Clinical trial results:
Open, non-controlled, dose escalating Phase I trial to evaluate the pharmacokinetics, pharmacodynamics, tolerability and toxicity of Volasertib in paediatric patients from 2 years to less than 18 years of age with acute leukaemia or advanced solid tumour, for whom no effective treatment is known

Summary

EudraCT number	2013-001291-38
Trial protocol	DE IT CZ AT SK BE NL GB FR
Global end of trial date	31 January 2017

Results information

Result version number	v1 (current)
This version publication date	06 August 2017
First version publication date	06 August 2017

Trial information

Trial identification

Sponsor protocol code	1230.27

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01971476
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	QRPE Processes and Systems Coordination, Clinical Trial Information Disclosure, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000044-PIP20-13
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?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	28 February 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 June 2015
Global end of trial reached?	Yes
Global end of trial date	31 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The present trial was performed according to an open design to determine the Maximum Tolerable Dose (MTD) by evaluation of Dose-Limiting Toxicity (DLT) of Volasertib in paediatric leukaemia and solid tumours in the age group 2 to less than 12 and 12 to less than 18 years. A further objective was to collect data on safety, tolerability, toxicity, efficacy (preliminary activity), pharmacokinetics and pharmacodynamics of Volasertib in paediatric cancer patients.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. If a subject continued to take trial medication, close monitoring was adhered to and all adverse events recorded. Rules were implemented in all trials whereby doses would be reduced if required. Thereafter, if further events were reported, the subject would be withdrawn from the trial. Symptomatic treatment of tumour associated symptoms were allowed throughout.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 October 2013
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	12 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 13
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 2
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	United Kingdom: 2
Worldwide total number of subjects	29
EEA total number of subjects	29

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)	15
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

In the age group 2 to <12 years, 12 patients were entered and treated. In the age group 12 to <18 years, 10 patients were entered and treated.

Pre-assignment

Screening details:

In the age group 2 to <12 years, 15 patients were screened, with 3 screen failures. In the age group 12 to <18 years, 14 patients were screened, with 4 screen failures.

Period 1

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

Blinding implementation details:

The study was non-controlled, non-randomised, open label.

Arms

Are arms mutually exclusive?	Yes
Arm title	2 to <12 years: Volasertib 200 mg/m2

Arm description:

The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Arm type	Experimental
Investigational medicinal product name	Volasertib 200 mg/m2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients were administered Volasertib 200 mg/m2 over approximately 1 hour on Day 1 of 14-day cycle.

Arm title	2 to <12 years: Volasertib 250 mg/m2

Arm description:

The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Arm type	Experimental
Investigational medicinal product name	Volasertib 250 mg/m2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients were administered Volasertib 250 mg/m2 over approximately 1 hour on Day 1 of 14-day cycle.

Arm title	2 to <12 years: Volasertib 300 mg/m2

Arm description:

The patients were administered Volasertib 300 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Arm type	Experimental

Investigational medicinal product name	Volasertib 300 mg/m2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients were administered Volasertib 300 mg/m2 over approximately 1 hour on Day 1 of 14-day cycle.

Arm title	12 to <18 years: Volasertib 200 mg/m2

Arm description:

The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Arm type	Experimental
Investigational medicinal product name	Volasertib 200 mg/m2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients were administered Volasertib 200 mg/m2 over approximately 1 hour on Day 1 of 14-day cycle.

Arm title	12 to <18 years: Volasertib 250 mg/m2

Arm description:

The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Arm type	Experimental
Investigational medicinal product name	Volasertib 250 mg/m2
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients were administered Volasertib 250 mg/m2 over approximately 1 hour on Day 1 of 14-day cycle.

Number of subjects in period 1[1]	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2
Started	3	3	6
Completed	0	0	0
Not completed	3	3	6
Dose Limiting Toxicity (DLT)	-	-	-
Non-fatal Adverse Event (AE)	-	-	-
Other reason not defined above	-	1	-
Progressive disease/relapse	3	2	6

Number of subjects in period 1[1]	12 to <18 years: Volasertib 200 mg/m2	12 to <18 years: Volasertib 250 mg/m2
Started	6	4

Completed	0	0
Not completed	6	4
Dose Limiting Toxicity (DLT)	-	1
Non-fatal Adverse Event (AE)	-	1
Other reason not defined above	-	-
Progressive disease/relapse	6	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Baseline characteristics are based on patients who were randomised after successfully completing the screening period and received at least one dose of the trial medication.

Baseline characteristics

Reporting groups	
Reporting group title	2 to <12 years: Volasertib 200 mg/m2
Reporting group description:	
The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	2 to <12 years: Volasertib 250 mg/m2
Reporting group description:	
The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	2 to <12 years: Volasertib 300 mg/m2
Reporting group description:	
The patients were administered Volasertib 300 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	12 to <18 years: Volasertib 200 mg/m2
Reporting group description:	
The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	12 to <18 years: Volasertib 250 mg/m2
Reporting group description:	
The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	

Reporting group values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2
Number of subjects	3	3	6
Age categorical			
Units: Subjects			

Age Continuous			
Treated Set: The treated set consisted of all patients who have received at least 1 dose of trial medication at the time of clinical cut-off.			
Units: Years			
arithmetic mean	7	6.3	7
standard deviation	± 3.6	± 3.1	± 3.3
Gender categorical			
Units: Subjects			
Female	1	2	3
Male	2	1	3

Reporting group values	12 to <18 years: Volasertib 200 mg/m2	12 to <18 years: Volasertib 250 mg/m2	Total
Number of subjects	6	4	22
Age categorical			
Units: Subjects			

Age Continuous			
Treated Set: The treated set consisted of all patients who have received at least 1 dose of trial medication at the time of clinical cut-off.			
Units: Years			

arithmetic mean	14.3	15.8	
standard deviation	± 2.3	± 1.5	-

Gender categorical Units: Subjects			
Female	2	0	8
Male	4	4	14

End points

End points reporting groups

Reporting group title	2 to <12 years: Volasertib 200 mg/m2
Reporting group description:	
The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	2 to <12 years: Volasertib 250 mg/m2
Reporting group description:	
The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	2 to <12 years: Volasertib 300 mg/m2
Reporting group description:	
The patients were administered Volasertib 300 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	12 to <18 years: Volasertib 200 mg/m2
Reporting group description:	
The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	
Reporting group title	12 to <18 years: Volasertib 250 mg/m2
Reporting group description:	
The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.	

Primary: Number of Participants with Dose Limiting Toxicities (DLTs) in the First Cycle for the Determination of the Maximum Tolerated Dose (MTD)

End point title	Number of Participants with Dose Limiting Toxicities (DLTs) in the First Cycle for the Determination of the Maximum Tolerated Dose (MTD)[1]
End point description:	
This outcome measure presents number of participants with DLTs in the first cycle for the determination of MTD. DLTs were defined as drug related Common Terminology Criteria for Adverse Events (CTCAE) ≥Grade 3 (haematological and nonhaematological) Adverse Events (AEs) with the exception of a) Reduced blood cell count (any grade) without associated clinical complications qualifying for DLT. b) Febrile neutropenia Grade 3. c) Infection Grade 3 with neutrophil count <1000/mm3. d) Uric acid Grade ≥3. e) Nausea, vomiting and/or diarrhoea managed by adequate therapy (i.e. recovery to CTCAE Grade ≤2). Treated Set (TS): The treated set consisted of all patients who have received at least 1 dose of trial medication at the time of clinical cut-off.	
End point type	Primary
End point timeframe:	
Up to 14 days.	

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[2]	3[3]	6[4]	6[5]
Units: Participants				

number (not applicable)	0	0	0	0

Notes:

[2] - TS

[3] - TS

[4] - TS

[5] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[6]			
Units: Participants				
number (not applicable)	2			

Notes:

[6] - TS

Statistical analyses

No statistical analyses for this end point

Primary: Maximum Tolerated Dose of Volasertib

End point title	Maximum Tolerated Dose of Volasertib[7]

End point description:

This outcome measure presents MTD of Volasertib. The MTD was defined as the highest dose level at which DLTs were reported in not more than 1 in 6 evaluable patients during Cycle 1.
99999: The recommended dose for Volasertib in patients of 2 to <12 years of age was 300 mg/m2.
99999: The MTD for Volasertib in patients of 12 to <18 years of age was 200 mg/m2.

End point type	Primary

End point timeframe:

Up to 14 days.

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[8]	3[9]	6[10]	6[11]
Units: mg				
number (not applicable)	99999	99999	99999	99999

Notes:

[8] - TS

[9] - TS

[10] - TS

[11] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[12]			
Units: mg				
number (not applicable)	99999			

Notes:

[12] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Hepatic Injury Defined as Adverse Events of Special Interest (AESI)

End point title	Number of Patients with Hepatic Injury Defined as Adverse Events of Special Interest (AESI)

End point description:

This outcome measure presents number of patients with hepatic injury defined as AESI. Hepatic injury was defined by the following alterations of liver parameters: an elevation of (Aspartate Transaminase) AST and/or (Alanine Transaminase) ALT >3x Upper Limit of Normal (ULN) combined with an elevation of total bilirubin >2x ULN measured in the same blood sample.

End point type	Secondary

End point timeframe:

Up to 879 days.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[13]	3[14]	6[15]	6[16]
Units: Participants				
number (not applicable)				
Total AEs in grouped category hepatic impairment	0	1	1	3
Alanine aminotransferase increased	0	1	0	2
Aspartate aminotransferase increased	0	1	0	0
Blood alkaline phosphatase increased	0	0	1	0
Metabolism and nutrition disorders	0	0	0	0
Hypoalbuminaemia	0	0	0	0
Hepatobiliary disorders	0	0	0	1
Hyperbilirubinaemia	0	0	0	1
Blood bilirubin increased	0	0	0	1
Gamma-glutamyltransferase increased	0	0	0	1

Notes:
[13] - TS
[14] - TS
[15] - TS
[16] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[17]			
Units: Participants				
number (not applicable)				
Total AEs in grouped category hepatic impairment	1			
Alanine aminotransferase increased	0			
Aspartate aminotransferase increased	0			
Blood alkaline phosphatase increased	0			
Metabolism and nutrition disorders	1			
Hypoalbuminaemia	1			
Hepatobiliary disorders	0			
Hyperbilirubinaemia	0			
Blood bilirubin increased	0			
Gamma-glutamyltransferase increased	0			

Notes:
[17] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Patients with Clinically Relevant Laboratory Value Changes of Calcium (hyper- and/or hypocalcaemia) as Judged by the Investigator and Reported as AEs, CTCAE Grade ≥3

End point title	Number of Patients with Clinically Relevant Laboratory Value Changes of Calcium (hyper- and/or hypocalcaemia) as Judged by the Investigator and Reported as AEs, CTCAE Grade ≥3

End point description:

This outcome measure presents number of patients with clinically relevant laboratory value changes of calcium (hyper- and/or hypocalcaemia) as judged by the investigator and reported as AEs, CTCAE Grade ≥3. CTCAE Grade 3 (severe AE), 4 (life-threatening or disabling AE), 5 (death related to AE).

End point type	Secondary

End point timeframe:

Up to 879 days.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[18]	3[19]	6[20]	6[21]
Units: Participants				
number (not applicable)				
Total AEs clinically relevant changes of calcium	0	0	0	0
Metabolism and nutrition disorders	0	0	0	0
Hypocalcaemia	0	0	0	0
Hypercalcaemia	0	0	0	0

Notes:

[18] - TS

[19] - TS

[20] - TS

[21] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[22]			
Units: Participants				
number (not applicable)				
Total AEs clinically relevant changes of calcium	0			
Metabolism and nutrition disorders	0			
Hypocalcaemia	0			
Hypercalcaemia	0			

Notes:

[22] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: The Number of Patients with Changes in Cardiac Activity (prolonged QTc interval) Reported as Clinically Relevant Observations

End point title	The Number of Patients with Changes in Cardiac Activity (prolonged QTc interval) Reported as Clinically Relevant Observations

End point description:

This outcome measure presents the number of patients with changes in cardiac activity (prolonged QTc interval) reported as clinically relevant observations to assess cardiac activity based on Electrocardiogram (ECG) recordings (digital, triplicate) before and at the end of each Volasertib administration and at least at 2 more time-points within the first 24 hours after end of the first Volasertib administration. Two methods of heart rate correction of the QT interval were used: the fixed corrections QTcF (Fridericia's correction) and QTcB (Bazett's correction).
SMQ: Standardised Medical Dictionary for Regulatory Activities (MedDRA) query.

End point type	Secondary

End point timeframe:

Up to 879 days.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[23]	3[24]	6[25]	6[26]
Units: Participants				
number (not applicable)				
Total AEs in the MedDRA SMQ of QT prolongation	0	0	1	2
Electrocardiogram QT prolonged	0	0	1	1
Cardiac disorders	0	0	0	1
Conduction disorder	0	0	0	1

Notes:

[23] - TS

[24] - TS

[25] - TS

[26] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[27]			
Units: Participants				
number (not applicable)				
Total AEs in the MedDRA SMQ of QT prolongation	1			
Electrocardiogram QT prolonged	1			
Cardiac disorders	0			
Conduction disorder	0			

Notes:

[27] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Best Overall Response [in leukaemia patients]: (Complete Remission (CR)), CR with incomplete neutrophil or platelet recovery (CRi), Partial Remission (PR), Stable Disease (SD), Progressive Disease (PD) and Death in aplasia

End point title	Best Overall Response [in leukaemia patients]: (Complete Remission (CR)), CR with incomplete neutrophil or platelet recovery (CRi), Partial Remission (PR), Stable Disease (SD), Progressive Disease (PD) and Death in aplasia

End point description:

This outcome measure includes, CR: Bone marrow blasts <5%; absence of blasts with Auer rods; absence of extramedullary (EM) disease; absolute neutrophil count ≥ 1.0 x 109/L (1000/µL); platelet count ≥80 x 109/L (80000/µL); independence of red blood cells transfusions. CRi: All CR criteria except for residual neutropenia (<1.0 x 109/L [1000/µL]) or thrombocytopenia (<800 x 109/L [80000/µL]), independence of red blood cell transfusions not required. PR: Decrease of bone marrow blast percentage

to 5%-25%; decrease of pretreatment bone marrow (baseline) blast percentage by at least 50%; absence of EM disease. SD: Neither qualifies for CR, CRi, PR or PD. PD: At least one of the criteria a) 50% increase in bone marrow blast count over baseline b) 50% increase in peripheral blast count over baseline - evidence of new EM disease - clinically PD based on the judgment of the investigator. Death in aplasia: Deaths occurring ≥7 days after last administration of the trial drug while cytopenic.

End point type	Secondary

End point timeframe:

Up to 849 days.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[28]	2[29]	0[30]	2[31]
Units: Participants				
number (not applicable)				
Complete remission	0	0		0
CRi*	0	0		0
Partial remission	0	0		0
Stable disease	2	2		1
Progressive disease	0	0		1
Death in aplasia	0	0		0
Not evaluable	0	0		0
Missing	0	0		0

Notes:

[28] - TS

[29] - TS

[30] - TS
No subjects analysed.

[31] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	1[32]			
Units: Participants				
number (not applicable)				
Complete remission	0			
CRi*	0			
Partial remission	0			
Stable disease	0			
Progressive disease	1			
Death in aplasia	0			
Not evaluable	0			
Missing	0			

Notes:

[32] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Event-Free Survival (EFS) [in leukaemia patients]

End point title	Event-Free Survival (EFS) [in leukaemia patients]

End point description:

EFS was defined as the time from the first infusion of Volasertib to the date of PD or relapse, occurrence of secondary malignancy, or death from any cause, whichever occurred first. EFS was censored at the date of last disease assessment for patients who were not reported with PD, relapse, occurrence of secondary malignancy or death.
99999: Median EFS not estimated due to small number of patients per treatment arm.

End point type	Secondary

End point timeframe:

Up to 849 days.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[33]	2[34]	0[35]	2[36]
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	(to)	99999 (99999 to 99999)

Notes:

[33] - TS

[34] - TS

[35] - TS

[36] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	1[37]			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[37] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival (OS) [in leukaemia patients]

End point title	Overall Survival (OS) [in leukaemia patients]

End point description:

Overall survival was defined as time from first infusion of Volasertib to death from any cause. For patients who were lost to follow-up, OS were censored on the last date the patients were known to be alive.

99999: Median OS not estimated due to small number of patients per treatment arm.

End point type	Secondary

End point timeframe:

Up to 849 days.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	2[38]	2[39]	0[40]	2[41]
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)	99999 (99999 to 99999)	(to)	99999 (99999 to 99999)

Notes:

[38] - TS

[39] - TS

[40] - TS
No subjects analysed.
[41] - TS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	1[42]			
Units: Months				
median (confidence interval 95%)	99999 (99999 to 99999)			

Notes:

[42] - TS

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Measured Concentration (Cmax, norm) of Volasertib

End point title	Maximum Measured Concentration (Cmax, norm) of Volasertib

End point description:

This outcome measure presents dose normalized maximum measured concentration of Volasertib in plasma (Cmax, norm).
Pharmacokinetic Set (PKS): All evaluable patients were included in the PK analysis. A patient was considered to be not evaluable, if the patient had an important protocol violation relevant to the evaluation of PK or had insufficient data.

End point type	Secondary

End point timeframe:

Cycle 1: -0:05 (hour/s: minute/s) before drug administration and 1:00, 1:30, 3:00, 24:00, 96:00, 216:00 after drug administration. Cycle >=2: -0:05 (hour/s: minute/s) before drug administration and 1:00 after drug administration.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[43]	3[44]	6[45]	6[46]
Units: ng/mL/mg				
geometric mean (geometric coefficient of variation)	5.34 (± 22)	9.71 (± 128)	3.6 (± 35.1)	2.46 (± 54.9)

Notes:

[43] - PKS

[44] - PKS

[45] - PKS

[46] - PKS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[47]			
Units: ng/mL/mg				
geometric mean (geometric coefficient of variation)	2.5 (± 94.6)			

Notes:

[47] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Trough Concentration (Cpre, 2) of Volasertib

End point title	Trough Concentration (Cpre, 2) of Volasertib

End point description:

This outcome measure presents pre-dose concentration of Volasertib in plasma immediately before administration of the second dose (Cpre,2).
The number of participants analysed are the number of participants with available data at the time-point of interest.

End point type	Secondary

End point timeframe:

Cycle 1: -0:05 (hour/s: minute/s) before drug administration and 1:00, 1:30, 3:00, 24:00, 96:00, 216:00 after drug administration. Cycle >=2: -0:05 (hour/s: minute/s) before drug administration and 1:00 after drug administration.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[48]	2[49]	0[50]	0[51]
Units: ng/mL				
geometric mean (geometric coefficient of variation)	1.48 (± 60.3)	1.13 (± 17.6)	()	()

Notes:

[48] - PKS

[49] - PKS

[50] - PKS
No subjects analysed.

[51] - PKS
No subjects analysed.

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	0[52]			
Units: ng/mL				
geometric mean (geometric coefficient of variation)	()			

Notes:

[52] - PKS
No subjects analysed.

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Concentration-Time Curve (AUC0-∞, norm) of Volasertib in Plasma

End point title	Area Under the Concentration-Time Curve (AUC0-∞, norm) of Volasertib in Plasma

End point description:

This outcome measure presents dose normalized area under the concentration-time curve of Volasertib in plasma over the time interval from zero extrapolated to infinity.

End point type	Secondary

End point timeframe:

Cycle 1: -0:05 (hour/s: minute/s) before drug administration and 1:00, 1:30, 3:00, 24:00, 96:00, 216:00 after drug administration. Cycle >=2: -0:05 (hour/s: minute/s) before drug administration and 1:00 after drug administration.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[53]	3[54]	6[55]	6[56]
Units: ng*h/mL/mg				

geometric mean (geometric coefficient of variation)	41.7 (± 40.1)	51.2 (± 69.8)	36.4 (± 28.2)	28.6 (± 19)

Notes:

[53] - PKS

[54] - PKS

[55] - PKS

[56] - PKS

End point values	12 to <18 years: Volasertib 250 mg/m2			
Subject group type	Reporting group			
Number of subjects analysed	4[57]			
Units: ng*h/mL/mg				
geometric mean (geometric coefficient of variation)	22.1 (± 37.9)			

Notes:

[57] - PKS

Statistical analyses

No statistical analyses for this end point

Secondary: Half-Life (t1/2) of Volasertib

End point title	Half-Life (t1/2) of Volasertib

End point description:

This outcome measure presents half-life of Volasertib.

End point type	Secondary

End point timeframe:

Cycle 1: -0:05 (hour/s: minute/s) before drug administration and 1:00, 1:30, 3:00, 24:00, 96:00, 216:00 after drug administration. Cycle >=2: -0:05 (hour/s: minute/s) before drug administration and 1:00 after drug administration.

End point values	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2	12 to <18 years: Volasertib 200 mg/m2
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	3[58]	3[59]	6[60]	6[61]
Units: hx				
geometric mean (geometric coefficient of variation)	102 (± 28.6)	130 (± 14.1)	54.8 (± 27.2)	78.6 (± 27.3)

Notes:

[58] - PKS

[59] - PKS

[60] - PKS

[61] - PKS

End point values	12 to <18 years: Volasertib 250 mg/m2			

Subject group type	Reporting group			
Number of subjects analysed	4[62]			
Units: hx				
geometric mean (geometric coefficient of variation)	52.7 (± 17.7)			

Notes:

[62] - PKS

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the first drug administration until 30 days after the last drug administration.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	2 to <12 years: Volasertib 200 mg/m2

Reporting group description:

The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Reporting group title	2 to <12 years: Volasertib 250 mg/m2

Reporting group description:

The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Reporting group title	2 to <12 years: Volasertib 300 mg/m2

Reporting group description:

The patients were administered Volasertib 300 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Reporting group title	2 to <12 years: Volasertib Pooled Total

Reporting group description:

The pooled total of patients administered Volasertib 200 mg/m2/250 mg/m2/300 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Reporting group title	12 to <18 years: Volasertib 200 mg/m2

Reporting group description:

The patients were administered Volasertib 200 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Reporting group title	12 to <18 years: Volasertib 250 mg/m2

Reporting group description:

The patients were administered Volasertib 250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 1-day cycle.

Reporting group title	12 to <18 years: Volasertib Pooled Total

Reporting group description:

The pooled total of patients administered Volasertib 200 mg/m2/250 mg/m2 (solution for infusion) by intravenous infusion over approximately 1 hour on Day 1 of 14-day cycle.

Serious adverse events	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	5 / 6 (83.33%)
number of deaths (all causes)	3	3	6
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Lower limb fracture			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Tongue injury			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 2
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pneumonitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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 and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Bone marrow toxicity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1

deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	1 / 3 (33.33%)	3 / 6 (50.00%)
occurrences causally related to treatment / all	3 / 3	1 / 1	3 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Headache			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Paraplegia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences causally related to	0 / 0	0 / 1	0 / 0

treatment / all			
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Mouth haemorrhage			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Nausea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Vomiting			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)

occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hydronephrosis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Renal impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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			
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Soft tissue infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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
Viral infection			

subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (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

Serious adverse events	2 to <12 years: Volasertib Pooled Total	12 to <18 years: Volasertib 200 mg/m2	12 to <18 years: Volasertib 250 mg/m2
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 12 (58.33%)	6 / 6 (100.00%)	4 / 4 (100.00%)
number of deaths (all causes)	12	5	4
number of deaths resulting from adverse events	0	0	1
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tongue injury			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
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			
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 1	0 / 0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (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
Pneumonitis			

subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone marrow toxicity			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Febrile neutropenia			
subjects affected / exposed	5 / 12 (41.67%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	7 / 7	1 / 2	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neutropenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thrombocytopenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Headache			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 4 (50.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraplegia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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			
Asthenia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mouth haemorrhage			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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

Nausea			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Vomiting			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (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
Hydronephrosis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Renal impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Musculoskeletal and connective tissue disorders			
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abscess neck			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Pharyngitis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
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	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (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
Soft tissue infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (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
Viral infection			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	12 to <18 years: Volasertib Pooled Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	10 / 10 (100.00%)		
number of deaths (all causes)	9		
number of deaths resulting from adverse events	1		
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Tongue injury			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Electrocardiogram QT prolonged			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Neoplasms benign, malignant and			

unspecified (incl cyst and polyps)			
Malignant neoplasm progression			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Pneumonitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Bone marrow toxicity			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences causally related to treatment / all	3 / 4		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Neutropenia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		

deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Headache			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Paraplegia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		

occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Gastrointestinal haemorrhage				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Mouth haemorrhage				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Nausea				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Vomiting				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Haematuria				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Hydronephrosis				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Renal impairment				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Myalgia				

subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abscess neck			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pharyngitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Soft tissue infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral infection			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	2 to <12 years: Volasertib 200 mg/m2	2 to <12 years: Volasertib 250 mg/m2	2 to <12 years: Volasertib 300 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 3 (100.00%)	3 / 3 (100.00%)	6 / 6 (100.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Chills			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Fatigue			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Influenza like illness			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Malaise			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Mucosal inflammation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Pyrexia			
subjects affected / exposed	2 / 3 (66.67%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
Psychiatric disorders			

Agitation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Insomnia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alanine aminotransferase decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Alanine aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Antithrombin III decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Blood bilirubin increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood creatinine increased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood phosphorus decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood pressure increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Body temperature increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Electrocardiogram QT prolonged			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Haemoglobin decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
International normalised ratio increased			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphocyte count decreased			

subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Neutrophil count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Platelet count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Weight decreased			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
White blood cell count decreased			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	1	0	1
Cardiac disorders			
Conduction disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Sinus tachycardia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Epistaxis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Respiratory disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Respiratory failure			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)

occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 3 (33.33%)	2 / 3 (66.67%)	3 / 6 (50.00%)
occurrences (all)	1	2	3
Febrile neutropenia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Leukopenia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Lymphadenopathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Neutropenia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	3 / 6 (50.00%)
occurrences (all)	2	0	3
Thrombocytopenia			
subjects affected / exposed	0 / 3 (0.00%)	2 / 3 (66.67%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Dysaesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	2	0	0
IIIrd nerve disorder			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Paraesthesia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	4
Abdominal pain upper			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Anal inflammation			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Constipation			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	1 / 6 (16.67%)
occurrences (all)	0	2	1
Dyspepsia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Glossodynia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Nausea			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)

occurrences (all)	2	0	1
Oral pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stomatitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	2 / 6 (33.33%)
occurrences (all)	1	0	2
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Urinary retention			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Erythema			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Exfoliative rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Ingrowing nail			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Mechanical urticaria			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Petechiae			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	1	0	0
Pruritus			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Rash			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Scar pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Skin ulcer			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Back pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Groin pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pain in extremity			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	2 / 6 (33.33%)
occurrences (all)	0	1	2
Hypercalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hyperglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hyperkalaemia			
subjects affected / exposed	0 / 3 (0.00%)	1 / 3 (33.33%)	0 / 6 (0.00%)
occurrences (all)	0	1	0
Hyperuricaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypocalcaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	2
Hypoglycaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Hypokalaemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Hyponatraemia			
subjects affected / exposed	1 / 3 (33.33%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	2	0	1
Hypophosphataemia			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)

occurrences (all)	0	0	0
Conjunctivitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	1 / 6 (16.67%)
occurrences (all)	0	0	1
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Pharyngitis			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0
Stoma site infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 6 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	2 to <12 years: Volasertib Pooled Total	12 to <18 years: Volasertib 200 mg/m2	12 to <18 years: Volasertib 250 mg/m2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 12 (100.00%)	6 / 6 (100.00%)	3 / 4 (75.00%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	2
Chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	3

Chills			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Fatigue			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	2	1	2
Influenza like illness			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Malaise			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	4
Mucosal inflammation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Pyrexia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	2	3	2
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Allergic transfusion reaction			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Investigations			
Activated partial thromboplastin time prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0

Alanine aminotransferase decreased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Alanine aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	1	2	0
Antithrombin III decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Blood bilirubin increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood creatine increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Blood creatine phosphokinase MB increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood creatinine increased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	2	2	0
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Blood phosphorus decreased			

subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Blood pressure increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Body temperature increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Electrocardiogram QT prolonged			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	15
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Haemoglobin decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
International normalised ratio increased			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	23
Neutrophil count decreased			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	1	23
Platelet count decreased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	22
Weight decreased			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	18

Cardiac disorders			
Conduction disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	12	1	0
Sinus tachycardia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	3
Epistaxis			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	4
Oropharyngeal pain			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Respiratory disorder			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Respiratory failure			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Rhinorrhoea			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 12 (50.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	6	2	4
Febrile neutropenia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Leukopenia			

subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	1	6	0
Lymphadenopathy			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Neutropenia			
subjects affected / exposed	4 / 12 (33.33%)	3 / 6 (50.00%)	1 / 4 (25.00%)
occurrences (all)	5	14	1
Thrombocytopenia			
subjects affected / exposed	3 / 12 (25.00%)	3 / 6 (50.00%)	1 / 4 (25.00%)
occurrences (all)	3	4	1
Nervous system disorders			
Cranial nerve disorder			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Dysaesthesia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Headache			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	2 / 4 (50.00%)
occurrences (all)	2	2	10
IIIrd nerve disorder			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Paraesthesia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	6
Peripheral sensory neuropathy			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Eye disorders			
Visual impairment			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	3 / 12 (25.00%)	2 / 6 (33.33%)	1 / 4 (25.00%)
occurrences (all)	5	2	11
Abdominal pain upper			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Anal inflammation			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Aphthous ulcer			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	0 / 12 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Diarrhoea			
subjects affected / exposed	2 / 12 (16.67%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	3	0	15
Dyspepsia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Glossodynia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 12 (16.67%)	2 / 6 (33.33%)	2 / 4 (50.00%)
occurrences (all)	3	3	4
Oral pain			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Stomatitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Vomiting			
subjects affected / exposed	3 / 12 (25.00%)	2 / 6 (33.33%)	3 / 4 (75.00%)
occurrences (all)	3	2	5

Renal and urinary disorders			
Oliguria			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Urinary retention			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Exfoliative rash			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Ingrowing nail			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Mechanical urticaria			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Petechiae			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Pruritus			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	1	2	4
Rash			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Scar pain			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Skin ulcer			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	0	1	1
Back pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal chest pain			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Myalgia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	2 / 4 (50.00%)
occurrences (all)	0	0	2
Pain in extremity			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	3 / 12 (25.00%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	3	0	0
Hypercalcaemia			
subjects affected / exposed	0 / 12 (0.00%)	2 / 6 (33.33%)	0 / 4 (0.00%)
occurrences (all)	0	2	0
Hyperglycaemia			
subjects affected / exposed	1 / 12 (8.33%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	2	1	5
Hyperkalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)

occurrences (all)	1	0	1
Hyperuricaemia			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Hypoalbuminaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypocalcaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	2	0	0
Hypoglycaemia			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Hypokalaemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	1	0	1
Hyponatraemia			
subjects affected / exposed	2 / 12 (16.67%)	1 / 6 (16.67%)	1 / 4 (25.00%)
occurrences (all)	3	1	7
Hypophosphataemia			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	1
Conjunctivitis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	1 / 12 (8.33%)	0 / 6 (0.00%)	0 / 4 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal candidiasis			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0
Pharyngitis			

subjects affected / exposed	0 / 12 (0.00%)	0 / 6 (0.00%)	1 / 4 (25.00%)
occurrences (all)	0	0	3
Stoma site infection			
subjects affected / exposed	0 / 12 (0.00%)	1 / 6 (16.67%)	0 / 4 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	12 to <18 years: Volasertib Pooled Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 10 (90.00%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leukaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	2		
Chest pain			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
Chills			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	3		
Influenza like illness			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Malaise			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	4		

Mucosal inflammation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Pain subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Pyrexia subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 5		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Insomnia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Injury, poisoning and procedural complications Allergic transfusion reaction subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Investigations Activated partial thromboplastin time prolonged subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Alanine aminotransferase decreased subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Alanine aminotransferase increased subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 2		
Antithrombin III decreased subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Aspartate aminotransferase increased subjects affected / exposed	0 / 10 (0.00%)		

occurrences (all)	0			
Blood alkaline phosphatase increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Blood bilirubin increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Blood creatine increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Blood creatine phosphokinase MB increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	2			
Blood creatine phosphokinase increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	1			
Blood creatinine increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	2			
Blood lactate dehydrogenase increased				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	2			
Blood phosphorus decreased				
subjects affected / exposed	2 / 10 (20.00%)			
occurrences (all)	2			
Blood pressure increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Body temperature increased				
subjects affected / exposed	0 / 10 (0.00%)			
occurrences (all)	0			
Electrocardiogram QT prolonged				
subjects affected / exposed	1 / 10 (10.00%)			
occurrences (all)	15			

Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Haemoglobin decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
International normalised ratio increased			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Lymphocyte count decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	24		
Neutrophil count decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	24		
Platelet count decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	23		
Weight decreased			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
White blood cell count decreased			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	19		
Cardiac disorders			
Conduction disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Sinus tachycardia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	3		

Epistaxis			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	4		
Oropharyngeal pain			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Respiratory disorder			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Respiratory failure			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Rhinorrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	3 / 10 (30.00%)		
occurrences (all)	6		
Febrile neutropenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Leukopenia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	6		
Lymphadenopathy			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Neutropenia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	15		
Thrombocytopenia			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	5		
Nervous system disorders			

Cranial nerve disorder subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Dysaesthesia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Headache subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 12		
IIIrd nerve disorder subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Paraesthesia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 6		
Peripheral sensory neuropathy subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Eye disorders Visual impairment subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)	3 / 10 (30.00%) 13		
Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Anal inflammation subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Aphthous ulcer subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Constipation subjects affected / exposed	2 / 10 (20.00%)		

occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	15		
Dyspepsia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Glossodynia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Nausea			
subjects affected / exposed	4 / 10 (40.00%)		
occurrences (all)	7		
Oral pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Stomatitis			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	5 / 10 (50.00%)		
occurrences (all)	7		
Renal and urinary disorders			
Oliguria			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Urinary retention			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hepatobiliary disorders			
Hyperbilirubinaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Dermatitis acneiform			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Erythema			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Exfoliative rash			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Ingrowing nail			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Mechanical urticaria			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Petechiae			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Pruritus			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	6		
Rash			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Scar pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Skin ulcer			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Back pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Groin pain			

subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Musculoskeletal chest pain			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypercalcaemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	2		
Hyperglycaemia			
subjects affected / exposed	2 / 10 (20.00%)		
occurrences (all)	6		
Hyperkalaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hyperuricaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hypoalbuminaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	0 / 10 (0.00%)		
occurrences (all)	0		
Hypoglycaemia			
subjects affected / exposed	1 / 10 (10.00%)		
occurrences (all)	1		

Hypokalaemia subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Hyponatraemia subjects affected / exposed occurrences (all)	2 / 10 (20.00%) 8		
Hypophosphataemia subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Infections and infestations Anal abscess subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Conjunctivitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 10 (0.00%) 0		
Oropharyngeal candidiasis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		
Pharyngitis subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 3		
Stoma site infection subjects affected / exposed occurrences (all)	1 / 10 (10.00%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 May 2014	One global amendment to the Clinical Trial Protocol (CTP) was issued before Database Lock (DBL)(08 May 2014); it was implemented only after approval of the Institutional Review Board (IRB)/ Independent Ethics Committee (IEC)/Competent Authorities. The major changes were: • the alignment of the new reporting times for concomitant medication and Adverse Events (AEs), • a change in time for the End of Treatment (EoT) visit, to align the CTP with the Case Report Form (CRF) and to ensure that the residual effect period could be applied, • the addition of blood pressure and heart rate measurements during infusion of Volasertib, as requested by the German competent authority, • the addition of echocardiography after every 4th treatment cycle, as requested by Medicines and Healthcare products Regulatory Agency, United Kingdom (UK), • a change in wording for clarification: left ventricular ejection fraction <25% updated to left ventricular shortening fraction <30%, • an update of exclusion criterion 18 regarding the contraception, according to the Investigator's Brochure (IB) of Volasertib, • to clarify that bone marrow sampling was not required if Progressive Disease (PD) was diagnosed due to increased peripheral blasts, evidence of new extramedullary disease or clinical PD based on the investigator's judgement, • the clarification of reporting of clinically relevant Electro Cardio Gram (ECG) findings.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported