I. Synopsis

TITLE OF STUDY	A prospective Phase II clinical study to assess the efficacy and toxicity of high-dose chemotherapy followed by allogeneic stem cell transplantation as treatment of primary progressive and relapsed aggressive non-Hodgkin lymphoma**. A**llogeneic **S**tem Cell **T**ransplantation in **R**elapsed **A**ggressive Non-Hodgkin **L**ymphoma (ASTRAL)
CONDITION	Aggressive B- and T-cell lymphoma, primary progressive or relapsed
OBJECTIVE(S)	To determine the efficacy and toxicity of defined high-dose chemotherapy followed by allogeneic stem cell transplantation (alloSCT) in treatment of primary progressive and relapsed aggressive B- and T-cell lymphoma
INTERVENTION(S)	**High-dose therapy** prior to alloSCT will consist of fludarabine (5 x 25 mg/m^2), thiotepa (3 x 5 mg/kg), cyclophosphamide (2 x 60 mg/kg) Graft-versus-host (GvH) prophylaxis is done according to local standards and national as well as international guidelines.
INCLUSION AND EXCLUSION CRITERIA	**Inclusion criteria:** 1. Provision of written informed consent and specifically the consent to the collection and processing of health-related data 2. Age 18 years and older 3. Gender: Male and female patients 4. Histology: Diagnosis of aggressive non-Hodgkin lymphoma (aNHL), based on an excisional biopsy of a lymph node or on an appropriate sample of a lymph node or of an extranodal involvement at relapse or progression (recommended) or at initial diagnosis. It will be possible to treat the following entities in this study as defined by the 2016 revision of WHO classification of lymphoid neoplasms (written histology report must be sent to Trial office prior registration). 5. Diagnosis of relapsed or primary progressive aggressive B- or T-cell lymphoma including: **a) <u>Criteria for B-NHL:</u>** • Follicular lymphoma grade IIIb • Diffuse large B-cell lymphoma (DLBCL), not otherwise specified (NOS) • T-cell/histiocyte-rich large B-cell lymphoma • Primary cutaneous DLBCL, leg type

	• Epstein-Barr virus (EBV) positive DLBCL, NOS • DLBCL associated with chronic inflammation • Primary mediastinal (thymic) large B-cell lymphoma • Intravascular large B-cell lymphoma • ALK-positive large B-cell lymphoma • Plasmablastic lymphoma • Primary effusion lymphoma • High-grade B-cell lymphoma, with MYC and BCL2 and/or BCL6 rearrangements • High-grade B-cell lymphoma, NOS • B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma • Mantle cell lymphoma (MCL) **b) <u>Criteria for T-NHL:</u>** • Aggressive natural killer cell leukemia (ANKL) • Enteropathy-associated T-cell lymphoma • Hepatosplenic T-cell lymphoma • Primary cutaneous gamma-delta T-cell lymphoma • Peripheral T-cell lymphoma, NOS • Angioimmunoblastic T-cell lymphoma • Anaplastic large cell lymphoma, ALK-positive • Anaplastic large cell lymphoma, ALK-negative • Peripheral T-cell lymphoma with TFH phenotype • Monomorphic epitheliotropic intestinal T-cell lymphoma • Subcutaneous panniculitis-like T-cell lymphoma 6. Knowledge of staging data at relapse or progression (data should not be older than 4 weeks): • Knowledge of all 5 factors of the International Prognostic Index (IPI) • Information on involved bulky diseases 7. Staging after 2 or 3 cycles of salvage treatment: • Information on all 5 IPI factors • Information on type and start date of salvage therapy • Results of a staging procedure according to the Lugano classification 2014 have to be available • Prior failed autoSCT OR • Progressive disease (PD) after 2 or 3 cycles of salvage treatment OR • Remission duration ≤ 12 months and complete response (CR) (CT based only), partial

	response (PR) or stable disease (SD) after 2 or 3 cycles of salvage treatment OR • Remission duration > 12 months and PR or SD after 2 or 3 cycles of salvage treatment • Performance Status ECOG 0-3 8. Fully matched donor (10/10 HLA-loci) available 9. Females of childbearing potential (FCBP) must: • Understand the potential teratogenic risk to the unborn child • Understand the need and agree to utilize two reliable forms of contraception simultaneously without interruption for at least 28 days before starting study drug and until 2 years after end of treatment (EoT) in this study • Understand and agree to inform the investigator if a change or stop of method of contraception is needed • Be capable of complying with effective contraceptive measures • Be informed and understand the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy • Understand the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test • Understand the need and accept to undergo pregnancy testing based on the frequency outlined in this protocol • Agree to abstain from breastfeeding during study participation 10. Males must: • Agree to use a latex condom during any sexual contact with females of childbearing potential • Agree to refrain from donating semen or sperm while on the study drugs and should seek for sperm cryopreservation before therapy is started and should not father a child while treated and during one year after end of study treatment 11. Females of non-childbearing potential: • Childbearing potential ends with sterilization or for women who have been in the menopause for more than one year as well as for women who are post-menopausal. Women will be considered post-menopausal if they have been amenorrheic for at least 24 consecutive months without an alternative medical cause.

	Exclusion criteria: 1. Pregnant females; lactating women must end breast feeding before start of study treatment 2. Serious accompanying disorder or impaired organ function (due to any reason including lymphoma progression) causing significant clinical problems and reduced life expectancy (< 1 month) 3. CNS involvement of lymphoma - to be examined in case of clinical symptoms 4. History of severe cardiac diseases, and cardiac function impairment (NYHA III and IV) 5. Severe kidney disease (creatinine clearance < 30 ml/min) 6. HIV-positivity 7. Hepatitis B and C as defined by seropositivity (HBsAg and anti-HBe / anti-HBc; anti-Hc); in case of false positive serology (transfused antibodies), negative PCR-results will allow patient inclusion 8. Patients under legal guardianship regarding medical decisions 9. Ongoing treatment or study procedures within any other clinical trial with the exception of follow-up 10. Ongoing exclusion periods of other clinical studies after end of treatment 11. In patients tested: Metabolic CR in a PET-CT scan after the last cycle of therapy prior to planned SCT 12. Known hypersensitivity to the study drugs (active substances, or excipients of the preparations) 13. Criteria which in the opinion of the investigator precluded participation for scientific reasons, for reasons of compliance, or for reasons of the subject's safety 14. Commitment to an institution by virtue of an order issued either by the judicial or the administrative authorities 15. Dependency on the sponsor, trial site or investigator 16. Additional exclusion criteria with respect to SmPC of the IMPs Fludarabin, Thiotepa, Cyclophosphamid: a) Known hypersensitivity to fludarabine, Thiotepa, cyclophosphamide or one of their metabolites b) Renal impairment with a glomerular filtration rate of less than 30 ml/min c) Decompensated haemolytic anaemia d) Concurrent application of vital vaccines e) Cystitis f) Renal tract obstruction g) Active and uncontrolled infection h) Notice: myelosuppression and impaired hematopoietic function is not an exclusion

	criterion as this usual contraindication to the application to any of the IMPs will be overcome by the stem cell transplantation following conditioning therapy.
OUTCOME(S)	Primary endpoint: Progression free survival (PFS) at 1 year of defined high-dose chemotherapy (FTC) in treatment of primary progressive and relapsed aggressive B- or T-cell lymphoma Secondary efficacy endpoints: • Rate of complete remission (CR) • Rate of partial remission (PR) • Overall response rate (ORR; CR+PR) • Rate of progressive disease (PD) • Relapse rate (RR) • Rate of treatment-related mortality • Event free and overall survival at 1 year (EFS and OS)
STUDY TYPE	Open-label, multicenter, prospective phase II study
STATISTICAL ANALYSIS	PFS will be analyzed according to the Kaplan-Meier method. 1-year PFS rate with 95% confidence interval (CI) will be determined.
SAMPLE SIZE	It is hypothesized that PFS at 1 year is 50% for alloSCT. With a sample size of 70 patients, the 95% CI would range from about 38% to 62% and allows excluding a true value of PFS at 1 year below 38%. Sample size: To be assessed for eligibility: n = 100 To be allocated to trial: n = 70
TRIAL DURATION	First patient inclusion: 02/2019 End of recruitment: 12/2019 Last patient, end of treatment: 03/2020 End of follow-up: 03/2021 Final Report: 03/2022
PARTICIPATING CENTERS	10 centers in Germany

GCP CONFORMANCE	The present trial will be conducted in accordance with the valid versions of the trial protocol, the internationally recognized Good Clinical Practice Guidelines (ICH-GCP) and any applicable laws.
FINANCING	Riemser Pharma GmbH