

# **LCH-IV**

## **International Collaborative Treatment Protocol for Children and Adolescents with LANGERHANS CELL HISTIOCYTOSIS**

**EudraCT Nr.: .....**

**International Sponsor: St. Anna Kinderkrebsforschung**

**Children's Cancer Research Institute  
Vienna, Austria**

**Protocol Version 1.0 from March 2011**

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Start of the Study: \_\_\_\_\_.\_\_\_\_\_.2011

## LCH-IV

### INTERNATIONAL COLLABORATIVE TREATMENT PROTOCOL FOR CHILDREN AND ADOLESCENTS WITH LANGERHANS CELL HISTIOCYTOSIS

Version 1.0 of the therapy protocol from April 15<sup>th</sup> 2011

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The registration, trial enrollment and randomization will be performed on-line through the remote clinical trial database: <https://www.hs-lch-database.org> (for detailed instructions see **Appendix A-I\_1**).

##### **1.1.2.2 Contact Information for SAE Reporting**

The SAE reporting (for detailed instructions see SOP, Appendix A-II\_1) will be managed by a specific tool of the remote clinical trial database: <https://www.hs-lch-database.org> (for detailed instructions see **Appendix A-I\_2**).

The reporting investigator must log in, complete, sign and send the SAE report form. The system will automatically notify the National Principal Investigator and the International LCH-IV Study Management Center in Vienna.

If for some reasons the use of the remote database system is not possible, the paper SAE report form (**Appendix A-II\_2**) has to be filled in and sent by **Fax** to:

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## 2 LCH-IV STUDY SYNOPSIS

### 2.1 Summary (English)

<b>Full title of the trial</b>	LCH-IV International Collaborative Treatment Protocol for Langerhans Cell Histiocytosis
<b>EudraCT number</b>	
<b>Disease</b>	Langerhans cell histiocytosis
<b>Background</b>	<p>LCH is a rare disease of the immune system that may affect any age group. It can affect many different organs, including the skeleton, skin, lymph nodes, liver, lungs, spleen, hematopoiesis, or central nervous system (CNS). Accordingly, the range of clinical symptoms is wide. There are two widely recognized disease extent categories: single-system LCH (involvement of a single organ or system) and multisystem LCH (involvement of 2 or more organ systems). Patients with SS-LCH of the skeleton, skin, or the lymph nodes have an excellent prognosis and are felt to need a minimum or sometimes even no treatment at all.</p> <p>The course of multisystem LCH (MS-LCH) is unpredictable upon diagnosis, ranging from spontaneous resolution to fulminant progression and fatal outcome. Involvement of crucial organs like the hematopoietic system, liver, or spleen has been found to herald a poor prognosis in different studies. Recent large clinical trials have shown that the response to initial treatment is a highly important prognostic factor. Patients with MS-LCH without involvement of “risk organs” have very high (&gt;95%) probability of survival when treated with a standard regimen consisting of vinblastine and steroids. In contrast, involvement of risk organs carries the risk of unfavourable outcome.</p> <p>Patients with reactivations or chronic disease may experience severe permanent consequences (PC) reducing the patient's quality of life, in particular when they affect the CNS or lungs and lead to hormone deficiencies, a neurodegenerative syndrome, lung fibrosis, etc.</p> <p>The international efforts of the past 20 years have shown that combination therapy with vinblastine and prednisone is an effective therapy for MS-LCH. The previous prospective trial LCH-III confirmed this regimen as a standard regimen for MS-LCH in patients with and without risk organ involvement. It also showed that prolonged treatment in the latter group (treatment duration of 12 vs. 6 months) is superior in preventing disease reactivations. The results of this trial are encouraging and serve as a basis for the LCH-IV study design.</p> <p>Due to the complexity of the disease presentations and</p>

	<p>outcomes, the LCH-IV study seeks to tailor treatment based on features at presentation and on response to treatment, leading to seven strata:</p> <ul style="list-style-type: none"> <li>• <b>Stratum I:</b> First-line treatment for MS-LCH patients (Group 1) and patients with SS-LCH with multifocal bone or “CNS-risk” lesions (Group 2)</li> <li>• <b>Stratum II:</b> Second-line treatment for non-risk patients (patients without risk organ involvement who fail first-line therapy or have a reactivation after completion of first-line therapy)</li> <li>• <b>Stratum III:</b> Salvage treatment for risk LCH (patients with dysfunction of risk organs who fail first-line therapy)</li> <li>• <b>Stratum IV:</b> Stem cell transplantation for risk LCH (patients with dysfunction of risk organs who fail first-line therapy)</li> <li>• <b>Stratum V:</b> Monitoring and treatment of isolated tumorous and neurodegenerative CNS-LCH</li> <li>• <b>Stratum VI:</b> Natural history and management of “other” SS-LCH (patients who do not need systemic therapy at the time of diagnosis)</li> <li>• <b>Stratum VII:</b> Long-term Follow up (all patients irrespective of previous therapy will be followed for reactivation or permanent consequences once complete disease resolution has been achieved and the respective protocol treatment completed)</li> </ul>
<b>Primary objectives</b>	<ul style="list-style-type: none"> <li>• To decrease mortality in MS-LCH by an early switch of patients with risk organ involvement, who do not respond to front-line therapy, to a more intensive treatment (Stratum III or Stratum IV).</li> <li>• To reduce reactivation rates and permanent consequences in MS-LCH (Group 1) through prolongation (12 vs. 24 months) and intensification (+/- 6-MP) of continuation treatment (2x2 factorial randomized trial)</li> <li>• To reduce reactivation rates and permanent consequences in a subset of SS-LCH (multifocal bone or isolated “CNS-Risk” lesions (Group 2) through prolongation (6 vs. 12 months) of continuation therapy (randomized trial)</li> <li>• To investigate the value of a uniform second-line therapy with PRED/ARA-C/VCR followed by randomized continuation therapy (24 months of Indomethacin vs. 6-MP/MTX) in patients with non-risk organ LCH (both non-responders to first-line regimen and those who experience disease reactivation in non-risk organs after its completion) with respect to achievement of complete disease resolution, prevention of further reactivations and permanent consequences</li> </ul>

	<ul style="list-style-type: none"> <li>To evaluate whether systemic therapy with intravenous immunoglobulin (IVIG) or low dose cytarabine can achieve improvement of the neuropsychological symptoms in patients with clinically manifest neurodegenerative CNS-LCH.</li> <li>To describe the spectrum and incidence of permanent consequences in systemically treated patients, identify possible risk factors, and assess the role of systemic treatment in their prevention</li> <li>To prospectively study the natural course of SS-LCH in patients who initially are not candidates for systemic therapy, with respect to disease progression, reactivations, need for medical interventions, as well as permanent consequences, at any time after diagnosis.</li> </ul>
<b>Inclusion criteria</b>	<ul style="list-style-type: none"> <li>Definitive diagnosis of Langerhans cell histiocytosis</li> <li>Age less 18 years at time of definitive diagnosis</li> <li>Met inclusion criteria for the respective stratum</li> <li>Signed written informed consent</li> </ul>
<b>Exclusion criteria</b>	Stratum-dependent
<b>Study period</b>	2011-2018
<b>Expected accrual</b>	800 patients in the first-line treatment (Stratum I), 400 each for Group 1 and Group 2. Patients failing Stratum I may be eligible for the other interventional Strata (Stratum II, III, IV, V)
<b>Study chairs (international)</b>	Milen Minkov, MD, PhD Email: <a href="mailto:LCH@ccri.at">LCH@ccri.at</a> Carlos Rodriguez-Galindo, MD Email: <a href="mailto:carlos_rodriguez-galindo@dfci.harvard.edu">carlos_rodriguez-galindo@dfci.harvard.edu</a>
<b>Participating countries / subcenters</b>	Argentina, Australia, Austria, Belarus, Belgium, Canada, Czech Republic, Denmark, France, Germany, Great Britain, India, Israel, Italy, Netherlands, New Zealand, Norway, Russia, Spain, Sweden, Turkey, USA

## 2.2 Summary in the national language (*Study synopsis in the appropriate language to be added to the national protocol version*)

### **3 GENERAL INFORMATION ON ADMINISTRATIVE AND ORGANIZATIONAL ISSUES**

#### **3.1 Disclaimer**

This document describes a prospective clinical study including five treatment and two observational Strata for patients with Langerhans cell histiocytosis and provides information about the procedures for enrollment. This is a research study and thus it is not intended for use as an aide-memoire or as a guide for the treatment of non-registered patients. Every care was taken in the design and drafting of the protocol but corrections or amendments may be necessary. These will be circulated to known investigators in the trial, but centers entering patients for the first time are advised to contact their appropriate (National) Study Center to confirm the accuracy of their version of the protocol, and to obtain the necessary authorization to enter patients onto the trial. Participants are required to maintain confidentiality regarding the contents of this protocol. The protocol or any of its parts may not be reproduced or circulated without prior authorization by the Study Management Group. Responsibility for the administration of the protocol treatments lies with the participating investigators. Before entering patients onto the trial, investigators must ensure that the study protocol has received approval by the local committees for protection of human research subjects. Please note that this trial is a collaboration between American and European trial groups. For consistency, American spelling is used throughout the protocol.

#### **3.2 Organization of the LCH-IV Study Management**

The trial will be managed by an International Study Management Group (SMG). The SMG is responsible for the study design, execution, as well as for decisions on all other study-related issues. Decisions can be made by simple majority (50+1) on voting.

The SMG consists of the study Chair and Co-chair (selected among the Coordinating Principal Investigators), the Coordinating Principal Investigators, and the National Principal Investigators (for contact information refer to Section 1.2.3, page 4).

The operative execution of the study will be done by the International LCH-IV Study Management Center in Vienna.

The SMG will execute the study in cooperation with an independent Data Safety Monitoring Committee (DSMC).

Valuable experts (Advisors) contributing to the study conception and design will be appropriately acknowledged in the protocol.

### **3.2.1 Study Chair/ Co-Chair**

The SMG Chair/ Co-chair act as the intermediary between external authorities and the SMG, as well as within the SMG. They administer and supervise the execution of the study. They have a representative function and act on behalf of and in accordance with decisions of the SMG.

### **3.2.2 Principal Investigators**

Due to the complexity of the study design and the participation of national groups with different regulatory systems, three levels of Investigators are defined:

#### **3.2.2.1 Coordinating PI**

A Coordinating PI will have responsibility for the design and execution of a defined Stratum of the Study. For each Stratum two Coordinating PIs will be appointed: one for Americas and one for Europe and other countries except Americas. The Coordinating PIs will be responsible for the evaluation of the SAE reports concerning their Stratum.

#### **3.2.2.2 National PI**

A National PI will have responsibility for the organization and execution of the LCH-IV Study for his/her country (in some exceptional case this will represent a single big tertiary reference center). Therefore, he/she will act on behalf of the national (institutional) Co-Sponsor and carry the respective responsibilities, which will be delegated by the International Sponsor through a contract. Among other duties he will be responsible to arrange for indemnity to cover the liability of the Investigators as well as to organize study monitoring according to GCP requirements.

#### **3.2.2.3 Investigator**

A person responsible for the conduct of the LCH-IV Study at a study site.

The organization of the collaboration among the National PI and the Investigators (e.g. contracts etc) can differ from country to country and has to be defined on a local level. With respect to SAE reporting the Investigators will have to notify both their National

PI and the International LCH-IV Study Management Center.

### **3.2.3 International LCH-IV Study Management Center**

The International LCH-IV Study Management Center situated at the Children's Cancer Research Institute (the International Sponsor) in Vienna will be responsible for the operation and administration of the study including the SAE management coordination at an international level.

### **3.2.4 Participating Institutions/Sites**

For a complete list of the participating institutions and contact information see **Appendix A-III**. Each institution will be represented by an Investigator.

### **3.2.5 Monitors**

A monitor is responsible for overseeing the progress of the LCH-IV Study, and ensuring conformity with GCP and applicable regulatory requirements. The monitoring will be organized at a national level.

## **3.3 Data Safety Monitoring Committee (DMSC)**

An independent DMSC constituted to serve the clinical trials of the Histiocyte Society will cover the LCH-IV study.

## **3.4 Advisors**

These are established experts with valuable contribution to the conception and design of the LCH-IV Study, who are not actively involved in its execution. They have advisory functions and do not vote. Their contribution has to be appropriately acknowledged in future publications related to the LCH-IV Study.

## 4 INTRODUCTION

### 4.1 Background

#### 4.1.1 Biology

Langerhans Cell Histiocytosis (LCH) is a disorder with highly variable clinical presentation and biological behavior (1). It is characterized by proliferation and accumulation of cells phenotypically and functionally similar to the activated normal Langerhans cells (LCs).

The histopathology varies depending on localization and evolution stage of the lesions, but does not allow discrimination with respect to clinical course and severity. A typical lesion consists of collections of LCs, interdigitating cells and macrophages, accompanied by T lymphocytes with variable numbers of multinucleated giant histiocytes and eosinophils (2). The pathogenesis of LCH is poorly understood. Because LCH has been demonstrated to be a clonal disease, the possibility exists that it is a neoplastic disorder (3). However, different patterns of clinical involvement and natural course are consistent with other pathogenetic mechanisms. The occurrence of spontaneous remission (4) and the benign histopathological appearance of the lesions in LCH suggest a reactive clonal disorder rather than a malignant process. LCs, like other dendritic cells, have a critical role in the immune system, and it has been suggested that LCH could be the result of immune dysregulation. Although no consistent immunologic abnormalities have been described, there is increasing evidence that LCH may be the result of an uncontrolled and abnormal proliferation of LCs secondary to either immune dysregulation or following exposure to an as yet undetermined stimulus (5;6).

#### 4.1.2 Course and prognosis

The course in the individual patient is unpredictable upon diagnosis. It ranges from spontaneous regression to multiple bouts of disease activity over many years, to rapid deterioration with lethal outcome within weeks.

The early clinical observations on LCH, however, revealed some correlation between disease extent, localization and severity at presentation on the one hand, and course and prognosis on the other hand (1, 2). It has been empirically found that LCH initially confined to the skeleton usually does not evolve into the severe life-threatening multisystem form (3). Such patients presenting with single bone LCH have a benign course and an excellent survival, independent of the therapy. At the other end of the

disease spectrum, patients who present with multisystem LCH (MS-LCH) with involvement/dysfunction of critical organs (e.g. liver, spleen, hematopoietic system) have a significant risk of mortality, particularly if they do not respond to systemic therapy. In the middle of the spectrum are patients with multifocal bone or multisystem LCH without risk organ involvement who may have a progressive or protracted course and a risk of significant permanent sequelae. Even MS-LCH patients who initially respond well to treatment may experience disease reactivations that can lead to permanent consequences such as orthopedic problems, hormone loss or neurologic deficits, which can significantly affect their quality of life. Accordingly, an individual patient might be in need of different therapeutic strategies during his/her disease course.

#### **4.1.3 Clinical classification**

The LCH Study Group of the Histiocyte Society adopted a simple pragmatic clinical classification which divided the LCH population into two general groups: patients with “single-system” LCH (SS-LCH) and patients with “multisystem” LCH (MS-LCH). The current version of this classification is presented in Table I.

**Table I: Current clinical classification of LCH**

<b>Single System LCH (SS-LCH)</b>	<b>One organ/system involved (uni- or multifocal):</b> <ul style="list-style-type: none"> <li>• Bone unifocal (single bone) or multifocal (&gt;1 bone)</li> <li>• Skin</li> <li>• Lymph node (excluding draining lymph node of another LCH lesion), single (one group) or multiple (more than one group)</li> <li>• Lungs</li> <li>• Central nervous system</li> <li>• Other (e.g. thyroid, thymus)</li> </ul>
<b>Multisystem LCH (MS-LCH)</b>	<b>Two or more organs/systems involved</b> With or without involvement of “Risk Organs” (e.g. hematopoietic system, liver, and/or spleen)

## 4.2 Therapeutic trials in LCH

The evolution of LCH therapy over the years has closely reflected the paradigm shifts in the understanding of LCH biology. Indeed, the difficulties in developing optimal therapies are, at least in part, due to the gaps in the understanding of the pathogenesis of LCH.

### 4.2.1 The era before the Histiocyte Society

LCH has been treated with a wide range of therapeutic strategies over the time, reflecting the changing understanding of the disease process (4, 5). The first multi-institutional trials were conducted in the early 1980s. Due to a lack of uniform criteria for patient evaluation and stratification, the patient populations reported in these early trials varied greatly with respect to extent of disease thus precluding precise comparison of the reported data, and making any conclusions regarding a superior treatment approach elusive. Nevertheless, these clinical studies resulted in important observations, which formed the basis for development of more recent therapeutic strategies and large-scale prospective trials.

The largest co-operative prospective clinical trials of the 1980s were those of the Italian AIEOP Group (AIEOP-CNR-HX 83) (6) and of the DAL-HX group (DAL-HX 83) (7), both applying systemic chemotherapy promptly after establishment of the diagnosis. Overall mortality was low in both of these series (8% and 9%, respectively). The low incidence of disease reactivation seen in the DAL-HX 83 trial (overall 23%) provides evidence that early treatment intensification and prolonged treatment duration (12 months in the DAL studies) may positively influence the natural course of the disease. Disease related permanent consequences were encountered in 48% of patients in the AIEOP series and in 33% of the DAL group. Strikingly, diabetes insipidus (DI) occurred in only 20% and 10% of the cases, respectively (6, 7).

### 4.2.2 The era of international prospective clinical trials

Three prospective therapeutic trials for MS-LCH have been conducted to date by the Histiocyte Society. Their achievements and key finding are summarized below:

#### 4.2.2.1 LCH-I Study (April 1, 1991 – October 1, 1995)

In the first international trial for the treatment of MS-LCH, LCH-I eligible patients were randomly assigned to receive 24 weeks treatment of vinblastine (Arm A) or etoposide

(Arm B) (8). An initial pulse of high-dose methyl-prednisolone was given in both arms to treat constitutional symptoms. Five hundred and twenty-three patients were registered on LCH-I, of whom 210 had multisystem disease and 143 were randomized. A comparison of the two regimens showed no significant difference with respect to initial response (57% vs. 49%), probability of reactivation (61% vs. 55%), mortality (24% vs. 20%), and permanent consequences (39% vs. 51%), including diabetes insipidus (22% vs. 23%), in Arm A and Arm B, respectively.

The LCH-I trial demonstrated that:

- Vinblastine and Etoposide, used as monotherapy, are equally effective in MS-LCH
- a poor prognosis is clearly associated with the involvement at diagnosis of at least one “risk organ” (liver, lungs, hematological system, and/or spleen)
- response at 6 weeks is a very powerful and independent predictor of outcome

The results of LCH-I were compared also to the DAL-HX 83 and DAL-HX 90 studies (Table II). The DAL-HX series was used as the historical control because of strict and uniform criteria for diagnosis, uniform methods of evaluation of disease extent, and the application of standard, risk-adapted chemotherapy. Extensive data collection allowed re-evaluation of the DAL-HX 83/90 cohort according to the criteria for disease extension and therapy response used in the LCH-I study.

Although the LCH-I trial achieved comparable survival rates, it compared unfavorably to the historical DAL-HX studies in some other aspects. There was a higher response rate after 6 weeks of therapy in the DAL-HX studies (80% vs. 51%) and the DAL-HX initial therapy lead to a clearer discrimination between responders and non-responders (with only 6% of patients with intermediate response vs. 30% in the LCH-I study). The comparison suggested that patients with severe MS-LCH may benefit from a more intensive initial chemotherapy. It was additionally speculated that a rapid control of the disease activity could reduce the incidence of the permanent consequences. In the LCH-I study a higher incidence of disease-related sequelae was observed after a shorter observation time. While the overall survival rates were similar, there was a disappointing high incidence of disease reactivation in the LCH-I study. All these aspects suggested that therapy for MS-LCH should be intensified.

**Table II: Results of the LCH-I study compared to DAL-HX studies**

	<b>DAL-HX Studies</b>	<b>LCH-I study</b>
Number of MS-LCH patients	63	135
Gender (M:F)	1.1 : 1	1 : 1
Age at diagnosis	median 11 mo (birth-13 yrs 2 mo)	median 17 mo (birth – 14 yrs 5 mo)
Response at week 6:		
NAD	13 (21%)	17 (13%)
AD better	37 (59%)	52 (38%)
AD intermediate	4 ( 6%)	41 (30%)
AD worse	9 (14%)	25 (19%)
Reactivations after NAD	15 / 63 (24%)	45 / 90 (50%)
Outcome (at last follow-up):		
NAD	50 (79%)	73 (54%)
AD better	-	9 ( 7%)
AD intermediate	1 ( 2%)	11 ( 8%)
AD worse	-	14 (10%)
Deaths	12 (19%)	28 (21%)
Sequelae developed after diagnosis	20 / 59 (34%)	41 / 112 (37%)
Observation time	median 7.5 yrs (4 yrs – 11 yrs 8 mo)	median 3 yrs (4 mo – 6 yrs)

**Legend:** NAD = non-active disease, AD = active disease

Even after extended analysis, however, it remained unclear whether the superiority of the DAL-HX studies was attributable to the administration of continuous steroids, to the combination of vinblastine and etoposide, or to the prolonged continuation therapy (total therapy duration of 12 months) including 6-mercaptopurine (6-MP).

#### **4.2.2.2 LCH-II Study (May 1, 1996 – March 31, 2001)**

The LCH-II study investigated the value of the addition of etoposide (Arm B) to the standard combination of prednisolone and vinblastine (Arm A) in patients with MS-LCH. The randomized trial focused on risk patients including patients with risk organ (RO) involvement (liver, spleen, hematopoietic system and lung) and patients younger than 2 years of age. The continuation therapy included 6-MP in addition to the prednisolone/ vinblastine pulses for a total treatment duration of 6 months (9).

The randomized trial for risk patients revealed similar outcomes in both treatment arms including a rapid response at week 6 (arm A vs. arm B 63% and 71%, respectively), 5-year survival probability (74% vs. 79%), reactivation frequency (46% vs. 46%) and permanent consequences (43% vs. 37%). Interestingly, patients younger than 2 years without RO involvement had a high response rate (>80%) and a

100% survival. Patients with RO involvement and non-response within 6 weeks had the highest mortality.

In contrast to the preliminary comparison between treatment arms as a whole, subsequent analysis of the subgroup of patients with RO involvement showed that complete disease resolution (NAD) was greater in arm B both within the first year (arm A 49% vs. arm B 62%) and over the entire 5-year study period ( $p<0.036$ ). Survival was also better with a 5-year pSU of 0.64 ( $\pm 0.06$ ) in arm A and 0.73 ( $\pm 0.05$ ) in arm B ( $p<0.036$ ) indicating that the 3-drug arm was associated with an improved outcome in this patient subgroup. The toxicity was similar in both arms (9).

The main lessons from the LCH-II trial were:

- The age at diagnosis <2 years is not of independent prognostic significance in multivariable analysis and, therefore, the risk group can be reliably defined by the presence of “risk organ involvement” only.
- Patients with RO involvement have a significant disease-related mortality and therapy intensification in this group is reasonable
- The overall treatment duration of 6 months in the LCH-II study resulted in a higher reactivation rate than the 12 month DAL-HX studies, despite similar initial therapy

#### **4.2.2.3 LCH- III Study (April 1, 2001 – February 6, 2008)**

The LCH III study included three separate patient groups:

- **Group 1: “Risk Group” patients (MS-LCH with risk organ involvement)**

The trial was planned before the final evaluation of LCH II and it was decided not to include etoposide due to its leukemogenic potential and the lack of benefit shown in the preliminary analyses. Based on preliminary but promising data on the beneficial effects of MTX in the DAL-HX studies, the LCH-III study was designed to test in risk patients in a randomized fashion the effect of the addition of intermediate dose (500 mg/m<sup>2</sup>) methotrexate (MTX) to the “standard arm” of vinblastine (VBL) and prednisolone (PDN) during induction, and the addition of low-dose weekly oral MTX to the “standard” continuation arm of prednisolone, vinblastine, and 6-mercaptopurine (6-MP).

A total of 489 patients with multisystem disease were enrolled on the study; 234 Risk patients were randomized between the “standard” 2-drug induction (Arm A) with

vinblastine and prednisolone (VBL/PDN) and the experimental 3-drug induction (Arm B) with addition of methotrexate (VBL/PDN/MTX). The continuation therapy consisted of PDN, VBL and 6-MP in the standard arm and of PDN, VBL, 6-MP, and MTX in the experimental arm, given for a total treatment duration of 12 months in both arms.

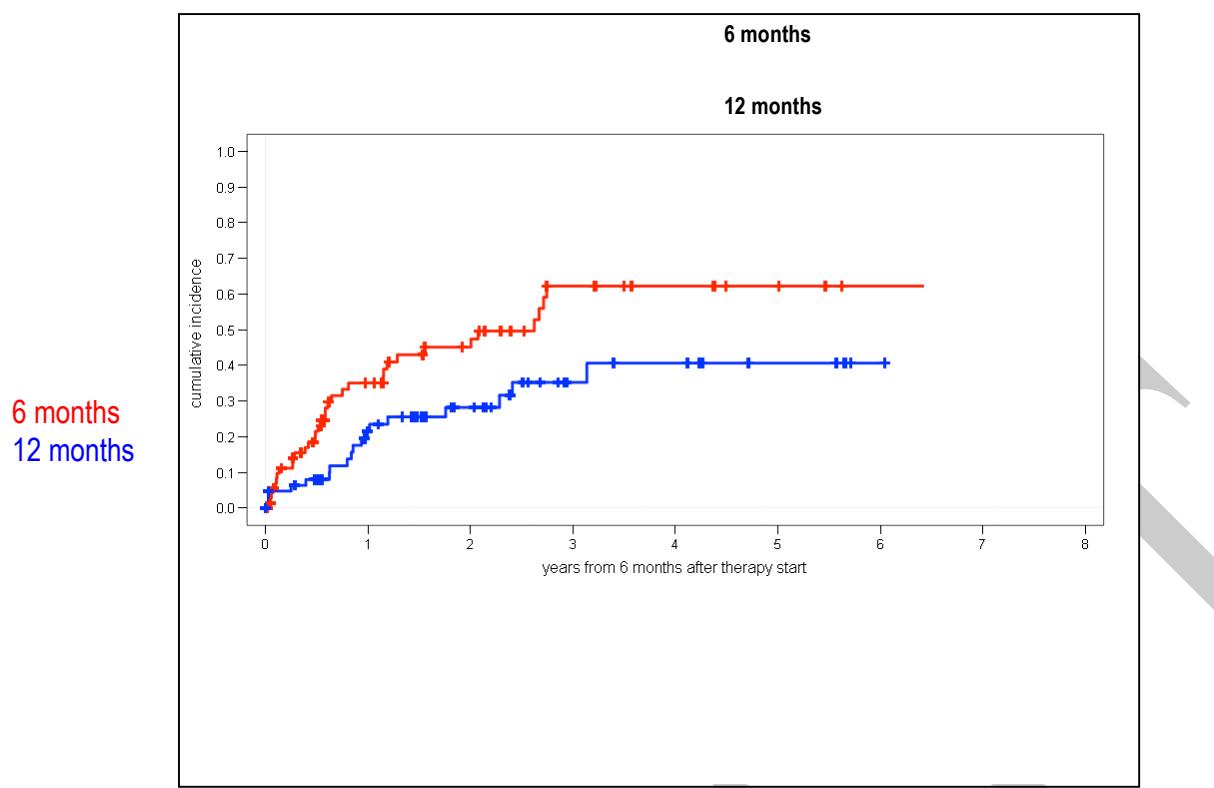
A new concept tested in LCH III was the intensification of initial therapy for patients who did not achieve a complete resolution (NAD) after 6 weeks of therapy by delivering a second course of initial therapy with an additional 6 weeks of weekly vinblastine with weekly 3-day pulses of  $40\text{mg}/\text{m}^2/\text{d}$  prednisolone. Patients who deteriorated after 6 or 12 weeks of initial therapy were switched to intensive salvage therapy without delay.

Preliminary evaluation of the LCH III results is very encouraging. Most importantly, over the past 3 trials a reduction of mortality in MS-LCH patients with risk organ involvement has been achieved, with a decline from 40% in LCH I to 30% in LCH II and 20% in LCH III. The survival estimates for patients with MS-LCH and RO involvement is almost identical in both LCH III arms, with a pSU of  $0.85 \pm 0.04$  in arm A and a pSU of  $0.82 \pm 0.04$  in arm B. Importantly, the retrospective comparison with the previous studies clearly showed that pSU in LCH III (with and without methotrexate) was superior to arm B of LCH II (with etoposide). The reasons for the superiority of LCH III remain speculative. The improved survival could be related to improved supportive care, intensification of initial therapy by the 2<sup>nd</sup> initial course, to earlier institution of more effective salvage treatment, or a combination of all three factors.

- **Group 2: “Low Risk Group” patients (MS-LCH without risk organ involvement)**

The 234 low risk patients received initial treatment with the “standard” arm. Non-responders at week 6 (AD stable and AD worse) received a second course of initial therapy with another 6 weeks of weekly vinblastine with weekly 3-day pulses of  $40\text{mg}/\text{m}^2/\text{d}$  prednisolone. Responders (NAD, AD better) were randomized between 6 months and 12 months of continuation therapy to test the effect of prolonged treatment duration on the prevention of reactivation and permanent sequelae.

One-hundred and eighty-six patients were randomized in this trial (97 to the 6-month and 89 to the 12-month treatment arm). The probability of reactivation at 3 years was significantly higher in the 6-month arm (0.50 vs. 0.35, log-rank test  $p=0.019$ ) (**Figure 1**).



**Figure 1. Risk for reactivation in the Low risk group of the LCH-III Study**

Therefore, the preliminary evaluation of the results of this trial shows a benefit from prolongation of the treatment duration. In support of this conclusion, the probability of reactivation in the “Risk Group” (both treatment arms for risk patients had total treatment duration of 12 months) was similar to the 12-month treatment arm of the “Low risk” trial (**Figure 2**).

The curves appear to have stabilized after 3-years; nonetheless, the possibility exists that the longer therapy merely delays reactivations and longer follow-up to assess the rate of reactivations and permanent consequences is necessary to answer these important questions.

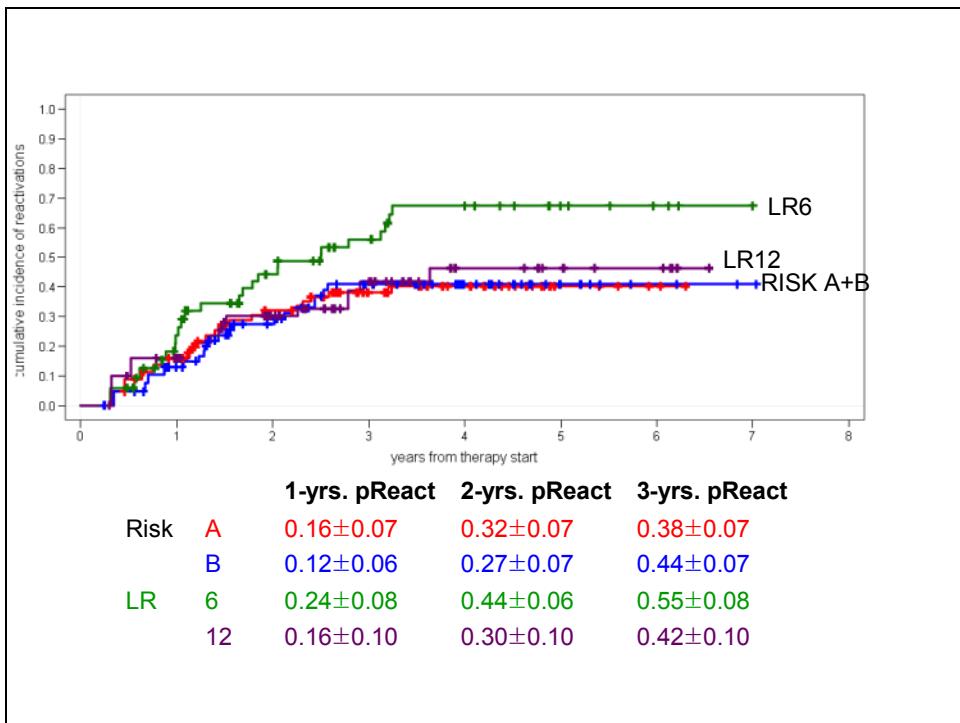


Figure 2. Risk for reactivation in patients with MS-LCH in the LCH-III Study

- **Group III: Multifocal bone disease and “special sites” (this group included patients with single-system LCH who have an indication for systemic therapy)**

LCH-III also included a stratum for patients with multifocal bone disease and so-called “special site” disease. The term “special site” was used for i) vertebral lesions with significant intraspinal soft tissue component and ii) for patients with “CNS risk lesions” i.e. lesions in the facial bones and skull base with intracranial soft tissue extension, shown to be associated with an increased risk of development of diabetes insipidus (DI) (10). To avoid risky and potentially mutilating procedures, 6 months of systemic “standard” chemotherapy was recommended for such patients, without randomization. Detailed considerations on “CNS risk” lesions are given below (see Section 4.2.4).

#### 4.2.3 Histiocyte Society’s Salvage Trials

##### 4.2.3.1 LCH-I-S

A salvage therapy trial, **LCH-I-S**, was introduced by the Histiocyte Society in 1994, in which the questions asked were whether it was possible to improve survival for MS-

LCH patients whose disease progressed on current “best” therapy, and whether it was possible to cure these patients. This salvage trial proposed a switch to bone marrow transplantation for patients with available matched sibling donor, or to immunosuppressive therapy (IST) with antithymocyte globulin, prednisone and cyclosporine (CSA) for patients without matched sibling donor (11). Due to poor patient entry this trial was closed prematurely in 1998. From the composite data available and under the conditions it was used, the only conclusion possible was that CSA is not remarkably effective in the treatment of resistant MS-LCH.

#### **4.2.3.2 LCH-S-98 Study**

LCH-S-98 was a non-randomized phase II study which evaluated the activity of 2-Chlorodeoxyadenosine (2-CdA) in patients with risk organ involvement (RO+) whose disease progressed after combination therapy with prednisolone, vinblastine and etoposide and in patients without risk organ involvement (RO-) with multiple reactivations of their disease. Forty-six RO+ and 37 RO- patients were evaluable. 2-CdA as monotherapy was significantly more effective in RO- patients with a response in 62% compared to 22% in RO+ patients. Two-year predicted survival is 48% for RO+, 97% for RO- patients, 100% for RO+ patients reactivating in non-risk organs and 67% for RO- patients reactivating in risk organs (12).

#### **4.2.3.3 Emerging salvage options**

Promising results in the treatment of patients with severe, resistant to conventional therapy MS-LCH have been recently reported for a regimen using a combination of 2-chlorodeoxyadenosine (2-CdA, Cladribin®, Leustatin®) and cytarabine (Ara-C) (13) and for hematopoietic stem cell transplantation after reduced intensity conditioning regimen (RIC-HSCT) (14). However, both reports are based on limited observations and need validation from prospective clinical trials.

#### **4.2.4 CNS-LCH Studies**

In 2000 the Histiocytose Society launched the LCH-CNS study to better characterize CNS disease and its natural course in LCH. The study proposed a uniform diagnostic and follow-up program including serial MRI-studies, repeated neurological examination with standardized tests including the EDSS (15) and the International Cooperative Ataxia Rating Scale (ICARS) (16), psychological tests and

electrophysiological studies, and collected information on the natural history and underlying pathological mechanisms of the disease and outcome of patients with CNS-LCH treated with various therapeutic regimens.

Due to the efforts of this study and some single and multi-institutional collaborative efforts it was possible to better characterize the radiological and clinical presentations of LCH-associated CNS disease and to gain better insights in its nature. CNS-LCH encompasses endocrine manifestations (e.g. diabetes insipidus, anterior pituitary dysfunction), tumorous lesions of the brain, as well as a late neurodegenerative syndrome. The last may be present only on imaging (radiographic neurodegeneration) or result in significant clinical manifestations (clinical neurodegeneration). Pathologically, tumorous lesions have been shown to be active LCH, while neurodegenerative lesions are thought to represent a cytotoxic or antigen-antibody reaction (usually lymphocytes but not LCH cells found on biopsy), or the late effects of cytokine damage.

Recent knowledge suggests that involvement of skull bones (excluding those in the calvarium) predisposes to development of DI and other CNS manifestations. In a study by Grois et al. (10) patients with MS-LCH and "craniofacial involvement" at diagnosis, in particular of the "ear," "eye," and the "oral" region carried a significantly increased risk to develop DI during their course. In a bivariate model adjusted for the extent of disease (MS-LCH vs. SS-LCH), the authors found that the influence of lesions in "ears" (RHR 1.8, P1/4 0.005), "eyes" (RHR 1.7; P1/4 0.024), and "oral cavity" (RHR 1.8; P1/4 0.007), and combined "craniofacial lesions" (RHR 1.6; P1/4 0.030) are statistically significant. This risk is augmented when the disease remains active for a longer period or reactivates (10, 17-19). Therefore, lesions involving the orbital, temporal, sphenoid, ethmoid or mastoid bones as well as the paranasal sinuses and anterior or middle cranial fossa are regarded as "CNS risk lesions" (20). The impact of such lesions on the risk of developing DI or radiologic neurodegeneration and their appropriate treatment are still a controversial issue and can only be assessed by systematic long-term follow-up studies, including MRI examinations. Therefore such studies will be requested in the upcoming LCH-IV protocol.

DI is the key symptom of hypothalamic-pituitary disease. It is usually irreversible and seen in up to 25% of all LCH patients or in up to 50% of patients with multisystem disease (18, 21-23). In up to 60% of DI patients additional anterior pituitary hormone

deficits (APD), such as growth hormone deficiency, secondary hypothyroidism, hypogonadism, and hyperprolactinemia occur (17, 18, 24, 25). On MRI of patients with DI or APD, tumorous lesions might be seen, but even in the absence of visible tumors, an infiltration in the hypothalamic pituitary region is now regarded as responsible for the usually irreversible hormone loss.

Grois et al found a remarkably high frequency (76%) of signs of radiologic neurodegeneration on MRIs of patients with DI, who had been observed for more than 5 years (26). Donadieu et al. found LCH-associated neurodegeneration in almost 10% of patients with pituitary involvement (14/145) as opposed to 0.2% in those without pituitary involvement (1/444) (17). Fahrner et al found neurodegeneration in all cases of 22 patients with pronounced hypothalamus-pituitary tumors > 6.5mm diameter (unpublished data). These observations indicate an increased risk for LCH-associated neurodegeneration in patients with hypothalamus-pituitary involvement.

The incidence of neurodegeneration in the international LCH studies is unclear as not all patients are routinely examined with MRI during their course. Those who are studied are patients with craniofacial lesions or already manifest neuroendocrine problems and actually may overrepresent the population at risk. Recent studies suggest a frequency between 20-24% of MS-LCH patients or 57% of patients studied by MRI (27-29). In a small population-based Swedish study in children with LCH, the minimal prevalence of radiological neurodegeneration was 24% among all LCH patients (including patients with single system LCH). Thus the frequency might be higher than expected and the clinical impact of the radiologic findings needs to be further determined by prospective long-term follow-up studies.

A recent long-term study on a limited number of properly assessed patients showed that neurodegenerative lesions on MRI are irreversible in all patients. The lesions could be stable over years or progressive. At least 25% of the patients with radiologic neurodegeneration develop overt clinical neuropsychological symptoms and disabilities (29, 30), defined above as clinical neurodegeneration. However, the study of Allen CE et al using vincristine/cytarabine or cytarabine alone suggests that early treatment of patients with clinical neurodegenerative disease may provide clinical improvement and reversal of MRI findings (31). In a neuropsychological study of patients with CNS-LCH verified by MRI, the vast majority have cognitive defects, most typically affecting verbal working memory and visual-spatial working memory (32).

After almost 20 years of research on CNS-LCH there are still considerable gaps in

understanding the disease process and its course. The best therapy to prevent irreversible permanent consequences like hormone loss or neuropsychological disabilities severely impairing the quality of life of affected patients is still to be determined.

### **4.3 Rationale**

Based on the data discussed above the following issues will be addressed in the LCH-IV study:

#### **4.3.1 Rationale for the First-line Treatment (Stratum I)**

Systemic therapy is indicated for disease control in all patients with MS-LCH and for a certain subgroup of patients with SS-LCH (isolated CNS-risk lesion or multifocal bone lesions). The combination of steroids and vinblastine is the standard first-line combination for patients needing systemic therapy (Stratum I).

Due to high mortality in previous studies, patients with MS-LCH and involvement of risk organs, who do not respond to 6-12 weeks of standard therapy, will be immediately switched to alternative treatment approaches (Stratum III or Stratum IV).

The LCH-III trial showed significant reduction of the reactivation rate by prolongation of treatment duration (6 vs. 12 months). Therefore, the LCH-IV study will test whether a further therapy prolongation (12 vs. 24 months) and intensification ( $\pm$  mercaptopurine) will further reduce the reactivation rate and the permanent consequences.

A need for more objective criteria for disease severity and response has been recognized. For this purpose a scoring system will be prospectively assessed in this study. The data needed for the prospective validation will be collected through the Case Report Forms of the LCH-IV Study.

#### **4.3.2 Rationale for the Second-line Treatment for non-risk LCH (Stratum II)**

The previous studies of the Histiocytosis Society (LCH I, LCH-II, and LCH-III) have contributed significantly to optimization of the treatment and care for children with LCH. However, some of the patients still do not (optimally) respond to standard treatment and a proportion of those who initially respond will eventually experience recurrence of the disease. For both these disease course scenarios prospective studies are limited and hence the optimal management remains to be established.

Stratum II of the LCH-IV Study is aimed at confirming effective treatment for patients without life-threatening disease (e.g. no involvement of risk organs such as liver, hematologic system, or spleen), who do not respond to initial standard first-line therapy (Stratum I) or experience disease reactivation after its completion. The second-line treatment has to target both efficient disease control and reduction of further reactivations and disease-related morbidity. A combination of drugs which is different from the standard first-line combination, but is comparable for its intensity and side effects will be evaluated. The individual drugs (prednisolone, vincristine, and cytosine-arabinoside) have been used in the past in different treatment concepts for MS-LCH, and even a combination of them has already been applied, although in a somewhat different schedule (33).

A uniform “intensive” 24-week course consisting of prednisolone, vincristine and cytosine-arabinoside will be introduced in Stratum II for eligible patients. It will be followed by a continuation therapy to total treatment duration of 24 months. The continuation therapy for LCH is traditionally based on repetition of pulses (steroids/vinblastine ± other drugs) and/or continuous application of oral drugs (e.g. mercaptopurine and methotrexate). Experience of the UK group suggests that indomethacin could be an acceptable non-toxic alternative to the traditional drugs, especially in non-risk patients (34, 35). According to the published evidence and the personal experience of the members of the LCH-IV Study Committee, patients eligible for a second-line therapy seem to need less intensive, but prolonged therapy. Therefore, the efficacy of indomethacin to prevent further reactivations will be tested against the “standard” mercaptopurine/ methotrexate combination in a randomized trial.

#### **4.3.3 Salvage Treatment for Risk MS-LCH (Stratum III)**

Patients with involvement of risk organs at diagnosis, and especially those who do not respond to standard treatment, have a dismal prognosis, with survival chances of less than 30% at 2 years from diagnosis (1, 7, 8, 21, 36).

However, the progression pattern of the disease is unpredictable. The disease usually retains some sensitivity to treatment, but with only partial control followed by further progression and deterioration. Many of these patients suffer profound and refractory pancytopenia and usually die from sepsis or bleeding. The serum albumin level is also profoundly decreased, related to digestive tract leak and/or to lack of production due

to liver dysfunction. Both nutritional status and an enhanced catabolic state contribute to the progressive deterioration.

Over the last 15 years, several new drugs (e.g. cyclosporine A, interferon alpha and 2-Chlorodeoxyadenosine) (12, 37-42) have been reported as being useful in the treatment of patients with LCH. Most of them were tested in individual cases or small series and unfortunately, further evaluations in a larger group of patients did not confirm initial reports. The results were especially disappointing in patients with hematological dysfunction and failure to respond to standard therapy, who represent the majority of early deaths in LCH.

New strategies for the treatment of patients with refractory LCH are therefore urgently needed. One promising strategy is a combination of 2-CdA and cytosine-arabinoside (cytarabine, Ara-C). A pilot study (13) suggests that patients with MS-LCH who fail standard therapy may respond to this combination. The main limitation of the study is the small number of patients enrolled. Nevertheless, its results are significantly better from the reported historical outcome for this group of patients. In addition, there is a good pharmacological rationale for the combination of 2-CdA and Ara-C. 2-CdA is a deoxyadenosine analogue phosphorylated by the enzyme deoxycytidine kinase (dCK), leading to the formation of 2-CdA mono-, di- and triphosphate (2-CdAMP, 2-CdADP, and 2-CdATP). These nucleotides are resistant to deoxyadenosine aminase, and their accumulation results in inhibition of DNA synthesis and cell death. 2-CdA thus has an antiproliferative effect on histiocytes and lymphocytes (43). Ara-C is a drug also phosphorylated by dCK and has been used successfully, together with vincristine and prednisolone, as first line treatment of children with disseminated LCH and organ dysfunction (33). In other in vitro and in vivo studies, pretreatment with 2-CdA resulted in increased accumulation of Ara-CTP (the active form of Ara-C) in circulating blasts from relapsed adults with refractory acute myelogenous leukemia (44).

#### **4.3.4 RIC-HSCT for Risk MS-LCH (Stratum IV)**

Despite the considerable advances made in the management of MS-LCH and the use of salvage protocols, the most considerable challenge remains the development of effective treatments for patients with refractory disease. There have been several "case-reports" reporting sustained complete remissions after myeloablative conditioning followed by hematopoietic stem cell transplantation (HSCT) (45-54). A review of the literature revealed 29 pediatric patients with risk organ involvement, who

underwent myeloablative allogeneic HSCT (14). The overall survival was 48% (14/29 patients) with exceedingly high transplant-related mortality of 45% (13/29 patients).

Reduced intensity conditioning (RIC) regimens have been developed with the aim to reduce toxicity and transplant-related mortality in pediatric patients with non-malignant disorders. Experience with this approach in children with primary immunodeficiency disorders has been published (55). Thirty-three patients with a variety of immune disorders received an unrelated donor bone marrow transplant after a reduced intensity fludarabine (FLU) and melphalan (MEL) conditioning with either anti-thymocyte globulin (ATG) or campath 1H. In this study, outcomes were compared to a retrospective control cohort of 19 patients who underwent transplantation with myeloablative conditioning between 1994 and 1998. All children in both groups had primary engraftment. There was no statistical difference in the speed of immune reconstitution or incidence of graft-versus-host disease between the 2 groups. Overall survival was significantly better in the reduced-intensity conditioning group, 31/33 (94%) patients survived, compared with 10/19 (53%) in the myeloablative conditioning group ( $P = .014$ ).

This approach has already been successfully applied to patients with refractory MS-LCH. Steiner et al reported on the experience with RIC-HCT in 9 high-risk LCH patients (14). The conditioning regimen utilized was similar to what will be used in this protocol. The conditioning regimen was well tolerated with regard to common transplant-related complications. Two patients died at 50 and 69 days after RIC-HCT. Seven out of the nine (78%) patients survived and showed no signs of disease activity (including one with non-engraftment who experienced full autologous hematopoietic recovery) after median follow-up of 390 days post-HCT. The investigators concluded that RIC-HCT is a feasible procedure with low transplant-related morbidity and mortality, which represents a very promising new approach for high-risk LCH patients that have resistant risk organ involvement.

Based on the above described experience with RIC-HCT in patients with congenital immunodeficiencies and MS-LCH, a similar approach will be offered in Stratum IV to patients with MS-LCH and risk organ involvement after front-line therapy of this protocol has failed.

It is not yet clear whether the 2-CdA/Ara-C salvage therapy (Stratum III) or RIC-HSCT (Stratum IV) is the superior approach in refractory disease in risk organs, and therefore both options will be available as part of the LCH-IV Study, depending on

physician's choice and donor availability. Patient numbers are too small to allow a randomization between there two treatment options.

#### **4.3.5 Monitoring and Treatment of isolated tumorous and neurodegenerative CNS-LCH (Stratum V)**

In addition to rare tumorous (space occupying) lesions, LCH involvement of the CNS may result in multiple endocrine deficits as well as neurodegenerative changes (ND-CNS-LCH) with cognitive, motor, and psycho-social dysfunctions that may be severe, as detailed in Section 4.2.4. While tumorous lesions usually respond to therapy, endocrine and neurodegenerative dysfunctions are typically persistent or progressive (56). Patients with ND-CNS-LCH pose a special challenge with respect to evaluation and treatment.

For patients with CNS involvement (both tumorous and neurodegenerative type) and those who are at risk for CNS involvement (e.g. bone lesions at the skull base), a uniform evaluation will be implemented.

Special regimens will be offered to patients with isolated tumorous CNS-LCH (repeated 2-CdA courses) and to patients with clinically manifested ND-CNS-LCH (+/- extracranial LCH manifestations). For the last group monotherapy with Ara-C courses or IVIG will be offered depending on physician's choice.

#### **4.3.6 Natural History and Management of "Other" SS-LCH (Stratum VI)**

Patients with SS-LCH are traditionally considered to have excellent prognosis and have no need for systemic therapy (except those fulfilling the criteria for Group 2 of Stratum I, for definition see Section 6.7.2). However, prospective studies of high quality are still lacking. In the LCH-IV study these patients will be registered in the observational Stratum VI in order to study the natural course, with special emphasis on: disease reactivation, need for systemic therapy later in the disease course, and permanent consequences.

#### **4.3.7 Long-term Follow-up (Stratum VII)**

It is well known that patients with LCH are at risk for developing permanent consequences (PC) either due to disease itself or to the applied systemic therapy. Stratum VII should encompass all patients enrolled in any of the LCH-IV study strata (I-VI) and collect prospectively in a uniform way follow-up information as long as

possible (at least 5 to 10 years). This information in turn should be correlated to specific variables (e.g. disease extend at diagnosis, lesions at certain location, intensity and duration of treatment, reactivations etc.) in order to validate known risk factors, identify further risk factors and assess the role of systemic treatment in preventing permanent disabilities.

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## 5 STUDY OBJECTIVES

### 5.1 Primary Objectives

- To investigate whether mortality in MS-LCH can be further decreased by an early switch of patients with risk organ involvement who do not respond to front-line therapy to more intensive salvage treatment (Stratum III or Stratum IV).
- To investigate in a randomized fashion whether further prolongation (12 vs. 24 months) and intensification ( $\pm$  mercaptopurine) of continuation therapy will reduce the reactivation rate and permanent consequences in MS-LCH.
- To investigate in a randomized fashion whether prolongation of continuation therapy (6 vs. 12 months) will reduce the reactivation rate and permanent consequences in SS-LCH patients with isolated “CNS-Risk” lesion or multifocal bone lesions.
- To investigate whether second-line therapy with PRED/ARA-C/VCR for 24 weeks, followed by 24 months of continuation therapy (Indomethacin vs. 6-MP/MTX) can help achieve disease resolution, prevent further reactivations and permanent consequences in patients with non-risk LCH (MS-LCH without risk organ involvement, isolated “CNS-Risk” lesion, or multifocal bone lesions), who are non-responders to first-line therapy, or experience disease progression/reactivation in non-risk organs on or off first-line therapy.
- To study whether systemic therapy with intravenous immunoglobulin (IVIG) or low dose cytarabine for patients with clinically manifest neurodegenerative CNS-LCH can achieve improvement of the neuro-psychological symptoms.
- To study the spectrum and incidence of permanent consequences in systemically treated patients, identify possible risk factors, and assess the role of systemic treatment in their prevention
- To prospectively study the natural course of SS-LCH in patients who initially are not candidates for systemic therapy, with respect to disease progression, reactivations, need for medical interventions, as well as permanent consequences, at any time after diagnosis.

### 5.2 Secondary Objectives

- To validate prospectively a new scoring system for disease activity and treatment response assessment.

- To investigate the cumulative incidence of radiographic and clinical neurodegeneration in patients with “CNS-Risk” bone lesions and endocrine deficits.
- To study the natural history of LCH in patients not needing upfront systemic therapy and the long-term consequences and quality of life of all registered (with and without systemic therapy) patients.

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## **6 DIAGNOSTIC EVALUATION AND RESPONSE ASSESSMENT**

### **6.1 Confirmation of Diagnosis**

The diagnosis of LCH is based on histological and immunohistochemical examination of lesional tissue. The main feature is the morphologic identification of the characteristic LCH cells. Additionally, positive staining of the lesional cells with CD1a and/or Langerin (CD207) is mandatory for definitive diagnosis (57-59). Since it has been demonstrated that the expression of Langerin confirms the presence of Birbeck granules (60), the previous diagnostic “gold standard”, namely ultrastructural demonstration of cytoplasmic Birbeck granules, is no longer essential.

In the case of isolated vertebra plana without a soft tissue component the risk of biopsy may outweigh the need for a tissue diagnosis. In this case the patient should be closely observed to exclude malignancy. Such cases will be eligible for the observational Stratum VI without a tissue diagnosis, but diagnostic confirmation has to be done in case of progression or reactivation at later time point, particularly if systemic therapy is indicated.

### **6.2 Pre-treatment Diagnostic Evaluation**

The pre-treatment diagnostic evaluation must include:

#### **6.2.1 Complete History**

A complete history should include special reference to: duration of symptoms, pain, swelling, skin rashes, otorrhea, irritability, fever, loss of appetite, weight loss or poor weight gain, growth failure, polydipsia, polyuria, diarrhea, changes in activity level, dyspnea, cigarette smoke exposure, behavioral and neurological changes.

#### **6.2.2 Complete Physical Examination**

The complete physical examination should include measurement of temperature, height, and weight. Special attention should be paid to pubertal status (Tanner staging), characterization of skin and scalp rashes, presence of jaundice, pallor, edema, lymphadenopathy, ear discharge, orbital abnormalities, gum and palatal lesions, dentition, soft tissue swelling, lesions on the genital and anal mucosa, tachypnea, intercostal retractions, ascites, liver and spleen size, presence of neurological signs and/or symptoms. A complete clinical evaluation should be

performed depending on disease localization and severity, as well as on individual risks. During treatment it should be performed as required by the respective treatment Stratum, and during follow-up as prescribed by Stratum VII.

### **6.2.3 Laboratory and Radiographic Evaluation**

#### **6.2.3.1 Mandatory baseline evaluation**

The investigations listed in Table III are mandatory for all patients at initial presentation, as well as at reactivation or disease progression.

**Table III: Mandatory baseline evaluation upon initial diagnosis, reactivation or progression**

**Full blood count:**

- hemoglobin, white blood cell and differential count, platelet count
- ESR

**Blood chemistry:**

- total protein, albumin, bilirubin, ALT (SGPT), AST (SGOT), alkaline phosphatase, γGT
- BUN, creatinine, electrolytes
- Ferritin

**Coagulation studies:**

- PT, APTT/PTT, fibrinogen

**Early morning urine sample:**

- Specific gravity and osmolality

**Abdominal ultrasound:**

- Size and structure of liver and spleen

**Chest radiograph (CXR)**

**Skeletal radiograph survey\***

\* functional imaging like bone scan or PET is optional and can be performed in addition to skeletal survey

### 6.2.3.2 Investigations upon specific indications

Investigations to be performed upon specific indications are summarized in

**Table IV.**

**Table IV: Laboratory investigations, imaging and special clinical assessments recommended upon specific indications**

Indication	Assessment test
<b>Risk organ involvement</b>	<ul style="list-style-type: none"> <li>HLA tissue typing</li> </ul>
<b>Bi- or pancytopenia, or persistent unexplained single cytopenia</b>	<ul style="list-style-type: none"> <li>Bone marrow aspirate &amp; trephine biopsy to exclude causes other than LCH</li> </ul>
<b>Liver dysfunction</b>	<ul style="list-style-type: none"> <li>Liver biopsy only recommended if there is clinically significant liver involvement and the result will alter treatment i.e. to differentiate between active LCH and sclerosing cholangitis</li> </ul>
<b>Lung involvement</b> (abnormal CXR or symptoms/signs suggestive for lung involvement)	<ul style="list-style-type: none"> <li>Low dose multi-detector volume-CT if available is preferable to high resolution computed tomography (HR-CT) of the lungs</li> <li>Lung function test (if age appropriate)</li> </ul>
<b>Abnormal lung CT AND findings not characteristic for LCH or suspicion for atypical infection*</b>	<ul style="list-style-type: none"> <li>Bronchoalveolar lavage (BAL), &gt;5% CD1a-positive cells in BAL fluid is diagnostic in non-smokers</li> <li>Lung biopsy (if BAL not diagnostic)</li> </ul>
<b>Suspected craniofacial bone lesions including maxilla and mandible</b>	<ul style="list-style-type: none"> <li>MRI of head**</li> <li>CT could be considered in addition, if needed for better view of skeletal lesions</li> </ul>
<b>Suspected vertebral lesions</b>	<ul style="list-style-type: none"> <li>MRI of spine (to exclude spinal cord compression and evaluate soft tissue masses)</li> </ul>
<b>Visual or neurological abnormalities</b>	<ul style="list-style-type: none"> <li>MRI of head*</li> <li>Neurology assessment</li> <li>Neuropsychometric assessment</li> </ul>
<b>Suspected endocrine abnormality (i.e. short stature, growth failure, polyuria, polydipsia, hypothalamic syndromes, precocious or delayed puberty) and/or Imaging abnormality of hypothalamus/ pituitary</b>	<ul style="list-style-type: none"> <li>Endocrine assessment (including water deprivation test and dynamic tests of the anterior pituitary)</li> <li>MRI of head*</li> </ul>
<b>Aural discharge or suspected hearing impairment/mastoid involvement</b>	<ul style="list-style-type: none"> <li>Formal hearing assessment</li> <li>MRI of head*</li> <li>CT of temporal bone</li> </ul>
<b>Unexplained chronic diarrhea, failure to thrive or evidence of malabsorption</b>	<ul style="list-style-type: none"> <li>Endoscopy and biopsy</li> </ul>

\* In case of verified LCH in other organs, biopsy is indicated **ONLY** if the pulmonary findings on CT are inconsistent with LCH or atypical infection is suspected

\*\*MRI of head has to be performed according to the uniform Guidelines specified in Section 12.6.2.1

### 6.3 Diagnostic Evaluation During Treatment and at Follow-up

The evaluation and the respective intervals and time points during therapy can vary depending on disease severity and treatment, and are therefore specified in the Roadmaps of each therapeutic Stratum (see Appendix A-IV).

The long-term follow-up evaluation scheme after end of systemic treatment is specified in Stratum VII (Section 14). The evaluation scheme is based on the assumption that patients have non-active disease (NAD) at the time being included in Stratum VII. In the case of complaints, signs and/or symptoms suggesting disease reactivation a basic evaluation as described in Section 6.2 has to be performed.

### 6.4 Definition of Organ Involvement

#### 6.4.1 Risk organs

The definition of risk organs in the LCH-IV protocol is different from that of the previous study, since **lung** will no longer be considered a **risk organ**. The reason is the frequent association of pulmonary involvement with involvement of other risk organs, the low relative hazard ratio in a multivariate analysis, and last but not least, the very difficult and subjective evaluation of disease activity and therapy response in this organ.

A patient is considered to have risk organ involvement if at least one of the risk organs is involved. The current definition of involvement of the risk organs is presented in **Table V**.

**Table V: Definition of Risk Organ Involvement**

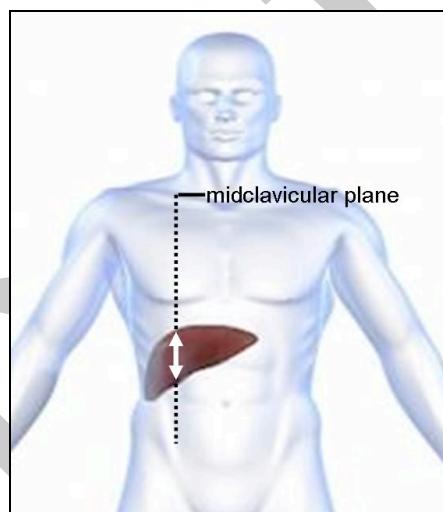
<b>Hematopoietic involvement:</b> (with or without bone marrow involvement*)	<b>At least 2 of the following:</b> <ul style="list-style-type: none"> <li>• <b>anemia:</b> hemoglobin &lt;100 g/L (&lt;10 g/dL), infants &lt;90 g/L (&lt;9.0 g/dL), not due to other causes e.g. iron deficiency</li> <li>• <b>leukocytopenia:</b> leukocytes &lt;4.0 x10<sup>9</sup>/l (4,000/<math>\mu</math>L)</li> <li>• <b>thrombocytopenia:</b> platelets &lt;100 x10<sup>9</sup>/l (100,000/<math>\mu</math>L)</li> </ul>
<b>Spleen involvement:</b>	<ul style="list-style-type: none"> <li>• <b>enlargement</b> &gt;2 cm below costal margin in the midclavicular line**</li> </ul>
<b>Liver involvement:</b>	<ul style="list-style-type: none"> <li>• <b>enlargement</b> &gt;3 cm below costal margin in the midclavicular line** and/or</li> <li>• <b>dysfunction</b> (i.e. hypoproteinemia &lt;55 g/L, hypoalbuminemia &lt;25 g/L, not due to other causes and/or</li> <li>• <b>histopathological findings</b> of active disease</li> </ul>

\*Bone marrow involvement is defined as presence of CD1a positive cells on marrow slides. The clinical significance of marrow CD1a positivity is still unclear. Hemophagocytosis may be prominent in severe progressive cases prominent hemophagocytosis, as well as hypocellularity, myelodysplasia or myelofibrosis may be found.

\*\* Enlargement in **cm below the costal margin** as assessed by palpation is used for definition of organ involvement. *Sonographic measurements of liver and spleen as defined below will be collected for prospective evaluation, but will not be considered for definition of liver and spleen enlargement in this protocol.*

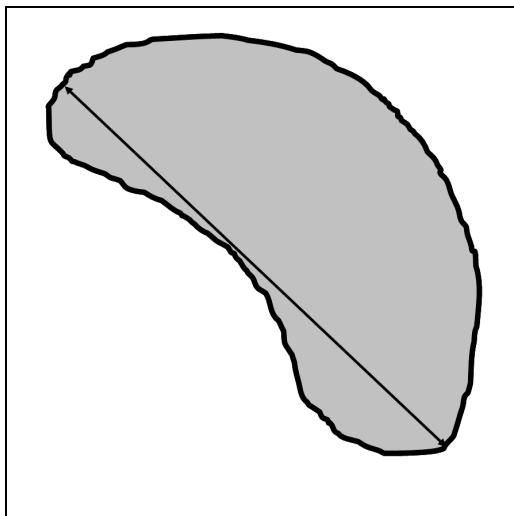
### **Guidelines for standardized sonographic measurement of the longitudinal dimension of liver and spleen:**

- Liver measurement is to be performed with convex transducer in a subject lying in the supine position. Longitudinal dimension has to be obtained in the right midclavicular plane. The upper margin of the liver is defined as the uppermost edge under the dome of the diaphragm, whereas the lower margin is defined as the lowermost edge of the lobe (Figure 3).



**Figure 3. Measurement the longitudinal dimension of the liver**

- Spleen measurement is to be performed with convex transducer in a subject lying in the supine or slightly right lateral decubitus position (the hilum has to be optimally visualized). Longitudinal size measurement is to be performed between the most superomedial and the most inferolateral points of the spleen in a coronal section passing through the splenic hilum (Figure 4).



**Figure 4.** Measurement the longitudinal dimension of the spleen

The reference values for the sonographic measurements of the liver and spleen longitudinal size depending of body height and age according to Konus et al. (61) are presented in **Table VI** and **Table VII**.

**Table VI: Longitudinal Dimensions of Right Lobe of Liver vs. Height and Age according to Reference (61)**

Subjects		Longitudinal dimensions [mm] of right lobe of liver							
Body height [cm]	Age range [mo]	Mean	SD	Minimum	Maximum	Percentile		Suggested limits of normal	
		5th	95th	Lower	Upper				
47-64	1-3	64	10.4	45	90	48	82	40	90
54-73	4-6	73	10.8	44	92	53	86	45	95
65-78	7-9	79	8.0	68	100	70	90	60	100
71-92	12-30	85	10.0	67	104	68	98	65	105
85-109	36-59	86	11.8	69	109	63	105	65	115
100-130	60-83	100	13.6	73	125	77	124	70	125
110-131	84-107	105	10.6	81	128	90	123	75	130
124-149	108-131	105	12.5	76	135	83	128	75	135
137-153	132-155	115	14.0	93	137	95	136	85	140
143-168	156-179	118	14.6	87	137	94	136	85	140
152-175	180-200	121	11.7	100	141	104	139	95	145

**Table VII: Longitudinal Dimensions of Spleen vs. Height and Age according to Reference (61)**

Subjects		Longitudinal dimensions [mm] of spleen							
Body height [cm]	Age range [mo]	Mean	SD	Minimum	Maximum	Percentile		Suggested limits of normal	
		5th	95th	Lower	Upper				
48-64	1-3	53	7.8	33	71	40	65	30	70
54-73	4-6	59	6.3	45	71	47	67	40	75
65-78	7-9	63	7.6	50	77	53	74	45	80
71-92	12-30	70	9.6	54	86	55	82	50	85
85-109	36-59	75	8.4	60	91	61	88	55	95
100-130	60-83	84	9.0	61	100	70	100	60	105
110-131	84-107	85	10.5	65	102	69	100	65	105
125-149	108-131	86	10.7	64	114	70	100	65	110
137-153	132-155	97	9.7	72	100	81	108	75	115
143-168	156-179	101	11.7	84	120	85	118	80	120
152-175	180-200	101	10.3	88	120	88	115	85	120

#### **6.4.2 Non-Risk organ involvement**

##### **6.4.2.1 Lung involvement**

Lung involvement in patients with verified LCH is defined by computer tomography (HR-CT or in small children preferably low dose multi-detector volume-CT).(62) Histopathological confirmation is obligatory in patients with isolated pulmonary LCH.

In a case of verified LCH in other organs, biopsy is indicated only if the radiological pulmonary findings are considered atypical or inconsistent with LCH.

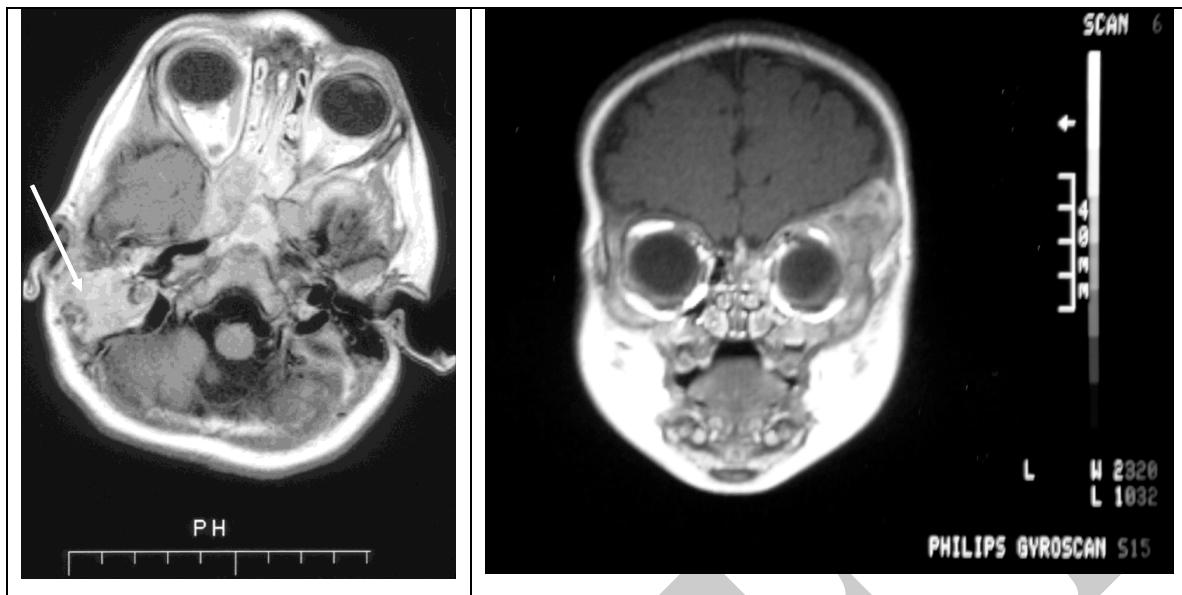
##### **6.4.2.2 Single system (SS) LCH lesions of the skeleton indicating systemic therapy**

The following categories have been defined due to the need for systemic therapy (all other patients with SS-LCH will be treated with local therapies or followed without treatment):

###### **6.4.2.2.1 Isolated “CNS-risk” lesion**

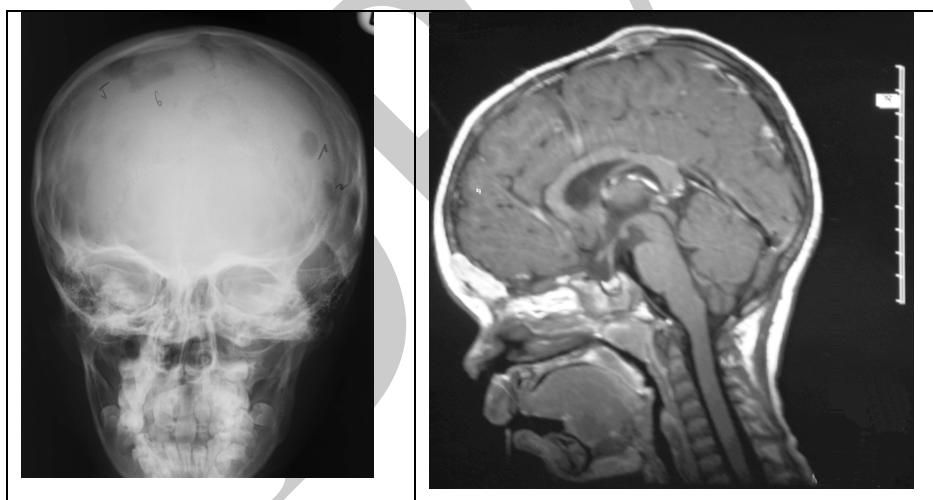
This category was coined for isolated lesions in one of the craniofacial bones (i.e. orbit, temporal bone, mastoid, sphenoid, zygomatic, ethmoid, maxilla, paranasal sinuses, or cranial fossa) with or without intracranial soft tissue extension (Figure 5). Systemic therapy for effective disease control is considered important, due to the

increased risk for diabetes insipidus and neurodegenerative CNS-LCH (10).



**Figure 5 Example of CNS-risk lesions**

*Lesions in the calvarium (frontal, parietal, and occipital bone) are not considered as “CNS-risk” lesions (Figure 6).*



**Figure 6. Example of non-CNS-risk lesions**

#### **6.4.2.2.2 Multifocal bone disease:**

Multifocal bone (MFB) LCH is defined as two or more lesions in two or more different bones. The rare occurrence of two lesions within one anatomical bone is considered as a single lesion.

### **6.4.2.3 Central Nervous System LCH (CNS – LCH)**

#### **6.4.2.3.1 Neurodegenerative CNS-LCH (ND-CNS-LCH)**

- **Radiological neurodegeneration**

The **radiological neurodegeneration** requires the detection of typical signal changes (63) on 2 consecutive MRI scans performed within an interval of at least 3 months. For classification of severity see Section 12.6.2.1.2.

- **Clinical neurodegeneration**

**Clinical neurodegeneration** is defined as the presence of acquired neurological deficits (EDSS, International Cooperative Ataxia rating scale ICARS, Movement ABC-2, see 10.6.2.2) or neuropsychological deficits (Full Scale IQ, Verbal IQ or Performance IQ, or both Verbal and Visual-Spatial Working Memory Functions below 1 SD for age) in the context of consistent radiological findings.

#### **6.4.2.3.2 Isolated tumorous CNS-LCH**

Tumorous lesions of the CNS are defined as space-occupying lesions involving brain structures. Any of the following brain regions may be involved either by isolated lesions or in the context of multisystem disease: hypothalamic-pituitary region (HPR), pineal gland, meninges or choroid plexus.

***This definition excludes dural enhancement caused by a skull lesion, as often seen in skull vault lesions.***

Patients with isolated tumorous CNS-LCH will be treated in Stratum V (for details refer to Section 0) and those who have such lesions in the context of MS-LCH will be treated according to Stratum I (initially) or Stratum II (in the setting of a reactivation).

## **6.5 Response Evaluation**

### **6.5.1 Definition of disease state**

Disease state categories to be used in LCH-IV study are summarized in Table VIII.

**Table VIII: Disease state categories**

Main Category	Sub-categories	Definition
NON ACTIVE DISEASE (NAD)		Resolution of all signs/ symptoms (no evidence of disease)
ACTIVE DISEASE (AD)		
Better	Regressive disease	Regression of signs/ symptoms, no new lesions
Stable	Stable disease	Persistence of signs or symptoms, no new lesions
Worse	Progressive disease*	Progression of signs or symptoms and/or appearance of new lesions

\* Progression of skeletal lesions is defined as unequivocal enlargement of the size of existing lesions and/or appearance of new lesions

### 6.5.2 Response categories

Assessment of disease response is based on the three categories of response: Better, Intermediate and Worse (**Table IX**). They express a comparison of a current disease state to that at the last previous evaluation and are mandatory for therapeutic decisions!

**Table IX: Definition of response categories**

Response category	Definition
BETTER	<ul style="list-style-type: none"> <li>• Complete disease resolution (NAD)</li> <li>• Regression (AD better)</li> </ul>
INTERMEDIATE	<ul style="list-style-type: none"> <li>• Stable (unchanged)</li> </ul>
WORSE	<ul style="list-style-type: none"> <li>• Progression*</li> </ul>

\* Progression of skeletal lesions is defined as unequivocal enlargement of the size of existing lesions and/or appearance of new lesions; in patients with risk organ involvement the overall response (and hence the therapeutic decision) depends on response in risk organs.

For evaluation of severity and response in neurodegenerative CNS LCH (ND-CNS-LCH), please refer to Section 12.

## 6.6 Clinical Classification of LCH

The clinical classification of LCH is presented in Table X

Lymph-node involvement is counted as separate organ involvement, except for the draining lymph-nodes of bone or skin lesions.

A bone lesion with contiguous soft tissue involvement is considered as a single lesion.

**Table X: Clinical classification of LCH**

Disease categories:	Definitions:
<b>Single System LCH (SS-LCH)</b>	<b>One organ/system involved (uni- or multifocal):</b> <ul style="list-style-type: none"> <li>• Bone unifocal (single bone) or multifocal (&gt;1 bone)</li> <li>• Skin</li> <li>• Lymph node (not the draining lymph node of another LCH lesion)</li> <li>• Lungs</li> <li>• Central nervous system</li> <li>• Other (e.g. thyroid, thymus)</li> </ul>
<b>Multisystem LCH (MS-LCH)</b>	<b>Two or more organs/systems involved</b> With or without involvement of “Risk Organs” (e.g. hematopoietic system, liver, spleen)

## 6.7 Stratification for the First-Line Therapy

Patients with indication for systemic therapy are stratified at diagnosis into two groups:

### 6.7.1 GROUP 1 – Multisystem LCH

- Two or more organs/systems involved, with or without involvement of “Risk Organs” (e.g. hematopoietic system, liver, or spleen)

### 6.7.2 GROUP 2 –Single-system LCH

- isolated “CNS-risk” lesion
- multifocal bone lesions (MFB)

## 7 OVERALL TREATMENT CONCEPT

The LCH-IV is an international, multicenter, prospective clinical study for pediatric LCH (age < 18 years).

All patients will be enrolled through a “Registration and Stratification” Step. Depending on stratification and indication for treatment at the next step the patients will be assigned to the following Strata:

- **STRATUM I:** First-line therapy for patients with MS-LCH (Group 1) and patients with SS-LCH (isolated CNS-risk or multifocal bone lesions) (Group 2). Treatment includes randomized comparisons in both Groups
- **STRATUM II:** Second-line treatment for non-risk LCH. Treatment includes randomized comparison of two continuation treatment regimens.
- **STRATUM III:** Salvage treatment for risk LCH
- **STRATUM IV:** RIC-HSCT for risk LCH
- **STRATUM V:** Monitoring and Treatment of isolated tumorous and neurodegenerative CNS-LCH
- **STRATUM VI:** Natural history and management of “other” SS-LCH not eligible for stratum I group 2
- **STRATUM VII:** Long-term follow-up

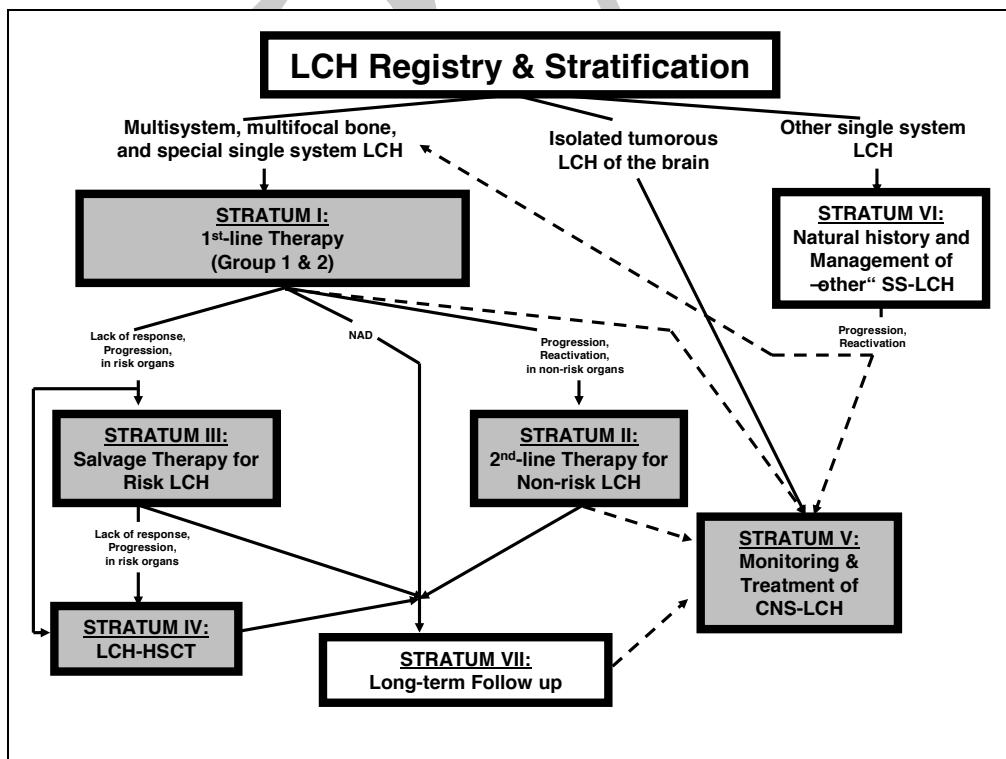


Figure 7. Overall concept for newly diagnosed patients with LCH

Patients may be enrolled in multiple strata sequentially as dictated by the course of their disease. Treatment on any stratum requires a separate enrollment process, including provision of informed consent at the time of each enrollment, regardless of prior enrollments on LCH-IV. The only exception will be the long-term follow-up stratum, to which all eligible patients (i. completed therapy, ii. complete disease resolution, and iii. signed consent) will be automatically assigned (consent for long-term follow up will be obtained at enrollment to any other stratum) regardless of previous treatment.

In addition to the above therapeutic or observational strata, all patients are eligible for optional biological studies.

DRAFT

## 8 STRATUM I: FIRST-LINE TREATMENT

### 8.1 Study Hypothesis

- Prolongation and intensification of the continuation therapy will reduce the cumulative incidence of reactivations in children with LCH.

### 8.2 Study Endpoints

#### 8.2.1 Primary endpoint

- Reactivation-free survival (please refer to Section 8.9.3.1)

#### 8.2.2 Secondary endpoints

For both groups, secondary aims are the investigation of following secondary endpoints:

- Overall survival
- Incidence of permanent consequences
- Toxicity of treatment
- The proportion of patients alive and free of disease without permanent consequences
- Cumulative incidence of reactivations in risk organs

### 8.3 Eligibility Criteria and Enrollment

#### 8.3.1 Eligibility criteria

- Age

Patients must be less than 18 years of age at the time of diagnosis.

- Diagnosis

Patients must have histological verification of the diagnosis of Langerhans cell histiocytosis according to the criteria described in Section 6.1

- Prior therapy

No prior systemic therapy for LCH

- Signed informed consent form

#### 8.3.2 Exclusion criteria

- Pregnancy (patients of child-bearing age must be appropriately tested before

**All drugs given in Group 1 and 2 of Stratum I of the LCH-IV Study are non-investigative medical products<sup>52</sup>**

chemotherapy)

- LCH-related permanent consequences (e.g. vertebra plana, sclerosing cholangitis, lung fibrosis, etc.) in the absence of active disease
- Prior systemic therapy

### **8.3.3 Enrollment procedures**

- **IRB Approval**

Approval from appropriate regulatory administrations (e.g. national or institutional IRB) is required of each participating institution prior to accrual of patients. A copy of the official approval document must be sent to the National Coordinator (will be kept there and must be available for monitoring, audits, and inspections).

- **Informed consent**

The parents or the legal guardians of the patients must sign a written informed consent, which has to be kept in the patient's records. The respective entry (checkbox) in the clinical trial database has to be performed.

- **Enrollment**

Enrollment will be managed through the **web-based central clinical trial database** on <https://www.hs-lch-database.org> (for detailed instructions see **Appendix A-I\_2**).

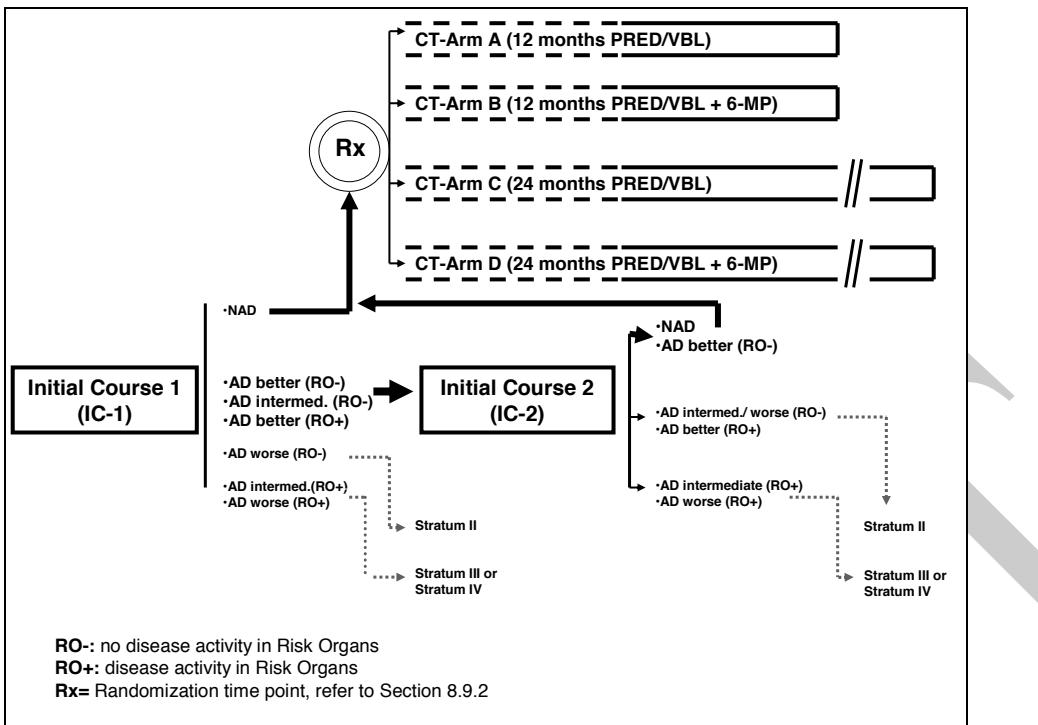
***Enrollment by paper Case Report Forms could be exceptionally granted only by the National Coordinator, who will have to enter the data into the database by himself.***

## **8.4 First-Line Therapy**

The treatment plans for Group 1 (MS-LCH) and Group 2 (SS-LCH) will be separately described.

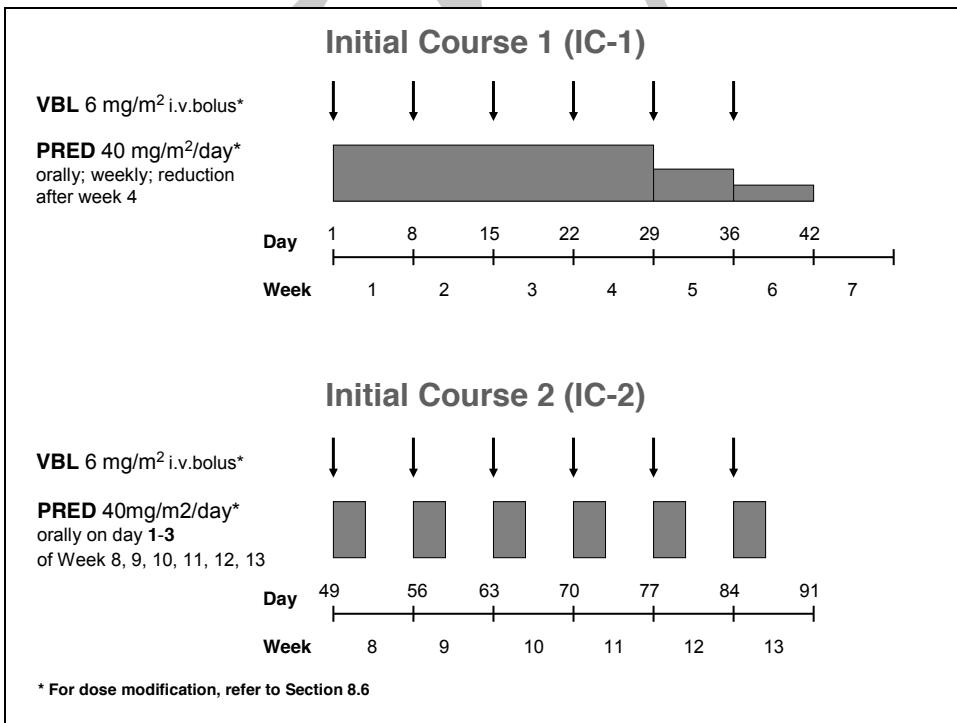
### **8.4.1 First-Line therapy for Group 1 (MS-LCH)**

The overall therapy plan for Group 1 is presented in **Figure 8**.



**Figure 8.** Stratum I: Overall therapy plan for Group 1 (MS-LCH)

#### 8.4.1.1 Group 1: Initial Treatment



**Figure 9.** Stratum I: Initial Course 1 (IC-1) and Initial Course 2 (IC-2)

#### 8.4.1.1.1 Initial Course 1 (IC-1)

IC-1 is presented on **Figure 9**. It consists of:

- Continuous oral prednisone (PRED) 40mg/m<sup>2</sup> daily in three divided doses for 4 weeks, tapering over a period of 2 weeks.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 of weeks 1, 2, 3, 4, 5, 6.

(For dose modification refer to **Section 8.6**)

*There will be a one week break in treatment after IC-1 whatever the next treatment step, allowing for the response assessment at week 6.*

**Further therapy depends on Response at week 6:**

⇒ Patients with NAD proceed to **Continuation therapy**.

⇒ Patients with **AD better** or **intermediate** in **non-risk organs** and those with **AD better in risk organs** proceed to **Initial Course 2**

⇒ Patients with AD **worse in non-risk organs** proceed to **STRATUM II**

⇒ Patients with **AD intermediate** or **worse in risk organs**, proceed to **STRATUM III** or **STRATUM IV** depending on physician's choice and donor availability.

#### 8.4.1.1.2 Group 1: Initial Course 2 (IC-2)

IC-2 is presented on Figure 9. It consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses for 3 days every week, weeks 8-13.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 of week 8, 9, 10, 11, 12, and 13.

(For dose modification refer to **Section 8.6**)

**Further therapy depends on Response at week 13:**

⇒ Patients with NAD and those with AD better in non-risk organs proceed to **Continuation therapy**.

⇒ Patients with AD intermediate or worse in non-risk organs, and those with AD better

in risk organs, proceed to **STRATUM II**

⇒ Patients with AD intermediate or worse in risk organs, proceed to **STRATUM III** or **STRATUM IV** depending on physician's choice and donor availability.

#### **8.4.1.2 Group 1: Continuation Therapy**

Patients who have NAD after Course 1 (week 6) and those who have NAD or AD better in non-risk organs after Course 2 (week 13) are eligible for continuation therapy and will be randomly assigned to one of the arms A-D.

The randomization will be performed on-line through the remote data-base (<https://www.hs-lch-database.org>).

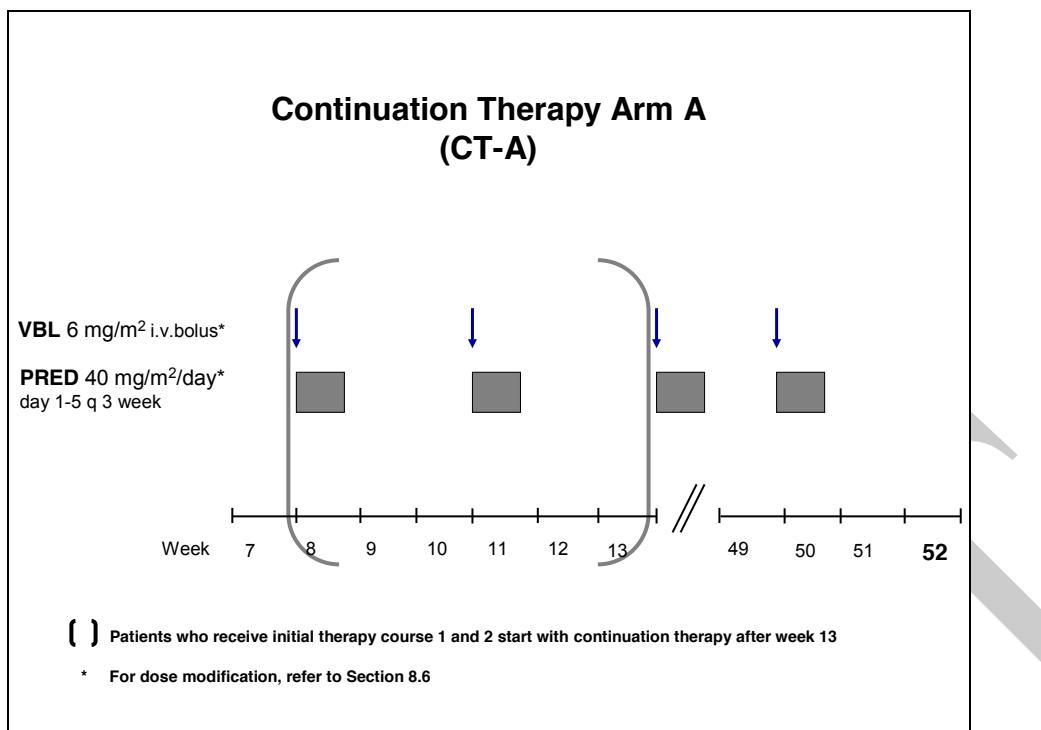
##### **8.4.1.2.1 Continuation therapy Arm A**

Continuation therapy starts at week 8 or 14 as stated above and lasts for total therapy duration of **12 months** (calculated from start of the Initial Course 1).

Continuation Arm A (**Figure 10**) consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses, day 1-5 q 3 weeks, starting at day 1 of week 8 or 14.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 q 3 weeks, starting at day 1 of week 8 or 14.

(For dose modifications refer to Section 8.6)



**Figure 10. Stratum I: Continuation therapy Arm A (CT-A) for Group 1**

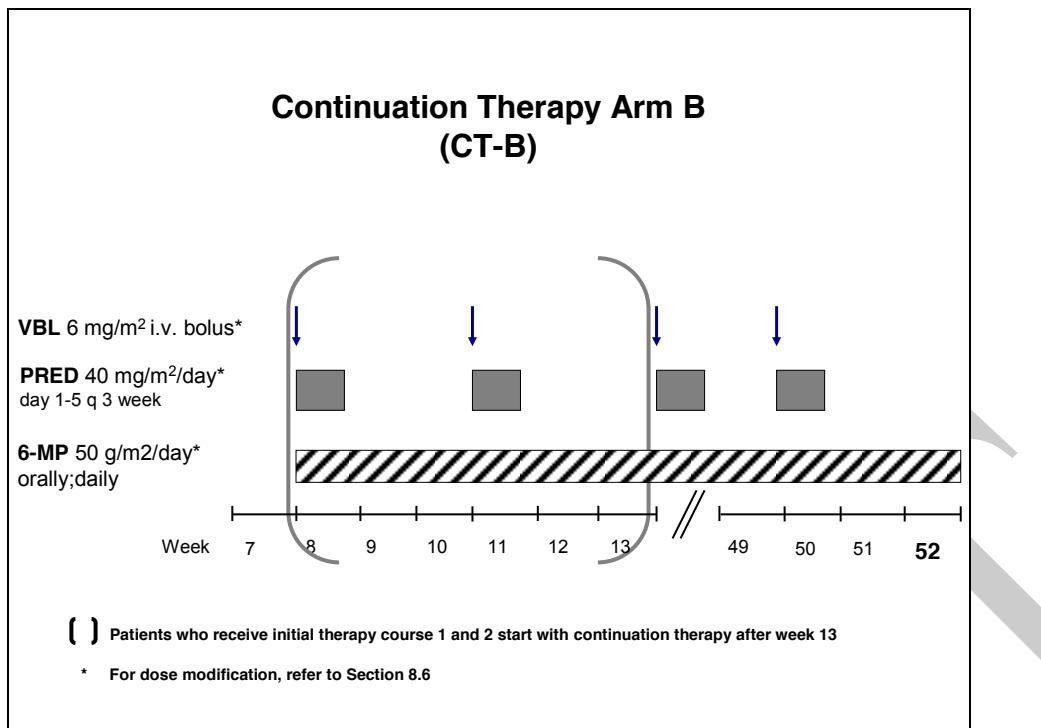
#### 8.4.1.2.2 Continuation therapy Arm B

Continuation therapy starts at week 8 or 14 as stated above and lasts for a total therapy duration of **12 months** (calculated from start of the Initial Course 1).

Continuation Arm B (**Figure 11**) consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses, day 1-5 q 3 weeks, starting at day 1 of week 8 or 14.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 q 3 weeks, starting at day 1 of week 8 or 14.
- Continuous oral mercaptopurine (6-MP) 50mg/m<sup>2</sup> daily, starting at day 1 of week 8 or 14.

*(For dose modifications refer to Section 8.6)*



**Figure 11.** Stratum I: Continuation therapy Arm B (CT-B) for Group 1

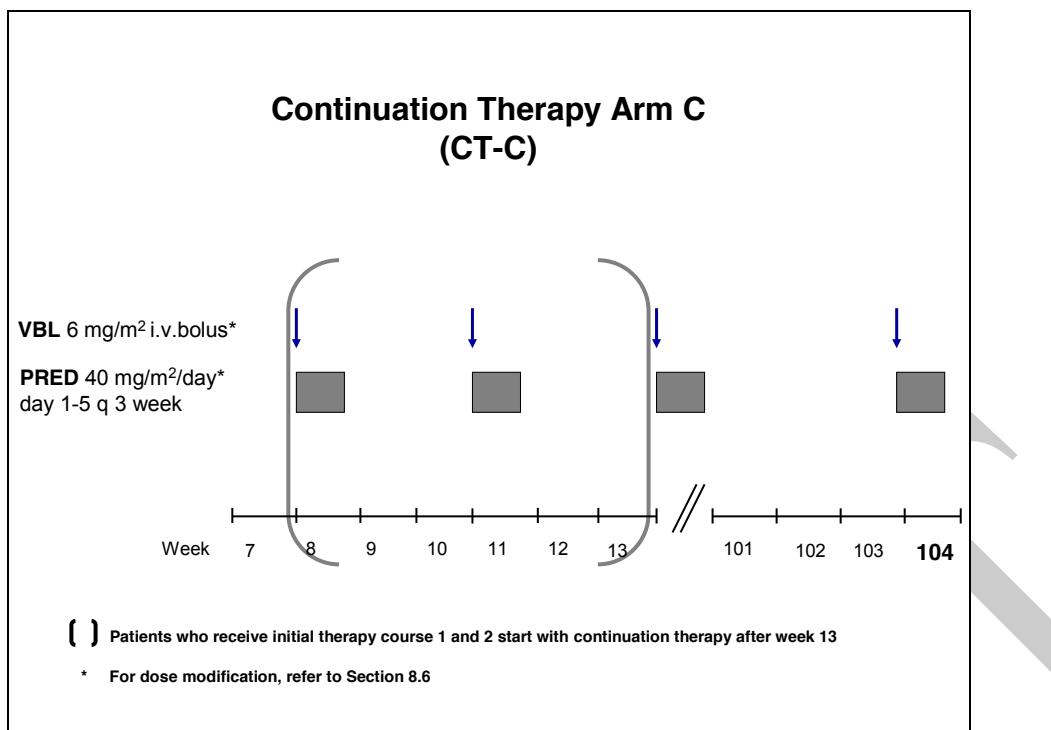
#### 8.4.1.2.3 Continuation therapy Arm C

Continuation therapy starts at week 8 or 14 as stated above and lasts for total therapy duration of **24 months** (calculated from start of the Initial Course 1).

Continuation Arm C (**Figure 12**) consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses, day 1-5 q 3 weeks, starting at day 1 of week 8 or 14.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 q 3 weeks, starting at day 1 of week 8 or 14.

(For dose modifications refer to **Section 8.6**)



**Figure 12. Stratum I: Continuation therapy Arm C (CT-C) for Group 1**

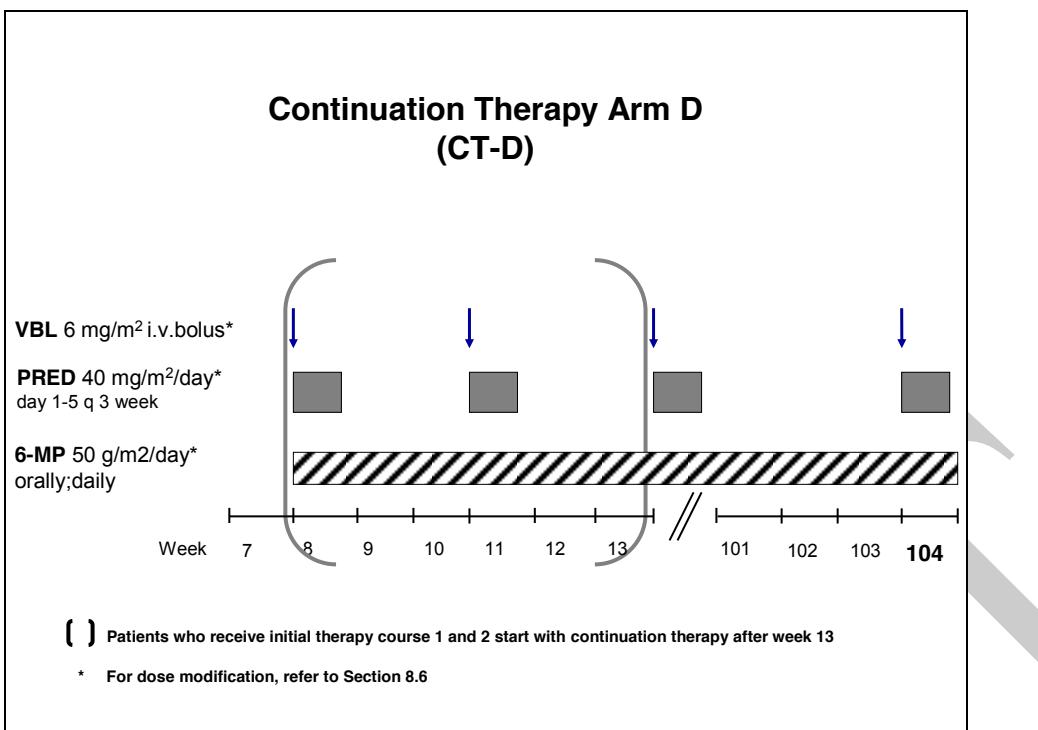
#### 8.4.1.2.4 Continuation therapy Arm D

Continuation therapy starts at week 8 or 14 as stated above and lasts for total therapy duration of **24 months** (calculated from start of the Initial Course 1).

Continuation Arm D (**Figure 13**) consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses, day 1-5 q 3 weeks, starting at day 1 of week 8 or 14.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 q 3 weeks, starting at day 1 of week 8 or 14.
- Continuous oral mercaptopurine (6-MP) 50mg/m<sup>2</sup> daily, starting at day 1 of week 8 or 14.

*(For dose modifications refer to Section 8.6)*



**Figure 13. Stratum I: Continuation therapy Arm D (CT-D) for Group 1**

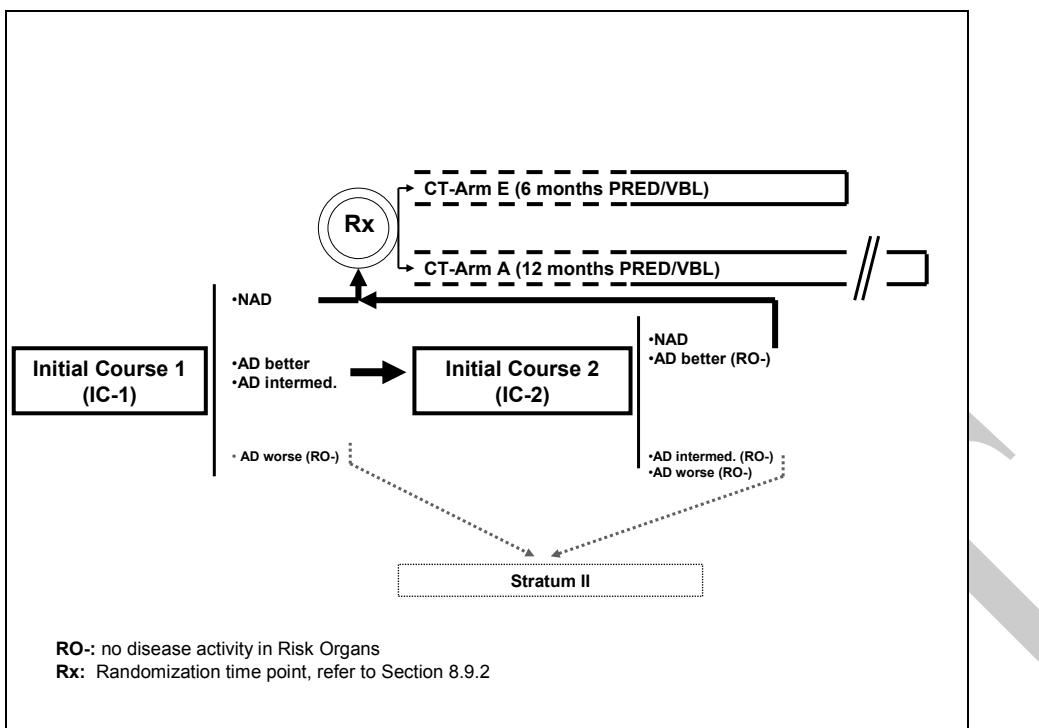
#### 8.4.1.3 Evaluation of disease activity and therapy response in Group 1

Please refer to the respective Road-map (Appendix A\_IV). The Road-maps are intended for use by the treating physicians (can be printed out, put into the patients charts and used for documentation of the therapy).

#### 8.4.2 First Line therapy for Group 2: SS-LCH (patients with isolated “CNS-risk” or multifocal bone lesions)

The overall therapy plan for Group 2 is presented in **Figure 14**.

Initial course 1 (IC-1) and Initial Course 2 (IC-2) for patients assigned to Group2 are identical to those used in Group 1.



**Figure 14. Stratum I: Overall therapy plan for Group 2 (SS-LCH with isolated “CNS-Risk” or multifocal bone lesions)**

#### 8.4.2.1 Group 2: Initial treatment

##### 8.4.2.1.1 Group 2: Initial Course 1 (IC-1)

This course is identical to Initial course 1 (IC-1) in Group 1 (**Figure 9**):

IC-1 consists of:

- Continuous oral prednisone (PRED)  $40\text{mg}/\text{m}^2$  daily in three divided doses for 4 weeks, tapering over a period of 2 weeks.
- Vinblastine (VBL)  $6\text{mg}/\text{m}^2/\text{dose}$  i.v. bolus on day 1 of weeks 1, 2, 3, 4, 5, 6.

(*For dose modifications refer to Section 8.6*)

***There will be a one week break in treatment after IC-1 whatever the next treatment step, allowing for the response assessment at week 6.***

Further therapy depends on Response at week 6:

⇒ Patients with NAD proceed to **Group 2 Continuation therapy**.

⇒ Patients with **AD better** or **intermediate** proceed to Initial treatment **Course 2**

⇒ Patients with AD worse **in non-risk organs**, proceed to **STRATUM II**

⇒ Patients who develop risk organ involvement under systemic therapy (very unlikely scenario) have to proceed to **STRATUM III** or **STRATUM IV** depending on physician's choice or donor availability. Please discuss such unusual SS-LCH cases with your National Coordinator.

#### **8.4.2.1.2 Group 2: Initial Course 2 (IC-2)**

This course is identical to Initial Course 2 (IC-2) in Group 1 (see **Figure 9**):

IC-2 consists of:

- Oral prednisone (PRED)  $40\text{mg}/\text{m}^2$  in three divided doses for 3 days every week, weeks 8-13.
- Vinblastine (VBL)  $6\text{mg}/\text{m}^2/\text{dose}$  i.v. bolus on day 1 of week 8, 9, 10, 11, 12, and 13.

(*For dose modifications refer to Section 8.6*)

Further therapy depends on Response at week 13:

⇒ Patients with NAD and those with AD better proceed to **continuation therapy**.

⇒ Patients with AD intermediate or worse in non-risk organs, proceed to **STRATUM II**.

⇒ Patients who develop risk organ involvement under systemic therapy (very unlikely scenario) have to proceed to **STRATUM III** or **STRATUM IV** depending on physician's choice or donor availability. Please discuss such unusual SS-LCH cases with your National Coordinator.

#### **8.4.2.2 Group 2: Continuation therapy**

Patients who are NAD after Course 1 (week 6) and those who are NAD or AD better after Course 2 (week 13) are eligible for continuation therapy and will be randomly assigned to the arms A and E.

The randomization will be performed on-line through the remote data base (<https://www.hs-lch-database.org>).

##### **8.4.2.2.1 Group 2: Continuation therapy Arm A**

Continuation therapy starts at week 8 or 14 as stated above and lasts for total therapy duration of **12 months** (calculated from start of the Initial Course 1).

This course is identical to Arm A of Group 1 (**Figure 10**) and consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses, day 1-5 q 3 weeks, starting at day 1 of week 8 or 14, respectively.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 q 3 weeks, starting at day 1 of week 8 or 14, respectively.

(*For dose modifications refer to Section 8.6*)

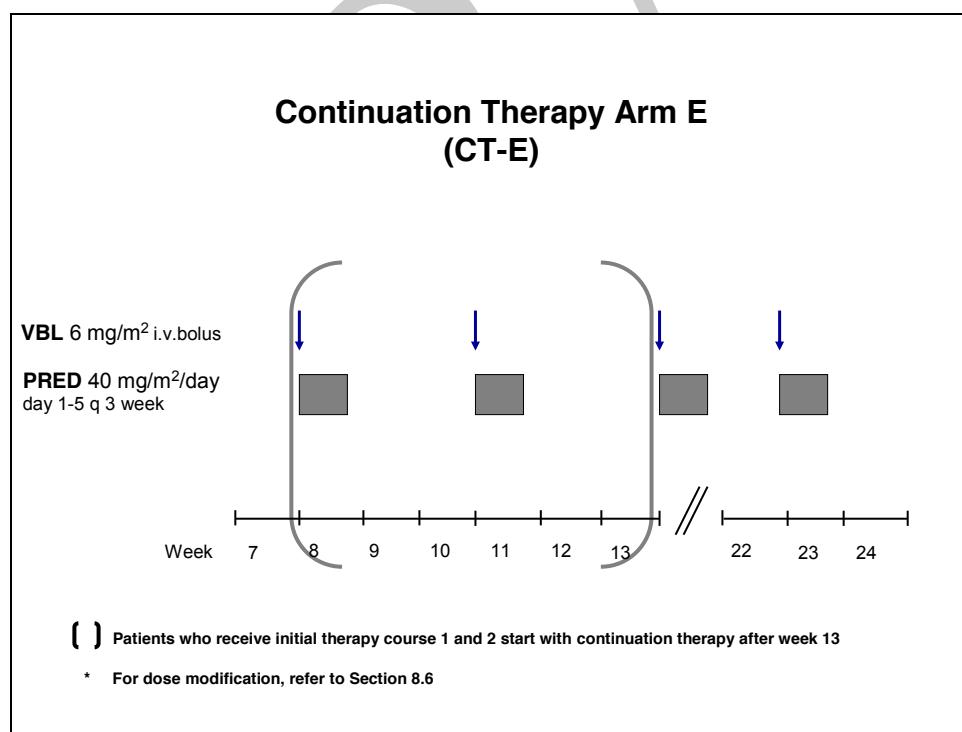
#### 8.4.2.2.2 Group 2: Continuation therapy Arm E

Continuation therapy starts at week 8 or 14 as stated above and lasts for total therapy duration of **6 months** (calculated from start of the Initial Course 1).

This treatment arm is presented on (**Figure 15**) and consists of:

- Oral prednisone (PRED) 40mg/m<sup>2</sup> in three divided doses, day 1-5 q 3 weeks, starting at day 1 of week 8 or 14, respectively.
- Vinblastine (VBL) 6mg/m<sup>2</sup>/dose i.v. bolus on day 1 q 3 weeks, starting at day 1 of week 8 or 14, respectively.

(*For dose modifications refer to Section 8.6*)



**Figure 15. Stratum I: Continuation therapy Arm E (CT-E) for Group 2**

#### **8.4.2.3 Assessment of disease activity and therapy response in Group 2**

**Please refer to the respective Road-map (Appendix A\_IV). The Road-maps are intended for use by the treating physicians (can be printed out, put into the patients charts and used for documentation of the therapy).**

### **8.5 Criteria for Removal From Protocol Therapy and Off-Study Criteria**

#### **8.5.1 Criteria for Removal from Protocol Treatment**

- Progressive disease
- Excessive toxicity
- Diagnosis of a malignant neoplasm
- Refusal of further protocol therapy by patient/ parent/ guardian
- Completion of planned therapy
- Physician determines it is in patient's best interest

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

#### **8.5.2 Off-Study Criteria**

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission

### **8.6 Dose Modifications**

#### **8.6.1 Dose modifications for age and body weight**

**For children weighing less than 10 Kg:**

Prednisone (PRED): 1.3 mg/Kg/day in three divided doses

Vinblastine (VBL): 0.2 mg/Kg/dose

6-mercaptopurine (6-MP): 1.7 mg/Kg/day in a single dose

#### **8.6.2 Dose modifications for toxicity**

##### **Prednisone**

- Hypertension:

Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to

their potential prohemorrhagic effect.

- Hyperglycemia:

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

- Pancreatitis:

Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain >72 hours and  $\geq$  Grade 3 amylase elevation ( $\geq$  2.0x ULN)).

- Varicella:

Steroids should be held during active infection. Do not hold during incubation period following exposure.

- Inability to use oral doses:

Substitute IV methyl-prednisolone at 80% of the oral prednisone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is converted in the liver to prednisolone.

- Severe infection:

Do not hold or discontinue steroids during Induction without serious consideration.

- Severe psychosis:

Steroid dose may be reduced by 50%.

### **Vinblastine**

Please use the modified “Balis” scale for grading peripheral neuropathy in children (**Appendix A-V\_1**).

Following dose reduction is suggested:

- **Severe neuropathic pain (Grade 3 or greater):**

Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated.

- **Vocal Cord paralysis:**

Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated.

- **Foot Drop, paresis:**

Should be Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vinblastine and/or

lowering the dose may not result in rapid resolution of symptoms and may compromise cure.

- **Jaw pain:**

Treat with analgesics; do not modify vinblastine dose.

- **Hyperbilirubinemia**

Direct Bilirubin		Dose reduction
[μmol/L]	[mg/dL]	
< 53.0	< 3.1	FULL dose
53.0-85.5	3.1-5.0	50%
85.6-103.0	5.1-6.0	75%
>103	> 6.0	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

- **Constipation or ileus (≥ Grade 3) or typhlitis:**

Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms **abate resume at 50% dose and escalate to full dose as tolerated.**

### **6-mercaptopurine (6-MP)**

- **Hematologic toxicity:**

If absolute neutrophil count (ANC) falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ) or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ), 6-MP will be held until recovery above these levels.

For the first drop in ANC or platelets, resume chemotherapy at 100% after ANC is  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ). If ANC falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ), or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ) for a second time, discontinue doses until ANC is  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets are  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ). Restart 6-MP at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided ANC remains  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets remain  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ).

If ANC falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ) or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ) on  $\geq 2$  occasions, thiopurine pharmacology testing should be considered. Should therapy be withheld for myelosuppression or elevated transaminases, do not "make up" that week. Resume therapy at the correct point, chronologically.

- **Hepatic toxicity:**

For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin every 4 weeks as long as transaminases remain over 5x ULN. Continue full dose therapy unless either of the following occurs:

- 1) Direct bilirubin >34.2 µmol/L (>2.0 mg/dL)
- 2) SGPT/ALT or SGOT/AST > 20x ULN (consistent with Grade 4 toxicity) on two determinations at least one week apart.

If either of these occurs, hold 6-MP and monitor labs (as above) weekly. Restart therapy at full dose when the transaminase is less than 5x ULN and bilirubin is normal.

If liver dysfunction persists sclerosing cholangitis should be considered and excluded and alternative therapy should be considered.

## **8.7 Supportive Care**

### **8.7.1 Gastric protection**

Gastric protection concomitant to steroids is recommended. H-2 inhibitors (e.g. Ranitidine), proton pump blockers (e.g. Omeprazole), or Sucralfate could be used depending on local preferences.

### **8.7.2 Pneumocystis jiroveci prophylaxis**

Oral sulphamethoxazole/trimethoprim, 5 mg/kg/day of the trimethoprim, divided into 2 doses/day, on 3 days per week (or per local protocol) is recommended throughout the study period and for 12 weeks thereafter.

### **8.7.3 Antiemetics**

Antiemetics according to local practices should be given as necessary.

### **8.7.4 Transfusions of packed red blood cells and platelets**

Blood cell components should be filtered and irradiated (>25 Gy) for prevention of GvHD according to local practice.

### **8.7.5 G-CSF**

In case of prolonged neutropenia, G-CSF may be given subcutaneously or intravenously. The use of GM-CSF is discouraged.

### **8.7.6 Intravenous immunoglobulin**

Intravenous immunoglobulin may be given upon discretion of the treating physician in cases of hypoimmunoglobulinemia.

## **8.8 Drug Information**

The drug information leaflets of all drugs used in the LCH-IV Study are provided in alphabetical order in **Appendix A-VI**.

## **8.9 Statistical Considerations**

The International LCH-IV Study Management Center in Vienna will carry out all analyses for Stratum I. The results will be sent to the Data Safety Monitoring Committee (DSMC) of the Histiocyte Society for an independent review after the interim-analyses and at least three weeks before a meeting of the Study Management Group (SMG).

### **8.9.1 Statistical design for the First Line protocol**

#### **8.9.1.1 Group 1 (MS-LCH)**

The design of this randomized clinical trial is 2x2 factorial, aiming to investigate two research questions:

- The role of the prolongation of continuation therapy from a total treatment duration of 12 months to 24 months
- The role of the addition of continuous oral 6-mercaptopurine (6-MP) on the rate of patients, who will survive without reactivation of disease (= cured individuals).

#### ***Rationale of the study design for Group 1***

In the LCH-III study 12 months of therapy proved to be superior to 6 months of therapy. The LCH-IV Study aims to investigate whether a further prolongation of therapy will result in an additional reduction of the reactivation rate.

In the LCH-III study 6-MP was given to patients with risk organ involvement at initial evaluation; patients without risk organ involvement did not receive 6-MP. The impact of 6-MP on the reactivation rate has never been investigated prospectively and thus, is still unclear.

The factorial design allows to:

- Evaluate, whether the addition of 6-MP influences the reactivation rate
- Ensure that the LCH-III reference arm is included in LCH-IV for both, patients with and without risk organ involvement.

Although 6-MP has been previously given to patients with risk organ involvement only, it is not anticipated that there is an interaction between risk organ involvement and 6-MP use with respect to occurrence of LCH reactivations.

In addition, it is not expected, that there will be an interaction between treatment duration and the addition of 6-MP.

The primary aim of this study is to investigate the main effect, i.e. the average effect of treatment duration on one hand, and the role of 6-MP on the other hand. In a secondary analysis, the investigation of interaction between treatment duration and 6-MP will be investigated.

### **8.9.1.2 Group 2 (SS-LCH)**

This randomized clinical trial with 2 arms aims to investigate

- the impact of prolongation of total treatment duration from 6 months to 12 months on the rate of patients, who will survive without reactivation of disease (= cured individuals).

## **8.9.2 Randomization**

### **8.9.2.1 Eligibility for Randomization**

#### **Group 1 MS-LCH**

- 1) A response “NAD” after Initial Course 1 (Week 7), or “NAD” or “AD Better” in non-risk organs after Initial Course 2 (Week 13). This means that at the time-point for randomization the patient has no more risk organ involvement. Hence, patients with residual RO involvement are not eligible for this randomization and will accordingly proceed to Stratum II, Stratum III, or Stratum IV.
- 2) signed informed consent for randomization

#### **Group 2 SS-LCH (isolated tumorous CNS lesion or multifocal bone lesions)**

- 1) A response “NAD” after Initial Course 1 (Week 7), or “NAD” or “AD

"Better" after Initial Course 2 (Week 13).

- 2) signed informed consent for randomization

### **8.9.2.2 Randomization time-point**

**For both Group 1 and Group 2:**

- at week 7 (after Initial Course 1)
 

or
- at week 13 (after Initial Course 2), but not later than at week 15 after therapy start

### **8.9.2.3 Randomization procedure**

The randomization will be managed through the **web-based central clinical trial database** on <https://www.hs-lch-database.org> for detailed instruction see **Appendix A-I\_3.**

The randomization will be done by random permuted blocks stratified according to

- National group
- The Application of Initial Course 2
- Age at diagnosis ( $\leq 2$  years vs.  $> 2$  years)  
and for Group 1 additionally
- Risk-organ involvement at diagnosis/ initial evaluation

### **8.9.3 Aims and endpoints**

#### **8.9.3.1 Primary end-points and hypothesis**

For Group 1 and Group 2, the primary end-point is the reactivation free survival.

**Reactivation free survival** is defined as the time from randomization to reactivation or death. Patients without events are censored at their last follow-up evaluation.

If the null hypothesis is true, the rate of patients, who survived without reactivation are equal. If the alternative hypothesis is true, there is a difference between the two arms in terms of reactivation-free survival. The primary aim of the study is a reduction of the reactivation rate.

The study aim is not reached, if treatment extends the period of non-active disease without an influence on the proportion of patients with reactivation (with other words just postpones reactivations but does not reduce their rate).

### 8.9.3.2 Secondary aims and endpoints

Besides the secondary endpoints defined in 6.2.2, for Group 1 (factorial design) an additional secondary aim is the investigation of interactions between

- treatment duration and the addition of 6-MP
- risk-organ involvement at diagnosis and addition of 6-MP

and to study the impact of treatment on reactivation times in uncured individuals.

### 8.9.4 Analyses

Analyses of the primary and secondary endpoints will be done according to the intention-to-treat principle, i.e. the patients will be analyzed in their allocated treatment group, even in case of non-compliance or protocol violations.

The statistical analyses of the primary endpoint will be done with a two-sided significance level of 5%. The statistical analyses of the secondary endpoints are exploratory. In addition to the intention-to-treat analyzes a secondary per protocol analyses will be done including all patients who were treated according to the originally assigned treatment arm without protocol violations.

#### 8.9.4.1 Analysis approach to the primary endpoints

Reactivation (or progression) in any organ and death will be considered as events for the calculation of Reactivation Free Survival. The interval will start at randomization.

The reactivation free survival rate will be estimated according to the method of Kaplan-Meier and confidence intervals according to Dorey and Korn (64) will be given.

The primary statistical evaluation of the treatment effect will be done with a proportional hazard mixture cure model with a logistic link function for the proportion of cured individuals, i.e. survivors without reactivations (65, 66).

The primary analysis will be done adjusted for age-group, the addition of the initial course 2, national group and for Group 1 initial risk organ involvement.

For Group 1, the main effects for the assigned treatment, i.e. assigned treatment duration and the whether or not the patient is randomized to receive 6-MP are included in the model. This analysis is based on the assumption, that there is no interaction between the interventions, in other words, the effect of treatment duration on the reactivation rate is similar in patients with and without 6-MP.

#### **8.9.4.2 Analysis approach to the secondary endpoints**

The cure models separately address the secondary question whether a prolonged therapy or the addition of 6-MP can slow down the speed of reactivation.

The overall survival time will be calculated from the date of randomization to death or the last response evaluation. The proportion of survival will be estimated by the method of Kaplan Meier. Comparison of arms will be done by Cox regression analysis. The cumulative incidence of permanent consequences will be calculated from the date of randomization to the diagnosis of permanent consequences. Deaths without permanent consequences will be considered as competing events. For all other censored patients the interval will be calculated until the date of the last response evaluation. For the comparison of treatment arms patients with permanent consequences which are already present at therapy start will not be considered in the analysis. For the statistical evaluation, the model according to Fine and Gray will be used (67).

The proportion of patients with severe organ toxicity (WHO score grade III-IV) within the first 12 weeks of treatment will be compared with Fisher's exact test.

For Group 1, in a secondary analysis, appropriate interaction terms between

- 1) treatment duration and the addition of 6-MP
- 2) risk-organ involvement at diagnosis and 6-MP will be included in the cure model.

#### **8.9.5 Power Consideration**

Monte Carlo methods are used to estimate the statistical power.

##### **8.9.5.1 Group 1**

According to our previous experience 100 MS-patients/year are anticipated. 65-70 patients will respond to initial treatment course 1 and 2 and be eligible for randomization. With a randomization rate of 85-90%, we expect that 55-65 randomizations/year will be performed.

Based on the LCH-III experience, the estimated event rate (reactivations and deaths) with 12 months of continuation therapy without 6-MP is 40%.

With 400 randomized patients and a minimum follow-up of 2 years, the study is able to demonstrate main effects with odds ratios of 0.5 with a power of 80% or more (Monte-Carlo simulations).

### **8.9.5.2 Group 2**

According to our previous experience, we expect that 50-60 randomization/year will be performed.

Based on the LCH-III experience, the estimated event rate (reactivations and deaths) with 6 months of continuation therapy without 6-MP is again 40%.

With 400 randomized patients, the study is able to demonstrate effects with odds ratios of 0.5 with a power of 80% or more (Monte-Carlo simulations).

### **8.9.6 Interim-analysis**

The primary aims of the two trials will be monitored according to a group sequential plan.

In addition to the final analysis, one interim-analysis will be done after 4 years. Early stopping will be implemented to retain the null hypotheses (68) and the study will be stopped if the upper limit of the 95% CI for the OR is below the targeted treatment effect of 2. In case, this boundary is crossed for one of the two randomized questions (i.e. therapy length or the addition of 6-MP), the randomization for this question will be stopped, however the randomization will continue for the other question.

Simulation studies showed that this approach will have a limited influence on type-I error rates and power.

### **8.9.7 Stopping Rules**

#### **8.9.7.1 Group 1**

In LCH-III all patients with risk-organ involvement at diagnosis received 6-MP during continuation treatment. In this population, about 15% of the patients will have a reactivation in risk-organs within 2-years after start of continuation treatment.

We wish to avoid continuation therapy without 6-MP in MS-patients with risk-organ involvement, if the rate of reactivations in risk organs or death is inferior for patients without 6-MP. Thus, stopping rules for the rate of reactivation in risk organs or death will be implemented:

Annually a Log-Rank test will be used to compare the patients randomized to receive or not receive 6-MP. This analysis will be performed six times during the course of the trial at annual intervals. A group sequential design according to Pocock will be applied.

With this approach the power to detect a difference of 20-25% will be near 80%.

The event-rates (reactivations in risk organs or death) will be monitored continuously and this will be implemented in the remote data entry system. The cumulative years of follow-up are calculated from date of randomization to the current date. Therefore reactivations, particularly those in risk organs have to be reported immediately. This is needed to be able to judge on event rates correctly.

#### **8.10 Consent Forms**

For consent forms refer to **Appendix A-VII\_1**

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## **9 STRATUM II: SECOND LINE TREATMENT FOR NON-RISK LCH**

### **9.1 Aims**

To achieve disease resolution, prevent/reduce further reactivations and/or permanent consequences in patients without risk organ involvement, who fail first-line therapy or have a reactivation after completion of first-line therapy.

### **9.2 Study Endpoints for Second Line treatment (Stratum II)**

#### **9.2.1 Primary endpoint**

- Reactivation-free survival (for definition please refer to 8.9.3.1, page 69)

#### **9.2.2 Secondary endpoints**

- To determine the response rate to the combination of prednisone, vincristine and cytarabine
- The proportion of patients alive and free of disease without permanent consequences (e.g. diabetes insipidus, anterior pituitary dysfunction, radiological or clinical neurodegeneration)
- To describe treatment-related toxicities
- To compare reactivation rates after continuation treatment with Indomethacin vs. 6-MP/MTX.

### **9.3 Eligibility Criteria and Enrolment for Second Line treatment (Stratum II)**

#### **9.3.1 Eligibility criteria**

Patients of Stratum I who have:

- Progressive disease (AD worse) in non-risk organs after 6 weeks (Initial Course 1)
- AD intermediate or worse in non-risk organs or AD better in risk organs after 12 weeks (Initial Course 2)
- Disease progression (AD worse) in non-risk organs at any time during continuation treatment
- Active disease at the end of Stratum I treatment

- Disease reactivation in non-risk organs at any time after completion of Stratum I treatment

### 9.3.2 Exclusion Criteria

- Patients with progressive disease in risk organs
- Permanent consequences (e.g. sclerosing cholangitis, lung fibrosis, etc.) without evidence of active LCH in the same organ or in any other locations
- No written consent of the patient or his/her parents or legal guardian

### 9.3.3 Enrollment procedure

- **IRB Approval of LCH-IV study protocol**

Approval from appropriate regulatory administrations (e.g. national or institutional IRB) is required of each participating institution prior to accrual of patients. A copy of the official approval document must be sent to the National Coordinator (will be kept there and must be available for monitoring, audits, and inspections).

- **Informed consent**

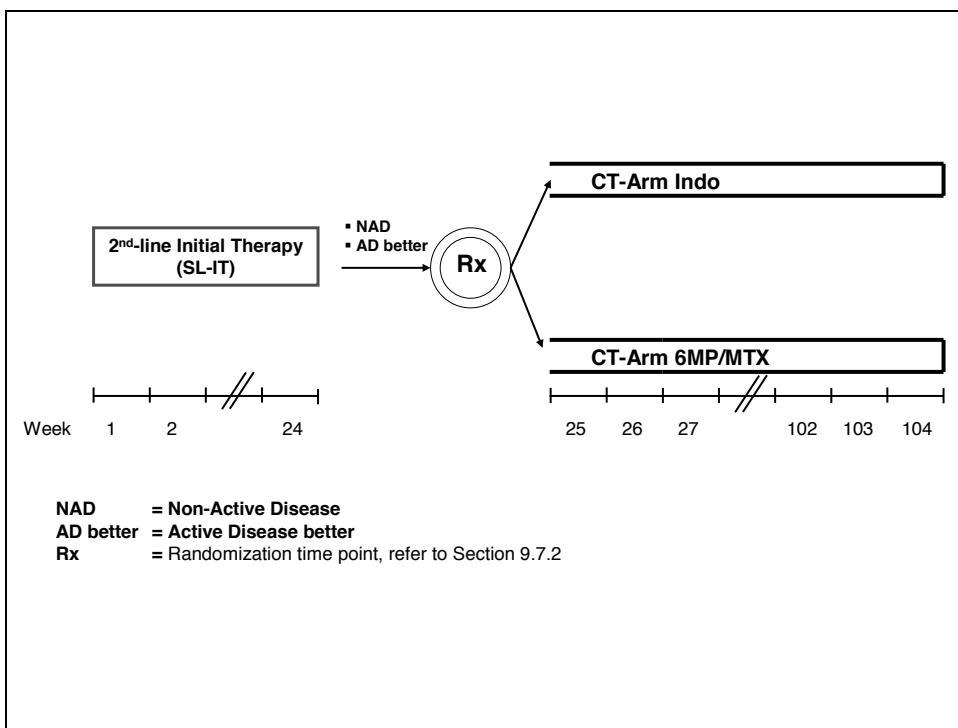
The parents or the legal guardians of the patients must sign a written informed consent, which has to be kept in the patient's records. The respective entry (checkbox) in the clinical trial database has to be performed.

- **Enrollment**

**Enrollment will be managed through the web-based central clinical trial database on <https://www.hs-lch-database.org> (for detailed instructions see Appendix A-1\_2).** Enrolment by paper Case Report Forms could be exceptionally granted by the National Coordinator, who will have to enter the data into the database by himself.

## 9.4 Stratum II: Treatment Plan

The overall treatment plan for patients enrolled to Stratum II is presented on **Figure 16**. All patients will receive a 24-week initial course (SL-IT). After this course response assessment will be performed. Those who have responded (NAD and AD better) will be randomly assigned to one of the two continuation arms (Indomethacin vs. Mercaptopurine/Methotrexate) and treated to total treatment duration of 2 years.



**Figure 16.** Stratum II: Overall therapy plan

#### 9.4.1 Second-line Initial Therapy (SL-IT)

The 24-week SL-IT is presented on **Figure 17**. It consists of:

- Prednisone (PRED) 40mg/m<sup>2</sup>/d orally in three doses, daily for 2 weeks, tapering over a period of 6 weeks.
- Cytosine-arabinoside (Ara-C) 100mg/m<sup>2</sup>/dose as an i.v. push for 4 days on weeks 1, 4, 7, 10, 13, 16, 19, 22. **Ara-C can be given subcutaneously without need for dose adjustment.**
- Vincristine (VCR) 1.5mg/m<sup>2</sup>/dose (max. 2.0mg) as an i.v. push on day 1 of weeks 1, 4, 7, 10, 13, 16, 19, 22.

(For dose modifications refer to **Section 9.4.3**)

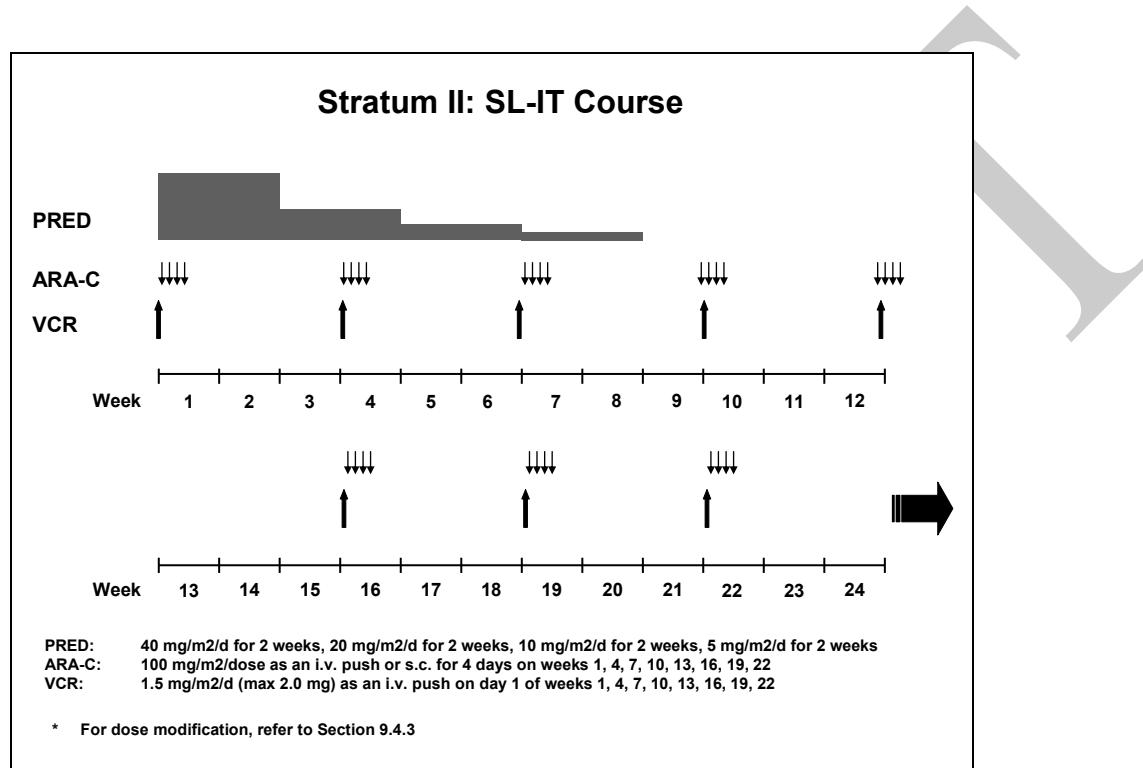
**Response evaluation at week 13:** Treatment discontinuation and switch to another treatment only in case of unequivocal progression (new lesions or unequivocal enlargement of the size of existing lesions). All other patients have to continue the protocol treatment according to Stratum II.

**Response evaluation at week 24:** Patients with NAD and AD Better will be randomized for the continuation treatment. In the case of AD Intermediate (no changes in bone lesions since six months) verification of disease activity has to be

performed by functional imaging (PET) and/or biopsy.

In the case of active disease alternative options should be discussed with the National Coordinator.

In case of AD Worse (disease progression or reactivation) at any time after week 13 the patient will be off study and alternative options should be discussed with the National Coordinator.

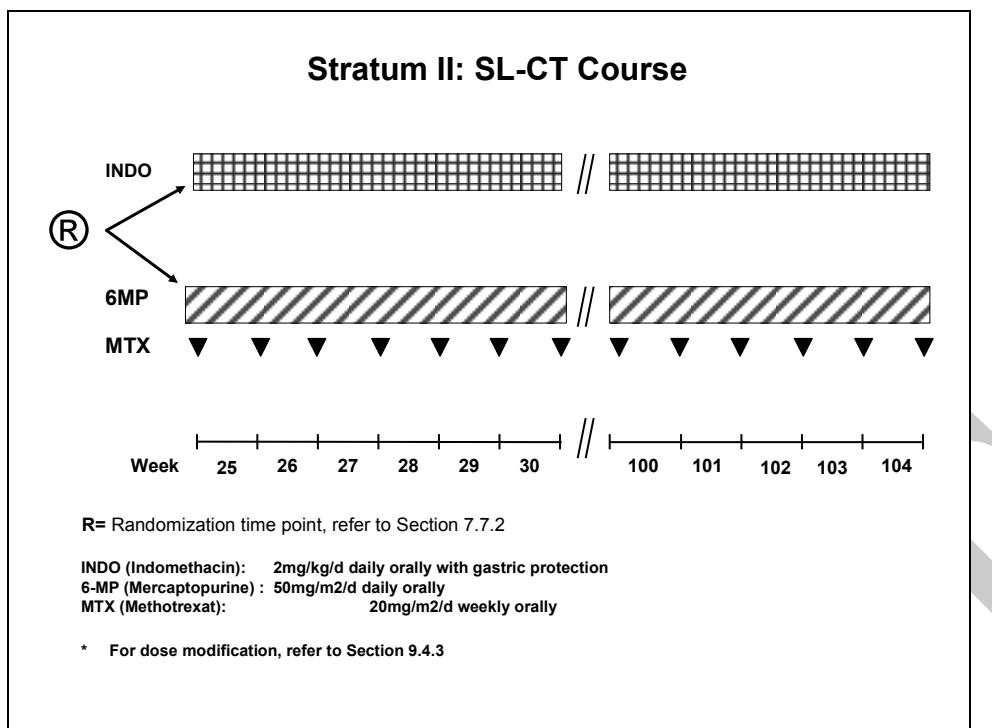


**Figure 17. Stratum II: Second-line Initial Therapy (SL-IT)**

#### 9.4.2 Second-line Continuation Therapy (SL-CT)

Patients who after SL-IT (week 24) have a response (NAD or AD better) are eligible for randomization between the continuation arms “INDOMETHACIN” and “6-MP/MTX”.

For details on randomization refer to **Section 9.7**



**Figure 18. Stratum II: Second-line Continuation Therapy (SL-CT)**

#### 9.4.2.1 Treatment Arm “INDOMETHACIN”

Indomethacin 2mg/kg/day given daily orally in two divided doses with gastric protection for total treatment duration of 24 months.

#### 9.4.2.2 Treatment Arm “6-MP/MTX”

- 6-mercaptopurine 50mg/m<sup>2</sup>/dose daily orally for total treatment duration of 24 months.
- Methotrexate 20mg/m<sup>2</sup>/dose weekly orally for total treatment duration of 24 months.

(*For dose modifications refer to Section 9.4.3*)

#### 9.4.2.3 Evaluation of disease activity and therapy response during treatment.

Please refer to the respective Road-map (Appendix A\_IV). The Road-maps are intended for use by the treating physicians (can be printed out, put into the patients charts and used for documentation of the therapy).

#### 9.4.3 Dose Modifications

#### **9.4.3.1 Dose modifications for age and body weight**

##### **For children weighing less than 10 kg:**

- Prednisone 1.5mg/kg/day in three divided oral doses for 2 weeks, tapering over a period of 6 weeks (reduction by 50% every 2 weeks).
- Cytosine-arabinoside (Ara-C) 3.3mg/kg/dose daily as an i.v. push or s.c. for 4 days on weeks 1, 4, 7, 10, 13, 16, 19, 22.
- Vincristine (VCR) 0.05mg/kg/dose daily (max. 2.0mg) as an i.v. push on day 1 of weeks 1, 4, 7, 10, 13, 16, 19, 22.
- 6-mercaptopurine (6-MP) 1.7mg/kg/dose daily orally to total treatment duration of 24 months.
- Methotrexate (MTX) 0.67mg/kg/dose weekly orally to total treatment duration of 24 months.
- Indomethacin dose is calculated per kg body weight and no modification is required for patients weighing less than 10kg.

#### **9.4.3.2 Dose modifications for toxicity**

##### **Prednisolone**

- Hypertension:

Dose should not be reduced. Sodium restriction and anti-hypertensives should be employed in an effort to control hypertension. Avoid calcium channel blockers due to their potential prohemorrhagic effect.

- Hyperglycemia:

Dose should not be reduced for hyperglycemia. Rather, insulin therapy should be employed to control the blood glucose level.

Pancreatitis: Do not modify dose for asymptomatic elevations of amylase and/or lipase. Discontinue steroids, except for stress doses, in the presence of hemorrhagic pancreatitis or severe pancreatitis (abdominal pain >72 hours and  $\geq$  Grade 3 amylase elevation ( $\geq$  2.0x ULN)).

- Varicella:

Steroids should be held during active infection. Do not hold during incubation period following exposure.

- Inability to use oral doses:

Substitute IV methyl-prednisolone at 80% of the oral prednisolone dose. Note that if substituting oral prednisolone for prednisone, the doses are the same; prednisone is

converted in the liver to prednisolone.

- Severe infection:

Do not hold or discontinue steroids during Induction without serious consideration.

- Severe psychosis:

Steroid dose may be reduced by 50%.

### **Vincristine**

Please use the modified “BALIS” scale for grading peripheral neuropathy in children

#### **(Appendix A-V\_1)**

- Severe neuropathic pain (Grade 3 or greater):

Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated.

- Vocal Cord paralysis:

Hold dose(s). When symptoms subside, resume at 50% previous dose, then escalate to full dose as tolerated.

- Foot Drop, paresis:

Should be Grade 3 to consider holding or decreasing dose. These toxicities are largely reversible but over months to years. Accordingly, holding doses of vincristine and/or lowering the dose may not result in rapid resolution of symptoms and may compromise cure.

- Jaw pain:

Treat with analgesics; do not modify vincristine dose.

- **Hyperbilirubinemia**

Direct Bilirubin		Dose reduction
[μmol/L]	[mg/dl]	
< 53.0	< 3.1	FULL dose
53.0-85.5	3.1-5.0	50%
85.6-103.0	5.1-6.0	75%
>103	> 6.0	Withhold dose and administer next scheduled dose if toxicity has resolved. Do not make up missed doses.

- **Constipation or ileus (≥ Grade 3) or typhlitis:**

Hold dose(s); institute aggressive regimen to treat constipation if present. When symptoms abate resume at 50% dose and escalate to full dose as tolerated.

### **Cytarabine (Ara-C)**

Do not withhold Ara-C for fever if it is likely to have been caused by the Ara-C. For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved.

Consider pre-medication with Tylenol if patient develops fevers.

### **Indomethacin**

There is no established dose adjustment for toxicity. Liver toxicity has been reported in chronic use in children <14 years, so liver function panel monitoring during maintenance visits is required. Indomethacin should be used with gut protection.

### **Methotrexate (MTX) and 6-Mercaptopurine (6-MP)**

- **Hematologic toxicity**

If absolute neutrophil count (ANC) falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ) or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ), 6-MP and MTX will be held until recovery above these levels.

For the first drop in ANC or platelets, resume chemotherapy at 100% after ANC is  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ). If ANC falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ) or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ) for a second time, discontinue doses until ANC is  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets are  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ). Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided ANC remains  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets remain  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ).

If ANC falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ) or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ) on  $\geq 2$  occasions, perform thiopurine pharmacology testing as described below. Should therapy be withheld for myelosuppression or elevated transaminases, do not “make up” that week. Resume therapy at the correct point, chronologically.

- **Hepatic toxicity**

For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin every 4 weeks as long as transaminases remain over 5x ULN. Continue full dose therapy unless either of the following occurs:

- 1) Direct bilirubin 34.2  $\mu mol/L$  ( $> 2.0 mg/dL$ )
- 2) SGPT/ALT or SGOT/AST  $> 20x$  ULN (consistent with Grade 4 toxicity) on two

determinations at least one week apart.

If either of these occurs, hold MTX and monitor labs as above, weekly. Restart at full dose therapy when the transaminase is less than 5x ULN and bilirubin is normal. If liver dysfunction persists, alternative therapy should be considered.

## **9.5 Supportive Care**

The supportive care recommendations are the same as for Stratum I (see 8.7, page 66).

## **9.6 Drug Information**

For drug information see package inserts provided in **Appendix A-VI**

## **9.7 Randomization**

### **9.7.1 Eligibility for Randomization**

Eligible for randomization are all patients who have completed the SL-IT course and are NAD or AD better at week 24.

The randomization will be done by random permuted blocks stratified according to:

- National group
- Age at diagnosis ( $\leq$  2 years vs.  $>$  2 years)

### **9.7.2 Randomization time point**

Randomization will be performed at week 24 of Stratum II (no later than two weeks after completion of SL-IT course).

### **9.7.3 Randomization procedure**

The randomization will be performed on-line through the remote data base (<https://www.hs-lch-database.org>).

For detailed instructions see **Appendix A-I\_3**.

## **9.8 Statistical Considerations**

This randomized clinical trial with two arms of continuation therapy aims to investigate

- the role of Indomethacin and 6-MP/MTX during continuation therapy on the rate of patients, who will survive without reactivation of disease (= cured individuals).

### **9.8.1 Aims and endpoints**

#### **9.8.1.1 Primary Endpoints**

Reactivation or progression in any organ and death will be considered as events for the calculation of Reactivation Free Survival. The interval will start at randomization. Patients without events are censored at their last follow-up evaluation.

The reactivation-free survival rate will be estimated according to the method of Kaplan-Meier and confidence intervals according to Dorey and Korn will be given.

The primary statistical evaluation of the treatment effect will be done with a proportional hazard mixture cure model with a logistic link function for the proportion of cured individuals, i.e. survivors without reactivations.

The primary analysis will be done adjusted for age-group, initial treatment failure or relapse, and national group.

#### **9.8.1.2 Secondary Endpoints**

The same approaches as described in chapter 8.9.4.2 will be used.

#### **9.8.1.3 Evaluation approach to the endpoints and hypothesis**

If the null hypothesis is true, the rates of patients in the two arms who survive without reactivation are equal. If the alternative hypothesis is true, there is a difference between the two arms in terms of reactivation-free survival rate. The primary aim of this stratum is a reduction of the reactivation rate.

The response to initial treatment with PRED/ARA-C/VCR (week 24) will be investigated in all patients of Stratum II, regardless whether or not randomized for the continuation therapy.

The analysis of the primary and secondary endpoints will be done according to the intention-to-treat principle, i.e. the patients will be analyzed in their allocated treatment group, even in case of non-compliance or protocol violations.

The statistical analysis of the primary endpoint will be done with a two-sided significance level of 5 %. The statistical analyses of the secondary endpoints are exploratory. In addition to the intention-to-treat analyses a secondary per protocol

analyses will be done including all patients who were treated according to the originally assigned treatment arm without protocol violations.

### **9.8.2 Power Consideration**

Monte Carlo methods are used to estimate the statistical power.

According to our previous experience about 50 randomizations/year are to be expected.

Based on the LCH-III experience, the estimated event rate (reactivations and deaths) after a first reactivation is similar as for patients in first NAD, and is anticipated to be about 40%.

With 400 randomized patients and the minimum follow up of 2 years, the study is able to demonstrate main effects with odds ratios of 0.5 with a power of 80% (Monte-Carlo simulations).

### **9.8.3 Interim-analyses**

The primary aims of the two trials will be monitored according to a group sequential plan.

In addition to the final analysis, one interim-analysis will be done after 4 years. Early stopping will be implemented to retain the null hypothesis (68) and the study will be stopped if the upper limit of the 95% CI for the OR is below the targeted treatment effect of 2.

## **9.9 Criteria For Removal From Protocol Therapy and Off Study Criteria**

### **9.9.1 Criteria for removal from protocol therapy**

- Progressive disease with involvement of risk organs at any time
- Progression in non-risk organs after at least 12 weeks of therapy
- Diagnosis of a malignant neoplasm
- Refusal of further protocol therapy by patient/ parent/guardian
- Completion of planned therapy
- Excessive toxicity
- Physician determines it is in patient's best interest

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

### **9.9.2 Off Study criteria**

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission

### **9.10 Consent forms**

For consent forms refer to **Appendix A-VII\_2**

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## 10 STRATUM III: SALVAGE TREATMENT FOR RISK LCH

### 10.1 Aims

To assess the efficacy of the combination 2-CdA/Ara-C in MS-LCH patients with risk organ involvement, who fail to respond to front-line (Stratum I) therapy.

### 10.2 Study Endpoints for Salvage Treatment for Risk LCH (Stratum III)

#### 10.2.1 Primary endpoint

**The primary endpoint is the response rate after two courses of therapy.**

The response will be evaluated at 4-5 weeks from the initiation of the second cycle (about 9-10 weeks from start of Stratum III).

For response criteria refer to **Section 10.4**

#### 10.2.2 Secondary endpoints

- Time to complete disease resolution (Non-Active Disease)
- The type of subsequent intensive and/or maintenance therapy utilized
- The early and late mortality
- The early and late toxicity

### 10.3 Eligibility Criteria and Enrolment to Stratum III

The inclusion criteria for this Stratum are very restrictive due to important considerations. First, the group of patients as defined below has an extremely poor outcome with standard approaches, and this justifies experimental approaches with higher toxicity. Secondly, the expected toxicities of the drug combination being evaluated in this study are significantly greater than the complications seen with standard first-line therapy in LCH.

Therefore, the restrictive inclusion criteria are used here to protect patients with better prognosis from an unduly toxic treatment.

#### 10.3.1 Eligibility Criteria

Patients from Stratum I who fulfill the following criteria:

- AD worse in risk organs after week 6 (after Initial Course 1), or AD worse or AD intermediate in risk organs after week 12 (after Initial Course 2).

- Presence of unequivocally severe organ dysfunction at the above mentioned evaluation points (hematological dysfunction, liver dysfunction, or both of them) as defined in **Table XI**.

**Table XI: Organ dysfunction eligibility criteria for enrolment in Stratum III**

<ul style="list-style-type: none"> <li>• <b>Hematologic dysfunction</b> <ul style="list-style-type: none"> <li>• Hb &lt;70 g/L (&lt;7.0 g/dl) and/or transfusion dependency</li> <li>• PLT &lt;20 x10<sup>9</sup>/L (20,000/<math>\mu</math>L) and/or transfusion dependency <i>(both criteria have to be fulfilled)</i></li> </ul> </li> </ul>
AND/OR
<ul style="list-style-type: none"> <li>• <b>Liver dysfunction</b> (or digestive involvement with protein loss)           <ul style="list-style-type: none"> <li>• Total protein &lt;55 g/L or substitution dependency</li> <li>• Albumin &lt;25 g/L or substitution dependency <i>(at least one of the two criteria to be fulfilled)</i></li> </ul> </li> </ul>

### 10.3.2 Exclusion criteria

The presence of any of the following criteria will exclude the patient from the study:

- Isolated sclerosing cholangitis without evidence of active hepatic LCH as the only evidence of risk organ involvement.
- Inadequate renal function as defined by serum creatinine > 3x normal for age

Age	Maximum serum creatinine			
	Male		Female	
	[ $\mu$ mol/L]	[mg/dl]	[ $\mu$ mol/L]	[mg/dl]
1 month to < 6 months	35.4	0.4	35.4	0.4
6 months to < 1 year	44.2	0.5	44.2	0.5
1 to < 2 years	53.0	0.6	53.0	0.6
2 to < 6 years	70.7	0.8	70.7	0.8
6 to < 10 years	88.4	1	88.4	1
10 to < 13 years	106.1	1.2	106.1	1.2
13 to < 16 years	132.6	1.5	123.8	1.4
≥ 16 years	150.3	1.7	123.8	1.4

The threshold creatinine values in this table are derived from the Schwartz formula for estimating GFR (69) utilizing child length and stature data published by the CDC. The SI values [ $\mu$ mol/L] were converted from the respective [mg/dl] values

### 10.3.3 Enrollment

- **IRB Approval**

Approval from appropriate regulatory administrations (e.g. national or institutional IRB) is required of each participating institution prior to accrual of patients. A copy of the official approval document must be sent to the National Coordinator (will be kept there and must be available for monitoring, audits, and inspections).

- **Informed consent**

The parents or the legal guardians of the patients must sign a written informed consent that has to be sent to the National Coordinator without delay and the respective entry (checkbox) in the clinical trial database has to be performed.

- **Enrollment**

Enrollment will be managed through the web-based central clinical trial database on <https://www.hs-lch-database.org> (for detailed instructions see **Appendix A-I\_2**). ***Enrollment by paper Case Report Forms could be exceptionally granted only by the National Coordinator, who will have to enter the data into the database by himself.***

### 10.4 Response criteria in Stratum III

The response categories NAD, AD better, AD intermediate, and AD worse as defined in Section 6.5.2 will be applied also in Stratum III. Accordingly, response is defined as NAD or AD Better. AD intermediate and AD worse, as well as any early death, whatever the cause, are considered as non-response (treatment failure).

In order to allow comparison to an already published pilot trial (13) disease severity and response to salvage therapy will be additionally assessed by a disease activity score developed by J. Donadieu et al. (70). This score allows for a more exact and objective assessment of the patient's general condition and of therapy response in cases with very severe disease.

A translation between the two response assessment systems is given in **Table XIII**.

**Table XII: Disease Activity Score (from Donadieu et al.(70))**

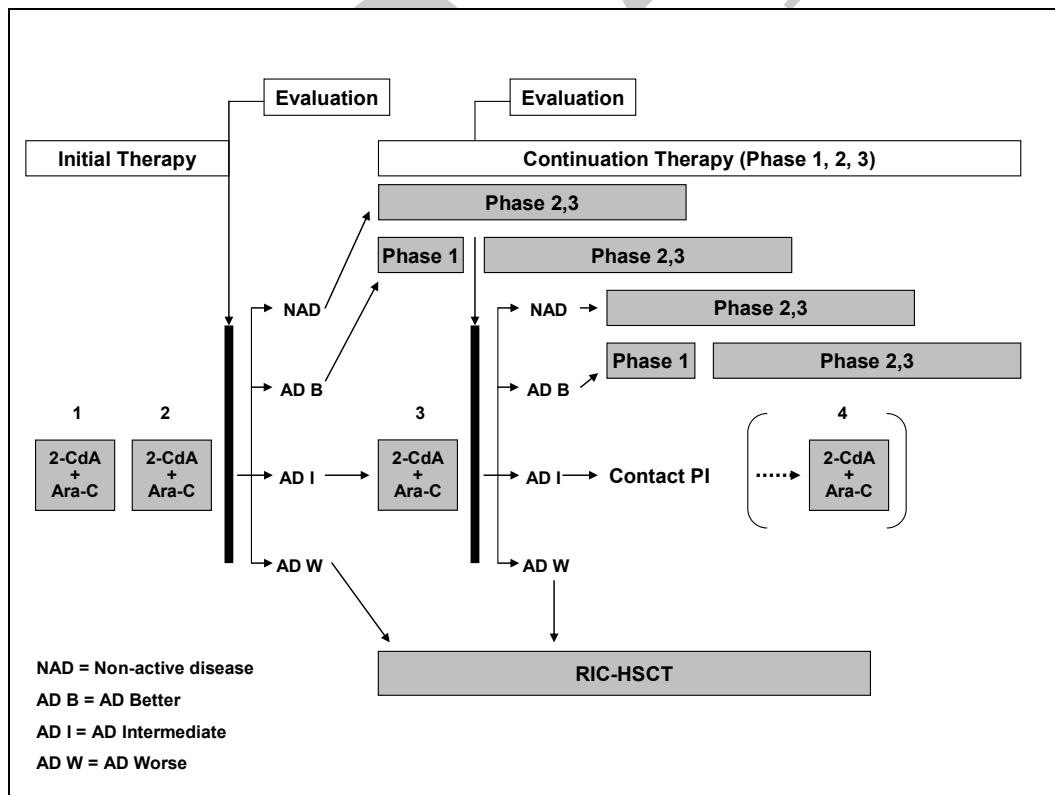
<b>Variable</b>	<b>Modality</b>	<b>Score</b>
<b>Bone (a)</b>	Pain No pain	1 0
<b>Bone (b)</b>	Compressing other organs (orbit or spine) No compression	2 0
<b>Fever (&gt;38.5 °C)</b>	Yes No	1 0
<b>Lung: iconography</b>	Pneumothorax Interstitial lesion on chest x-ray film or lung CT scan Normal chest x-ray film or lung CT scan	2 1 0
<b>Lung: function</b>	Mechanical ventilation or PFT <50% Supplemental oxygen or PFT between 50-80% No dysfunction, no cyanosis, no supplemental oxygen	5 2 0
<b>Skin: area</b>	25% 5-25% Below 5%	2 1 0
<b>Soft tissue tumor (including CNS)</b>	5 cm max diameter 2-5 cm max diameter 0-2 cm max diameter	2 1 0
<b>Nodes (&gt; 2 cm)</b>	Yes No	1 0
<b>Liver</b>	Below umbilicus Enlarged above umbilicus Not enlarged	2 1 0
<b>Spleen</b>	Below umbilicus Enlarged above umbilicus Not enlarged	2 1 0
<b>Liver (enzymes)</b>	>10 N 3 - 10 N < 3 N	2 1 0
<b>Liver (gamma GT)</b>	> 10 N 3 - 10 N < 3 N	2 1 0
<b>Albumin</b>	Perfusion required in past week No perfusion, but < 30 g/L > 30 g/L	3 1 0
<b>Platelet: requirements in past week</b>	More than 2 transfusions 1 or 2 transfusions Low platelet count (PLT < 100 x10 <sup>9</sup> /L), no transfusion Normal count	4 3 2 0
<b>Red cells: requirements in past week</b>	more than 2 units (> 20 ml/kg/week) 1 or 2 units (10-20 ml/kg/week) Hb below 100 g/L, no transfusion No transfusion	4 3 1 0

**Table XIII: Response assessment in Stratum III**

Response category (HS criteria)		Disease severity score
Response	Non-Active Disease	Absolute Score 0-1
	AD better	Absolute Score 2-7 AND decrease of $\geq 4$ points compared to pre-salvage evaluation
Non-response	AD intermediate	Absolute Score 2-7 AND decrease of <4 points or Absolute Score >7 AND no increase of score compared to pre-salvage evaluation
	AD worse	Any increase of score compared to pre-salvage evaluation

## 10.5 Treatment Plan

The treatment concept of Stratum III is presented on **Figure 19**.

**Figure 19. Stratum III: Overall Salvage therapy plan for RISK-LCH**

### 10.5.1 Initial Salvage therapy:

The initial therapy consists of 2 courses of 2-CdA/Ara-C.

Each 2-CdA/Ara-C course (**Figure 20**) consists of:

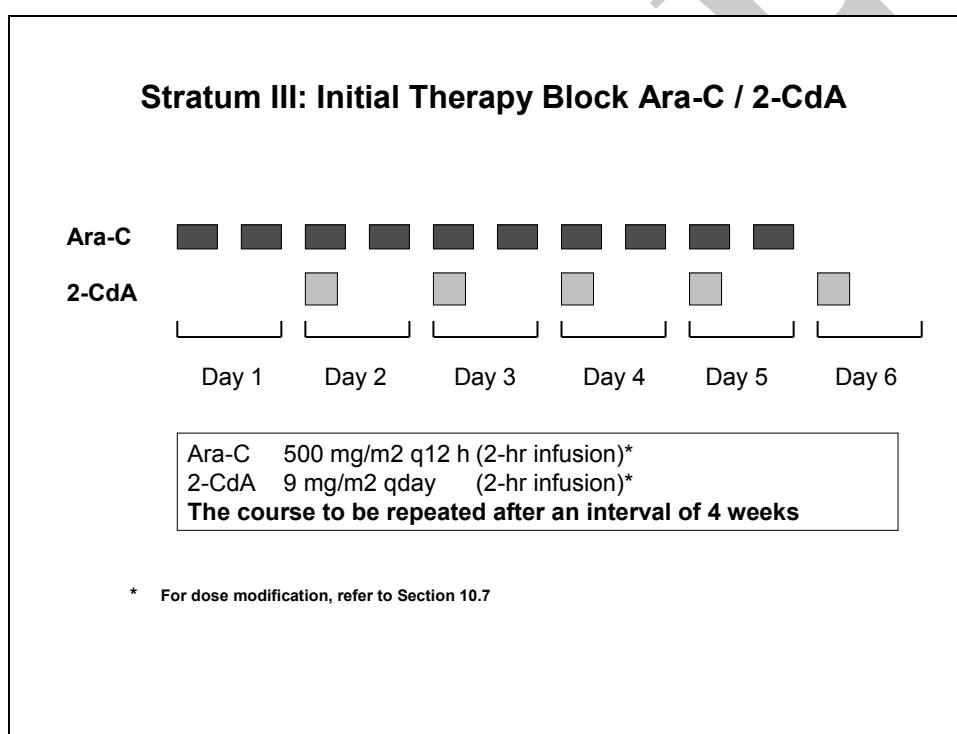
- **Cytosine Arabinoside** (Cytarabine, Ara-C)

500 mg/m<sup>2</sup>/dose in 250 ml/m<sup>2</sup> normal saline twice a day for 5 days, as a 2 hour i.v. infusion, at hours 1, 13, 25, 37, 49, 61, 73, 85, 97 and 109. Thus Ara-C dose will be 1000mg /m<sup>2</sup>/day. Ara-C is started on the first day of the course.

- **2-chlorodeoxyadenosine** (2-CdA, Cladribin®, Leustatin®)

9 mg/m<sup>2</sup>/day as a 2 hour i.v. infusion given daily for 5 days. 2-CdA is started on the second day of the course and is given at hours 23, 47, 71, 95 & 119 (***thus, infusion of 2-CdA should not be given at the same time as Ara-C***).

(For dose modifications see **Section 10.7**).



**Figure 20. Stratum III: Schedule of a single course of Initial Salvage Therapy (2-CdA/Ara-C course)**

Response evaluation before start of the second course has to be recorded for a prospective evaluation, but the second course is to be given regardless of response. The interval between the first and second cycle is usually 4 weeks. The second course is started at the **fifth week** after the initiation of therapy, whatever the hematological

values. The interval can be extended only in cases of uncontrolled infectious or other severe complications.

#### **10.5.1.1 Response after 2 courses of 2-CdA/Ara-C and decision about further therapy**

The evaluation after the second course must be done at week five after the start of the 2<sup>nd</sup> course (i.e. week 9-10 from the start of the salvage therapy, or as appropriate in the case of therapy delay). Further therapy depends on response at this time point.

These are the following possible scenarios:

- **AD Worse** (compared to pre-salvage assessment).

For those patients RIC-HSCT according to Stratum IV is recommended.

- **AD Intermediate** (compared to pre-salvage assessment).

Patients with AD intermediate will receive a third course of 2-CdA/Ara-C starting between 28 and 35 days after the 2<sup>nd</sup> course. Hematopoietic regeneration (ANC >0.75  $\times 10^9/L$  and platelets > 75  $\times 10^9/L$ ) is required for start of the 3<sup>rd</sup> course.

- **AD Better** (compared to pre-salvage assessment).

Those patients will move to Part 1 of the continuation therapy according to Section 10.5.2

- **NAD** (compared to pre-salvage assessment).

Those patients will skip Part 1 and move directly to Part 2 of the continuation therapy according to Section 10.5.2

#### **10.5.1.2 Response evaluation after the 3<sup>rd</sup> 2-CdA/Ara-C course**

The response evaluation has to be done 4-5 weeks after start of the 3<sup>rd</sup> course.

There are following possible scenarios:

- **AD Worse** compared to pre-salvage assessment.

For those patients RIC-HSCT (Stratum IV) is recommended.

- **AD Intermediate** compared to pre-salvage assessment.

***Those patients will have to be discussed with the Principal Investigator. A 4<sup>th</sup> course of 2-CdA/Ara-C starting between 28 and 35 days after the 3<sup>rd</sup> course could be***

given after careful consideration. Hematopoietic regeneration (ANC  $>0.75 \times 10^9/L$  and platelets  $> 75 \times 10^9/L$ ) is required for start of the 4<sup>th</sup> course.

- **AD Better** compared to pre-salvage assessment.

Those patients will move to Part 1 of the continuation therapy according to Section 10.5.2

- **NAD** compared to pre-salvage assessment.

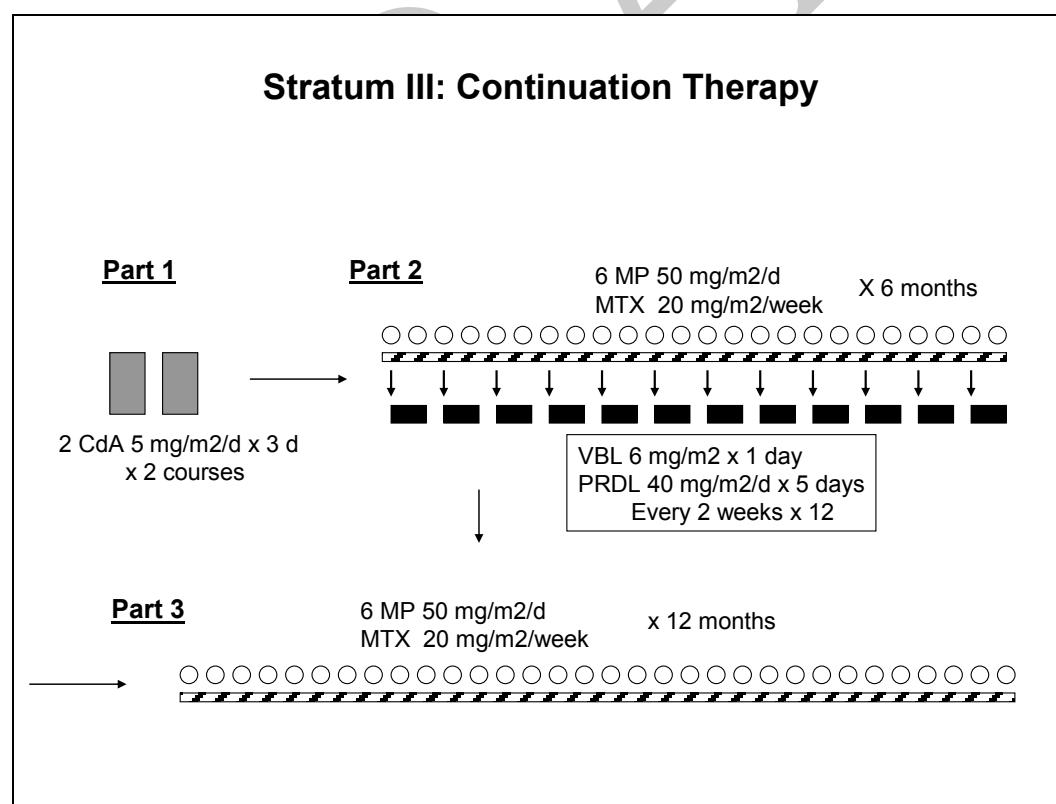
Those patients will skip Part 1 and move directly to Part 2 of the continuation therapy according to Section 10.5.2

#### 10.5.1.3 Further response evaluations

If 4<sup>th</sup> 2-CdA/Ara-C course given response evaluation and documentation have to be performed 4-5 weeks after its start.

#### 10.5.2 Continuation Therapy

The continuation therapy of Stratum III is presented on **Figure 21**



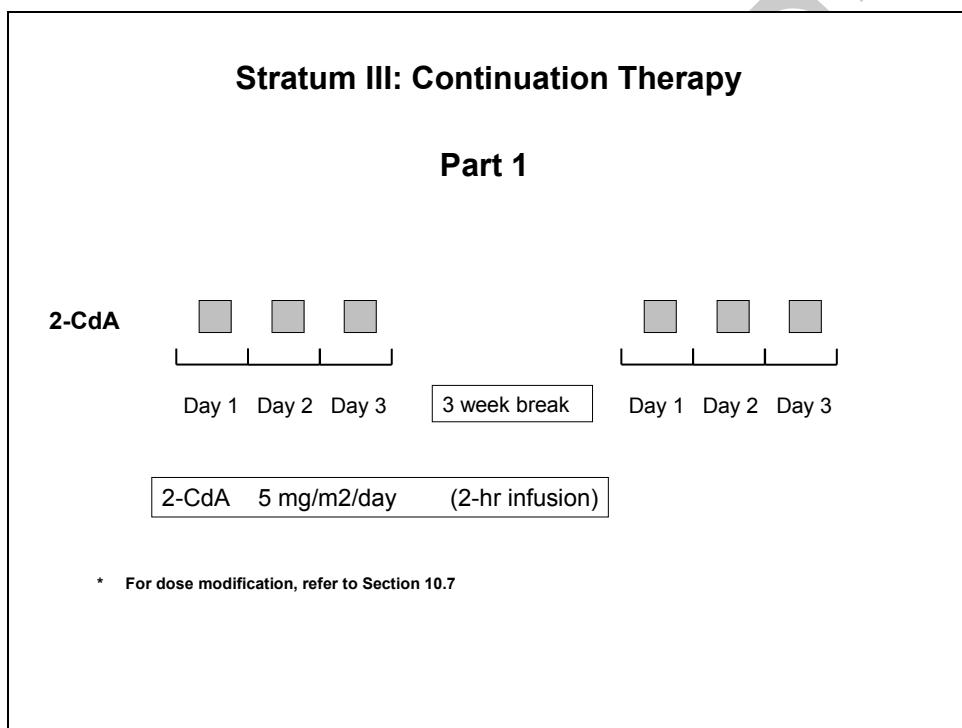
**Figure 21. Continuation Therapy**

### 10.5.2.1 Continuation Therapy/ Part 1

Part 1 starts at day 21 from the start of the 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> course of 2-CdA/Ara-C in patients with response AD Better (please beware the ***different dose and duration*** compared to the 2CdA/Ara-C courses). The second course is started on day 21 after the start of the first one, provided the blood counts have recovered to ANC >0.75 x10<sup>9</sup>/L and platelets > 75 x10<sup>9</sup>/L (Figure 22). Each course consists of:

- **2-chlorodeoxyadenosine** (2-CdA, Cladribin®, Leustatin®)  
5 mg/m<sup>2</sup>/day as a 2 hour i.v. infusion given daily for 3 days

(For dose modifications refer to **Section 10.7**)



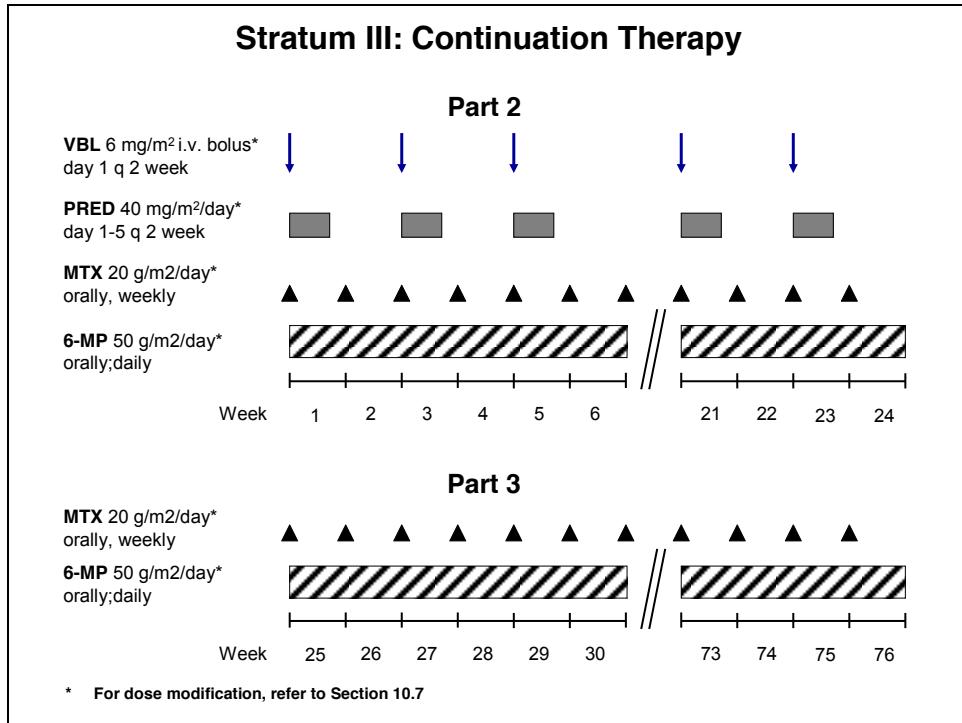
**Figure 22. Continuation Therapy/ Part 1**

### 10.5.2.2 Continuation Therapy/ Part 2

Part 2 starts at day 21 from the start of the 2<sup>nd</sup>, 3<sup>rd</sup>, or 4<sup>th</sup> course of 2-CdA/Ara-C (in those who have response NAD, respectively) or after Part 1 of the continuation therapy (in those who have received it for incomplete response), and will be given for 24 weeks (**Figure 23**):

- Vinblastine 6 mg/m<sup>2</sup> i.v. every two weeks
- Prednisone 40 mg/m<sup>2</sup>/day, divided into 3 oral doses, days 1-5, every two weeks (therefore a total of 12 pulses VBL/PRED will be given)

- Mercaptopurine (6-MP) at a dose of  $50 \text{ mg/m}^2$  orally daily for 24 weeks
  - Methotrexate (MTX) at a dose of  $20 \text{ mg/m}^2$  orally weekly for 24 weeks
- (For dose modifications refer to **Section 10.7**)



**Figure 23.** Continuation Therapy/ Part 2 and Part 3

#### 10.5.2.3 Continuation Therapy/ Part 3

Part 3 begins after the end of Part 2 in all patients and will be given for 12 months (**Figure 23**).

Part 3 consists of oral treatment with mercaptopurine and methotrexate:

- Mercaptopurine (6-MP) at a dose of  $50 \text{ mg/m}^2$  orally daily for 12 months
- Methotrexate (MTX) at a dose of  $20 \text{ mg/m}^2$  orally weekly for 12 months

(For dose modification refer to **Section 10.7**)

#### 10.5.2.4 Evaluation of disease activity and therapy response during continuation treatment.

Response evaluation and documentation have to be performed after Part 1, Part 2, and Part 3 of the continuation therapy, respectively.

Please refer to the respective Road-map (Appendix A\_IV). The Road-maps are intended for use by the treating physicians (can be printed out, put into the patients

*(charts and used for documentation of the therapy).*

## **10.6 Criteria for Removal From Protocol Therapy and Off-Study Criteria**

### **10.6.1 Criteria for Removal from Protocol Treatment**

- Progressive disease
- Excessive toxicity
- Diagnosis of a malignant neoplasm
- Refusal of further protocol therapy by patient/ parent/ guardian
- Completion of planned therapy
- Physician determines it is in patient's best interest

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

### **10.6.2 Off-Study Criteria**

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission

## **10.7 Dose Modifications**

### **10.7.1 Dose modification for weight and age:**

- Ara-C:

Children who are <10 kg body weight do not require dose reduction except in the first month of life, where the dose of Ara-C will be 16.5 mg/kg/dose corresponding to 33mg/kg/day.

- 2-CdA:

In children who are <10 kg body weight the dose of 2-CdA will be:

- 0.3mg/Kg/day in the 2-CdA/Ara-C courses (standard 2-CdA dose 9mg/m<sup>2</sup>/day)
- 0.15mg/Kg/day in the 2-CdA courses of the Phase 1 (standard 2-CdA dose 5mg/m<sup>2</sup>/day)

### **10.7.2 Dose modification for toxicity**

#### **10.7.2.1 Initial 2 courses 2-CdA/Ara-C**

The treating physician always has the responsibility to adjust therapy according to the precise clinical condition of the patient. As this protocol is aimed at a group of patients in a life-threatening situation, with numerous potential complications, decisions to delay therapy or decrease doses are not recommended, except to manage an acute infection, or a metabolic complication. Any significant deviation from the protocol (delay more than 2 weeks or administration of less than 80% of recommended dose) has to be reported to the Principal Investigator.

#### **10.7.2.2 Oral therapy with 6-MP and MTX**

- **Hematologic toxicity**

If the absolute neutrophil count (ANC) falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ), or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ), 6-MP and MTX will be held until recovery above these levels.

For the first drop in ANC or platelets, resume chemotherapy at 100% after ANC is  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ). If ANC falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ), or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ) for a second time, discontinue doses until ANC is  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets are  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ). Restart 6-MP and/or MTX at 50% of the original dose on the same day the counts recover. Increase to 75% and then 100% of the original dose at 2-4 week intervals provided ANC remains  $\geq 0.75 \times 10^9/L$  (750/ $\mu L$ ) and platelets remain  $\geq 75 \times 10^9/L$  (75,000/ $\mu L$ ).

If ANC falls below  $0.5 \times 10^9/L$  (500/ $\mu L$ ), or if platelet count falls below  $50 \times 10^9/L$  (50,000/ $\mu L$ ) on  $\geq 2$  occasions, perform thiopurine pharmacology testing as described below. Should therapy be withheld for myelosuppression or elevated transaminases, do not “make up” that week. Resume therapy at the correct point, chronologically.

- **Hepatic toxicity**

For increase in hepatic transaminases (SGPT/ALT or SGOT/AST) to greater than 5x ULN consistent with Grade 3 toxicity, obtain total bilirubin. Monitor SGPT/ALT or SGOT/AST and total bilirubin every 4 weeks as long as transaminases remain over 5x ULN. Continue full dose therapy unless either of the following occurs:

- 1) Direct bilirubin  $> 34.2 \mu mol/L$  ( $> 2.0 \text{ mg/dL}$ ).
- 2) SGPT/ALT or SGOT/AST  $> 20x$  ULN (consistent with Grade 4 toxicity) on two

determinations at least one week apart.

If either of these occurs, hold MTX and monitor labs as above, weekly. Restart at full dose therapy when the transaminase is less than 5x ULN and bilirubin is normal. If liver dysfunction persists, alternative therapy should be considered.

## **10.8 Supportive Care**

### **10.8.1 Fluids and parenteral nutrition**

The insertion of a one or two-lumen central venous catheter or infusion port, prior to therapy start, is encouraged.

During the chemotherapy courses, twice maintenance fluids (i.e.  $3\text{L}/\text{m}^2/24\text{ hours i.v.}$  or  $200\text{ ml/Kg}$  for children under  $10\text{ Kg}$  body weight) should be given, except during high volume chemotherapy infusions.

Urine output should be maintained at least 60% of input, measured 4-6 hourly.

- If the urine output is insufficient, furosemide  $0.5\text{ mg/Kg}$  (maximum  $20\text{ mg/dose}$ ), should be given.
- Blood count, renal and liver function studies and electrolytes are to be measured daily until the results are stable, or more frequently if clinically indicated.
- Parenteral nutritional support is encouraged.
- Albumin infusions are recommended for hypoalbuminemia until the albumin level remains stable above  $30\text{g/L}$  (ie  $3.0\text{g/dl}$ ).
- Intravenous immunoglobulin support is recommended  $400\text{ mg/kg}$  every 3-4 weeks or as per local guidelines.

### **10.8.2 Antibiotics**

Wide spectrum antibiotic and antifungal therapy is recommended to treat febrile neutropenia according to local policy.

Prophylactic therapy for prevention of fungal disease, particularly aspergillosis infection, is highly recommended, according to local policy.

#### Pneumocystis jiroveci prophylaxis:

Oral sulphamethoxazole/trimethoprim  $5\text{mg/kg/day}$  of the trimethoprim, divided into 2 doses/day, on 3 consecutive days per week, has to be given throughout the treatment period and for 12 weeks thereafter.

### 10.8.3 Blood products

All cellular blood products are to be given according to the local transfusion policies for immunocompromised patients. Leukocyte-depletion and irradiation with > 2.5 Gy is recommended.

### 10.8.4 Dexamethasone eye drops

Dexamethasone eye drops 0.1% or saline eye drops (investigator's choice) to both eyes three times daily for 6 days are recommended during Ara-C. Eye drops could be administered for more than 6 days according to local policy.

### 10.8.5 Antiemetics

Could be provided following local policy.

### 10.8.6 G-CSF

Administration of G-CSF 5 µg/kg/dose, subcutaneously or intravenously, given daily until neutrophil recovery, is not contraindicated and is provided following local policy. Its use, however, **must** be clearly recorded.

*The use of GM-CSF and Peg G-CSF is discouraged as could unfavorably influence underlying disease.*

## 10.9 Drug Information

See Appendix A-VI

### 10.10 Statistical considerations

Stratum III represents the best available treatment for severe MS-LCH which is refractory to first-line therapy (13).

From published surveys of LCH patients, it is apparent that the inclusion criteria used here will restrict this study to a very limited subset of the patients, likely representing less than 5% of all newly diagnosed LCH. There will likely be no more than 10 patients a year eligible for the study, if all the participating countries include all their eligible patients. The limited expected enrolment does not allow for a randomized trial.

The short term response rate will be used as the major end point of the study, based on the standard criteria for response in risk organs used in the previous LCH clinical

trials (Non Active Disease/ Active Disease better or stable or worse). With regards to literature, the best response rate of historical controls in this group of patient is about 25%. Therefore, a response rate of less than 25% is unacceptable. With this protocol we expect to achieve a response rate of 50%.

A Simon two-stage phase II study is designed with an unacceptable response rate of 25% and a promising response rate of 50%.

13 patients will be included in the first stage. If  $\leq$  3 responses are observed, the study will be stopped and the treatment declared ineffective. If  $\geq$  4 responses are observed, 17 additional patients will be included.

At the end of the study (after the inclusion of 30 patients), the treatment will be declared promising if  $\geq$  11 responses are observed and ineffective if  $\leq$  10 responses are observed.

#### **10.11 Consent forms**

See **Appendix A-VII\_3**.

## 11 STRATUM IV: STEM CELL TRANSPLANTATION FOR RISK LCH (HSCT)

### 11.1 Aims

To establish an effective salvage treatment option for MS-LCH patients with risk organ involvement, who fail to respond to front-line therapy (Stratum I) OR to the salvage 2-CdA/Ara-C regimen (Stratum III).

### 11.2 Study Endpoints

#### 11.2.1 Primary endpoint

- To determine the overall and disease free survival at 1 and 3 years after reduced intensity conditioning hematopoietic stem cell transplantation (RIC-HSCT)

#### 11.2.2 Secondary endpoints

- To determine d+100 transplant related mortality
- To determine the incidence of hematopoietic recovery, and donor chimerism at d+100 and 1 year post RIC-HSCT
- To determine the incidence of grades II-IV and III-IV acute GVHD
- To determine the incidence of chronic GVHD

### 11.3 Eligibility Criteria and Enrollment

#### 11.3.1 Eligibility Criteria

Patients from Stratum I or Stratum III who fulfill the following criteria:

- AD worse in risk organs after week 6 (after Initial Course 1), or AD worse or AD intermediate in risk organs after week 12 (after Initial Course 2) of Stratum I

OR

- AD worse after the 2<sup>nd</sup> and 3<sup>rd</sup> 2-CdA/Ara-C course, and those AD worse or AD intermediate after the 4<sup>th</sup> 2-CdA/Ara-C course of Stratum III

AND

- Presence of unequivocally severe organ dysfunction at the above mentioned evaluation points (hematological dysfunction, liver dysfunction, or both of them) as defined in **Table XI**.
- Informed consent: All patients or their legal guardians (if the patient is <18 years of age) must sign an Ethics or institutional Review Board approved consent form indicating their awareness of the investigational nature and the risks of this study.

When appropriate, younger patients will be included in all discussions in order to obtain assent.

- **Adequate organ function:** Patients should have adequate hepatic, renal, cardiac and pulmonary function to undergo reduced intensity HCT based upon local institutional guidelines, or at a minimum meet requirements noted in eligibility checklist **Appendix A-VIII\_1**. However, significant hepatic and pulmonary dysfunction, if secondary to underlying LCH disease activity, will not exclude patients from protocol enrolment and should be discussed with the National Study Coordinator and the Principal Investigator.

### **11.3.2 Exclusion Criteria**

- Pulmonary failure (requiring mechanical ventilation) not due to active LCH.
- Isolated liver sclerosis or pulmonary fibrosis, without active LCH.
- Uncontrolled active life-threatening infection.
- Decreased renal function with a GFR of less than 50ml/1.73m<sup>2</sup>/min.
- Pregnancy or active breast feeding
- Failure to provide signed informed consent

### **11.3.3 Enrollment procedure**

The enrollment will be managed through the **web-based central clinical trial database** on <https://www.hs-lch-database.org>.

For detailed instructions see **Appendix A-I\_2**.

## **11.4 HLA-Typing and Choice of Donors**

HLA typing of the patient should be performed as soon as progression of disease develops including typing of family members (full siblings and parents).

Class I and Class II antigens should be determined using high-resolution molecular techniques. For family member donors, Class I antigens determined with medium resolution techniques will be allowed. Guidelines for donor selection is shown below.

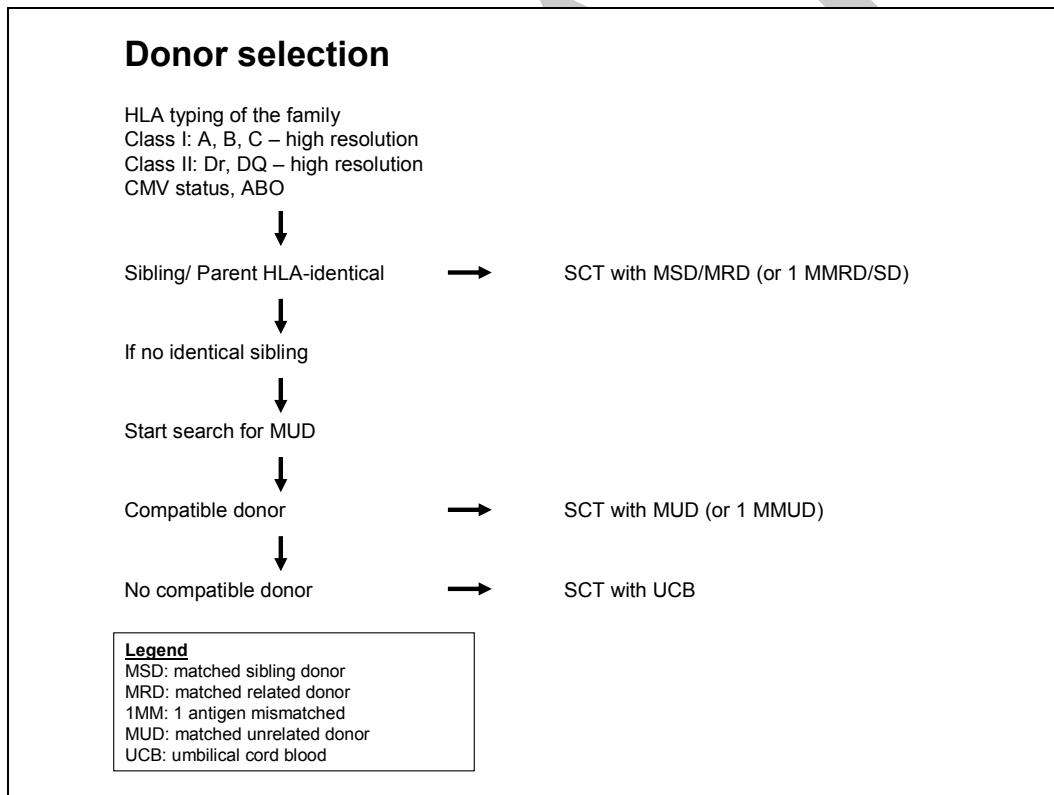
On the basis of the following considerations the following **HSCT groups** are formed:

- **MSD** Matched **Sibling Donor** (MSD) or one locus mismatched sibling donor (1MMSD)
- **MRD** Matched **Related Donor** (MRD) or one locus mismatched related donor (1MMRD).
- **MUD** Matched **Unrelated Donor** (MUD) or one locus **Mismatched Unrelated Donor** (1MMUD)
- **UCB** Unrelated Umbilical Cord Blood (UCB), Unrelated umbilical cord blood unit with adequate cell dose and up to two locus mismatched (see 9.5.4)

As some institutions do not test for both HLA-C and DQ, 7 out 8 matched donors (A,B,C,Dr) will be allowed with allele level mismatch at any locus.

#### 11.4.1 Donor selection

The process of donor selection is presented in **Figure 24**.



**Figure 24. Donor selection process**

In the selection process, further consideration may be given to the CMV status of the donor and recipient, to the age and sex of the donor and in certain cases the preference of the donor for bone marrow or peripheral stem cell donation based upon

institutional policies.

#### **11.4.2 Donor hierarchy**

One should always aim at the best possible match between donor and recipient. A matched sibling or related donor (MSD) should always be preferred to matched unrelated donor (MUD), and a MUD in turn should always be preferred to a mismatched donor (MMD). Further, a 10/10 identical MD is better than a 9/10 donor, an allele mismatch is better than an antigen mismatch. The preference hierarchy is presented in Table XII, although local institutional donor matching hierarchy may be followed.

**Table XIV:** Donor hierarchy

Preference	HLA match	HSCT groups
1	HLA-identical sibling	MSD
2	8/8 or 10/10 identical unrelated or related donor	MUD, MRD
3	7/8 or 9/10 identical unrelated or related donor	MMRD, MMUD
4	0-2 antigen matched or mismatched cord blood	UCB
In case of a mismatch:		
1	Allele-mismatch	MUD, MMD, UCB
2	Antigen mismatch	MUD, MMD, UCB

#### **11.4.3 Graft Type and Cell Dose**

##### **11.4.3.1 Stem cell source**

The preferred stem cells source is bone marrow. The use of peripheral blood stem cells is discouraged, but will be allowed utilizing the same HLA matching criteria.

##### **11.4.3.2 Stem cell dose**

The total number of unfractionated allogeneic bone marrow mononuclear cells infused on day 0 should be  $> 5 \times 10^8$  nucleated cells/ per kg, but not more than  $7 \times 10^8$  nucleated cells/ per kg. If using PBSCT the dose should be  $> 4 \times 10^6$  CD34+ cells per kg.

#### **11.4.4 Unrelated Umbilical Cord Blood**

Unit selection based on cryopreserved nucleated cell dose. HLA-A, B, DRB1 match using intermediate resolution A, B antigen and DRB1 allele typing.

**Unit selection Priority:**

- 1<sup>st</sup> 6/6 or 5/6 single unit graft with cell dose  $\geq 3.5 \times 10^7$  nucleated cells/kg
- 2<sup>nd</sup> 6/6 or 5/6 single unit graft with cell dose  $\geq 2.5 \times 10^7$  nucleated cells/kg
- 3<sup>rd</sup> 4/6 single unit graft with cell dose  $\geq 3.0 \times 10^7$  nucleated cells/kg
- 4<sup>th</sup> Double Unit Graft: Each unit must be  $\geq 1.5 \times 10^7$  nucleated cells/kg and the total graft dose must be  $\geq 3.0 \times 10^7$  nucleated cells/kg. Unit 1: Choose the best HLA matched unit for all units with a dose  $\geq 1.5 \times 10^7$  nucleated cells/kg. Unit 2: Choose best HLA matched unit for all remaining units with a dose  $\geq 1.5 \times 10^7$  nucleated cells/kg unless there is a unit with a 1 antigen lesser match that has a cell dose twice that of a better matched unit (ie, 5/6 with cell dose of  $4.1 \times 10^7$  nucleated cells/kg over 6/6 with a cell dose of  $2.0 \times 10^7$  nucleated cells/kg, or 4/6 with a dose of  $5.0 \times 10^7$  nucleated cells/kg over a 5/6 with a dose of  $2.4 \times 10^7$  nucleated cells/kg). Due to concerns regarding graft failure/rejection, UCB should never be chosen as graft source if a marrow donor is available.

**11.5 Pretransplant evaluation**

- A complete history, physical examination, and neurologic examination is necessary.
- Evaluation of organ disease by appropriate radiologic evaluation (CT, MRI, nuclear medicine) with documentation of measurable disease, as well as disease related signs and symptoms is required.
- Bone marrow aspirate and biopsy to determine LCH involvement. CD1a staining of biopsy specimen is recommended.
- Height, weight and body surface area should be recorded.
- Hematology - complete blood count, platelet count, differential, PT, PTT.
- Chemistries – ALT, AST, total bilirubin, alkaline phosphatase, albumin, total protein, electrolytes, urea nitrogen, creatinine, calcium, phosphate, uric acid.
- Other pre-HSCT studies as required by local institutional standards.

**11.6 Treatment Plan**

The conditioning therapy consists of the following:

<b>Day</b>	<b>Drug</b>	<b>Dose</b>
-8	Campath	0.2 mg/kg
-7	Campath Fludarabine	0.2 mg/kg 30 mg/m <sup>2</sup> IV over 30-60 min (dose adjust if age <12 months)*
-6	Campath Fludarabine	0.2 mg/kg 30 mg/m <sup>2</sup> IV over 30-60 min
-5	Campath Fludarabine	0.2 mg/kg 30 mg/m <sup>2</sup> IV over 30-60 min
-4	Campath Fludarabine	0.2 mg/kg 30 mg/m <sup>2</sup> IV over 30-60 min
-3	Fludarabine CsA/MMF	30 mg/m <sup>2</sup> IV over 30-60 min Start CsA (and MMF if mismatched donor or PBSC)
-2	Melphalan	140 mg/m <sup>2</sup> IV over 30 min (dose adjust if age <12 months)*
-1	Rest	
0	Stem cell infusion	
+8		GCSF 5mcg/kg/d until ANC>1000

\* for respective dose adjustment refer to Section 9.11

#### **11.6.1 Melphalan:**

Melphalan will be administered intravenously on day -2 over 15-30 minutes. Preparation, administration and monitoring will be according to standard practice procedures of local institution.

#### **11.6.2 Fludarabine:**

Fludarabine will be given IV daily on days -7, -6, -5, -4, -3, over 30-60 minutes. Preparation, administration and monitoring will be according to standard practice procedures of local institution.

#### **11.6.3 Campath1H (Alemtuzumab):**

Prepare Campath-1H for IV infusion immediately prior to use. The required dose

should be drawn up into a syringe from the ampule or vial and further diluted in 100 mL of 0.9% Sodium Chloride or 5% Dextrose, USP. Gently invert the bag to mix the solution; do not shake. Administer dose over 2 hours on days -8, -7, -6, -5, -4.

#### **11.6.3.1 Premedication:**

Twelve hours prior to start of infusion of Campath administer methylprednisolone 1mg/kg IV, then one hour prior to each dose of campath, repeat dose of methylprednisolone (1 mg/kg IV). 30 minutes prior to start of each infusion administer acetaminophen (paracetamol) 15mg/kg/dose and diphenhydramine 1.25 mg/kg/dose, may repeat Tylenol, and diphenhydramine 4-6 hrs after start of the infusion. Administer dose over 2 hours. In case of reactions, dose of methylprednisolone dose may be increased to 2mg/kg or other institutional management methods may be instituted.

#### **11.6.3.2 Campath 1H substitution**

For institutions where Campath 1H is not available, or if severe reactions not manageable with intensification of premedications, Thymoglobulin may be substituted at a dose of 2.5 mg/kg given on days -6, -5, -4, -3, -2. Use same premedications as for Campath (**Section 11.6.3.1**).

### **11.7 GVHD Prophylaxis, Supplemental therapy and Supportive Care**

11.7.1 Prophylaxis against GvHD will be cyclosporine administered intravenously divided into 2 or 3 doses starting on day -3 and continue until day + 50 and tapering over 8 weeks.

**11.7.1.1** CsA administration guidelines: starting dose is 2.5 mg/kg IV every 8 hours for patients less than 40kg or 2.5mg/kg/dose IV every 12 hours for patients over 40 kg, maintain serum trough levels at 200-400 ng/ml. When patients are able to take oral medication they may be converted to oral cyclosporine A. (CSA starting doses and serum levels may be administered and monitored according local institutional standards).

**11.7.1.2** In the absence of GvHD, cyclosporine A will be tapered at day 50 post transplantation over 8 weeks if no evidence of GvHD, however, CSA taper should be held if DLI is given for decreasing donor chimerism.

**11.7.2** For mismatched donors (any source) and peripheral blood stem cells mycophenolate mofetil (MMF) also will be given for additional GVHD prophylaxis and immunosuppression.

**11.7.2.1** Start MMF on day -3 at a dose of 3 gram/day for patients who are  $\geq$  40 kg divided in 2 or 3 doses. Patient <40 kilograms will receive MMF at the dose of 15 mg/kg/dose IV every 8 hours. IV route between days -3 and +5, then may change to PO between days +6 and +30.

**11.7.2.2** Stop MMF at day +30 or 7 days after engraftment, whichever day is later, if no acute GVHD. (Definition of engraftment is 1st day of 3 consecutive days of absolute neutrophil count [ANC]  $>$  0.5  $\times$  10<sup>9</sup> /L).

**11.7.2.3** If the patient has acute GVHD requiring systemic therapy, MMF may be stopped 7 days after initiation of systemic therapy for acute GVHD (e.g. resolution of skin rash, vomiting, diarrhea).

**11.7.3** Antimicrobial, anti-viral and anti-fungal (including mold) prophylaxis and monitoring (i.e. HSV, CMV, EBV, adenovirus, etc.) during the transplant period and in follow-up should be provided according to current local institutional standards and practices.

**11.7.4** Immunoglobulin (IVIG) substitution should be provided at a dose of 500 mg/kg every 3 weeks (begin within first 7 days post stem cell infusion), continue through day +100 and after that monitor IgG levels and treat with IVIG every 3-4 weeks if levels are below normal range.

**11.7.5** During the entire transplantation period up to day +100, no other anti-LCH chemotherapy agents such as methotrexate may be used in patients while they are enrolled in this study as some responses may take several weeks to months to be evident after HSCT.

11.7.6 GCSF 5 mcg/kg SQ or IV daily start day +8, continue until ANC >1x10<sup>9</sup>/L x 2days

## **11.8 Donor Lymphocyte Infusion (DLI)**

DLI is permitted for patients with mixed chimerism. Treating investigators may administer DLI as per institutional protocols. However, the following guidelines are also provided and may be utilized:

11.8.1 Patients with mixed chimerism (< 95% donor) and those with <50% donor T-cell engraftment at any engraftment assessment time point in the absence of GvHD are eligible for Donor Lymphocyte Infusions (DLI). Escalating doses of CD3+ lymphocytes will be administered at 3–4 week intervals in the absence of development of GvHD if mixed chimerism persists.

11.8.2 CD3+ lymphocytes will be administered in escalating dosages ( $1 \times 10^5$ ,  $5 \times 10^5$ ,  $1 \times 10^6$ ).

11.8.3 Lineage-specific chimerism (in T-cell, B-cell and myeloid lineages, if available) shall be assessed by means of PCR analysis of informative minisatellite regions or sex chromosome FISH prior to every DLI as well as every 3 months during follow-up until stable for 12 months.

## **11.9 Response Assessment**

For definitions of response categories with respect to LCH refer to Section 6.5.2

## **11.10 Follow up evaluations**

With respect to follow up schedule please refer to **Appendix A-IV\_4**

## **11.11 Dose Modifications**

**For infants < 12 months:**

Fludarabine dose = 1 mg/kg

Melphalan dose = 4.7 mg/kg

### **11.12 Drug Information**

Refer to **Appendix A-VI.**

For potential toxicity associated with HSCT see Appendix A-V\_2.

### **11.13 Autopsy report is required, if available, if death occurs during the follow-up period**

### **11.14 Data Collection and Reporting**

The enrolment will be managed through the **web-based central clinical trial database on <https://www.hs-lch-database.org>**

**For detailed instructions refer to Appendix A-I\_2**

This will serve concomitantly as a pre-transplant follow up with respect to LCH. Further follow up with respect to LCH (containing information of patient status, disease status and permanent consequences) is required at day 100, 1 year and than annually after HSCT. All additional transplant-oriented detailed information will be collected on CIBMTR collection forms, which have to be sent along with a copy of the signed consent form to Dr. Scott Baker at FAX +1-206-667-5899 or [ksbaker@fhcrc.org](mailto:ksbaker@fhcrc.org). All forms can be accessed for PDF file downloads at the following website:

<http://www.cibmtr.org/DataManagement/DataCollectionForms/index.html>

The following forms are required for submission:

Form to be completed at:	Required Forms	Where to Obtain
Study entry	Study Registration Form, Patient Eligibility Checklist	<a href="https://www.hs-lch-database.org">https://www.hs-lch-database.org</a> For detailed instruction see Appendix A-I 2
	CIBMTR LCH Disease Insert Form (2040)	<a href="https://www.cibmtr.org/DataManagement/DataCollectionForms/index.html">https://www.cibmtr.org/DataManagement/DataCollectionForms/index.html</a>
	Recipient Baseline Data Form (2100)	<a href="https://www.cibmtr.org/DataManagement/DataCollectionForms/index.html">https://www.cibmtr.org/DataManagement/DataCollectionForms/index.html</a>
	Confirmation of HLA Typing (2005)	<a href="https://www.cibmtr.org/DataManagement/DataCollectionForms/index.html">https://www.cibmtr.org/DataManagement/DataCollectionForms/index.html</a>

	HLA Typing Form (2005)	Submit for patient and donor
Day +100	100 Days post-HSCT Data Form (2100)	<a href="#">100 Days post-HSCT Data Form (2100)</a>
	CIBMTR LCH Follow-up Form (2140)	<a href="#">CIBMTR LCH Follow-up Form (2140)</a>
Day +180	6 mo to 2 yrs Post-HSCT Data Form (2200)	<a href="#">6 mo to 2 yrs Post-HSCT Data Form (2200)</a>
	CIBMTR LCH Follow-up Form (2140)	<a href="#">CIBMTR LCH Follow-up Form (2140)</a>
Day +360	6 mo to 2 yrs Post-HSCT Data Form (2200)	<a href="#">6 mo to 2 yrs Post-HSCT Data Form (2200)</a>
	CIBMTR LCH Follow-up Form (2140)	<a href="http://www.cibmtr.org/DataManagement/DataCollectionForms/2140/Rev1.0/combine_2140_LCH.pdf">http://www.cibmtr.org/DataManagement/DataCollectionForms/2140/Rev1.0/combine_2140_LCH.pdf</a>
Day +720	Yearly Follow-up for greater than 2 yrs Post-HSCT Data Form (2300)	<a href="http://www.cibmtr.org/DataManagement/DataCollectionForms/2300/Rev2.0/combine-2300-Follow-.pdf">http://www.cibmtr.org/DataManagement/DataCollectionForms/2300/Rev2.0/combine-2300-Follow-.pdf</a>
	CIBMTR LCH Follow-up Form (2140)	<a href="http://www.cibmtr.org/DataManagement/DataCollectionForms/2140/Rev1.0/combine_2140_LCH.pdf">http://www.cibmtr.org/DataManagement/DataCollectionForms/2140/Rev1.0/combine_2140_LCH.pdf</a>

### 11.15 Serious Adverse Event Definition

For this study, serious adverse events will be defined as graft failure, acute graft vs. host disease grade 3 or 4, or death from any cause in the first 100 days post-HSCT, and must be reported to the PI within 10 working days of the occurrence of the event, as well as to any local regulatory board as required at each institution. Toxicities, complications of therapy and other adverse events which are considered expected as part of therapy in general are listed in Appendix A-V\_2 and will not be reported as SAE's. After day 100, investigators must notify the PI of any death, disease recurrence

or graft rejection, acute or chronic GVHD within 30 days.

For SAE reporting form see **Appendix A-II\_2**.

## **11.16 Statistical considerations**

### **11.16.1 Definition of Endpoints**

#### **11.16.1.1 Hematopoietic recovery**

Neutrophil and platelet recovery will be analyzed separately. Achievement of absolute neutrophil count  $>0.5 \times 10^9/L$  and of untransfused platelet count  $>50 \times 10^9/L$  on three consecutive days are considered events. Patients without recovery of ANC  $>0.5 \times 10^9/L$  by day 42 will be censored as **graft failure**. Patients receiving a second transplant for non-engraftment will be censored at the time of conditioning for the second transplant or, if no additional conditioning is given, at the time of second transplant. Late graft failures (loss of haematopoiesis after initial recovery) will also be described. The degree of donor-recipient chimerism will be analyzed in those recipients for whom testing was done in the first 100 days post transplant. Presence of  $> 95\%$  donor cells will be considered full chimerism. Chimerism studies (on either bone marrow or peripheral blood by means of VNTR or FISH) should be performed at days +28, +60, +100, +360 and +720.

#### **11.16.1.2 Acute Graft Versus Host Disease (GvHD)**

The occurrence of skin, gastrointestinal or liver abnormalities fulfilling the criteria of Grades II, III and/or IV acute GVHD are considered events (**Appendix A-VIII\_2**). Patients without acute GvHD will be censored at the time of death or last follow-up. Patients that survive  $<21$  days and listed as not evaluable will be excluded. Patients receiving a second transplant will be censored at the time of second transplant.

#### **11.16.1.3 Chronic GVHD**

Occurrence of symptoms in any organ system fulfilling the criteria of limited or extensive chronic GvHD (**Appendix A-VIII\_3**), among patients surviving  $\geq 90$  days with evidence of engraftment. Patients without chronic GvHD will be censored at time of death or last follow-up.

#### **11.16.1.4 Disease-free survival**

This outcome is defined as survival with resolution of LCH at 12 months post

transplant. Unresolved disease for over 12 months post-transplant, progressive disease after this time period, recurrence of disease and death from any cause are considered events. Those who survive with resolution of disease are censored at the date of last contact.

#### **11.16.1.5 Overall survival**

Deaths from any cause are events. Surviving patients are censored at the date of last contact.

#### **11.16.2 Statistical Analysis**

Survival and disease-free survival will be estimated by the Kaplan-Meier method. Non-relapse mortality, relapse, neutrophil and platelet engraftment, acute and chronic GVHD will be estimated by cumulative incidence using competing risk methods. Chimerism will be evaluated both by simple proportions and median (range) values among assessable patients. 95% confidence intervals will be used to make inferences. Comparisons of time-to-event endpoints by various factors will be completed by the Log-rank test. Comparison of simple proportions will be evaluated by the Chi-square test and the general Wilcoxon test will be used to evaluate continuous factors.

#### **11.16.3 Rationale for Sample Size**

It is hypothesized that this new regimen will result in an overall disease-free survival rate of at least 50%. Historical survival rates in this very poor risk group of patients without RIC-HSCT are approximately 25% (11-34%). The sample size estimation is conducted using empirical 95% confidence limits after performing 1000 Monte-Carlo simulations.

Assuming a sample size of 25 patients, 5 years of enrolment, uniform censoring after 3 years and time to progression or death which follows an exponential distribution with a cure fraction by 3 years post transplant of 50%, the simulation gives a lower 95% empirical confidence limit of 26%. This will give us confidence in showing an improvement over historical rates.

Based on accrual to LCH salvage regimens and expected response (failure) rates on LCH III, we expect to enroll 5 patients per year over a 5 year period for a total enrolment of 25 subjects.

## 11.16.4 Stopping Rules

### 11.16.4.1 Graft Failure by day 42

Given a hypothesized graft failure (defined as failing to achieve an ANC >500/uL of donor origin by day 42) rate of 10%, a maximum tolerated rate of 25% and a maximum sample size of 25 patients, the trial will be stopped and reviewed if: 4/9, 5/16, 6/22 or 7/25 patients fail to engraft. This has a type I error rate of 5% and a power of 80%.

### 11.16.4.2 Treatment Related Mortality by 100 days

Given a hypothesized treatment related mortality rate of 30%, a maximum tolerated rate of 50% and a sample size of 25 patients, the trial will be stopped and reviewed if: 5/5, 6/7, 7/10, 8/12, 9/15, 10/17, 11/20, 12/22 or 13/25 patients have treatment related mortality by day 100. This has a type I error rate of 5% and a power of 80% (71).

## 12 STRATUM V: MONITORING AND TREATMENT OF ISOLATED TUMOROUS AND NEURODEGENERATIVE CNS-LCH

### 12.1 Aim

The overall aim is to better understand CNS-LCH (presentation, risk factors, course), in particular neurodegenerative CNS-LCH (ND-CNS-LCH). Additionally the effectiveness of 2-CdA in tumorous CNS-LCH (72) and of intravenous immunoglobulin (IVIG) (73, 74) and intravenous cytarabine (Ara-C) (75) in ND-CNS-LCH will be prospectively studied.

### 12.2 Study objectives

#### 12.2.1 Primary objective

- To study the course of ND-CNS-LCH (both radiological and clinical neurodegeneration).
- To study the impact of 2-CdA on the response of isolated tumorous CNS lesions. (***Nota bene!*** Patients with tumorous CNS LCH within the setting of extended disease will be treated according to Stratum I).

#### 12.2.2 Secondary objectives

- To assess whether systemic therapy can be beneficial for patients with clinically manifest ND-CNS-LCH.
- To assess the role of 2-CdA in preventing ND-CNS-LCH in patients with isolated tumorous CNS-LCH
- To study the efficacy of intravenous immunoglobulin and intravenous cytarabine in the treatment of ND-CNS-LCH (by both radiological and clinical assessment).
- To assess markers of neurodegeneration and LCH activity in the spinal fluid of patients who have diabetes insipidus as well as patients with radiologic and/or clinical signs of CNS-LCH.

### 12.3 Study Endpoints

### **12.3.1 Primary endpoints**

- The cumulative incidence of radiological and clinical neurodegeneration in patients with isolated tumorous CNS-LCH, DI, anterior pituitary dysfunction, and those with CNS-risk lesions and the respective presenting features.
- The time interval and cumulative incidence of progression of radiological neurodegeneration to clinically manifested ND-CNS-LCH

### **12.3.2 Secondary endpoints**

- Response to ND-CNS-targeted therapy at 12 and 24 months after start of therapy.
- Response of isolated tumorous CNS-LCH to 2-CDA (for response criteria refer to section 10.7.1.3)
- Frequency of ND-LCH in patients with isolated tumorous CNS-LCH
- Exploration of the value of neurochemistry, neurophysiology, and neuropsychology methods in early identification of ND-CNS-LCH and in assessing its severity, and comparison to MRI findings.

## **12.4 Eligibility Criteria and Enrollment**

- All patients with verified diagnosis of LCH and MRI findings consistent with ND-CNS-LCH irrespective of previous treatments (also those not registered to other Strata of LCH-IV).
- Patients with isolated tumorous CNS-LCH (including isolated DI with mass lesion in the hypothalamus-pituitary axis). In patients with already established diagnosis of LCH and radiologic finding of CNS lesions compatible with LCH a biopsy of the lesion is not obligatory. In all other cases a biopsy of the lesion is needed for inclusion into the study (see also 12.6.1 for more information).

## **12.5 Enrollment procedure**

### **12.5.1 IRB Approval**

Approval from appropriate authorities (e.g. national or institutional IRB) is required from each participating institution prior to accrual of patients. A copy of the official approval document must be sent to the National Coordinator (will be kept there and

must be available for monitoring, audits, and inspections).

### **12.5.2 Informed consent**

The patient, or a parent or the legal guardian of the patient, must sign a written informed consent.

### **12.5.3 Enrollment**

Enrollment will be managed through the **web-based central clinical trial database** on <https://www.hs-lch-database.org> (for detailed instructions see **Appendix A-I\_2**). **Enrolment by paper Case Report Forms could be exceptionally granted by the National Coordinator, who will have to enter the data into the database by himself.**

## **12.6 Pretreatment Evaluation**

### **12.6.1 Brain biopsy**

Brain biopsy is only indicated in patients without established diagnosis of LCH who have a negative diagnostic workup for extracranial LCH lesions.

In parenchymal lesions, in particular in the brain stem, stereotactic biopsies are rarely indicated in the context of a history of LCH outside the CNS. If a physician decides to perform a biopsy it should solely be based on clinical indications, and it is then suggested that a central expert of the study also reviews the biopsy (contact the Study Coordinators in Stockholm or Houston for contact addresses) (see **Appendix A-IX\_2**). In fatal cases of LCH with evidence of CNS-LCH, a carefully planned and executed autopsy should be done as soon as possible after death and the reports should be sent to the Study Coordinators in Vienna, Stockholm, or Houston.

### **12.6.2 Evaluation of patients with isolated tumorous CNS-LCH**

Baseline investigation performed prior to therapy should include the following:

#### **12.6.2.1 Craniospinal MRI (see “Guidelines for MRI studies” below)**

Strict following of the standardized “Guidelines for MRI studies” is recommended and will enable optimal review and most importantly optimal treatment recommendations for the individual patient.

### **12.6.2.1.1 Guidelines for MRI Studies:**

It is the aim to systematically seek neuro-degenerative involvement (cerebellum, basal ganglia, brain stem) and tumorous (hypothalamic-pituitary region, meninges, pineal gland, choroid plexus) involvement. Therefore, the MRI protocol for the examination of the brain of patients with CNS-LCH - especially for a first exploration - must be able to assess both the hypothalamic-pituitary axis and the entire brain (63). It must include:

- thin axial T1-weighted sequences with magnetization transfer contrast (MTC)
- thin coronal and sagittal T1-weighted sequences ( $\leq 3$  mm slice thickness) for the hypothalamic-pituitary region
- axial T2-weighted and FLAIR sequences ( $\leq 5$  mm slice thickness) over the entire brain
- contrast enhanced coronal and sagittal T1 weighted sequence brain and hypothalamic-pituitary region

Additional sequences may be used if indicated. It is not recommended to use magnetization transfer contrast (MTC). If MTC is done, the same technique has to be used every time and this information has to be specified on the report.

### **12.6.2.1.2 Radiological grading of ND-CNS-LCH severity**

There are three **categories of severity** of ND-CNS-LCH based on extension and pattern of MRI findings:

- **Mild:** Increased signal in basal ganglia and dentate nucleus (T1-weighted) and locally increased signal (T2-weighted) in the cerebellar white matter, predominantly in connection with dentate nucleus.
- **Moderate:** As ("mild") and in addition abnormally increased signal in brainstem, thalami and corpus callosum
- **Severe:** As ("moderate") and in addition subcortical and periventricular white matter and grey matter changes

Second opinion for MRI reviews can be provided. Send the complete MRI examination in digital format via CD, in addition to the specific radiological report sheet (**Appendix A-X\_1**) to:

**In Europe, et al:**

<b>Stockholm</b>	<b>Vienna</b>
Evaldas Laurencikas, MD, PhD Department of Radiology Danderyd Hospital SE-182 88 STOCKHOLM, Sweden Phone: +46 – 8 655 5879 Email: <a href="mailto:Evaldas.Laurencikas@ki.se">Evaldas.Laurencikas@ki.se</a>	Professor Daniela Prayer, MD or Helmut Prosch, MD Department of Radiology (771) Medical University Vienna Währinger Gürtel 18-20 A-1180 Vienna Phone: +43 -1 40 400 7620 Email: <a href="mailto:Daniela.Prayer@meduniwien.ac.at">Daniela.Prayer@meduniwien.ac.at</a> Email: <a href="mailto:Helmut.Prosch@meduniwien.ac.at">Helmut.Prosch@meduniwien.ac.at</a>

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**12.6.2.2 Baseline neurological evaluation**

The baseline neurological evaluation will be performed by the use of the ICARS (International Cooperative Ataxia Rating Scale) (16), which allows assessing postural and gait disturbances, kinetic function, speech disorders and oculomotor disorders, and in children less than 17 years also by applying the Movement Assessment Battery for Children (Movement ABC-2), which is developed as a clinical and educational tool to provide an indication of motor functioning across a range of fine and gross motor tasks among children 3-16 years old (76, 77). In addition, evaluation with the EDSS (Extended Disability Status Scale) (15), which is a method of evaluating the neurological impairment paying attention to pyramidal, cerebellar, brain stem, sensory, bowel and bladder, visual or optic, cerebral or mental functions, will be performed in both children and adults.

**12.6.2.3 Baseline neuropsychological testing**

It includes assessing of full scale intelligence quotient (IQ), verbal and performance IQ (also termed verbal factor and perceptual factor), as well as sustained attention tests, speed of processing tests, and verbal and visual-spatial working memory tests applying age-appropriate tests according to the institutions preference and giving the results in percentiles.

**12.6.2.4 Endocrine evaluation**

The endocrine evaluation includes patient's height and weight, urine osmolality after overnight water deprivation, IGF1, TSH, T4, FSH, LH, and others, as clinically indicated.

**12.6.2.5 Ophthalmologic evaluation**

It is indicated in case of hypothalamic lesions extending to the optic chiasm to assess visual impairment, scotoma, and strabismus.

#### **12.6.2.6 Brain stem evoked potentials**

The brain stem evoked potential testing (27, 78, 79) is optional. Electroencephalogram (EEG), visual evoked potentials (VEP), and brain stem acoustic-evoked potentials (BAEP) are recommended.

### **12.6.3 Patients with Neurodegenerative (ND)-CNS-LCH**

Baseline investigation at diagnosis and prior therapy of ND-CNS-LCH should include the investigations as in **Section 12.6.2**.

Cerebrospinal fluid (CSF) studies in addition to the studies recommended in **Section 12.6.2** are suggested in patients with ND-CNS-LCH.

#### **12.6.3.1 Indication for CSF examination**

Examination of CSF may be indicated in cases with isolated extraaxial mass lesions (hypothalamic pituitary region, choroid plexus, meninges) for differential diagnostic purposes. It is also suggested, but optional, in patients with diabetes insipidus, or radiological or clinical neurodegenerative disease (80). It is recommended to perform lumbar punctures with thin, non-traumatic needles and to measure the spinal fluid pressure (80).

#### **12.6.3.2 CSF diagnostic work-up**

- Measure and report the spinal fluid pressure.
- Analyze the CSF cell counts and the CSF protein levels at your local laboratory.
- We suggest also measuring albumin levels in CSF and blood, for albumin quotient.

#### **12.6.3.3 Optional CNS studies of biomarkers in CSF**

In addition to the routine CSF analyzes suggested above, two coordinated research projects will evaluate CSF biomarkers in these patients. The sampling is optional and should be obtained after a respective written consent (see Appendix A-VII\_5). Instructions for sample collection, handling and shipping, as well as appropriate contact information are provided in **Appendix A-IX\_3**.

European project: The aim of this project is to evaluate the value of CSF biomarkers for i.) An early identification of neurodegeneration, and ii.) Monitoring of treatment response in patients with ND-CNS-LCH. The neurodegenerative CSF biomarkers to

be studied include neurofilament protein light chain (NF-L), glial fibrillary acid protein (GFAp), and total tau protein (TAU), as well as inflammatory cytokines. A recent Swedish study in a small patient number preliminary indicates that in particular NF-L may be of value in to monitor ongoing neurodegeneration (80). For sampling instructions see **Appendix A-IX\_3**.

North American project: Studies on CSF and plasma are based upon current findings on cell-specific gene expression (81). Several of the most highly expressed genes will be assayed in patient specimens and compared to controls. The aim is to define markers of LCH in the CSF that will aid in diagnosing LCH as well as the response to therapy. For sampling instructions see **Appendix A-IX\_3**.

## 12.7 Treatment

Due to the rarity and heterogeneity of CNS-LCH a randomized study is not feasible. The following therapeutic options are proposed based on the limited therapeutic experience from the former CNS-LCH Study and that of single centers. It is therefore strongly recommended to submit reports at onset of therapy and follow-up, even if other treatments than those listed below are administered.



### 12.7.1 Treatment of isolated tumorous CNS-LCH

Any of the following brain regions may be involved as isolated lesions or in the context of multisystem disease: hypothalamic-pituitary region (HPR), pineal gland, meninges or choroid plexus.

Patients who have tumorous CNS-LCH within the context of a multisystem disease will be treated according to Stratum I (initially) or Stratum II (in case of a reactivation).

#### 12.7.1.1 Indication

The treatment option specified below is indicated in cases of isolated tumorous CNS-LCH (no active extracranial LCH at the time of therapeutic decision).

#### 12.7.1.2 Treatment plan

2-Chlorodeoxyadenosine: 5mg/m<sup>2</sup>/day in 250 ml/m<sup>2</sup> normal saline, given as a 2-hour

i.v. infusion daily for 5 days per course.

**For dose modifications refer to Section 10.8**

Six courses (**maximum**) in intervals of 4 weeks are recommended, with MRI response evaluation after two, four, and six courses.

All patients will receive at least 2 courses with further treatment decision depending on response.

**After two courses:**

- Those who after two courses have a complete or partial response will receive another two courses.
- Those with progressive disease should discuss further treatment with the PIs.

**After four courses:**

- those patients who have had complete response after 2 courses and retained it after four courses will stop treatment and will be followed
- those who had partial response after 2 courses and complete response after 4 courses will receive another 2 courses
- those with partial response after four courses will receive another 2 courses
- those with progressive disease after four courses have to be discussed with the PIs

**After six courses:**

Those who have not achieved complete response have to be discussed with the PIs

#### **12.7.1.3 Response criteria in isolated tumorous CNS-LCH**

Being aware of the drawbacks of tumor size reduction as a response criterion, for a uniform response evaluation we will adopt modified RECIST criteria (82-85) will be adopted for their simplicity and reproducibility (Table XV).

**Table XV: Radiological response criteria for tumorous CNS-LCH lesions**

<b>Response categories</b>	<b>Response definitions</b>
Complete response (CR)	Disappearance of all tumorous CNS-LCH lesions
Partial response (PR)	At least 30% decrease in longest diameter (LD) of single lesion or sum of the LDs of multiple masses
Stable disease (SD)	Neither PR nor PD criteria met
Progressive disease (PD)	Greater than 20% increase in LD of single

	tumor or the sum of LDs in multiple masses, or appearance of new lesions
--	--------------------------------------------------------------------------

## 12.7.2 Treatment of ND-CNS-LCH

There is currently no consensus on whether to recommend therapy for patients with isolated radiological neurodegeneration if there are no clinical signs of neurodegeneration. Follow up with a battery of standardized examinations (see Section 12.6.3) is recommended in order to detect clinical neurodegeneration.

### 12.7.2.1 Indication for therapy

The therapy options specified below are indicated **ONLY** in patients with **clinical** neurodegeneration (for definitions see chapter 6.4.2.3 “Definition of organ involvement”) in combination with typical imaging findings. In case of progressing MRI findings (unequivocal progression on at least 3 MRI studies performed over a time period of at least 6 months) without clinical signs of ND-CNS-LCH discussion with the National Study Coordinator and the Principal Investigator is recommended.

### 12.7.2.2 Treatment options

Two therapy options reported in the literature are suggested at the choice of the treating physician:

- **Cytosine arabinoside (Ara-C):** 150 mg/m<sup>2</sup>/day daily for 5 days. This course should be repeated every 4 weeks for 12 months (75).
- **Intravenous immunoglobulin (IVIG):** a dosage of 0.5 g/kg/dose repeated every 4 weeks for 12 months. One may also give additional VBL with or without 6-MP and/or MTX when other sites of active LCH exist (74).

**See section 10.8 for dose modifications.**

### 12.7.2.3 Response assessment for treated patients with ND-CNS-LCH

- MRI at 6, 12, and 24 months from therapy start, then yearly for 5 years, and if stable every 2 years for additional 5 years, then as clinically indicated.
- Neurological evaluation (the ICARS and the EDSS) - after 6, 12, and 24 months from therapy start, then yearly for 5 years, and if stable every 2 years

for additional 5 years, then as clinically indicated. Movement ABC-2 is suggested to be used in parallel in children less than 17 years.

- Neuropsychological testing – every 2 years.
- Endocrine evaluation yearly including urine osmolality after overnight water deprivation, IGF1, TSH, T4, FSH, LH, and others as clinically indicated.
- Brain stem evoked potentials – 6, 12, and 24 months from therapy start, then yearly (optional).
- CSF studies (see below) – 6, 12, and 24 months from therapy start, then yearly (optional) (80).

#### **12.7.2.4 Response criteria for clinical ND-CNS-LCH**

Regression of clinical ND is defined as:

- EDSS - a loss of 0.5 steps is defined as “better”
- ICARS - a loss of 2 points is defined as “better”
- Movement ABC-2 – change from one percentile category\* to the next upper is defined as “better”
- Neuropsychological Tests – improvement to be judged by the testing psychologist
- Radiological (MRI) findings (see below)

**Progression of clinical ND-CNS-LCH is defined as:**

- EDSS - a gain of 0.5 steps is defined as “worse”
- ICARS - a gain of 2 points is defined as “worse”
- Movement ABC-2 – change from one percentile category\* to the next lower is defined as “worse”
- Neuropsychological Tests – worsening to be judged by the testing psychologist
- Radiological (MRI) findings (see below)

\* The Movement ABC-2 is assessed in age-specific percentiles. The test results expressed in percentiles are usually grouped into the following categories:

- **0-5 Perc. = impaired**
- **5-15 Perc. = at risk**
- **>15 Perc. = normal**

### **Radiological (MRI) response criteria in ND-CNS-LCH.**

Judgment of MRI response is based on number, extension and signal intensity of the neurodegenerative lesions (Table XVI).

**Table XVI Radiological response criteria in ND-CNS-LCH**

<b>Response category</b>	<b>Regression</b>	<b>Progression</b>
<b>Mild</b>	regression within same category*	progression within same category*
<b>Moderate</b>	downgrade of the category* (severe to moderate, or moderate to mild)	upgrade of the category* (mild to moderate, or moderate to severe)
<b>Marked</b>	from severe to mild	from mild to severe

\* Severity categories as defined in section 12.6.2.1.2

In case of progressive neurodegeneration while on protocol treatment please contact the National Study Coordinator and the Principal Investigator to discuss other experimental options.

## **12.8 Dose Modifications**

### **12.8.1 Dose modification for age**

In children who are < 10 kg body weight:

- Ara-C: 5 mg/kg/day
- 2-CdA: 0,17 mg/kg/day

### **12.8.2 Dose modification for treatment-related toxicities**

- 2-CdA

If platelet count drops to <  $50 \times 10^9/L$  and does not increase between courses, hold next course until platelet count  $> 100 \times 10^9/L$  and reduce dose of 2-CdA by 50%. If on subsequent courses the platelet count drops to  $50 \times 10^9/L$  and does not rise, stop 2-CdA and discuss case with European or North American Principal Investigator for alternative therapy.

If absolute lymphocyte counts (ALC) drops to less than  $1.0 \times 10^9/L$  initiate monthly treatment with IVIG at 500mg/kg until ALC rises and immunoglobulin levels before the next scheduled dose of IVIG have normalized.

- ARA-C:

Do not withhold Ara-C for fever if it is likely to have been caused by the Ara-C. For rash or conjunctivitis, withhold for Grade 3-4 toxicity until resolved. Consider pre-

medication with paracetamol (acetaminophen) if patient develops fever.

If profound diarrhea is associated with Ara-C treatment notify National Study Coordinator and decrease dose by 25%. If symptoms persist despite this discuss case with regional coordinator. When patients have profound cytopenias that do not resolve during the 3-week rest period and treatment is delayed discuss with the National Study Coordinator for a dose modification plan or switch to alternative therapy.

### **12.9 Supportive Care**

Supportive care recommended as in section 6.9.

It is strongly recommended that patients treated by ARA-C or 2-CdA have to receive Pneumocystis jiroveci prophylaxis with TMP/SMZ.

### **12.10 Off-Therapy Criteria**

**A patient may be taken off therapy in case of clinical or radiological progression.**

- Progressive disease with involvement of risk organs at any time
- Diagnosis of a malignant neoplasm
- Refusal of further protocol therapy by patient/ parent/ guardian
- Completion of planned therapy
- Excessive toxicity
- Physician determines it is in patient's best interest

Patients who are off protocol therapy are to be followed until they meet the criteria for Off Study (see below). Follow-up data will be required unless consent was withdrawn.

**12.11 Off-Study Criteria**

- Death
- Lost to follow-up
- Withdrawal of consent for any further data submission

**12.12 Drug Information**

Refer to Appendix A-VI

**12.13 Consent forms**

Refer to Appendix A-VII-5

**12.14 Statistical Considerations**

This stratum will be evaluated by the means of descriptive statistics.

## **13 STRATUM VI: NATURAL HISTORY AND MANAGEMENT OF “OTHER” SS-LCH**

### **13.1 Aims**

To describe the natural history of single system LCH treated by conservative methods  
- “wait and watch” approach or local therapy.

### **13.2 Primary end-point**

Reactivation-free survival

(The reactivation free survival is defined as the time from diagnosis to progression, reactivation or death. Patients without events are censored at their last follow-up evaluation).

### **13.3 Secondary end-points**

- Need for systemic therapy later during disease course
- Spectrum and cumulative incidence of permanent consequences

### **13.4 Eligibility criteria**

Patients with newly diagnosed SS-LCH and localization other than “multifocal bone”, isolated tumorous CNS lesion, or isolated “CNS-risk” lesion.

### **13.5 Exclusion criteria**

- Patients with SS-LCH who have an isolated tumorous CNS lesion (they are eligible for Stratum V),
- Patients with isolated “CNS-risk” or multifocal bone lesions (they are eligible for Stratum I, Group 2)

### **13.6 Enrollment procedures**

#### **• IRB Approval**

Approval from appropriate regulatory administrations (e.g. national or institutional IRB) is required of each participating institution prior to accrual of patients. A copy of the official approval document must be sent to the National Coordinator.

- **Informed consent**

The parents or the legal guardians of the patients must sign a written informed consent prior to enrollment and the respective entry (checkbox) in the clinical trial database has to be performed. The signed original consent form has to be kept in the study records of the patient and be provided upon request by study monitor or competent authorities.

- **Enrollment**

Enrollment will be managed through the **web-based central clinical trial database** on <https://www.hs-lch-database.org> (for detailed instructions see **Appendix A-I\_2**). **Enrolment by paper Case Report Forms could be exceptionally granted by the National Coordinator, who will have to enter the data into the database by himself.**

## **13.7 Evaluation of disease**

### **13.7.1 Initial evaluation:**

Initial evaluation as in Section 6.2 is mandatory in order to exclude additional lesions

### **13.7.2 Follow-up evaluation**

The follow-up evaluation depends on site.

#### **13.7.2.1 Isolated (bone, soft tissue, other) lesion:**

- Clinical examination with recording of height, weight and pubertal status at 6 weeks, 3 months, 6 months and 1 year after diagnosis, and 6 monthly to total duration of at least 5 years. Special attention should be paid to signs or symptoms of characteristic permanent consequences (**Table XVII**).
- Imaging: x-ray or another appropriate technique (needs to be consistent with previous evaluation) after 3 months and thereafter at 6-month intervals or as clinically indicated, till healing.

#### **13.7.2.2 Isolated cutaneous LCH**

Skin involvement is assessed clinically every 2 –4 weeks until stable or resolved. Special attention should be paid to signs and symptoms suggesting generalization of the disease process (e.g. failure to thrive, pallor, enlarged organs, respiratory symptoms, etc). After complete disease healing 6 monthly check-ups for at least 5 years are recommended. Special attention should be paid to signs or symptoms of characteristic permanent consequences (**Table XVII**).

**Table XVII: Characteristic permanent consequences of LCH**

<b>LCH</b>	<b>Sequelae</b>
<b>Bone</b>	Deformity, facial asymmetry, dental problems
<b>Orbits</b>	Residual proptosis, visual loss or deficit
<b>Ear</b>	Deafness
<b>Skin</b>	Scarring, xanthomata
<b>Brain</b>	Cerebellar ataxia, learning difficulty, hydrocephalus, meningeal plaques, seizures
<b>Hypothalamus and Pituitary</b>	Diabetes insipidus, GH and other anterior pituitary deficiencies, hypothalamic syndrome
<b>Liver</b>	Sclerosing cholangitis
<b>Lung</b>	Pulmonary fibrosis, abnormal PFT, respiratory symptoms
<b>Lymph nodes</b>	Chronic discharging sinuses
<b>General</b>	Growth retardation
<b>Consequences of therapy</b>	Secondary malignancy
<b>Radiation sequelae</b>	Alopecia, scarring, lymphedema, xerostomia

### **13.7.3 Disease state definition**

Disease state should be defined according to the categories presented in Section 6.5.1

### **13.8 Treatment options**

**13.8.1 Management (mostly “wait & see” and topical treatment) is left to the discretion of the treating physician. All treatments and disease responses must be reported in the database. In the case of uncertainties please contact your National Coordinator.**

**13.8.2 Patients being followed on Stratum VI who have progression of disease to MS-LCH, multifocal bone disease or CNS-risk bone lesions should be enrolled on Stratum I therapy.**

**13.8.3 Patients being followed on Stratum VI who develop isolated tumorous or neurodegenerative CNS-LCH should be enrolled on Stratum V.**

## **14 STRATUM VII: LONG-TERM FOLLOW-UP**

### **14.1 Aim**

To collect data on the incidence and prevalence of sequelae/ permanent consequences (PC) in all patients registered on LCH IV depending on disease stratification/ organ involvement.

### **14.2 End points**

#### **14.2.1 Primary end point:**

Cumulative incidence of specific PC e.g. diabetes insipidus (DI), growth hormone deficiency (GHD), neuropsychological impairment, etc.

#### **14.2.2 Secondary end points:**

- Identify possible risk factors for PC
- Assess the role of systemic treatment in preventing PC

### **14.3 Eligibility criteria**

All patients registered in LCH IV (regardless of treatment) as long as consent for long-term follow-up has not been withheld.

### **14.4 Enrollment**

The need for a long-term follow-up will be explained in the consent form of each treatment stratum and respective consent will be obtained there. Therefore, no separate consent form will be available for the follow-up stratum. Each patient will be automatically put on Stratum VII once treatment has been completed, if i) consent available and ii) NAD (disease resolution) has been achieved.

### **14.5 Follow-up schedule**

#### **14.5.1 General schedule**

The follow up evaluation scheme after end of therapy is presented in **Table XVIII**. The evaluation scheme is based on the assumption that patients have non-active disease (NAD) at time of stop of therapy. In the case of signs and /or symptoms suggesting disease reactivation a basic evaluation as described in Section 6.2 has to be performed.

**Table XVIII: Follow-up evaluation after end of therapy**

<b>Test</b>	<b>Indication</b>	<b>Year 1</b>	<b>Years 2 – 5*</b>
Ask for history of polyuria/polydipsia	All patients	3 monthly	6 monthly
Clinical examination	All patients		
Height, weight, pubertal status	All patients	6 monthly	6 monthly
Blood counts	Hematological involvement	3 monthly	Yearly
liver tests (GPT, GGT, Bili, ALP)	Liver involvement		
Liver ultrasound	Liver involvement	6 monthly	Yearly
Low-dose multidetector CT or HR-CT	Pulmonary involvement	6 monthly	As clinically indicated, at least once at 5 years
Pulmonary function tests	Pulmonary involvement	6 monthly	Yearly
Radiographs/ MRT/ CT	Skeletal involvement	Only if new lesions or reactivation suspected	Only if new lesions or reactivation suspected
Audiology	Ear/mastoid involvement	End of therapy	At school entry and as clinically indicated
Dental assessment	Oral tissue/ jaw involvement	As clinically indicated	As clinically indicated, at least once at 5 years
Urine osmolality in an early morning sample, water deprivation test (WDT), MRI	History of polyuria/polydipsia	Once DI is confirmed WDT does not need to be repeated	See Stratum V
Brain MRI **	DI or other endocrinopathies or patients with CNS risk lesions	see Stratum V	See Stratum V
Neuropsychometric assessment	Radiological or clinical neurodegeneration***	See Section 12 (Stratum V)	See Section 12 (Stratum V)

\* A follow-up of at least 5 years is required. The follow-up should be continued preferably till the end of puberty (age of 18) in order to capture some possible late permanent consequences described below. Beyond 5 years of follow-up yearly examinations are recommended.

\*\* for MRI guidelines see Section 12.6.2.1.1

\*\*\* for detailed information see Section 12

#### **14.5.2 Diabetes insipidus**

Diabetes insipidus (DI) is the most frequent endocrinopathy associated with LCH. It is due to involvement of the posterior pituitary gland and may become manifest either before, concurrently or after LCH diagnosis. It is thus important to always investigate

thirst and polyuria in LCH patients, even many years after diagnosis. In case of symptoms investigate

- a. Early morning urine specific gravity and osmolality
- b. Blood electrolytes
- c. Water deprivation test if possible
- d. MRI head to assess the pituitary stalk and gland and look for disease reactivation

#### **14.5.3 Growth and puberty:**

Growth hormone deficiency is the most frequent anterior pituitary hormone loss and is seen in up to 10% of MS-LCH patients. Other problems include delayed puberty and rarely panhypopituitarism. Measurement of height and weight and assessment of puberty is therefore recommended every 6-12 months until growth is completed.

##### **14.5.3.1 Growth:**

Ideally, standardized equipment, such as a Harpenden stadiometer (86) or other similar stadiometer should be used, and by the same operator.

Measurements must be plotted onto appropriate growth charts (National growth charts if available, or WHO or Tanner charts) and assessed in relation to parents' heights.

Serial measurements should be plotted.

Standard deviation (SD) scores for age, sex and country should be calculated where possible and plan for investigations as below.

***Indications for investigation of growth:*** (Criteria for investigation are taken from the Consensus guidelines of the GH Research Society (87):

If SD scores are available:

- a) Any child with severe short stature defined as a height more than 3SD below the mean
- b) Height more than 1.5 SD below mid-parental height
- c) Height more than 2 SD below the mean and a height velocity > 1SD below mean for age
- d) In the absence of short stature, a height velocity more than 2SD below the mean over 1 year or 1.5 SD over 2 years

If SD scores are not available:

- a) Any child between the ages of 2 and 10 years who is growing at less than 5 cms per year (this child has a low height velocity, and will drop below the expected centile with time)
- b) Any child whose height is well below the expected centile for parents' heights
- c) Children with excessive weight gain in relation to height
- d) Any child who does not have an adequate pubertal growth spurt despite onset of puberty

#### **14.5.3.2 Puberty:**

Assess puberty according to Tanner stages starting from age 8 years in girls and 9 years in boys.

##### ***Indications for investigation of puberty:***

- a) Delayed onset of puberty (B2>13 years in girls, P2, T2> 14 years in boys)
- b) Delayed onset of periods (menarche) in girls (> 14 years)
- c) Precocious puberty (B2 <8 years in girls, P2, T2<9 years in boys)
- d) Arrest or regression of pubertal development. (A child who starts pubertal development at correct time, but then does not progress or has loss of secondary sexual characteristics)

##### ***Investigations for delayed growth / puberty:***

1. Bone age assessed on X ray (88)
2. Anterior pituitary function tests (in those with poor growth / delayed puberty depending on the suspected deficit)
  - a. Stimulation of GH secretion using Insulin, Glucagon, Clonidine or Arginine stimulation test
  - b. IGF-1 levels
  - c. Gonadotropin releasing hormone/ luteinizing hormone releasing hormone (GnRH, LHRH) to assess LH and FSH secretion in case of suspicion of hypogonadotropic hypogonadism
  - d. Thyroid function test
  - e. Cortisol levels
3. MRI scan of brain and pituitary (if there is any hormone deficiency)

4. Bone mineral density (DEXA) scan needs to be monitored in patients with GH deficiency, delayed puberty, panhypopituitarism
5. Consider karyotype analysis in girls with delayed puberty and short stature as they might have Turner syndrome

#### **14.5.4 Orthopedic**

Lesions of the vault of the skull and the long bones of the limbs usually heal without major problems. However, when vertebrae are affected scoliosis may become manifest later in life, in particular during periods of rapid growth such as puberty. Children should be assessed clinically at least annually in particular during puberty in order to identify any early signs of scoliosis. They should be referred to the orthopedic surgeon in order to start preventative physical therapies (e.g. orthopedic corset/ brace, or neck collar) in order to manage this proactively.

If facial bones are affected by the disease, facial asymmetry may become manifest as the child grows and reconstructive surgery may be required.

#### **14.5.5 Ears**

Subjects with involvement of the middle or inner ear should be monitored with audiology at diagnosis and at end of treatment and reassessed at start of school and if any new symptoms develop.

Early diagnosis and interventional strategies such as hearing aids can avoid deterioration of school performance and significantly improve outcome.

#### **14.5.6 Oral tissue and jaw**

Subjects with LCH involvement of gums and jaw should be monitored for dental development and growth of the jaw, as they might need orthodontic surgery.

#### **14.5.7 Neurological**

Children with multisystem LCH and those with single system LCH and cranio-facial (“CNS risk”) lesions are at risk of developing late neuropsychological sequelae, in particular cerebellar ataxia and learning difficulty. Therefore, they should be regularly followed up clinically. Children with CNS risk lesions and those with radiological and clinical neurological abnormality will be followed as recommended in Stratum V.

#### 14.5.8 Lungs

In those children with a history of lung involvement pulmonary function tests should be performed as recommended in **Table XVIII**.

If pulmonary function is abnormal perform low dose multidetector CT or HR-CT of chest.

The dangers of smoking should be explained and smoking avoided.

#### 14.5.9 Liver

Liver involvement is rare, but can result in serious morbidity. Only those with abnormal liver function might need further investigation including ultrasound of liver or cholangiography.

#### 14.5.10 Associated malignancies

There is a recognized association between LCH and malignancies (89-91). The malignancies may precede, occur concurrently or follow the diagnosis of LCH and should be considered at every clinical visit.

Acute leukemia should be considered in patients who develop signs of bone marrow involvement or hepatosplenomegaly. Acute lymphoblastic leukemia and lymphoma more often occur prior to the diagnosis of LCH, but may be diagnosed within 5 years after LCH.

Myeloid leukemias may follow LCH especially in those patients exposed to etoposide, alkylating agents and/or radiotherapy. With the current treatment strategy it is expected that these types of secondary malignancy will be exceptional.

Solid tumors may precede, occur concurrently or follow the diagnosis of LCH. Those that follow LCH develop in a previous radiation field e.g. sarcoma, skin or thyroid cancer.

### 14.6 Statistical analysis

The cumulative risk of developing a permanent consequence (PC) will be calculated overall and by system involvement starting from the date of LCH diagnosis by using the Kaplan-Meier method. Treatment exposure, age at diagnosis, and organ involvement will be used as covariates in a multivariable analysis to estimate the risk of developing PC.

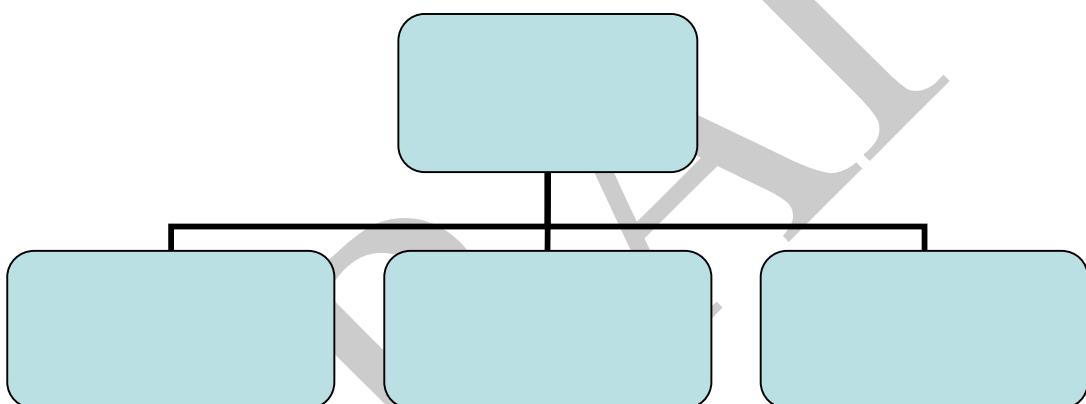
## 15 DATA SAFETY MONITORING COMMITTEE (DSMC)

The LCH-IV Study will be reviewed by the Data Safety Monitoring Committee (DSMC) of the Histiocyte Society. Thus, the respective SOPs and requirements of the DMC have to be followed (for details refer to [Appendix A XII](#): "The Charter and Standard Operating Procedures of the Data Safety Monitoring Committee (DSMC) of the Histiocyte Society").

Relevant implications for the LCH-IV Study management originating from the above mentioned document will be summarized below.

### 15.1 Organisational Diagram

The diagram refers to the relationships between the DSMC and the committees or functional areas involved in the trial



### 15.2 Reporting to the DSMC

„The DSMC will review all therapeutic trials prior to implementation for general scientific merit, with particularly attention to statistical design, feasibility, data monitoring plan and risk benefit assessment“

„Each “statistical considerations” section of Phase III protocols and Pilot studies of therapy for newly diagnosed patients must specify the time at which the study has reached its “information goal”. Typically, the information goal will be specified in terms of a total number of observed events.“

***Therefore, the protocol will be submitted for a review by the DSMC of the Histiocyte Society before submission to the competent Authorities.***

„At protocol-specified time points (annually at a minimum) the DSMC reviews reports of interim analyses of study toxicity and outcomes prepared by the study statistician, in conjunction with the study progress report. The DSMC will review the report and have access to the database, study statistician and study chair.“

***Therefore, interim study reports will be provided to the DSMC at least annually, or more frequently if in view of DSMC, the study chair(s), or the PIs, there is an obvious need for an extraordinary reporting and review.***

DRAFT

## 16 SAFETY REPORTING

### 16.1 Definitions

#### 16.1.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom or disease temporally associated with the use of an, whether or not related to the investigational medicinal product. (International Conference of Harmonization -ICH-Guideline E2A).

#### 16.1.2 Adverse Reaction (AR)

All untoward and unintended responses to an investigational medicinal product (IMP) related to any dose administered.

An AE judged by either the reporting Investigator or Sponsor as having causal relationship to the IMP qualifies as an AR. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

#### 16.1.3 Serious Adverse Event (SAE)

Any untoward medical occurrence or effect that at any dose:

- results in death unrelated to original disease
- is life-threatening\*

\* The term *life-threatening* in the definition of an SAE refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- requires hospitalization or prolongation of existing patient's hospitalization\*\*

\*\* Hospitalization is defined as an unplanned, formal inpatient admission, even if the hospitalization is a precautionary measure for continued observation. Thus hospitalization for protocol treatment (e.g. line insertion), elective procedures (unless brought forward because of worsening symptoms) or for social reasons (e.g. respite care) are not regarded as an

### SAE

- results in persistent or significant disability / incapacity
- is a congenital anomaly/birth defect in the offspring
- or is otherwise considered medically significant by the Investigator\*\*\*

\*\*\*Medical and scientific judgment should be exercised in deciding whether an AE is serious in other situations. Important AE that are not immediately life-threatening or do not result in death or hospitalization, but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above, should be considered serious (s. ICH guideline E2A, section IIB).

In case of any other events stated as serious by the treating physicians, the National Study Coordinator and the respective Principal Investigator should be consulted.

The most common **life-threatening events** as defined above are:

- circulatory/cardiac insufficiency requiring catecholamines /positive inotropes
- respiratory failure requiring intubation/ventilation
- other serious situations requiring immediate intervention, e.g.
  - gastrointestinal bleeding or perforation requiring immediate surgery
  - cerebral abscess/bleeding requiring immediate neurosurgical intervention

#### **16.1.4 Serious Adverse Reaction (SAR)**

An Adverse Reaction which also meets the definition of a Serious Adverse Event.

#### **16.1.5 Unexpected Adverse Reaction (UAR)**

An AR, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator Brochure for an unapproved IMP or (compendium of) Summary of Product Characteristics (SPC) for a licensed product).

When the outcome of an AR is not consistent with the applicable product information the AR should be considered unexpected.

#### **16.1.6 Suspected Unexpected Serious Adverse Reaction (SUSAR)**

A SAR that is unexpected i.e. the nature, or severity of the event is not consistent with the applicable product information.

A SUSAR should meet the definition of an AR, UAR and SAR.

### **16.1.7 Documentation and Reporting**

Adverse events will be documented on the chemotherapy and toxicity forms. If adverse events occur which are not explicitly named in the Case Report Forms, these events have to be named and classified using the severity levels mentioned in Section 16.5.1.

## **16.2 Reporting Requirements**

### **16.2.1 Adverse Events**

AEs are commonly encountered in patients receiving chemotherapy. As the safety profiles of the Investigational Medicinal Products used in this trial are well characterised, only Adverse Reactions (ARs) experienced during treatment will be reported.

### **16.2.2 Serious Adverse Events**

Investigators should report AEs that meet the definition of a Serious Adverse Event (SAE) and are not excluded from the reporting process as described below.

#### **16.2.2.1 Events that do not require expedited reporting**

Patients receiving chemotherapy may require admission to hospital for appropriate medical intervention following development of some of the more severe known side effects of treatment. For this reason the following SAEs do not require expedited (immediate) reporting by site and are not regarded as unexpected for the purpose of this trial:

- Admissions to control symptoms of nausea and vomiting unless the condition is life-threatening or proves fatal
- Admissions for supportive treatment during an episode of myelosuppression unless this proves fatal or requires admission to a high dependency or intensive care facility

An SAE Form should still be completed for these events, but can be sent at any time prior to completion of chemotherapy treatment.

#### **16.2.2.2 Events that do not require reporting on a SAE Form**

The following events are not to be considered as SAEs (please note that the recommendations given in the list below cannot cover all possible clinical events, but they represent examples of the more common adverse events not to be reported as

serious):

- Hospitalizations for:
  - a) Planned as per protocol medical/surgical procedure
  - b) Admission for medical events that, according to medical and scientific judgment, are neither immediately nor hypothetically life-threatening
  - c) Routine health assessment requiring admission for baseline/trending of health status documentation
  - d) Medical/surgical admission for purpose other than remedying ill health state (planned prior to entry into study trial)
  - e) Other life circumstances that carries no bearing on health status and requires no medical/surgical intervention (i.e. lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative reason)
  - f) Non life-threatening infections (except for all proven, probable or possible fungal infections, for severe local infections, and for infections of the central nervous system)
  - g) Uncomplicated drug-induced diabetes mellitus (except if requiring insulin treatment longer than 1 week)
  - h) Parenteral nutrition or i.v.-rehydration due to mucositis, inappetence/anorexia or vomiting/diarrhea
- Progression or death as a result of the underlying disease, as this information is captured elsewhere on the Case Report Form
- Common disease-related organ dysfunction (it will be captured in the patient's CRF):
  - Pancytopenia
  - liver dysfunction (hypoproteinemia, hypoalbuminemia; hyperbilirubinemia due to sclerosing cholangitis)
  - Pneumothorax, respiratory failure due to pulmonary involvement

An event requiring an intervention for preventing a life-threatening situation (e.g. dialysis due to acute renal failure) is not life-threatening *per definitionem*

#### **16.2.2.3 Monitoring pregnancies for potential SAE**

Most of the patients are expected to be prepubertal, and hence not in child-bearing age. Female patients who are in child-bearing age will be advised about the need of contraception and pregnancy testing will be performed before trial enrollment.

### **16.2.3 Reporting period**

Details of all AEs (except those listed above) will be documented and reported from the date of commencement of protocol defined treatment until 30 days after the administration of the last treatment.

## **16.3 Reporting Procedure**

### **16.3.1 Participating site**

#### **16.3.1.1 Adverse Events**

AEs experienced during the reporting period should be recorded in the toxicity section of the Treatment Form.

AEs will be reviewed using the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (see **Appendix A-V**). Any AEs experienced by the patient but not included in the CTCAE should be graded by an Investigator and recorded on the AE Form using the Severity Scale in **Section 16.5.1**. For each sign/symptom, the highest grade observed since the last visit should be recorded.

#### **16.3.1.2 Serious Adverse Events**

AEs defined as serious and which require reporting as an SAE (excluding events listed in **Sections 16.2.2.1 and 16.2.2.2**) should be reported on an SAE Form. When completing the form, the Investigator will be asked to define the causality and the severity of the AE which should be documented using the CTCAE version 4.0.

The SAE reporting will be managed by a specific tool of the remote database system at <https://www.hs-lch-database.org>. The reporting investigator must log in, complete and sign the electronic SAE report form. The system will automatically notify the National Principal Investigator and the International LCH-IV Study Management Center in Vienna.

If for some reasons the use of the remote data-base system is not possible, the paper SAE report form (**Appendix A-II\_2**) has to be filled in and sent by **Fax to**

- **Fax: +43 1 40470 7430**
- **Fax: to the respective National Principal Investigator**  
(Fax numbers provided in **Section 1.2.3**)

as soon as possible and no later than 24 hours after first becoming aware of the event. On receipt the International LCH-IV Study Management Center will allocate each SAE a unique reference number. This number will be sent back to the site as

proof of receipt by either the remote database system or Fax, depending on the way of transmission. If confirmation of receipt is not received within 1 working day please contact the International LCH-IV Study Management Center. The SAE reference number should be quoted on all correspondence and follow-up reports regarding the SAE. The SAE Form with its unique reference number should be filed in the patient's medical/study records and in the Investigator Site File (ISF).

For SAE Forms completed by someone other than the Investigator the Investigator will be required to countersign the original SAE Form to confirm agreement with the causality and severity assessments.

#### **16.3.1.3 Provision of follow-up information**

Patients should be followed up until resolution or stabilisation of the event. Follow-up information should be provided by a new SAE Report Form being marked as a follow-up report.

#### **16.3.2 International LCH-IV Study Management Center**

On receipt of a SAE Report Form seriousness and causality will be determined independently by the Coordinating Principal Investigator of the respective Stratum and by the National Principal Investigator. A SAE judged by the Investigator, the Coordinating Principal Investigator of the respective Stratum, or by the National Principal Investigator to have a reasonable causal relationship with the trial medication will be regarded as a Serious Adverse Reaction (SAR). The Coordinating Principal Investigator of the respective Stratum will also assess all SARs for expectedness. If the event meets the definition of a SAR that is unexpected (i.e. is not defined in the Drug Information provided in **Appendix A-VI**) it will be classified as a Suspected Unexpected Serious Adverse Reaction (SUSAR).

#### **16.3.3 Reporting to the Competent Authority and main Research Ethics Committee**

##### **16.3.3.1 Suspected Unexpected Serious Adverse Drug Reactions (SUSAR)**

The International LCH-IV Study Management Center will report a minimal data set of all individual events categorized as a fatal or life-threatening SUSAR to the Competent Authority and main Research Ethics Committee (REC) of Austria within 7 days. This report will be provided within the same time frame to all National Principal Investigators, who must submit it to the respective Competent Authorities and Ethics

Committees at a national level. Detailed follow-up information will be provided within an additional 8 days.

All other events categorized as SUSARs will be reported within 15 days.

#### **16.3.3.2 Serious Adverse Reactions (SARs)**

The International LCH-IV Study Management Center will report details of all SARs (including SUSARs) to the Competent Authority and main REC annually from the date of the Clinical Trial Authorization, in the form of an Annual Safety Report. This report will be distributed also to all National Principal Investigators for submission to the respective Competent Authorities and Ethics Committees at a national level.

#### **16.3.3.3 Adverse Events (AEs)**

Details of all AEs will be reported to the Competent Authority on request.

#### **16.3.3.4 Other safety issues identified during the course of the trial**

The Competent Authority and main REC will be notified immediately if a significant safety issue is identified during the course of the trial.

#### **16.3.4 Investigators**

Details of all SUSARs and any other safety issue which arises during the course of the trial will be reported to both the Coordinating and the National Principal Investigators. A copy of any such correspondence should be filed in the ISF.

#### **16.3.5 Data Safety Monitoring Committee**

The independent Data Safety Monitoring Committee (DSMC) will review all SAEs.

### **16.4 Therapeutic Procedures**

AEs requiring therapy must be treated with recognized standards of medical care to protect the health and well being of the subject. Appropriate resuscitation equipment and medicines must be available to ensure the best possible treatment of an emergency situation.

The action taken by the Investigator must be documented on the SAE forms according to the following classification.

## 16.5 Classification of an Adverse Event

### 16.5.1 Severity

The severity of adverse events will be assessed according to the CTC criteria. Adverse events which are not explicitly listed in the CTC criteria are assessed analogously by the following 5-point system.

Assessment of severity according to CTCAE v.4.0:

Adverse Event:

- |          |                                                                                                                                                                        |
|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Grade 1: | Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.                                                             |
| Grade 2: | Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL).                                |
| Grade 3: | Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care ADL. |
| Grade 4: | Life threatening consequences; urgent intervention indicated.                                                                                                          |
| Grade 5: | Death related to AE.                                                                                                                                                   |

### 16.5.2 Causal relationship

The investigator must judge whether or not, in his/her opinion, the adverse event was connected with the administration of the investigational product according to the classification given below.

- Definitely: There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.
- Probable: There is evidence to suggest a causal relationship and the influence of other factors is unlikely.
- Possible: There is some evidence to suggest a causal relationship (e.g. because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g. the patient's clinical condition, other concomitant treatments).
- Unlikely: There is little evidence to suggest there is a causal

relationship (e.g. the event did not occur with a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the patient's clinical condition, other concomitant treatments).

- Unrelated: There is no evidence of any causal relationship.
  - Unknown
- /Not assessable: There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

Each adverse event has to be reported, even if the Investigator feels that it is not related to the administration of the study drugs.

### **16.5.3 Expected / Unexpected**

An Unexpected AE is an AE, the nature or severity of which is not consistent with the applicable drug information (**Appendix A\_VI**).

For example the following events related to therapy are adverse but expected:

- Transitory treatment-related myelosuppression (anemia, leukopenia, thrombocytopenia)
- Diarrhoea
- Hepatic dysfunction
- Nausea/Vomiting
- Alopecia
- Infections
- Neurotoxicity
- Cardiomyopathy

### **16.5.4 Outcome**

The outcome of an AE has to be classified as follows:

- Recovered / resolved
- Recovering
- Not recovered / not resolved
- Recovered / resolved with sequelae

- Fatal\*

*\*A subject's death per se is not an event, but an outcome. The event which resulted in the subject's death must be fully documented and reported. This includes all cases where the death occurs within 30 days after the end of treatment.*

- Unknown

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## 17 ETHICAL BACKGROUND

### 17.1 Declaration of Helsinki

LCH-IV will be conducted in full accordance with the Declaration of Helsinki, last revised by 52<sup>nd</sup> WMA General Assembly, Edinburgh, Scotland, October 2008 ([www.wma.net](http://www.wma.net)).

### 17.2 Ethical Approval

Before being activated by a participating group, the protocol, patient information sheets, and consent forms must have been reviewed and accepted by the appropriate Ethics Committee of that group, in conformity with the laws and regulations of the country of the Chief Investigator and, for European investigators, the appropriate European laws and regulations.

The group for which this version of the protocol was issued will submit protocol, patient information sheets, and consent forms to the appropriate Ethics Committee.

The trial will not be activated before approval by that committee.

The Chief Investigator of the group will inform the named Ethics Committee and the competent authorities about all protocol amendments which might affect the safety of participating patients. The Ethics Committee will also be informed about all severe or unexpected adverse events made known to the Chief Investigator. Within 90 days after the end of the trial, the Chief Investigator(s) shall notify the competent authorities and the competent Ethics Committee that the clinical trial has ended. If the trial has to be terminated early, this period shall be reduced to 15 days and the reasons clearly explained.

Directive 2001/20/EC of the European parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use states that, “in the case of multi-center clinical trials carried out in more than one Member State (*of the European Union*) simultaneously, a single Ethics Committee opinion shall be given for each Member State concerned by the clinical trial”. Member States of the European Union shall adopt and publish before 1 May 2003 the laws, regulations and administrative provisions necessary to comply with this Directive. In Member States failing to comply

with these provisions and in participating countries which are not Member States of the European Union, multiple Ethics Committee opinions may be required. Before entering patients into the trial, clinicians must, therefore ensure that they have ethical approval to participate in the trial according to their national and, where applicable, European laws and regulations. It may be necessary to await the vote of the local Ethical Committee and to inform that board about protocol amendments, adverse events, and termination of the trial, as detailed above.

### **17.3 Patient Information**

Before entry into the trial and randomization, the trial subject or, when the person is not able to give informed consent, their legal representative, will be given the opportunity, in a prior interview with the investigator or a member of the investigating team, to understand the objectives, risks and inconveniences of the trial, and the conditions under which it is to be conducted and will also be informed of their right to withdraw from the trial at any time.

Minors are to receive information according to their capacity of understanding, from staff with experience with minors, regarding the trial, the risks and the benefits.

### **17.4 Informed Consent**

Prior to trial entry, the trial subject or, when the person is not able to give informed consent, their legal representative, must give their written consent after being informed of the nature, significance, implications and risks of the clinical trial, including treatment allocation and randomization. Sufficient time will be allowed to decide about trial participation and to solve open questions. If the individual is unable to write, oral consent in the presence of at least one witness may be given in exceptional cases, as provided for in national legislation.

The signature of the legal representative is required for children and adolescents below legal age. The explicit wish of a minor who is capable of forming an opinion and assessing this information to refuse participation or to be withdrawn from the clinical trial at any time is to be considered by the investigator or where appropriate the principal investigator.

Master versions of the Patient Information and Informed Consent Forms for the group for which this version of the protocol was issued are to be found in **Appendix B**. The

format may need to be modified according to the requirements of the participating institution. Any modified versions may need to be submitted to the appropriate Ethical Committee for evaluation. Patient Information and Informed Consent forms will be issued in two copies. One copy remains with the local investigator; one is handed to the patient.

### **17.5 Data Management, Storage and Transmission**

The patients will be informed about the fact that their trial based data will be stored, transmitted and used for scientific analyzes and publications, and that competent authorities may have the right to conduct an official review of documents, records, and any other resources that are deemed by the competent authority to be related to the clinical trial and that may be located at the site of the trial or at the Trials Center, or at other establishments which the competent authority sees fit to inspect.

Patients have the right to be informed about the data kept.

Consent for data management, storage and transmission will be asked for in addition to consent into trial participation (**see Appendix A-VII**).

### **17.6 Withdrawal from the trial**

The subject may without any resulting detriment withdraw from the clinical trial at any time by revoking their informed consent.

## **18    LEGAL AND ADMINISTRATIVE GUIDELINES**

### **18.1 Good Clinical Practice (GCP)**

The "Recommendations of Good Clinical Practice (ICH-GCP: International Conference on Harmonisation - Good Clinical Practice, effective since 17.1.1997)" and "Directive 2001/20/EC of the European Parliament and of the council of 4 April 2001 on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use" will be respected.

### **18.2 Legal background (National and International Regulations)**

The trial will be performed in accordance with the national laws and regulations of the countries in which it is being performed and applicable European laws and regulations. Before commencing the trial, the Chief Investigator for each of the participating groups shall submit a valid request for authorization to the competent authority of the country in which they plan to conduct the clinical trial. The trial will not start until the Ethics Committee has issued a favorable opinion and the competent authority of the country concerned has not informed the sponsor of any grounds for non-acceptance.

The Chief Investigators for each group are required to ensure that the laws, regulations and rules of their respective countries are being followed. The Chief Investigator for each cooperative group must be qualified for this position as required by the national laws and regulations of their country and, for European Chief Investigators, applicable European laws and regulations (for instance: adequate experience in the conduct of clinical trials).

### **18.3 Insurance**

Each National Group has ensured that appropriate arrangements for indemnity to cover the liability of the investigator, including insurance where necessary, have been made according to their national guidelines (the respective documents to be included in Appendix B).

#### **18.4 Ancillary studies**

Costs associated with ancillary studies will be the subject of separate grant applications.

#### **18.5 Compliance with the protocol**

The guidelines of the protocol are to be followed. Participating investigators must document all protocol violations and must give the reasons responsible for these violations, e.g. emergency measures, to be captured through the treatment report forms of the remote data-base system. Compliance will be checked as part of the on-site monitoring process.

#### **18.6 Protocol amendments**

Necessary amendments to the protocol have to be submitted to the responsible IRB for approval. For amendments related to patient safety or patient involvement, accrual to the relevant stratum of the study will be suspended at all participating sites, and accrual to that stratum will be blocked at an individual site, until documentation of approval of the amendment at that particular site is received by the LCH-IV Study Management Center.

#### **18.7 Publication policy**

##### **18.7.1 Premises**

It is a major commitment of the International LCH Study Group to collect relevant data concerning individuals with LCH and make them promptly available to the medical and scientific communities.

In order to avoid conflicts, publication of data derived from the LCH-IV Clinical Study should follow the guidelines detailed in this section. Failure to comply with or disregard of these guidelines could result in changes in the LCH Study Group membership status and collaborations within the Histiocytosis Society.

### **18.7.2 General rules**

An article focused on the primary endpoints of a clinical study (Stratum) should precede the publication of sub-set analyzes. Manuscripts should report the results of the final analysis of a study /Stratum concerning the primary hypotheses or the results of the analysis of incidental findings.

Publications and reporting of data not focused on primary study endpoints are allowed to be published independently from the main paper publication, but the manuscript topic and strategy must be approved by the LCH-IV Study Management Group prior to start the publication process.

Authorship and contributorship have to be inspired by the ethical considerations in the conduct and reporting of research stated in “Uniform requirements for manuscripts submitted to biomedical publication” of the International Committee of Medical Journal Editors (updated February 2006, <http://www.icmje.org>).

## **18.8 Publication of the LCH-IV Data**

### **18.8.1 Final report**

A final report will be written on each Stratum of the LCH-IV regardless of its outcome. It will include the relevant clinical and statistical issues, tables detailing results and the conclusions in accordance with the standards of the CONSORT Statement (Begg et al, 1997) or subsequent updates. It will be signed by the Chair of the LCH-IV Study Management Group, the respective Chief Investigator and the study statistician.

### **18.8.2 Authorship**

The authorship of the main study report will consist of the study chair, the respective principal investigator, the study statistician, and the national coordinators of the countries who have effectively enrolled patients. This will be the writing committee. The order of the authors will be: principle investigator, study statistician, followed by the others in alphabetical order, and the chair of the LCH-IV Study Management Group as a senior author.

The first author will provide a first draft of the report within 24 months of closure. The final report will be accompanied by an appendix identifying the LCH-IV Study Management Group and listing other contributors or associated committees.

### 18.8.3 Additional publications

Other publications using data collected within the LCH-IV Study are possible after approval by the LCH-IV Study Management Group and published with authors and “on behalf of LCH-IV”.

No national group will independently use data from LCH-IV for separate publication before publication of the final report of the respective Stratum. After the EFS and OS reports have been published, each national group can report analyzes of their own data without consulting the LCH-IV Study Management Group. Analyzes of the whole trial data set require the permission of the LCH-IV Study Management Group.

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## **19 APPENDICES**

**19.1 Appendix A – International (separate SET OF FILES)**

**19.2 Appendix B – National (separate SET OF FILES)**

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