PLEASE NOTE: *This study has been imported from ClinicalTrials.gov without additional data checks.*

Trial Description

Title

International Collaborative Treatment Protocol For Children And Adolescents With Acute Lymphoblastic Leukemia

Trial Acronym

[---]*

URL of the trial

[---]*

Brief Summary in Lay Language

Rationale/Purpose: Drugs used in chemotherapy work in different ways to stop the growth of cancer cells, either by killing the cells or by stopping them from dividing. Giving more than one drug (combination chemotherapy) may kill more cancer cells. It is not yet known which combination chemotherapy regimen is more effective in treating young patients with acute lymphoblastic leukemia (ALL).

This trial is studying several different combination chemotherapy regimens to compare how well they work in treating young patients with ALL.

Study objectives

Primary study questions:

- Non high-risk (non-HR) precursor-B ALL (pB-ALL) patients with TEL/AML1-negative ALL or unknown TEL/AML1 status and flow cytometry minimal residual disease (MRD) in bone marrow on day 15 <0.1% or with TEL/AML1-positive ALL (randomized study question R1):
Can the daunorubicin dose in Protocol IA be safely reduced by 50 % with a non-inferior EFS and a reduction of toxicity (treatment-related mortality and AE/SAE in Protocol I)?

- Patients with pB-ALL and risk group medium risk (MR) (randomized study question R2):
Can the clinical outcome be improved by protracted asparagine depletion

achieved through application of intensified PEG-L-asparaginase during reintensification and early maintenance?

- High-risk (HR) patients (as identified by day 33 - randomized study question RHR): Can the clinical outcome be improved by protracted exposure to PEG-L-asparaginase during Protocol IB?

Secondary study questions:

- Standard risk (SR) patients identified by at least one sensitive marker: Is the clinical outcome comparable to that obtained in SR patients (identified with two sensitive markers) in AIEOP-BFM ALL 2000, or can the outcome even be improved with the use of PEG-L-asparaginase instead of native E. coli L-ASP?

- T-ALL non-HR patients: Can the high level of outcome which was obtained for these patients in study AIEOP-BFM ALL 2000 be preserved or even improved with the use of PEG-L-ASP instead of native E. coli L-ASP?

- HR patients with persisting high MRD levels despite the use of the HR blocks in the intensified consolidation phase "MRD Non-Responders": Is it possible to improve the outcome and to achieve a further reduction of leukemic cell burden by administration of an innovative treatment schedule (DNX-FLA)?

- Patients participating in the randomized asparaginase studies (pB-ALL/MR, HR): Are asparaginase activity and asparaginase antibodies associated with development of allergic reactions, and do they have an effect on the outcome of the patients?

- What is the relative value of different methods of MRD monitoring in the definition of alternative stratification systems within a BFM-oriented protocol?

Brief Summary in Scientific Language

Risk Stratification

- T/non-HR: T-ALL in absence of any HR criteria (see below)

- pB/non-HR: pB-ALL in absence of any HR criteria (see below).

- SR (polymerase chain reaction(PCR)-MRD-SR (MRD-negative on day 33 and 78) or, if

no PCR-MRD result available, FCM d15 < 0.1%)

- MR (no SR)

- HR: Prednisone poor-response (≥1000 blast cells/µl in peripheral blood on day 8), blast cells ≥10% in bone marrow on day 15 as measured by FCM, non-remission on day 33, positivity for MLL/AF4 or t(4;11), hypodiploidy (< 45 chromosomes), PCR-MRD-HR (MRD ≥10E-3 on day 78) or PCR-MRD-MR SER (only in pB-ALL, MRD ≥ 10-3 on day 33 and MRD positive at a level of < 10E-3 on day 78)

Chemotherapy

According to the risk group, patients receive the following chemotherapy elements:

T/non-HR: Protocol I, Protocol M, Protocol II and Maintenance pB/non-HR: Protocol I, Protocol M, Protocol II and Maintenance HR: Protocol I, HR-1', HR-2', HR-3', 3x Protocol III, Maintenance Patients of the HR group with PCR-MRD ≥10E-3 after element HR-3' are eligible for treatment with element DNX-FLA.

Protocol I Cytoreductive prephase: Prednisone (PDN) on days 1-7 and one dose of methotrexate (MTX) intrathecal (IT) on day 1 Protocol IA: Prednisone (PDN) on days 8 to 28 (21 days); vincristine (VCR) on days 8, 15, 22, 29 (4 doses); daunorubicin (DNR) on days 8, 15, 22 and 29 (4 doses); pegylated L-asparaginase (PEG-L-ASP) on days 12 and 26; MTX IT on days 12 and 33 and in case of blast cells in cerebrospinal fluid at diagnosis additional IT MTX is given on days 19 and 26.

Protocol IA': Only two doses of DNR on days 8 and 15 given to patients eligible for randomization R1 and randomized into the experimental arm Protocol IA-CPM: additional cyclophosphamide (CPM) on day 10 only in T-ALL patients with prednisone poor-response Protocol IA-Dexa (IAD): Dexamethasone (DXM) instead of PDN is given to all patients with T-ALL without any high-risk criteria as identified by day 8.

Protocol IB: CPM on days 36 and 64; cytarabine (ARA-C) on days 38-41, 45-48, 52-55 and 59-62; 6-mercaptopurine (6-MP) on days 36 to 63 (28 days); MTX IT on day 45 and 59 Protocol IB-ASP+: additional PEG-L-ASP on days 40, 47, 54, and 61 (4 doses) are given to the patients

eligible for randomization RHR and randomized into the experimental arm.

Protocol M 6-MP on days 1- 56, high-dose MTX (HD-MTX) on days 8, 22, 36, 50 and MTX IT on days 8, 22, 36 and 50 Protocol II Protocol IIA: DXM on days 1 to 21 (21 days); VCR on days 8, 15, 22, 29 (4 doses); doxorubicine (DOX) on days 8, 15, 22 and 29 (4 doses); PEG-L-ASP on day 8 (1 dose); MTX IT on days 1 and 18 only in patients with initial CNS involvement.

Protocol IIA-ASP+: additional PEG-L-ASP on day 22 for patients eligible for randomization R2 and randomized into the experimental arm.

Protocol IIB: CPM on day 36; ARA-C on days 38-41 and 45-48; thioguanine (TG) on days 36 to 49 (14 days) and MTX IT on days 38 and 45.

Protocol IIB-ASP+: additional PEG-L-ASP on days 36 and 50 for eligible for randomization R2 and randomized into the experimental arm.

Protocol III DXM on days 1-15; VCR on days 1 and 8; DOX on days 1 and 8; PEG-L-ASP on day 1; CPM on day 15; ARA-C on days 17-20 and 24-27; TG on days 15 - 28 and MTX IT on days 17 and 24, also on day 1 in patients with initial CNS involvement HR-1' DXM on days 1-5; VCR on days 1 and 6; HD-MTX on day 1; CPM every 12 hours on days 2-4 (5 doses); HD-ARA-C every 12 hours on day 5 (2 doses); PEG-L-ASP on day 6, MTX IT on day 1 HR-2' DXM on days 1 to 5; VDS on days 1 and 6; HD-MTX on day 1; IFO every 12 hours on days 2-4 (5 doses); DNR on day 5; PEG-L-ASP on day 6; MTX IT on day 1 and 1 in patients with initial CNS involvement also day 5 HR-3' DXM on days 1-5; ARA-C 4 x on days 1-2 in 12 h intervals; etoposide (VP-16) every 12 hours on days 3-5 (5 doses); PEG-L-ASP on day 6; MTX IT on day 1 DNX-FLA Flucytosine (FLU) on days 1-5 (5 doses); HD-ARA-C on days 1 to 5 (5 doses); liposomal daunorubicin (DNX) on days 1, 3 and 5 (3 doses); MTX IT on day 1

Interim/Maintenance (until week 104):

6-MP p.o. daily; MTX p.o. once a week, doses adjusted to white blood cell count; PEG-L-ASP: every second week (6 doses), only for patients eligible for randomization R2 and randomized into the experimental arm; MTX IT every 6 weeks up to a total of 6 doses for the following subgroups (all CNS-negative):

- T-ALL (HR or non-HR) with < 2 years of age at start of maintenance,

- T-ALL, non-HR and initial WBC < 100 000/µl

- pB-ALL with PPR and/or FCM-MRD day 15 ≥ 10 % and/or PCR-MRDMR SER as only HR criteria

Radiotherapy Patients without CNS involvement and

- T-ALL/non-HR, WBC ≥ 100 000/µl, and age ≥ 2 years at start of pCRT or

- with risk group HR and age ≥ 2 years at start of pCRT except pB-ALL with PPR and/or FCM-MRD day 15 ≥ 10 % and/or PCR-MRD-MR SER as only HR criteria receive preventive cranial radiotherapy with 12 Gy

Patients with CNS involvement receive therapeutic cranial radiotherapy with 18 Gy (age 1 to <2 years 12 Gy).

Organizational Data

- DRKS-ID: **DRKS00003772**
- Date of Registration in DRKS: **2012/04/24**
- Date of Registration in Partner Registry or other Primary Registry: **2010/05/03**
- Investigator Sponsored/Initiated Trial (IST/IIT): **yes**
- Ethics Approval/Approval of the Ethics Committee: **[---]***
- (leading) Ethics Committee Nr.: **[---]***

Secondary IDs

- Primary Registry-ID: **NCT01117441 (ClinicalTrials.gov)**
- Sponsor-ID: **AIEOP-BFM ALL 2009 (University of Schleswig-Holstein)**

Health condition or Problem studied

- Free text: **Leukemia**
- ICD10: **C91.0 - Acute lymphoblastic leukaemia**

Interventions/Observational Groups

- Arm 1: **Drug: PEG-L-asparaginase**
- Arm 2: **Drug: cyclophosphamide**

- Arm 3: **Drug: cytarabine**
- Arm 4: **Drug: daunorubicin hydrochloride**
- Arm 5: **Drug: dexamethasone**
- Arm 6: **Drug: doxorubicin hydrochloride**
- Arm 7: **Drug: etoposide**
- Arm 8: **Drug: ifosfamide**
- Arm 9: **Drug: mercaptopurine**
- Arm 10: **Drug: methotrexate**
- Arm 11: **Drug: prednisone**
- Arm 12: **Drug: thioguanine**
- Arm 13: **Drug: vincristine sulfate**
- Arm 14: **Drug: vindesine**
- Arm 15: **Drug: daunoxome**
- Arm 16: **Drug: fludarabine**
- Arm 17: **Radiation: Radiation Therapy**

Characteristics

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

Primary Outcome

- Event-free survival; time frame: 10 years from the start of recruitment; Randomization R1: Event-free survival from time of randomization Historical comparison non-HR T-ALL: Event-free survival from diagnosis Historical comparison "MRD Non-Responders": Event-free survival from start of DNX-FLA (morphological non-response after HR-3' is no event for this study question)
- Disease-free survival; time frame: 10 years from the start of recruitment; Randomization R2: Disease-free survival from time of randomization Historical comparison SR: Disease-free survival from start of Protocol M

- minimal residual disease (MRD); time frame: week 12 of treatment; Randomization RHR: rate of MRD highly positive patients (MRD ≥ 10-3) at TP2 (week 12)

Secondary Outcome

- survival; time frame: 10 years from the start of recruitment; All randomized and historical comparisons: Survival
- treatment-related mortality; time frame: up to 25 months from the diagnosis; All randomized and historical comparisons: treatment-related mortality in induction or CCR (overall and by chemotherapy/SCT)
- adverse events; time frame: up to 25 months from the diagnosis; All randomized and historical comparisons: incidence and frequency of adverse events of interest and serious adverse events
- event-free survival; time frame: 10 years from the start of recruitment; Randomization R-HR: Event-free survival from time of randomization
- minimal residual disease; time frame: after 24 weeks of treatment; "MRD Non-Responders": MRD levels after DNX-FLA

Countries of recruitment

- AU **Australia**
- AT **Austria**
- CZ **Czech Republic**
- DE **Germany**
- IL **Israel**
- IT **Italy**
- CH **Switzerland**

Locations of Recruitment

- **Kinderklinik der med. Fakultät der RWTH, Bereich Hämatologie/Onkologie, Aachen**
- **I. Klinik für Kinder u. Jugendliche, Klinikum Augsburg, Hämatologie/ Onkologie, Augsburg**
- **Klinikum Bayreuth, Kinderklinik, Bayreuth**
- **Kinderklinik der Charité, Campus Virchow Klinikum (CVK), Abt.: Kinderhämatologie, Berlin**
- **Klinikum Berlin-Buch II. Kinderklinik, Bereich Onkologie/Allg. Pädiatrie, Berlin**
- **Zentrum für Kinderheilkunde der Universität Bonn, Päd. Hämatologie / Onkologie, Bonn**
- **Städtisches Krankenhaus, Kinderklinik, Braunschweig**

- **Klinikum Chemnitz gGmbH, Klinik für Kinder- und Jugendmedizin, Hämatologie / Onkologie, Chemnitz**
- **Carl-Thiem-Klinikum, Kinderklinik, Abt. Hämatologie/Onkologie, Cottbus**
- **Vestische Kinder- u. Jugendklinik, Universitätsklinik Witten/Herdecke, Datteln**
- **Klinikum Lippe-Detmold, Kinder- und Jugendmedizin, Detmold**
- **Klinikum Dortmund, Klinik f. Kinder- und Jugendmedizin, Dortmund**
- **Uni.Klinik Carl Gustav Carus, Klinik f. Kinderheilkunde, Dresden**
- **Universitätskinderklinik, Düsseldorf**
- **Helios Klinikum Erfurt GmbH, Klinik für Kinderheilkunde, Erfurt**
- **Universitätsklinikum Erlangen, Kinder- und Jugendmedizin, Abt. für Onkologie/ Hämatologie/Immunologie, Erlangen**
- **Universitätsklinikum Essen, Kinderklinik, Hämatologie/Onkologie, Essen**
- **Universitäts-Kinderklinik, Klinik für Kinderheilkunde III, Pädiatrische Hämatologie/Onkologie, Frankfurt**
- **Universitäts-Kinderklinik, Haematologie/ Onkologie, Freiburg**
- **Klinikum der Justus-Liebig-Universität, Zentrum für Kinderheilkunde, Abt. Hämatologie/Onkologie, Gießen**
- **Klinik und Poliklinik für Kinder und Jugendmedizin, Allgemeine Pädiatrie mit Poliklinik/Pädiatrische Onkologie und Hämatologie, Greifswald**
- **Universitäts-Kinderklinik Päd. I, Hämatologie/Onkologie, Göttingen**
- **Uniklinikum d. Martin Luther Universität, Halle Wittenberg, Univ.-und Poliklinik für Kinder- und Jugendmedizin, Halle**
- **Medizinische Hochschule Hannover, Zentrum Kinderheilkunde u. Jugendmedizin, Hannover**
- **Universitäts-Kinderklinik, Päd. Onkologie, Hämatologie, und Immunologie, Heidelberg**
- **Klinikum Heilbronn GmbH, Klinik für Kinderheilkunde und Jugendmedizin/Perinatalzentrum, Heilbronn**
- **Gemeinschaftskrankenhaus Herdecke, Kinderabteilung, Herdecke**
- **Universitätsklinik für, Kinder- und Jugendmedizin, Päd. Hämatologie/ Onkologie, Homburg / Saar**
- **Klinikum, der Friedrich-Schiller-Universität, Klinik für Kinder- und Jugendmedizin, Jena**
- **Städtisches Klinikum Karlsruhe, Kinderklinik, Karlsruhe**
- **Klinikum Kassel, Kinderklinik, Kassel**
- **Klinik für Allgemeine Paediatrie, Univ.-Klinikum Schleswig-Holstein, Campus Kiel, Kiel**
- **Städtisches Krankenhaus Kemperhof, Kinderklinik, Koblenz**
- **Kliniken der Stadt Köln GmbH, Kinderkrankenhaus Riehl, Köln**

- **Med. Einrichtungen der Universität zu Köln, Klinik für Allg. Kinderheilkunde, Onkologisch-hämatologische Station, Köln**
- **Universität zu Lübeck, Klinik für Kinder- u. Jugendmedizin, Abt. Hämatologie/ Onkologie/Immunologie, Lübeck**
- **Universitätsklinikum Magdeburg, Klinik für Päd. Hämatologie/Onkologie, Magdeburg**
- **Klinikum Mannheim gGmbH, Kinderklinik, Abt. Hämatologie/Onkologie, Mannheim**
- **Universitätskliniken, Giessen und Marburg GmbH, Marburg**
- **Johannes Wesling Klinikum Minden, Minden**
- **Städt. Krankenhaus München GmbH, Krankenhaus München-Schwabingen, Kinderklinik d. TU, München**
- **Universitäts-Kinderklinik, Päd. Hämatologie und Onkologie, Münster**
- **Cnopf'sche Kinderklinik, Onkologie, Nürnberg**
- **Klinikum Oldenburg gGmbH, Zentrum für Kinder- u. Jugendmedizin, (Elisabeth Kinderkrankenhaus), Oldenburg**
- **Universitäts-Kinderklinik, Rostock**
- **Asklepios-Klinik, Sankt Augustin GmbH, Sankt Augustin**
- **HELIOS Kliniken Schwerin, Klinik f. Kinder-u. Jugendmedizin, Schwerin**
- **Deutsches Rotes Kreuz, Kinderklinik, Siegen**
- **Olga-Hospital, Kinderklinik, Pädiatrisches Zentrum, Abt. Hämatologie/Onkologie, Stuttgart**
- **Krankenanstalt Trier, Mutterhaus der Borromaeerinnen, Pädiatrische Abteilung, Trier**
- **Universitäts-Kinderklinik, Abt. Kinderheilkunde II, Hämatologie/Onkologie, Tübingen**
- **Universitäts-Kinderklinik, Ulm**
- **Stadtkrankenhaus, Kinderklinik, Wolfsburg**
- **Universitäts-Kinderklinik, Würzburg**

Recruitment

- Planned/Actual: **[---]***
- (Anticipated or Actual) Date of First Enrollment: **2010/06/30**
- Target Sample Size: **4750**
- Monocenter/Multicenter trial: **Multicenter trial**
- National/International: **International**

Inclusion Criteria

- Gender: **Both, male and female**
- Minimum Age: **1 Years**

Gender: **Both, male and female**

Minimum Age: **1 Years**

■ Maximum Age: **18 Years**

Additional Inclusion Criteria

- newly diagnosed acute lymphoblastic leukemia

- age ≥ 1 year (> 365 days) and < 18 years old (up to 17 years old and 365 days)

- no Ph+ (BCR/ABL or t(9;22)-positive) ALL

- no evidence of pregnancy or lactation period

- no participation in another clinical study

- patient enrolled in a participating center

- written informed consent

Exclusion criteria

- pre-treatment with cytostatic drugs

- pre-treatment with cytostatic drugs

- steroid pre-treatment with ≥ 1 mg/kg/d for more than two weeks during the last month before diagnosis

- treatment started according to another protocol

- underlying diseases that prohibit treatment according to the protocol

- ALL diagnosed as second malignancy steroid pre-treatment with ≥ 1 mg/kg/d for more than two weeks during the last month before diagnosis

Addresses

■ **Primary Sponsor**

University of Schleswig-Holstein

Primary Sponsor

University of Schleswig-Holstein

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Contact for Scientific Queries**

Department of Pediatrics, University Hospital of Schleswig-Holstein, Campus Kiel
Martin Schrappe, MD PhD

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Contact for Public Queries**

Department of Pediatrics, University Hospital of Schleswig-Holstein, Campus Kiel
Martin Schrappe, MD PhD

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Collaborator, Other Address**

Deutsche Krebshilfe e.V., Bonn (Germany)

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

■ **Collaborator, Other Address**

SIGMA TAU RARE DISEASES, S.A.

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***

Collaborator, Other Address

SIGMA TAU RARE DISEASES, S.A.

Telephone: **[---]***
Fax: **[---]***
E-mail: **[---]***
URL: **[---]***

- **Collaborator, Other Address**

  medac GmbH

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

Sources of Monetary or Material Support

- **[---]***

  Bitte wenden Sie sich an den Sponsor / Please refer to primary sponsor

  Telephone: **[---]***
  Fax: **[---]***
  E-mail: **[---]***
  URL: **[---]***

Status

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

Trial Publications, Results and other documents

- Further trial documents **Conter V, Bartram CR, Valsecchi MG, Schrauder A, Panzer-Grümayer R, Möricke A, Aricò M, Zimmermann M, Mann G, De Rossi G, Stanulla M, Locatelli F, Basso G, Niggli F, Barisone E, Henze G, Ludwig WD, Haas OA, Cazzaniga G, Koehler R, Silvestri D, Bradtke J, Parasole R, Beier R, van Dongen JJ, Biondi A, Schrappe M. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010 Apr 22;115(16):3206-14. Epub 2010 Feb 12.; 20154213**
- Further trial documents **Flohr T, Schrauder A, Cazzaniga G, Panzer-Grümayer R, van der Velden V, Fischer S, Stanulla M, Basso G, Niggli FK, Schäfer BW, Sutton R, Koehler R, Zimmermann M, Valsecchi MG, Gadner H, Masera G, Schrappe M, van Dongen JJ, Biondi A, Bartram CR; International BFM Study Group (I-BFM-SG). Minimal residual disease-directed risk stratification using real-time quantitative**

PCR analysis of immunoglobulin and T-cell receptor gene rearrangements in the international multicenter trial AIEOP-BFM ALL 2000 for childhood acute lymphoblastic leukemia. Leukemia. 2008 Apr;22(4):771-82. Epub 2008 Jan 31.; 18239620

- Further trial documents **Möricke A, Zimmermann M, Reiter A, Henze G, Schrauder A, Gadner H, Ludwig WD, Ritter J, Harbott J, Mann G, Klingebiel T, Zintl F, Niemeyer C, Kremens B, Niggli F, Niethammer D, Welte K, Stanulla M, Odenwald E, Riehm H, Schrappe M. Long-term results of five consecutive trials in childhood acute lymphoblastic leukemia performed by the ALL-BFM study group from 1981 to 2000. Leukemia. 2010 Feb;24(2):265-84. Epub 2009 Dec 10.; 20010625**