**Trial Description**

**Title**
German Treatment Optimization Study for Children with De Novo and Relapsed Langerhans cell Histiocytosis (LCH) as Part of the International Study LCH-IV

**Trial Acronym**
LCH-IV-G-2016

**URL of the trial**
http://---

**Brief Summary in Lay Language**
[---]*

**Brief Summary in Scientific Language**
Langerhans cell Histiocytosis (LCH) is a malignant disorder affecting 3-5/1 million children. Previous trials decreased mortality by intensifying induction chemotherapy, but up to 40% of patients with LCH still reactivate, and permanent sequelae occur in up to 40% of patients. Permanent consequences include hormone deficiencies, orthopedic and pulmonary problems. Previous studies have demonstrated in patients with multisystem (MS)-LCH that prolongation of maintenance therapy results in a decreased risk of reactivation. In addition, retrospective and non-randomized studies suggest that the administration of 6-mercaptopurine decreases the risk of reactivation as well. Therefore, the proposed phase III open-label multicenter randomized trial will evaluate in pediatric patients (< 18 years) with de novo MS-LCH (Stratum I, Group 1) whether prolongation (12 vs 24 months)±intensification with 6-mercaptopurine will decrease the risk of reactivation and the incidence of permanent consequences. In patients with de novo single system (SS) LCH (Stratum I, Group 2), it will be evaluated whether prolongation of maintenance therapy (12 versus 6 months) will result in a clinical benefit (decreased risk of reactivation). The study will further evaluate whether in patients with de relapsed LCH (no involvement of risk organs such as bone marrow, liver, spleen; Stratum II), a new compound (indomethacin) will perform better than standard therapy with 6-mercaptopurine/methotrexate to decrease further reactivations and the risk of permanent consequences. Primary endpoint is reactivation-free survival, secondary endpoints include toxicity and risk of permanent consequences.

**Organizational Data**

- **DRKS-ID:** DRKS00012701
- **Date of Registration in DRKS:** 2017/11/23
- **Date of Registration in Partner Registry or other Primary Registry:** [---]*
Secondary IDs

- EudraCT-No. (for studies acc. to Drug Law): 2016-003568-38

Health condition or Problem studied

- ICD10: C96.0 - Multifocal and multisystemic (disseminated) Langerhans-cell histiocytosis [Letterer-Siwe disease]
- ICD10: C96.5 - Multifocal and unisystemic Langerhans-cell histiocytosis
- ICD10: C96.6 - Unifocal Langerhans-cell histiocytosis

Interventions/Observational Groups

- Arm 1: Stratum I, Group 1: Prednisone/Vinblastine for 12 months of total therapy (prednisone 40 mg/sqm day 1-5 und vinblastine 6 mg/sqm day 1 every 3 weeks)
  Stratum I, Group 2: Prednisone/Vinblastine for 6 months of total therapy (prednisone 40 mg/sqm day 1-5 und vinblastine 6 mg/sqm day 1 every 3 weeks)
  Stratum II: 6-Mercaptopurine/Methotrexate for 2 years of total therapy (mercaptopurine 50 mg/sqm daily and methotrexate 20 mg/sqm once a week)
- Arm 2: Stratum I, Group 1: Prednisone/Vinblastine for 24 months of total therapy (prednisone 40 mg/sqm day 1-5 und vinblastine 6 mg/sqm day 1 every 3 weeks)
  Stratum I, Group 2: Prednisone/Vinblastine for 12 months of total therapy (prednisone 40 mg/sqm day 1-5 und vinblastine 6 mg/sqm day 1 every 3 weeks)
  Stratum II: Indometacin for 2 years of total therapy (dosage 2 mg/kg/day)
- Arm 3: Stratum I, Group 1: Addition of 6-mercaptopurine to arm 1 and arm 2, respectively (dosage 50 mg/sqm daily)

Characteristics

- Study Type: Interventional
- Study Type Non-Interventional: [---]*
Study Type: **Interventional**  
Study Type Non-Interventional: [---]*  
- Allocation: **Randomized controlled trial**  
- Blinding: [---]*  
- Who is blinded: [---]*  
- Control: **Active control (effective treatment of control group)**  
- Purpose: **Treatment**  
- Assignment: **Other**  
- Phase: **III**  
- Off-label use (Zulassungsüberschreitende Anwendung eines Arzneimittels): **Yes**

**Primary Outcome**

- Reactivation-free survival

**Secondary Outcome**

**Stratum I, Group 1 and 2**
- Overall survival
- Incidence of permanent consequences (Diabetes insipidus, neurodegeneration)
- The proportion of patients alive and free of disease without permanent consequences
- Cumulative incidence of reactivations in risk organs
- Treatment-related toxicity

**Stratum II:**
- Overall survival
- The proportion of patients alive and free of disease without permanent consequences (e.g. diabetes insipidus, radiological or clinical neurodegeneration)
- Incidence of reactivation of the disease in the experimental arm
- Treatment-related toxicity

**Countries of recruitment**

- DE Germany

**Locations of Recruitment**

- University Medical Center **Klinikum d. J. W. Goethe-Universität, Frankfurt a.M.**
- Medical Center **I. Kinderklinik des KZVA, Augsburg**
University Medical Center Kinderklinik u. Poliklinik im Dr. v. Haunerschen Kinderspital, München
University Medical Center Charité CVK , Berlin
Medical Center Klinikum Bremen-Mitte gGmbH, Bremen
Medical Center Städt. Kliniken Dortmund, Dortmund
University Medical Center Univ.-Kinderklinik, Münster
University Medical Center Universitätsklinikum Carl-Gustav-Carus, Dresden
University Medical Center Klinik für Kinder-Onkologie, -Hämatologie und Klinische Immunologie, Düsseldorf
University Medical Center Klinik u. Poliklinik f. Kinder- u. Jugendmed.; Kinderklinik III, Essen
University Medical Center Zentrum f. Kinderheilkde u. Jugendmed., Freiburg im Breisgau
University Medical Center Päd. Hämatologie u. Onkologie, Gießen
University Medical Center Georg-August-Universität Göttingen, Göttingen
University Medical Center Universitätsklinikum Hamburg-Eppendorf; Klinik u. Poliklinik f. Kinder- u. Jugendmed., Hamburg
University Medical Center Medizinische Hochschule Hannover; Zentrum für Kinderheilkunde und Jugendmedizin, Hannover
University Medical Center Kinderklinik III - Päd. Onkologie, Hämatologie, Immunologie, Heidelberg
University Medical Center Campus Kiel Klinik für Allgemeine Pädiatrie, Kiel
University Medical Center Univ.-Kinderklinik, Kinderonk. u. -hämatol., Köln
University Medical Center Universitätsmedizin der Johannes Gutenberg-Universität Mainz; Zentrum für Kinder- und Jugendmedizin, Mainz
University Medical Center Kinder- u. Poliklinik des Klinikums rechts der Isar der Technischen Universität München Kinderklinik Schwabing, München
Medical Center Klinikum Oldenburg gGmbH, Oldenburg
University Medical Center Abt. Päd. Hämatologie, Onkologie und SZT, Regensburg
Medical Center Olgahospital - Klinik f. Kinder- u. Jugendmedizin, Pädiatrie 5, Stuttgart
University Medical Center Univ.-Kinderklinik, Tübingen
University Medical Center Univ.-Kinderklinik, Klinikbereich Michelsberg, Ulm
University Medical Center Päd. Onkologie, Hämatologie, Stammzelltransplantation, Würzburg

Recruitment

- Planned/Actual: **Actual**
- (Anticipated or Actual) Date of First Enrollment: **2018/06/26**
- Target Sample Size: **300**
- Monocenter/Multicenter trial: **Multicenter trial**
Planned/Actual: **Actual**

(Anticipated or Actual) Date of First Enrollment: **2018/06/26**

Target Sample Size: **300**

Monocenter/Multicenter trial: **Multicenter trial**

National/International: **National**

### Inclusion Criteria

- **Gender:** Both, male and female
- **Minimum Age:** no minimum age
- **Maximum Age:** 18 Years

### Additional Inclusion Criteria

**Stratum I:**
- **Age:** Patients must be less than 18 years of age at the time of enrollment.
- **No systemic therapy for LCH prior to the standardized induction therapy, e.g., prior to Initial Course 1 (IC-1) and, eventually, Initial Course 2 (IC-2) (pre-study)**
- **Evaluation demonstrates non-active disease after IC-1 (independent of involvement of risk organs) or non-active disease or active disease better (only for patients without involvement of risk organs) after IC-2 [imaging studies need to be referenced regarding treatment response to initial course(s) (pre-study)]**

**Stratum II:**
- **Age:** Patients must be older than 2 years and less than 18 years of age at the time of enrollment
- **No systemic therapy for progression/relapse of LCH prior to the standardized second line therapy, e.g., standardized 24-week second-line initial course (SL-IT), which is NOT part of the study**
- **Evaluation demonstrates non-active disease or active disease better after SL-IT [imaging studies need to be referenced regarding treatment response to second-line initial course (pre-study)].**

**Both Strata:**
- **Patients must have a referenced histological verification of the diagnosis of LCH (pre-study)**
- **Male subjects able to father children and female subjects of childbearing potential and at risk for pregnancy must agree to use a highly effective method of contraception (e.g., barrier contraception for males, contraceptive pill (“Pill”) for female) throughout the study and for at least 90 days (male subjects) and 30 days (female subjects) after the last dose of assigned study treatment.**
- **Signed informed consent of parent(s)/legal guardian(s) and/or patient (when applicable depending on age and patient’s compliance) prior to any protocol procedure**

### Exclusion criteria

**Stratum I:**
Patients with any active disease after IC-1 or patients with active disease intermediate/worse (for patients without involvement of risk organs) or any active disease for patients with involvement of risk organs after IC-2
- Hypersensitivity for one of the trial drugs or any of its excipients or hypersensitivity to any other vinca-alkaloid or any of its excipients
- Leukopenia, which is not caused by LCH
- Severe uncontrolled infection
- Stomatitis or ulcer of the gastrointestinal tract
- Pregnancy (patients of child-bearing age must be appropriately tested before chemotherapy)
- Breastfeeding
- Participation in other clinical trials according to German drug law (§§40ff AMG)

Stratum II:
- Patients with progressive disease in risk organs
- Patients with active disease intermediate/worse after second-line intensive course
- Hypersensitivity for one of the trial drugs or any of its excipients
- Pregnancy (patients of child-bearing age must be appropriately tested before chemotherapy)
- Breastfeeding
- History of severe bleeding, ulcer of the gastrointestinal tract, history of CNS bleeding or other bleeding disorders unrelated to LCH
- Patient suffering from Crohn’s disease or Colitis ulcerosa
- History of asthma, urticaria, or other allergic-type reactions after taking acetylsalicylic acid or other non-steroidal anti-inflammatory drugs.
- Known severe immunodeficiency, untreated blood disorders not caused by LCH or untreated functional disorders of the hematopoietic system*
- Severe impairment of liver, chronic liver disease, increased alcohol consumption
- Renal impairment (creatinine-clearance < 60 ml/min)
- Heart insufficiency
- Severe uncontrolled infection
- Participation in other clinical trials according to German drug law (§§40ff AMG)

*Note: Both LCH and preceding chemotherapy for LCH, which is mandatory for the cure of the patient, may cause blood disorders/functional disorders of the hematopoietic system as well as clotting disorders. This is similar to other hematological diseases such as acute lymphoblastic leukemia, in which standard treatment consists of cytotoxic agents such as methotrexate. Therefore, the inclusion of patients with blood disorders unrelated to LCH depends on the careful evaluation of the treating investigator, if the patient is in stable condition and the disorder is sufficiently treated.

Addresses

Primary Sponsor
Johann Wolfgang Goethe-Universität Frankfurt am Main
Ms. Prof. Dr. Birgitte Wolf
Theodor-W.-Adorno Platz 1
60323 Frankfurt
Germany
Telephone: +496979811100
Fax: +496979811109
Primary Sponsor

Johann Wolfgang Goethe-Universität Frankfurt am Main
Ms. Prof. Dr. Birgitte Wolf
Theodor-W.- Adorno Platz 1
60323 Frankfurt
Germany

Telephone: +496979811100
Fax: +496979811109
E-mail: praesidentin at uni-frankfurt.de
URL: www.uni-frankfurt.de/

Contact for Scientific Queries

University Hospital Frankfurt Hospital for Children and Adolescents Pediatric Hematology and Oncology
Mr. Prof. Dr. Thomas Lehrnbecher
Theodor Stern Kai 7
60590 Frankfurt
Germany

Telephone: +49 69 6301 83481
Fax: +49 69 6301 6700
E-mail: Thomas.Lehrnbecher at kgu.de
URL: [--]*

Contact for Public Queries

Pädiatrisches Forschungsnetzwerk gGmbH GPOH gGmbH
Ms. Katharina Waack-Buchholz
Hufelandstr 17
45147 Essen
Germany

Telephone: +49 201 7494 9611
Fax: +49 201 8777 5484
E-mail: studienbuero at lch-studie.de
URL: www.gpoh.de

Sources of Monetary or Material Support

Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)

Deutsche Forschungsgemeinschaft
Kennedyallee 40
53175 Bonn
Germany
Public funding institutions financed by tax money/Government funding body (German Research Foundation (DFG), Federal Ministry of Education and Research (BMBF), etc.)

Deutsche Forschungsgemeinschaft
Kennedyallee 40
53175 Bonn
Germany

Telephone: [---]*
Fax: [---]*
E-mail: [---]*
URL: www.dfg.de

Status

- Recruitment Status: Recruiting ongoing
- Study Closing (LPLV): [---]*

Trial Publications, Results and other documents

- trial protocol (mandatory for transfer to Studybox) Prüfplan LCH-IV-G_2016

* This entry means the parameter is not applicable or has not been set.
*** This entry means that data is not displayed due to insufficient data privacy clearing.