CLINICAL TRIAL PROTOCOL

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

Vorinostat in children

Clinical Trial Code:  NCT-2007-11-02-1004
EudraCT No.:  2007-005537-11
ISRCTN number:  [will be added]
Clinical Phase:  Phase I/II
Version:  Final 2.3, dated 09.06.2011

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SIGNATURES
The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:
- the current risk-benefit assessment of the investigational medicinal product
- the moral, ethical, and scientific principles governing clinical research as set out in the applicable version of Declaration of Helsinki and the principles of GCP.

The investigator will be supplied with details of any significant or new finding including Adverse Events relating to treatment with the investigational medicinal product.

Principal Investigator

Date Prof. Dr. Olaf Witt

Sponsor

Date I. Gürkan

Biometrician

Date I. Karapanagiotou- Schenkel
## PROTOCOL OUTLINE

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

**Trial code:** NCT-2007-11-02-1004

### Phase
Phase I/II

### Sponsor
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### Financing/ Status of the Sponsor
Non-commercial, pending funding application at the Deutsche Kinderkrebsstiftung Bonn

### Indication
*C00-C75: Malignant neoplasms, stated or presumed to be primary, of specified sites, except of lymphoid, haematopoietic and related tissue*
*C81-C96: Malignant neoplasms of lymphoid, haematopoietic and related tissue*

### Trial Population
#### Inclusion Criteria
- Children and adolescents (3-18 years) with relapsed or therapy-refractory solid tumor, lymphoma or leukemia following standard first-line or relapse protocols in pediatric oncology
- Diagnosis confirmed by one of the Pathological, Radiological or Study Reference Centers recognized by the German Society of Pediatric Oncology and Hematology (GPOH)
**Vorinostat in Children**

**Version:** Final 2.3   09.06.2011

**EudraCT:** 2007-005537-11

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**Inclusion Criteria**

- No other simultaneous anti-neoplastic treatment or radiation during the study and 1 month before enrolment
- Sufficient general condition (Lansky Score > 50%)
- Life expectancy > 3 months
- Liver enzymes (ALT or AST) < 5x upper limit of normal reference value, bilirubin and creatinine < 3x upper limit of normal reference value
- Solid tumors: leukocytes > 2000/µl, thrombocytes > 50,000/µl and adequate bone marrow function to permit evaluations of haematopoietic toxicity
- Normal electrocardiogram
- No common toxicity criteria (CTC) grade 3 or 4 toxicity from previous treatment
- Written informed consent of the legal representatives and the patient if the patient is able to understand the study situation and to give consent (must be available before enrolment in the trial)
- Women with childbearing potential agree to use adequate contraception or to abstain from heterosexual activity throughout the study, starting with Visit 1.
- Sexually active male patient agrees to use an adequate method of contraception for the duration of the study.
- Solid tumors: measurable disease activity according to RECIST criteria

**Exclusion Criteria**

- History of deep vein thrombosis or pulmonary embolism
- Pregnancy and lactation
- Patients with concomitant treatments and/or anti-neoplastic treatment such as chemotherapy, immune therapy, and differentiation therapy, other targeted therapy, radiation, anti-epileptic treatment with valproic acid. The use of valproic acid as prior antiepileptic therapy is allowed with a 30-day washout period.
- Prior exposure to Histone Deacetylase Inhibitors
- Known active HBV, HCV or HIV infection
- Patients with concomitant treatments such as amber [Hypericum perforatum], plant extracts, vitamins, and other anti-oxidative compounds
- Participation in other clinical trials or observation period of competing trials, respectively
- Patient is unable to swallow vorinostat suspension or capsules
- Patients on coumarin-derivative anticoagulants
- Any other medication which could accentuate known dose-dependent adverse effects of the study drug, for instance bone marrow depression or QT-prolongation

**Objectives**

**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 ≥ 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.

Additional biomarker studies for the prediction of vorinostat response (IL-6, IL-10, BMP4) induction, basal histone acetylation level) will be performed.

**Trial Design**

Open-label single-arm, intra-patient dose escalation, multi-centre, national Phase I/II clinical trial.

**Investigational Medicinal Product(s)**

Vorinostat, SAHA (suberoylanilide hydroxamic acid)

Suspension at 50mg/ml oral administration qd (once per day) with food

Capsules at 100mg oral administration qd (once per day) with food

Starting dose: 180 mg/m²/d, individual dose escalation every 2 weeks until MTD is reached. Thereafter each patient will receive a maintenance therapy at this individually determined MTD for at least 3 months.

Minimum dose: 30 mg/m²/d.

Maximum dose: 580 mg/m²/d.

Responding patients: continuation of vorinostat for a maximum of 9 months or withdrawal from study for other reasons.

**Sample Size**

The sample size calculation in this study was based on the accuracy requirements for the toxicity rate associated with the safe dose for the routine application. 50 pediatric patients ≥ 3 years will be included in the trial. If dose limiting toxicity (DLT) (i.e. ≥ grade 3 toxicity) is observed at a given dose d in 1/50 patients (this defines the safe dose for routine application) then the 95% confidence interval for the true rate r of DLT at this dose is [0.05;10.65]%.

Additionally, this is a feasible number of patients to be recruited by the participating trial centers within 2 years.

**Statistical Analysis**

Estimation of toxicity rates with 95%-CI.

**Trial Duration and Dates**

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FLOW CHART

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

**Enrolment**
- In/Exclusion criteria?
- Baseline: MRI, blood count, clinical chemistry, tumor marker, ECG, MiBG (in neuroblastoma), 3ml citrate-blood for biomarker
- bone marrow cytology if infiltrated or in neuroblastoma

**Phase I: start**
- Vorinostat: 180mg/m²/d for 2 weeks
- weekly physical exam, blood count and clinical chemistry, ECG after 1 week

**Phase I: dose escalation**
- (de)escalate dose every 14 days: ± 50mg/m²/d
- weekly physical exam, blood count and clinical chemistry,
- ECG: at MTD
- establish maximum tolerated dose (MTD)

**Phase II: start treatment at MTD**
- start treatment with maximum tolerated dose (MTD) immediately after Phase I
- treat for 3 months
- weekly physical exam, blood count and clinical chemistry
- if grade 3 or 4 toxicity occurs, reduce dose by 50mg/m²/d

**Pharmacokinetics I**
- on day 8 of vorinostat treatment
- 2ml citrate-blood (green coagulation monovette) at 0, 30, 60, 90, 120min, 4, 6, 8h after intake
- 0.5ml CSF 0, 30, 60, 90, 120min, 4, 6, 8h after intake

**Biomarker I**
- extra 3ml citrate-blood

**Pharmacokinetics II**
- following establishment of MTD
- 2ml citrate-blood (green coagulation monovette) at 0, 30, 60, 90, 120min, 4, 6, 8h after intake
- 0.5ml CSF 0, 60, 90, 120min, 4, 6, 8h after intake

**Biomarker II**
- extra 3ml citrate-blood

**Response evaluation**
- 3 months after start of treatment with MTD
- MRI, tumor marker, bone marrow, MiBG
- response evaluation by central review

**No progression (CR, PR, SD)**
- continue vorinostat treatment
- 2 weekly: physical exam, blood count, clinical chemistry
- 3 monthly: tumor evaluation
- stop treatment in case of progression

**Progression (PD)**
- stop vorinostat treatment

**End of Treatment**

**Follow-up**
- 3 months follow up, routine supportive care
- 2 weekly: physical exam, blood count, clinical chemistry

**End of Study**