NATIONALES CENTRUM FÜR TUMORERKRANKUNGEN HEIDELBERG

getragen von:
Deutsches Krebsforschungszentrum
Universitätsklinikum Heidelberg
Thoraxklinik-Heidelberg
Deutsche Krebshilfe

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

Short Title/ Acronym: Vorinostat in children

Final Study Report

Version Number, Date: Final, 27.02.2018
Investigational product: Vorinostat (SAHA)
Eudra-CT Number: EudraCT number: 2007-005537-11
Protocol-Number: Final 2.5, dated 12.06.2014
Register-Number: ClinicalTrials.gov identifer NCT01422499

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Study Initiation and Completion Dates:
Date of first enrollment (FPI): 11.05.2012
Date of last enrollment (LPI): 28.09.2016
Date of last completed (LPO): 24.03.2017

CONFIDENTIAL

Signatures

The present trial study report was subject to critical review and has been approved in the present version. The information contained is consistent with the ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki (current version), the principles of ICH-GCP and all local regulatory requirements.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of this study.

Report Version / Date: Final/ 27.02.2018

Sponsor / or Designated Representatives (Reviewer)	Prof. Witt Name, Title	Heidelberg 27.02.18 Place, Date
Principal or Coordinating Investigator (Reviewer)	Prof. Witt Name, Title	Heidelberg 28.2.18 Place, Date
Biostatistician (Author)	J. L. Sehl Name, Title	Heidelberg, 27.02.18 Place, Date

Synopsis

Name of Sponsor/Company:
University of Heidelberg represented in law by its Commercial Director Mrs. Irmtraut Gürkan
Im Neuenheimer Feld 672
69120 Heidelberg, Germany

Name of Finished Product:
Vorinostat(SAHA)
Suspension at 50mg/ml oral administration qd (once per day) with food
Capsules at 100mg oral administration qd (once per day) with food

Name of Active Ingredient:
Suberoylanilide hydroxamic acid

Title of Study:
Phase I/II intra-patient dose escalation study of vorinostat in children with relapsed solid tumor, lymphoma, or leukemia - vorinostat in children.
Protocol Version Number: Final 2.5, dated 12.06.2014

Study Center(s) and Principle Investigator(s): Please refer Attachment 1

Publication (Reference):
Phase I/II Intra-patient Dose Escalation Study of Vorinostat in Children with Relapsed Solid Tumor, Lymphoma or Leukemia. Phase I/II intra-individuelle Dosiseskalationstudie von Vorinostat bei Kindern mit rezidivierten soliden Tumoren, Lymphomen oder Leukämien.
O. Witt, T. Milde , H. E. Deubzer , I. Oehme , R. Witt , A. Kulozik , A. Eisenmenger , U. Abel, I. Karapanagiotou-Schenkel, Klinische. Pädiatrie.

Studied Period (years):	**Phase of Development**:
Date of first enrollment (FPI): 11.05.2012 Date of last enrollment (LPI): 28.09.2016 Date of last completed (LPO): 24.03.2017	Study Phase I/II

Objectives:
The study „Phase I/II Trial of Vorinostat in children with relapsed solid tumor, lymphoma or leukemia" was a single-arm, multi-center study. The primary objective of this study was to define a safe dose recommendation involving subsequent individual dose escalation regimen of Vorinostat in pediatric oncology. Secondary objectives included pharmacokinetics of Vorinostat in children, and to determine tumor response rates, safety and feasibility

Methodology:
The study proceeded in two phases: Phase I was an intra-patient dose (de)escalation period with daily study drug administration until the individual maximum tolerated dose (MTD) was reached, followed by Phase II, during which Vorinostat was administered daily at the MTD. During Phase II disease assessments were performed every 3 months. Patients without progressive disease could continue the therapy at the MTD, consisting of daily Vorinostat administration until disease progression. In case of toxicity grade 3-4, the dose was reduced by 50mg/m^2/d. Treatment was discontinued in case of safety concerns, withdrawal of consent, or death.

Pharmacokinetic studies were performed in plasma. Biomarkers (BMP4, IL-6, IL-10 induction following Vorinostat treatment, basal histokine acetylation, HDACs and H23B) in

archived tumor samples were determined.

Number of Patients (planned and analyzed):

- Planned: 50 patients were planned to be included in the trial.
- Screened: 58 patients were assessed for eligibility.
- Included: 52 patients have been included. Two patients were enrolled but did not receive any study medication and were excluded from all analysis sets
- Analyzed: 50 patients

Diagnosis and Main Criteria for Inclusion:

Relapsed or therapy-refractory solid tumor, lymphoma or leukemia following standard treatment protocols in pediatric (children and adolescents (3-18 years) oncology.

Investigational Product, Dose and Mode of Administration, Batch Numbers:

- Vorinostat, SAHA (suberoylanilide hydroxamic acid).
- Suspension at 50 mg/ml oral administration qd (once per day) with food.
- Capsules at 100 mg oral administration qd (once per day) with food.
- Minimum dose: 30 mg/m²/d.
- Maximum dose: 580 mg/m²/d.
- Starting dose: 180 mg/m²/d

Vorinostat was taken orally once per day on an outpatient basis and the dose was de/escalated until the individual maximum tolerated dose was established. This dose was then applied for 3 months, when tumor response was evaluated. Patients without progression at first response evaluation continued the treatment for a maximum of 9 months.

Duration of Treatment: Phase I: individual dose escalation until individual MTD reached. Phase II: maximum 12 months (3 months until response evaluation plus up to 9 months maintenance in case of SD or better response). Individual patients with clinical benefit were allowed to continue treatment beyond 12 months after discussion with sponsor.

Reference Therapy, Dose and Mode of Administration, Batch Numbers: n.a.

Criteria for Evaluation:

Safety:

- Determination of a safe dose recommended (SDR) for the routine application of oral Vorinostat in individual dose escalation regimen. SDR was defined as the highest dose with no DLT (Dose Limiting Toxicity) in no more than 1/50 patient.
- Pharmacokinetics and the distribution of individual maximum tolerated doses (MTD)

Efficacy:

- Antitumor effectiveness of Vorinostat as measured by treatment response rate. Response was evaluated in each patient three months after start of treatment with the individual MTD. Treatment response rate was defined as the proportion of patients with confirmed complete response (CR) or confirmed partial response (PR) according to RECIST v1.1. Overall response rate (ORR) was determined as the proportion of patients with established response (CR, PR, or SD).
- PFS, OS

Statistical methods:

The justification for the sample size outlined in the study protocol was based on accuracy requirements for the toxicity rate associated with the safe dose for the routine application. The following specifications regarding sample size and stopping rules were defined in the study protocol:

- 50 pediatric patients were to be included in the trial. If dose limiting toxicity (DLT) is

observed at a given dose d in no more than 1/50 patients (this defines the safe dose for routine application) then the upper bound of the 95% confidence interval for the true rate r of DLT at this dose is ≤ 10.65 %.

- The toxicity associated with the starting dose (180 mg/m²/d) chosen in this study was to be continuously monitored using a Bayesian criterion with a non-informative 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 95% or higher, the starting dose used for the following patients has to be lowered by 50 mg/m^2. This decision process was repeated, i.e., it was applied to the lowered starting dose in an analogous way.
- In case of DLT, the trial drug was discontinued until toxicity declined to at least grade 2 or less, and treatment was then continued at the last dose without DLT. This dose was defined as the MTD.
- If DLT already occurs at the starting dose, the trial drug discontinued until toxicity declined to at least grade 2 or less and treatment was then continued with 130 mg/m²/d.
- De-escalation was done in steps of 50 mg/m²/d until 30 mg/m²/d. If de-escalation results in a dosage < 30mg/m²/d patient treatment was to be discontinued.
- If, during dose escalation, a patient experiences drug-related life threatening symptoms or death, dose escalation for the following patients has to be stopped one dose step below this toxic dose.

SUMMARY - CONCLUSIONS

The study complied with the Declaration of Helsinki, the ICH-GCP Guideline, and was approved by local ethics committees. An independent DMC reviewed tabulated aggregate safety and efficacy data as well as recruitment and the study progress at regular intervals during the trial.

Analysis Population

Children and adolescents patients (56% males and 44% females) aged between 3 and 18 (mean: 10.9, SD: 4.1) years with relapsed or therapy refractory tumors were recruited from 10 centers in Germany. The most of the patients 19 (38%) had high grade glioma (WHO III-IV), 2 patients (4%) had low grade glioma (WHO II-I), 8 (16%) had medulloblastoma, 4 (8%) had Ewing sarcoma, 4 (8%) had osteosarcoma, 3 (6%) had ependymoma, 2 (4%) had neuroblastoma and 8 (16%) patients had other entities in singular cases.

Patients receiving at least one dose of study drug were included in the safety analysis. This was the primary analysis. Patients completed the escalation/de-escalation period and had at least one visit in phase II part of the trial formed the efficacy set.

A total of 58 patients were screened, of them 52 patients have been included in the trial. Two patients were enrolled but did not receive any study medication and were excluded from all analysis sets. Of the 50 patients, of the safety set only 7 (14%) patients have reached the end of the observation period (3 months after end of treatment). All other patients (43, 86%) have terminated the study prematurely, 20 (46.5%) due to death, 12 (27.9%) due to occurrence of exclusion criteria, 4 (9.3%) due to withdrawal of informed consent, 3 (7.0%) due to lost to follow-up, 1 (2.3%) due to SAE and 3 (3.0%) due to other reasons. Overall 27/50 patients completed the escalation/de-escalation period and had at least one visit in phase II part of the trial. These patients were included in the efficacy set. Please refer also the CONSORT Flow Diagram in Attachment 2.

Study Treatment:

Ten different dose levels were administered from 130 mg/m^2/day to 580 mg/m^2/day, most of the patients had 3 (28%) or 4 (18%) different dose levels. 48/50 (96%) of patients had a start dose of 180 mg/m^2/day, the highest start dose level was 230 mg/m^2/day (one patient). The highest maximum tolerated dose (MTD) was 580 mg/m^2/day (median 280 mg/m^2/day).

Primary Analysis

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^2/day. Disorders related to the Blood and lymphatic system were the most frequently reported DLTs. The most common DLT was thrombocytopenia. In singular cases anaemia, leukopenia, abdominal pain, nausea, vomiting, fatigue, febrile infection, aggression, apathy, metabolism and nutrition disorders were reported as a DLT.

Efficacy Analysis

Overall response (CR, PR, SD) was observed in 6 (12%, 95% CI: 4.53, 24.31) of the 50 patients of the safety set, corresponding to 22.2% (95% CI: 8.62, 42.26) of the 27 patients of the efficacy set. According to the worst case analysis the treatment response rate (CR+PR) was 4%, with a 95% CI of (0.49, 13.71) in the safety set, corresponding to 7.4% (95% CI: 0.91, 24.29) in the efficacy set.

Safety Analysis

Almost all patients (n=49, 98%) experienced at least one (all causality) adverse event (AE). All causalities serious adverse events (SAEs) occurred in 19 (38%) patients. The majority of the patients (n=48, 96%) experienced severe adverse events (CTCAE grade 3 or 4). 38 (76%) patients had dose reductions or temporary discontinuations due to adverse events, and 9 (18%) patients discontinued the study due to AEs.

The majority of the patients (N=46, 92%) experienced treatment related AES, 6 (12%) of them had treatment related SAEs. A total of 42 (84%) patients experienced severe adverse events (CTCAE grade 3 or 4). 6 (12%) patients discontinued the study drug due to treatment related AEs. 35 (70%) patients had dose reductions or temporary discontinuations due to treatment related AEs.

PK, PD and biomarker analysis: PK will be reported separately.

CONCLUSION:

Vorinostat has been approved by the FDA for the treatment of cutaneous T-cell lymphoma at a dose of 400mg/d with a favorable safety profile. In children, phase I study determined a corresponding recommended dose of 230 mg/m^2/d. PK studies in adults and children demonstrated linear pharmacokinetics and plasma peak levels of 1-2 µM maintained for a brief period of 30-60 min only due to the short half-life. According to our own data, significant anti-tumoral activity in pediatric cancer models require higher concentrations [1, 2]. The aim of this study therefore was to intra-individually dose escalate vorinostat in pediatric patients to obtain for each patient the individual MTD to potentially increase the likelihood of response while maintaining an acceptable risk for each enrolled patient.

In phase I part of the study, a safe starting dose of 130 mg/m^2/d for individual dose escalation regimen of increments of 50 mg/m^2 per week was determined. 27/50 patients reached their individual MTD. Median MTD was 280 mg/m^2/d (Ranged from 130 mg/m^2/d to 580 mg/m^2/d). 25/27 (92.6%) patients treated at their individual MTD experienced all causalities AEs. In 4/27 (14.8%) patients AEs were judged as serious adverse events. 18/27 (66.7%) patients experienced severe adverse events (CTCAE grade 3 or 4). 19 (70.4%) patients had dose reductions or temporary discontinuations due to adverse events, and 2 (7.4%) patients discontinued the study due to AEs. Almost all of these AEs were treatment related. Overall response rate (ORR) in this heavily pretreated population was 22.2% (95% CI: 8.62, 42.26).

In summary, the study has determined a safe starting dose for an individual dose escalation regimen in children. In comparison to the current approved adult dose and recommended phase II doses in children, individual patients tolerated higher doses of Vorinostat with acceptable toxicity profiles associated with higher response rates. Our study confirms relatively low drug exposure associated with no clinical activity of Vorinostat when applied standard doses compared with previously published phase I data of single agent Vorinostat in children [3].

Substantial Amendments:

BfArM (Federal Institute for Drugs and Medical Devices) Approvals of

Amendment No.	Approval Date
Amendment 1	14.07.2011
Amendment 2	20.03.2012
Amendment 3	10.05.2013
Amendment 4	01.07.2014
Amendment 5	02.03.2015

IEC Independent Ethics Committee(s) Consent of Amendments:

Amendment No.	Approval Date
Amnedment 1	12.07.2011
Amendment 2	22.12.2011
Amendment 3	06.03.2012
Amendment 4	02.05.2012
Amendment 5	14.05.2012
Amendment 6	24.05.2012
Amendment 7	03.08.2012
Amendment 8	28.08.2012
Amendment 9	12.10.2012
Amendment 10	14.06.2013
Amendment 11	27.06.2013
Amendment 12	09.05.2014
Amendment 13	15.07.2014
Amendment 14	12.12.2014

Interruptions or early Termination: None

Version / **Date of Report**: Final, 27.01.2018

Attachments (Study Synopsis)

Attachment 1: List of study centers

01 Klinikum **Augsburg**, I.Klinik für Kinder und Jugendliche, Stenglinstr. 2, 86156 Augsburg
Prüfer: Prof. Dr. Michael Frühwald

02 Klinikum **Bremen**-Mitte gGmbH, Prof. -Hess-Kinderklinik/Kinderonkologie, St.-Jürgen-Str. 1, 28177 Bremen
Prüfer: Prof. Dr. Arnulf Pekrun

03 Universitätsklinikum **Münster**, Klinik und Poliklinik für Kinder- und Jugendmedizin, Hämatologie und Onkologie, Albert-Schweitzer-Campus 1, Geb. A1, 48149 Münster
Prüfer: Prof. Dr. Claudia Rössig

04 Universitätsklinikum **Essen**, Klinik für Kinderheilkunde III, Hämatologie/Onkologie, Hufelandstr. 55, 45122 Essen
Prüferin: Dr. Regina Wieland

05 Universitätsklinikum **Freiburg**, Zentrum für Kinder- und Jugendmedizin, Hämatologie und Onkologie, Mathildenstr. 1, 79106 Freiburg
Prüfer: Prof. Dr. Christian Flotho

06 Universitätsklinikum **Hamburg** (UKE), Pädiatrische Hämatologie/Onkologie, Haus NORD 21, Martinistr. 52, 20246 Hamburg
Prüfer: Dr. Uwe Kordes

07 Universitätsklinikum **Heidelberg**, Zentrum für Kinder- und Jugendmedizin, Angelika-Lautenschläger-Klinik, Klinik für Kinderheilkunde III, Onkologie, Hämatologie, Immunologie und Pneumologie, Im Neuenheimer Feld 430, 69120 Heidelberg
Prüfer: Prof. Dr. Olaf Witt

08 Universitätsklinikum **Jena**, Klinik für Kinder und Jugendmedizin, Hämatologie/Onkologie, Kochstr. 2, 07745 Jena
Prüfer: Prof. Dr. James F. Beck

09 Universitätsklinikum **Köln**, Klinik und Poliklinik für Kinder- und Jugendmedizin, Kinderonkologie, Kerpener Str. 62, Neubau Haus 26, 50924 Köln
Prüfer: Prof. Dr. Thorsten Simon

10 Medizinische Hochschule **Hannover** (MHH), Zentrum Kinderheilkunde und Jugendmedizin, Pädiatrische Hämatologie und Onkologie, Carl-Neuberg-Str. 1, 30625 Hannover
Prüferin: Dr. Christin Linderkamp

Attachment 2: Patient Disposition CONSORT Flow Diagram

The flow diagram was prepared according to the most recent version of the CONSORT statement (Schulz et al. 2010).