CLINICAL STUDY REPORT

PHASE II MULTICENTER STUDY OF EXTRACORPOREAL PHOTOPHERESIS WITH UVADEX™ PLUS STANDARD STEROID TREATMENT FOR HIGH-RISK ACUTE GRAFT-VERSUS-HOST DISEASE

A prospective, multicenter, open label, single arm clinical study

Investigational Product:	Extracorporeal photopheresis with UVADEX™
Study Protocol:	MAGIC-HR-ECP
Study Phase:	Phase II
EudraCT No:	2019-000894-22
Report Version:	Final (31-Mar-2026)
First Patient Enrolled:	18-May-2020
Last Patient Completed:	24-Jun-2024
Coordinating Investigator:	Francis A. Ayuk, MD Department of Stem Cell Transplantation University Medical Center Hamburg-Eppendorf Martinistr. 52, 20246 Hamburg, Germany Tel: +4940741055250 Fax. +4940741053795 Email: ayuketan@uke.de
Sponsor:	University Medical Center Hamburg-Eppendorf Martinistraße 52 20246 Hamburg Germany
Date of this report:	31-Mar-2026

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1. SYNOPSIS

Name of Sponsor: University Medical Center Hamburg-Eppendorf Martinistraße 52, 20246 Hamburg, Germany	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of finished product: Extracorporeal photopheresis with UVADEX™	Volume:	
Name of active ingredient: Methoxsalen 20 mcg	Page:	

Title of Study:

Phase II multicenter study of extracorporeal photopheresis with UVADEX™ plus standard steroid treatment for high-risk acute graft-versus-host disease.

Investigator:

Francis A. Ayuk, MD
Department of Stem Cell Transplantation
University Medical Center Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg, Germany

Study Center(s):

Francis A. Ayuk, MD
Department of Stem Cell Transplantation
University Medical Center Hamburg-Eppendorf
Martinistr. 52, 20246 Hamburg, Germany

Matthias Edinger, MD
Department of Internal Medicine III and Stem Cell Transplantation
University Hospital Regensburg
Franz-Josef-Strauß-Allee 11, 93053 Regensburg, Germany

Ingrid Vasova, MD
Department of Internal Medicine 5
University Hospital Erlangen
Ulmenweg 18, 91054 Erlangen, Germany

Hildegard Greinix, MD
Internal Medicine, Department of Hematology
University Hospital Graz
Auenbruggerplatz 38, 8036 Graz, Austria

Publication (reference):

Not applicable

Studied Period (years):

Date of first patient enrolled: 18-May-2020
Date of last patient completed: 24-Jun-2024

Phase of Development:

II

Objectives:

The primary objective of this study was to improve Day 28 Graft-versus-Host Disease (GvHD) complete response rate for Ann Arbor score 2 or 3 GvHD patients from the historical rate of 37% to 52% by treatment with extracorporeal photopheresis (ECP) and high dose methylprednisolone (2 mg/kg) or equivalent dose prednisolone.

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Methodology:

This study was conducted as a prospective, multicenter, open label, single arm clinical study.

Patients with new onset of high risk acute GvHD (aGvHD) (Ann Arbor score 2 or 3) following allogeneic stem cell transplantation (SCT) were included. Patients were treated with ECP 3x/week in Weeks 1+2, 2x/week thereafter until Day 28 and 1x/week till Day 56 and with methylprednisolone 2 mg/kg/d (or prednisolone equivalent) from Day 0 to Day 3, then tapered according to clinical criteria. Treatment on protocol per patient was 2 months with a follow-up period of 1 year.

The study procedures comprised prescreening, screening (to be performed within 5 working days prior to baseline) and baseline procedures (Day 0, start of ECP treatment), treatment period (Days 0-56: 3x/week in Week 1 and Week 2, 2x/week in Week 3 and Week 4, then once weekly until Day 56) and a follow-up period (Weeks 10, 12, and Months 6, 9, 12).

Prescreening Process:

The local study sites were required to prescreen patients for the study on a regular basis. This process could take place as part of routine practice for all new aGvHD diagnosed patients and served to identify potential patients for study screening. No study related examinations were performed at this stage.

Screening and Enrollment Process (Day -5 (working days) to Day 0):

The screening process started after the patient was diagnosed with aGvHD (Glucksberg grade II-IV) and after Informed Consent was collected.

For Ann Arbor scoring 5 mL of serum was collected on either the day of diagnosis (preferable) or the following day. The sample had to be shipped priority overnight to the laboratory of Dr. Holler in Regensburg for early AM arrival. Once received in the laboratory, the GvHD biomarkers used to assign the Ann Arbor GvHD score were measured by ELISA using standard technical procedures. Once the Ann Arbor score was confirmed, the local site investigator and the Study Coordination Center (University Medical Center Hamburg-Eppendorf) were notified of the Ann Arbor score by telephone (local site) and by E-mail through the laboratory of Dr. Holler in Regensburg.

To be eligible for study enrollment, patients had to be diagnosed with Ann Arbor score 2 or 3. As soon as confirmation was received by the laboratory in Regensburg, the patient could start with study treatment. First ECP had to be performed by the end of 5 working days after starting systemic steroid treatment for aGvHD, therefore investigators were encouraged to begin the informed consent and screening process immediately when aGvHD was diagnosed. Patient eligibility was centrally monitored by the Study Coordinating Center in Hamburg.

Treatment Period (Days 0-56: ECP 3x/week in Week 1 and Week 2, 2x/week in Week 3 and Week 4, then once weekly until Day 56):

Protocol treatment with ECP had to start within 5 working days after initiation of systemic steroid treatment for aGvHD. Study treatment consisted of two drugs: methylprednisolone (or prednisone) which is standard treatment for aGvHD and ECP.

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Corticosteroid dosing and taper: All patients enrolled on this study received steroids at a dose of methylprednisolone 2 mg/kg/day orally or i.v. (or prednisone equivalent). The dose of steroids could not be tapered before 3 days of initiation of study therapy (Day 0 was defined as the day of the first ECP), but afterwards local institutional tapering practices could be followed. Steroid therapy could be given up to 7 days prior to the first ECP (Day -6 to -0), i.e., during the period from the initiation of systemic steroid treatment for aGvHD until study therapy began.

ECP procedure and schedule: The ECP procedure was performed according to manufacturer's guidelines as outlined in the investigators' brochure. ECP treatment began within 5 working days of initiation of steroid treatment. ECP was performed 3x weekly during the first 2 weeks, 2 x weekly thereafter until Day 28 and 1x weekly until Day 56. The first day of ECP was defined as Day 0 of the study. Prior to an ECP treatment each patient was assessed by a physician to verify that the patient was acceptable for ECP treatment. This assessment included vital signs (diastolic and systolic blood pressures, pulse, temperature) which were taken prior to and at the end of each ECP treatment. Blood cell counts were analyzed prior to each treatment. If a patient's WBC count was below 1 x 10^9/L or platelet count was below 20 x 10^9/L, ECP was postponed until rise in WBC or platelet counts. Platelet transfusions and use of cytokines was permitted. Whenever possible, peripheral venous access was preferable to central venous catheters. In patients with platelet counts below 40 x 10^9/L, acid citrate dextrose (ACD) instead of heparin was used for ECP. When severe acute infections occurred during the study, ECP should be discontinued until the infection had been controlled under appropriate therapy. During the ECP treatment, the patient's tolerance to the extracorporeal treatment was monitored according to manufacturer's guidelines and centers' routine practice. Supportive care guidelines were defined for patients in addition to the application of study drug plus corticosteroids.

Follow-up Period (Weeks 10, 12, and Months 6, 9, 12):

Patients were followed for 1 year after removal from treatment or until death, whichever occurred first. Patients with aGvHD were followed closely and frequent clinical evaluations were the norm. In the following, the minimum frequency of follow-up evaluations is outlined, however, in most cases patients were evaluated more frequently: During the first 8 weeks of participation (i.e., up to the last ECP), patients were evaluated at least weekly for acute toxicity assessment, GvHD staging and management. For the next 6 weeks, patients were evaluated at least every other week for GvHD staging and management. Thereafter, patients were evaluated every 3 months (±2 weeks) until 1 year from start of study treatment.

Number of patients (planned and analyzed):

Sample size was determined based on the primary endpoint of a conservatively estimated magnitude of improvement in Day 28 CR of 15% (from 37% to 52%) as well as on feasibility and power requirements. Over the recruitment period of three years, it was planned to recruit 25 patients with grade 2 or 3 aGvHD per year, resulting in 72 patients. Based on previous knowledge from the ongoing US-trial (MAGIC USA), 172 patients needed to be screened to realize the final sample size of 72 patients. This sample size should provide 85% power to detect a 15% difference in CR rates, assuming a Type I error rate of 5% (one-sided).

Due to recruitment problems, recruitment phase was extended for 1 year (Protocol Amendment 3, 20-Apr-2023). After this, recruitment phase ended on 31-Mar-2024 with the inclusion of 24 patients.

Diagnosis and Main Criteria for Inclusion:

The study included patients with new onset of high risk aGvHD (Ann Arbor score 2 or 3) following allogeneic SCT. Any clinical severity in accordance with Glucksberg grade II-IV was eligible.

Test Products, Dose and Mode of Administration, Batch Number:

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Investigational product was UVADEX™ (methoxsalen, 8-methoxypsoralen). UVADEX™ was supplied as a sterile solution containing methoxsalen 20 mcg, propylene glycol 50 mg, sodium chloride 8 mg, sodium acetate 1.75 mg, ethanol 40.550 mg, glacial acetic acid 1.260 mg, and water for injection q.s. to 1.0 mL. Glacial acetic acid and sodium hydroxide were used to adjust the pH of the solution if necessary. UVADEX™ is a clear, colorless to pale yellow liquid. Patients received ECP 3x/week in weeks 1+2, 2x/week thereafter until Day 28 and 1x/week until Day 56.

Duration of Treatment:

ECP was performed 3x weekly during the first 2 weeks, 2 x weekly thereafter until Day 28 and 1x weekly until Day 56.

Methylprednisolone at a dose of 2 mg/kg/d (or prednisolone equivalent) was given from Day 0 to Day 3 and then tapered according to clinical criteria.

Reference Therapy, Dose and Mode of Administration, Batch Number:

Not applicable.

Criteria for Evaluation:

Efficacy:

Primary objective:

The primary objective of the study was to improve Day 28 GvHD complete response rate for Ann Arbor score 2 or 3 GvHD patients from the historical rate of 37% to 52% by treatment with ECP and high dose methylprednisolone (2 mg/kg) or equivalent dose prednisolone.

Secondary objectives:

Secondary objectives were:

- to decrease 6-month NRM from the historical rate of 30% to 20%
- to determine the overall survival and NRM rates at 1 year and the cumulative incidence of treatment-refractory GvHD by 6 months (defined as no improvement or worsening in any target organ or who receive additional immunosuppression prior to 6 months), the Day 28 and Day 56 overall response rate (CR + PR), time to discontinuation of steroid therapy over a period of 1 year, number of lines of GvHD therapy by 1 year, and cumulative incidence of chronic GvHD by 1 year
- to determine the cumulative incidence of severe GI aGvHD stage 3 or 4 at 6 months
- to determine the cumulative incidence of 6 months and 1 year relapse and the incidence of serious infections by 6 months
- to assess the safety of ECP for the treatment of high risk GvHD.

Safety:

Tolerability and safety were assessed by the frequency of relapses, the frequency of infections, toxicity and hematologic abnormalities and the number of AEs, AEs with CTCAE grade ≥3, and SAEs.

Statistical Methods:

The primary endpoint was tested with a binomial test with a one-sided Type I error rate of 5%. The estimated CR rate at Day 28 was presented together with a two-sided 90% exact Clopper-Pearson confidence interval (CI). The lower limit of the 90% CI should not include the historical rate of 0.37.

Analyses of secondary outcomes were performed exploratively. Corresponding p-values and CIs were considered as descriptive measures and were therefore not adjusted for multiplicity.

Categorical data were summarized by absolute and relative frequencies. Continuous data were summarized by mean, standard deviation, median, inter quartile range (IQR), minimum, and maximum.

Statistical analyses were based on the Full Analysis Set (FAS), Per Protocol Population (PP), and the Evaluated for Safety Set (EFS).

SUMMARY

Efficacy Results:

The primary endpoint objective of this study, improvement in Day 28 GvHD complete response rate for Ann Arbor score 2 or 3 GvHD patients from the historical rate of 37% to 52% by treatment with ECP and high dose methylprednisolone or equivalent dose prednisolone was clearly reached in this study. The CR proportion was significantly higher in MAGIC-HR-ECP compared to the historical rate (87.5% vs. 37%), with a p-value of < 0.001.

Also, with respect to secondary endpoints, favorable results were obtained for ECP treatment.

Overall response was achieved at Day 28 in 91.7% of patients and at Day 56 in 78.3% of patients.

In the MAGIC-HR-ECP study, the estimated incidence of NRM was lower than the historical rate of 30%, with an incidence of 8% at both 6 and 12 months.

The incidence of treatment refractory GvHD was low at Day 28 (0.042, 95% CI [0.003;0.176]) and Day 56 (0.219, 95% CI [0.062;0.436]).

After 1 year, 3 deaths were documented, resulting in a survivor function of 87.5%.

Relapse was restricted to one case after 12 months.

Subsequently, the MAGIC cohort was compared to the historical controls of the C1a cohort with regard to the primary efficacy endpoint as well as the secondary endpoints OR at Day 28 and Day 56, OS at 1 year, and NRM at 6 and 12 months, respectively. Analyses were conducted adjusted for the propensity score and unadjusted as sensitivity analysis. With respect to the primary efficacy endpoint, CR at Day 28, a difference was obtained in favor of the MAGIC cohort (OR=11.11, 95% CI [1.76;70.29], p=0.011). Similar results were obtained in the unadjusted analysis. Accordingly, the MAGIC cohort was superior to the C1a cohort with respect to CR at Day 28, the primary efficacy endpoint. The cohorts did not differ for the secondary endpoints.

Safety Results:

In total, 19 of 24 patients experienced CTCAE grade ≥3 AEs during total study duration (62 events) and 13 of 24 patients experienced CTCAE grade ≥3 AEs during treatment period (17 events).

Predominantly, CTCAE grade ≥3 was grade 3 with 55 of 62 events (88.7%) during total study duration and 16 of 62 events (25.8%) during treatment period. CTCAE AEs grade 4 and grade 5 were restricted to single cases.

The most frequent CTCAE grade ≥3 AEs related to the MedDRA System Organ Class infections and infestations in both total study duration (N=15, 78.9%) and treatment period (N=7, 36.8%). Regarding Preferred

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Terms, infection, sepsis (N=5, 26.3%, each), and pneumonia (N=4, 21.1%) during total study duration and infection (N=3, 15.8%) during treatment period were most frequently documented.

SAEs were recorded in 20 of 24 patients during total study duration and in 14 of 24 patients during treatment period, most frequently related to the MedDRA System Organ Class infections and infestations in both total study duration (N=13, 65.0%) and treatment period (N=7, 35.0%).

Three patients died during the study. The underlying causes of death were cardiac arrest, myelodysplastic syndrome progression, and sepsis. As other significant adverse events hepatotoxicity (59 events in 50.0% of the patients), hematologic abnormalities (5 events in 20.8% of the patients), and serious (grade 3) infections (2 events in 8.3% of the patients) were documented.

In general, it can be stated that therapy with ECP was well tolerated.

CONCLUSIONS:

It can be concluded from this study that extracorporeal photopheresis with UVADEX™ plus standard steroid treatment for high-risk acute graft-versus-host disease is an effective and safe treatment in patients with new onset of high risk aGvHD (Ann Arbor score 2 or 3) following allogeneic stem cell transplantation.

Date of the Report:

31-Mar-2026

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