



## Clinical trial results:

### Phase I/II intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma or leukemia

#### Summary

EudraCT number	2007-005537-11
Trial protocol	DE
Global end of trial date	24 March 2017

#### Results information

Result version number	v1 (current)
This version publication date	01 February 2019
First version publication date	01 February 2019
Summary attachment (see zip file)	Vorinostat_CTR (Vorinostat Ergebnisbericht_27022018.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	NCT-2007-11-02-1004
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01422499
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	University of Heidelberg
Sponsor organisation address	Im Neuenheimer Feld 672, Heidelberg, Germany, 69120
Public contact	Commercial Director Mrs. Irmtraut Gürkan, University of Heidelberg, Irmtraut.Guerkan@uni-heidelberg.de
Scientific contact	Clinical Trial Unit, Hopp-Kindertumorzentrum Heidelberg (KITZ) , 06221 567294, ruth.witt@kitz-heidelberg.de

Notes:

#### Paediatric regulatory details

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

Notes:

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## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	27 February 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	24 March 2017
Was the trial ended prematurely?	No

Notes:

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## General information about the trial

Main objective of the trial:

Primary:

To determine a safe dose recommended (SDR) for the routine application of oral vorinostat (involving dose escalation) in children and adolescents (3-18 years) with relapsed/refractory solid tumor, lymphoma or leukemia. A SDR is defined as the highest dose with no  $\geq$  grade 3 toxicity according to CTC criteria in no more than 1/50 patient in this study (for details refer chapter 2.1).

Secondary:

To determine the

- pharmacokinetics and the distribution of individual maximum tolerated doses (MTD), which is the maximum dose with no grade 3 or 4 toxicity according to CTC criteria.
- antitumor effectiveness of vorinostat as measured by treatment response rate. Response will be evaluated in each patient three months after start of treatment with the individual MTD.
- association of the histone deacetylase (HDAC)-inhibiting activity with the dose administered, toxicity, and treatment response.
- feasibility and safety
- duration of response in responding patients.

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Protection of trial subjects:

Continuous risk assessment: The toxicity associated with the starting dose chosen in this study will be continuously monitored using a Bayesian criterion with a noninformative prior and a binomial-beta model for the toxicity rate  $r$ . If, for the second and following patients, the posterior probability that  $r > 10\%$  is 90% or higher, the starting dose used for the following patients will be lowered by 50mg/m<sup>2</sup>. This decision process is repeated, i.e., it is applied to the lowered starting dose in an analogous way.

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Background therapy:

During vorinostat dose escalation and 3 months maintenance treatment at individual MTD, patients will receive a routine pediatric physical examination including vital signs, body weight, concomitant treatment and AEs once per week. Blood will be taken once per week for full blood counting including differential, serum electrolytes, glucose, AST, ALT, protein, bilirubin, LDH and creatinine. An ECG will be done at day 8 and 15 of vorinostat treatment and when the MTD is reached, to rule out QT-changes. Collection of blood and cerebrospinal fluid for pharmacokinetic evaluation will be done after 1 week of vorinostat treatment and at the time when individual MTD is established. This material will be sent to the reference pharmacokinetic laboratory. 3 months after start of vorinostat treatment at MTD, response will be evaluated by MRI imaging using the RECIST criteria and bone marrow cytology if indicated. In patients with neuroblastoma, a MIBG scan will also be performed and response additionally evaluated according to the International Neuroblastoma Response Criteria (INRC). Furthermore, full blood counting including differential, serum electrolytes, glucose, AST, ALT, protein, bilirubin, LDH, creatinine, and tumor marker (if indicated). Biomarker (IL-6, IL-10, BMP4) will be determined at month 1 and 3 of MTD. Patients showing CR, PR, or SD on response evaluation will continue with vorinostat treatment for a maximum of 9 months or until disease progression. In these patients, tumor manifestations (MRI, tumor markers, bone marrow if indicated, MIBG) will be determined every three months until end of treatment (EOT). During this time, patients will receive routine pediatric oncological care including physical examination including body weight, full blood counting including differential, serum electrolytes, glucose, AST, ALT, protein, bilirubin, LDH and creatinine every 2 weeks.

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Evidence for comparator:

no comparator

Actual start date of recruitment	11 May 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

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### Population of trial subjects

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#### Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 50
Worldwide total number of subjects	50
EEA total number of subjects	50

Notes:

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#### Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	26
Adolescents (12-17 years)	23
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Recruitment of patients started in October 2011 and was continue until 50 patients will be enrolled.

### Pre-assignment

Screening details:

After obtaining patient informed consent, screening evaluations and procedures must be performed within 14 days prior to initiating study drug treatment.

### Period 1

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

### Arms

Arm title	single-arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Vorinostat study
Investigational medicinal product code	0006-0568-40
Other name	
Pharmaceutical forms	Capsule, Capsule, hard
Routes of administration	Oral use

Dosage and administration details:

Starting dose will be 180 mg/m<sup>2</sup>/d in children  $\geq$  3 years. The drug is provided as suspension of 50mg/ml or as capsules of 100 mg vorinostat and will be centrally distributed by the Department of Pharmacy, University of Heidelberg. A dosing schedule of vorinostat suspension or 100mg capsules based on body surface area is provided in the appendix section of the protocol.

Number of subjects in period 1	single-arm
Started	50
Completed	7
Not completed	43
Adverse event, serious fatal	1
Consent withdrawn by subject	4
other reasons	3
Death	20
occurrence of exclusion criterion	12
Lost to follow-up	3

## Baseline characteristics

### Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	50	50	
Age categorical			
Units: Subjects			
Children (2-11 years)	26	26	
Adolescents (12-17 years)	23	23	
Adults (18-64 years)	1	1	
Age continuous			
Units: years			
arithmetic mean	10.9		
standard deviation	± 4.13	-	
Gender categorical			
Units: Subjects			
Female	22	22	
Male	28	28	

## End points

### End points reporting groups

Reporting group title	single-arm
Reporting group description: -	

### Primary: Dose Limiting Toxicity

End point title	Dose Limiting Toxicity <sup>[1]</sup>
End point description: Number of Patients with DLT N at respective dose of Vorinostat (mg/m <sup>2</sup> /day) (N=50) Number of Patients with at least one DLT observed	
End point type	Primary
End point timeframe: dose escalation scheme was changed from 2 weekly to weekly	

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: The primary endpoint was the determination of a safe dose recommended (SDR) for the routine application of oral Vorinostat in children and adolescents. SDR was defined as the highest dose with no DLT (Dose Limiting Toxicity) in no more than 1/50 patient. According to this definition the SDR was 130 mg/m<sup>2</sup>/day. Disorders related to the Blood and lymphatic system were the most frequently reported DLTs.

End point values	single-arm			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Number of Patient number (not applicable)				
130 mg/m <sup>2</sup> /day	1			
180 mg/m <sup>2</sup> /day	10			
230 mg/m <sup>2</sup> /day	14			
280 mg/m <sup>2</sup> /day	15			
330 mg/m <sup>2</sup> /day	10			
380 mg/m <sup>2</sup> /day	5			
430 mg/m <sup>2</sup> /day	6			
480 mg/m <sup>2</sup> /day	4			
530 mg/m <sup>2</sup> /day	4			
580 mg/m <sup>2</sup> /day	5			

<b>Attachments (see zip file)</b>	Dose Limiting Toxicity(Preferred Terms) by Dosage /13. DLT observed by Dosage - Safety Set/13.4.1.4.1.1
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### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All AEs reported by the subject or detected by the investigator, will be collected during the trial and must be documented on the appropriate pages of the CRF. AEs must also be documented until the completion of the trial

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
Dictionary version	20.1

### Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Serious adverse events	overall trial		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 50 (38.00%)		
number of deaths (all causes)	20		
number of deaths resulting from adverse events			
Investigations			
C-reactive protein increased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Platelet count decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 20		
Weight decreased			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 20		
Nervous system disorders			
Aphasia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		

Ataxia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Cerebral haemorrhage			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	1 / 20		
Depressed level of consciousness			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Headache			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 20		
Hydrocephalus			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Seizure			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 20		
Blood and lymphatic system disorders			
Febrile neutropenia			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Thrombocytopenia			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 20		
General disorders and administration			



site conditions			
Fatigue			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 20		
General physical health deterioration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Pain			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Pyrexia			
subjects affected / exposed	3 / 50 (6.00%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 20		
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 20		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 50 (4.00%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 20		
Dyspnoea			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Pleural effusion			

subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Skin and subcutaneous tissue disorders			
Swelling face			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Infections and infestations			
Catheter site infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Herpes zoster			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 20		
Rhinitis			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Tooth infection			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Wound abscess			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		
Product issues			
Device malfunction			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 20		

Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 50 (2.00%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 20		

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

<b>Non-serious adverse events</b>	overall trial		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 50 (72.00%)		
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Blood creatine increased			
subjects affected / exposed	5 / 50 (10.00%)		
occurrences (all)	5		
Platelet count decreased			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Weight decreased			
subjects affected / exposed	10 / 50 (20.00%)		
occurrences (all)	10		
Nervous system disorders			
Headache			
subjects affected / exposed	19 / 50 (38.00%)		
occurrences (all)	19		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	12 / 50 (24.00%)		
occurrences (all)	12		
Leukopenia			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
Thrombocytopenia			

subjects affected / exposed occurrences (all)	31 / 50 (62.00%) 31		
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	20 / 50 (40.00%)		
occurrences (all)	20		
General physical health deterioration			
subjects affected / exposed	9 / 50 (18.00%)		
occurrences (all)	9		
Pain			
subjects affected / exposed	8 / 50 (16.00%)		
occurrences (all)	8		
Pyrexia			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Constipation			
subjects affected / exposed	7 / 50 (14.00%)		
occurrences (all)	7		
Diarrhoea			
subjects affected / exposed	15 / 50 (30.00%)		
occurrences (all)	15		
Nausea			
subjects affected / exposed	20 / 50 (40.00%)		
occurrences (all)	20		
Vomiting			
subjects affected / exposed	14 / 50 (28.00%)		
occurrences (all)	14		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	6 / 50 (12.00%)		
occurrences (all)	6		
Skin and subcutaneous tissue disorders			

Alopecia	subjects affected / exposed	9 / 50 (18.00%)		
	occurrences (all)	9		
Dry skin	subjects affected / exposed	6 / 50 (12.00%)		
	occurrences (all)	6		
Infections and infestations				
Infection	subjects affected / exposed	5 / 50 (10.00%)		
	occurrences (all)	5		
Rhinitis	subjects affected / exposed	5 / 50 (10.00%)		
	occurrences (all)	5		
Metabolism and nutrition disorders				
Decreased appetite	subjects affected / exposed	8 / 50 (16.00%)		
	occurrences (all)	8		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 April 2013	<p>The patient cohort enrolled in this trial turned out to have progressive disease under first/secondline therapy predominantly. These patients require immediate onset of vorinostat treatment in order to increase the likelihood of therapy response before fatal outcome of the disease. Other pediatric relapse protocols (i.e. HIT REZ 2005 trial) therefore have two week time interval to previous treatment as inclusion criterion. Changing the inclusion criterion "1 months interval from previous treatment" to two weeks has a safety and an efficacy response evaluation aspect.</p> <p>Safety: A 2 week interval is sufficiently long enough to ensure wash out of previous drug treatment, which in the case of valproic acid will additionally be ensured by determination of plasma drug levels. Also, the inclusion criteria "sufficient bone marrow, liver, kidney function etc." ensures patient safety by enrolling only patients that show recovered organ functions from previous treatments.</p> <p>Efficacy: Disease progression under previous treatment already proofs non-efficacy of previous treatment modality ensuring that response assessment of the study drug does not interfere with effects from previous treatments.</p>
12 June 2014	<p>Up to now we have included 35 patients into the trial and observed 3 responses. All responses occurred at very high doses (530 and 580mg/d/m<sup>2</sup>) and no responses at lower doses. The almost exclusive dose limiting toxicity (DLT) observed were reversible thrombocytopenia. After discontinuation of treatment, all side effects and symptoms (thrombocytopenia and other changes in blood counts, gastrointestinal symptoms, fatigue) completely resolved within 1 week which corresponds with observations in the literature (see protocol p. 21). In addition, preliminary PK analyses in the present trial demonstrate no accumulation of vorinostat in plasma and rapid clearance of the drug within 8h also at higher doses. Most patients haven't reached higher dosage due to disease progression or DLT. Importantly, the occurrence of toxicities showed no correlation with the dose received. To give patients with poor life expectancy a chance to reach effective doses in a shorter time period without additional risk, dose escalation scheme was changed from 2 weekly to weekly.</p>

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/22915450>