	9		
Hyperglycaemia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Hyperkalaemia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Hypermagnesaemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hyperphosphataemia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	5		
Hypocalcaemia			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	3		
Hypokalaemia			
subjects affected / exposed	4 / 32 (12.50%)		
occurrences (all)	4		
Hypomagnesaemia			

subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Hyponatraemia			
subjects affected / exposed	8 / 32 (25.00%)		
occurrences (all)	12		
Hypophosphataemia			
subjects affected / exposed	6 / 32 (18.75%)		
occurrences (all)	10		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 July 2013	The primary purpose of this amendment was to add additional timepoints to the ECG monitoring to better evaluate and characterize the cardiac repolarization effects of LEE011. In addition, the eligibility criterion was modified to allow the enrollment of patients with tumors other than malignant rhabdoid tumor (MRT) and neuroblastoma who had documented aberrations in the D-cyclin-CDK4/6-INK4a-Rb pathway to the dose escalation part of the study. Information on alternate formulations was added and language around continuous dosing regimen was removed. In addition, updates to some sections, and minor revisions and corrections were made to improve the consistency and clarity of the protocol.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported