**EuroNet-Paediatric Hodgkin’s Lymphoma Group**

First international Inter-Group Study for nodular lymphocyte-predominant Hodgkin’s Lymphoma in Children and Adolescents

- Surgery alone for stage IA disease and complete resection
- Low dose chemotherapy with CVP for patients with stage IA and incomplete resection or stage IIA disease

EudraCT-No.: 2007-004092-19

---

**Inter-group chairpersons**

**Prof. Dr. Dieter Körholz**  
(Co-ordinating investigator)  
Zentrum für Kinderheilkunde  
Universitätsklinik und Poliklinik für Kinder- und Jugendmedizin  
Ernst-Grube-Straße 40, 06120 Halle (Saale)  
Germany

**Prof. W. Hamish Wallace**  
Royal Hospital for Sick Children,  
Sciennes Road, Edinburgh EH9 1LF,  
Scotland, UK.

**Prof. Dr. Judith Landman-Parker**  
Service d’hématologie et d’oncologie pédiatrique  
Hopital d’Enfants Armand Trousseau  
26, Avenue du Dr Arnold Netter  
75571 Paris Cedex 12, France

---

Planned period of accrual: 5 years per country  
Start of study: 2009-11-01  
End of accrual (Germany): 2014-10-31  
End of accrual (last country): 2015-10-31  
End of study: 2020-10-31  
Date of Version: 2011-06-29  
Version: final version  
(Working copy incl. Amendment01 of 2009-11-06 and Amendment02 of 2011-06-29 to Trial protocol of 2009-08-19)
**Confidentiality**

The content of the protocol and the case report forms must be treated confidentially and may not be imparted to uninvolved persons without consent of the study chairpersons neither in oral nor in written form.

**Important information**

The protocol was written by the trial steering committee to the best of their knowledge and belief. Nevertheless mistakes can never be completely excluded.

Therefore every doctor is responsible for checking the treatment plans of the protocol before treating a patient.
CONTENTS

1  GENERAL INFORMATION..........................................................................................10
   1.1  RESPONSIBILITIES.........................................................................................11
   1.2  REFERENCE FACILITIES..............................................................................14
      1.2.1  Reference pathology................................................................................14
      1.2.2  Central staging and response assessment ..............................................16
   1.3  TRIAL RELATED COMMITTEES....................................................................17
      1.3.1  Inter-group trial steering committee.......................................................17
      1.3.2  Committees of the pre-existing study groups .........................................17
      1.3.3  Scientific side projects (Scientific Advisory Board)...............................17
      1.3.4  Data Monitoring Committee .................................................................17
   1.4  PROTOCOL SYNOPSIS..................................................................................19
   1.5  FLOWCHART OF THE STUDY ....................................................................22

2  STUDY OBJECTIVES............................................................................................23
   2.1  MAIN GOALS OF THE STUDY ....................................................................23

3  RATIONALE OF THE STUDY ............................................................................25
   3.1  RATIONALE AND PRIOR EXPERIENCE WITH SURGERY ALONE IN EARLY STAGE LPHL 25
   3.2  RATIONALE AND PRIOR EXPERIENCE WITH NON-INTENSIVE CHEMOTHERAPY (CVP). 27
   3.3  RESPONSE ASSESSMENT AFTER 3 CVP ......................................................28

4  TRIAL DESIGN AND DESCRIPTION...................................................................29
   4.1  TRIAL DESIGN.............................................................................................29
   4.2  REQUIREMENTS FOR PARTICIPATING INVESTIGATORS AND TRIAL SITES ............29
   4.3  TRIAL SITES AND NUMBER OF TRIAL SUBJECTS .........................................30
   4.4  EXPECTED DURATION OF TRIAL .................................................................30
   4.5  PREMATURE TERMINATION .......................................................................30
      4.5.1  Premature closure of a trial site ..............................................................30
      4.5.2  Premature termination of the trial or of trial arms ..................................31

5  SELECTION OF TRIAL SUBJECTS ....................................................................32
   5.1  INCLUSION CRITERIA ..................................................................................32
   5.2  EXCLUSION CRITERIA ................................................................................32
   5.3  SUBSEQUENT EXCLUSION OF PATIENTS ...............................................33
5.4 Gender Distribution ........................................................................................................... 33

6 DIAGNOSTICS ...................................................................................................................... 34

6.1 Confirmation of Diagnosis ................................................................................................ 34

6.2 Clinical and laboratory diagnostics before / during therapy ........................................ 34

6.2.1 Diagnostics prior to chemotherapy .............................................................................. 34

6.2.2 Diagnostic assessment before each course of chemotherapy ...................................... 35

6.3 Imaging diagnostics ......................................................................................................... 35

6.3.1 Initial staging .............................................................................................................. 35

6.3.2 FDG-PET examination .............................................................................................. 37

6.4 Assessment of involved regions ...................................................................................... 37

6.4.1 Assessment of nodal involvement .............................................................................. 38

6.4.2 Assessment of extra-nodal involvement ...................................................................... 38

6.4.3 Organ involvement ..................................................................................................... 39

6.4.4 PET evaluation in the region of the biopsy .................................................................. 40

6.5 Indications for invasive diagnostics ................................................................................. 40

6.6 Guidance to surgeons on additional surgery for resectable nodes ............................... 41

6.7 Restaging ......................................................................................................................... 41

6.7.1 General information .................................................................................................... 41

6.7.2 Complete resection after additional surgery .............................................................. 41

6.7.3 Response assessment after CVP ................................................................................. 41

6.7.4 Follow-up ................................................................................................................... 42

7 STAGE CLASSIFICATION AND DEFINITION OF THERAPY OUTCOME...43

7.1 Stage classification .......................................................................................................... 43

7.2 Definition of treatment response .................................................................................... 44

7.2.1 Definition of complete resection ................................................................................ 44

7.2.2 Local response after chemotherapy ............................................................................ 44

7.2.3 Overall (patient level) response definitions ................................................................ 46

7.3 FDG-PET response assessment ....................................................................................... 49

7.3.1 Definition local FDG-PET response ........................................................................... 49

7.3.2 Definition local FDG-PET response ........................................................................... 50

7.4 Definition of good response ........................................................................................... 50

8 TREATMENT PLAN ............................................................................................................. 51
8.1 SURGERY ONLY FOR SELECTED STAGE IA PATIENTS ............................................. 51
8.2 CVP CHEMOTHERAPY ....................................................................................... 51
8.3 PROCEDURE AFTER CVP .................................................................................. 53
8.4 DOSE MODIFICATIONS ...................................................................................... 53
8.5 CONTRACEPTION ............................................................................................... 53
8.6 SIDE EFFECTS OF CHEMOTHERAPY ................................................................... 53
  8.6.1 Vinblastine ................................................................................................ 54
  8.6.2 Cyclophosphamide ..................................................................................... 54
  8.6.3 Prednisone/Prednisolone ......................................................................... 54
8.7 SUPPORTIVE CARE ........................................................................................... 54
  8.7.1 Antibacterial prophylaxis (optional, as per national guidelines) ............... 54
  8.7.2 Prevention of GvH reaction / infection through blood transfusions ..........54
  8.7.3 Antifungal prophylaxis .............................................................................. 55
8.8 RECOMMENDATIONS FOR PATIENTS WITH TREATMENT FAILURE ............... 55

9 ORGANISATION ................................................................................................. 56
  9.1 INFORMED CONSENT ...................................................................................... 56
    9.1.1 Withdrawal of informed consent ............................................................. 57
  9.2 THERAPY .......................................................................................................... 58
    9.2.1 Procedures for all patients ....................................................................... 58
    9.2.2 Further procedures ................................................................................... 60
  9.3 PREMATURE TERMINATION OF THERAPY OR FOLLOW-UP ......................... 60
    9.3.1 Premature termination of trial therapy .................................................... 60
    9.3.2 Premature termination of follow-up ....................................................... 61
    9.3.3 Organisation of FDG-PET examinations ................................................ 61

10 ADVERSE EVENTS (AE/SAE) ........................................................................... 62
  10.1 SAFETY MONITORING ................................................................................... 62
  10.2 ADVERSE EVENT (AE) .................................................................................. 62
    10.2.1 Definition ............................................................................................... 62
    10.2.2 Documentation and Reporting .............................................................. 62
  10.3 SERIOUS ADVERSE EVENT (SAE) ................................................................. 62
    10.3.1 Definition ............................................................................................... 62
    10.3.2 Documentation and reporting ............................................................... 63
  10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS (SUSAR) .... 65
10.4.1 Definition ..................................................................................................65
10.4.2 Evaluation and reporting .......................................................................... 65
10.5 OTHER SAFETY RELEVANT ISSUES...............................................................66
10.6 ANNUAL SAFETY REPORT ............................................................................66
10.7 PERIODIC SUSAR REPORTS FOR ETHIC COMMITTEES.................................67
10.8 THERAPEUTIC PROCEDURES .....................................................................67
10.9 CLASSIFICATION OF THE ADVERSE EVENT ..............................................67
  10.9.1 Severity ..................................................................................................67
  10.9.2 Causal relationship .................................................................................. 68
  10.9.3 Expected/Unexpected .............................................................................. 69
  10.9.4 Outcome .................................................................................................. 69
10.10 PREGNANCIES...............................................................................................70

11 BIOMETRICAL ASPECTS ..............................................................................71
  11.1 GENERAL STUDY DESIGN CONSIDERATIONS ..........................................71
  11.1.1 Clinical hypotheses and respective endpoints.........................................71
  11.1.2 Stratification by method of staging and response assessment (central versus local) ..................................................................................................................73
  11.1.3 Allocation to study populations...................................................................73
  11.1.4 Expected number of patients.....................................................................74
  11.1.5 Precision of estimate considerations.......................................................75
  11.2 END POINT DEFINITIONS ..........................................................................76
  11.3 STATISTICAL INFERENCE AND METHODS ..............................................77
  11.4 INTERIM AND SAFETY ANALYSIS .............................................................77
  11.5 SPECIAL CASES AND DROP-OUTS ...........................................................78

12 REFERENCE EVALUATION ............................................................................79
  12.1 CENTRAL STAGING AND RESPONSE ASSESSMENT ................................79
    12.1.1 Determination of reference stage and response to CVP .........................79
    12.1.2 Organisation of the tumour conference .................................................79
  12.2 REFERENCE PATHOLOGY .............................................................................80

13 SCIENTIFIC AND BIOLOGICAL ADD ON STUDIES ..................................81

14 ETHICAL AND LEGAL ASPECTS AND AGREEMENTS .................................82
  14.1 SPONSORSHIP ............................................................................................82
14.2 REQUEST OF AUTHORISATION TO THE COMPETENT AUTHORITIES ..................82
14.3 APPLICATION FOR NATIONAL ETHICS COMMITTEE OPINIONS ...............83
14.4 NOTIFICATION OF SUBSTANTIAL AMENDMENTS.................................83
14.5 DECLARATION OF THE END OF TRIAL..................................................83
14.6 INSURANCE .........................................................................................84
14.7 FURTHER AGREEMENTS .....................................................................84

15 DATA HANDLING AND RECORD KEEPING.................................................85
15.1 CASE REPORT FORMS (CRF) .................................................................85
15.2 DATA MANAGEMENT ............................................................................86
15.3 ARCHIVING ..........................................................................................86

16 QUALITY CONTROL AND QUALITY ASSURANCE.................................87
16.1 DIRECT ACCESS TO SOURCE DATA .....................................................87
16.2 MONITORING ......................................................................................87
16.3 AUDITS ................................................................................................87
16.4 INSPECTIONS ......................................................................................88

17 DATA PROTECTION ................................................................................89
17.1 CONFIRMATION OF DATA PROTECTION ...............................................89

18 ADMINISTRATIVE AGREEMENTS .............................................................90
18.1 ADHERENCE TO THE PROTOCOL .......................................................90
18.2 PROTOCOL AMENDMENTS ..................................................................90
18.3 PUBLICATION POLICY .........................................................................91

19 REFERENCES ..........................................................................................92

20 CONFIRMATION OF THE FINAL PROTOCOL ...........................................94

21 PROTOCOL AGREEMENT .......................................................................95

22 APPENDIX ...............................................................................................96
22.1 ABBREVIATIONS ..................................................................................96
22.2 GPOH-HD HODGKIN’S LYMPHOMA WORKING GROUP ......................101
22.3 NCRI LYMPHOMA CLINICAL STUDY GROUP .....................................102
22.4 SFCE HODGKIN’S LYMPHOMA WORKING GROUP .............................103
22.5 PPLLSG HODGKIN’S LYMPHOMA WORKING GROUP .......................104
LIST OF TABLES

<table>
<thead>
<tr>
<th>Table</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>TABLE 1</td>
<td>PLANNED THERAPY DURATION</td>
<td>30</td>
</tr>
<tr>
<td>TABLE 2</td>
<td>RECOMMENDATIONS FOR FOLLOW-UP EXAMINATIONS</td>
<td>42</td>
</tr>
<tr>
<td>TABLE 3</td>
<td>INDEPENDENT LYMPH NODE REGIONS</td>
<td>43</td>
</tr>
<tr>
<td>TABLE 4</td>
<td>STAGE CLASSIFICATION HODGKIN’S LYMPHOMA</td>
<td>43</td>
</tr>
<tr>
<td>TABLE 5</td>
<td>ANNOTATIONS TO STAGE DEFINITIONS</td>
<td>44</td>
</tr>
<tr>
<td>TABLE 6</td>
<td>CVP</td>
<td>52</td>
</tr>
<tr>
<td>TABLE 7</td>
<td>DETAILS OF THE CALCULATION OF EXPECTED NUMBER OF PATIENTS PER GROUP</td>
<td>74</td>
</tr>
</tbody>
</table>

LIST OF FIGURES

<table>
<thead>
<tr>
<th>Figure</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIGURE 1</td>
<td>FLOWCHART</td>
<td>22</td>
</tr>
<tr>
<td>FIGURE 2</td>
<td>PROGRESSION FREE SURVIVAL</td>
<td>26</td>
</tr>
<tr>
<td>FIGURE 3</td>
<td>DEFINITION OF OVERALL RESPONSE</td>
<td>47</td>
</tr>
<tr>
<td>FIGURE 4</td>
<td>DEFINITION LOCAL FDG-PET RESPONSE</td>
<td>49</td>
</tr>
<tr>
<td>FIGURE 5</td>
<td>EXPECTED PRECISION</td>
<td>75</td>
</tr>
</tbody>
</table>
1 GENERAL INFORMATION

On 16 Sept 2005 in Leipzig the GPOH-HD group and study groups from Poland, Italy, Spain, France and the UK agreed to run a European protocol in children and young people with nodular lymphocyte-predominant Hodgkin’s lymphoma within the EuroNet-Paediatric Hodgkin’s Lymphoma group (EuroNet-PHL). Further study groups are encouraged to join.

The EuroNet-PHL-LP1 trial is a multinational inter-group trial, involving pre-existing national or cross-national study groups.

The study groups involved are:

- **GPOH-HD (Central Review)**
  German Society for Paediatric Oncology and Haematology – Study Group for Hodgkin’s lymphoma. This group involves centres from Germany, Austria, Switzerland, and the NOPHO group. These countries are committed to central review of diagnostic staging and response assessment.

- **National Cancer Research Institute (NCRI) Lymphoma Clinical Study Group (Central review of imaging) - England, Scotland, Ireland and Wales**

- **France - SFCE (Non-central review)**
  Société Française de lutte contre les cancers et les leucémies de L’Enfant et de l’adolescent (SFCE)

- **Czech Republic (central review)**

- **Slovakia (central review)**

- **Italy (non-central review)**
  Italian Association of Pediatric Hematology and Oncology

- **Poland (Non-central review)**
  Polish Pediatric Leukemia/Lymphoma Study Group

- **Spain (Central review)**
  Spanish Society of Pediatric Oncology (SEOP)

- **Belgium (central review)**
  Belgian Society for Paediatric Hematology and Oncology (BSPHO)

- **The Netherlands (central review)**
  Dutch Children’s Oncology Group (DCOG)

Further study groups may join either the central or the non-central review group after the start of the study.
### 1.1 RESPONSIBILITIES

| Sponsor according to GCP | Martin Luther University of Halle/Wittenberg  
|                         | Medizinische Fakultät, Prodekanat Forschung  
|                         | Magdeburger Str. 27  
|                         | 06097 Halle (Saale)  
|                         | Tel +49-345-5575420, Fax +49-345-5575424  
|                         | siegfried.bauer@medizin.uni-halle.de  
| Representative of the sponsor: | Prof. Dr. D. Körholz  
| Co-ordinating investigator and Inter-group chairperson | Prof. Dr. Dieter Körholz  
| Study chairperson GPOH-HD | Zentrum für Kinderheilkunde  
|                         | Universitätsklinik und Poliklinik für Kinder- und Jugendmedizin  
|                         | Ernst-Grube-Straße 40, 06120 Halle (Saale)  
|                         | Tel: +49-345-5572387, Fax +49-345-5572389  
|                         | Email: dieter.koerholz@medizin.uni-halle.de  
| Inter-group chairperson and National chairperson NCRI UK | Prof. W. Hamish Wallace  
|                         | Consultant Paediatric Oncologist  
|                         | Royal Hospital for Sick Children, Sciennes Road, Edinburgh EH9 1LF, Scotland, UK. Tel +44-131 536 0426, Fax +44-131 536 0430  
|                         | Email: hamish.wallace@luht.scot.nhs.uk  
| Study chairpersons in UK NCRI | Dr Georgina W Hall  
|                         | Dept of Paediatric Haematology/Oncology  
|                         | Oxford children’s hospital  
|                         | John Radcliffe Hospital, Headley Way, Headington, Oxford OX3 9DU, United Kingdom  
|                         | Tel: +44 (0)1865 221066, Fax: +44 (0)1865 221083  
|                         | Email: georgina.hall@paediatrics.ox.ac.uk  
|                         | Dr A. G. Shankar  
|                         | Department of Paediatric and Adolescent Oncology, UCL Hospitals NHS Trust  
|                         | 250 Euston Road, London, NW1 2PQ, United Kingdom  
|                         | Tel: +44 (0) 20 7380 9950, Fax:+44 (00 20 7380 9064  
|                         | Email: ananth.shankar@uclh.nhs.uk  
| Inter-group chairperson and Study chairperson France SFCE | Prof. Dr. Judith Landman-Parker  
|                         | Hopital d’Enfants Armand Trousseau  
|                         | 26, Avenue du Dr Arnold Netter  
|                         | 75571 Paris Cedex 12, France  
|                         | Tel +33-1-44737475, Fax +33-1-44736573  
|                         | Email : judith.landman-parker@trs.ap-hop-paris.fr  
| Study chairperson Austria | Dr. Georg Mann  
|                         | St. Anna Kinderspital, Zentrum f. Kinder und Jugendheilkunde Kinderspitalgasse 6A  
|                         | A-1090 Wien, Austria  
|                         | Tel +43-1-401704780, Fax +43-1-401707430
| Study chairperson Belgium | Dr Anne Uyttebroeck  
Paediatric haemato-oncology  
University Hospitals of Leuven  
Herestraat 49  
3000 Leuven  
Belgium  
Tel +32 00 343972, Fax +32 16 343842  
Email: Anne.uyttebroeck@uz.kuleuven.be |
| Study chairperson Czech Republic | Dr. Michaela Cepelová  
Dpt. of Pediatric Hematology and Oncology, Faculty Hospital Motol,  
V Úvalu 84, Prague 5, 150 06, Czech Republic  
Tel +420 224 436 454, Fax: + 420 224 436 420  
Email: michaela.cepelova@fnmotol.cz  
Study office  
Tel +420 224 436 401, Fax: + 420 224 436 420 |
| Study chairperson Denmark | Dr. Harald Thomassen  
Rigshospitalet  
Copenhagen University Hospital  
The Juliane Marie Centre  
Pediatric Clinic II  
Haem. Amb. 5051  
Blegdamsvej 9  
DK-2100 Copenhagen  
Email: harald.thomassen@rh.dk |
| Study Chairperson Italy | Dr. Roberta Burnelli  
Department of Pediatrics  
University of Ferrara  
S.Anna Hospital  
Corso Giovecca 203  
44100 Ferrara  
Tel +39-0532-236856  
E-mail: roberta.burnelli@unife.it |
| Study chairperson Netherlands DCOG | Dr. Auke Beishaizen  
Erasmus MC - Sophia Childrens Hospital University Medical Center Rotterdam, Dept of Pediatric Oncology/Hematology, PO-Box 2060, 3000 CB Rotterdam, The Netherlands,  
e-mail: a.beishaizen@erasusmc.nl |
| Study chairperson Norway | Alexander Fosså, MD PhD  
Department of Medical Oncology and Radiotherapy  
Rikshospitalet - Radiumhospitalet HF  
Montebello, 0310 Oslo, Norway  
Phone: +4722934000  
Fax: +4722935599  
E-mail: alexander.fossa@radiumhospitalet.no |
<table>
<thead>
<tr>
<th>Study chairperson Poland</th>
<th>Prof. Dr. Walentyna Balwierz</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Head of Department of Pediatric Oncology and</td>
</tr>
<tr>
<td></td>
<td>Hematology, Polish-American Pediatric Institute,</td>
</tr>
<tr>
<td></td>
<td>Jagiellonian University Medical Faculty</td>
</tr>
<tr>
<td></td>
<td>Wielicka Str. 265, 30-663 Krakow, Poland</td>
</tr>
<tr>
<td></td>
<td>Tel./Fax +48-12-65802-61, Email: <a href="mailto:balwierz@mp.pl">balwierz@mp.pl</a></td>
</tr>
<tr>
<td>Study chairperson Slovakia</td>
<td>Dr. Andrea Hraskova</td>
</tr>
<tr>
<td></td>
<td>Clinic of Pediatric Oncology</td>
</tr>
<tr>
<td></td>
<td>University Children’s Hospital</td>
</tr>
<tr>
<td></td>
<td>Limbova 1, 83340 Bratislava</td>
</tr>
<tr>
<td></td>
<td>Tel +4212-59371230, Fax +421254788000 Email: <a href="mailto:andrea.hraskova@zoznam.sk">andrea.hraskova@zoznam.sk</a></td>
</tr>
<tr>
<td>Study chairperson Spain</td>
<td>Dr. Ana Fernández-Teijeiro Álvarez</td>
</tr>
<tr>
<td></td>
<td>Jefe de Sección de Onco-Hematología Pediátrica</td>
</tr>
<tr>
<td></td>
<td>Hospital Universitario Virgen Macarena</td>
</tr>
<tr>
<td></td>
<td>Avda. Dr. Fedriani nº 3</td>
</tr>
<tr>
<td></td>
<td>41071-Sevilla</td>
</tr>
<tr>
<td></td>
<td>Tel: +34677903132, Fax: +34954370892 Email: <a href="mailto:anateijeiro@hotmail.com">anateijeiro@hotmail.com</a></td>
</tr>
<tr>
<td>Study chairperson Sweden</td>
<td>Dr. Jonas Karlén</td>
</tr>
<tr>
<td></td>
<td>Pediatric Cancer Unit, Astrid Lindgrens Childrens</td>
</tr>
<tr>
<td></td>
<td>Hospital, Karolinska University Hospital,</td>
</tr>
<tr>
<td></td>
<td>S-171 76 Stockholm, Sweden</td>
</tr>
<tr>
<td></td>
<td>Tel +46-8-51773016, Fax +46-8-51774467 Email: <a href="mailto:jonas.karlen@karolinska.se">jonas.karlen@karolinska.se</a></td>
</tr>
<tr>
<td>Study chairperson Switzerland</td>
<td>Dr. Eva Bergsträsser</td>
</tr>
<tr>
<td></td>
<td>Abteilung Onkologie, Universitäts-Kinderklinik Zürich</td>
</tr>
<tr>
<td></td>
<td>Steinwiesstr. 75, CH-8032 Zürich, Switzerland</td>
</tr>
<tr>
<td></td>
<td>Tel. +41 44 266 7723, Fax: +41-44-2667171 Email: <a href="mailto:eva.bergstraesser@kispi.uzh.ch">eva.bergstraesser@kispi.uzh.ch</a></td>
</tr>
<tr>
<td>Study Secretary</td>
<td>PD Dr. Christine Mauz-Körholz</td>
</tr>
<tr>
<td></td>
<td>Zentrum für Kinderheilkunde</td>
</tr>
<tr>
<td></td>
<td>Universitätsklinik und Poliklinik für Kinder- und</td>
</tr>
<tr>
<td></td>
<td>Jugendmedizin</td>
</tr>
<tr>
<td></td>
<td>Ernst-Grube-Straße 40, 06120 Halle (Saale)</td>
</tr>
<tr>
<td></td>
<td>Tel +49-345-5572746, Fax +49-345-5572389 Email: <a href="mailto:christine.mauz-koerholz@medizin.uni-halle.de">christine.mauz-koerholz@medizin.uni-halle.de</a> Email: <a href="mailto:hodgkin@medizin.uni-halle.de">hodgkin@medizin.uni-halle.de</a></td>
</tr>
<tr>
<td>Responsible Biometrician</td>
<td>Dr. Dirk Hasenclever</td>
</tr>
<tr>
<td></td>
<td>Institut für Medizinische Informatik, Statistik und</td>
</tr>
<tr>
<td></td>
<td>Epidemiologie, Universität Leipzig</td>
</tr>
<tr>
<td></td>
<td>Härtelstr.16-18, D-04107 Leipzig, Germany</td>
</tr>
<tr>
<td></td>
<td>Tel +49-341-9716121, Fax +49-341-9716109 Email: <a href="mailto:dirk.hasenclever@imise.uni-leipzig.de">dirk.hasenclever@imise.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Study office GPOH-HD Central data base</td>
<td>Dr. Oana Brosteanu</td>
</tr>
<tr>
<td></td>
<td>Koordinierungszentrum für Klinische Studien Leipzig,</td>
</tr>
<tr>
<td></td>
<td>Universität Leipzig</td>
</tr>
</tbody>
</table>
1.2 REFERENCE FACILITIES

1.2.1 Reference pathology

<table>
<thead>
<tr>
<th>Reference pathology</th>
<th>Association of German Lymphoma reference pathologists. Co-ordinating reference pathologist:</th>
</tr>
</thead>
<tbody>
<tr>
<td>GPOH-HD</td>
<td>Prof. Dr. Feller</td>
</tr>
<tr>
<td></td>
<td>Universitätsklinikum Schleswig-Holstein</td>
</tr>
<tr>
<td></td>
<td>Campus Lübeck, Institut für Pathologie</td>
</tr>
<tr>
<td></td>
<td>Ratzeburger Allee 160</td>
</tr>
<tr>
<td></td>
<td>23538 Lübeck</td>
</tr>
<tr>
<td></td>
<td>Tel: +49 451 500 2705</td>
</tr>
<tr>
<td></td>
<td>Fax: +49 451 500 3328</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference pathology</th>
<th>Dr Alan Ramsay</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCRI</td>
<td>Consultant Histopathologist</td>
</tr>
<tr>
<td></td>
<td>Department of Pathology</td>
</tr>
<tr>
<td></td>
<td>Rockefeller Building</td>
</tr>
<tr>
<td></td>
<td>University College London Hospitals NHS Foundation Trust</td>
</tr>
<tr>
<td></td>
<td>235 Euston Road, London, NW1 2BU</td>
</tr>
<tr>
<td>Reference pathology</td>
<td>Email: <a href="mailto:alan.ramsay@uclh.nhs.uk">alan.ramsay@uclh.nhs.uk</a></td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>SFCE</td>
<td>Dr Josette Brière</td>
</tr>
<tr>
<td></td>
<td>Laboratoire d’anatomie pathologique</td>
</tr>
<tr>
<td></td>
<td>GELA comité Hodgkin pédiatrique</td>
</tr>
<tr>
<td></td>
<td>Hôpital Saint Louis 1 av Claude Vellefaux</td>
</tr>
<tr>
<td></td>
<td>75010 Paris</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:josette.briere@sls.aphp.fr">josette.briere@sls.aphp.fr</a></td>
</tr>
<tr>
<td>Czech Republic</td>
<td>Prof. Dr. Roman Kodet</td>
</tr>
<tr>
<td></td>
<td>Dept. of pathology and molecular biology</td>
</tr>
<tr>
<td></td>
<td>Faculty Hospital Motol,</td>
</tr>
<tr>
<td></td>
<td>V Úvalu 84, Prague 5, 150 06, Czech Republic</td>
</tr>
<tr>
<td></td>
<td>Tel +420 224 435 601, Fax: +420 224 435 620</td>
</tr>
<tr>
<td></td>
<td>e-mail: <a href="mailto:roman.kodet@ffmotol.cuni.cz">roman.kodet@ffmotol.cuni.cz</a></td>
</tr>
<tr>
<td>Italy</td>
<td>Prof. S. Pileri</td>
</tr>
<tr>
<td></td>
<td>Haemo-lymphopathology Unit</td>
</tr>
<tr>
<td></td>
<td>Haematology-Oncology Institut &quot;L&amp;A Seragnoli&quot;</td>
</tr>
<tr>
<td></td>
<td>S. Orsola-Malpighi Hospital</td>
</tr>
<tr>
<td></td>
<td>Via Massarenti, 11 - 40138 Bologna</td>
</tr>
<tr>
<td></td>
<td>Tel: 0039 051 6364674 Fax: 0039 051 6363606</td>
</tr>
<tr>
<td></td>
<td>E-mail: <a href="mailto:pileri@aosp.bo.it">pileri@aosp.bo.it</a></td>
</tr>
<tr>
<td>Netherlands DCOG</td>
<td>Prof. Dr. Philip M. Kluin,</td>
</tr>
<tr>
<td></td>
<td>University Medical Center Groningen, Dept. of Pathology, Hanzeplein 1, 9713 GZ (PO Box 30001, 9700 RB) Groningen, The Netherlands,</td>
</tr>
<tr>
<td></td>
<td>Tel +31 50 3611766,</td>
</tr>
<tr>
<td></td>
<td>E-mail <a href="mailto:p.m.kluin@path.umcg.nl">mailto:p.m.kluin@path.umcg.nl</a></td>
</tr>
<tr>
<td>Poland</td>
<td>Jadwiga Maldyk, MD, PhD</td>
</tr>
<tr>
<td>PPLLSG</td>
<td>Department of Pediatric Pathology</td>
</tr>
<tr>
<td></td>
<td>Medical College</td>
</tr>
<tr>
<td></td>
<td>ul. Marszałkowska 24, 00-828 Warszawa, Poland</td>
</tr>
<tr>
<td></td>
<td>Tel.: +4822 6291040</td>
</tr>
<tr>
<td></td>
<td>Email: <a href="mailto:jagusiamaldyk@wp.pl">jagusiamaldyk@wp.pl</a></td>
</tr>
<tr>
<td>Spain</td>
<td>Miguel Angel Martinez Gonzalez</td>
</tr>
<tr>
<td></td>
<td>Departamento de Anatomía Patológica</td>
</tr>
<tr>
<td></td>
<td>Hospital &quot;12 de Octubre&quot;</td>
</tr>
<tr>
<td></td>
<td>Ctra. de Andalucía Km 5,4</td>
</tr>
<tr>
<td></td>
<td>28041-MADRID</td>
</tr>
<tr>
<td></td>
<td>Tel.:913908000</td>
</tr>
<tr>
<td></td>
<td>E-mail: <a href="mailto:mmartinezg.hdoc@salud.madrid.org">mmartinezg.hdoc@salud.madrid.org</a></td>
</tr>
<tr>
<td>Sweden</td>
<td>Prof. Dr Anja Porwit</td>
</tr>
<tr>
<td></td>
<td>Dept of Pathology, Karolinska University Hospital,</td>
</tr>
<tr>
<td></td>
<td>S-17176 Stockholm, Sweden,</td>
</tr>
<tr>
<td></td>
<td>Tel: +46-8-51774518,</td>
</tr>
<tr>
<td></td>
<td>Fax: +46-8-51775843</td>
</tr>
</tbody>
</table>
### 1.2.2 Central staging and response assessment

| Central review co-ordinator | PD Dr. Christine Mauz-Körholz  
Zentrum für Kinderheilkunde  
Universitätsklinik und Poliklinik für Kinder- und Jugendmedizin  
Ernst-Grube-Straße 40, 06120 Halle (Saale)  
Tel +49-345-5572746, Fax +49-345-5572389  
Email: hodgkin@medizin.uni-halle.de |
|-----------------------------|----------------------------------------------------------------------------------|
| Radiology                   | Prof. Dr. Rolf Peter Spielmann  
Universitätsklinikum der  
Martin-Luther-Universität Halle-Wittenberg  
Universitätsklinik und Poliklinik für Diagnostische Radiologie  
Ernst-Grube-Straße 40  
06120 Halle (Saale) Germany  
Tel +49-345-5572441, Fax +49-345-5572157  
Email: rolf.spielmann@medizin.uni-halle.de |
| Nuclear medicine            | Prof. Dr. Regine Kluge  
Klinik und Poliklinik für Nuklearmedizin  
Universitätsklinikum Leipzig  
Liebigstr. 20a, D-04103 Leipzig, Germany  
Tel. +49-341- 97 18 031 or 97 18 000, Fax +49-341- 97 18 009  
Email: klur@medizin.uni-leipzig.de |
1.3 TRIAL RELATED COMMITTEES

1.3.1 Inter-group trial steering committee

The inter-group trial steering committee is responsible for writing the protocol and organizing the study in the participating countries.

The inter-group trial steering committee consists of the study chairpersons of the participating national study groups and the responsible biometrician.

The study secretary is responsible for the minutes of inter-group trial steering committee meetings.

Further experts can be invited to participate as consultants.

1.3.2 Committees of the pre-existing study groups

The GPOH-HD committee as well as the other national committees of the pre-existing study groups are responsible for endorsing and implementing EuroNet–PHL approved protocols. The members of the GPOH-HD committee, of the NCRI, SFCE and PPLLSG Hodgkin's lymphoma working parties are listed in the Appendix.

1.3.3 Scientific side projects (Scientific Advisory Board)

The Scientific Advisory Board (SAB) of EuroNet-PHL-LP1 evaluates applications of interested working teams and decides on the eligibility of applications in agreement with the study chairpersons and the biometrician of the study. This advisory panel consists of representatives of the study groups, reference pathology and biometry as well as of further recognized experts in the field of malignant lymphomas and paediatric oncology.

Collection of tumour tissue and serum will be handled by different national protocols which will include national regulation for personal data safety. These protocols will be closely related to the EuroNet-PHL-LP1 protocol. Scientific study projects that have been favourably reviewed by the SAB will be provided with anonymous clinical data from the study database (see chapter 13).

The current members of the Scientific Advisory Board are listed in the Appendix.

1.3.4 Data Monitoring Committee

The Data Monitoring Committee (DMC) consists of independent medical and biometrical experts.
The DMC receives confidential information on the progress of the study at annual intervals and has the following tasks:

- assessment of the study’s progress
- assessment of safety
- advise on serious adverse events
- assessment of the results of interim analyses if stopping rules are met.

The DMC gives recommendations to the study chairpersons referring to conduct, modification or early termination of the study. These recommendations are discussed and decided upon by the inter-group trial steering committee.
1.4 PROTOCOL SYNOPSIS

<table>
<thead>
<tr>
<th><strong>Title of the study</strong></th>
<th>First international Inter-Group Study for nodular lymphocyte-predominant Hodgkin’s Lymphoma in Children and Adolescents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acronym</strong></td>
<td>EuroNet-PHL-LP1</td>
</tr>
<tr>
<td><strong>Sponsor</strong></td>
<td>Martin-Luther-University of Halle/Wittenberg, Germany</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Nodular lymphocyte-predominant Hodgkin’s lymphoma in childhood and adolescence</td>
</tr>
<tr>
<td><strong>Objective</strong></td>
<td>Building on the experience of the European PHL study groups since 1978, first line therapy for childhood nodular lymphocyte-predominant Hodgkin’s lymphoma shall be further optimised to avoid over-treatment and decrease long-term complications.</td>
</tr>
<tr>
<td></td>
<td>- Surgery alone for patients with stage IA disease and complete resection.</td>
</tr>
<tr>
<td></td>
<td>- Low intensity chemotherapy with CVP (Cyclophosphamide, Vinblastine and Prednisolone (or Prednisone)) for patients with stage IA and incomplete resection or stage IIA disease</td>
</tr>
<tr>
<td><strong>Primary objectives</strong></td>
<td>Patients with complete resection group:</td>
</tr>
<tr>
<td></td>
<td>Statistically estimate the five year event free survival rate with meaningful precision and show it is at least above 50% (target 70%).</td>
</tr>
<tr>
<td></td>
<td>Patients with residual disease receiving 3 CVP:</td>
</tr>
<tr>
<td></td>
<td>Statistically estimate the 5 year event free survival rate in all patients receiving CVP chemotherapy.</td>
</tr>
<tr>
<td></td>
<td>Note: failure includes not achieving a good response (cf. 7.4) to 3 CVP.</td>
</tr>
<tr>
<td><strong>Secondary objectives</strong></td>
<td>Low intensity of treatment of early stage LPHL does not result in reduction in overall OS rates or in significant upstaging at relapse or increased rates of histological transformation.</td>
</tr>
<tr>
<td><strong>Study design</strong></td>
<td>Uncontrolled study to estimate success rates assuming that the study population will be representative of LPHL patients in the participating countries and that it is thus meaningful to estimate absolute success rates.</td>
</tr>
<tr>
<td><strong>Study population</strong></td>
<td>Patients with nodular lymphocyte-predominant Hodgkin’s lymphoma stage IA and IIA under 18 years of age. (Further details cf. 5.1)</td>
</tr>
</tbody>
</table>
**Sample size** | At least 200 patients will be included in the study  

**Therapy** | In patients with stage IA disease complete resection of involved lymph nodes is considered. After complete resection these patients enter follow-up without further treatment.  
All other patients receive three cycles of CVP. Patients with good response to CVP enter follow-up.  
Patients without a good response to CVP have failed and are off protocol. Suggestions on further management of such patients to be obtained from national trial co-ordinators.  
Cyclophosphamide, vinblastine and prednisolone (or prednisone) are investigational medicinal products (IMPs) in this trial.  

**Primary end point** | Event free survival (EFS):= time from registration until the first of the following events:  
- additional treatment for Hodgkin’s Lymphoma  
- progression/relapse of disease  
- occurrence of a secondary malignancy  
- death by any cause  
For patients allocated to the CVP group failure to achieve a good response constitutes an indication for additional treatment and counts as event.  

**Secondary end points**  
1. Significant upstaging at relapse defined as development of B-symptoms or extra-nodal disease or relapse stage > II.  
2. Overall survival (OS)  
3. CTC (Common toxicity criteria) toxicity levels of therapy elements  
4. Complications of surgery  

**Biometry** | For the surgery only group we expect about 80 patients and a long-term event free rate of about 70%. With 90% power a precision of the 5 year EFS estimate of less than ± 11% can be achieved. We then have 94% power to exclude 50% from the two-sided 95% confidence interval.  
For the CVP group we expect about 120 patients, a rate of 90-95% of good response and an EFS rate of about 70%. The precision of the good-responder rate estimate is thus expected to be in the order ± 5%. With 95% power a precision of the 5 year EFS estimate of
less than ± 9% can be achieved. We then have 90% power to exclude 55% EFS from the two-sided 95% confidence interval.

| Schedule | The study is scheduled to start on 2009-11-01. For insurance reasons in Germany the recruitment period is limited to 5 years (minus 1 day), i.e. probably until 2014-10-31. Individual follow-up for 5 years after study entry is required for this protocol. Other countries join the study as soon as possible. Overall accrual stops on 2015-10-31. Long-term follow-up is strongly recommended and will be organised according to national circumstances. The study is scheduled to end on 2020-10-31. If the start of the study is delayed, given dates change accordingly. |
| Financial support for GPOH-HD group | Main support: Deutsche Krebshilfe e.V. / Dr. Mildred Scheel Foundation |
1.5 FLOWCHART OF THE STUDY

EuroNet-PHL-LP1

![Flowchart]

Figure 1  Flowchart
For explanation of good response, please refer to section 7.4

Histology is centrally reviewed (nationally) prior to registration. Staging includes CT/MRI & PET. Stages > IIA, i.e. stage III or higher and/or any B or E involvement are not eligible for study. Complete surgical resection post diagnostic biopsy must be uncomplicated see text (section 6.6).
2 STUDY OBJECTIVES

2.1 MAIN GOALS OF THE STUDY

Satisfactory disease control rates (>90%) can be achieved in paediatric Hodgkin’s lymphoma with established therapeutic modalities (documented for the GPOH-HD study group since the DAL-HD-82 study).

The remaining challenges for further treatment optimisation are:

- Reduction of acute and long-term toxicity of the chemotherapy and radiotherapy employed.
- Reduction of the amount of treatment in those children who are currently being over-treated.

This study aims to reduce intensity of treatment for the majority of patients with early stage LPHL:

- In about 40% of patients with early stage disease complete resection can be achieved. A recent retrospective EuroNet-PHL case collection suggests that such patients can safely enter a follow up (Watch & Wait) period after surgery alone and that two thirds of these achieve long term remission. The patients, who experienced relapse represented with relapse at stage IA / IIA, i.e. had no significant upstaging. Without significant upstaging at relapse treatment of the relapse should not be compromised. It is hoped that this study can confirm these promising preliminary results in patients with resectable stage IA disease.

- We hypothesise that patients with non-resectable stage IA/IIA disease are currently over-treated with the standard treatment for classical HL. In this study patients will receive 3 courses of non-intensive chemotherapy (3 CVP). Pilot data (17/18 complete remission) suggests an excellent response rate. Treatment stops for patients achieving a good response who then enter a follow up period. Patients without a good response to 3 courses of CVP have failed and go off protocol but long-term follow up and monitoring is recommended to evaluate late effects. Guidance on further treatment for patients who fail this protocol can be obtained from the national trial co-ordinators.

The objectives of the EuroNet-PHL-LP1 study are to statistically estimate the following rates:
In patients with complete resection

1. The five year Event Free Survival rate (EFS)
2. The rate of significant upstaging at relapse (i.e. development of B symptoms or extranodal disease or stage greater than II).

In patients with residual tumour

1. The 5 year Event Free survival rate in all patients receiving 3 CVP chemotherapy. Not achieving a ‘good response’ to 3 CVP implying need for further treatment counts as event.
2. The ‘good response’ rate after CVP
3. The five year Event Free Survival rate (EFS) after documented ‘good response’
4. The rate of significant upstaging at relapse (i.e. development of B symptoms, extranodal disease or stage greater than II) after a ‘good response’ to 3 CVP.
3 RATIONALE OF THE STUDY

Lymphocyte-predominant Hodgkin’s lymphoma (LPHL) is a rare CD20 positive sub-type of Hodgkin’s lymphoma which was recently recognised as a distinct entity (Harris NL et al., 1999). LP is characterized by the presence of lymphocytic and histiocytic (L&H) cells, with polylobular nuclei, within nodules composed of small mature B lymphocytes. Reed-Sternberg cells are rare or absent. The L&H cells are frequently negative for CD15, CD30, and EBV genome, but positive for B cell antigens (CD20, CD79a, and CD75), leucocytes (CD45) and epithelial membrane antigen (EMA) (Bodis JCO 1997, Poppema Semin Diagn Pathi 1992).

There is a high predominance of male patients. Typically patients present with peripheral, early stage disease, mainly IA with cervical involvement. Mediastinal disease is exceptional and suggestive of more advanced stage. LPHL has an indolent course and the prognosis for patients with early stage disease [IA and IIA] is very favourable. Few patients die from LPHL (Regula NEJM 1988, Borg-Grech JCO 1989, Franklin Ann Onco 1998, Pappa Ann onco 1995, Sextro Ann Oncol 1996, Trudel Cancer 1987, Karayalcin MPO 1997) but rather from secondary malignancies or transformation to aggressive B cell lymphoma. In the past patients with LPHL have been treated with chemotherapy and radiotherapy using standard classical Hodgkin’s lymphoma (HL) protocols (Nogova Eur J Haematol 2005, Gobbi Cancer 2005, Feugier Blood 2004). Early stage patients have also been treated with radiotherapy (Wirth Cancer 2005, Schlembach Cancer 2002, Wilder Cancer 2002), or chemotherapy alone (Nachman JCO 2002) or more recently with a monoclonal antibody (Rituximab) (Ekstrand Blood 2003, Rehwald Blood 2003). With these strategies, progression free survival between 80% and 95% (Feugier Blood 2004, Schlembach Cancer 2002) and overall survival between 83% and 100% (Wirth Cancer 2005, Schlembach Cancer 2002) has been reported.

3.1 RATIONALE AND PRIOR EXPERIENCE WITH SURGERY ALONE IN EARLY STAGE LPHL

Surgery alone is based on the following rationale: Nodular lymphocyte-predominant Hodgkin’s lymphoma presents typically with peripheral, localised stage IA or IIA disease. Thus local therapy such as surgery alone is an option. In addition, at relapse, the disease tends to remain localised. Therefore surgery alone as first line treatment should be a safe option even if a certain proportion of the patients experiences relapse. If the relapse is still localised (without significant upstaging) then efficacy of alternative treatment modalities should not be compromised when used as a second line approach. A localised approach is particularly pertinent in children with LPHL in order to avoid the growth disturbances and severe long term sequelae of more aggressive treatment modalities.
The working hypothesis of this trial is fully supported by pilot data of our study group [Mauz-Koerholz 2007]: European study groups participating in the EuroNet-PHL inter-group were asked to report their experience with surgery alone in paediatric nodular lymphocyte-predominant Hodgkin's lymphoma. Surgery as a single treatment modality has been systematically used for several years by the SFCE (France), the DAL / GPOH Germany + Sweden, and more recently by the former CCLG (UK). The approach has not been used so far in Italy, Poland, Spain, the Czech Republic and Slovakia. Individual data from 58 patients were collected using a common CRF. The 13 cases already published by Pellegrino 2003 were updated and included.

When complete resection was documented, a substantial proportion (about 2/3) of surgically treated stage IA LPHL cases experienced long-term remission. Patients with incomplete resection had a high probability of relapse (Fig 2). The surgery alone strategy appears to be safe as all patients are alive and all relapses from completely resected stage IA cases were either strictly local or relapsed at stage II A. Hence no significant upstaging was observed.

Figure 2  Progression free survival
___ CR after surgery 14/51 events; ----- incomplete resection 7/ 7 events.
Logrank test p=0.011.
3 RATIONALE OF THE STUDY

Had the above mentioned cases been included in treatment programs for classical Hodgkin’s lymphoma they would have received polychemotherapy possibly followed by radiotherapy. Surgery alone, therefore, offers the potential of avoiding acute and, in particular, long-term side-effects associated with standard chemo-radiotherapy. In most of the cases reported above FDG-PET was not routinely performed. Using routine FDG-PET to confirm complete resection may further improve results. The EuroNet-PHL-LP1 study, using surgery alone in Stage IA patients is designed to prospectively confirm these promising results

We expect that about 40% of the early stage patients will present with resectable disease.

3.2 RATIONALE AND PRIOR EXPERIENCE WITH NON-INTENSIVE CHEMOTHERAPY (CVP)

The optimum therapy for early stage LPHL is not known, but it is likely that current therapy for classical Hodgkin’s lymphoma is unnecessarily toxic and intensive for this indolent, slowly progressive, peripheral CD20 positive disease. Adverse treatment-related late effects are the major causes of morbidity and death in patients treated with standard chemo-radiotherapy. Consequently, children with early stage LPHL are ideal candidates for low intensity treatment.

CVP consists of cyclophosphamide [500 mg/m²- day 1], vinblastine [6 mg/m² –day 1 & 8] and Prednisolone [40 mg/m² - days 1-7]. These agents are all well-known drugs, with established efficacy in HL and favourable toxicity profiles. Anthracyclines are not used in this protocol to avoid cardiotoxicity. CVP was designed to assess whether a short course of non-intensive chemotherapy with minimal toxicity could replace standard chemotherapy protocols used for treatment of classical HL without compromising efficacy of outcome in children and young people with LPHL.

Between May 2004 and April 2007 20 patients with stages IA [n=14] and IIA [n=6] biopsy proven LPHL were treated with 3 cycles of CVP chemotherapy (Shankar et al., 2006). Six of the twenty patients were treated initially with surgical resection alone and received CVP at first relapse. Twelve patients were males and the median age at diagnosis was 11 years (range 4-17 years). Staging investigations at diagnosis included both conventional cross sectional, as well as 18 fluro-deoxyglucose [FDG] PET, imaging. Remission status at the end of 3 cycles of CVP was confirmed by both conventional cross sectional and FDG PET imaging.
19 patients achieved a complete remission [CR] after 3 courses of CVP and 1 patient a very good partial remission [VGPR]. To date, only 2 patients have relapsed whilst 18 patients remain in continuous CR. Median duration of follow up is 12 months (range 12-36 months). The overall survival is 100% and event free survival is 90%. No significant early or late toxicity has been observed to date (including no hair loss).

Notwithstanding the relatively short follow up period, CVP appears to be an effective non toxic chemotherapy regimen with 95% of patients with early stage LPHL achieving a CR after 3 courses. Based on these preliminary results, we want to confirm prospectively these results on response, and investigate long-term outcome, in a larger cohort of patients.

### 3.3 RESPONSE ASSESSMENT AFTER 3 CVP

Functional FDG-PET imaging has been used increasingly in Hodgkin’s lymphoma since 1995. It is now routinely used in most EuroNet-PHL centres.

FDG-PET can better distinguish between vital and fibrotic/necrotic residual masses and thus may resolve the problem of low specificity with CT/MRI. The EuroNet-PHL-LP1 study essentially follows the approach developed for the EuroNet-PHL-C1 study in classical HL in how FDG-PET is formally integrated into staging and response assessment. In order to safeguard against possible uptake artefacts and to avoid a major upshift in staging, the integration of FDG-PET results into staging and response assessment is based on two principles:

1. All functional FDG-PET information formally used in staging and response assessment must be paired with findings on conventional imaging.

2. At diagnosis FDG-PET results are only used to decide on involvement in regions that are suspicious but inconclusive by conventional imaging.

Sites in which FDG-PET is not informative require particular attention. For details on how these principles are implemented see chapter 6 and 7.
4 TRIAL DESIGN AND DESCRIPTION

4.1 TRIAL DESIGN

Nodular lymphocyte-predominant Hodgkin’s lymphoma is a rare disease in adults as well as children. Any reasonably sized paediatric study requires Europe-wide cooperation of regional or national study groups. A randomised comparative trial addressing the study questions (treatment reduction) is not feasible.

In paediatric practice, nearly all patients with Hodgkin’s lymphoma are included in ongoing studies/clinical trials. The participating study groups will make all possible efforts to include all eligible patients into this study.

The study design therefore assumes that the study population will be representative of LPHL patients in the participating countries. Estimating absolute success rates in a prospective uncontrolled study is thus meaningful. The excellent prognosis of patients with LPHL receiving treatment for classical HL is well documented elsewhere.

4.2 REQUIREMENTS FOR PARTICIPATING INVESTIGATORS AND TRIAL SITES

The principal investigators have to be specialised in paediatric haematology/oncology.

Requirements for trial sites:

- Access to intensive care unit,
- Access to diagnostic facilities: CT, MRI, FDG-PET

In addition in Germany the GPOH requires:

- 24h on-call service in paediatric haematology/oncology
- At least two investigators specialised in paediatric haematology/oncology per trial site

The common qualification criteria required by ICH-GCP and the pertinent national laws will be assessed by the involved ethics committees before start of the trial. There are no further specific requirements for participating investigators or trial sites.

The study chairpersons involved are responsible for the selection of qualified investigators and trials sites in their country.

The co-ordinating investigator on behalf of the sponsor is responsible for setting up written agreements with every trial site involved in Germany. The authorised institutions (cf. chapter 14)
in all other participating countries are responsible for setting up written agreements with every trial site involved in the respective country.

### 4.3 TRIAL SITES AND NUMBER OF TRIAL SUBJECTS

At least 200 trial sites, associated with the participating study groups, are expected to take part in the EuroNet-PHL-LP1 study.

At least 200 patients are expected. The expected number of annually recruited patients is approximately 40-50.

### 4.4 EXPECTED DURATION OF TRIAL

The EuroNet-PHL-LP1 study is planned to run for 5 years.

For all patients, including those who come off protocol, an individual 5-year follow-up plan will be followed. In addition, long-term follow up and monitoring is recommended to evaluate late effects.

The EuroNet-PHL-LP1 trial formally ends after 5 years of follow up on the last patient registered into the trial. The duration of treatment varies according to the patient’s response. Table 1 gives an overview on the planned treatment duration.

**Table 1 Planned therapy duration**

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Planned therapy period (according to response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery only</td>
<td>No chemotherapy, just follow up</td>
</tr>
<tr>
<td>CVP</td>
<td>3 cycles (6-9 weeks)</td>
</tr>
</tbody>
</table>

### 4.5 PREMATURE TERMINATION

#### 4.5.1 Premature closure of a trial site

Premature closure of a trial site is to be considered if:

- it does not meet the technical requirements of the protocol
- the conduct of the study is not compliant with the protocol
- data quality does not meet required standards
- data return is insufficient for trial purposes.
The premature closure of a site will be decided by the study chairperson of the respective
country after consultation with the responsible biometrician and the inter-group chairpersons.

Investigators and trial sites deciding not to take part in the trial any longer have to inform the co-
ordinating investigator immediately.

Details on further treatment and follow-up of patients registered on study have to be discussed
with the co-ordinating investigator.

4.5.2 Premature termination of the trial or of trial arms

If the following occurs, the premature termination of the trial or of trial arms will have to be
considered:

- Serious adverse drug reactions leading to substantial changes in risk-benefit
  considerations
- Unacceptable toxicity (e.g. cumulative occurrence of deaths conditional on therapy)
- Poor efficacy
- New developments from other trials in childhood HL /LPHL
- Insufficient recruitment rate
- Unsustainable trial organisation

The Data Monitoring Committee will monitor the study conduct and the safety aspects of the
trial on a regular basis, and will give recommendations to the Inter-Group Trial Steering
Committee whether to stop the trial or to change the trial protocol. The Inter-Group Trial
Steering Committee will then decide on the actions to be taken.
5 SELECTION OF TRIAL SUBJECTS

5.1 INCLUSION CRITERIA

Trial sites register patients at their corresponding study office if the following requirements are met:

- initial stage IA/IIA (according to local staging) or relapse stage IA or IIA and residual tumour after relapse biopsy and no additional surgery planned in nLP patients relapsing after surgery alone
- patient aged under 18 years at time of diagnosis
- written informed consent of the patient and/or the patient’s parents or guardian according to national laws

In certain European countries very young patients may have to be excluded in order to comply with national laws or formal insurance requirements.

5.2 EXCLUSION CRITERIA

Patients with one of the following circumstances are excluded:

- pre-treatment of Hodgkin’s lymphoma differing from study protocol
- Any extra-nodal involvement
- Inability to fulfil protocol requirements for imaging (CT, MRI, FDG-PET) at staging and response assessment
- known hypersensitivity or contraindication to study drugs
- prior chemotherapy or radiotherapy
- Current or recent therapy (within 30 days prior to the start of trial treatment) with steroids
- Current or recent (within 30 days prior to the start of trial treatment) treatment with another investigational drug or participation in another investigational trial
- other (simultaneous) malignancies
- severe concomitant diseases (e.g. immune deficiency syndrome)
- known HIV positivity
5 SELECTION OF TRIAL SUBJECTS

- pregnancy and / or lactation
- females who are sexually active refusing to use effective contraception (oral contraception, intrauterine devices, barrier method of contraception in conjunction with spermicidal jelly or surgical sterile) (except for surgery only)

5.3 SUBSEQUENT EXCLUSION OF PATIENTS

Patients are excluded from the study after registration if

- documents or material ascertained before study inclusion show that an exclusion criterion was fulfilled or an inclusion criterion was not met
- the patient and/or the patient’s parents or guardian withdraw(s) his/her/their consent to further study participation

If central review results in upstaging above stage IA/IIA the patient is still documented in the scope of the study but not eligible for treatment in the study. The patient’s physician then decides together with the patient/parents or guardian as to the most appropriate therapy.

The study chairpersons decide on the exclusion along with the biometrician of the study. Subsequent exclusion of a patient can be requested by a trial site only in writing.

Subsequent exclusion of a patient differs from an individual therapy withdrawal. In the latter case the treatment of the patient according to protocol is terminated, but follow-up and documentation (data collection in the CRF) is continued according to protocol and the patient appears in all relevant analyses.

5.4 GENDER DISTRIBUTION

All eligible patients (and his/her parents / guardian) will be asked for informed consent for participation in the trial independent of gender. Therefore, the gender distribution will reflect the underlying gender distribution in paediatric nodular lymphocyte-predominant Hodgkin’s lymphoma.
6 DIAGNOSTICS

If nodular lymphocyte-predominant Hodgkin’s lymphoma is suspected, an open biopsy should be obtained as soon as possible.

After confirmation of the diagnosis by the local pathologist the patient is staged. Staging includes CT/MRI and FDG-PET scanning performed before treatment starts.

6.1 CONFIRMATION OF DIAGNOSIS

The histopathological diagnosis is based on a biopsy of a lymph node or as the case may be of a biopsy of another primarily involved organ. Biopsies using a fine needle are not appropriate.

Reference pathology is mandatory and is organised in each country as detailed in the pathology manual.

Treatment MUST NOT be started on any patient with CD 20+ positive, stage IA or IIA Hodgkin’s lymphoma until the differential diagnosis of classic Hodgkin’s lymphoma (versus nodular lymphocyte-predominant HL) has been excluded by central reference pathology review. Patients with c-HL may be treated on the EuroNet-PHL-C1 study.

If a nodular lymphocyte-predominant Hodgkin’s lymphoma is diagnosed and the patient and his / her parents / guardian declare his / her consent the investigator registers the patient in the corresponding study office of the EuroNet-PHL-LP1 study.

6.2 CLINICAL AND LABORATORY DIAGNOSTICS BEFORE / DURING THERAPY

6.2.1 Diagnostics prior to chemotherapy

Exact clinical history including:

- previous and concomitant diseases (e.g. paraneoplastic phenomena such as nephrotic syndromes and other autoimmune diseases),
- systemic symptoms and
- prior treatment.
Clinical examination

- detailed documentation of all palpable lymph nodes and their localisation.
- examination and inspection of Waldeyer’s ring preferably by ENT-physician.
- Palpation of spleen and liver

Laboratory examinations:

- Complete blood count, erythrocyte sedimentation rate, ALT, AST, GGT, LDH, AP, creatinine and albumin in the serum, fibrinogen, Immunoglobulin A, G, M
- Protein electrophoresis: gamma-globulin and alpha-2-globulin
- Baseline virology recommended to include serologic examinations for antibodies against VZV, EBV, CMV, HSV, HIV, toxoplasmosis, hepatitis A, B, C (HCV-PCR).

6.2.2 Diagnostic assessment before each course of chemotherapy

Before start of each chemotherapy cycle:

- Presence of infections
- detailed clinical examination
- Lansky/Karnofsky’s score depending on age
- blood counts including differential blood count
- ALT, AST, GGT, bilirubin, creatinine

Further diagnostic measures are carried out according to the individual circumstances of the patient.

6.3 IMAGING DIAGNOSTICS

6.3.1 Initial staging

After diagnostic biopsy/resection, complete staging including CT/MRI and FDG-PET examination is needed prior to any further treatment. The site of biopsy must be re-examined by cross-sectional imaging.

Cross sectional imaging should preferably be performed according to options A and B, see below.

Low dose chest CT should be performed with weight-dependent dosage if possible.

A) CT chest with mediastinum, MRI neck / abdomen / pelvis
CT examination:

CT examination of thorax is mandatory, since lung foci can be best diagnosed with CT. (Recommendations for CT examination performance see B).

MRI examinations should include the following sequences:

- **neck**: transversal and coronal T2 fat saturated T2 (T2-TIRM, T2-STIR)
- **thorax**: If performed in addition to chest CT an MRI examination of lung and mediastinum should provide ECG triggered transversal sequences to avoid pulsation artefacts.
- **abdomen**: transversal T2 fat saturated and T1-FLASH 2d dynamic in arterial, portal venous and venous phase
- **pelvis**: T1-SE transversal, T2- fat saturated transversal and coronal, T1-SE-transversal after contrast agent with fat saturation

### B) CT neck / thorax / abdomen / pelvis

Recommendation for examination performance:

<table>
<thead>
<tr>
<th>Examination Region</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>examination region</td>
<td>epipharynx to lower edge of symphysis</td>
</tr>
<tr>
<td>layer thickness</td>
<td>reconstructed 5 mm layers</td>
</tr>
<tr>
<td>oral contrasting</td>
<td>yes</td>
</tr>
<tr>
<td>i.v. contrasting</td>
<td>depending on KG 1.5 – 2.0 ml/kg KG</td>
</tr>
<tr>
<td></td>
<td>(recommended up to 10 kg body weight 2 ml/kg, up to 40 kg body weight 1.5 ml/kg, from 40 kg 60 ml; choose delay according to device so that a parenchymal phase of liver and spleen is achieved)</td>
</tr>
<tr>
<td>reconstruction</td>
<td>lung: sharp kernel and pulmonary window, mediastinum with involvement of axillae, supra- and infraclavicular region: soft kernel and mediastinal window, abdomen and pelvis involving inguinal region: abdominal window ( e.g. W 400/C 60)</td>
</tr>
</tbody>
</table>

### C) CT in combination with PET:

If only a PET-CT is performed, the CT-images have to be in “state of the art” quality. This includes: oral and i.v. contrasting (as described in B), the choice of an adequate mAs dose (not low dose) and a slice thickness not higher than 5 mm. The imaging quality of the PET-CT-images has to be comparable to normal diagnostic CT.

### D) Whole body-MRI
Whole body-MRI (WB-MRI) is a promising technique for initial staging and restaging. The real value of WB-MRI is currently under investigation. Thus, it should not replace staging options A to C.

Additional imaging procedures
Ultrasonography of spleen and liver are mandatory

Additional points to consider
For central review digital transmission of cross sectional imaging and bone scans is appreciated (CD with automatically opening (DICOM) viewer if necessary as teleradiology link). If this is not possible central review is performed on the basis of original or copied images. The original report of the local radiologist should be included for orientation.

At trial sites not taking part in the central review the tumour volume is determined at the local hospital as a prerequisite for response assessment. PET positive regions not investigated by cross-sectional imaging (e.g. extremities) must be examined using conventional imaging (CT or MRI) before starting therapy.

6.3.2 FDG-PET examination
For detailed instructions please confer to the FDG-PET procedural manual.

6.4 ASSESSMENT OF INVOLVED REGIONS
The EuroNet-PHL-LP1 study is an inter-group trial. While the GPOH-HD group pursues a quality assurance strategy with real time central review of staging and restaging, other involved study groups do not.

Depending on country patients qualify for either central staging and response assessment (CSRA) or only local staging and response assessment (LSRA).

For all patients the clinical stage is determined by the local investigator. In CSRA patients the reference stage is defined by the GPOH-HD central review. Decision on treatment group is determined by the clinical stage (LSRA) or if available the reference stage (CSRA).
6.4.1 **Assessment of nodal involvement**

6.4.1.1 **Assessment of lymph node involvement**

1. If the largest diameter of a lymph node or a lymph node conglomerate is smaller than 1 cm the region is considered not involved – independent of the PET result. If however several such small lymph nodes are present in a region and are FDG-PET positive then they are considered involved.

2. If the largest diameter of a lymph node or a lymph node conglomerate exceeds 2.0 cm the region is considered involved. If such an involved region is FDG-PET-negative this discordance must be documented, since this is relevant for response assessment.

3. If a lymph node or a lymph node conglomerate has a diameter of 1.0 – 2.0 cm the region is considered
   - **involved** if it is FDG-PET positive.
   - **not involved** if it is FDG-PET negative
   - **doubtfully involved** if the FDG-PET has not been performed or is not evaluable (e.g. in muscle artefacts). In these cases the decision on involvement of this region is made including further criteria, such as clinical data, ultrasound findings, proximity to larger involved region.

6.4.1.2 **Assessment of Waldeyer’s ring**

1. Involvement is defined by clinical assessment preferably by ENT physician and is **not** measurable: involvement yes/ no; localisation left/right;

2. FDG-PET assessment is irrelevant.

3. Biopsy is not required and not advised since too invasive.

6.4.2 **Assessment of extra-nodal involvement**

Definitions of extranodal involvement are mentioned in this protocol to define patients’ exclusion criteria. Patients with extranodal disease are not eligible for this trial.

6.4.2.1 **Pleura and pericardium**

Involvement of the pleura is assumed if
• the lymphoma is contiguous with the pleura without fat lamella or
• the lymphoma invades the chest wall or
• a pleural effusion occurs which can not be explained by a venous congestion.

Pericardial involvement is assumed if

• the lymphoma has a broad area of close contact towards the heart surface beyond the valve level (ventriculus area) or
• a pericardial effusion occurs.

Pleura and/or pericardial involvement are generally considered E-lesions.

6.4.2.2 Extra-nodal involvement

Extra-lymphatic structures or organs that are infiltrated per continuum out of a lymphatic mass are termed E-lesion (examples: lung, intestine, bones) and do not automatically qualify for stage IV. Exceptions: Liver or bone marrow involvement always implies stage IV disease.

6.4.3 Organ involvement

Definitions of organ involvement are mentioned in this protocol to find out whether patient fulfil an exclusion criterion.

6.4.3.1 Lung involvement

Lung involvement is assumed if any intrapulmonary focus is detectable.

Note: This definition differs from EuroNet-PHL-C1 definitions for classical HL because minimal involvements may be important when minimal therapy is being given.

E-lesion of the lung is restricted to one pulmonary lobe or perihilar extension with homolateral hilar lymphadenopathy.

6.4.3.2 Liver and spleen involvement

• Liver involvement always implies stage IV.
• Mere enlargement of liver / spleen only is not considered as involvement.
• Focal changes in the liver / spleen structure that are tumour suspicious in ultrasonography are considered involved – independent of the FDG-PET result.
• In case of doubtful involvement of liver or spleen (e.g. structures atypical of tumour in sonography or MRI) the liver / spleen is considered involved (biopsy at discretion of
treated by the treating clinician) and the patient is excluded from the trial (if stage would be above IIA in case of involvement).

Note: This definition differs from EuroNet-PHL-C1 definitions for classical HL because minimal involvements may be important with minimal therapy.

6.4.3.3 Bone / bone marrow involvement

**Bone involvement** or **Bone marrow involvement** is assumed if:

- A bone biopsy or bone marrow biopsy is positive or
- CT bony window is positive or
- MRI is positive in bone and adjacent soft tissue (T2 fat saturated sequences) or
- FDG-PET of bone region is positive

Note: This definition differs from EuroNet-PHL-C1 definitions for classical HL because minimal involvements may be important with minimal therapy.

In the event of an isolated lesion or relevant history (e.g. trauma) only a positive biopsy indicates bony involvement.

Bone marrow involvement implies stage IV and exclusion of the patient from the trial.

Note: Patients with assumed bone or bone marrow involvement are excluded from this trial although, if treated according to EuroNet-PHL-C1 these patients might not be classified as having bone/bone marrow involvement. The reason for this exclusion is that within this protocol only low intensity chemotherapy is given. Thus, the protocol should be restricted to patients in whom no doubt exists about an early stage.

6.4.4 PET evaluation in the region of the biopsy

The region of the diagnostic biopsy is involved by histological evidence. If staging FDG-PET was performed after the biopsy and the biopsy region is not PET-positive then the region is considered PET-unclear and does not constitute a discordantly negative PET result.

6.5 INDICATIONS FOR INVASIVE DIAGNOSTICS

Bone marrow biopsy is not required for protocol patients.
6.6 GUIDANCE TO SURGEONS ON ADDITIONAL SURGERY FOR RESECTABLE NODES

Any additional, i.e. post diagnostic biopsy, surgery should be performed by the surgeon(s) working with the multidisciplinary paediatric haematology/oncology team. If one or two nodes, or part of a large node, remain(s) then additional surgery can be attempted, provided complete resection is easy and will not cause morbidity to the patient. Neck dissection, for example, should not be attempted. If the node(s) is not easily resectable then CVP chemotherapy should be given instead.

6.7 RESTAGING

6.7.1 General information

The following cross-sectional imaging procedure is recommended for reassessment of initially involved regions:

- neck: MRI / (CT)
- thorax: MRI
- abdomen: MRI + sonography / (CT)
- pelvis (inguinal): MRI / (CT)

6.7.2 Complete resection after additional surgery

Complete resection (7.2.1) is documented by the surgeon. If in doubt CT/MRI imaging is recommended.

6.7.3 Response assessment after CVP

After CVP treatment all initially involved regions are assessed by CT/MRI and those patients not in CR but in CRu or less need a **FDG-PET scan (between day 14 and day 17 after the last dose of chemotherapy)**.
6.7.4 Follow-up

Follow-up starts six weeks after completion of therapy according to the recommendations (Table 2; cf. section 9.2).

Table 2 Recommendations for follow-up examinations

<table>
<thead>
<tr>
<th>Procedures</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>In 1st year</td>
</tr>
<tr>
<td></td>
<td>First follow-up 6 weeks</td>
</tr>
<tr>
<td></td>
<td>after end of treatment</td>
</tr>
<tr>
<td></td>
<td>In 2nd year</td>
</tr>
<tr>
<td></td>
<td>In 3rd year</td>
</tr>
<tr>
<td></td>
<td>In 4th year</td>
</tr>
<tr>
<td></td>
<td>In 5th year</td>
</tr>
<tr>
<td></td>
<td>from 6th year on</td>
</tr>
<tr>
<td>Clinical history and examination</td>
<td>4 - 8x</td>
</tr>
<tr>
<td>Blood counts, ESR</td>
<td>4x</td>
</tr>
<tr>
<td>CT/MRI or Ultrasound of involved region</td>
<td>2-4x</td>
</tr>
<tr>
<td>FDG-PET</td>
<td>Only if relapse confirmed by biopsy</td>
</tr>
</tbody>
</table>

Many countries may consider it appropriate to perform fewer and less frequent follow up investigations.
7 STAGE CLASSIFICATION AND DEFINITION OF THERAPY OUTCOME

7.1 STAGE CLASSIFICATION

Stage classification is performed according to Cotswolds revision of the classical Ann Arbor staging system.

The diagnostic criteria for involvement formally integrating FDG-PET results are explained in chapter 6.4.

Table 3 details the definition of lymph node regions and extra-nodal sites on which staging is based.

Table 3 Independent lymph node regions

<table>
<thead>
<tr>
<th>Independent lymph node regions are:</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Waldeyer’s ring (left and right)</td>
</tr>
<tr>
<td>- cervical (left and right) with sub-regions relevant for irradiation:</td>
</tr>
<tr>
<td>- upper neck: up to upper edge of larynx</td>
</tr>
<tr>
<td>- lower neck: up to supraclavicular fossa</td>
</tr>
<tr>
<td>- supraclavicular (left and right)</td>
</tr>
<tr>
<td>- infraclavicular (left and right): subpectoral on the thoracic wall</td>
</tr>
<tr>
<td>- axillar (left and right)</td>
</tr>
<tr>
<td>- lung hilus (left and right): bronchopulmonary LN</td>
</tr>
<tr>
<td>- mediastinum with sub-regions relevant for irradiation:</td>
</tr>
<tr>
<td>- upper mediastinum: down to bifurcation</td>
</tr>
<tr>
<td>- middle mediastinum: hilus down to subcarinal region</td>
</tr>
<tr>
<td>- lower mediastinum: down to diaphragm</td>
</tr>
<tr>
<td>- supradiaphragmatic: diaphragmatic recessus</td>
</tr>
<tr>
<td>- spleen</td>
</tr>
<tr>
<td>- splenic hilus</td>
</tr>
<tr>
<td>- liver hilus</td>
</tr>
<tr>
<td>- mesenteric: mesentery, mesocolon</td>
</tr>
<tr>
<td>- paraortic: coeliac, paraaortocaval, pararenal, paralienal, parapancreatic</td>
</tr>
<tr>
<td>- iliac (left and right): parailiac</td>
</tr>
<tr>
<td>- inguinal (left and right): inguinal, femoral</td>
</tr>
</tbody>
</table>

Table 4 Stage classification Hodgkin’s lymphoma
Stages of Hodgkin’s lymphoma according to the Cotswolds revision of the Ann Arbor staging system

I  Involvement of a single independent lymph node region or lymph node structure
II  Involvement of 2 or more lymph node regions on the same side of the diaphragm
III Involvement of lymph node regions or lymph node structures on both sides of the diaphragm
IV  Involvement of extra-nodal sites beyond “E”-sites

Table 5 Annotations to stage definitions

A. No B symptoms

B. At least one of the following systemic symptoms
   a. Inexplicable weight loss of more than 10% within the last 6 months
   b. Unexplained persisting or recurrent temperature above 38 °C
   c. Drenching night sweats

E. Involvement of a single extra-nodal site contiguous or proximal to known nodal site.
   (For the distinction between stage IV and the E-stages see chapter 6.4.2.)

7.2 DEFINITION OF TREATMENT RESPONSE

7.2.1 Definition of complete resection

Complete resection is achieved if all initially involved lymph-nodes have been removed.

7.2.2 Local response after chemotherapy

7.2.2.1 Local response definition for nodal involvement with measurable tumour volume

In this protocol overall response to treatment is determined according to a systematic assessment of tumour response in all involved sites, using CT/MRI and PET.
In those sites where the tumour is measurable from CT/MRI scanning the change in tumour volume is compared with the original pre-treatment reference volume and then assigned a treatment response for that local site.

At initial staging all measurable nodal sites (i.e. all nodal except for the spleen and Waldeyer’s ring) are grouped in separately measurable reference volumes. Reference volumes can include multiple sites if these are contiguous.

The composition of these reference volumes is defined and documented. Initial volumes of reference volumes are measured.

Volumes are approximated as ellipsoids. If a, b, c denote the principal axes of the ellipsoid the volume is calculated as $V = \frac{a \times b \times c}{2}$.

**Local Complete remission (local CR)**

A reference volume is in "local complete remission" (in short: local CR) if:

- the residual tumour volume is less than, or equal to, 5% of the initial reference volume at diagnosis (CT/MRI) and
- the residual tumour volume is less than, or equal to, 2 ml.

**Local complete remission unconfirmed (local CRu)**

A reference volume is in "local complete remission unconfirmed" (in short: local CRu) if:

- No local CR and
  - the residual tumour volume is less than, or equal to, 25% of the reference volume (CT/MRI) or
  - the residual tumour volume is less or equal to 2 ml

**Local partial remission (local PR)**

A reference volume is in "local partial remission" (in short: local PR) if:

- No local CR or local CRu and
  - the residual tumour volume is less than, or equal to, 50% of the reference tumour volume (on CT/MRI) or
  - the residual tumour volume is between 2 - 5 ml (to safeguard against artefacts due to measurement errors).
Local no change (local NC)

A reference volume is in "local no change" (in short: local NC) if

- no local CR or local CRu or local PR and
- no local Progression

Local Progression (local PRO)

A reference volume is in "local progression" (in short: local PRO) if

- The residual tumour volume is larger than >125% of the reference volume or significantly increases compared to the best previous response – be aware of possible measurement error in small tumour volume.

7.2.2.2 Local response definitions for nodal involvement with non-measurable tumour volume

For all nodal involvement with non-measurable tumour volume (e.g. spleen, Waldeyer’s ring) three response categories are distinguished by radiological or clinical criteria:

- Locally undetectable
- Locally detectable
- Locally progressive

Only “Locally undetectable” is consistent with overall CR.

7.2.3 Overall (patient level) response definitions

Overall (patient level) response categories are obtained from the worst local response in reference volumes and the worst local response in non measurable nodal disease as illustrated in the following figure:
Figure 3  Definition of overall response

<table>
<thead>
<tr>
<th>Worst local response in nodal reference volumes</th>
<th>No involvement</th>
<th>Local CR</th>
<th>Local CRu</th>
<th>Local PR</th>
<th>Local NC</th>
<th>Local PRO</th>
</tr>
</thead>
<tbody>
<tr>
<td>No involvement</td>
<td>Overall CR</td>
<td>Overall CRu</td>
<td>Overall PR</td>
<td>Overall NC</td>
<td>Overall PRO</td>
<td></td>
</tr>
<tr>
<td>Undetectable</td>
<td>Overall CR</td>
<td>Overall CRu</td>
<td>Overall PR</td>
<td>Overall NC</td>
<td>Overall PRO</td>
<td></td>
</tr>
<tr>
<td>Still detectable</td>
<td>Overall CRu</td>
<td>Overall CRu</td>
<td>Overall PR</td>
<td>Overall NC</td>
<td>Overall PRO</td>
<td></td>
</tr>
<tr>
<td>Local PRO</td>
<td>Overall PRO</td>
<td>Overall PRO</td>
<td>Overall PRO</td>
<td>Overall PRO</td>
<td>Overall PRO</td>
<td></td>
</tr>
</tbody>
</table>

Legend: overall CR, overall CRu, overall PR, overall NC, overall PRO

**Complete remission (CR)**

“Complete remission” (in short: CR) is achieved if in restaging

- all disease symptoms have disappeared **and**
- no new lymphatic lesions have occurred **and**
- **all** initially involved regions with non-measurable tumour volume are locally undetectable **and**
- **all** reference volumes are in local CR

**Complete remission unconfirmed (CRu)**

“CR unconfirmed” (in short: CRu) is achieved if in restaging

- no CR **and**
- all disease symptoms have disappeared **and**
- no new lymphatic lesions have occurred **and**
- **all** initially involved regions with non-measurable tumour volume are not locally progressive **and**
- **all** reference volumes are at least in local CR
**Partial remission (PR)**

"Partial remission" (in short: PR) is achieved if in restaging

- no CR or CRu and
- all disease symptoms have disappeared and
- no new lymphatic lesions have occurred and
- all initially involved regions with non-measurable tumour volume are not locally progressive and
- all reference volumes are at least in local PR

**No change (NC)**

"No change" (in short: NC) is achieved if in restaging

- no CR or CRu or PR and
- no PRO

**Progression (PRO) / Relapse (R)**

Progression / Relapse of the disease occurs if

- recurrence or occurrence of new disease symptoms which can not be explained otherwise or
- occurrence of new lymphatic or extra-lymphatic lesions or
- at least one initially involved region with non-measurable tumour volume is locally progressive or
- at least one reference volume is in local PRO

**Biopsy of an enlarging region or new lesion is mandatory.**

**A progression / relapse of the disease is called**

- **progression** if it occurs within three months of the end of therapy (date of surgery or last day of chemotherapy application (including prednisone/prednisolone))
- **early relapse** if it occurs between three and twelve months after the end of therapy.
- **late relapse** if it occurs later than twelve months after the end of therapy.
7.3 FDG-PET RESPONSE ASSESSMENT

After three cycles of CVP response reassessment including FDG-PET is performed. **FDG-PET examinations are assessed only for initially involved regions** (except in case of suspected progression).

7.3.1 Definition local FDG-PET response

For each initially involved reference volume or non-measurable nodal site a local PET response is defined based on the initial PET and the response assessment PET results as illustrated in:

**Figure 4  Definition local FDG-PET response**

<table>
<thead>
<tr>
<th>initial PET – involved regions only</th>
<th>+</th>
<th>-</th>
<th>? / nd</th>
</tr>
</thead>
<tbody>
<tr>
<td>response assessment PET</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>? / nd</td>
<td>?</td>
<td>?</td>
<td>?</td>
</tr>
</tbody>
</table>

+ = positive FDG-PET
- = negative FDG-PET
? / nd = questionable FDG-PET or FDG-PET not done
7.3.2 Definition local FDG-PET response

- **Local PET response positive** if the response assessment PET is positive anywhere in the reference volume or involvement site.
- **Local PET response unclear**, if the response assessment PET is unclear or the response assessment PET is negative, but the initial PET was discordantly negative.
- **Local PET response negative** if the response assessment PET is negative and the initial PET was positive or unclear (i.e. not discordantly negative).

**NOTE:** A PET examination is locally unclear if

- Not done
- Not evaluable due to technical problems

in rare cases of questionable PET results.

7.4 DEFINITION OF GOOD RESPONSE

Patients have a good response if they are

- in overall CR

  or

- CRu and all initially involved regions are
  - PET-negative or
  - PET-unclear and either in local CR or undetectable

All other patients are considered poor responder.
8 TREATMENT PLAN

Do not start treatment in patients with early stage CD20+ Hodgkin’s lymphoma until the differential diagnosis of classical Hodgkin’s lymphoma (versus nodular lymphocyte-predominant HL) has been excluded by reference pathology. Patients with c-HL qualify for the EuroNet-PHL-C1 study.

Once the diagnosis of LPHL is made patient eligibility for this protocol needs to be established.

8.1 SURGERY ONLY FOR SELECTED STAGE IA PATIENTS

All patients in stage IA that
- either achieve a complete resection by diagnostic biopsy or
- or achieve a complete resection by additional (post biopsy) surgery
receive no further treatment and enter immediately follow-up.

Additional surgery is performed if complete resection (see 6.6.) is considered feasible and uncomplicated, i.e. should not cause unacceptable morbidity or permanent functional impairment. Ideally surgery should be performed by surgeons who are part of the multidisciplinary paediatric haematology/oncology team who follow the guidance for surgeons in section 6.6. Patients in complete resection do not enter the CVP study population.

8.2 CVP CHEMOTHERAPY

Cyclophosphamide, vinblastine and prednisolone (or prednisone) will each be considered Investigational Medicinal Products (IMPs).

All patients with stage IIA disease and
all patients with unresected stage IA disease in whom
- additional surgery is deemed not feasible
- additional surgery was attempted but not successful
- additional surgery is not accepted by the patient
receive CVP chemotherapy.
The first cycle of CVP (\textbf{C}yclophosphamide, \textbf{V}inblastine, \textbf{P}rednisolone (or Prednisone)) should start once the indication for chemotherapy has been established. Three cycles of CVP are given.

The patient should be weighed at study entry and the body surface area (BSA) calculated using actual body weight according to national standards (e.g., the UK-standard CCLG paediatric BSA tables “Estimation of Body-Surface Area in Infants and Children”). Dose capping for obese patients is not recommended. Treatment of infants <1 year old is not expected in this trial but dosing in these patients should follow established local practice, or may be discussed with the CI. The patient should be reweighed and the BSA recalculated before each cycle of CVP.

Subsequent cycles are started if all the following criteria are fulfilled:
\begin{itemize}
  \item Lansky/Karnovski Index >70%
  \item WBC > 1.8/nl or \( x \times 10^9/L \)
  \item ANC > 1.0/nl or \( x \times 10^9/L \)
  \item Platelets > 100/nl or \( x \times 10^9/L \)
  \item No protocol drug contraindications
\end{itemize}

(Chemotherapy should be interrupted if more serious intercurrent illnesses occur i.e., pneumonia, suspected sepsis, varicella, Herpes zoster etc...)

Drug schedule for CVP is illustrated in Table 6.

\textbf{Table 6 CVP}

\begin{center}
\begin{tabular}{|l|c|c|c|c|c|c|c|}
\hline
\textbf{Prednisolone (or Prednisone)} & 1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
\textbf{40 mg/m²/day p.o. divided into 3 doses} & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \bullet & \\
\textbf{Day 1 - 8} & & & & & & & & \\
\hline
\textbf{Vinblastine} & & & & & & & & \\
\textbf{6 mg/m2 intravenous, (max single dose 9 mg)} & \bullet & & & & & \bullet & \\
\textbf{Day 1 + 8} & & & & & & & & \\
\hline
\textbf{Cyclophosphamide} & & & & & & & & \\
\textbf{500 mg/m² as 1-hr IV Infusion} & \bullet & & & & & & & \\
\textbf{Day 1} & & & & & & & & \\
\hline
\end{tabular}
\end{center}

Hydration fluids should be given according to local practice.

Vinblastine must be given by the intravenous route ONLY – fatal if given by other routes.
(Country specific information: In UK trial sites must prepare vinca alkaloid doses in accordance with NPSA/2008/RRR004 when treatment is delivered in Adult/Adolescent Units – refer to Pharmacy Manual).

Prednisolone (or prednisone) **should be stopped** on day 8 and **should not be tapered**.

The next cycle can start by day 15 of each cycle provided the above criteria are satisfied. Patients who show clinical progression during CVP come off protocol and should immediately switch to treatment on a classical HL protocol (e.g. according to EuroNetPHL-C1 protocol).

### 8.3 PROCEDURE AFTER CVP

After receiving 3 courses of CVP patients are restaged as in section 6.7.3 and those with
- good response receive no further treatment and enter follow up.
- poor response are considered to have failed CVP. In these patients further treatment with two courses of ABVD combined with Rituximab (375 mg/m²) given on day one of each cycle of ABVD is recommended.

### 8.4 DOSE MODIFICATIONS

Since chemotherapy is well tolerated no detailed provisions for dose modifications are given, even in patients with haematotoxicity CTC grade 4. A short (7 days) therapy delay may be indicated in a few cases. Delays beyond 7 days should be discussed with the CI.

### 8.5 CONTRACEPTION

All patients are advised that during chemotherapy and up to one year afterwards procreation of children is not recommended, there is a risk of an adverse effect on the foetus. The treating physician should advise about methods of contraception individually. The occurrence of pregnancy in patients or their partners should be reported to the study office.

### 8.6 SIDE EFFECTS OF CHEMOTHERAPY

General acute side effects of chemotherapy include: nausea, vomiting, weight loss and alopecia. General late side effects of chemotherapy include: increased risk of secondary malignancies, infertility or premature menopause.

For additional information on side effects please refer to the summary of product characteristics.
8.6.1  Vinblastine
Acute side effects are constipation, abdominal pain and leucocytopenia. Occasionally mild peripheral neuropathy, thrombocytopenia and anaemia can occur. Rarely, nausea and vomiting, alopecia and paralytic ileus can occur.

8.6.2  Cyclophosphamide
The following side effects can occur: bone marrow suppression, increased infection risk, and haemorrhagic cystitis.

8.6.3  Prednisone/Prednisolone
Changes in the bone metabolism have been detected (especially in patients treated for acute lymphoblastic leukaemia) which can lead to osteonecrosis. In rare cases an artificial joint replacement may be required. In addition, the Prednisone/Prednisolone therapy can lead to reversible retention of water, increase in weight, hypertension, glucose intolerance, increased infection risk and psychosis/mental disorders.

8.7  SUPPORTIVE CARE
Management of febrile neutropenia is according to locally agreed guidelines. Antiemetics should be given according to local policy.

8.7.1  Antibacterial prophylaxis (optional, as per national guidelines)
Patients may receive Trimethoprim / Sulfamethoxazole orally during chemo- and radiotherapy and up to three months after end of chemotherapy, as per local/national guidelines. If WBC is below 1000/ mm³, 1 x 10⁹/L, patients may receive, e.g. oral colistin sulphate (100.000E/kg, max. 4.000.000 E) optional as per local/national guidelines.

8.7.2  Prevention of GvH reaction / infection through blood transfusions
Transfusions of packed red cells or platelets should be leukocyte-depleted and irradiated with 30 Gy.
8.7.3 **Antifungal prophylaxis**

During treatment patients may receive antifungal prophylaxis according to local/national recommendations.

8.8 **RECOMMENDATIONS FOR PATIENTS WITH TREATMENT FAILURE**

All patients with a good response to treatment, be it surgery alone or 3 CVPs, enter a follow up (watch and wait) period. Patients failing to achieve a good response will come off protocol but long-term follow up and monitoring is recommended to evaluate late effects.

Patients who relapse in the follow up period are treated according to physician’s decision. Patients relapsing after surgery alone with relapse stage IA or IIA and residual tumour after diagnostic biopsy for relapse and no additional surgery planned may enter into the CVP study population. This requires new registration and informed consent.

Guidance and recommendations for management of all other relapses during follow up can be obtained from national study group in each country, and might include further surgery, CVP (in CVP naïve patients), monoclonal antibody therapy with Rituximab or standard classical HL therapy.
9 ORGANISATION

9.1 INFORMED CONSENT

All patients admitted to the trial site with suspected or diagnosed lymphocyte-predominant Hodgkin’s lymphoma are to be considered for enrolment and the inclusion and exclusion criteria to be checked.

NOTE: If any eligibility criteria can be checked only by study specific invasive procedures that are not part of standard care, eligibility check has to be finished after receiving written informed consent from the patient and his/her parents or guardian. No study related procedures are allowed before informed consent has been obtained.

The investigator must explain to each patient and his/her parents or guardian the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each patient and his/her parents or guardian must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship to the treating physician. The patient and his/her parents or guardian should be provided with enough time to think about the participation in the study.

The informed consent is documented on a standard form, written in non-technical language. The patient (if applicable) and his/her parents or guardian should read the statement and consider his/her decision before signing and dating the document, and should be given a copy of the signed document. No patient can enter the study before informed consent in compliance with the pertinent national laws has been obtained.

Informed consent forms are provided in the investigator site file. The signed informed consent form has to be duplicated to provide one version to the trial subject and one original for the trial site which has to be filed in the investigator site file.

The informed consent of the patient and his/her parents or guardian must also refer specifically to the assessment and processing of data on the patients’ health. The patient and his/her parents or guardian are to be informed explicitly on the purpose and extent of the data collection and the use of his/her personal data, especially the health-related data.

NOTE: The following procedures apply only to German patients.

The patient and his/her parents or guardian are additionally asked to give consent that the personal and health related data is transmitted to the:

- German Childhood Cancer Registry in Mainz (Dr. Kaatsch),
Furthermore, patients who are treated in trial sites taking part in Central review and their parents or guardian are informed on the central staging and response assessment performed in the study office in Halle. For this purpose, all medical experts involved in the central review process need to have access to all required medical files and images. The aims and purposes of this data collection are explained to the patient and their parents or guardian.

One of the main objectives of the EuroNet-PHL-LP1 trial is to reduce long-term sequelae of therapy without compromising cure rates. To monitor this, complete follow-up data are crucial. Therefore, the patient and his/her parents or guardian are additionally asked for their consent to be contacted directly by the corresponding study office, in case no follow-up has been provided by the responsible trial site.

9.1.1 Withdrawal of informed consent

Patients and their parents or guardian may withdraw their consent to participate at any time of the trial without giving the reason for it. Nevertheless, the patient and his/her parents or guardian should be asked for the reason of the premature termination but they should also be aware, that they need not answer this question. The patient and his/her parents or guardian must be informed that choosing not to participate or to withdraw the consent will not affect his/her subsequent medical treatment or relationship to the treating physician.

Date of enrolment and date of and reason for withdrawal (if available) are to be documented in any case. The patient and his/her parents or guardian is to be informed that in case of revocation of his/her consent, the data already stored will be used further, as may be necessary:

- to assess effects of the study drug to be tested
- to guarantee that the interests of the patient are not impaired
- to comply with the regulatory requirements.
### 9.2 THERAPY

#### 9.2.1 Procedures for all patients

<table>
<thead>
<tr>
<th>Registration</th>
<th>Immediately after informed consent has been obtained and the diagnostic procedures (cf. chapter 6) have been completed and preferably before start of therapy, the investigator registers the patient in the respective study office (fax of the patient registration form). Note: reference pathology is required. The investigator receives a return fax with the assigned patient ID. The patient ID has to be entered in the patient identification list (PIL) in the investigator site file together with the patient’s name and date of birth. Note: In Germany, the patient should be registered simultaneously in the German Childhood Cancer Registry in Mainz, according to the common procedure for all paediatric-oncological studies.</th>
</tr>
</thead>
</table>
| Staging | Staging is performed according to chapter 6.  
*Procedures for trial sites with central review*  
Immediately after registration, the investigator has to send all required documents and images concerning the initial staging to the corresponding study office. These documents are an indispensable precondition for the central staging.  
As soon as possible after central review, the investigator receives the reference staging results necessary for treating according to protocol as well as documents necessary for further documentation. The few patients who may be upstaged by central review will be off study irrespective of prior treatment with CVP. These patients will then be treated according to national recommendations.  
*Procedures for trial sites without central review*  
Once the diagnosis is confirmed and the staging investigations completed the staging is documented on the staging form and sent to the corresponding study office. |
| Surgery alone | Patients qualify for surgery only a) if after diagnostic biopsy no residual |
tumour is found at staging or b) if complete resection is achieved by additional surgery. In this case the surgeon decides on complete resection. A restaging after additional surgery is not required. Surgery only patients enter follow-up without further therapy.

In case of incomplete resection the patient should go on with CVP.

| **CVP chemotherapy** | **Immediately after** decision for chemotherapy is made, the first **CVP cycle** is started.  
All patients receive **3 CVP cycles**.  
After completion of CVP chemotherapy, the respective chemotherapy and chemotherapy-toxicity forms have to be sent to the corresponding study office immediately. |
|----------------------|----------------------------------------------------------------------------------------------------------------|

| **Restaging after CVP** | The dates of **first restaging** (sonography, CT/MRI, FDG-PET) are **time-critical** and therefore should be fixed **by the start of the first CVP cycle**.  
After CVP treatment all initially involved regions are assessed by CT/MRI and those patients not in CR but in CRu or less need a FDG-PET scan (between day 14 and day 17 after the last dose of chemotherapy/ Prednisone/Prednisolone of the third CVP cycle).  
**Procedures for trial sites with central review**  
All **required documents and images** concerning the **first restaging** have to be sent to the corresponding study office **at the latest by day 21** after the last dose of chemotherapy/ prednisone/Prednisolone of the third CVP cycle.  
**Procedures for trial sites without central review**  
Response assessment is the responsibility of the local investigator. Documentation should be completed and returned to the corresponding study office. |
|----------------------|----------------------------------------------------------------------------------------------------------------|

9.2.2 Further procedures

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>The first follow-up examination is scheduled <strong>6 weeks after end of therapy</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>After the first follow-up examination, the first follow-up form should be sent</td>
</tr>
<tr>
<td></td>
<td>to the corresponding study office as soon as possible.</td>
</tr>
<tr>
<td></td>
<td>Further follow-up visits are scheduled according to section 6.</td>
</tr>
<tr>
<td></td>
<td>Follow-up forms are due at latest four weeks after the follow-up visit has</td>
</tr>
<tr>
<td></td>
<td>been performed.</td>
</tr>
<tr>
<td></td>
<td>In case of relapse, progression after end of therapy or of death the study</td>
</tr>
<tr>
<td></td>
<td>office should be informed immediately by completing and sending a follow-up</td>
</tr>
<tr>
<td></td>
<td>form.</td>
</tr>
<tr>
<td></td>
<td><strong>Note:</strong> FDG-PET is not recommended for follow-up unless a relapse is confirmed by biopsy.</td>
</tr>
</tbody>
</table>

9.3 PREMATURE TERMINATION OF THERAPY OR FOLLOW-UP

Any premature termination of the trial therapy as well as any premature termination of follow-up has to be documented by the responsible investigator. If possible, date, circumstances of and reasons for the termination should be documented in detail, and communicated to the corresponding study office.

9.3.1 Premature termination of trial therapy

The premature termination of trial therapy may be considered for the following reasons:

- adverse / serious adverse event(s)
- no response to therapy according to protocol criteria
- excessive toxicity
- at the discretion of the investigator, for reasons of medical prudence
- severe protocol violation
- non-compliance of the patient
- administrative problems

In addition, the trial therapy may be terminated on request of the patient, in case of withdrawal of consent or in case of lost to follow-up.

Premature termination should be avoided. In case of premature termination of therapy, reasons/circumstances and if applicable the final status should be documented. If the patient
does not withdraw the consent for further follow-up, he or she should be followed-up as planned.

9.3.2 Premature termination of follow-up

Patients in whom no follow-up has been received for more than two years are directly contacted by the corresponding study office (if consent to this procedure has been given).

NOTE: In Germany, the German Childhood Cancer Registry in Mainz may be asked for current residence.

9.3.3 Organisation of FDG-PET examinations

FDG-PET examinations are time-critical. FDG-PET examinations immediately after chemotherapy can lead to false positive results. **FDG-PET examination** should be performed at the very earliest 14 days **after the last dose of chemotherapy/Prednisolone** and for organisational reasons the **examination date should be fixed in advance**.
10 ADVERSE EVENTS (AE/SAE)

10.1 SAFETY MONITORING

For safety reasons, all laboratory parameters relevant for the application of chemotherapeutic drugs should be measured before start of every new cycle of chemotherapy (cf. 6.2.2). Additionally, blood counts should be measured at least twice during every cycle, especially at time of nadir. The patient’s general condition (Lansky resp. Karnofsky index) should be documented before therapy and regularly during therapy.

10.2 ADVERSE EVENT (AE)

10.2.1 Definition

An Adverse Event (AE) is any untoward medical occurrence in a patient or clinical trial subject administered a pharmaceutical or medical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including abnormal laboratory findings for example), symptom, or disease temporarily associated with the use of a medicinal (investigational) or medical product, whether or not it is considered to be related to the medicinal (investigational) product. (ICH-Guideline E2A)

Adverse events encompass illness, signs of illness (including pathological laboratory findings) and symptoms that initiate during the trial or previous conditions that become worse.

10.2.2 Documentation and Reporting

Adverse events will be documented on the chemotherapy toxicity form. If adverse events occur which are not explicitly named in case report forms, these events have to be named and classified using the severity levels mentioned in section 10.9.1.

Reporting of adverse events is restricted to events occurring within 3 months after the end of the study treatment.

10.3 SERIOUS ADVERSE EVENT (SAE)

10.3.1 Definition

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:
10 ADVERSE EVENTS

- results in death
- is life-threatening

**NOTE**: The term "life-threatening" in the definition of "serious" 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 in-patient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect or
- other medical important condition (see below)

**NOTE**: Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation, but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. (See ICH guideline E2A, section IIB)

In case of further events stated as serious by the treating doctors the study chairpersons should be consulted.

**Events exclusively related to tumour progression are not stated as SAE.**

**SAE reporting is restricted to events occurring within 3 months after the end of the study treatment.**

### 10.3.2 Documentation and reporting

The occurrence of ANY serious adverse event (including death, irrespective of the reason) has to be reported by the investigator immediately (within 24 h) at latest on the next working day.

**Exceptions:**

Hospitalisation due to diagnostic procedures or standard supportive care (e.g. implant of central venous catheter) does not constitute an SAE.

In-patient hospitalisation or prolongation of existing hospitalisation due to **adverse reactions explicitly covered on the toxicity forms** need not be reported as an SAE:

The chemotherapy regimen CVP is known to be associated with the following acute adverse reactions:
- Changes in laboratory parameters (haemoglobin, WBC, neutrophils, platelets, creatinine, bilirubin, liver enzymes)
- Fever
- Infection
- Stomatitis / pharyngitis
- Vomiting
- Diarrhoea
- Constipation
- Sensory neuropathy
- Motor neuropathy

These toxicities are documented on the chemotherapy toxicity form. These **expected adverse reactions** are to be **reported immediately on the SAE pages only** if they:

- result in death
- are life-threatening
- result in persistent or significant disability/incapacity

Every SAE must be documented by the investigator on the SAE pages to be found in the investigator site file. The Serious Adverse Event Report Form must be completed, signed and sent to the corresponding study office immediately by fax (see further details in the investigator site file). The initial report shall be promptly followed by detailed, written reports. The initial and follow-up reports shall identify the trial subjects by unique code numbers assigned to the latter.

The investigator shall supply the corresponding study office, the national study chairperson, the co-ordinating investigator and the Ethics Committee(s) with any additionally requested information.

The corresponding study office shall forward the SAE form and all further reports immediately upon receipt to the coordinating investigator (see further details in the investigator site file). The corresponding study office is responsible for the timely provision of all information required by the coordinating investigator for the evaluation of the SAE.

The study secretary on behalf of the coordinating investigator keeps detailed records of all SAEs reported by the investigators and performs an evaluation with respect to seriousness, causality and expectedness.

The evaluation is documented on an assessment-sheet, which the study secretary submits to the KKSL (pharmacovigilance department) together with the SAE-CRF within two calendar days after the study secretary received the SAE-CRF.

**KKSL / pharmacovigilance**

Universität Leipzig
Query process and closure of open Serious Adverse Events:
Queries regarding all open Serious Adverse Events will be asked in the following frequency:

1. 2 weeks after receipt of SAE-CRF
2. 2 weeks after first query
3. 1 week after second query

Each case will be closed after the third query even if there is no information about outcome and stop date. There will be no further queries.

The case will be closed if the outcome is declared as “recovered”, “recovered with sequel”, or “fatal” and the stop date is known. After consultation of the study secretary, cases will be closed also if the query process described above does not provide the necessary information.

10.4 SUSPECTED UNEXPECTED SERIOUS ADVERSE DRUG REACTIONS (SUSAR)

10.4.1 Definition

Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) are side effects (probably or definitely connected with the administration of the investigational product), the nature or severity of which are inconsistent with the information available about the product. Information about the trial product contained in the SmPC (Summary of Product Characteristics) should be used to verify if the adverse reaction has been previously described.

10.4.2 Evaluation and reporting

The study secretary submits via the KKSL all information available about a SUSAR immediately, at latest within 15 days after the event becomes known to the sponsor, to the competent authorities and the study offices concerned. In case of death or immediate danger of life caused by a SUSAR the competent authorities and the study offices concerned must be informed within 7 days after the event becomes known to the sponsor. Additional information has to be given within further 8 days.
The involved study offices are responsible for information of the Ethics Committee(s) concerned as well as of the respective investigators. The reporting procedure has to comply with the national legislation.

The competent regulatory authorities obtains an electronic report of the SUSARs, if possible. The leading ethics committee will be informed paper-based by the CIOMS-I form. The investigators will be informed by e-mail concerning SUSARs by using the CIOMS-I form.

### 10.5 OTHER SAFETY RELEVANT ISSUES

In addition, other safety issues may also qualify for expedited reporting if they materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the investigational product administration or in the overall conduct of the trial, for instance:

- an increase in the rate of occurrence or a qualitative change of an expected serious adverse reaction, which is judged to be clinically important,
- post-study SUSARs that occur after the patient has completed a clinical trial and are reported by the investigator to the sponsor,
- new events related to the conduct of the trial or the development of the investigational medicinal products and likely to affect the safety of the subjects, such as:
  - a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial,
  - a significant hazard to the subject population such as lack of efficacy of an investigational medicinal products used for the treatment of a life-threatening disease,
  - a major safety finding from a newly completed animal study (such as carcinogenicity)
  - any anticipated end or temporally halt of a trial for safety reasons and conducted with the same investigational medicinal products in another country by the same sponsor,
  - recommendations of the Data Monitoring Committee, if any, where relevant for the safety of the subjects.

The study secretary is responsible for reporting such issues as described above.

### 10.6 ANNUAL SAFETY REPORT

The study secretary on behalf of the coordinating investigator writes an annual (or upon request) safety report (following the “detailed guidance on the collection, verification and presentation of adverse events reports arising from clinical trials on medicinal products for human use”). This report comprises a detailed risk-benefit-analysis, a line listing of all serious adverse reactions (SARs) registered during the report period of the ASR as well as an aggregate summary tabulation containing all documented SARs in the course of the trial. The
study secretary submits this report detailing the safety of the tested medicinal products to the leading ethics committee as well as to the competent regulatory authorities via the national study offices.

The yearly cut-off date refers to the date of the first authorization of the clinical trial by a competent regulatory authority. All data obtained up to this time point will be included in the ASR. Beginning with the cut-off date, there is a time-limit of 60 days for the preparation and submission of the ASR to the competent regulatory authorities and ethic committees.

The ASR is prepared by the study secretary in cooperation with the project management at the KKSL and the responsible biometrician.

10.7 PERIODIC SUSAR REPORTS FOR ETHIC COMMITTEES

The study secretary on behalf of the coordinating investigator submits every 6 months a list of all SUSARs occurred in the period covered by the report accompanied by a brief report to the concerned competent authorities and Ethics Committee(s) via the national study offices.

10.8 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:

a) in general

- the action taken has to be documented by the investigator in the appropriate section of the CRF and/or by additional documents

b) on the investigational product

- drug withdrawn
- dose reduced
- dose increased
- dose not changed
- unknown
- not applicable

10.9 CLASSIFICATION OF THE ADVERSE EVENT

10.9.1 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 V3.0
### 10.9.2 Causal relationship

The investigator must judge whether or not, in his opinion, the Adverse Event was connected with the administration of the investigational product according to the classification given below (Venulet and Ham, 1996).

- Possible
- Not possible

The relationship is **possible**, if one of the following criteria according to WHO-UMC is fulfilled:

- plausible timing, and can not be explained by concomitant diseases or other products, and known pharmacological or phenomenological reaction and positive re-application of the product, if necessary

- plausible timing, and unlikely connection to concomitant diseases or other products, and positive reaction upon withdrawal

- Plausible timing, but could be explained by concomitant diseases or other products, information on withdrawal is incomplete or unclear.

- For a complete evaluation, further information is necessary

- Evaluation is impossible due to inadequate or contradictory information

The relationship is not possible, if the following criterion according to WHO-UMC is fulfilled:

| Mild Adverse Event | • No special medical treatment necessary  
|                   | • All laboratory parameters or x-ray diagnoses without clinical symptoms  
|                   | • Low medical relevance |
| Moderate Adverse Event | • minimal or local medical treatment necessary  
|                    | • exclusively non-invasive treatment (e.g. bandages) necessary |
| Severe and undesirable Adverse Event | • significant symptoms, leading to in-patient treatment or invasive therapy  
|                      | • e.g. transfusions, elective interventional radiology treatment, therapeutic endoscopy or surgery |
| Life-threatening or disabling Adverse Event | • exacerbated by acute life-threatening complications affecting the metabolism or circulation, e.g. break down of the circulation, haemorrhage, sepsis  
|                           | • life-threatening physiological consequences  
|                           | • necessity of intensive care, immediate invasive, interventional or radiotherapy, therapeutic endoscopy or surgery |
| Death related to Adverse Event | • Death caused by the AE |
The timing renders a causal relationship unlikely and concomitant disease or other products can serve as a plausible explanation.

Each Adverse Event has to be reported, even if the investigator feels that it is not related to the administration of study drugs.

### 10.9.3 Expected/Unexpected

An Unexpected AE is an AE, the nature or severity of which is not consistent with the applicable product information (SmPC).

The distinction expected/unexpected only depends on whether the untoward reactions have been previously described.

The following events related to therapy are adverse but expected:

- myelosuppression
- nausea / vomiting
- alopecia
- infections, especially during leukopenic phases
- hemorrhagic cystitis
- cardiomyopathy
- necroses in paravasal injection
- peripheral polyneuropathy, paralytic ileus
- radiation consequences in lung, pericardium or intestine

Expected AEs are also described in 8.6.

### 10.9.4 Outcome

The outcome of an AE has to be classified as follows:

- recovered/resolved
- recovering
- not recovered/not resolved
- recovered/resolved with sequelae
- fatal*
- unknown

*NOTE: A subject's death per se is not an event, but an outcome. The event which resulted into subject's death must be fully documented and reported, even in case the death occurs within
four weeks after test drug treatment end, and without respect of being considered treatment-related or not.

10.10 PREGNANCIES

It is highly unlikely that pregnancies occur during treatment in this study. In the surgery only stratum of the trial, there is no treatment beside the extirpation of a lymph node. In the CVP stratum, chemotherapy lasts for only 6 weeks and failure to use effective contraception methods is an exclusion criterion.

We will document pregnancies on the follow-up forms. Expedited reporting is not required.
11 BIOMETRICAL ASPECTS

11.1 GENERAL STUDY DESIGN CONSIDERATIONS

Nodular lymphocyte-predominant Hodgkin's lymphoma in children is a rare disease. Any reasonably sized study requires Europe-wide co-operation of regional or national study groups. Even with pan-European participation, realistic patient numbers do not suffice to run a comparative randomised trial. Fortunately in children, nearly all patients with Hodgkin's lymphoma are included in ongoing studies. The participating study groups will make all possible efforts to include consecutively into the study all patients that fit the inclusion criteria.

For study design we may therefore assume that the study population will be representative of LPHL patients in the participating countries and that it is thus meaningful to estimate absolute success rates.

Estimating absolute success rates is wholly adequate for the study questions addressed here: In the past, LPHL patients have been treated identical to patients with classical HL. It is well documented that long-term event free survival with treatment for classical HL is very high (~90 - 95%) in the patient population studied here and we are confident that this treatment option as back-up is not relevantly compromised in case of relapse after the treatments investigated here. The main clinical question is thus: Are results with markedly reduced treatment good enough to accept that some patients experience a first relapse and only then receive the very effective standard treatment for classical HL?

In the study we therefore estimate long-term event free survival rates and estimate the rate of relevant upstaging to support the claim that relapse treatment is not relevantly compromised by the first line of therapy employed here.

11.1.1 Clinical hypotheses and respective endpoints

Patients will be allocated to two main study populations:

- Completely resected stage IA patients
- Stage IA / IIA patients with residual tumour.

We expect that about 40% of the early stage patients will present with completely resectable disease.

The clinical hypotheses in this “completely resected” group are:
• A substantial proportion of these patients (> 50% at least, target 70%) can be cured by surgery alone thus sparing them the acute and long-term side effects of chemotherapy and/or radiotherapy currently used in classical Hodgkin’s lymphoma.

• Those that suffer a relapse will still represent in early stages of the disease and thus treatment options at relapse will not be compromised.

Statistically, in this group we will estimate the five year event free survival rate with meaningful precision.

Secondarily we will estimate the rate of clinically significant upstaging in those patients that relapse i.e. whether the disease comes back at a more advanced stage. Clinically significant upstaging means relapse with B symptoms or extranodal disease or stage greater than IIA.

In patients with residual disease the clinical hypotheses are:

• Low intensity (non-antracycline containing) chemotherapy (3 CVP) can achieve a good response ((Overall CR or CRu) AND (PET-negative or PET-unclear and local CR)) in a high (>90%) proportion of patients.

• Patients who achieve a good response after low intensity chemotherapy remain in long-term remission in a substantial proportion (>80%) of cases.

• Patients relapsing after a good response to low intensity chemotherapy rarely show upstaging and still have an excellent prognosis with treatment for classical HL if required.

Firstly we will estimate the 5 year Event free survival rate in all patients receiving CVP chemotherapy. Note failure includes not achieving a good response to 3 CVP. We expect an EFS rate in the order of 70%.

Secondly we will estimate separately the good-response rate after low dose CVP chemotherapy (Based on pilot data this rate should be high (~90%)) and the event free survival rate of patients with documented good response to 3 CVP only.

In addition we will estimate the rate of upstaging (B symptoms or extra-nodal disease or stage > II) in those patients who relapse and document their overall survival.

The outcome of the few patients without good response after low dose CVP chemotherapy will be documented and described.
11.1.2 Stratification by method of staging and response assessment (central versus local)

The study population of this inter-group trial will consist of two strata corresponding to how countries organise staging and response assessment (SRA).

Patients from those national study groups that agree to submit all images to real-time central staging and response assessment (CSRA) in the GPOH-HD study office form the CSRA stratum.

Patients from countries that rely on local decision making concerning staging and response assessment (LSRA) form the LSRA stratum. Most patients in this group will be entered by the SFCE and PPLLSG.

Both strata will be jointly analysed. Staging results and the quality of the decisions concerning complete resection and good response may or may not turn out to be stratum dependent. Impact of stratum on results will be explored. In case of marked differences at an interim safety analysis, a stratum specific discontinuation of the trial may be considered.

11.1.3 Allocation to study populations

Patients are allocated into two study populations

**Completely resected stage IA patients**

All patients in stage IA that

- either achieve a complete resection by diagnostic biopsy or
- or achieve a complete resection by additional surgery

In all stage IA patients with residual disease the feasibility of additional surgery should be assessed. If surgery is deemed possibly successful it should be recommended to the patient.

**Stage IA / IIA patients with residual tumour**

All patients in stage IIA and all patients in IA in whom

- additional surgery is deemed not feasible
- additional surgery was attempted but not successful
- additional surgery is not accepted by the patient

Patients with complete resection cannot enter the CVP study population.

Patients relapsing after surgery alone with relapse stage IA or IIA who have residual tumour after diagnostic biopsy for relapse may be registered into the CVP study population. Indeed,
any patient with relapsed, even multiply relapsed, LPHL who has residual disease after surgery, can be entered into the CVP study, provided they have never received chemo- and/or radio-therapy for HL.

Patients relapsing after surgery alone, who achieve a second complete resection after diagnostic biopsy for relapse can NOT re-enter the study.

Primary analyses concern only the two main study populations.

### 11.1.4 Expected number of patients

Based on the past experiences of the participating study groups we expect at least 200 limited stage LP cases within 5 years of accrual, 80 with complete resection and 120 for CVP treatment.

#### Table 7 Details of the calculation of expected number of patients per group

**Anticipated parameters for LP-Study**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL (all subtypes) cases per year</td>
<td>600</td>
</tr>
<tr>
<td>Proportion LP of HL</td>
<td>0.08</td>
</tr>
<tr>
<td>LP cases over 5 years(all)</td>
<td>240</td>
</tr>
<tr>
<td>Proportion limited stage IA/IIA</td>
<td>0.85</td>
</tr>
<tr>
<td>Accrual limited stage LP cases</td>
<td>204</td>
</tr>
<tr>
<td>Proportion resectable</td>
<td>0.4</td>
</tr>
<tr>
<td>Accrual for W&amp;W after surgery only</td>
<td>82</td>
</tr>
<tr>
<td>Proportion non resectable</td>
<td>0.6</td>
</tr>
<tr>
<td>Accrual for CVP</td>
<td>122</td>
</tr>
<tr>
<td>Rate of no good response to CVP</td>
<td>0.1</td>
</tr>
<tr>
<td>Patient without good response to CVP</td>
<td>12</td>
</tr>
</tbody>
</table>
### 11.1.5 Precision of estimate considerations

**Figure 5**  
**Expected precision of rate estimate**  
(Half width of 95% confidence interval) of rate estimates as a function of sample size and assumed rate: 90%: black, 80%: blue, 75%: green, 70%: orange, 65%: red. Vertical lines indicate expected sample sizes for surgery only (N≈80), CVP (N≈120) and CVP-good responder (N≈110)

For the surgery only group we expect about 80 patients and a long-term event free rate of about 70%. With 90% power a precision of the 5 year EFS estimate of less than ± 11% can be achieved. We then have 94% power to exclude 50% from the two-sided 95% confidence interval.

For the CVP group we expect about 120 patients, a rate of 90-95% of good response and an EFS rate of about 70%. The precision of the good-responder rate estimate is thus expected to be in the order ± 5%. With 95% power a precision of the 5 year EFS estimate of less than ± 9% can be achieved. We then have 90% power to exclude 55% EFS from the two-sided 95% confidence interval.
In the CVP good responder group we expect about 110 patients and a long-term event free rate of >80%. Thus with 90% power a precision of the conditional 5 year EFS estimate of less than ± 8.5% can be achieved.

We expect 10-24 relapses from the surgery only group and less than 3 patients with relevant upstaging. Precision will be in the order of 20% -12%. Similar expectations hold for relapses after good response to 3 CVP.

Overall Survival is a secondary endpoint; 5 year Overall Survival rates will be estimated with a 95%-lower confidence limit. We expect an Overall Survival rate of ca. 98% after 5 years.

For the CVP study population we will thus have 93% Power to exclude 90% from the one-sided exact 95%-confidence interval. For the smaller surgery-only population the expected respective power is 78.7%.

### 11.2 END POINT DEFINITIONS

**Event free survival (EFS)**

EFS: = time from registration until the first of the following events:

- Additional treatment for Hodgkin’s Lymphoma
- progression/relapse of disease
- occurrence of a secondary malignancy
- death by any cause

For patients allocated to the CVP group failure to achieve a good response constitutes an indication for additional treatment and counts as failure.

**Overall survival (OS)**

OS: = time period from registration until death of any cause

**Relevant upstaging**

Relevant upstaging at relapse is defined as

- B-symptoms or
- extra-nodal disease or
- relapse stage > II.

**Further endpoints**

- Acute toxicity of CVP, documented by CTC criteria
• Frequency and success rate of additional surgery beyond diagnostic biopsy in stage IA patients.

• Complications of additional surgery

11.3 STATISTICAL INFERENCE AND METHODS

For all the above endpoints the underlying probability will be estimated and a two-sided 95% confidence interval be calculated.

The allocation process will be described. The main analyses will be performed on an intention to treat basis based on the allocation to surgery only and CVP.

Time-to-event end points are described with the Kaplan-Meier estimator and 5-year survival rates are stated with 95% confidence interval. Regression analyses are performed with the proportional hazard model.

Qualitative variables are described by frequency tables (with 95% confidence interval where relevant) and compared using contingency tables (Chi²-test if relevant).

Metric variables are described by adequate measures of location (average, median) and of spread (standard deviation, inter-quartile range). Histograms or box-plots are used for graphic representation. For comparisons adequately chosen difference measures with 95% confidence interval can be estimated and t-test or Mann-Whitney-U-test can be used respectively.

A detailed analysis plan is developed on occasion of the first safety interim analysis. The final evaluation concerning EFS is performed as soon as at least 95% of patients have more than five years of follow-up.

11.4 INTERIM AND SAFETY ANALYSIS

Given the promising long-term pilot data a safety problem in the surgery only group would be rather surprising. But no long-term data after CVP is available. Therefore annually interim and safety analyses are planned.

In both study populations a higher than usual (5-10%) relapse rate is accepted to reduce the overall toxicity burden because treatment for classical HL is thought to be a safe back-up option for cure.

Alarming events are thus

- relevant upstaging at relapse,
- failure after treatment for classical HL (EuroNet-PHL-C1 or similar) or
- transformation to NHL at relapse
- death from any treatment or disease related causes
Each such event has to be reported immediately and commented in detail. If 5 alarming events occur in one of the study populations the opinion of the DMC has to be requested.

In addition relapses will be monitored: As the relapses will occur within the first five years a formal monitoring with immature data is difficult without assuming a certain form of the underlying hazard function. The following procedure will be used as a trigger to request a comment from the DMC: We will assume that the hazard function for LPHL is roughly the same as for classical HL. As the data evolve we will compare EFS-curves with surgery only as well as CVP with a typical HL curve levelling off at 50% at 5 years using a proportional hazard model. If the one-sided one-sample test against this reference curve is significant at alpha=0.1% alarm is triggered and an opinion of the DMC requested. The final analysis will thereby remain unaffected (Peto-sequential testing scheme). This analysis will be performed annually, but only if at least 30 patients have a follow-up of more than 12 months past the end of therapy in the respective group.

11.5 SPECIAL CASES AND DROP-OUTS

Upstaging by central review
Registration for the study is based on local staging (IA or IIA). We expect less than 3% upstaging in those patients whose final staging is based on central review. This assumption is based on pilot data. These patients do not qualify for the treatment options under study and should be treated according to standard treatment for classical HL of the respective stage. Basic follow up data of these cases should be collected if feasible. This selection may contribute to possible differences between local and central decision making strata.

Additional surgery attempted, but no complete resection
An unknown proportion of stage IA patients will require additional surgery to achieve a complete resection. In the pilot data this concerned 6/54 cases but this rate may be higher in the current study. Additional surgery may be unsuccessful. The failure rate of additional surgery will be described. These cases will then be included into the CVP study population.
12 REFERENCE EVALUATION

12.1 CENTRAL STAGING AND RESPONSE ASSESSMENT

For those groups not using central review (e.g. SFCE, PLLSG), the determination of the stage and assessment of response is the responsibility of the local investigator after discussion if necessary with the national study chairperson or his/her deputy. Stage and response assessment will be checked by the corresponding study office based on information provided on the staging form.

12.1.1 Determination of reference stage and response to CVP

For every patient the reference stage and the response to CVP will be determined by the central review panel during tumour conferences taking place regularly (at least weekly) at the GPOH-HD study office. The following information and material is required for the central staging and response assessment, and has to be provided by the treating investigator:

- Results of clinical examination (including ENT findings)
- Results of sonography
- Results and images (preferably electronically) of all CT / MRI examinations and FDG-PET data sets

The relapse reference stage is determined by the same procedure.

12.1.2 Organisation of the tumour conference

12.1.2.1 Preparations before tumour conference

Participating trial sites send the necessary written results and films or data sets (except: PET images – these are transmitted directly by the local nuclear medicine physician) to the GPOH-HD study office (see PET-Manual and checklists in the investigator site file).

The central review coordinator checks the documents for completeness. If necessary documents are missing, a reminder telephone call is made immediately. As soon as all necessary documents are available the patient is scheduled by the coordinator for the weekly tumour conference.
Prior to the tumour conference both the reference radiologist and the reference nuclear medicine physician independently evaluate the submitted images or data sets (being aware of the written reports of the local centre).

12.1.2.2  **Tumour conference**

Participants of the tumour conference are: the central review coordinator, the reference radiologist, the reference nuclear medicine physician and the reference radiotherapist or their respective deputies.

In the tumour conference in a first step the clinical findings and the findings collected in sonography are presented by the study secretary. Next the reference radiologist reports and compares the results based on his CT/MRI evaluation. Then these data are related to the PET results by the reference nuclear medicine physician. Finally the reference stage and/or the response to treatment is determined in consultation with the study chairperson or his deputy considering all results applying the rules of chapter 6.4 and 7.4.

12.1.2.3  **Transmission of information to the investigators**

The result of the tumour conference is documented on the staging / response assessment forms – tumour conference. Subsequent to the tumour conference these forms are sent to the investigators by fax and/or mail within maximal two working days with corresponding annotations by the central review coordinator after consultation of the study chairperson.

The GPOH-HD study office is responsible for establishing the reference stage after final evaluation of the PET / CT / MRI examination findings in synopsis with clinical findings.

**12.2 REFERENCE PATHOLOGY**

 Histologic diagnosis confirmation is an indispensable basic requirement for admission of a patient to the study. The participating reference pathology centres as well as the diagnostic criteria and markers are described within the reference pathology manual.
13 SCIENTIFIC AND BIOLOGICAL ADD ON STUDIES

It is planned to collect tumour material and serum from patients for scientific and biological add on studies. Side projects need approval by the scientific advisory board. A separate protocol and respective informed consent form will be developed and submitted to the relevant ethics committees.
14 ETHICAL AND LEGAL ASPECTS AND AGREEMENTS


14.1 SPONSORSHIP

The Martin Luther University of Halle/Wittenberg is sponsor of the international clinical trial EuroNet-PHL-LP1 in the legal sense as defined by the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001. The sponsor internally transfers his duties for every participating country to an authorised institution (as nominated by the national study group and / or the national study chairperson) by written agreement.

The authorised institution will fulfil the transferred duties for the sponsor and warrants the compliance with all the statutory provisions relevant for the sponsor. The authorised institution is responsible for pointing out to the sponsor those duties required by a respective national regulation that were not transferred to the authorised institution by the written agreement and has to support the sponsor in fulfilling these duties as required.

Beginning with the date of the agreement the authorised institution will semi-annually draw up a written report on the progress of the clinical trial in the respective country, the fulfilment of the transferred duties and the compliance with legal requirements. In addition the authorised institution will on demand provide all documents (if applicable as copy) necessary for the Trial Master File of the sponsor.

The sponsor reserves the right to audit the authorised institution to control adherence to all legal requirements.

14.2 REQUEST OF AUTHORISATION TO THE COMPETENT AUTHORITIES

The co-ordinating investigator is responsible for the request of authorisation to the competent authority in Germany, taking into account the German laws. Furthermore, the co-ordinating investigator will provide all authorised institutions of the participating countries with all documents necessary for request of authorisation according to German law.

The authorised institutions of the participating countries are responsible for provision of all further documents required by national law and for request of authorisation to the competent authority in the respective country, taking into account the national laws.
14.3 APPLICATION FOR NATIONAL ETHICS COMMITTEE OPINIONS

The co-ordinating investigator on behalf of the sponsor is responsible for the application for an Ethics Committee opinion in Germany, taking into account the German laws. Furthermore, the co-ordinating investigator will provide all authorised institutions of the participating countries with all documents required for application for an Ethics Committee opinion according to German law.

The authorised institutions of the participating countries are responsible for provision of all further documents required by national law and for application for an Ethics Committee opinion in the respective country, taking into account the national laws.

14.4 NOTIFICATION OF SUBSTANTIAL AMENDMENTS

Any protocol amendments prepared by the Inter-Group Trial Steering Committee, which are likely to have an impact on the safety of the trial subjects or to change the interpretation of the scientific documents in support of the conduct of the trial, or which are otherwise significant, require an authorisation of the competent authorities of the participating countries, as well as approval of the concerned Ethics Committees.

The co-ordinating investigator on behalf of the sponsor is responsible for the request of authorisation to the competent authority in Germany as well as for application for an Ethics Committee opinion in Germany, taking into account the German laws. Furthermore, the co-ordinating investigator will provide all authorised institutions of the participating countries with all documents for request of authorisation respectively for application for an Ethics Committee opinion according to German law.

The authorised institutions of the participating countries are responsible for provision of all further documents required by national law and for request of authorisation to the competent authority as well as for application for an Ethics Committee opinion in the respective country, taking into account the national laws.

14.5 DECLARATION OF THE END OF TRIAL

The co-ordinating investigator on behalf of the sponsor is responsible for providing all documents required for the notification of the regular or premature termination of the trial. The co-ordinating investigator is responsible for notification of the end of trial to the competent authority and the Ethics Committee concerned in Germany, according to German laws.
The authorised institutions of the participating countries are responsible for notification of the end of trial to the competent authority and the ethics Committee concerned in the respective country, taking into account the national laws.

### 14.6 INSURANCE

In Germany, patients are insured by the insurance company HDI Gerling Industrie Versicherungs AG Am Schönenkamp 45, 40599 Düsseldorf. The number of the certificate is 70-005 890 284-7. A copy of the certificate of insurance and the insurance conditions will be filed in the investigator site file. Copies of both documents should be handed over to the patients and/or their parents or guardian.

The authorised institutions of all other participating countries are responsible for the provision of insurance or indemnity to cover the liability of the investigator and the sponsor in the respective country (if necessary according to national law), as required by the Directive 2001/20/EC of the European Parliament and of the Council of 4 April 2001 and the corresponding national laws.

### 14.7 FURTHER AGREEMENTS

Procedures and agreements for safety management are described in chapter 10, for archiving in section 15.3, for selection of qualified investigators and trial sites in section 4.2.
15 DATA HANDLING AND RECORD KEEPING

15.1 CASE REPORT FORMS (CRF)

The CRF will be prepared by the KKSL and printed on 3-part, no carbon required (NCR) paper. The regional study offices receive the original and the first copy (yellow) of the CRF pages and the second copy (blue) is retained in the trial site.

Case report forms (CRFs) should always be completed with a black ballpoint pen. Pens or pencils cannot be used. Attention has to be paid to a clear, legible script, preferably block letters. Mistakes in completion of CRFs are cancelled with a simple horizontal line and correction is written above or next to it. All corrections have to be clearly signed and dated. The use of correction fluid is not permitted. Data fields which can not be completed due to missing information have to be annotated. The forms have to be completed timely and finally checked and signed with date by the investigator.

The signatures serve to attest that the information contained in the CRF is true and has not been falsified. In case of a major correction or missing data, the reason for it shall also be given. The investigator must assure completion, review and approval of all CRFs. At all times the principal investigator has final responsibility for the accuracy and authenticity of all clinical and laboratory data entered in the CRF. Even if there are no changes from a previous examination the questions which are repeated in each section of the case report forms should be answered completely.

The carefully completed case report forms (original and first copy (yellow)) are sent to the regional study office at the scheduled time points.

As source data are regarded:

- all data contained in the patient’s medical record
- all data provided by the reference pathology
- all data provided by the tumour conference (in countries were a centralized staging and response assessment procedure is installed)

Further information on data collection and CRFs is given in specific handling guidelines, which are stored in the investigator site file.
15.2 DATA MANAGEMENT

Each participating study group has to specify a regional study office. Data management will be performed by the regional study offices according to common working instructions (WIs).

The study management software Oracle Forms will be used for creation of the study database. The database will be validated according to the corresponding SOPs of the KKSL prior to data capture. The regional study offices will be linked through internet to this common data base. The communication will be realized using a standard web protocol (https); in most cases no configuration of firewalls will be necessary. The local installation will be supported by a detailed to-do-list and email/telephone support.

The responsibilities of the regional study offices include:

- Handling of registrations from its participating local trial sites
- Shipment of investigator site file, CRFs etc. to local trial sites
- Data entry (if applicable)
- Collection of paper CRFs including reminder-campaigns
  (Reminder lists will be generated automatically from the database)
- Clinical check of CRFs and queries on missing or implausible data
  (Queries will be generated automatically from the database)
- DB access to own data (views, reports)

An audit trail of all changes concerning the contents of the study database will be automatically recorded.

Once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between the co-ordinating investigator, the biometrician and the data manager.

15.3 ARCHIVING

The archiving of all study relevant documents at the trial site, at the regional study offices and at the co-ordinating investigator will be performed according to the requirements of ICH-GCP, the Commission directive 2005/28/EC of 8 April 2005, and the pertinent national laws.

In countries were a central staging and response assessment procedure is installed, all CT/MRI/PET images sent to the study office will be archived electronically by the responsible reference radiologist and the responsible reference nuclear medicine physician.
16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 DIRECT ACCESS TO SOURCE DATA

According to ICH-GCP and to the applicable European laws, the principal investigator must permit all authorised third parties access to the trial site and insight into the medical records of the trial subjects (source data). This permission includes the clinical trial monitors, auditors and other authorised employees of the sponsor, as well as members of the competent authorities. All these persons are sworn to secrecy.

16.2 MONITORING

The authorised institutions (cf. chapter 14) are responsible for the organisation of an adequate monitoring process in the respective country.

In general, only a random on-site monitoring is provided in the context of this study. Nevertheless, in case of frequent protocol violations, incomplete documentation, unanswered queries or other problems, for cause monitoring visits may be performed.

The main emphasis of on-site monitoring should lie on the check of the informed consent forms and of the inclusion and exclusion criteria, as well as on the main efficacy and safety endpoints. In addition on-site monitoring visits make sure that the study is performed according to ICH-GCP, and that the protocol is adhered to. Thus, on-site monitoring plays an important role in the support and training of participating trial sites.

Details of the country specific monitoring procedures will be provided within a monitoring manual.

16.3 AUDITS

In order to guarantee that the conduct of the study is in accordance with ICH-GCP and the national laws, the sponsor or his legal representatives reserves the right to audit selected trial sites. The auditor will be independent from the staff involved in the proceedings of this clinical study. In addition, the sponsor reserves the right to audit national study offices at any time during the study in order to check fulfilment of duties delegated from the sponsor to the national chairpersons.
16.4 INSPECTIONS

According to the pertinent European legislation, inspections of the trial sites may be performed by the competent authorities at any time during or after completion of the trial.
17 DATA PROTECTION

Within this study personal data of the trial subjects (initials, date of birth) and data regarding the therapy and the course of disease will be collected.

If the patients and their parents or guardian have consented, the name and address of the patient are stored in the study office, in order to allow for direct contact in case of overdue follow-up information. Name and address of the trial subjects will be handled strictly confidentially. They will be stored in a protected part of the database access to which is restricted to the study secretary and her documentation assistant.

All data will be stored electronically and handled strictly confidentially. Throughout documentation and analysis, subjects will be identified only by the individual patient code, whereas all subject names will be kept secret by the investigator.

In countries where a central staging and response assessment is installed, the members of the reference team will have access to the patients’ full name.

The investigators are obliged to keep all study data and information confidential and to use those data only in context with the persons involved in the trial conduct. Study material or information generated in this trial must not be made available to third parties, except for official representatives of the sponsor or regulatory authorities.

Data will be processed in the KKSL, according to the written safety concept of this institution. Access to the data will be strictly limited to authorised persons. Extensive back-up procedures are installed to prevent loss of data. All legal requirements concerning data protection and confidentiality will be respected. All authorised persons are sworn to secrecy.

All data are completely backed up every day. By applying a hierarchic role-based access method unauthorised access to patient data is excluded as far as possible. Anonymity of data in the scope of statistical analysis is ensured.

17.1 CONFIRMATION OF DATA PROTECTION

During data entry, handling and analysis in the KKSL all requirements of the data protection act will be taken into account. Access to the data is strictly limited to authorized persons. Data are protected against unauthorised access.
18 ADMINISTRATIVE AGREEMENTS

18.1 ADHERENCE TO THE PROTOCOL

Protocol violations are any deviations from the procedures outlined in this document:

- missed evaluations/ incorrect timing of evaluations
- non-compliance with study medications/ intake of prohibited medications

After a patient has been enrolled, it is the investigator’s responsibility to make a reasonable effort to avoid any protocol violation in order to keep the subject in the study.

Major protocol violations will be reported immediately to the corresponding study chairperson and the co-ordinating investigator during the course of the study. All protocol violations will be listed and discussed with the co-ordinating investigator and the biometrician prior to statistical analysis.

The investigator makes every effort to record data according to the protocol. Under practical working conditions, however, some minor variations may occur due to circumstances beyond the control of the investigator. Every attempt will be made to rectify missing, contradictory and non-sense data but data inconsistencies will not be considered protocol deviations, but may constitute a serious breach of GCP if they are repetitive.

18.2 PROTOCOL AMENDMENTS

In order to ensure most comparable conditions during all stages of the trial and in the interests of valid statistical analysis, the investigators, the co-ordinating investigator or any other person involved in the trial conduct may not alter the study conditions agreed upon and set out in this protocol.

Amendments should be made only in exceptional cases and by mutual agreement within the steering committee EuroNet-PHL. Any amendment and the reasons therefore must be set out in writing, and signed by all parties concerned. The amendment then becomes part of the study protocol, and is to be filed in the Trial Master File (TMF).

The Inter-Group Trial Steering Committee also decides when such protocol changes become effective. If protocol changes are profound, i.e. if they regard modifications of a therapy arm, inclusion or exclusion criteria, period or the closing of a therapy arm or of the whole study the vote of the DMC must be obtained as a matter of principle.

Amendments which might have an impact on the well-being of the trial subject (major amendments) such as the use of additional invasive diagnostic procedures require an
additional approval by the Ethics Committees (EC) and by the competent authorities concerned. In addition, a further informed consent form is to be signed by all trial subjects already enrolled in the trial that might be affected by the amendment. Minor changes will only be submitted to the Ethics Committees and the competent authorities in a written form (for further details see section 14.4).

The investigator may implement a deviation from, or a change of the protocol to eliminate an immediate hazard(s) to trial subjects without prior EC approval. As soon as possible, the implemented deviation or change, the reason for it, and if appropriate, the proposed protocol amendment(s) should be submitted to the co-ordinating investigator for agreement.

### 18.3 PUBLICATION POLICY

Participating centres may if they wish publish their own cases but will agree to allow the clinical board of EuroNet-PHL exclusive right to publish the major results of the EuroNet-PHL-LP1 study (primary and secondary study questions as detailed in the protocol) in part or in total.

All such publications will acknowledge the contribution of the participating clinicians. Authorship of such publications, including abstracts, will represent members of the intergroup trial steering committee, members of the central review panel and other persons who made a major contribution to the design of the trial, the preparation of the data, its analysis or the writing of the manuscript. Every author should have participated sufficiently to take public responsibility for the content. It is the responsibility of the clinical board of EuroNet-PHL to determine and agree the composition of writing committees.

Additional specific publications from the contributing medical disciplines (e.g. reference facilities, quality assurance) are welcome as long as they do not preclude the publication of major study results. Authorship of such publications, including abstracts, will represent those persons who made a major contribution to the preparation of the data, its analysis or the writing of the manuscript.

All publications (abstracts or manuscripts) require written approval of the intergroup chairpersons.
REFERENCES


Schwarze EW, Wickmann L. Preliminary results of the multicenter trial GPOH-HD 95 for the treatment
Jun;215(3):139-45.


Feugier P, Labourye E, Djeridane M et al. Comparison of initial characteristics and long term outcome
of Lymphocyte-predominant Hodgkin’s lymphoma patients at clinical stage IA and IIA prospectively
104: 2675-2681.

Franklin J, Tesch H, Hansmann ML, et al. Lymphocyte predominant Hodgkin's disease: pathology and


Harris NL, Jaffe ES, Diebold J, Flandrin G, Muller-Hermelink HK, Vardiman J, Lister TA, Bloomfield
CD. World Health Organization classification of neoplastic diseases of the hematopoietic and lymphoid
Clin Oncol.* 1999 Dec;17(12):3835-49.)

Mendenhall NP, Chauvenet A, Murphy SB. Lymphocyte predominant Hodgkin disease: clinico-
pathologic features and results of treatment—the Pediatric Oncology Group experience. *Med Pediatr

G, Robert A , Koerholz D, Oberlin O, Hall GW and Landman-Parker J. Resection Alone In 58 Children
With Limited Stage Lymphocyte Predominant Hodgkin’s Lymphoma – Experience from the European

Nachman JB, Sposto R, Herzog P, et al. Randomized Comparison of low-dose Involved-Field
Radiotherapy and no Radiotherapy for children with Hodgkin's disease Who achieve a complete


Pappa VI, Norton AJ, Gupta RK et al. Nodular type of lymphocyte predominant Hodgkin's disease. A

Pellegrino B, Terrier-Lacombe MJ, Oberlin O et al. Lymphocyte-predominant Hodgkin's lymphoma in
children: therapeutic abstention after initial lymph node resection--a Study of the French Society of

64


Declaration of Helsinki: Guiding Physicians in Biomedical Research Involving Human Subjects. Adopted by the 18th World Medical Assembly, Helsinki (Finland), June 1964. Last amendment by the 48th General Assembly, Somerset West (Rep. of South Africa) 1996


20  CONFIRMATION OF THE FINAL PROTOCOL

The signatories declare that they agree to fulfil their responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented.

Co-ordinating investigator  
Inter-group Chairperson  
GPOH-HD  
Prof. Dr. Dieter Koerholz  

Inter-group Chairperson  
NCRI  
Hamish Wallace MD, FRCPCH, FRCP (Edin)  

Inter-group Chairperson  
SFCE  
Prof. Dr. Judith Landman-Parker  

Responsible Biometrician  
Dr. Dirk Hasenclever  

Date  Signature  
Date  Signature  
Date  Signature  
Date  Signature
21 PROTOCOL AGREEMENT

The signatory declares

- that he/she agrees to conduct his/her responsibilities within this study in accordance with local law, the declaration of Helsinki, ICH-GCP and the study protocol as presented
- that he/she has familiarised his/herself with the results of the pharmacological and toxicological trials of the investigational product and the results of other studies carried out to date
- that he/she has read the study protocol and agrees to it in its entirety
- that he/she intends to adhere to the schedule as specified below.
- that he/she will make sure that all investigators involved at the trial site will act according to the protocol.

Date: _________________________

Signature of the principal investigator: _________________________

Affiliation /address:

_________________________
_________________________
_________________________
### 22.1 ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ABVD</td>
<td>Chemotherapy cycle: Adriamycin, Bleomycin, Vinblastin, Dacarbazine</td>
</tr>
<tr>
<td>ADR</td>
<td>Adverse Drug Reaction</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse Event</td>
</tr>
<tr>
<td>ALAT</td>
<td>Alanine-amino-transferase</td>
</tr>
<tr>
<td>AMG</td>
<td>German Drug Law</td>
</tr>
<tr>
<td>AML</td>
<td>Acute Myeloid Leukemia</td>
</tr>
<tr>
<td>AP</td>
<td>Alkaline Phosphatase</td>
</tr>
<tr>
<td>AR</td>
<td>Adequate response</td>
</tr>
<tr>
<td>ASAT</td>
<td>Aspartate-amino-transferase</td>
</tr>
<tr>
<td>ASR</td>
<td>Annual safety report</td>
</tr>
<tr>
<td>BfArM</td>
<td>Bundesinstitut für Arzneimittel und Medizinprodukte</td>
</tr>
<tr>
<td>B (B-symptoms)</td>
<td>Systemic symptoms: unexplained fever, weight loss, night sweats</td>
</tr>
<tr>
<td>BSPHO</td>
<td>Belgian Society for Paediatric Hematology and Oncology</td>
</tr>
<tr>
<td>°C</td>
<td>Degree Celsius (temperature dimension unit)</td>
</tr>
<tr>
<td>Ca</td>
<td>Calcium</td>
</tr>
<tr>
<td>CCS</td>
<td>Children’s Cancer Study</td>
</tr>
<tr>
<td>CCLG</td>
<td>Children’s Cancer &amp; Leukaemia Group (England, Scotland, Ireland, Wales)</td>
</tr>
<tr>
<td>CD</td>
<td>Compact Disc</td>
</tr>
<tr>
<td>cf.</td>
<td>Confer</td>
</tr>
<tr>
<td>c-HL</td>
<td>Classical Hodgkin’s Lymphoma</td>
</tr>
<tr>
<td>CIOMS</td>
<td>Council for International Organizations of Medical Sciences</td>
</tr>
<tr>
<td>cm</td>
<td>Centimeter</td>
</tr>
<tr>
<td>CMV</td>
<td>Cytomegalovirus</td>
</tr>
<tr>
<td>CNS</td>
<td>Central Nervous System</td>
</tr>
<tr>
<td>Cp</td>
<td>Compare</td>
</tr>
<tr>
<td>CR</td>
<td>Complete remission</td>
</tr>
<tr>
<td>CRF</td>
<td>Case Report Form</td>
</tr>
<tr>
<td>CRu</td>
<td>Complete remission unconfirmed</td>
</tr>
<tr>
<td>CRCTU</td>
<td>Cancer Research UK Clinical Trials Unit</td>
</tr>
<tr>
<td>CSRA</td>
<td>Central staging and response assessment</td>
</tr>
<tr>
<td>CT</td>
<td>Computed tomography</td>
</tr>
<tr>
<td>CTC</td>
<td>Common Toxicity Criteria</td>
</tr>
<tr>
<td>CTCAE</td>
<td>Common Terminology Criteria for Adverse Events</td>
</tr>
<tr>
<td>Cum.</td>
<td>Cumulative</td>
</tr>
<tr>
<td>CV</td>
<td>Curriculum Vitae</td>
</tr>
</tbody>
</table>
CVP Chemotherapy cycle: Cyclophosphamide, Vinblastine, Prednisone
DCOG Dutch Children's Oncology Group
DD Differential diagnosis
DFS Disease free survival
DICOM Digital imaging file format
DMC Data Monitoring Committee
DNA Desoxyribonucleic acid
EBV Epstein Barr Virus
EC Ethics Committee
ECG Electrocardiogramme
Echo Echocardiogramme
Echo-CG Echocardiogramme
ED Einzeldosis (single dose)
EEG Electroencephalogramme
EFS Event free survival
e.g. Example given
E-lesions Extranodal lesions by contiguous involvement
ENT Ear, Nose and Throat
et al. et altra (and others)
Eudra-CT European ClinicalTrials Data Base
Euro-Net European Network
Euro-Net-PHL-C1 European Network on Pediatric Hodgkin's Lymphoma-Classical Hodgkin-1
FAB French-American British (classification for acute leukemias)
FDG-PET Fluoro-Deoxyglucose-Positron emission tomography
FFTF Freedom from treatment failure
FF2F Freedom from second failure
Fig. Figure
FSH Follicle stimulating hormone
fT4 Free Tetra-iodineThyionine
GCP Good Clinical Practice
GGT Gamma Glutamyl transferase
GMP Good Manufacturing Practice
GOT Synonyme for ASAT (Aspartate-amino-transferase)
GPOH Gesellschaft für Pädiatrische Onkologie und Hämatologie, (German Society for Paediatric Oncology and Haematology)
GPOH-HD GPOH-HodgkinStudiengruppe (GPOH-Hodgkin's study group)
GPT Synonyme for ALAT (Alanine-amino-transferase)
h Hour
HCV Hepatitis C Virus
HIV Humane Immunodeficiency Virus
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>HL</td>
<td>Hodgkin's Lymphoma</td>
</tr>
<tr>
<td>HLA</td>
<td>Human Leukocyte Antigen</td>
</tr>
<tr>
<td>HSV</td>
<td>Herpes simplex virus</td>
</tr>
<tr>
<td>5-HT-3 antagonist</td>
<td>Serotonin-antagonist</td>
</tr>
<tr>
<td>ICH</td>
<td>International Conference on Harmonisation</td>
</tr>
<tr>
<td>ID</td>
<td>Identification code</td>
</tr>
<tr>
<td>i.e.</td>
<td>id est</td>
</tr>
<tr>
<td>Incl.</td>
<td>Including</td>
</tr>
<tr>
<td>ISF</td>
<td>Investigator Site File</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention-to-treat</td>
</tr>
<tr>
<td>i.v.</td>
<td>Intravenously</td>
</tr>
<tr>
<td>KCL</td>
<td>Potassium chloride</td>
</tr>
<tr>
<td>Kg</td>
<td>Kilogram</td>
</tr>
<tr>
<td>KKSL</td>
<td>Koordinierungszentrum für Klinische Studien Leipzig</td>
</tr>
<tr>
<td>L</td>
<td>Litre</td>
</tr>
<tr>
<td>LDH</td>
<td>Lactate dehydrogenase</td>
</tr>
<tr>
<td>LESG</td>
<td>Late Effect Study Group</td>
</tr>
<tr>
<td>LH</td>
<td>Luteinizing Hormone</td>
</tr>
<tr>
<td>LH-RH</td>
<td>Luteinizing Hormone Releasing Hormone</td>
</tr>
<tr>
<td>LN</td>
<td>Lymph node</td>
</tr>
<tr>
<td>LPHL</td>
<td>Lymphocyte-predominant paediatric Hodgkin's Lymphoma</td>
</tr>
<tr>
<td>LSRA</td>
<td>Local staging and response assessment</td>
</tr>
<tr>
<td>m²</td>
<td>Square meter</td>
</tr>
<tr>
<td>mAS</td>
<td>milli Ampere seconds</td>
</tr>
<tr>
<td>MedDRA</td>
<td>Medical Dictionary for Regulatory Activities</td>
</tr>
<tr>
<td>mg</td>
<td>Milligram</td>
</tr>
<tr>
<td>MHD</td>
<td>French Hodgkin's Lymphoma trial name</td>
</tr>
<tr>
<td>min</td>
<td>Minimum</td>
</tr>
<tr>
<td>ml</td>
<td>Milliliter</td>
</tr>
<tr>
<td>mm</td>
<td>Millimeter</td>
</tr>
<tr>
<td>MRI</td>
<td>Magnetic Resonance Imaging</td>
</tr>
<tr>
<td>NC</td>
<td>No change</td>
</tr>
<tr>
<td>NCI</td>
<td>National cancer institute</td>
</tr>
<tr>
<td>NCR</td>
<td>No carbon required</td>
</tr>
<tr>
<td>NRCI</td>
<td>National Cancer Research Institute, Lymphoma Clinical Study Group</td>
</tr>
<tr>
<td>ND</td>
<td>Not done</td>
</tr>
<tr>
<td>NHL</td>
<td>Non Hodgkin's lymphoma</td>
</tr>
<tr>
<td>NOPHO</td>
<td>Nordic Society for Pediatric Hematology and Oncology</td>
</tr>
<tr>
<td>OEPA</td>
<td>Chemotherapy cycle: Vincristine, Etoposide, Prednisone, Adriamycine</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
</tr>
</tbody>
</table>
PCR  Polymerase Chain Reaction
PD   Progressive disease
PET  Positron emission tomography
PFS  Progression free survival
p.i.  Per injectionem
PIL  Patient identification list
p.o.  Per os (by mouth)
PP   Per-protocol
PR   Partial remission
Prog.  Progression
Resid.  Residual, residuum
Resp.  Respective(ly)
RNA  Ribonucleic acid
SAE  Serious Adverse Event
SAR  Serious Adverse Reaction
sd   Standard deviation
se   Standard error
SEOP Spanish Society of Pediatric Oncology
SFCE Société Française de lutte contre les cancers et les leucémies de l’enfant et de l’adolescent
SmPC Summary of Product Characteristics
Sono Sonography, ultrasound
SOP  Standard Operating Procedures
SRA  Staging and response assessment
SST  Secondary solid tumour
STAR strategy for treatment adapted to response
T2-STIR  Fat saturated T2-weighted spin echo sequence (MRI)
SUSAR Suspected Unexpected Serious Adverse Drug Reaction
T1-Flash  T1-weighted gradient echo sequence (MRI)
T2-TIRM  Fat saturated T2-weighted spin echo sequence (MRI)
TMF  Trial Master File
TOX  Toxicity
T1-SE  T1-weighted spin echo sequence (MRI)
TSH  Thyroid stimulating hormone
TTT  Therapy titration study
UICC Unité Internationale contre le Cancre
UK  United Kingdom
vs.  Versus
WB-MRI Whole body MRI
WHO World Health Organisation
VZV Varicella zoster Virus
X-ray Two-dimensional radiogramme
### 22.2 GPOH-HD HODGKIN’S LYMPHOMA WORKING GROUP

Members of the GPOH-HD Committee (status quo November 2008):

<table>
<thead>
<tr>
<th>Name</th>
<th>Email Address</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. Bergsträsser (paediatrician, Zürich, Switzerland)</td>
<td><a href="mailto:eva.bergstraesser@kispi.uzh.ch">eva.bergstraesser@kispi.uzh.ch</a></td>
</tr>
<tr>
<td>Dr. Bredenfeld (medical haematologist, Cologne)</td>
<td><a href="mailto:bredenfeld@gmx.de">bredenfeld@gmx.de</a></td>
</tr>
<tr>
<td>Dr. Brosteanu (biometrician, Leipzig)</td>
<td><a href="mailto:oana.brosteanu@kksl.uni-leipzig.de">oana.brosteanu@kksl.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Schultz (paediatrician, Lübeck)</td>
<td><a href="mailto:schultz@paedia.ukl.mu-luebeck.de">schultz@paedia.ukl.mu-luebeck.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Burdach (paediatrician, Munich)</td>
<td><a href="mailto:stefan.burdach@lrz.tu-muenchen.de">stefan.burdach@lrz.tu-muenchen.de</a></td>
</tr>
<tr>
<td>PD Dr. Claviez (paediatrician, Kiel)</td>
<td><a href="mailto:a.claviez@pediatrics.uni-kiel.de">a.claviez@pediatrics.uni-kiel.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Karin Dieckmann (radiotherapist, Wien)</td>
<td><a href="mailto:Karin.dieckmann@meduniwien.ac.at">Karin.dieckmann@meduniwien.ac.at</a></td>
</tr>
<tr>
<td>Dr. Dörfel (paediatrician, Berlin)</td>
<td><a href="mailto:w.doerffel@arcor.de">w.doerffel@arcor.de</a></td>
</tr>
<tr>
<td>Dr. Hasenclever (biometrician, Leipzig)</td>
<td><a href="mailto:dirk.hasenclever@imise.uni-leipzig.de">dirk.hasenclever@imise.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Spielmann (radiology, Halle)</td>
<td><a href="mailto:rolf-peter.spielmann@medizin.uni-halle.de">rolf-peter.spielmann@medizin.uni-halle.de</a></td>
</tr>
<tr>
<td>Dr. Gabriele Escherich (paediatrician, Hamburg)</td>
<td><a href="mailto:escheric@uke.uni-hamburg.de">escheric@uke.uni-hamburg.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Jürgens (paediatrician, Münster)</td>
<td><a href="mailto:jurgh@uni-muenster.de">jurgh@uni-muenster.de</a></td>
</tr>
<tr>
<td>Dr. Thomas Kuhnt (radiotherapist, Halle)</td>
<td><a href="mailto:thomas.kuhnt@medizin.uni-halle.de">thomas.kuhnt@medizin.uni-halle.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Körholz (paediatrician, Halle)</td>
<td><a href="mailto:dieter.koerholz@medizin.uni-halle.de">dieter.koerholz@medizin.uni-halle.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Kluge (nuclear physician, Leipzig)</td>
<td><a href="mailto:klur@medizin.uni-leipzig.de">klur@medizin.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Lehrnbecher (paediatrician; Frankfurt)</td>
<td><a href="mailto:thomas_lehrnbecher@yahoo.com">thomas_lehrnbecher@yahoo.com</a></td>
</tr>
<tr>
<td>Mrs. Heike Lüders (physicist, Berlin)</td>
<td><a href="mailto:hlueders@berlin.helios-kliniken.de">hlueders@berlin.helios-kliniken.de</a></td>
</tr>
<tr>
<td>Dr. Georg Mann (paediatrician, Vienna, Austria)</td>
<td><a href="mailto:georg.mann@stanna.at">georg.mann@stanna.at</a></td>
</tr>
<tr>
<td>Dr. Marciniak (radiologist, Berlin)</td>
<td><a href="mailto:hmarciniak@berlin.helios-kliniken.de">hmarciniak@berlin.helios-kliniken.de</a></td>
</tr>
<tr>
<td>PD Dr. Mauz-Körholz (paediatrician, Halle)</td>
<td><a href="mailto:christine.mauz-koerholz@medizin.uni-halle.de">christine.mauz-koerholz@medizin.uni-halle.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Pötter (radiotherapist; Vienna, Austria)</td>
<td><a href="mailto:richard.poetter@univie.ac.at">richard.poetter@univie.ac.at</a></td>
</tr>
<tr>
<td>Dr. Ursula Rühl (radiotherapist, Berlin)</td>
<td><a href="mailto:ursula.ruehl@vivantes.de">ursula.ruehl@vivantes.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Sabri (nuclear physician, Leipzig)</td>
<td><a href="mailto:sabri@medizin.uni-leipzig.de">sabri@medizin.uni-leipzig.de</a></td>
</tr>
<tr>
<td>Dr. Scheel-Walter (paediatrician, Tübingen)</td>
<td><a href="mailto:hgscheel@med.uni-tuebingen.de">hgscheel@med.uni-tuebingen.de</a></td>
</tr>
<tr>
<td>Prof. Dr. G. Schellong (paediatrician, Münster)</td>
<td><a href="mailto:schellon@uni-muenster.de">schellon@uni-muenster.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Schlegel (paediatrician, Würzburg)</td>
<td><a href="mailto:schlegel@mail.uni-wuerzburg.de">schlegel@mail.uni-wuerzburg.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Sykora (paediatrician, Hannover)</td>
<td><a href="mailto:sykora.karl-walter@mh-hannover.de">sykora.karl-walter@mh-hannover.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Stein (pathologist, Berlin)</td>
<td><a href="mailto:Harald.stein@charite.de">Harald.stein@charite.de</a></td>
</tr>
<tr>
<td>Dr. Lutz Wickmann (paediatrician, Berlin)</td>
<td><a href="mailto:lwickmann@berlin.helios-kliniken.de">lwickmann@berlin.helios-kliniken.de</a></td>
</tr>
<tr>
<td>Prof. Dr. Willich (radiotherapist, Münster)</td>
<td><a href="mailto:willich@uni-muenster.de">willich@uni-muenster.de</a></td>
</tr>
</tbody>
</table>
### 22.3 NCRI LYMPHOMA CLINICAL STUDY GROUP

<table>
<thead>
<tr>
<th>Name</th>
<th>City</th>
<th>Specialization</th>
<th>Position</th>
</tr>
</thead>
<tbody>
<tr>
<td>W. Hamish Wallace</td>
<td>Edinburgh</td>
<td>Oncology</td>
<td>Chairman</td>
</tr>
<tr>
<td>Martin Hewitt</td>
<td>Nottingham</td>
<td>Oncology</td>
<td></td>
</tr>
<tr>
<td>Ananth Shankar</td>
<td>London</td>
<td>Oncology</td>
<td></td>
</tr>
<tr>
<td>Mike Williams</td>
<td>Cambridge</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Helen Lucraft</td>
<td>Newcastle</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Alan Ramsay</td>
<td>London</td>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Ken MacLennan</td>
<td>Leeds</td>
<td>Pathology</td>
<td></td>
</tr>
<tr>
<td>Stephen Daw</td>
<td>Middlesex</td>
<td>Oncology</td>
<td></td>
</tr>
<tr>
<td>Georgina Hall</td>
<td>Oxford</td>
<td>Haematology</td>
<td></td>
</tr>
<tr>
<td>Sally Barrington</td>
<td>London</td>
<td>Nuclear Medicine</td>
<td></td>
</tr>
<tr>
<td>Eve Gallop-Evans</td>
<td>Cardiff</td>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Malcolm Taylor</td>
<td>Manchester</td>
<td>Biology</td>
<td></td>
</tr>
<tr>
<td>Elizabeth Chalmers</td>
<td>Glasgow</td>
<td>Haematology</td>
<td></td>
</tr>
<tr>
<td>Delwar Hussain</td>
<td>CRCTU</td>
<td>Trial Coordinator</td>
<td></td>
</tr>
</tbody>
</table>
### 22.4 SFCE HODGKIN’S LYMPHOMA WORKING GROUP

<table>
<thead>
<tr>
<th>Name</th>
<th>Email</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alain Robert</td>
<td><a href="mailto:robert.a@chu-toulouse.fr">robert.a@chu-toulouse.fr</a></td>
</tr>
<tr>
<td>Andre Baruchel</td>
<td><a href="mailto:andre.baruchel@sls.ap-hop-paris.fr">andre.baruchel@sls.ap-hop-paris.fr</a></td>
</tr>
<tr>
<td>Carrie Christian</td>
<td><a href="mailto:carrie@lyon.fnclcc.fr">carrie@lyon.fnclcc.fr</a></td>
</tr>
<tr>
<td>Claudine Schmitt</td>
<td><a href="mailto:c.schmitt@chu-nancy.fr">c.schmitt@chu-nancy.fr</a></td>
</tr>
<tr>
<td>Christine Edan</td>
<td><a href="mailto:christine.edan@wanadoo.fr">christine.edan@wanadoo.fr</a></td>
</tr>
<tr>
<td>Francoise Montravers</td>
<td><a href="mailto:francoise.montravers@tnn.aphp.fr">francoise.montravers@tnn.aphp.fr</a></td>
</tr>
<tr>
<td>Gérard Michel</td>
<td><a href="mailto:gmichel@ap-hm.fr">gmichel@ap-hm.fr</a></td>
</tr>
<tr>
<td>Guy Leverger</td>
<td><a href="mailto:guy.leverger@trs.ap-hop-paris.fr">guy.leverger@trs.ap-hop-paris.fr</a></td>
</tr>
<tr>
<td>Helene Pacquement</td>
<td><a href="mailto:helene.pacquement@curie.net">helene.pacquement@curie.net</a></td>
</tr>
<tr>
<td>JL Habrand</td>
<td><a href="mailto:habrand@igr.fr">habrand@igr.fr</a></td>
</tr>
<tr>
<td>Anne Lambilliotte</td>
<td><a href="mailto:a-lambilliotte@chru-lille.fr">a-lambilliotte@chru-lille.fr</a></td>
</tr>
<tr>
<td>Nathalie Aladjidi</td>
<td><a href="mailto:n.aladjidi@hotmail.com">n.aladjidi@hotmail.com</a></td>
</tr>
<tr>
<td>Odile Oberlin</td>
<td><a href="mailto:oberlin@igr.fr">oberlin@igr.fr</a></td>
</tr>
<tr>
<td>Schell Mathias</td>
<td><a href="mailto:schell@lyon.fnclcc.fr">schell@lyon.fnclcc.fr</a></td>
</tr>
<tr>
<td>Sylvie.Helfre</td>
<td><a href="mailto:sylvie.helfre@curie.net">sylvie.helfre@curie.net</a></td>
</tr>
<tr>
<td>Thierry Leblanc</td>
<td><a href="mailto:thierry.leblanc@sls.ap-hop-paris.fr">thierry.leblanc@sls.ap-hop-paris.fr</a></td>
</tr>
<tr>
<td>Yves Perel</td>
<td><a href="mailto:yves.perel@chu-bordeaux.fr">yves.perel@chu-bordeaux.fr</a></td>
</tr>
</tbody>
</table>
22.5 PPLLSG Hodgkin's Lymphoma Working Group

Walentyna Balwierz      balwierz@mp.pl
Jerzy Kowalczyk      jkowalcz@dsk.lublin.pl
Alicja Chybicka      klin@pedhemat.am.wroc.pl
Jacek Wachowiak      jacek.wachowiak@plusnet.pl
Danuta. Sonta-Jakimczyk      edziubek@sk1.zabrze.pl
Anna Balcerska      hemonkp@amg.gda.pl
Michal. Matysiak      mmatysiak@litewska.edu.pl
Mariusz Wysocki      hematonko@by.home.pl
Maryna Krawczuk-Rybak      rybak@amb.edu.pl
Tomasz Urasinski      urasin@sci.pam.szczecin.pl
Jerzy Bodalski      jot@toya.net.pl
Grazyna Sobol      onkohematologia@wp.pl
Grazyna Karolczyk      karolczyk@chok.kielce.pl
Maria Wieczorek      mariawiecz@poczta.onet.pl
Anna Skowronska Gardas      agardas@coi.waw.pl
Krzysztof Paprota      lek kp@gazeta.pl
Jadwiga Maldyk      jagusiamaldy@wp.pl
Małgorzata Kaczmarek-Kanold      mkanold@neostrada.pl
Angelina Moryl-Bujakowska      amb6000@op.pl
22.6 INTERNATIONAL SCIENTIFIC ADVISORY BOARD

Current members of the Scientific Advisory Board are listed below (status quo November 2005). Further members can be appointed by the clinical board of the EuroNet-PHL-group.

*Chairpersons:* Prof. Dr. S. Burdach, Munich  
Prof. Dr. W. H. Wallace  
Prof. Dr. D. Körholz

*Members of the Scientific Advisory Board*

- Prof. Dr. Stein, Berlin  
- Dr. Hasenclever, Leipzig  
- PD Dr. Berger (Switzerland)  
- Dr. Malcolm Taylor, Manchester, UK  
- Dr. Paul Murray, Birmingham, UK  
- Dr. D Machin, UK.  
- Prof. Judith Landman-Parker, F  
- Prof. Dr. Walentyna Balwierz