

Official Title: Single-Arm Study to Assess the Efficacy of UVADEX® (methoxsalen) Sterile Solution in Conjunction with the THERAKOS® CELLEX® Photopheresis System in Pediatric Patients with Steroid-Refractory Acute Graft-vs-host Disease (aGvHD)

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Development Phase: III
Date of Protocol Amendment 2: 27 July 2017
Date of Protocol Amendment 1: 15 March 2016
Date of Original Protocol: 12 June 2015

The study will be conducted according to the protocol and in compliance with Good Clinical Practice (GCP), the Declaration of Helsinki, and other applicable regulatory requirements.

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PROTOCOL AMENDMENT 2 DATED: 27 July 2017**SUMMARY OF CHANGES**

Protocol Amendment 2 was developed to modify the existing protocol. Amendment 2 will make the clinical study more successful and the protocol will be more detailed for the Investigators. The major protocol changes are summarized below. Additional minor revisions were made to the protocol to improve other descriptions and tables.

The major protocol changes are summarized as follows:

1. Modified inclusion criterion #2 from Grade B-C to Grade B-D, specified that Grade D organ involvement would be limited to liver and skin and updated language related to the assessment of steroid refractory status ([Section 4.1](#)).
2. Modified inclusion criterion #3 to specify that the Lansky Scale will be used in the study ([Section 4.1](#)).
3. Modified the recording period for adverse events from ICF signing to Week 16 of the study ([Section 8.1.4](#)).
4. Modified the descriptive language in exclusion criterion (#21, systemic therapy) and prohibited medications from: immunomodulatory to immunosuppressive ([Sections 4.2](#) and [6.5.1](#)).
5. Modified the SUSARs definition and description ([Section 8.1.8](#)).
6. Removed the requirement for biomarkers from the study protocol ([Sections 3.2.3](#) and [9.3.3](#)).
7. Added an inclusion criterion related to Patients with a lack of complete response after 2 weeks of steroid treatment ([Section 4.1](#)).
8. Removed prior exclusion criterion #4 (Development of aGvHD after donor lymphocyte infusion) ([Section 4.2](#)).

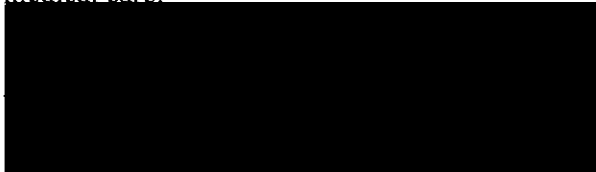
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Declaration of Sponsor or Responsible Medical Officer

Title: Single-Arm Study to Assess the Efficacy of UVADEX® (methoxsalen) Sterile Solution in Conjunction with the THERAKOS® CELLEX® Photopheresis System in Pediatric Patients with Steroid-Refractory Acute Graft-vs-host Disease (aGvHD)

My signature, in conjunction with the signature of the investigator, confirms the agreement of both parties that the clinical study will be conducted in accordance with the protocol and applicable laws and other regulations including, but not limited to, the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice (GCP), the US Code of Federal Regulations (CFR), protections for privacy, and generally accepted ethical principles for human research such as the Declaration of Helsinki.

Nothing in this document is intended to limit the authority of a physician to provide emergency medical care.



28 JUL 2017

Date of Signature
(DD Month YYYY)



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Declaration of the Principal Investigator

Title: Single-Arm Study to Assess the Efficacy of UVADEX[®] (methoxsalen) Sterile Solution in Conjunction with the THERAKOS[®] CELLEX[®] Photopheresis System in Pediatric Patients with Steroid-Refractory Acute Graft-vs-host Disease (aGvHD)

This study protocol, TKS-2014-001 Amendment 2, was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product(s), as well as with the moral, ethical, and scientific principles governing clinical research as set out in the Declaration of Helsinki, 1996, and the guidelines on Good Clinical Practice and other applicable regulatory requirements.

Principal Investigator (signature)

Date

Principal Investigator (printed name)

Site

PROTOCOL SYNOPSIS

Title	Single-Arm Study to Assess the Efficacy of UVADEX[®] (methoxsalen) Sterile Solution in Conjunction with the THERAKOS[®] CELLEX[®] Photopheresis System in Pediatric Patients with Steroid-Refractory Acute Graft-vs-host Disease (aGvHD)
Study duration	Treatment duration per patient: 12 weeks
Study center	Multicenter
Objectives	<p>Primary objective:</p> <ul style="list-style-type: none"> To evaluate the efficacy of extracorporeal photopheresis (ECP) in pediatric patients with steroid-refractory aGvHD. <p>Secondary objectives:</p> <ul style="list-style-type: none"> To assess the safety of ECP. To assess the duration of response to ECP. To assess the steroid-sparing effect of ECP. To assess the organ-specific response to ECP.
Study endpoints	<p>Primary:</p> <ul style="list-style-type: none"> The primary endpoint is the proportion of patients who achieve an overall response (complete response [CR] + partial response [PR]) after 4 weeks (Day 28) of ECP treatment, or fewer treatments if they discontinued treatment. <p>Patients will be evaluated by the treating physician for the presence or absence of aGvHD manifestations of the skin, liver, and gut. Source data will be collected for each patient and entered into the electronic Case Report Form (eCRF), and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified International Bone Marrow Transplant Registry (IBMTR) Severity Index (Appendix A: Modified IBMTR Severity Index). Patients weighing < 50 kg will be evaluated according to a modified version of the IBMTR criteria that accounts for stool output on an mL/kg/day basis.</p> <p>Secondary:</p> <ul style="list-style-type: none"> Safety parameters including vital signs, laboratory tests, and spontaneously reported adverse events (AEs) and serious adverse events (SAEs). Proportion of patients who achieve an overall response 8 weeks (Day 56) and 12 weeks (Day 84) after initiation of ECP treatment. Duration of response (defined as the length of time a patient maintains a response through Week 16 of the Follow-up Period on a per-patient basis). Proportion of patients who achieve an overall response after 4 weeks (Day 28), 8 weeks (Day 56), and 12 weeks (Day 84) of ECP treatment according to the modified Glucksberg criteria (Appendix B: Modified Glucksberg Criteria). <ul style="list-style-type: none"> Source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified Glucksberg Criteria. Cumulative dose of daily steroids administered from diagnosis of aGvHD to 12 weeks (Day 84) after initiation of ECP treatment. Organ-specific grade at 4 weeks (Day 28), 8 weeks (Day 56), and 12

	<p>weeks (Day 84) after initiation of ECP treatment.</p> <p>Exploratory:</p> <p>█ [REDACTED]</p> <p>█ [REDACTED]</p> <p>█ [REDACTED]</p> <p>█ [REDACTED]</p> <p>█ [REDACTED]</p>
<p>Number of patients</p>	<p>48 patients with steroid-refractory aGvHD grade B-D.</p>
<p>Study design</p>	<p>This is a single-arm, open-label, multicenter study of the efficacy of UVADEX (methoxsalen) Sterile Solution in conjunction with THERAKOS CELLEX Photopheresis Systems in pediatric patients with steroid-refractory aGvHD. The study is composed of Screening, Treatment, and Follow-up Periods.</p> <p>Screening:</p> <p>After the informed consent/assent form (ICF) is signed, the screening assessments will be performed in a single visit to establish the eligibility of the patient, based on inclusion and exclusion criteria, as well as aGvHD grading. Scheduling of the first week of ECP treatments and the arrangements for availability of typed and cross-matched donor packed red blood cells (PRBCs) for transfusion, if required, will be made in advance of patients entering the Treatment Period.</p> <p>Treatment Period:</p> <p>Once eligibility is established, patients will enter the 12-week ECP Treatment Period. The availability of typed and cross-matched donor PRBCs for transfusion during treatment, if needed, should be established prior to the scheduling of ECP treatments.</p> <p>Patients will be allowed to continue standard aGvHD prophylaxis regimens (e.g., cyclosporine, tacrolimus, methotrexate, mycophenolate mofetil) without the addition of new therapies. Patients will be allowed to discontinue prophylaxis regimens for reasons of toxicity, and will also be allowed to switch to another prophylaxis medication within the same class (e.g., the calcineurin inhibitors cyclosporine and tacrolimus) for reasons of toxicity.</p> <p>All patients enrolled in this trial will have received corticosteroids for the treatment of aGvHD. After entering the treatment period on study, it is suggested that the steroid dose be decreased by 12.5% to 25% of the dose after the initiation of ECP therapy if a sustained response of aGvHD has been observed for at least 3 consecutive days. The suggested goal is to have decreased the starting steroid dose by at least 50% at 4 weeks after initiation of ECP.</p> <p><u>Special Warnings and Precautions for Use</u></p> <p>Patients should be explicitly instructed to wear ultraviolet A (UVA)-absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SPF 15 or higher) for the 24 hour period following treatment with methoxsalen, whether exposed to direct sunlight, or indirect sunlight through a glass window.</p>

		<p>Follow-Up Period: After completion of the 12-week Treatment Period, patients may continue ECP treatment on commercial product at the discretion of the Principal Investigator. Acute GvHD status will be assessed 4 weeks after completion of the Treatment Period. Patient survival will be assessed by passive follow-up (chart review) 26 weeks after initiation of ECP treatment.</p>
<p>Patient population</p>	<p>Inclusion criteria</p>	<p>Patients must meet all of the following criteria:</p> <ol style="list-style-type: none"> 1. Male or female 1 to 21 years of age at the time of consent. 2. Steroid-refractory grade B-D aGvHD <ul style="list-style-type: none"> • Steroid-refractory is defined as a failure to respond to steroid treatment, with failure to respond defined as any grade B-D (IBMTR grading) aGvHD that shows progression ≥ 3 days, or no improvement by 5 days of treatment with 2 mg/kg/day of methylprednisolone or equivalent in patients with lower GI or liver disease, or skin disease associated with bullae. Grade D organ involvement will be limited to skin and liver. • Steroid refractory may also be defined as a failure to respond to 1 mg/kg/day of methylprednisolone or equivalent in patients with disease confined to upper GI disease or lesser degrees of skin GvHD. • Patients with lack of complete response after 2 weeks of steroid treatment. 3. A Lansky Scale Performance Status score ≥ 30. 4. Laboratory values are within the following limits, assessed within 3 days of the first study treatment: <ul style="list-style-type: none"> • Absolute neutrophil count $> 0.5 \times 10^9/L$ • Creatinine level < 2 times the upper limit of normal 5. For patients with isolated upper gastrointestinal (GI) symptoms, pre-Screening biopsy results to confirm diagnosis of aGvHD. 6. Female patients of childbearing potential and nonsterilized males who are sexually active with a female partner must be practicing highly effective, reliable, and medically approved contraceptive regimen throughout their participation in the study and for 3 months following the last ECP treatment. Or, for the US only, abstinence may be used in place of an approved contraceptive regimen. Females of childbearing potential are those who have reached the onset of menarche, or 8 years of age, whichever comes first. Approved contraceptive methods for female patients of childbearing potential or nonsterilized males who are sexually active with a female partner are as follows: <ul style="list-style-type: none"> • Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository. • Established use of oral, injectable, or implanted hormonal methods of contraception. • Placement of an intrauterine device or intrauterine system. 7. Signed informed consent/assent is obtained before conducting any study procedures; the parent, legal guardian, or legally authorized representative of a minor must also provide written informed consent.
	<p>Exclusion criteria</p>	<p>Any of the following would exclude the patient from participation in the study:</p> <ol style="list-style-type: none"> 1. Currently enrolled in another clinical trial for the treatment of aGvHD. 2. Use of any experimental regimens or medication(s) for aGvHD

		<p>treatment.</p> <ol style="list-style-type: none"> 3. Treatment with > 2.0 mg/kg/day of methylprednisolone equivalents for aGvHD within 30 days prior to the first study treatment. 4. Overt signs of relapse of the underlying condition. 5. Uncontrolled viral, fungal, or bacterial infection. 6. Platelet count < $20.0 \times 10^9/L$, despite platelet transfusion. 7. Total bilirubin value ≥ 15 mg/dL. 8. Inability to tolerate the extracorporeal volume shifts associated with ECP treatment. 9. Uncontrolled GI bleeding. 10. Veno-occlusive liver disease. 11. Life expectancy < 4 weeks. 12. Patient requires invasive ventilation or vasopressor support. 13. Known human immunodeficiency virus (HIV) or hepatitis B or C virus infection (proof of seronegativity within 6 months of screening is required). 14. Known allergy or hypersensitivity to methoxsalen, Uvadex, or its excipients. 15. Known hypersensitivity or allergy to heparin and Anticoagulant Citrate Dextrose Formula-A (ACD-A). 16. Co-existing photosensitive disease (e.g., porphyria, systemic lupus erythematosus, albinism) or aphakia. 17. Coagulation disorders that cannot be corrected with simple transfusion. 18. Co-existing melanoma, basal cell, or squamous cell skin carcinoma. 19. Previous splenectomy. 20. White blood cell count greater than $25,000 \text{ mm}^3$. 21. Currently being treated with any systemic immunosuppressive or biologic therapy for the treatment of a medical condition other than aGvHD. 22. Female patient is breastfeeding or pregnant. 23. Any medical concerns that may pose risk to the patient. 24. Any psychological, familial, sociological, and/or geographical condition that may potentially hamper compliance with the study protocol and the follow-up schedule.
Study treatment		<p>Patients will receive ECP (UVADEX [methoxsalen] Sterile Solution) in conjunction with the CELLEX System.</p>
Dosage and frequency of administration		<p>The dose of UVADEX (methoxsalen) Sterile Solution used to inoculate the buffy coat will be calculated according to the CELLEX System Operator's Manual based on the treatment volume collected during the plasma/buffy coat collection process using the following formula:</p> <p style="padding-left: 40px;">Treatment Volume in mL $\times 0.017 =$ Dose of UVADEX (methoxsalen) Sterile Solution (in mL) required for administration into the recirculation bag. Each mL of solution contains 20 μg of UVADEX (methoxsalen) Sterile Solution.</p> <p>After the cells are inoculated with UVADEX (methoxsalen) Sterile Solution, the buffy coat/plasma suspension is irradiated with ultraviolet A (UVA) light and then re-infused back into the patient.</p> <p>Extracorporeal photopheresis will be administered using the CELLEX System and UVADEX (methoxsalen) Sterile Solution in the mode of administration recommended by the approved labeling for UVADEX (methoxsalen) Sterile Solution, except for the treatment frequency. ECP will be administered by trained ECP operators only.</p> <p style="padding-left: 40px;">Extracorporeal photopheresis will be administered as follows:</p>

	<ul style="list-style-type: none"> • Weeks 1-4: 3 treatments per week. • Weeks 5-12: 2 treatments per week. <p>Week 1 (7 days) begins when the first ECP treatment is received (Day 1 of Week 1). The availability of typed and cross-matched donor PRBCs for transfusion during treatment, if needed, should be established prior to the scheduling of ECP treatments.</p> <p>Extracorporeal photopheresis treatments given within \pm 2 days of the expected treatment week will not be considered a protocol deviation.</p> <p>Patients must be enrolled and receive their first ECP treatment within 1 week (7 days) after being diagnosed as having steroid-refractory aGvHD.</p> <p>All patients will be evaluated for a response in their aGvHD manifestations at least once each week through Week 12, or the visit at which a patient ceases to receive treatment, if before Week 12. The assessment of aGvHD status should occur after the last ECP treatment of the week has been completed.</p> <p>Principal Investigators should consult Appendix D: Fluid Balance Management and the CELLEX System Operator's Manual for information on minimum hematocrit and extracorporeal volume.</p> <p>It is anticipated that most patients will receive ECP treatments in this protocol via a central venous catheter. However, Principal Investigators may choose to administer ECP treatments via peripheral venous access if clinically prudent.</p>
Study assessments	<p>Grading and Assessment of aGvHD:</p> <ul style="list-style-type: none"> • Acute GvHD will be assessed for each organ system by the treating physician, and source data will be collected for each patient and entered into the eCRF. A scoring algorithm will then be applied to calculate the grade of aGvHD using the modified IBMTR Severity Index and the modified Glucksberg criteria. Acute GvHD status will be assessed at screening and once per week throughout the Treatment and at each Follow-up Period by the treating physician. • The formal statistical analysis and evaluation of response is based on at least 4-weeks of ECP treatment only. <p>Cumulative Steroid Dose:</p> <p>Cumulative daily steroid dose from diagnosis of aGvHD along with all other concomitant medications will be recorded every week during the Treatment Period (Week 12).</p> <p>Adverse Events:</p> <p>Adverse events will only be recorded from ICF signing until Week 16. Following Week 16, there will be a passive chart review which will not include the collection of AEs.</p> <p>Treatment Failure:</p> <p>Treatment failure is defined as the addition of next-line systemic therapy for the treatment of aGvHD. Next-line treatment is defined as any additional systemic treatment not used for initial treatment of aGvHD, or for prophylaxis. Next-line treatment also includes an increase in steroid dose to $>$ 2.0 mg/kg/day of methylprednisolone equivalents because of a flare during steroid tapering. A flare is defined as any increase in aGvHD symptoms after an initial response (CR or PR).</p>
Power and sample size	<p>A total of 48 patients with steroid-refractory grade B-D aGvHD will be enrolled and receive at least one ECP treatment. The trial is designed to test the null hypothesis that standard therapy has an overall response (CR+PR)</p>

	<p>rate of 10% versus the alternate hypothesis that ECP plus standard therapy has a CR+PR rate not equal to 10% (the expected rate $\geq 27\%$). The overall Type I error rate and power for this design are 5% and 90.4%, respectively.</p> <p>This single-arm trial will have 1 interim analysis and a final analysis. After the first 24 patients enrolled into the study have completed at least 4 weeks of ECP treatment, significance will be declared if the CR+PR 2-sided <i>P</i> value vs the stated alternative is < 0.005, corresponding to an observed CR+PR rate $> 48\%$. A final analysis will be performed after all 48 patients enrolled into the study have been treated for at least 4 weeks. In this final analysis, significance will be declared if the CR+PR 2-sided <i>P</i> value vs the stated null is < 0.049.</p>
Statistical methods	<p>All baseline demographic and disease characteristics will be summarized. The primary endpoint of overall response (CR+PR) at Day 28 (Week 4) will be summarized by frequency tabulation and analyzed using exact Binomial test and confidence interval. Secondary endpoints of response at Week 8 (Day 56) and Week 12 (Day 84) will be analyzed in the same manner. Other endpoint data collected in the Treatment and Follow-up Period will be summarized appropriately.</p> <p>All AE data will be fully listed by investigator terms and Medical Dictionary for Regulatory Activities (MedDRA) preferred term. Adverse event data will be summarized by system organ classification and preferred term. Vital signs and laboratory values will be summarized by visit and numbers of patients, with excursions outside the normal reference range summarized.</p> <p>Patients who voluntarily cease to receive treatment early will not be replaced. Patients may be replaced if they are enrolled in the trial but are not treated. If a patient has received any ECP treatments and is administered a second-line therapy other than ECP, or discontinues study treatment, that patient will be considered a nonresponder and may not be replaced.</p>

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LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

ACD-A	Anticoagulant citrate dextrose formula-A
AE	Adverse event
aGvHD	Acute graft-vs-host disease
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BSA	Body surface area
BUN	Blood urea nitrogen
CBC	Complete blood count
cGvHD	Chronic graft-vs-host disease
CR	Complete response
CTCAE	Common Terminology Criteria for Adverse Events
CTCL	Cutaneous T-cell lymphoma
CVL	Central venous line
DRL	Drug Reference List
DSMB	Data Safety Monitoring Board
ECP	Extracorporeal photopheresis
eCRF	Electronic case report form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GvHD	Graft-vs-host disease
HCG	Human chorionic gonadotropin
HIV	Human immunodeficiency virus
HSCT	Hematopoietic stem cell transplantation
IBMTR	International Bone Marrow Transplant Registry
ICF	Informed consent/assent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional Review Board
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary of Regulatory Activities
NIH	National Institutes of Health
OR	Overall response
PR	Partial response
PRBCs	Packed red blood cells
PT/PTT	Prothrombin time/partial thromboplastin time
SAE	Serious adverse event
SUSAR	Suspected unexpected serious adverse reaction
Treg	Regulatory T cell
UVA	Ultraviolet A
WBC	White blood cell

VGPR	Very good partial response
WHO	World Health Organization

1. INTRODUCTION

1.1 BACKGROUND

Graft-vs-host Disease

Graft-vs-host disease is the major complication of allogeneic hematopoietic stem cell transplantation (HSCT), in which newly transplanted donor T cells recognize and attack host histocompatibility antigens on the transplant recipient's organs [Ferrara et al., 2009]. Graft-versus-host disease is clinically separated into an acute form (aGvHD) and a chronic form (cGvHD) that were historically defined as GvHD before or after Day 100, respectively. Advances in HSCT practice have altered the presentation and natural history of aGvHD and cGvHD; therefore, clinical manifestations and histologic findings are now used to differentiate between the 2 diseases [Filipovich et al., 2005]. Acute GvHD can present as classic aGvHD (occurring within 100 days after transplant) or as persistent, recurrent, or late-onset aGvHD (occurring more than 100 days after transplant), without diagnostic or distinctive signs of cGvHD [Hart et al., 2013].

Incidence rates of aGvHD in adults range from 10% to 80% following allogeneic HSCT, with symptoms typically presenting 2 to 3 weeks posttransplant [Garnett et al., 2013]. Acute GvHD also occurs in a substantial proportion of children. Reports from large pediatric transplant studies have demonstrated a cumulative incidence of grade II-IV aGvHD ranging from 28% to 56% [Giebel et al., 2003, Rocha et al., 2000, Kanold et al., 2003]. While bone marrow is predominantly used as the source for HSCT in pediatric patients, the risk of aGvHD is greater when alternative donor sources are used, including unrelated cord blood and peripheral blood stem cells [Jacobsohn, 2008].

A recent study evaluating the risk and prognostic factors for development of aGvHD based on the National Institutes of Health (NIH) consensus criteria found that the incidence of aGvHD in patients (N = 775) who underwent allogeneic HSCT was 44.7% overall [Lee et al., 2013]. Among patients with aGvHD, classic presentation was associated with lower survival than late-onset ($P = 0.044$). Additionally, more pronounced disease (e.g., visceral organ involvement [$P = 0.002$], severity at onset [$P = 0.035$], and advanced disease [$P < 0.001$]) were significantly associated with lower survival [Lee et al., 2013]. Acute GvHD is also an important risk factor for the later development of cGvHD. The primary target organs of aGvHD are skin, gut, and liver, and disease severity is graded from I to IV [Przepiorka et al., 1995] using the modified Glucksberg criteria, or from A to D [Rowlings et al., 1997] using the International Bone Marrow Transplant Registry (IBMTR) Severity Index. The grade of aGvHD correlates to overall survival, as an analysis of 1,294 patients receiving an allogeneic transplant for chronic myelogenous leukemia demonstrated that transplant-related mortality for aGvHD grades 0 to IV was 28%, 27%, 43%, 68%, and 92%, respectively, with a distinct separation between grades 0 to I and II to IV [Gratwohl et al., 1995]. In a retrospective comparison of the IBMTR Severity Index with the Glucksberg criteria in 2,129 patients receiving cyclosporine and methotrexate for GvHD prophylaxis, the relative risk of treatment failure for grade A to D was 0.85, 1.21, 2.19, and 5.68, respectively [Rowlings et al., 1997]. Patients with grade A aGvHD have a similar risk of treatment failure compared with patients without aGvHD, and those with grade B to D aGvHD have incrementally increased risks [Rowlings et al., 1997]. Furthermore, patients with grade IV aGvHD have a markedly increased transplant-related mortality compared with grades 0 to III

[Gratwohl et al., 1995], and grade D patients have decreased leukemia-free survival compared with grades A to C [Rowlings et al., 1997].

Although the treatment of aGvHD with corticosteroids has long been accepted as a first-line systemic therapy, a complete response (CR) to first-line systemic corticosteroids was observed in only 20% (92/456) of evaluable patients with aGvHD in a retrospective study (median age [range] of entire patient population, 23 years [0.8 to 62]) [Martin et al., 1990]. Steroids are associated with a number of side effects, including immunosuppression, hyperglycemia, osteopenia, and avascular bone necrosis [Garnett et al., 2013], and long-term use of these agents can cause growth retardation and delayed puberty in pediatric patients [Lawitschka et al., 2012]. Current research evaluating second-line agents based on a number of clinical endpoints does not support or exclude any of these agents from consideration as a second-line therapy for steroid-refractory aGvHD [Martin et al., 2012].

The pathophysiology of aGvHD is thought to involve excessive inflammation caused by activation of alloreactive donor T cells [Ferrara et al., 1996]. Modulation of this reaction by means other than medication could provide benefit in the GvHD population. Extracorporeal photopheresis in combination with conventional corticosteroids is a second-line option for patients with aGvHD. This is an especially promising approach for the pediatric patient population due to the toxic effects of prolonged treatment with steroids or other immunosuppressive agents currently used for the treatment of aGvHD.

Extracorporeal Photopheresis

Extracorporeal photopheresis is a leukapheresis-based immunomodulatory therapy indicated for the palliative treatment of skin manifestations in patients with cutaneous T-cell lymphoma (CTCL) unresponsive to other forms of treatment [Ferrara et al., 1996]. Extracorporeal photopheresis has been studied in a number of other autoimmune-mediated disorders, including acute and chronic GvHD in both adult and pediatric patients, rejection after solid organ transplantation, systemic sclerosis, Crohn's disease, and type 1 diabetes [Knobler et al., 2014].

Extracorporeal photopheresis consists of the *ex vivo* exposure of autologous peripheral leukocytes to UVADEX[®] (methoxsalen) Sterile Solution and UVA irradiation, followed by reinfusion of the cells to the patient. Photoactivated UVADEX (methoxsalen) Sterile Solution covalently binds to DNA, causing apoptosis of treated cells after reinfusion [Bladon and Taylor, 1999].

Systemic exposure to UVADEX (methoxsalen) Sterile Solution following extracorporeal photopheresis (ECP) is minimal. The total dose of methoxsalen used to inoculate cells in conjunction with the THERAKOS integrated system is less than 1/200th of the oral dose. Plasma levels obtained as part of other clinical studies have shown no detectable level (< 10 ng/mL) 30 minutes after reinfusion of the treated cell suspension containing the UVADEX (methoxsalen) Sterile Solution in > 80% of patients [Moon et al., 2014, Therakos Inc., 2013].

Evidence from preclinical and clinical studies supports a role for systemic immunomodulation as the mechanism of action in GvHD patients treated with ECP. Broadly, the complex mechanism by which ECP induces immunomodulation in GvHD can be described by its effects on shifting the immunologic milieu from a pro-inflammatory, type 1 T-helper cell (Th1)-mediated response to an anti-inflammatory, type 2 T-helper cell (Th2)-mediated environment, and inducing a degree

of lasting immune tolerance via upregulation of regulatory T cells (Tregs) [Bruserud et al., 2014].

Extracorporeal photopheresis has been studied as a second-line treatment for acute and chronic GvHD, although the majority of studies have been small and retrospective in nature. In a prospective Phase 2 study of ECP as second-line therapy in 59 adult patients with aGvHD, a CR after 3 months of ECP treatment was observed in 82% of patients with skin involvement and in 61% of patients with either liver or gut involvement [Greinix et al., 2006]. Furthermore, patients achieving a CR had a significantly higher overall 4-year survival compared with those who did not achieve a CR (59% versus 11%, $P < 0.0001$) [Greinix et al., 2006]. A more recent retrospective study demonstrated an overall response (complete+partial response; CR+PR) of 66% and a CR of 54% in 57 adult and pediatric patients receiving ECP for aGvHD [Jagasia et al., 2013]. In a retrospective study of 33 pediatric patients treated with ECP for aGvHD, the overall response rate after a median of 8 treatments (range 2 to 20 treatments) was 76% and a CR was observed in 76%, 75%, and 60% of patients with skin, gut, and liver involvement, respectively [Messina et al., 2003]. Furthermore, the 5-year overall survival was significantly better in ECP responders compared with nonresponders (69% versus 12%, $P = 0.001$) [Messina et al., 2003]. Extracorporeal photopheresis is well tolerated, with an excellent safety profile in children and adults. In a prospective analysis of 27 children who underwent ECP for acute ($n = 12$) or chronic ($n = 15$) GvHD, clinical adverse events (AEs) were observed in 11% and 9% of patients, respectively; no infectious events could be attributed to the ECP procedure [Kanold et al., 2007]. Furthermore, no significant differences in clinical tolerance were found in 8 GvHD patients with low body weight (< 25 kg) versus other patients [Kanold et al., 2007].

A number of factors should be considered when performing ECP on pediatric patients. Several studies have emphasized that the use of ECP in children presents specific challenges, including low body weight, vascular access, extracorporeal volume, metabolic and hematologic problems, and psychological tolerance [Messina et al., 2003, Kanold et al., 2007, Schneiderman et al., 2010]. The newer CELLEX[®] System is equipped with continuous flow separation that reduces treatment times and extracorporeal volumes compared with the UVAR XTS[®] System [Bohbot et al., 2012, Kapadia et al., 2015] and has also been shown to treat an increased percentage of mononuclear cells and reduce the incidence of patient-related complications compared with the UVAR XTS System based on a retrospective chart review of 10 patients with steroid-refractory acute or chronic GvHD [Kapadia et al., 2015]. Although the optimal treatment schedule and duration of ECP treatment have yet to be established, aGvHD patients are routinely administered ECP 2 to 3 times a week initially, followed by progressive tapering. Early initiation of ECP has also been associated with better outcomes [Gonzalez Vicent et al., 2010]. Clinical practice guidelines recommend ECP as first-line therapy for pediatric patients with grade IV aGvHD along with conventional immunosuppressants, and as second-line therapy for grade II to III steroid-refractory aGvHD [Kanold et al., 2007].

The safety, tolerability, and efficacy of the CELLEX System alone have also recently been investigated [Rangarajan et al., 2013, Uygun et al., 2014]. Rangarajan et al reported on the safety of 385 ECP procedures performed in 9 children and young adults treated for acute or chronic GvHD [Rangarajan et al., 2013]. The median age was 13.5 years (range, 3.7 to years) and median weight was 49.2 kg (range, 18.5 to 86.3 kg). The mean duration per procedure was 106 minutes (range, 60 to 205 minutes). The study reported 1 episode of central venous line (CVL)-associated thrombosis and 1 episode of delayed bleeding. Furthermore, 4 episodes of viral

reactivation, 4 CVL-associated infections (over 1,142 catheter days), and 1 episode of systemic inflammatory response syndrome were reported. No patient experienced symptomatic hypotension or hypocalcemia [Rangarajan et al., 2013]. The study concluded that use of the CELLEX System for the treatment of children and young adults with GvHD was safe and well tolerated.

Uygun et al reported on 12 pediatric patients with aGvHD, cGvHD, or overlap syndrome [Uygun et al., 2014]. The age of patients with aGvHD ranged from 1.5 to 12 years, and weight ranged from 7 to 68 kg. Improvement was observed in 70% of aGvHD patients (7/10, including 4 patients with overlap syndrome) and in 66% of cGvHD patients (4/6, including 4 patients with overlap syndrome), and the initial response to ECP was observed after a median of 4 treatments (range, 2 to 10). Nine of 11 patients with skin involvement and 5 of 8 patients with gastrointestinal (GI) involvement responded to treatment; all 4 patients with liver involvement failed to respond to ECP. No deterioration in general health conditions were observed, except in 1 patient who had GI GvHD with bloody diarrhea. The study concluded that the CELLEX System is a safe and effective treatment option for pediatric patients [Uygun et al., 2014].

2. STUDY OBJECTIVES

2.1 PRIMARY OBJECTIVE

- To evaluate the efficacy of ECP in pediatric patients with steroid-refractory aGvHD.

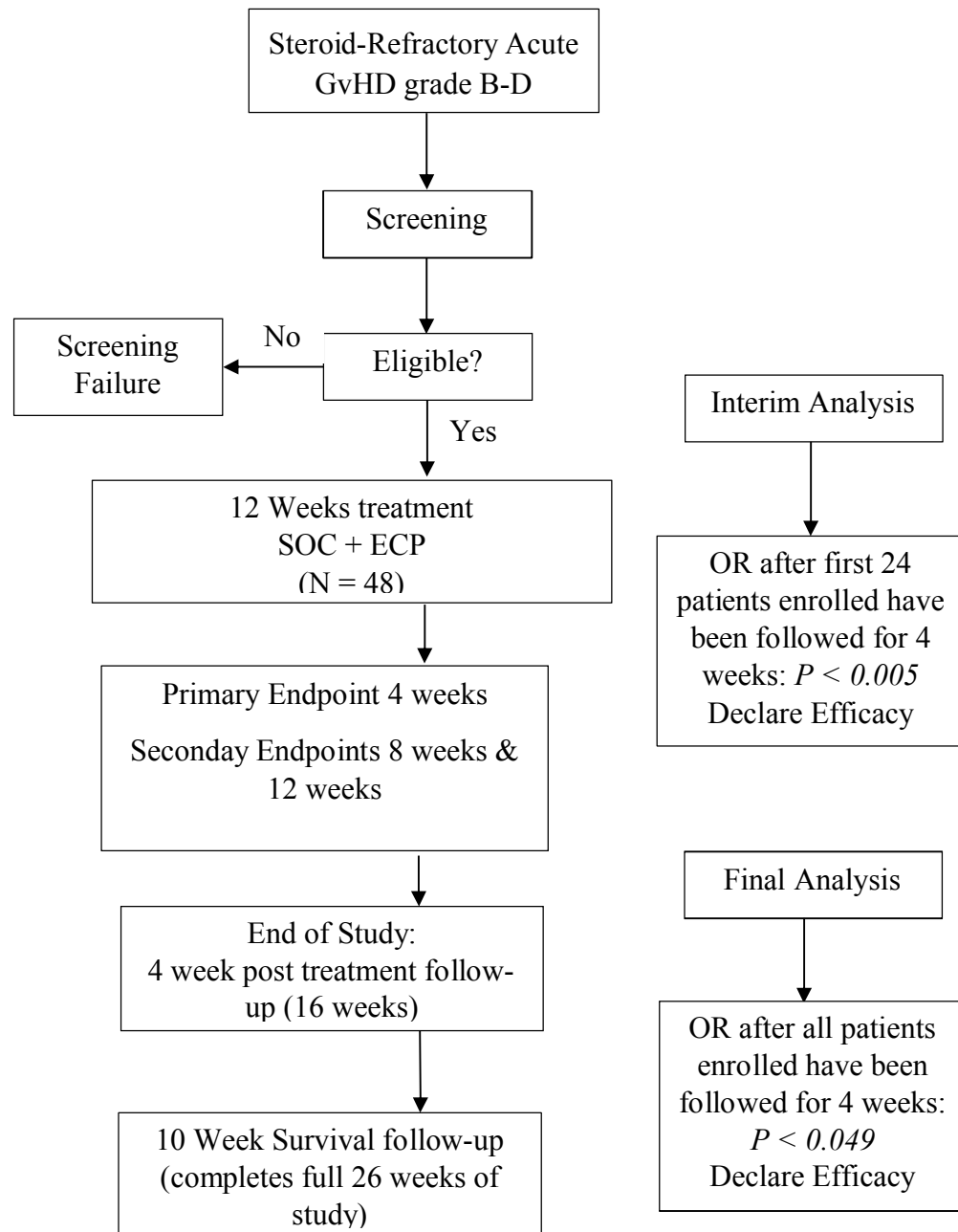
2.2 SECONDARY OBJECTIVES

- To assess the safety of ECP.
- To assess the duration of response to ECP.
- To assess the steroid-sparing effect of ECP.
- To assess the organ-specific response to ECP.

3. OVERALL DESIGN AND PLAN OF THE STUDY

This is a single-arm, open-label, multicenter study to demonstrate the efficacy of UVADEX (methoxsalen) Sterile Solution in conjunction with the THERAKOS CELLEX Photopheresis System in pediatric patients with steroid-refractory aGvHD having received the existing standard of care (Figure 1).

Figure 1. Study Schematic



ECP, extracorporeal photopheresis; GvHD, graft versus host disease; OR, overall response.

3.1 OVERVIEW

Screening will occur in a single visit during which patients will be evaluated for eligibility and for the grading of aGvHD. Patients with steroid-refractory aGvHD grade B-D who meet the eligibility criteria will be treated with UVADEX (methoxsalen) Sterile Solution in conjunction with the CELLEX System. Patients must be enrolled and receive their first ECP treatment within 1 week (7 days) after being diagnosed as having steroid-refractory aGvHD. Patients are expected to receive the stated number of ECP treatments per treatment week (7 days) \pm 2 days, and a total of no more than 12 ECP treatments for the first 28 days. A maximum of 28 ECP treatments will be given per patient during the 12-week treatment period. Conventional steroids will continue to be administered and tapered based on a sustained response to ECP. The primary endpoint is the proportion of patients reaching an overall response (CR+PR) after 4 weeks (Day 28) of ECP treatment, or fewer treatments if they discontinued treatment, regardless of steroid tapering.

The addition of next-line systemic therapy for aGvHD will be considered a treatment failure. Next-line treatment is defined as any additional systemic treatment not used for initial treatment of aGvHD, or for prophylaxis. Next-line treatment also includes an increase in steroid dose to > 2.0 mg/kg/day of methylprednisolone equivalents because of a flare during steroid tapering. A flare is defined as any increase in aGvHD symptoms after an initial response (CR or PR). Patients will be allowed to continue standard aGvHD prophylaxis regimens (e.g., cyclosporine, tacrolimus, methotrexate, and mycophenolate mofetil) without the addition of new therapies. Patients will be allowed to discontinue prophylaxis regimens for reasons of toxicity, and will also be allowed to switch to another prophylaxis medication within the same class (e.g., the calcineurin inhibitors cyclosporine and tacrolimus) for reasons of toxicity.

After completion of the 12-week Treatment Period, patients may continue ECP treatment on commercial product at the discretion of the Principal Investigator. Acute GvHD status will be assessed 4 weeks after completion of the Treatment Period, and survival will be assessed by passive follow-up (chart review) 26 weeks after initiation of ECP treatment.

3.2 ENDPOINTS

3.2.1 Primary Endpoint

- The proportion of patients who achieve an overall response (CR+PR) after 4 weeks (Day 28) of ECP treatment, or fewer treatments if they discontinued treatment
 - Patients will be evaluated by the treating physician for the presence or absence of aGvHD manifestations of the skin, liver, and gut. Source data will be collected for each patient and entered into the electronic Case Report Form (eCRF) and a scoring algorithm will be applied to calculate the aGvHD grade using the modified IBMTR Severity Index ([Appendix A: Modified IBMTR Severity Index](#)). Patients weighing < 50 kg will be evaluated according to a modified version of the IBMTR criteria that accounts for stool output on an mL/kg/day basis.

3.2.2 Secondary Endpoints

- Safety parameters including vital signs, laboratory tests, and spontaneously reported AEs and SAEs.

- Proportion of patients who achieve an overall response 8 weeks (Day 56) and 12 weeks (Day 84) after initiation of ECP treatment.
- Duration of response (defined as the length of time a patient maintains a response through Week 16 of the Follow-up Period on a per-patient basis).
- Proportion of patients who achieve an overall response after 4 weeks (Day 28), 8 weeks (Day 56), and 12 weeks (Day 84) of ECP treatment according to the modified Glucksberg criteria ([Appendix B: Modified Glucksberg Criteria](#)).
 - Source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified Glucksberg Criteria.
- Cumulative dose of daily steroids administered from diagnosis of aGvHD to 12 weeks (Day 84) after initiation of ECP treatment.
- Organ-specific grade at 4 weeks (Day 28), 8 weeks (Day 56), and 12 weeks (Day 84) after initiation of ECP treatment.

3.2.3 Exploratory Endpoints



3.3 CRITERIA FOR DEFINING RESPONSE

The criteria for defining response are as follows:

- Overall response: CR + PR
 - CR: complete resolution of all signs and symptoms of aGvHD in all evaluable organs without addition of next-line systemic treatment.
 - PR: improvement of 1 stage in 1 or more aGvHD target organs without progression in others and without addition of next-line systemic treatment (see [Section 3.1](#) for information regarding next-line treatment).
- No response: Mixed Response or Stable Disease or Progression
 - Mixed Response: at least 1 stage improvement of at least 1 organ, with at least 1 stage worsening in at least 1 other organ.
 - Stable Disease: no significant change in any organ system.
 - Progression: worsening in 1 or more organs by 1 or more stage without improvement in any involved organ.
- Very good partial response (VGPR) [[Martin et al., 2009](#)]:
 - Skin: no rash, or residual erythematous rash involving < 25% of the body surface, without bullae (residual faint erythema and hyperpigmentation do not count).

- Liver: total serum bilirubin concentration < 2 mg/dL or < 25% of baseline at enrollment.
- Gut: tolerating food or enteral feeding, predominantly formed stools, no overt GI bleeding or abdominal discomfort, and no more than occasional nausea or vomiting.

3.4 RATIONALE FOR THE STUDY DESIGN

Although the treatment of aGvHD with corticosteroids has long been accepted as a first-line systemic therapy, a durable CR to corticosteroids has been reported in only 24% to 40% of aGvHD patients [Greinix et al., 2006]. There is also an unmet need in patients with steroid-refractory aGvHD, as many of the second-line treatment options are associated with infrequent durable response rates and increased risk of life-threatening infection and viral reactivation [Martin et al., 2012]. Furthermore, long-term use of steroids can cause growth retardation and delayed puberty in pediatric patients [Lawitschka et al., 2012]. There are currently no approved agents for the treatment of aGvHD. However, in clinical practice guidelines and expert consensus recommendations, ECP is recommended as second-line therapy in combination with corticosteroids for patients with steroid-refractory aGvHD [Dignan et al., 2012, Das-Gupta et al., 2014a], including pediatric patients [Kanold et al., 2007, Pierelli et al., 2013, Bredeson et al., 2014].

The clinical efficacy that has been reported in the literature on the use of ECP in pediatric patients with steroid-refractory aGvHD, as previously described, has provided the rationale for further investigation of this treatment approach in these patients. This single-arm trial will be the first prospective, multicenter investigation of ECP in pediatric patients with steroid-refractory aGvHD. Guidance received from the U.S. Food and Drug Administration (FDA) indicated that a single-arm trial that shows a meaningful rate of durable response in an endpoint reasonably likely to predict clinical benefit in a population with no available therapy could support an application for accelerated approval. The primary endpoint of overall response (CR+PR) after 4 weeks (28 days) of ECP treatment was chosen because this has been qualified as reasonably likely to predict long-term outcomes for steroid-refractory aGvHD [MacMillan et al., 2002, Levine et al., 2008, Inamoto et al., 2014]. Two interim analyses will occur after approximately 1/3 (N=19) and 2/3 (N=38) of the patients have completed at least 4 weeks of ECP treatment, or fewer treatments if they discontinued treatment, for steroid-refractory aGvHD. Standard therapy has an overall response (CR+PR) rate of 10%.

3.5 RISK/BENEFIT RATIO

Pediatric patients with steroid refractory aGvHD are an underserved patient population for whom there is a lack of controlled data on the risks associated with treatment options. Current therapies used for the treatment of steroid refractory aGvHD have ranged from increasing the dose of steroids, to the addition of polyclonal or monoclonal antibodies, or additional immunosuppressive/chemotherapeutic interventions. These therapies are associated with high rates of infection, including invasive fungal, bacterial, and viral infections. In addition to immunosuppression, the use of steroids in pediatric patients is associated with a number of serious and oftentimes lasting side effects including: hyperglycemia, osteopenia, and avascular bone necrosis [Garnett et al., 2013].

The UVADEX with CELLEX technology being evaluated in this trial has a well-established safety profile based on both post-marketing data and off-label pediatric use. In addition, there is

published literature that suggests that ECP has effectiveness and tolerability in the steroid refractory pediatric aGvHD patient population.

The benefit of this proposed trial is to evaluate a safety and efficacy of a promising alternative treatment for the treatment of pediatric patients with aGvHD. A further benefit of the proposed trial is the opportunity to produce validated results for this rare disease by collecting controlled data from multiple international sites.

4. STUDY POPULATION

4.1 INCLUSION CRITERIA

Males and females 1 to 21 years of age who have steroid-refractory grade B-D aGvHD. Steroid-refractory is defined as a failure to respond to steroid treatment, with failure to respond defined as any grade B-D (IBMTR grading) aGvHD that shows progression ≥ 3 days or no improvement by 5 days, of treatment with 2 mg/kg/day methylprednisolone or equivalent in patients with lower GI or liver disease, or skin disease associated with bullae. Grade D organ involvement will be limited to skin and liver. Steroid refractory may also be defined as a failure to respond to 1 mg/kg/day of methylprednisolone or equivalent in patients with disease confined to upper GI disease or lesser degrees of skin GvHD.

Patients must meet all of the following criteria:

1. Male or female 1 to 21 years of age at the time of consent
2. Steroid-refractory grade B-D aGvHD.
 - Steroid-refractory is defined as a failure to respond to steroid treatment, with failure to respond defined as any grade B-D (IBMTR grading) aGvHD that shows progression ≥ 3 days, or no improvement by 5 days of treatment with 2 mg/kg/day methylprednisolone or equivalent in patients with lower GI or liver disease, or skin disease associated with bullae. Grade D organ involvement will be limited to skin and liver.
 - Steroid refractory may also be defined as a failure to respond to 1 mg/kg/day of methylprednisolone or equivalent in patients with disease confined to upper GI disease or lesser degrees of skin GvHD.
 - Patients with lack of complete response after 2 weeks of steroid treatment.
3. A Lansky scale Performance Status score ≥ 30 .
4. Laboratory values are within the following limits, assessed within 3 days of the first study treatment:
 - Absolute neutrophil count $> 0.5 \times 10^9/L$.
 - Creatinine level < 2 times the upper limit of normal.
5. For patients with isolated upper GI symptoms, pre-Screening biopsy results to confirm diagnosis of aGvHD.
6. Female patients of childbearing potential and nonsterilized males who are sexually active with a female partner must be practicing highly effective, reliable, and medically approved contraceptive regimen throughout their participation in the study and for 3 months following the last ECP treatment. Or, for the US only, abstinence may be used in place of an approved contraceptive regimen. Females of childbearing potential are those who have reached the onset of menarche, or 8 years of age, whichever comes first. Approved contraceptive methods for female patients of childbearing potential or nonsterilized males who are sexually active with a female partner are as follows:
 - Barrier methods of contraception: condom or occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository.
 - Established use of oral, injectable, or implanted hormonal methods of contraception.
 - Placement of an intrauterine device or intrauterine system.

7. Signed informed consent/assent is obtained before conducting any study procedures; the parent, legal guardian, or legally authorized representative of a minor must also provide written informed consent.

4.2 EXCLUSION CRITERIA

Any of the following would exclude the patient from participation in the study:

1. Currently enrolled in another clinical trial for the treatment of aGvHD.
2. Use of any experimental regimens or medication(s) for aGvHD treatment.
3. Treatment with > 2.0 mg/kg/day of methylprednisolone equivalents for aGvHD within 30 days prior to the first study treatment.
4. Overt signs of relapse of the underlying condition.
5. Uncontrolled viral, fungal, or bacterial infection.
6. Platelet count $< 20.0 \times 10^9/L$, despite platelet transfusion.
7. Total bilirubin value ≥ 15 mg/dL.
8. Inability to tolerate the extracorporeal volume shifts associated with ECP treatment.
9. Uncontrolled GI bleeding.
10. Veno-occlusive liver disease.
11. Life expectancy < 4 weeks.
12. Patient requires invasive ventilation or vasopressor support.
13. Known human immunodeficiency virus (HIV) or hepatitis B or C virus infection (proof of seronegativity within 6 months of screening is required).
14. Known allergy or hypersensitivity to methoxsalen, Uvadex, or its excipients.
15. Known hypersensitivity and allergy to heparin and Anticoagulant Citrate Dextrose Formula-A (ACD-A).
16. Co-existing photosensitive disease (e.g., porphyria, systemic lupus erythematosus, albinism) or aphakia.
17. Coagulation disorders that cannot be corrected with simple transfusion.
18. Co-existing melanoma, basal cell, or squamous cell skin carcinoma.
19. Previous splenectomy.
20. White blood cell count greater than $25,000 \text{ mm}^3$.
21. Currently being treated with any systemic immunosuppressive or biologic therapy for the treatment of a medical condition other than aGvHD.
22. Female patient is breastfeeding or pregnant.
23. Any medical concerns that may pose risk to the patient.
24. Any psychological, familial, sociological, and/or geographical condition that may potentially hamper compliance with the study protocol and follow-up schedule.

5. STUDY PRODUCT

5.1 IDENTITY

UVADEX (methoxsalen) Sterile Solution will be supplied by Therakos, Inc. at no cost.

5.1.1 UVADEX (methoxsalen) Sterile Solution

The active ingredient in UVADEX (methoxsalen) Sterile Solution is 8-methoxypsoralen (methoxsalen). Methoxsalen is a naturally occurring photoactive substance found in the seed of the *Ammi majus* (umbelliferae plant). It belongs to a class of compounds known as psoralens or furocoumarins. The chemical name is 9-methoxy-7H-furo[3,2-g][1]-benzopyran-7-one. The formulation of the drug is a sterile liquid at a concentration of 20 µg/mL in a 10-mL vial. A complete description of the pharmacokinetic activity of methoxsalen is available in the Investigator's Brochure.

Adverse events associated with the ECP process during CTCL clinical trials in adult patients include venous access complications, transient fever and worsening of the underlying CTCL skin rash, and transient hypotension associated with hypovolemia. A complete description of the AEs documented in studies using UVADEX (methoxsalen) Sterile Solution is provided in the Investigator's Brochure.

UVADEX (methoxsalen) Sterile Solution is currently approved and marketed in the United States, Canada, United Kingdom, Germany, France, Denmark, Italy, and Austria for use in the palliative treatment of the skin manifestations of CTCL unresponsive to other therapies. The safety of UVADEX (methoxsalen) Sterile Solution has not been established in the pediatric population.

5.2 PACKAGING, LABELING, AND STORAGE

UVADEX (methoxsalen) Sterile Solution is packaged in 10-mL, 13-mm, U.S. Pharmacopeia Type I borosilicate amber glass vials. The closure is a 13-mm, gray butyl rubber stopper laminated with 0.1-mm fluorocarbon polymer film. A 13-mm aluminum flip-off cap, with a clear lacquer foil and purple plastic flip-off button, is used to seal the stoppered vials. UVADEX (methoxsalen) Sterile Solution must be stored at between 15°C and 30°C (U.S. labeling) or < 25°C (European labeling). UVADEX (methoxsalen) Sterile Solution will be labeled according to country-specific guidelines and language and will be labeled as "Investigational Product."

5.3 DRUG AND DEVICE ACCOUNTABILITY

5.3.1 Shipment and Receipt

Clinical supplies, including UVADEX (methoxsalen) Sterile Solution and CELLEX System Procedural Kits (DAK), will be initially shipped and re-supplied automatically through the Interactive Web Response System (IWRS). Once a shipment has been initiated, the site designee will receive an email notification with the contents and tracking number of the incoming shipment.

When clinical supplies, including UVADEX (methoxsalen) Sterile Solution and CELLEX System Procedural Kits (DAK), are received at each study site, the receipt of supplies should be confirmed within the IWRS. This receipt will include the total number of supplies received, the

date received, and the condition of the supplies at time of receipt. The supplies should also be recorded on the Investigational Drug and Device Log, respectively. This receipt is to be confirmed by a staff member appointed by the Principal Investigator to account for investigational supplies. The packing list of this shipment should be kept at the site and filed with the Investigational Drug/Device Log.

Note: UVADEX must be stored in a temperature controlled setting upon receipt as soon as possible. If this does not occur ≤ 1 week from the ship date, the product will be invalid.

In the event that drug or devices do not arrive at a study site, the [REDACTED] study monitor should be notified immediately. If the number of investigational products received at a site does not correspond with the number indicated on the packing list, this should be confirmed in the IWRS.

5.3.2 Accountability Logs

An accurate record of all supplies received and used at each site should be maintained and updated regularly. The use of CELLEX System Procedural Kits will be recorded on the Investigational Device Inventory Log. UVADEX (methoxsalen) Sterile Solution use will be recorded on the Investigational Drug Log. In the event that study drugs or devices are damaged, an account should be made on the appropriate log and in the IWRS system.

At the conclusion of the study, all remaining CELLEX System Procedural Kits must be returned to the [REDACTED] or destroyed at the site according to the Clinical Monitoring Plan. Once all study products have been accounted for and verified by Therakos, Inc. or its designated agent, unused vials of UVADEX (methoxsalen) Sterile Solution will be destroyed.

6. TREATING THE PATIENT

6.1 INSTRUMENTS

A CELLEX System must be available for treatment of study patients for the duration of the study. Each site must have personnel who are technically competent in performing ECP.

6.1.1 Packaging, Labeling, and Storage of Procedural Kits

CELLEX System Procedural Kits will be supplied by Therakos, Inc. at no cost. CELLEX System Procedural Kits should be stored in a secure location, at room temperature. All supplied kits are labeled with “Clinical Trial Use Only.”

6.2 UVADEX ADMINISTRATION

Extracorporeal photopheresis will be administered using the CELLEX System and UVADEX (methoxsalen) Sterile Solution in the mode of administration recommended by the approved labeling for UVADEX (methoxsalen) Sterile Solution, except for the treatment frequency. ECP will be administered by trained ECP operators only.

During the ECP process, UVADEX (methoxsalen) Sterile Solution will be injected directly into the recirculation bag (each mL of solution contains 20 µg of methoxsalen) of the extracorporeal circuit after completion of the buffy coat collection, immediately before initiating photoactivation. The dose of UVADEX (methoxsalen) Sterile Solution used to inoculate these cells will be calculated according to the CELLEX System Operator’s Manual based on the treatment volume collected during the plasma/buffy coat collection process, using the following formula:

Treatment Volume, as displayed on the CELLEX System screen, in mL \times 0.017 = Dose of UVADEX (methoxsalen) Sterile Solution (in mL) required for administration into the recirculation bag. Each mL of solution contains 20 µg of methoxsalen.

After the cells are inoculated with UVADEX (methoxsalen) Sterile Solution, the buffy coat/plasma suspension is irradiated with ultraviolet A (UVA) light and then re-infused back into the patient.

For details on how patients should be treated, including information on minimum hematocrit and extracorporeal volume, Principal Investigators should consult the CELLEX System Operator’s Manual and [Appendix D: Fluid Balance Management](#).

The selection and timing of ECP treatments is based on the Principal Investigator’s assessment of patient status such that ECP will be administered according to the stated treatment schedule (\pm 2 days). The availability of typed and cross-matched donor PRBCs for transfusion during treatment, if needed, should be established prior to the scheduling of ECP treatments.

It is anticipated that most patients will receive ECP treatments in this protocol via a central venous catheter. However, Principal Investigators may choose to administer ECP treatments via peripheral venous access if clinically prudent.

6.2.1 Selection of Timing and ECP Treatment in the Study

The selection and timing of ECP treatments is based on the Principal Investigator's assessment of patient status such that ECP will be administered 3 times per week every week for 4 weeks (Weeks 1-4), followed by 2 times per week every week for 8 weeks (Weeks 5-12).

Patients must be enrolled and receive their first ECP treatment within 1 week (7 days) after being diagnosed as having steroid-refractory aGvHD. Patients are expected to receive the stated number of treatments per treatment week (7 days) \pm 2 days, and a total of no more than 12 ECP treatments for the first 28 days. A maximum of 28 and a minimum of 1 ECP treatments will be given per patient during the 12-week treatment period.

Week 1 (7 days) begins when the first ECP treatment is received (Day 1 of Week 1). Extracorporeal photopheresis treatments given within \pm 2 days of the expected treatment week will not be considered a protocol deviation.

After completion of the 12-week Treatment Period, patients may continue ECP treatment on commercial product at the discretion of the Principal Investigator.

6.2.2 Extracorporeal Photopheresis Stop/Hold Parameters

- **STOP:** If there is evidence of anaphylaxis or life-threatening allergic reaction thought to be related to ECP. ECP must be discontinued and cannot be restarted.
- **STOP:** If there is evidence of an urgent or life-threatening medical issue requiring immediate treatment. ECP may be restarted, at the discretion of the Principal Investigator, if the event is considered to be unrelated to ECP and the patient has been stable for at least 24 hours.
- **HOLD:** If a patient experiences a fever, i.e. a skin temperature of $> 101.3^{\circ}\text{F}$ (38.5°C), that is related to infection, the ECP should not be given until 24 hours after the skin temperature has decreased to 101.3°F (38.5°C).
- **HOLD:** ECP should not be given within 72 hours of a positive blood culture, unless there is clinical suspicion of a contaminant (e.g., staph coagulase negative species) rather than a true infection and repeat cultures are negative within 24 hours of the positive sample.
- **HOLD:** ECP should not be given in the setting of sepsis or hemodynamic instability but held and rescheduled when the patient has been hemodynamically stable for at least 24 hours.
- **HOLD:** ECP should not be given if the patient has clinically significant bleeding within 12 hours of a planned ECP treatment.
- **HOLD:** ECP should not be given on the same days as surgical or invasive procedures, including colonoscopy. At the discretion of the Principal Investigator, bone marrow biopsy and other procedures associated with low risk of bleeding may be performed on the same day as ECP.

6.2.3 Extracorporeal Volume

The American Association of Blood Banks' guidelines set a maximum extracorporeal blood volume to be $\leq 15\%$ of the patient's Total Blood Volume. A new calculation of Total Blood Volume is necessary before each treatment to estimate the safe extracorporeal blood volume that may be allowed for the patient undergoing treatment. These calculations should be performed

using the current weight and current hematocrit (the latter drawn after the last photopheresis treatment and within 48 hours before the next photopheresis treatment).

Maximum extracorporeal blood volume for patients weighing < 30 kg should not exceed 10% of the patient's Total Blood Volume. Patients who do not meet the safe minimal extracorporeal volumes listed in [Appendix D: Fluid Balance Management](#) should only be treated using a blood prime procedure. Patients who require but are not candidates for blood priming should not be enrolled and/or treated in the study. Please refer to [Appendix E: Blood Prime Technique Flow Sheet](#) for a worksheet to be used during the blood prime process and to [Appendix D: Fluid Balance Management](#) for detailed information on fluid management.

6.2.4 Anticoagulation During ECP

Anticoagulant Citrate Dextrose Formula-A (ACD-A) may be used instead of or in addition to heparin during ECP at the physician's discretion according to the patient's medical needs, provided that center-specific guidelines for the use of ACD-A with ECP and trained staff are available. Centers using ACD-A must have physician-approved protocols in place for managing hypocalcemia, a side effect of ACD-A administration. Protocols should include:

- Monitoring of ionized calcium levels.
- Determination of maximum RETURN flow rate parameters.
- Oral and/or intravenous calcium replacement.

General guidelines for monitoring and treating citrate toxicity are available in [Appendix F: ACD-A Recommendations for the Therakos CELLEX Photopheresis System](#); however, institutional guidelines and the judgment of medical staff must be used to dictate the appropriate intervention.

6.3 CORTICOSTEROIDS

6.3.1 Selection and Timing of Corticosteroid Doses in the Study

All patients enrolled in this trial will have received corticosteroids for the treatment of aGvHD. After entering the treatment period on study, it is suggested that the steroid dose be decreased by 12.5% to 25% of the dose after the initiation of ECP therapy if a sustained positive response to aGvHD has been observed for at least 3 consecutive days. The suggested goal is to have decreased the starting steroid dose by at least 50% at 4 weeks after initiation of ECP.

For patients taking a steroid other than methylprednisolone for the treatment of aGvHD, the daily dose should be converted to methylprednisolone equivalents at screening (to ensure the patient qualifies). Note, the steroid type and dose should be entered into the eCRF without this conversion.

6.4 ACUTE GVHD PROPHYLAXIS

Patients will be allowed to continue standard aGvHD prophylaxis regimens (e.g., cyclosporine, tacrolimus, methotrexate, and mycophenolate mofetil), without the addition of new therapies. Patients will be allowed to discontinue prophylaxis regimens for reasons of toxicity and will also be allowed to switch to another prophylaxis medication within the same class (e.g., the calcineurin inhibitors cyclosporine and tacrolimus) for reasons of toxicity.

6.5 CONCOMITANT MEDICATIONS

Any medication the patient takes, including herbal and other nontraditional remedies, during the 16-week study is considered a concomitant medication. All concomitant medications must be recorded in the eCRF. The following information must be recorded in the eCRF for each concomitant medication: generic name, route of administration, start date, stop date, dosage (average daily dose is acceptable), and indication. Any changes in the dosage or regimen of a concomitant medication must be recorded in the eCRF.

At Screening, medications that patients have taken during the last 30 days, including current medications, will be recorded. Prior administration of immunosuppressive agents to treat aGvHD other than steroids is not permitted. The prior use of non-absorbable corticosteroids is permitted. All concomitant medications taken by patients during the study to Week 16, including those medications taken between visits, will be recorded on the Prior and Concomitant Medication Report Form of the eCRF.

6.5.1 Prohibited Concomitant Medications

Prohibited concomitant medications include those used for the treatment of aGvHD (with the exception of steroids), medications that are not considered part of a standard prophylactic regimen, and systemic immunosuppressive or biologic therapies used for the treatment of other medical conditions.

6.6 EARLY CESSATION OF STUDY PARTICIPATION

If the Principal Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions that suggest a risk to safe participation in the study, study treatment will be discontinued. If the Principal Investigator, based on his/her medical judgment, determines there is a risk to the patient with continued participation in the study, the patient will be withdrawn. The study may also be terminated early for all patients at the Sponsor's discretion. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study.
- Failure to enroll patients at an acceptable rate.
- A decision on the part of the Sponsor to suspend or discontinue development of the drug.
- Recommendation by the Data Safety Monitoring Board (DSMB).

6.6.1 Early Cessation of Study Treatment

Patients *may* voluntarily stop receiving therapy at any time. The patient's legal guardian/legally authorized representative may choose to stop a patient's therapy at any time.

If a patient voluntarily ceases to receive therapy, the primary reason must be requested and, if provided, will be recorded on the Study Termination page of the eCRF.

The Principal Investigator and/or the Sponsor may also judge that early cessation of treatment is warranted for any one of the following reasons:

- Occurrence of AEs that pose a risk to safe participation.

- Abnormal laboratory value(s) that pose a risk to safe participation.
- Abnormal test procedure result(s) that pose a risk to safe participation.
- Unsatisfactory therapeutic effect.
- Condition no longer requires treatment.
- Significant protocol deviation.
- Patient non-compliance with protocol requirements.

Unless a patient/legal guardian/legally authorized representative withdraws study consent, patients will continue to be followed as per the trial protocol and clinical assessment schedule to ensure that full, intent-to-treat follow-up data are obtained.

For patients who are lost to follow-up, the Principal Investigator should show due diligence by documenting in the source documents steps taken to contact the patient (e.g., dates of telephone calls, emails).

Patients who voluntarily cease to receive treatment early will not be replaced. Patients will be replaced if they are enrolled in the trial but are not treated.

If a patient has received any ECP treatments and is administered a second-line therapy other than ECP for the treatment of aGvHD, or discontinues study treatment, that patient will be considered a nonresponder and may not be replaced.

7. STUDY CONDUCT

7.1 SCHEDULE OF ASSESSMENTS

Table 1. Schedule of Assessments

Assessments and Procedures	Screening	Treatment Period, weeks (+/- 2 days)												Follow-Up Period, weeks		Early Study Termination
		1	2	3	4 (Day 28) Primary Endpoint	5	6	7	8 (Day 56) Secondary Endpoint	9	10	11	12 (Day 84) Secondary Endpoint	16	26	
Informed consent/assent form	X															
Inclusion/exclusion criteria	X															
Focused medical history	X															
Transplant history	X															
Corticosteroid dosing	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Complete physical examination	X				X				X				X	X		X
Targeted physical examination		X	X	X		X	X	X		X	X	X				
Urine Pregnancy test ^a	X	X	X	X	X	X	X	X	X	X	X	X	X			X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Lansky Performance Status	X				X				X				X	X		X
Local laboratory analyses ^b	X	X	X	X	X	X	X	X	X	X ^h	X	X	X	X		X
Assess aGvHD status ^c	X	X	X	X	X	X	X	X	X	X	X	X	X ⁱ	X		X
Baseline total bilirubin level and aGvHD assessment ^d		X														
Total bilirubin level and primary endpoint aGvHD status assessment ^e					X											
Total bilirubin level and secondary endpoint aGvHD status assessment ^f									X				X			
Number of ECP treatments ^g		3	3	3	3	2	2	2	2	2	2	2	2			

Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Nonrelapse mortality		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Survival		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Early study termination ^j																X

^a If the result of the urine test is positive, blood must be drawn for a serum human chorionic gonadotropin (HCG) level and analyzed locally. A serum test may be performed in place of the urine test.

^b At a minimum, a bilirubin level should be checked before the first ECP treatment of each week to assist in assessing aGvHD status of the previous week. Platelets and total WBC count should be checked before each scheduled ECP treatment as clinically indicated to ensure that they meet pre-ECP safety parameters. Hematocrit should be checked according to the CELLEX System Operator’s Manual. Ionized calcium may be checked, at the discretion of the Principal Investigator. A new calculation of Total Blood Volume is necessary before each treatment to estimate the safe extracorporeal blood volume that may be allowed for the patient undergoing treatment. These calculations should be performed using the current weight (recorded at the first visit of the week) and current hematocrit (drawn after the last photopheresis treatment and within 48 hours before the next photopheresis treatment).

^c After the baseline aGvHD assessment at the beginning of Week 1, aGvHD assessments should be performed within the weekly treatment window (± 2 days) after the last ECP treatment of each treatment week.

^d A baseline aGvHD assessment, including blood sampling for total bilirubin should be performed before the first ECP treatment of Week 1.

^e The assessment of aGvHD for the primary endpoint must occur at Day 28 (± 2 days) and must include a total bilirubin level.

^f The assessment of aGvHD for the secondary endpoint must occur at Days 56 and 84 (± 2 days) and must include a total bilirubin level.

^g Patients should be told emphatically to wear UVA-absorbing, wrap-around sunglasses and to cover exposed skin or use a sunblock (SPF 15 or higher) for the 24 hour period following treatment with methoxsalen, whether exposed to direct or indirect sunlight in the open or through a glass window.

^h These laboratory assessments should be performed monthly, before the first ECP treatment of the week at Weeks 5 and 9:

- CBC with differential (WBC, platelets, hemoglobin, hematocrit, neutrophils, lymphocytes, basophils, eosinophils, and monocytes); absolute neutrophil count.
- Electrolyte panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose), BUN/creatinine ratio, calcium, phosphorous, and magnesium.
- AST, ALT, GGT, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and lactate dehydrogenase.

ⁱ The assessment of aGvHD must be +/- 2 days of the endpoint assessments

^j Early study termination applies to only to those patients who discontinue ECP prior to 12 weeks of treatment and do not remain on the study.

7.2 STUDY ASSESSMENTS AND PROCEDURES

7.2.1 Screening Period

The Screening Period begins once a patient signs the ICF, and will consist of at least one screening visit. If a patient does not meet the eligibility criteria, the patient will be considered a “screening failure” and will be discharged from the study. A small set of eCRF pages (i.e., a “Screening Failure Packet”) will be completed for those patients who are not eligible for this study.

Informed Consent/Assent

Patient consent/assent must be obtained before a patient’s participation in ANY study-related procedures. A copy of the signed and dated ICF will be given to the patient, legal guardian or legally authorized representative. The original signed and dated ICF will be maintained at the study site. The date(s) of signed consent must be recorded in the eCRF. For more information, see [Section 10.7 Informed Consent/Assent](#).

Inclusion/Exclusion Criteria

The inclusion and exclusion criteria MUST be assessed for patient eligibility at screening and recorded on the Inclusion Criteria and Exclusion Criteria Forms of the eCRF. Patients who do not meet the inclusion and exclusion criteria will be considered “screening failures” and will be discharged from the study.

Focused Medical History

The medical history should include any medical condition that the patient recalls or that is part of the medical record that is relevant to the condition under study. Any condition present at the onset of the study should be noted. Any condition NOT listed on the Medical History and Review of Symptoms Form of the eCRF will be considered an AE if it occurs during the course of the study (i.e., any time after the patient has signed the ICF). Any condition that increases in frequency or worsens as compared to the Medical History and Review of Symptoms Form of the eCRF will also be considered an AE.

Transplant History

Background information about a patient’s transplant (e.g., date of transplant, type of bone marrow transplant, underlying condition [malignant or non-malignant]) will be recorded on the Transplant History Form of the eCRF.

Corticosteroid Dosing History

The patient’s steroid dosing for the treatment of aGvHD for the 30 days prior to screening must be documented on the Corticosteroid Dosage Form of the eCRF. Dosages will be recorded as given in the eCRF, but the methylprednisolone equivalent dosage must be assessed to ensure compliance to the 2.0 mg/kg dosage required for inclusion into the study.

Physical Examination

A qualified health-care professional will give each patient a complete physical examination in order to capture general health by organ system. Patient height and weight will also be recorded.

Pregnancy Test

At the screening visit, a urine dipstick pregnancy test will be performed through local laboratory for all females of childbearing potential, defined as those who have reached the onset of menarche or 8 years of age, whichever comes first. A serum test may also be performed in place of a urine dipstick. If the urine dipstick result is positive, blood must be drawn for a serum human chorionic gonadotropin (HCG) level and analyzed locally. A positive serum HCG result will prohibit the patient from enrollment into the study.

Vital Signs

Diastolic and systolic blood pressure, pulse rate, respiratory rate, and temperature will be taken at the screening visit.

Lansky Performance Status

A qualified health-care professional (physician, physician's assistant, nurse practitioner) will evaluate the patient's Health Performance Status using the Lansky Performance Status Scale ([Appendix C: Lansky Scale](#)).

Local Laboratory Analyses

Laboratory assessments (including pregnancy tests) will be performed through a local laboratory. The data obtained should be entered into the eCRF.

Clinically significant laboratory abnormalities should be recorded as AEs according to the Principal Investigator's judgment. Blood samples may be obtained through standard venipuncture technique or through a venous access catheter, according to institutional guidelines.

At the screening visit, a blood sample will be collected for the purpose of assessing eligibility and processed for:

- CBC with differential (WBC, platelets, hemoglobin, hematocrit, neutrophils, lymphocytes, basophils, eosinophils, and monocytes) and an absolute neutrophil count.
- Electrolyte panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose), blood urea nitrogen (BUN)/creatinine ratio, calcium, phosphorus, and magnesium.
- AST, ALT, gamma-glutamyltransferase (GGT), total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and lactate dehydrogenase.
- Coagulation panel (PT/PTT, INR).

If any of these samples were drawn within the preceding 72 hours and the results are available, they do not have to be re-drawn and may be used to assess eligibility.

A total bilirubin level will also be assessed before the first ECP treatment of the study at Week 1, and this value will be used for the baseline assessment of a patient's aGvHD status.

Please refer to [Section 4.1](#) and [Section 4.2](#) for the values of specific local laboratory results that would exclude patients from this study.

Assessment of aGvHD Status

Patients will be evaluated to confirm that they have steroid-refractory aGvHD grade B-D. Steroid-refractory is defined as progressive aGvHD after 3 days of or no response after 5 days of starting systemic steroids at a dose of 1.0 mg/kg/day methylprednisolone or equivalent. Patients with grade A are not eligible for this study. Grade D organ involvement will be limited to skin and liver.

Patients will be evaluated by the treating physician for the presence or absence of aGvHD manifestations of the skin, liver, and gut. Source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will later be applied to calculate the grade of aGvHD using the modified IBMTR Severity Index and the modified Glucksberg criteria.

Skin aGvHD Staging

Only active rash (erythema) is considered in body surface area (BSA) calculations. Hyper- (e.g., brown/tanned rash) or hypopigmentation representing post-inflammatory changes are not included in the BSA assessment. Skin involvement will be reported as % BSA using the Rule of Nines ([Appendix G: Percent Body Surface Area Assessment](#)) [Waslen, 1986] and/or presence of bullae.

Other common etiologies for skin symptoms include drug rash, conditioning regimen toxicity, infection, and cytokine storm/engraftment syndrome.

Liver aGvHD Staging

Bilirubin will be assessed on the day of the first ECP treatment, and this value will be used for the baseline assessment of a patient's aGvHD status. Total bilirubin (not direct/conjugated bilirubin) will be used for staging.

Other common etiologies for liver symptoms include drug toxicity, conditioning regimen toxicity, veno-occlusive disease, total parenteral nutrition, cholestasis, and infection.

Gut aGvHD Staging

Stool output will be reported as volumes for all inpatients and as episodes (frequency and consistency) for all outpatients. Patients weighing ≥ 50 kg will be graded using total stool volume per day (mL/day), while patients weighing < 50 kg will be evaluated for gut symptoms according to mL/kg/day, as a function of body weight.

For patients who weigh < 50 kg, every effort should be made to collect stool volumes as a daily average in milliliters over a 3-day period. For diarrhea volumes, report liquid stool volume in the following order:

1. Average of 3 consecutive days, if available.
2. Otherwise, the 3 days closest to each other within 1 week.
3. Otherwise, the average of 2 consecutive days.
4. Otherwise, the maximum volume from the isolated day(s) available.

Formed or mostly formed stools should not be quantified or counted in the estimation of liquid stool volume. It will be noted on the source document, if urinary mixing is present.

For inpatients in diapers, the volume will be calculated from the weight of the diaper before and after use. For outpatients, Patient Stool Volume records will be provided, according to usual site practice, along with instructions for collection and measurements. Stool volume collection should be done without regard to the ECP treatment schedule.

When diarrhea is reported as episodes instead of individual volumes, episodes of non-quantified liquid stool will be counted as 200 mL each for patients ≥ 50 kg and 4 mL/kg for patients < 50 kg.

When gross blood is present:

- Bloody diarrhea is staged as 4, even if low volume.
- Blood-streaked low volume (< 500 mL/day or < 10 mL/kg/day) stools (as can be seen with bleeding hemorrhoids, for example) are staged as 0.

For stage D or stage 4 gut involvement, severe pain is defined as:

- Pain that requires the start of narcotic use, or an increase in on-going narcotic use PLUS.
- Pain that significantly impacts performance status, as determined by the treating physician.

Other common etiologies for GI symptoms include drug toxicity, conditioning regimen toxicity, and infection.

Upper GI aGvHD Staging

For patients with isolated upper GI symptoms, pre-Screening biopsy results will be used to confirm the diagnosis of aGvHD. The determination that nausea, vomiting and/or anorexia are persistent is based on clinical judgment. As a general rule, nausea lasting fewer than 3 days, fewer than 2 vomiting episodes per day for at least 2 days, and anorexia without weight loss should not be considered persistent.

Other common etiologies for upper GI symptoms include drug toxicity, conditioning regimen toxicity, infection, and total parenteral nutrition.

Concomitant Medications

Medications that patients have taken during the last 30 days, including current medications, will be recorded. Medications for the treatment of aGvHD will be captured individually on a separate eCRF page(s). Other medications that patients are taking at screening will be captured on the Concomitant Medication Form ([Section 6.5](#)). Concomitant medications for screening failures will not be recorded on the eCRF.

Adverse Events

Patients will be asked about AEs that may have occurred after the patient signed and dated the ICF. Each patient will be asked about AEs using the non-specific question, "How have you been since your last visit?" Any AEs elicited by this question will be recorded on the Adverse Event Report Form of the eCRF, as well as any AEs spontaneously volunteered by the patient or observed by the study staff.

7.2.2 Treatment Period

The following assessments and procedures should be performed during the Treatment Period. Not all of the assessments and procedures listed below are to be performed at every scheduled visit (e.g., selected assessments are performed at Weeks 4 and 8). For the timing of when to administer individual assessments and procedures, see the Schedule of Assessments in [Table 1, Section 7.1](#). Unless otherwise indicated, assessments should be performed before the first ECP treatment of the week.

Corticosteroid Dose Record

The patient's steroid dosing for the treatment of aGvHD must be documented on the Corticosteroid Dosage Form of the eCRF. Dosages should be recorded without modification (although average daily dose is acceptable). Methylprednisolone equivalence will be calculated later.

Physical Examination

A qualified health-care professional will give each patient a complete physical examination to document any changes in the general health of the patient by organ system. The complete physical examinations will be performed after all other assessments included in Weeks 4, 8, 12 and 16 have been completed. Targeted physical examinations will be performed after all other assessments included in Weeks 1, 2, 3, 5, 6, 7, 9, 10, and 11 have been completed. Patient height and weight will also be recorded each week. In those weeks when patients are reporting to the study site multiple times, height and body weight need only be recorded at the first visit.

A new calculation of Total Blood Volume is necessary before each treatment to estimate the safe extracorporeal blood volume that may be allowed for the patient undergoing treatment. These calculations should be performed using the current weight (recorded at the first visit of the week) and current hematocrit (drawn after the last photopheresis treatment and within 48 hours before the next photopheresis treatment).

Pregnancy Test

A urine dipstick pregnancy test will be performed at screening and weekly for all females of childbearing potential (defined as those who have reached the onset of menarche or 8 years of age, whichever comes first) on the day of the first scheduled treatment of the week, before the start of the day's therapy. A serum test may also be performed in place of a urine dipstick. If the urine dipstick result is positive, blood must be drawn for a serum HCG level and analyzed locally before any ECP treatment. A positive serum HCG result necessitates automatic withdrawal of the patient from active treatment, and no further ECP treatments can be performed.

Vital Signs

Vital signs (diastolic and systolic blood pressures, pulse rate, respiratory rate, and temperature) will be taken before and at the end of each ECP treatment.

Lansky Performance Status

A qualified health-care professional (physician, physician's assistant, nurse practitioner) will evaluate the patient's Health Performance Status using the Lansky Performance Status Scale ([Appendix C: Lansky Scale](#)) after 4, 8 and 12 weeks of ECP treatment.

Local Laboratory Analyses

Laboratory assessments (including pregnancy tests) will be performed through a local laboratory. The data obtained should be entered into the eCRF.

Clinically significant laboratory abnormalities should be recorded as AEs according to the Principal Investigator's judgment. Blood samples may be obtained through standard venipuncture technique or through a venous access catheter, according to institutional guidelines.

During the Treatment Period, blood will be collected at the indicated times and processed for the following:

Before the First Scheduled ECP Treatment of the Study at Week 1

- Total bilirubin, to be used for the baseline aGvHD status assessment.

Before Each Scheduled ECP Treatment (Weeks 1-12)

- Hematocrit, as indicated in the CELLEX System Operator's Manual.
- Platelets, as clinically indicated.
- WBC count, as clinically indicated.
- Ionized calcium, as clinically indicated and/or according to institutional guidelines (particularly for patients whose ECP treatments include the use of ACD-A as an anticoagulant).
- Total bilirubin, to be used for the prior weekly assessment of aGvHD status
 - Levels drawn before the first ECP treatment of Week 5 and Week 9 should be used for the Primary and Secondary Endpoint aGvHD status assessments, respectively. On Days 28 and 56, the bilirubin assessments must be done within ± 2 days.

Monthly Before the First ECP Treatment of the Week at Weeks 5 and 9

- CBC with differential (WBC, platelets, hemoglobin, hematocrit, neutrophils, lymphocytes, basophils, eosinophils, and monocytes) and an absolute neutrophil count.
- Electrolyte panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, and

glucose), BUN/creatinine ratio, calcium, phosphorous, and magnesium.

- AST, ALT, GGT, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and lactate dehydrogenase.

During ECP Treatments (Weeks 1-12)

- Laboratory analyses needed to assess patients should be drawn at the discretion of the Principle Investigator.

At Screening and Weekly (Weeks 1-12) for All Females of Childbearing Potential

- Urine dipstick pregnancy testing (for females age 8 or those who have reached the onset of menarche, whichever comes first). A serum test may also be performed in place of a urine dipstick.
- Serum HCG level immediately after any positive urine pregnancy test.

Any laboratory test results that are needed to manage aGvHD or other medical conditions should be drawn outside this schedule as clinically indicated.

Assessment of aGvHD Status

All patients will be evaluated for a response in their aGvHD manifestations at least once each week through Week 12 (or the visit at which the patient ceases to receive treatment, if before Week 12). The assessment of aGvHD status should occur after the last ECP treatment of the week, with the exception of bilirubin levels, which will be tested prior to the first ECP treatment of the following week.

Patients will be evaluated by the treating physician for the presence or absence of aGvHD manifestations of the skin, liver, and gut. Source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified IBMTR Severity Index and the modified Glucksberg criteria. Acute GvHD status will be assessed at baseline (at Week 1 before the first ECP treatment of the study) and once a week, after the last ECP treatment of each week (Weeks 1-12).

Skin aGvHD Staging

Only active rash (erythema) is considered in body surface area (BSA) calculations. Hyper- (e.g., brown/tanned rash) or hypopigmentation representing post-inflammatory changes are not included in the BSA assessment. Skin involvement will be reported as % BSA using the Rule of Nines ([Appendix G: Percent Body Surface Area Assessment](#)) and/or presence of bullae.

Other common etiologies for skin symptoms include drug rash, conditioning regimen toxicity, infection, and cytokine storm/engraftment syndrome.

Liver aGvHD Staging

Bilirubin will be determined from a single blood sample drawn before the first treatment of the following week. Total bilirubin (not direct/conjugated) will be used for staging.

Other common etiologies for liver symptoms include drug toxicity, conditioning regimen toxicity, veno-occlusive disease, total parenteral nutrition, cholestasis, and infection.

Gut aGvHD Staging

Stool output will be reported as volumes for all inpatients and as episodes (frequency and consistency) for all outpatients. Patients weighing ≥ 50 kg will be graded using total stool volume per day (mL/day), while patients weighing < 50 kg will be evaluated for gut symptoms according to mL/kg/day, as a function of body weight.

For patients who weigh < 50 kg, every effort should be made to collect stool volumes as a daily average in milliliters over a 3-day period and must be completed before the first ECP treatment of the next treatment week. For diarrhea volumes, report liquid stool volume in the following order:

1. Average of 3 consecutive days, if available.
2. Otherwise, the 3 days closest to each other within 1 week.
3. Otherwise, the average of 2 consecutive days.
4. Otherwise, the maximum volume from the isolated day(s) available.

Formed or mostly formed stools should not be quantified or counted in the estimation of liquid stool volume. It will be noted on the source documents, if urinary mixing is present. For patients in diapers, the volume will be calculated from the weight of the diaper before and after use. For outpatients, Patient Stool Volume Records will be provided, according to usual site practice, along with instructions for collection and measurements. Stool volume collection should be done without regard to the ECP treatment schedule.

When diarrhea is reported as episodes instead of individual volumes, episodes of non-quantified liquid stool will be counted as 200 mL each for patients ≥ 50 kg and 4 mL/kg for patients < 50 kg.

When gross blood is present:

- Bloody diarrhea is staged as 4, even if low volume.
- Blood-streaked low volume (< 500 mL/day or < 10 mL/kg/day) stools (as can be seen with bleeding hemorrhoids, for example) are staged as 0.

For stage D or stage 4 gut involvement, severe pain is defined as:

- Pain that requires the start of narcotic use, or an increase in on-going narcotic use PLUS.
- Pain that significantly impacts performance status, as determined by the treating physician.

Other common etiologies for GI symptoms include drug toxicity, conditioning regimen toxicity, and infection.

Upper GI aGvHD Staging

The determination that nausea, vomiting and/or anorexia are persistent is based on clinical judgment. As a general rule, nausea lasting fewer than 3 days, fewer than 2 vomiting episodes per day for at least 2 days, and anorexia without weight loss should not be considered persistent.

Other common etiologies for upper GI symptoms include drug toxicity, conditioning regimen toxicity, infection, and total parenteral nutrition.

ECP Treatments

Patients should be scheduled to receive the first ECP treatment as soon as possible upon confirmation of eligibility. Patients must be enrolled and receive their first ECP treatment within 1 week (7 days) after being diagnosed as having steroid-refractory aGvHD. Week 1 (7 days) begins on the day the first ECP treatment is received (Day 1 of Week 1). The availability of typed and cross-matched donor PRBCs for transfusion during treatment, if needed, should be established prior to the scheduling of ECP treatments.

Prior to an ECP treatment, each patient will be assessed by a qualified health-care professional to verify that the patient is acceptable for ECP treatment. This assessment will include vital signs (diastolic and systolic blood pressures, pulse rate, respiratory rate and temperature) that will be taken before and at the end of each ECP treatment. Local laboratory analyses will be drawn before each ECP treatment, as specified above. If a patient's WBC count is $< 1.0 \times 10^9/L$ or platelet count is $< 20.0 \times 10^9/L$, that patient should NOT be treated with ECP until the WBC count is $\geq 1.0 \times 10^9/L$ and platelet count is $\geq 20.0 \times 10^9/L$ (platelet transfusions ARE permitted). This stipulation may require that patients receive one or more transfusions before the first or subsequent ECP treatments. Principal Investigators must use a coagulation-screening test of their choice in verifying a patient as acceptable for ECP treatment. The threshold value of the coagulation-screening test used to allow a patient to receive ECP treatment will be based upon a Principal Investigator's own clinical judgment. Patient monitoring during ECP treatment will be done according to institutional protocols in alignment with the CELLEX System Operator's Manual. Ionized calcium, if applicable, will be assessed before and during ECP treatments at the discretion of the Principal Investigator and according to institutional protocols.

For more information on ECP treatments, see the CELLEX System Operator's Manual.

Scheduling

The study coordinator will arrange the scheduling of ECP treatments according to the following schedule:

- Weeks 1-4: 3 treatments per week.
- Weeks 5-12: 2 treatments per week.

Patients are expected to receive the stated number of treatments per treatment week (7 days) \pm 2 days, and a total of no more than 12 ECP treatments for the first 28 days.

Extracorporeal photopheresis treatments given within ± 2 days of the expected treatment week will not be considered a protocol deviation.

Week 1 (7 days) begins when the first ECP treatment is received (Day 1 of Week 1). The availability of typed and cross-matched donor PRBCs for transfusion during treatment, if needed, should be established prior to the scheduling of ECP treatments.

After completion of the 12-week Treatment Period, patients may continue ECP treatment on commercial product at the discretion of the Principal Investigator.

Special Warnings and Precautions for Use

Patients should be explicitly instructed to wear UVA-absorbing, wrap-around sunglasses and cover exposed skin or use a sunblock (SPF 15 or higher) for the 24 hour period following treatment with methoxsalen, whether exposed to direct sunlight or indirect sunlight through a glass window.

Primary and Secondary aGvHD Endpoint Assessments (Weeks 4, 8, and 12)

Assessments of aGvHD status (including total bilirubin, corticosteroid dosing, Lansky Performance Status, etc.) for the purpose of the primary and secondary endpoint analyses should be performed at Days 28 (± 2), 56 (± 2) and 84 (± 2), respectively.

Concomitant Medications

All concomitant medications taken by patients during the Treatment Period, including those medications taken between visits, will be recorded on the Prior and Concomitant Medication Report Form of the eCRF. Concomitant medications should be recorded on a weekly basis.

Adverse Events

Patients will be asked about AEs that may have occurred after the patient signed and dated the ICF. Each patient will be asked about AEs using the non-specific question, "How have you been since your last visit?" Any AEs elicited by this question will be recorded on the Adverse Event Report Form of the eCRF, as well as any AEs spontaneously volunteered by the patient or observed by the study staff.

Nonrelapse Mortality

Nonrelapse mortality is defined as death due to any cause, with death due to relapse as a competing risk [Das-Gupta et al., 2014b].

Survival

Recipient Death Information must be entered into the eCRF within 24 hours of knowledge of a patient's death. Once the cause of death is determined, the information must be recorded in the eCRF.

7.2.3 Follow-up Period

The following assessments and procedures should be performed during the Follow-up Period. Not all of the assessments and procedures listed below are to be performed at every scheduled

visit. For the timing of when to administer individual assessments and procedures, see the Schedule of Assessments in [Table 1, Section 7.1](#).

Corticosteroid Dose Record

The patient's steroid dosing for the treatment of aGvHD must be documented on the Corticosteroid Dosage Form of the eCRF. Dosages will be recorded as is (average daily dose is acceptable). Methylprednisolone equivalence will be calculated later.

Physical Examination

A qualified health-care professional will give each patient a complete physical examination to document any changes in the general health of the patient by organ system. Patient height and weight will also be recorded.

Local Laboratory Analyses

Laboratory assessments will be performed through a local laboratory. Clinically significant laboratory abnormalities should be recorded as AEs according to the Principal Investigator's judgment. Blood samples may be obtained through standard venipuncture technique or through a venous access catheter, according to institutional guidelines.

Blood will be collected and processed for the following:

- Total bilirubin, to be used for the weekly assessment of aGvHD status.
- CBC with differential (WBC, platelets, hemoglobin, hematocrit, neutrophils, lymphocytes, basophils, eosinophils, and monocytes) and an absolute neutrophil count.
- Electrolyte panel (sodium, potassium, chloride, bicarbonate, BUN, creatinine, and glucose), BUN/creatinine ratio, calcium, phosphorous, and magnesium.
- AST, ALT, GGT, total bilirubin, direct bilirubin, indirect bilirubin, alkaline phosphatase, and lactate dehydrogenase.

Any laboratory test results that are needed to manage aGvHD or other medical conditions should be drawn outside this schedule as clinically indicated.

Assessment of aGvHD Status

Patients will be evaluated by the treating physician for the presence or absence of aGvHD manifestations of the skin, liver, and gut. Source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified IBMTR Severity Index and the modified Glucksberg criteria.

Skin aGvHD Staging

Only active rash (erythema) is considered in body surface area (BSA) calculations. Hyper- (e.g., brown/tanned rash) or hypopigmentation representing post-inflammatory changes are not included in the BSA assessment. Skin involvement will be reported as % BSA using the Rule of Nines ([Appendix G: Percent Body Surface Area Assessment](#)) and/or presence of bullae.

Other common etiologies for skin symptoms include drug rash, conditioning regimen toxicity, infection, and cytokine storm/engraftment syndrome.

Liver aGvHD Staging

Bilirubin will be determined from a single blood sample. Total bilirubin (not direct/conjugated) will be used for staging.

Other common etiologies for liver symptoms include drug toxicity, conditioning regimen toxicity, veno-occlusive disease, total parenteral nutrition, cholestasis, and infection.

Gut aGvHD Staging

Stool output will be reported as volumes for all inpatients and as episodes (frequency and consistency) for all outpatients. Patients weighing ≥ 50 kg will be graded using total stool volume per day (mL/day), while patients weighing < 50 kg will be evaluated for gut symptoms according to mL/kg/day, as a function of body weight.

For patients who weigh < 50 kg, every effort should be made to collect stool volumes as a daily average in milliliters over a 3-day period. For diarrhea volumes, report liquid stool volume in the following order:

1. Average of 3 consecutive days, if available.
2. Otherwise, the 3 days closest to each other within 1 week.
3. Otherwise, the average of 2 consecutive days.
4. Otherwise, the maximum volume from the isolated day(s) available.

Formed or mostly formed stools should not be quantified or counted in the estimation of liquid stool volume. It will be noted on the source document, if urinary mixing is present. For patients in diapers, the volume will be calculated from the weight of the diaper before and after use. For outpatients, Patient Stool Volume Records will be provided, according to usual site practice, along with instructions for collection and measurements. Stool volume collection should be done without regard to the ECP treatment schedule.

When diarrhea is reported as episodes instead of individual volumes, episodes of non-quantified liquid stool will be counted as 200 mL each for patients ≥ 50 kg and 4 mL/kg for patients < 50 kg.

When gross blood is present:

- Bloody diarrhea is staged as 4, even if low volume.
- Blood-streaked low volume (< 500 mL/day or < 10 mL/kg/day) stools (as can be seen with bleeding hemorrhoids, for example) are staged as 0.

For stage D or stage 4 gut involvement, severe pain is defined as:

- Pain that requires the start of narcotic use, or an increase in on-going narcotic use PLUS.
- Pain that significantly impacts performance status, as determined by the treating physician.

Other common etiologies for GI symptoms include drug toxicity, conditioning regimen toxicity, and infection.

Upper GI aGvHD Staging

The determination that nausea, vomiting and/or anorexia are persistent is based on clinical judgment. As a general rule, nausea lasting fewer than 3 days, fewer than 2 vomiting episodes per day for at least 2 days, and anorexia without weight loss should not be considered persistent.

Other common etiologies for upper GI symptoms include drug toxicity, conditioning regimen toxicity, infection, and total parenteral nutrition.

Concomitant Medications

All concomitant medications taken by patients, including those medications taken between visits, will be recorded on the Prior and Concomitant Medication Report Form of the eCRF.

Adverse Events

Patients will be asked about AEs that may have occurred after the patient signed and dated the ICF. Each patient will be asked about AEs using the non-specific question, “How have you been since your last visit?” Any AEs elicited by this question will be recorded on the Adverse Event Report Form of the eCRF, as well as any AEs spontaneously volunteered by the patient or observed by the study staff.

Nonrelapse Mortality

Nonrelapse mortality is defined as death due to any cause, with death due to relapse as a competing risk [Das-Gupta et al., 2014b].

Survival

Recipient Death Information must be entered into the eCRF within 24 hours of knowledge a patient’s death. Once the cause of death is determined, the information must be recorded in the eCRF. Passive follow-up (chart review) will be performed to assess survival at Week 26.

7.2.4 Early Study Termination Visit

End of study assessments (Schedule of Assessments in [Table 1, Section 7.1](#)) will be completed for those patients who discontinue ECP, prior to completing 12 weeks of treatment, and will not remain in the study. The Early Study Termination page of the eCRF must be completed for these patients, with the reason for withdrawal from the study. For those patients who terminate early, every effort should be made to perform the early termination assessments.

8. SAFETY PARAMETERS

8.1 ADVERSE EVENTS

8.1.1 Collection of Adverse Events

It is the responsibility of the Principal Investigator to collect all AEs (both serious and nonserious) derived by spontaneous, unsolicited reports of patients, by observation, and by routine open questionings (e.g., “How have you felt since I last saw you?”).

8.1.2 Definitions

An AE is any untoward medical occurrence that occurs in a patient or clinical investigation patient administered a pharmaceutical product or an investigational medicinal product, and does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the product. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 and will be coded using MedDRA based on the verbatim term collected in the eCRF.

All AEs, including intercurrent illnesses, occurring during the study will be documented in the eCRF. Underlying disease, hospitalization for the study purpose, and abnormal laboratory results associated with an underlying disease will not be considered AEs. Relapse of underlying malignancy will not be considered an AE or serious AE (SAE) but will be captured and analyzed separately. Underlying disease will not be considered an AE unless it meets any of the seriousness criteria—in particular, hospitalization and deaths. Concomitant illnesses that existed before entry into the study will not be considered AEs unless they worsen during the treatment period. Pre-existing conditions will be recorded in the eCRF on the Medical History or appropriate page. Adverse events will be captured from the time of ICF signing until completion of the study (Week 16) or early cessation of treatment for any reason.

The underlying disease is defined as:

1. Clinical disease that was the reason for the bone marrow or stem cell transplant (e.g. malignancy, immunodeficiency disorder, Sickle Cell Disease, etc).
2. Typical, expected clinical manifestations of patients who have received bone marrow transplant or stem cell transplant.
3. Typical, expected clinical manifestations of patients with acute graft-vs-host disease.

The following signs, symptoms, laboratory results, and diseases are considered AEs:

1. Signs and symptoms not related to the underlying disease.
2. Signs and symptoms not typical following bone marrow transplant or stem cell transplant.
3. Abnormal laboratory results not related to the underlying disease that are clinically significant (expert clinical judgment required by the investigator to assess if an abnormal laboratory result is clinical significant/not clinically significant).

4. Underlying disease that worsens and meets criteria for a SAE during the study.
5. Concomitant illnesses that existed before entry into the study that worsen during the treatment period.
6. Death due to any cause.

The following signs, symptoms, laboratory results, diseases are not considered an AE:

1. Underlying disease that does not meet criteria for being a serious AE (see [Section 8.1.3.1](#)).
2. Hospitalization related to study enrollment procedures, treatments, etc.
3. Hospitalization for elective or planned procedure to treat a preexisting condition that has not worsened and does not result in another serious outcome (e.g. death, hospital prolongation, etc).
4. Abnormal laboratory results associated with the underlying disease (as determined by expert clinical judgment of the investigator).
5. Concomitant illnesses that existed before entry into the study that do not worsen during the treatment period.

8.1.3 Assessment of Adverse Events

Each AE will be assessed by the Principal Investigator with regard to seriousness, intensity, and causality.

8.1.3.1 *Seriousness*

An SAE is defined as any untoward medical occurrence that:

- Results in death.
- Is a life-threatening adverse drug/device experience (this means that the patient is at risk of death at the time of the event; it does not mean that the event hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability or incapacity.
- Is a congenital anomaly or birth defect.
- Is an important medical event that may not be immediately life-threatening or result in death or hospitalization, but that may jeopardize the patient or require intervention to prevent one of the above outcomes.

ANY SAE (INCLUDING DEATH) DUE TO ANY CAUSE, WHICH OCCURS DURING THE COURSE OF THIS INVESTIGATION, WHETHER OR NOT RELATED TO THE INVESTIGATIONAL DRUG, MUST BE REPORTED WITHIN 24 HOURS BY FAX TO

[REDACTED].

Medical and scientific judgment should be exercised in deciding whether a case is serious. Therakos, Inc. and/or its delegate (**[REDACTED]**) will determine if an event requires expedited reporting.

8.1.3.2 Intensity

The intensity of each AE must be assessed by the Principal Investigator using one of the following categories and recorded in the eCRF:

- Mild: an AE that does not interfere with usual activities.
- Moderate: an AE that interferes with usual activities.
- Severe: an AE that prevents usual activities.

8.1.3.3 Causality

The Principal Investigator will assess the causality/relationship between the study treatment and the AE, and record that assessment in the eCRF. The most likely cause of an SAE (e.g., disease under treatment, concomitant disease, and concomitant medications) will be indicated on the eCRF with details of the cause.

The causal relationship of the AE to study drug will be described for:

- Probable: the AE meets one of these criteria.
 - Follows a reasonable temporal sequence from administration of the study drug.
 - Could not be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient.
 - Disappears or decreases on cessation or reduction in dose of the study drug.
 - Follows a known pattern of response to the study drug.
 - Reappears or worsens on rechallenge.
- Possible: the AE meets one of these criteria
 - Follows a reasonable temporal sequence from administration of the study drug
 - Could be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient
 - Follows a known pattern of response to the study drug
- Unlikely: the AE meets one of these criteria
 - Does not follow a reasonable temporal sequence from administration of the study drug.
 - Could be reasonably explained by the patient's clinical state, environmental or toxic factors, or other therapies administered to the patient.
 - Does not follow a known pattern of response to the study drug.
 - Does not reappear or worsen on rechallenge.
- Not related:
 - The AE does not meet the above criteria.
 - There is sufficient information that the etiology of the AE is not related to the study drug.

For SAEs, the Principal Investigator will assess whether the event is related to UVADEX, the ECP procedure, concomitant medication, an underlying condition, other (specify), or unknown. If the SAE is assessed as related to UVADEX, the likelihood of the relationship will be assessed by the Principal Investigator as Probable, Possible, or Unlikely.

8.1.4 Recording Adverse Events

Adverse events will only be recorded from ICF signing until Week 16. Following Week 16 there will be a passive chart review which will not include the collection of AEs. Any AEs occurring after the end of the study should be reported to the Sponsor by the Investigator if the Principal Investigator considers that there is a causal relationship with the study treatment.

All AEs (including AEs resulting from active standard of care medication and study device), regardless of the relationship to study drug, will be recorded in the eCRF. In addition, the technician performing the ECP procedure will observe and record any AEs that occur during the procedure. Treatment will be stopped if the patient cannot tolerate the procedure.

All AEs recorded in the eCRF should contain a brief description of the event, date of onset, date of resolution, intensity, treatment required, relationship to study drug(s) and/or device, action taken with the study drug and/or device, outcome, and whether the event is classified as serious.

8.1.5 Reporting Serious Adverse Events

All SAEs will be recorded from the time of ICF signing until completion of the study. All SAEs, regardless of the relationship to the study drug(s) or study procedure(s), must be reported by the Principal Investigator, or his/her designee, within 24 hours of observation/discovery or notification of the event. Instructions for reporting an SAE are provided in this section. The name(s) and contact details of the individual(s) who should be contacted regarding safety issues or questions regarding the study are also included in [Table 2](#).

Table 2. Contact Information for Reporting Serious Adverse Events

	FAX all SAE Reports	SAE Hotline (questions)
Safety Fax Line:	US: [REDACTED]	US: [REDACTED]
	AT: [REDACTED]	AT: [REDACTED]
	HU: [REDACTED]	HU: [REDACTED]
	FR: [REDACTED]	FR: [REDACTED]
	GE: [REDACTED]	GE: [REDACTED]
	IT: [REDACTED]	IT: [REDACTED]
	SP: [REDACTED]	SP: [REDACTED]
	PL: [REDACTED]	PL: [REDACTED]
	UK: [REDACTED]	UK: [REDACTED]
Email (backup):	[REDACTED]	

Table 3. Contact Information US and EU Medical Monitors

[REDACTED], MD (US)	Office: [REDACTED] Fax: [REDACTED] Email: [REDACTED]
[REDACTED], MD, PhD (EU)	Office: [REDACTED] Fax: [REDACTED] Email: [REDACTED]

The Principal Investigator, Sponsor, and [REDACTED] Safety will review each SAE report and will evaluate the seriousness, causal relationship, and/or expectedness of the event to study treatment.

Hospitalization due to disease progression will be considered an SAE. Hospitalization for an elective or planned procedure to treat a preexisting condition will not be considered an SAE unless it results in one of the other outcomes previously described. Hospitalizations only for study agent administration will not be considered an SAE. Details for the reporting of suspected unexpected serious adverse reactions (SUSARs) can be found in [Section 8.1.8](#).

Serious AE reporting instructions:

- Provide the Medical Monitor with the Principal Investigator's name, your name, the telephone number where you can be reached, and the protocol number and title.
- Fax the SAE form and any supporting documentation to the Medical Monitor within 24 hours of becoming aware of the event.

The minimum information required for an initial report:

- Sender of the report (name, address of Principal Investigator).
- Patient identification (by enrollment number, initials, and/or birth date—NOT by patient name).
- Protocol number.
- Description of SAE.
- Causality assessment.

After receipt of the initial report, [REDACTED] Safety will review the information and, if necessary, contact the Principal Investigator to obtain further information for assessment of the event. [REDACTED] Safety will be responsible for all information processing and reporting according to local legal requirements following ICH E6 guidelines. Where necessary, Principal Investigators will inform the authorities in their own countries.

8.1.6 Follow-up of Serious Adverse Events

All SAEs experienced by a patient, irrespective of the suspected causality, will be monitored until the event has resolved, until any abnormal laboratory values have returned to baseline or stabilized at a level acceptable to the Principal Investigator and Medical Monitor, until there is a satisfactory explanation for the changes observed, or until the patient is lost to follow-up or the event is unlikely to resolve.

The Data Safety Monitoring Board (DSMB) meets on a quarterly basis to review all the SAEs (unblinded), the most frequent AEs (blinded aggregate data), and laboratory data of interest, and will make recommendation to the study team regarding the safety aspect of the study. The safety review team consists of medical experts who are not involved in the study.

8.1.7 Protocol-Specified Serious Adverse Events

In order to minimize expedited reporting on non-informative SAEs, the following list of events do not need to be reported individually in an expedited manner, as they are anticipated due to disease progression and/or the use of concomitant therapies. These events include:

- Relapse of an underlying pre-transplant malignant condition, progression of aGvHD symptoms, pancytopenia, vomiting, diarrhea, GI bleeding, bloody stools, GI perforation, myelosuppression, leukopenia, AST elevation ALT elevation, elevated bilirubin, hepatotoxicity, thrombocytopenia, red cell aplasia, hypogammaglobulinemia, anorexia, nephrotoxicity, seizures, and anemia;
- Tuberculosis infection, tuberculosis reactivation, CMV infection, VZV infection, herpes simplex virus infection, CMV reactivation, VZV reactivation, herpes simplex virus reactivation, parasitic infections, bacterial central line infection, bacterial sepsis, fungal central line infection, and fungal sepsis.

8.1.8 Suspected Unexpected Serious Adverse Reactions

A SUSAR is defined as any untoward and unintended response to a study drug, which is not listed in the applicable product information, which is assessed by the sponsor and or study investigator as being unexpected and meets one of the following serious criteria: results in death, is life-threatening, requires hospitalization or prolongation of an existing hospitalization, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect:

- If the SUSAR is fatal or life-threatening, regulatory authorities and ethics committees will be notified within 7 calendar days after the Sponsor learns of the event. Additional follow-up information (cause of death, autopsy report, and hospital report) should be reported within an additional 8 days (15 days total).
- If the SUSAR is not fatal or life-threatening but is otherwise serious (meets the other seriousness criteria in [Section 8.1.3.1](#)), regulatory authorities and ethics committees will be notified within 15 calendar days after the Sponsor learns of the event.

The Sponsor will notify the Principal Investigators of relevant information about SUSARs that could adversely affect the safety of patients in a timely fashion. Follow-up information may be submitted if necessary.

The Sponsor will also provide annual safety updates to the regulatory authorities and ethics committees responsible for the trial. These updates will include information on SUSARs and other relevant safety findings.

8.1.9 Pregnancy

The Sponsor has a responsibility to monitor the outcome of pregnancies where there has been maternal exposure to the investigational drug.

Pregnancy alone is not regarded as an AE unless there is a suspicion that the study drug(s) may have interfered with the effectiveness of a contraceptive medication.

Elective abortions without complications should not be handled as AEs unless they were therapeutic abortions (see below). Hospitalization for normal delivery of a healthy newborn should not be considered an SAE.

All pregnancies must be reported by the Principal Investigator to [REDACTED] Safety on the initial pregnancy report form within 30 days after becoming aware of the pregnancy. The Principal Investigator must follow up and document the course and the outcome of all pregnancies even if the patient was discontinued from the study or if the study has finished.

All outcomes of pregnancy must be reported by the Principal Investigator to [REDACTED] Safety on the pregnancy outcome report form within 30 days after he/she has gained knowledge of the normal delivery or elective abortion.

Any SAE that occurs during pregnancy must be recorded on the SAE report form (e.g., maternal serious complications, spontaneous or therapeutic abortion, ectopic pregnancy, stillbirth, neonatal death, congenital anomaly, birth defect) and reported within 24 hours in accordance with the procedure for reporting SAEs.

If a partner of a male study patient who has been exposed to study drug becomes pregnant, every effort should be made to monitor the pregnancy and outcome of pregnancy. A separate ICF will be provided for the partner before any data are collected regarding the pregnancy.

8.1.10 Medical Device Reporting

All device malfunctions during the 12-week study period should be reported to the Therakos, Inc. support hotline. The Mallinckrodt Critical Care Customer Care phone numbers are 877-566-9466 in the United States and 00800-843-725-67 in Europe. The caller should identify his/her involvement in this clinical study.

Device malfunctions should also be recorded in the eCRF. Any AEs resulting from the malfunction will be recorded in the eCRF.

8.2 DATA SAFETY MONITORING BOARD

A DSMB will be in place to oversee the study. The DSMB will be an external committee composed of various specialists (also relevant to the pediatric bone marrow transplant population being studied). Details will be provided in the DSMB Charter.

The DSMB will be responsible for ongoing review of enrollment, safety, and, if requested by the DSMB, efficacy data. They will provide regular assessments on the safety and overall risk-to-benefit ratio of the study conduct, advise Therakos, Inc. of the need for any protocol modifications/amendments to minimize potential risk for patients, and make recommendations including stopping of enrollment and/or treatment, if needed.

A [REDACTED] Safety designee will be responsible for the timely coordination and delivery of the data to the DSMB on a regular basis.

9. STATISTICAL METHODS

9.1 PLANNED SAMPLE SIZE

A total of 48 patients with steroid-refractory grade B-D aGvHD will be enrolled and receive at least one ECP treatment. The trial is designed to test the null hypothesis that standard therapy has an overall response (CR+PR) rate of 10% versus the alternate hypothesis that ECP plus standard therapy has a CR+PR rate not equal to 10% (the expected rate $\geq 27\%$). The overall Type I error rate and power for this design are 5% and 90.4%, respectively.

9.2 OVERVIEW OF STUDY DESIGN

This single-arm trial will have 1 planned interim analysis and a final analysis.

The primary endpoint is whether a patient achieves an overall response (defined as a complete response (CR) or partial response (PR)). The trial is designed to test the null hypothesis that standard therapy has an overall response (CR+PR) rate of 10% versus the alternate hypothesis that ECP plus standard therapy has a CR+PR rate not equal to 10% (the expected rate $\geq 27\%$). After the first 50% (24/48) of the patients have been treated for at least 4 weeks (or fewer if patients discontinued treatment), significance will be declared if the CR+PR 2-sided *P* value versus the stated alternative is < 0.005 , corresponding to an observed CR+PR rate $> 48\%$. Based on the primary endpoint analysis and review of the safety results available at the time of the interim analysis, consideration will be given, in the absence of safety concerns, to continue or stop the study for success or futility. Enrollment will not be placed on hold during the interim analysis. A final analysis will be performed after all 48 patients have been treated for at least 4 weeks. In this final analysis, significance will be declared if the CR+PR 2-sided *P* value versus the stated null is < 0.049 . The overall Type I error rate and power for this design are 5% and 90.4%, respectively.

9.3 EFFICACY ANALYSES

A formal statistical analysis plan will be developed prior to first patient entered that will provide full details of analysis methods and analysis populations.

9.3.1 Analysis of Primary Endpoint

The primary endpoint is the proportion of patients who achieve an overall response (CR+PR) after 4 weeks (Day 28), or fewer treatments if they discontinued treatment, of ECP treatment. Patients must receive at least one treatment. Patients will be evaluated by the treating physician for the presence or absence of aGvHD manifestations of the skin, liver, and gut; source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified IBMTR Severity Index. If a Patient is administered a second-line therapy other than ECP for the treatment of aGvHD, or discontinues study treatment, that Patient will be considered a nonresponder. The primary endpoint will be summarized by frequency tabulation and analyzed using exact Binomial test and confidence interval. The formal statistical analysis and evaluation of response is based on at least 4-weeks ECP treatment data only.

9.3.2 Analysis of Secondary Endpoints

The secondary endpoints are:

- Safety parameters including vital signs, laboratory tests, and spontaneously reported AEs and SAEs.
- Proportion of patients who achieve an overall response 8 weeks (Day 56) and 12 weeks (Day 84) after initiation of ECP treatment.
- Duration of response, defined as the length of time a patient maintains a response through Week 16 of the Follow-up Period on a per-patient basis.
- Proportion of patients who achieve an overall response after 4 weeks (Day 28), 8 weeks (Day 56) and 12 weeks (Day 84) of ECP treatment according to the modified Glucksberg criteria
 - Source data will be collected for each patient and entered into the eCRF, and a scoring algorithm will be applied to calculate the grade of aGvHD using the modified Glucksberg criteria.
- Cumulative dose of daily steroids administered from diagnosis of aGvHD to 12 weeks (Day 84) after initiation of ECP treatment.
- Organ-specific grade at 4 weeks (Day 28), 8 weeks (Day 56) and 12 weeks (Day 84) after initiation of ECP treatment.

Overall response (CR+PR) rate at 8 weeks (Day 56) and response determined by the Glucksberg criteria will be summarized by frequency tabulation and analyzed using exact Binomial test and confidence interval. Supportive analysis of response rates over time will be achieved by means of generalized linear mixed effects modelling. Daily steroid dose will be analyzed using mixed model repeated measures analysis. Duration of response will be summarized by Kaplan-Meier curve; the median duration of response and 95% confidence interval will be presented.

9.3.3 Analysis of Exploratory Endpoints

Exploratory endpoints include:

- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]
- █ [REDACTED]

9.4 SAFETY PARAMETERS

Safety parameters for each patient include vital signs, laboratory tests, and spontaneously reported AEs and SAEs. Adverse events will be graded according to the Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 and will be coded using MedDRA based on the verbatim term collected in the eCRF. Adverse event data will be summarized by system organ classification and preferred term. Vital signs and laboratory values will be summarized by visit and numbers of patients with excursions outside the normal reference range summarized.

10. ETHICAL, LEGAL, AND ADMINISTRATIVE ASPECTS

10.1 DATA QUALITY ASSURANCE

The Sponsor or Sponsor designee will conduct a site visit to verify the qualifications of each Principal Investigator, inspect the site facilities, and inform the Principal Investigator of the responsibilities and procedures for ensuring adequate and correct documentation.

The Principal Investigator is required to maintain adequate and accurate medical records which include all data collected for each study participant. All information recorded on the eCRFs for this study must be verifiable against original source documentation (i.e., medical records). Sponsor or designee Quality Assurance representatives may visit study sites to review data produced during the course of the study, and to assess compliance with applicable regulations pertaining to the conduct of clinical studies.

10.2 CASE REPORT FORMS AND SOURCE DOCUMENTATION

All data obtained during this study should be captured in the Electronic Data Capture (EDC) system promptly. All source documents from which EDC system entries are derived should be placed in the patients' medical records. Measurements for which source documents are usually available include laboratory assessments.

The original EDC system entries for each patient during the 12-week period may be checked against source documents at the study site by the designated site monitor. After review by the site monitor, completed EDC system entries will be uploaded for processing. Instances of missing or uninterpretable data will be discussed with the Principal Investigator for resolution.

The specific procedures to be used for data entry and query resolution using the EDC system will be provided to study sites in a training manual. In addition, site personnel will receive training on the EDC system.

10.2.1 Data Collection

Access to the eCRFs will be carefully controlled and configured according to each individual's role throughout the study. In general, only the Principal Investigator and authorized staff will be able to enter data and make corrections in the eCRFs.

The eCRF should be completed for each patient included in the study and should reflect the latest observations on the patients participating in the study. Therefore, the eCRFs are to be completed as soon as possible during or immediately after the patient's visit or assessment. The Principal Investigator must verify that all data entries in the eCRF are accurate and correct. If some assessments cannot be done, or if certain information is unavailable, not applicable, or unknown, the Principal Investigator should indicate this in the eCRF. Manual checks will identify any clinical data discrepancies for resolution. Corresponding queries will be loaded into the system and the site will be informed about new issues to be resolved on-line. All discrepancies will be solved on-line directly by the Investigator or by authorized staff. Off-line edit checks will be done to examine relationships over time and across panels to facilitate quality data.

After completion, the Principal Investigator will be required to approve the eCRF pages containing the clinical data.

Data about all study drugs dispensed to the patient will be tracked on eCRFs.

10.3 ACCESS TO SOURCE DATA

During the course of the study, a monitor will make site visits to review protocol compliance, compare eCRFs and individual patients' medical records, assess drug accountability, and ensure that the study is being conducted according to pertinent regulatory requirements. Electronic case report form entries will be verified with source documentation. The review of medical records will be performed in a manner to ensure that patient confidentiality is maintained.

Checking of the eCRFs for completeness and clarity, and cross-checking with source documents, will be required to monitor the progress of the study. Moreover, regulatory authorities of certain countries, Institutional Review Boards (IRBs), Independent Ethics Committees (IECs), and/or the Sponsor's Clinical Quality Assurance Group or designee may wish to carry out such source data checks and/or on-site audit inspections. Direct access to source data will be required for these inspections and audits; they will be carried out giving due consideration to data protection and medical confidentiality. The Principal Investigator assures the Sponsor and designee of the necessary support at all times. Local/country specific data protection law is applicable and will be followed.

10.4 DATA PROCESSING

All data will be entered by site personnel into the eCRFs.

The Data Cleaning Specification, to be developed during the initiation phase of the study, will include specifications for consistency and plausibility checks on data, and also include rules for data handling (e.g., what fields are entered for Screen Failures).

Previous and concomitant medications will be coded using the World Health Organization (WHO) Drug Reference List (DRL), which employs the Anatomical Therapeutic Chemical (ATC) classification system. Medical history/current medical conditions and AEs will be coded using MedDRA terminology.

The versions of the coding dictionaries can be obtained or provided by Therakos, Inc.

10.5 ARCHIVING STUDY RECORDS

According to ICH guidelines, essential documents should be retained for a minimum of 2 years after the last approval of a marketing application in an ICH region, and until there are no pending or contemplated marketing applications in an ICH region, or until at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. However, these documents should be retained for a longer period if deemed necessary by other applicable regulatory requirements.

10.6 GOOD CLINICAL PRACTICE

The procedures set out in this study protocol are designed to ensure that the Sponsor and Principal Investigator abide by the principles of the GCP guidelines of the ICH and the [Declaration of Helsinki \(1996\)](#). The study also will be carried out in compliance with local legal requirements.

10.7 INFORMED CONSENT/ASSENT

Before each patient is admitted to the study, informed consent/assent will be obtained from the patient (or his/her parent, legal guardian or legally authorized representative) according to the regulatory and legal requirements of the participating country. The ICF must be dated and retained by the Principal Investigator as part of the study records. The Principal Investigator will not undertake any investigation specifically required only for the clinical study until valid consent/assent has been obtained. The terms of the consent/assent and when it was obtained must also be documented in the eCRF.

If a protocol amendment is required, the ICF may need to be revised to reflect the changes to the protocol. If the ICF is revised, it must be reviewed and approved by the appropriate IRB and Ethics Committee and signed by all patients subsequently enrolled in the study as well as those currently enrolled in the study.

10.8 PROTOCOL APPROVAL AND AMENDMENT

Before the start of the study, the study protocol and/or other relevant documents will be approved by the IRBs, Ethics Committees and Competent Authorities (if applicable) in accordance with local legal requirements. The Sponsor must ensure that all ethical and legal requirements have been met before the first patient is enrolled in the study.

The protocol and IRB approval will be submitted to the Investigational New Drug (IND) application for the product to the U.S. Food and Drug Administration for notification/comment.

This protocol is to be followed exactly. To alter the protocol, amendments must be written, approval must be received from the appropriate personnel, and approval must be received from the IRB or Ethics Committees before implementation (if appropriate per regulatory requirements). Following approval, the protocol amendment(s) will also be submitted to the IND under which the study is being conducted and to Competent Authorities (if appropriate per regulatory requirements).

Administrative changes may be made without the need for a formal amendment. All amendments will be distributed to all protocol recipients, with appropriate instructions.

10.9 DURATION OF THE STUDY

For an individual patient, the maximum duration of treatment will be up to 12 weeks, not including the Week 26 Overall Survival assessment. The study is expected to last approximately 3 years.

10.10 PREMATURE TERMINATION OF THE STUDY

If the Principal Investigator, the Sponsor, or the Medical Monitor becomes aware of conditions or events that suggest a possible hazard to patients should the study continue, the study may be terminated after appropriate consultation among the relevant parties. The study may also be terminated early at the Sponsor's discretion in the absence of such findings.

Conditions that may warrant termination include, but are not limited to:

- Discovery of an unexpected, significant, or unacceptable risk to patients enrolled in the study.

- Failure to enroll patients at an acceptable rate.
- Recommendation of the DSMB.

10.11 CONFIDENTIALITY

All study findings and documents will be regarded as confidential. The Principal Investigator and members of his/her research team must not disclose such information without prior written approval from the Sponsor.

The anonymity of participating patients must be maintained. Patients will be identified on eCRFs and other documents submitted to [REDACTED] by their patient number, initials, and/or birth date—NOT by patient name. Documents not to be submitted to [REDACTED] that identify the patient (e.g., the signed ICF) must be maintained in confidence by the principal Investigator.

10.12 OTHER ETHICAL AND REGULATORY ISSUES

If a significant safety issue is identified, either from an individual case report or from a review of aggregate data, then the Sponsor will issue prompt notification to all parties—regulatory authorities, Principal Investigators, IRBs, Ethics Committees and Competent Authorities (if applicable).

A significant safety issue is one that has a significant effect on the course of the clinical trial or program (including the potential for suspension of the trial program or amendments to protocols) or warrants immediate update of informed consent/assent.

10.13 LIABILITY AND INSURANCE

It is assumed that the Principal Investigators have reasonable third-party liability insurance coverage in accordance with all local legal requirements. The civil liability of the Principal Investigator, the persons instructed by him/her, and the hospital, practice, or institution at which they are employed, with respect to financial loss due to personal injury and other damage that may arise as a result of the carrying out of this study, are governed by the applicable law.

10.14 PUBLICATION POLICY

As this is a Therakos, Inc.-sponsored study, Therakos, Inc. will be responsible for publication of study results. The results of this study may be published in a medical publication or journal or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority registries as well as for publication on health authority study registry Web sites as required by local health authority regulations.

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12. APPENDICES

12.1 APPENDIX A: MODIFIED IBMTR SEVERITY INDEX

Table 4. Criteria for Modified IBMTR Severity Index for aGvHD

Index ^a	Skin Involvement		Liver Involvement			GI Involvement			Upper GI Involvement			
	Stage	Extent of Rash	Stage	Total Bilirubin (mg/dL)	Stage	Volume of Diarrhea (stool output/day)		Stage	Clinical Features			
						Patients < 50 kg	Patients ≥ 50 kg					
A	1	< 25%	0	< 2 (< 34 μmol/L)	0	< 10 mL/kg/d	< 500 mL/d	0				
B ^b	2	25-50%	or	1-2	2-6 (34-102 μmol/L)	or	1-2	10-30 mL/kg/d	500-1500 mL/d	or	1	Nausea, vomiting, anorexia, epigastric pain or burning, and/or food intolerance with a positive upper GI biopsy
C	3	> 50%	or	3	6-15 (103-255 μmol/L)	or	3	> 30 mL/kg/d	> 1500 mL/d	–		
D	4	Bullae	or	4	> 15 (> 255 μmol/L)	or	4	Severe abdominal pain with or without ileus		–		

^a Assign Index based on maximum involvement in an individual organ.

^b Grade B aGvHD includes patients with stage 2 skin and no visceral aGvHD, or stage 0-2 skin and stage 1-2 visceral aGvHD.

12.2 APPENDIX B: MODIFIED GLUCKSBERG CRITERIA**Table 5. Modified Glucksberg Criteria for aGvHD**

Stage	Skin	Liver (bilirubin mg/dL)	Gut (stool output/day)	
			Patients < 50 kg	Patients ≥ 50 kg
0	No GvHD rash	< 2.0	< 10 mL/kg/day	< 500 mL/day or persistent nausea
1	Maculopapular rash < 25% BSA	2.0-3.0	< 10-19.9 mL/kg/day or persistent nausea, vomiting or anorexia, with a positive upper GI biopsy	500-999 mL/day or persistent nausea, vomiting or anorexia, with a positive upper GI biopsy
2	Maculopapular rash 25%-50% BSA	3.1-6.0	20-30 mL/kg/day	1000-1500 mL/day
3	Maculopapular rash > 50% BSA	6.1-15.0	> 30 mL/kg/day	> 1500 mL/day
4	Generalized erythroderma plus bullous formation	> 15.0	Severe abdominal pain with or without ileus	

Grade	Skin	Liver	Gut
I	Stages 1-2	None	None
II	Stage 3 or	Stage 1 or	Stage 1
III	—	Stages 2-3 or	Stage 2-4
IV	Stage 4 or	Stage 4	—

BSA, body surface area; GI, gastrointestinal; GvHD, graft-versus-host disease.

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