UKE HAMBURG

Der Vorstand

Summary final report **A randomised controlled trial to Compare Ocrelizumabor Alemtuzumab with autologous Hematopoietic Stem Cell Transplantation (aHSCT) in high inflammatory Multiple Sclerosis**	**7.3.10 Anlage 02** **Stand: 18.03.2019**

Name of Sponsor/Company: University Medical Center Hamburg-Eppendorf Martinistraße 52 20246 Hamburg Germany	Individual Study Table Referring to Part of the Dossier Volume: n.a. Page:n.a.	*(For Competent Authority only)*
Name of Finished Products: • autologous hematopoietic stem cells (aHSC) • Ocrevus • Lemtrada		
Name of Active Ingredient: • Morphologically and functionally intact stem and progenitor cells for reconstitution of hematopoiesis and immune system after myoablative or non-myoablative pretreatment. • ocrelizumab • alemtuzumab		
Title of Study	A randomised controlled trial to compare ocrelizumab or alemtuzumab with autologous Hematopoietic Stem Cell Transplantation (aHSCT) in high inflammatory Multiple Sclerosis (COAST)	
Principal Investigator	Prof. Dr. med. Nicolaus Kröger Department of Stem Cell Transplantation University Medical Center Hamburg-Eppendorf	

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Co-Principle Investigator	Prof. Dr. med. Christoph Heesen Multiple Sclerosis Day Hospital Clinical and Rehabilitative MS Research Institute of Neuroimmunology and Multiple Sclerosis Department of Neurology University Medical Center Hamburg-Eppendorf Martinistrasse 52 20246 Hamburg, Germany
Study centre(s)	1) University Medical Center Hamburg-Eppendorf Department of Stem Cell Transplantation and Multiple Sclerosis Day Hospital, Institute of Neuroimmunology and Multiple Sclerosis, Department of Neurology 2) University Hospital Mannheim, III. Medical Department, Clinic for Hematology and Oncology / Neurological Clinic (not active) 3) University Hospital Dresden, Department of Hematology and Blood Stem Cell Transplantation / Neurological Clinic and Polyclinic (not active)
Publication (reference)	n.a. / ClinicalTrials.gov Identifier: NCT04971005
Studied period (years):	Date of first enrolment: 01-SEP-2021
	Date of last completed: 04-FEB- 2022 Terminated (Lack of recruitment due to low acceptance of the control arm.)
Phase of development	Phase 2
Objectives	• To gain further evidence for clinical efficacy of aHSCT in active RRMS compared to ocrelizumab or alemtuzumab • To gain further knowledge on safety, tolerability and toxicity of aHSCT in MS • To gain further knowledge on the quality of life, daily functioning and long-term disability of patients treated with aHSCT with a special focus on neurocognitive functioning and on MRI measurements of neurodegeneration • To gain further knowledge on negative and positive predictors for aHSCT response in MS
Methodology	This is a randomised controlled aHSCT vs. ocrelizumab / alemtuzumab trial in subjects with highly active RRMS with clinical- or MRI signs of continuing inflammatory activity, who failed prior treatment as defined by the in- / exclusion criteria. After a screening period to evaluate in- / exclusion criteria for any of the three treatments, all patients will be randomised and treated. Randomisation will be either aHSCT or ocrelizumab/alemtuzumab following patient-physician decision in patients that are treatment naive for ocrelizumab and alemtzumab. In patients with a treatment failure under one of the two comparators, the other one is the control treatment. Ocrelizumab patients will receive 600 mg of the drug intravenously

	every 6 months. Alemtuzumab patients will receive 12 mg alemtuzumab on 5 consecutive days in year one and 12 mg alemtuzumab on 3 consecutive days in year 2. aHSCT patients will undergo mobilization with cyclophosphamide and G-CSF followed by harvesting of stem-cells with a minimum of 2.5x106/kg. Conditioning will be done with cyclophosphamide and ATG (Grafalon®). After treatment a follow-up is planned until the last patient completes 24 months of follow-up. Ocrelizumab and alemtuzumab have marketing authorizations and will be administered as directed in the current summary of product information (SmPC). All safety and monitoring that are defined in the SmPC will be performed through regular medical care. Safety visits and clinical follow-up of aHSCT including mobilisation will be performed within the clinical routine and according to the institutional standards.
Number of patients (planned and analysed)	Planned: 50 (1:1) Analysed: 0
Indication and main in- and exclusion criteria	Inclusion Criteria (Based on CARE-MS-II3, guidelines and Rio-criteria for treatment failure): • Written informed consent and agreement to comply to study protocol • Age: 18-55 years • EDSS: 0.0 - 6.0 • RRMS according to McDonald 2010 • < 10 years of disease course after symptom onset • Active disease with one of the following treatment failures occur-ring not earlier than 6 months after initiation of an approved DMT • 2 or more relapses within the last 12 months or • 1 relapse within the last 12 months and a Gd-enhancing lesion on MRI > 3 mm > 3 months before or after relapse onset or 2 new T2-lesions or • On-going signs of MRI activity in the last 6 months (either Gd-en-hancing of ≥ 3 mm lesion at any exam in the last year; or more than 5 new T2 lesions (≥ 3 mm) or • Patients stable under natalizumab but who have to stop treatment due to an increasing PML risk are defined as active, if a MRI within 6 months after termination of natalizumab shows new T2 or Gd-enhancing lesions and at least one other treatment failure prior to natalizumab is documented. Exclusion Criteria: • Secondary or primary progressive MS • Pregnancy, or other medical condition incompatible with aHSCT • Any treatment or medical condition that, according to the haematologist / transplant specialist precludes the use of aHSCT • John Cunningham virus (JCV) antibody index of > 1.5 in

	previ-ously natalizumab-treated patients, if a negative CSF JCV-PCR prior to screening is not available • Relapse during 30 days before initiation of treatment. If a relapse occurs during this period and eligibility criteria are otherwise ful-filled, start of treatment will be delayed until at least 30 days after receiving steroids. • Concurrent clinically significant (as determined by the investiga-tors and haematologist / transplant specialist) cardiac, immuno-logical, pulmonary, neurological, renal or other major disease such as: - Prominent cardial disease (Left ventricular ejection fraction (LVEF) < 40%, myocardial infarction or ischemia, uncontrolled arrhythmias, pericardial effusion > 1 cm) - Cerebrovascular disease - Renal disease (creatinine clearance < 30 ml/min/m2) - Respiratory disease (DLCO < 40% predicted) - Active bleeding or clotting disease - History of human immunodeficiency virus (HIV) or positive HIV antibody testing - Any uncontrolled acute or chronic infection, including HIV, hepatitis B surface antigen positivity and hepatitis C PCR positivity - Cancer except in situ cervix or cutaneous • Unwillingness or inability to comply with the requirements of this protocol including the presence of any condition (physical, men-tal, or social) that is likely to affect the patient returning for follow-up visits on schedule. Unwillingness to use contraception. • Previous participation in this study, previous treatment with aHSCT or already both comparators • Ongoing immunotherapy. Treatment with interferon or glatirameracetate will need no wash-out. Treatment pause before oc-relizumab/alemtuzumab or aHSCT will be: - for dimethylfumarate and fingolimod: 8 weeks - for natalizumab: 8 weeks - for ocrelizumab: 12 weeks - for alemtuzumab: 12 months - for teriflunomide: 4 weeks after elimination with cholestyramine - for cladribine: 24 weeks • Patients with cognitive impairments who are unable to provide written, informed consent prior to any testing under this protocol, including screening and baseline investigations that are not con-sidered part of routine patient care.
Test product, dose and mode of administration, batch number (planned)	autologous hematopoietic stem cells aHSC, 3.0x10e6 CD34 per kg body weight intravenous use, patient specific preparation
Duration of treatment (planned)	Once (aHSC)
Reference therapy, dose and mode of administration, batch number	Ocrevus (ocrelizumab, 600 mg every 6 months over a maximum of 4 years

(planned)	intravenous use Lemtrada (alemtuzumab) 12 mg/day for 5 consecutive days and again after 365 days for 3 days, intravenous use
Criteria for evaluation	Safety: Clinical safety will be assessed by neurological examination as well as standardised rating scales for multiple sclerosis (EDSS, MSFC), relapse rate, general physical examination, and vital signs (temperature, heart rate, body weight and blood pressure), adverse events (AEs) and serious adverse events (SAEs)
	Efficacy: Molecular mechanisms assessments in peripheral blood and CSF Disease activity, fatigue, QoL and mood/fatigue assessments, MRI, Neuropsychological assessments
Statistical methods (planned)	The primary endpoint will be visualized by Kaplan-Meier curves and assessed by Cox proportional hazards model with treatment and centre as factors based on an intention-to-treat (ITT) analysis. In the primary analysis dropout is assumed independent of the primary endpoint and will be dealt with as independent right censoring. If a sufficient number of dropouts is observed, at least 10, then the sensitivity of the results to this assumption will be assessed in shared random effects models accounting for a possible correlation between both processes. In supporting analyses adjustment for prognostic baseline variables (e.g. baseline Gd-lesions and number of relapses in the year before study entry) will be explored by adaptive regression. The treatment effect will be reported as hazard ratio with 95% confidence interval and p-value testing the null hypothesis of no treatment effect. The analyses of the time-to-event endpoints among the secondary endpoints will follow the same lines. Recurrent events such as relapses will be evaluated using negative binomial regression models with treatment and centre as factors including varying follow-up times as offset. Longitudinal assessments of continuous outcomes and scores will be analysed using the so-called mixed model repeated measures (MMRM) approach.
SUMMARY-CONCLUSIONS n.a. due to early termination, no therapeutic intervention and no analyses were performed in any of the study arms.	
Efficacy results	n.a
Safety results	n.a
Conclusion	n.a
Date of Report:	25.03.2022

PRINCIPAL OR COORDINATING INVESTIGATOR(S) SIGNATURE(S) OR SPONSOR'S RESPONSIBLE MEDICAL OFFICER

STUDY TITLE:

A randomised controlled trial to Compare Ocrelizumabor Alemtuzumab with autologous Hematopoietic Stem Cell Transplantation (aHSCT) in high inflammatory Multiple Sclerosis

STUDY AUTHOR(S): n.a.

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct ~~and results~~ of the study

Prof. Dr. med. Nicolaus Kröger
INVESTIGATOR OR SPONSORS
RESPONSIBLE MEDICAL OFFICER

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Date: 25.3.2022

CONSORT Flow Diagramm

Note: The flow chart is a recommendation of the CONSORT statement and not mandatory for the synopsis