

Request for Medicare National Coverage Determination:

Extracorporeal Photopheresis for the Treatment of
Refractory Chronic Graft-Versus-Host Disease

April 16, 2006

Submitted by:

Therakos Inc.
437 Creamery Way
Exton, PA 19341

Contact information:

Dennis DeCola
VP of Compliance and Scientific Affairs
Tel: 610-280-1004
Fax: 610-280-1087
E-Mail: ddecola@tksus.jnj.com

Statement of request

Under the National Coverage Determination process, Therakos requests that CMS expand its coverage of Extracorporeal photopheresis (ECP) to include extensive chronic graft-versus-host disease (cGVHD) that has failed to respond to corticosteroids and standard immunosuppressive drug therapy. Specifically, we propose coverage criteria that qualifying Medicare-eligible patients have documented extensive cGVHD that is refractory or resistant to conventional immunosuppressive drug therapy, or are corticosteroid-dependent and require dose reduction to abrogate or diminish the risk of infectious or other complications related to high-dose corticosteroid and other immunosuppressive drug therapy.

This application of photopheresis is (1) supported by an extensive publication record which documents both efficacy in achieving durable remissions and steroid- and drug-sparing benefit, (2) is widely used in clinical practice in the U.S., and (3) is almost universally covered by commercial U.S. insurers for the privately insured non-Medicare population.

Description of the extracorporeal photopheresis procedure

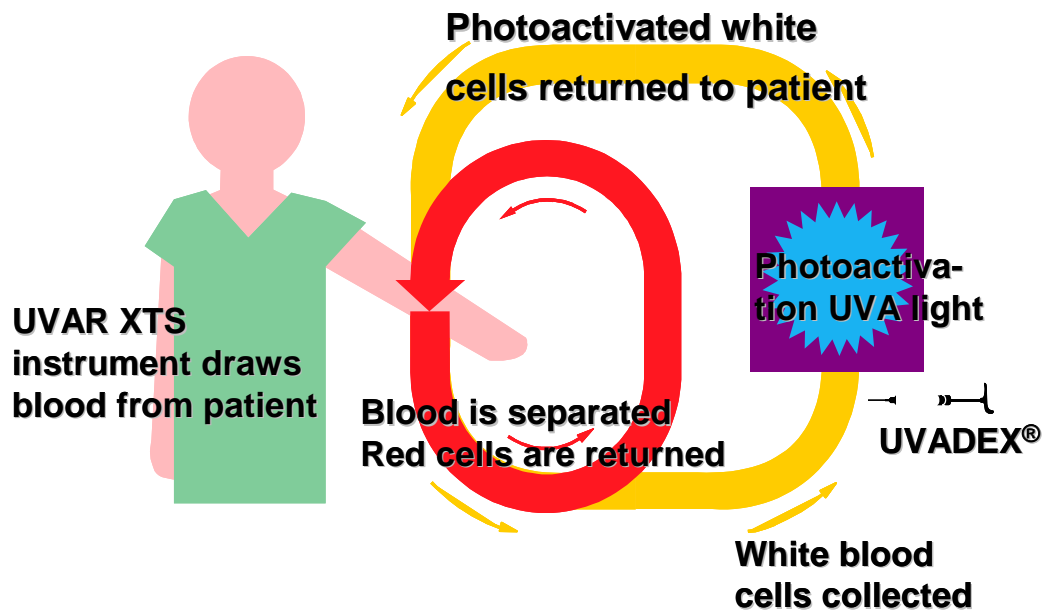
Extracorporeal photopheresis (ECP), also sometimes referred to as extracorporeal photochemotherapy, is a highly specialized procedure designed to induce apoptosis in approximately 10-15% of circulating T-lymphocytes and other leukocytes captured in the buffy coat phase of the patient's blood. This buffy coat is isolated from whole blood removed in a series of 100 mL aliquots by means of a blood cell separation process (apheresis).

As shown in the illustration below, 200 micrograms of liquid methoxsalen* is injected into the bag containing isolated buffy coat cells, then the cells are exposed to ultraviolet A (UVA) light to activate a cross-linking of chromosomal nucleotides and render these cells incapable of replication. The treated T-lymphocytes and other buffy coat cells are returned, along with all other blood components, to the patient's circulation.

A more detailed description of the proprietary Therakos UVAR® XTS System and its operation is presented in Appendix 1. This system received FDA Premarket application (PMA) approval on April 8, 1987 and a new drug application (NDA) for the UVADEX sterile methoxsalen solution was approved on February 25, 1999 (Appendix 2).

The Therakos UVAR XTS System is the sole ECP technology currently cleared by the FDA for marketing in the U.S.

* The trade name for this methoxsalen solution is UVADEX.®



After more than 400,000 procedures performed in the U.S. since 1987, the safety of ECP therapy has been well established. A database review for FDA medical device reportable (MDR) events, inclusive of adverse drug events, yields just 20 MDR events, for a frequency of less than 0.005%.

The most common side effects are transient non-serious hypotensive episodes related to the apheresis procedure and a slight transient decline in hematocrit or hemoglobin level. A single adverse event report relating to UVADEX was filed.

Most of the procedures completed with this system have been for treatment of cutaneous T-cell lymphoma and chronic graft-versus-host disease (cGVHD). The safety profile appears to be equivalent for patients with both diagnoses.

Photopheresis for its indicated use in cutaneous T-cell lymphoma

Cutaneous T-cell lymphoma (CTCL) represents a group of low-grade, non-Hodgkin's lymphomas, which are also identified as mycosis fungoides and Sézary syndrome. In responsive patients, ECP therapy mediates a partial or complete resolution of erythroderma, plaques and other skin manifestations which commonly occur in more advanced disease.

The formal indication for use of the UVAR XTS Photopheresis System is "the palliative treatment of the skin manifestations in cutaneous T-cell lymphoma (CTCL), in persons who have not been responsive to other therapy."

Cutaneous disease response rates have ranged between 50-71% in the significant reported patient series since the first report by Edelson et al in the *New England Journal of Medicine* in 1987:

<i>Study</i>	<i>Treatment response</i>
Edelson RL et al. <i>New Engl J Med</i> 1987; 316(6):297-303	59% (27/37)
Duvic M et al. <i>J Amer Acad Dermatol</i> 1996; 35(4):573-9	50% (17/34)
Zic J et al. <i>Amer Acad Dermatol</i> 1996; 35(6):935-45	50% (10/20)
Gottlieb S et al. <i>Amer Acad Dermatol</i> 1996; 35(6):946-57	71% (20/28)
Evans A et al. <i>Blood</i> 2001; 98(5):1298-1301	57% (13/23)

The standard ECP regimen for CTCL treatment is a “cycle” of two treatments on consecutive days every four weeks. While ECP protocols for cGVHD involve more intensive use of this procedure, a two-treatment cycle every two weeks – sometimes modified to single weekly treatments to address patient scheduling problems – has been adopted by many clinicians now employing this modality.

While the mechanism of action of ECP in CTCL is still not fully defined, it is believed that the combination of ultraviolet light and methoxsalen induces apoptosis in a small subset of circulating clonal tumor or autoreactive T-lymphocytes, resulting in a cytotoxic T-cell response against the larger clone.

A similar mechanism is thought to account for the efficacy of ECP in treatment-responsive patients with extensive cGVHD: a downmodulation of alloreactive donor T-lymphocytes mediated by a host immune response to reinfused apoptotic donor T-cells.

There is growing evidence that infusion of apoptotic cells decreases immune activity. “Immune tolerance” is a term used to describe specific unresponsiveness to antigens. In clinical situations such as graft-versus-host disease it may be useful to capitalize on these natural tolerance mechanisms to treat patients. These apoptotic cells are taken up by phagocytes (antigen presenting cells) in the body of the patient. Apoptotic cell engagement has been reported to induce several changes and functional activities in the engulfing antigen-presenting cell. These antigen-presenting cells: (1) decrease production of proinflammatory cytokines; (2) increase production of anti-inflammatory cytokines; (3) lower ability to stimulate T-cell responses; (4) delete CD8 T effector cells; and (5) induce regulatory T cells. Any and all of these mechanisms could explain the noted effect in graft-versus-host disease. It is still unclear which one or ones are truly responsible. Ongoing studies in animals and human trials will ultimately unravel these details. (Reference publication Maeda 2005 under appendix 5.)

Characterization of chronic GVHD

Chronic GVHD (cGVHD) is a frequent major complication of allogeneic hematopoietic stem cell transplantation (HSCT). It results when immunologically competent donor cells react against alloantigens present in the recipient but absent from the donor. The pathogenesis of this syndrome is incompletely understood, like CTCL, it is believed to involve a T cell-mediated immune dysfunction.

Patients with cGVHD present with features which closely resemble certain autoimmune and other immunologic disorders, such as scleroderma, wasting syndrome, primary biliary cirrhosis, bronchiolitis obliterans (BO) and chronic immunodeficiency.

Chronic GVHD can affect almost any organ. Most commonly it involves the immune system, skin, eyes, mouth, liver, gastrointestinal tract, lungs, and nerve and muscle tissue:

<i>Target organ</i>	<i>Typical manifestations</i>
Skin GVHD	<i>Lichenoid:</i> lichen planus; hypo- or hyperpigmentation; erythema <i>Sclerodermoid:</i> scleroderma; joint contractures; alopecia; nail loss
Liver GVHD	Predominantly cholestatic jaundice; abnormal liver enzymes (most commonly abnormalities in alkaline phosphatase)
Lung GVHD	Bronchiolitis obliterans (BO) and less commonly BO with organizing pneumonia (BOOP)
Oral GVHD	Dryness of mouth; leukoplakia ; lichenoid changes
GI tract GVHD	Esophageal stricture; diarrhea; weight loss
Ocular GVHD	Keratoconjunctivitis, sicca; dry eyes; vision changes
Musculoskeletal GVHD	Fasciitis

Initial diagnosis of cGVHD is generally based on the presence of one or more of these characteristic manifestations including:

- Lichenoid or sclerodermal skin involvement

- Ocular dryness that cannot be relieved by artificial tears
- Dryness or lichenoid involvement of oral and vaginal mucosa
- Gastrointestinal strictures

Confirmation of cGVHD affecting the liver is based on hyperbilirubinemia or alkaline phosphatase elevations with biopsy confirmation in the setting of one of these aforementioned manifestations. Chronic GVHD affecting the lungs invariably manifests as bronchiolitis obliterans, the diagnosis of which involves the presence of symptoms, functional deficits, radiological or pathological findings and the exclusion of active infection in the respiratory tract.

Symptoms of cGVHD almost invariably develop within the first three years after allogeneic HSCT, with as many as 95% of cases occurring within the first year.¹ With many exceptions, prognosis is generally better for *de novo* cGVHD than progressive or quiescent cGVHD which follows an acute GVHD phase. Aside from prior acute GVHD, there are other known risk factors for poor prognosis in patients with cGVHD, such as a female donor cell transplant into a male donor, liver dysfunction and thrombocytopenia.

Chronic GVHD can develop as a continuation of acute GVHD (“progressive” onset), after an episode of acute GVHD has fully resolved (“relapsing” or “quiescent” onset) or in patients who did not experience acute GVHD during the first 100 days post-transplant (“*de novo*” onset). A history of prior acute GVHD is itself a risk factor for cGVHD.

Reported incidence rates of cGVHD following allogeneic HSCT vary from 35-65% of allotransplanted patients, in accordance with the distribution of such risk factors as recipient age, donor type, prior acute GVHD experience, hematopoietic stem cell source (bone marrow, peripheral blood or cord blood), manipulation of the stem cell graft (e.g. T-cell depletion) and use of posttransplantation donor lymphocyte infusions. Each of these same variables may act to influence the prognosis of patients started on ECP after having failed immunosuppressive therapy. These multiple confounders, in conjunction with typically small reported case series and the lack of standardization in cGVHD treatment, make it impossible to evaluate ECP-related clinical outcomes by underlying leukemia, lymphoma or other diagnosis.

Currently, the severity of cGVHD is classified simply as *limited* or *extensive*, defined as follows:

Limited: Localized skin involvement and/or hepatic dysfunction

Extensive: Morbidity patterns as described in 1 and 2 below

¹ Lee S. New approaches for preventing and treating chronic graft-versus-host disease. *Blood* 2005; 105(11):4200-6.

1. Generalized skin involvement *or* localized skin + hepatic dysfunction
plus
2. Hepatic dysfunction and abnormal liver histology; *or* involvement of eye, minor salivary glands or oral mucosa on labial biopsy; *or* involvement of any other target organ.

In December 2005, in an attempt to better classify this heterogeneous disorder, an NIH Working Group published new proposed guidelines for global assessment of cGVHD.² Their model addresses the number of organs or sites involved and the degree of involvement in affected organs (mild, moderate or severe). However, this proposed scoring-based approach, intended to replace the current “limited” versus “extensive” categorization has not yet had a chance to be applied in clinical practice or widely incorporated into cGVHD research protocols.

Photopheresis therapy is currently used only in the management of *extensive* (moderate or severe) treatment-refractory cGVHD.

Post-transplant prophylaxis and immunosuppressive therapy for cGVHD

Shortly before and for at least six months following allogeneic HSCT, patients receive a prophylactic immunosuppressive drug regimen. While this regimen still has not been standardized, a 2002 survey of approximately 50% of U.S. transplant centers indicates that cyclosporine, tacrolimus, standard methotrexate, mini-methotrexate and T-cell depletion are the predominant modalities in use.³ Popular combinations include one of the two calcineurin inhibitors in combination with either methotrexate or mini-methotrexate.

Despite immunoprophylaxis, approximately 50% of post-HSCT patients develop acute GVHD, varying by such risk factors as stem cell source and degree of HLA match. Acute GVHD is in turn an important risk factor for cGVHD; one’s risk of developing cGVHD is roughly twice as high with than without prior acute GVHD (de novo form): about 60% versus 30% on an overall basis.

For patients who develop cGVHD despite this immunosuppressive therapy, corticosteroids (IV methylprednisolone or oral prednisone) are the first-line therapy, producing an approximately 30% complete response,⁴ as well as partial cutaneous and visceral im-

² Filipovich AH, Weisdorf D, Pavletic S et al. National Institutes of Health Consensus Development Project on Criteria for Clinical Trials in Chronic Graft-versus-Host Disease: I. Diagnosis and Staging Working Group Report. *Biol Blood Marrow Transplant* 2005; 945-56.

³ Lee SJ, Vogelsang G, Gilman A et al. A survey of diagnosis, management, and grading of chronic GVHD. *Biol Bone Marrow Transplant* 2002; 8:32-9.

⁴ Johnson ML, Farmer ER. Graft-versus-hos reactions in dermatology. *J Am Acad Dermatol* 1998;38:369-92.

provements determined to be adequate. However, cGVHD is frequently steroid-refractory (or the patient's steroid dose cannot be tapered without resurgence of disease).

Unfortunately, none of a number of immunosuppressive agents or other treatment modalities evaluated as potential second-line therapy appears to substantially improve the dismal prognosis of patients who require salvage therapy for cGVHD.^{5,6} Among the modalities that have recently been evaluated are mycophenolate mofetil (MMF), antithymocyte globulin, thalidomide, infliximab and PUVA.

Chronic GVHD is considered *steroid-refractory* or *steroid-resistant* (or drug-refractory or drug-resistant) when (1) patients have stable disease (i.e. no response) after one month of treatment, (2) no more than a partial response has occurred after two months of treatment or (3) progressive disease occurs within two weeks after initiation of steroid treatment or during the steroid taper.

Maintenance of patients on corticosteroid treatment predisposes them to avascular necrosis and to severe systemic infections. For this reason, once a clinical response has been achieved with corticosteroids they are usually tapered as tolerated, in order to reduce the rate of these serious and often life-threatening complications.

When corticosteroids cannot be tapered in a steroid-responsive patient without a cGVHD flare or relapse, the patient is said to be *steroid-dependent*.

Photopheresis for cGVHD: proposed mechanisms of action

The pathogenic and clinical similarities of cGVHD and CTCL prompted a number of investigators to evaluate ECP for treatment of cGVHD patients who had failed conventional drug therapy.

As described earlier, a possible mechanism by which ECP mediates its anti-cGVHD effect is through a down modulation of alloreactive donor T-lymphocyte activity by a host immune response to a subpopulation of reinfused apoptotic donor T-cells. Another hypothesis is that host phagocytes (antigen-presenting cells) take up apoptotic cells prepared by the ECP procedure, in turn inducing several functional changes in the engulfing antigen-presenting cell. These antigen-presenting cells mediate (1) decreased production of proinflammatory cytokines, (2) increased production of anti-inflammatory cytokines,

⁵ Flowers ME, Kansu E, Sullivan KM. Pathophysiology and treatment of graft-versus-host disease. *Hematol Oncol Clin North Am* 1999; 13(5):1091-1112.

⁶ Komanduri KV, Couriel D and Champlin RE. Graft-versus-host disease after allogeneic stem cell transplantation: evolving concepts and novel therapies including photopheresis. *Biol Blood Marrow Transplant* 2006; 12:1-6.

(3) reduced ability to stimulate T-cell responses, (4) anti-CD8 T effector cell deletion and (5) induction of regulatory T-cells. Any or some combination of these mechanisms could explain the effect of ECP therapy in responsive patients with cGVHD.

There is growing evidence that infusion of apoptotic cells decreases immune activity. "Immune tolerance" is a term used to describe specific unresponsiveness to antigens. In clinical situations such as graft-versus-host disease it may be useful to capitalize on these natural tolerance mechanisms to treat patients. These apoptotic cells are taken up by phagocytes (antigen presenting cells) in the body of the patient. Apoptotic cell engagement has been reported to induce several changes and functional activities in the engulfing antigen-presenting cell. These antigen-presenting cells: (1) decrease production of proinflammatory cytokines; (2) increase production of anti-inflammatory cytokines; (3) lower ability to stimulate T-cell responses; (4) delete CD8 T effector cells; and (5) induce regulatory T cells. Any and all of these mechanisms could explain the noted effect in graft-versus-host disease. It is still unclear which one or ones are truly responsible. Ongoing studies in animals and human trials will ultimately unravel these details.

Following several early case reports citing positive clinical outcomes,^{7,8,9} Greinix and colleagues at the University of Vienna reported complete or partial resolution of extensive cutaneous cGVHD in 15 patients, complete resolution of oral mucosal lesions in all 11 affected patients, and partial or complete resolution of hepatic cGVHD in 10 of 11 affected patients. This has been followed by several dozen subsequent case series and clinical reviews over the last eight years.

A complete bibliography of the ECP/cGVHD literature is attached as Appendix 3.

Limitations to ECP outcome assessment by underlying diagnosis or type of cGVHD

Because of (1) unusual heterogeneity relating to cGVHD risk and prognostic factors, (2) unusual heterogeneity in cGVHD disease presentations, (3) lack of standardization of GVHD prophylaxis and treatment regimens from center to center, (4) individualized tailoring of cGVHD treatment and (5) very small numbers of subjects with multiple underlying diagnoses in reported case series, it is not possible to comparatively assess the clinical utility of ECP by:

- Underlying hematological disease state or

⁷ Gerber M, Gmeinhardt B, Volc-Platzer B et al. Complete remission of lichen-planus-like graft-versus-host disease (GVHD) with extracorporeal photochemotherapy (ECP). *Bone Marrow Transplant* 1997; 19:517.

⁸ Besnier DP, Chabannes D, Mahe B et al. Treatment of graft-versus-host disease by Extracorporeal photochemotherapy. *Transplantation* 1997; 64:49.

⁹ Dall' Amico R, Rossetti F, Zulian F et al. Photopheresis in paediatric patients with drug-resistant chronic graft-versus-host disease. *Br J Haematol* 1997; 97:848.

- Type of chronic GVHD (de novo, progressive or relapsing/quiescent)

Pooling of case series to try to stratify the ECP-treated population by underlying disease or cGVHD type is additionally confounded by such factors as variable delay to ECP treatment and variations in HLA and gender matching.

Assessment of responsiveness to ECP therapy and analysis of the literature

Nearly all published case series define responsiveness to ECP therapy with the following descriptors:

- **Complete remission (CR):** resolution of all manifestations of cGVHD
- **Partial remission (PR):** $\geq 50\%$ improvement in at least one target organ without a CR
- **No response (NR)**

Investigators at one center defined PR by target organ as follows:

<i>Target organ</i>	<i>Typical manifestations</i>
Skin	<i>Lichenoid rashes:</i> minimum 50% reduction of body surface area <i>Sclerodermoid:</i> any improvement in skin score or range of motion, with an improvement of Zubrod performance status by 1
Liver and GI	Decrease by minimum of 50% in volume of diarrhea, bilirubin or alkaline phosphatase
Lung (BO)	Sustained improvement in pulmonary function tests (FEV1) and/or the ability to taper corticosteroids by 50% without deterioration of pulmonary function
Oral GVHD	Dryness of mouth; leukoplakia
Ocular GVHD	Subjective improvement and reduction in the frequency of artificial tear administration by 50%, or improvement in Schirmer's test for one or both eyes

While cGVHD manifestations may be limited only to the skin in one-third or more of patients with extensive disease, the majority have involvement of two or more target organs. In assessing overall response, patients identified as responders generally must have had improvement in at least one affected organ without progression in any other affected organs.

In addition to improvement or resolution of overt disease manifestations, another important ECP treatment outcome measure is ability to taper or entirely wean the patient from corticosteroids added to the immunosuppressive regimen to combat the cGVHD. Prolonged steroid dependence puts patients at very high risk of avascular necrosis and severe systemic infections; infections are the most frequent cause of death in non-relapsed patients.

Most significant reported case series have defined a steroid-sparing ECP treatment response as (1) discontinuation of corticosteroid therapy or (2) a minimum 50% corticosteroid dose tapering.

In nearly all reported case series, ECP treatment is initiated in patients with non-responsive or worsening cGVHD despite use of two or more lines of immunosuppression, including corticosteroids and calcineurin inhibitors (cyclosporine or tacrolimus).

The heterogeneity of cGVHD presentations and prognostic factors, a lack of a standardized treatment algorithm for cGVHD, and the fact that most centers perform fewer than 100 allogeneic stem cell transplants annually (and thus see very limited numbers of treatment-refractory cGVHD cases) account for a predominance of small ECP case series and individual case reports reported in the medical literature.

These factors, together with a general unwillingness by clinicians to randomize half of patients who have failed drug therapy to yet another course of drug therapy, have sharply limited interest in participation in a trial comparing ECP to salvage drug therapy.

With the publication of several case series, beginning in 1998,¹⁰ which documented very substantial PR/CR rates in patients with drug-resistant cGVHD, ECP is now widely considered standard therapy in cGVHD patients who have failed immunosuppressive drug and corticosteroid therapy.

Table 1 (attached) presents ECP/cGVHD outcomes from four single-center studies of adult patients (except where noted) who failed treatment with a calcineurin inhibitor plus corticosteroids, and in some cases failed additional drug therapies :

<i>Citation</i>	<i>Study design</i>	<i>n</i>
Couriel et al (2005) ¹¹	Uncontrolled case series	71
Foss et al (2005) ¹²	Prospective uncontrolled study	24

¹⁰ Greinix HT, Volc-Platzer B, Rabitsch W et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood* 1998; 92(9):3098-3104.

¹¹ Couriel DR, Hosing C, Saliba R et al. Extracorporeal photochemotherapy for the treatment of steroid resistant chronic GVHD. *Blood* 2005 Dec; prepublished online.

Seaton et al (2003) ¹³	Prospective uncontrolled study	34
Greinix et al (1998) ¹⁴	Prospective uncontrolled study	15

Additional uncontrolled case series exceeding 10 subjects have been reported by Abhyankar et al (1998),¹⁵ Child et al (1999),¹⁶ Sniecinski et al (1998)¹⁷ and others, and are summarized in the BlueCross BlueShield Association's 2001 technology assessment addressing ECP for graft-versus-host disease.¹⁸

Findings in these early studies are generally very consistent with findings in the selected case series. However, for various reasons, including non-description of objective outcome measures, selection of patients with a specific organ involvement, or use of a now-discontinued treatment regimen involving oral administration of 8-methoxypsoralen instead of the current extracorporeal mixing of drug with buffy coat cells, they are not reviewed in this request for coverage determination. Additionally, Appendix 6 contains a listing of 14 journal articles briefly summarized in table format. These publications provide further evidence that generally support the use of photopheresis in patients with steroid-immunosuppressive refractory cGVHD. We have provided reprints for these 14 publications. Appendix 7 contains a complete bibliography of all published articles on the subject of treating GVHD with photopheresis.

The 71-patient MD Anderson case series and other larger ECP/cGVHD case series

-
- ¹² Foss FM, DiVenuti GM, Chin K et al. Prospective study of Extracorporeal photopheresis in steroid-refractory or steroid-resistant extensive chronic graft-versus-host disease: analysis of response and survival incorporating prognostic factors. *Bone Marrow Transplantation* 2005; 35:1187-93.
- ¹³ Seaton ED, Szydlo RM, Kanfer E et al. Influence of Extracorporeal photopheresis on clinical and laboratory parameters in chronic graft-versus-host disease and analysis of predictors of response. *Blood* 2003; 102:1217-23.
- ¹⁴ Greinix HT, Volc-Platzer B, Rabitsch W et al. Successful use of extracorporeal photochemotherapy in the treatment of severe acute and chronic graft-versus-host disease. *Blood* 1998; 92(9):3098-3104.
- ¹⁵ Abhyankar S, Bishop M and the Photopheresis and GvHD Study Group. Adjunctive treatment of resistant chronic graft versus host disease, with extracorporeal photopheresis, using UVADEX sterile solution. *Blood* 1998; 92(Suppl 1):454a (abstract 1876).
- ¹⁶ Child FJ, Ratnavel R, Watkins P et al. Extracorporeal photopheresis (ECP) in the treatment of chronic graft-versus-host disease (GVHD). *Bone Marrow Transplant* 1999;23(9):881-7.
- ¹⁷ Sniecinski I, Parker P, Dgis A et al. Extracorporeal photopheresis for treatment of drug-resistant graft-vs.-host disease. *Blood* 1998; 92(10 Suppl 1):454a (abstract 1877).
- ¹⁸ Technology Evaluation Center. BlueCross BlueShield Association. Extracorporeal Photopheresis for Graft-Versus-Host Disease. November 2001; 16(9):1-21.

Because it now constitutes the largest-ever case series and present detailed clinical response data and risk assessments, a recently published report by Couriel et al at the University of Texas MD Anderson Cancer Center is reviewed below, with comparisons to findings from three other case series summarized in Table 1.

Seventy-one steroid-refractory cGVHD patients treated with ECP at MD Anderson between 1/98 and 10/02 were stratified into 2 groups according to number of prior immunosuppressive therapies, in order to minimize the confounding influence of multiple lines of immunosuppression and thus better understand the effects of ECP:

1. ≤ 3 lines of immunosuppression
2. > 3 lines of immunosuppression including calcineurin inhibitors and steroids

Mortality in MD Anderson case series. Overall non-relapse mortality in the eight “heavily pretreated” patients (treated with > 3 lines of immunosuppression before receiving ECP) was not significantly different compared with the less immunosuppressed subgroup of 63 patients (50% vs. 41%, NS). However, as shown in the table below, the cumulative incidence of progression after responding to ECP was 100% compared to 22% in patients who received ≤ 3 lines of immunosuppression.

The MD Anderson patient series found a highly significant reduction in mortality in ECP responders versus non-responders (24% non-relapse mortality in 37 responders vs. 65% in non-responders; $p < 0.0001$). Most of these deaths were related to cGVHD.

The association between extent of prior immunosuppression and non-relapse mortality over the median 34-month follow-up period was also pronounced, with a three-fold longer median survival (18 versus 6 months) in the group that received less immunosuppressive therapy prior to initiation of ECP:

	<u>> 3 lines (n = 8)</u>	<u>≤ 3 lines (n = 63)</u>	
Cumulative incidence of cGVHD progression after responding to ECP	100%	22%	
Nonrelapse mortality	50%	41%	p = 0.4 (NS)
Median survival post-ECP	6 months	18 months	

Sharply lower median survival in “heavily pretreated” cGVHD patients in this large MD Anderson patient series is partly a reflection of the fact that current immunosuppressive treatment options for cGVHD are generally poorly effective. In this small subset of 8 patients with multiple lines of prior immunosuppression, 7 had died at 19 months since initiation of ECP therapy.

Further, this evidence that median survival is reduced in patients treated longer and with more immunosuppressive is consistent with proposed mechanisms of action for ECP, all of which are predicated on host cellular immune responsiveness to reintroduced apoptotic donor T-lymphocytes. With prolonged and added lines of immunosuppression, host immune function is further compromised, and thus the direct or indirect suppression of the donor T-lymphocyte directed attack on host tissues and organs which manifests as cGVHD is also compromised.

Mortality experience in other case series. In their 25-patient prospective case series, Foss et al reported that, while not reaching statistical significance, 72-month mortality was approximately 35% in ECP responders and 55% in non-responders. These data are reasonably consistent with the MD Anderson experience (24% versus 65% non-relapse mortality in responders and non-responders). Correspondingly, median survival in ECP responders was 55 months versus 39 months in non-responders ($p=0.3$); responders received a median of 12 cycles of ECP therapy (24 treatments) versus a median of just 5 cycles in non-responders.

Disease remission rates. As summarized in Table 1, the overall response rate to a median of 32 ECP procedures (range 1-259 procedures) in the MD Anderson case series was 65% (disease remission in at least one target organ). Disease remission rates (both CR and PR) for skin, liver, oral and ocular cGVHD were 59%, 71%, 77% and 67%, respectively.

These results are generally consistent with response rates reported by Foss et al, Greinix et al (Table 1), as well as a large review of 20 older case reports and case series by Dall' Amico et al¹⁹. The 2002 Dall' Amico review of a total of 204 cGVHD patients treated with ECP (including non-UVAR XTS technologies available in Europe) documented regression of skin manifestations in 76% of patients with a complete remission in 35%. Improvement in liver and lung involvement was reported in 48% and 39% of affected patients, respectively. A review of nine early case series also found that ECP achieved very high skin and mucosal remission rates ($\geq 75\%$), but rates of partial or complete resolution of cGVHD of the liver, lung and other target organs were far more variable across individual case studies.²⁰

In an 2003 report on 32 of its eventual 71-patient series, MD Anderson investigators noted that there was a 13.1-month duration between onset of cGVHD and ECP therapy in non-responders, compared with a 5.9-month time gap for complete responders. However, there was no meaningful association between delay from cGVHD onset and initiation of ECP when they examined PR rate. This and other observations provide evidence that early initiation of ECP could be associated with higher CR rates, but PRs are still

¹⁹ Dall' Amico R and Messina C. Extracorporeal photochemotherapy for the treatment of graft-versus-host disease. *Therapeutic Apheresis* 2002; 6(4):296-304.

²⁰ Sciecinski I. Photochemotherapy for GvHD. *Intl J Artif Organs* 2000; 23(1):1-10.

frequently seen in patients who are started on ECP much later.²¹ Separately, Foss et al observed that response rates were similar (70% vs. 66%) in patients who started ECP earlier after onset of cGVHD (≤ 18 months) and later (>18 months).

Several lines of evidence strongly point to increased remission rates and increased likelihood of CR with earlier initiation of ECP, as opposed to delaying treatment to try additional immunosuppressive drugs or dosing alterations:

- The 2003 MD Anderson case series documented a much shorter duration from onset of cGVHD to ECP therapy in patients who experienced a CR than those with a PR or non-responders;
- In CTCL, patients who are immunocompromised are known not respond as well to ECP therapy;²²
- Couriel et al documented a trend toward increased CR/PR in patients with two prior drug treatments versus those with three prior treatments before initiating ECP (discussed below);
- Very high (80%) global CR was observed by Greinix et al, where ECP was initiated a median of only *12 months* after HSCT, while CR and CR/PR rates are much lower in the Seaton et al series, where the delay was *34 months* and 5 of the 25 patients were subjected to *four or more immunosuppressive drugs prior to initiation of ECP* (see figure on following page).

Again, while early initiation of ECP may offer incremental cGVHD outcomes benefit, at least two significant case series (Foss 2005 and Apisarnthanarax 2003) have respectively reported response rates of 50% and 80% in patients treated with ECP three or more years after the onset of cGVHD, supporting the use of ECP in patients with long-standing disease.

²¹ Apisarnthanarax N, Donato M, Körbling M et al. Extracorporeal photopheresis therapy in the management of steroid-refractory or steroid-dependent cutaneous chronic graft-versus-host disease after allogeneic stem cell transplantation: feasibility and results. *Bone Marrow Transplant* 2003; 31:459-65.

²² Heald P, Rook A, Perez M et al. Treatment of erythrodermic cutaneous T-cell lymphoma with extracorporeal photochemotherapy. *J am Acad Dermatol* 1992; 27:427-33.

Stratification by diagnosis, age and type of cGVHD disease. In a 63-patient subset of the 2005 MD Anderson patient series, all major subgroups by underlying cancer diagnosis experienced a CR/PR rate ranging between about 50-70%:

<u>Diagnosis</u>	<u>N</u>	<u>CR/PR (%)</u>	<u>P</u>
AML/MDS	23	12 (52%)	0.2
CML/MPD	21	14 (67%)	0.3
Lymphomas	13	9 (69%)	0.3

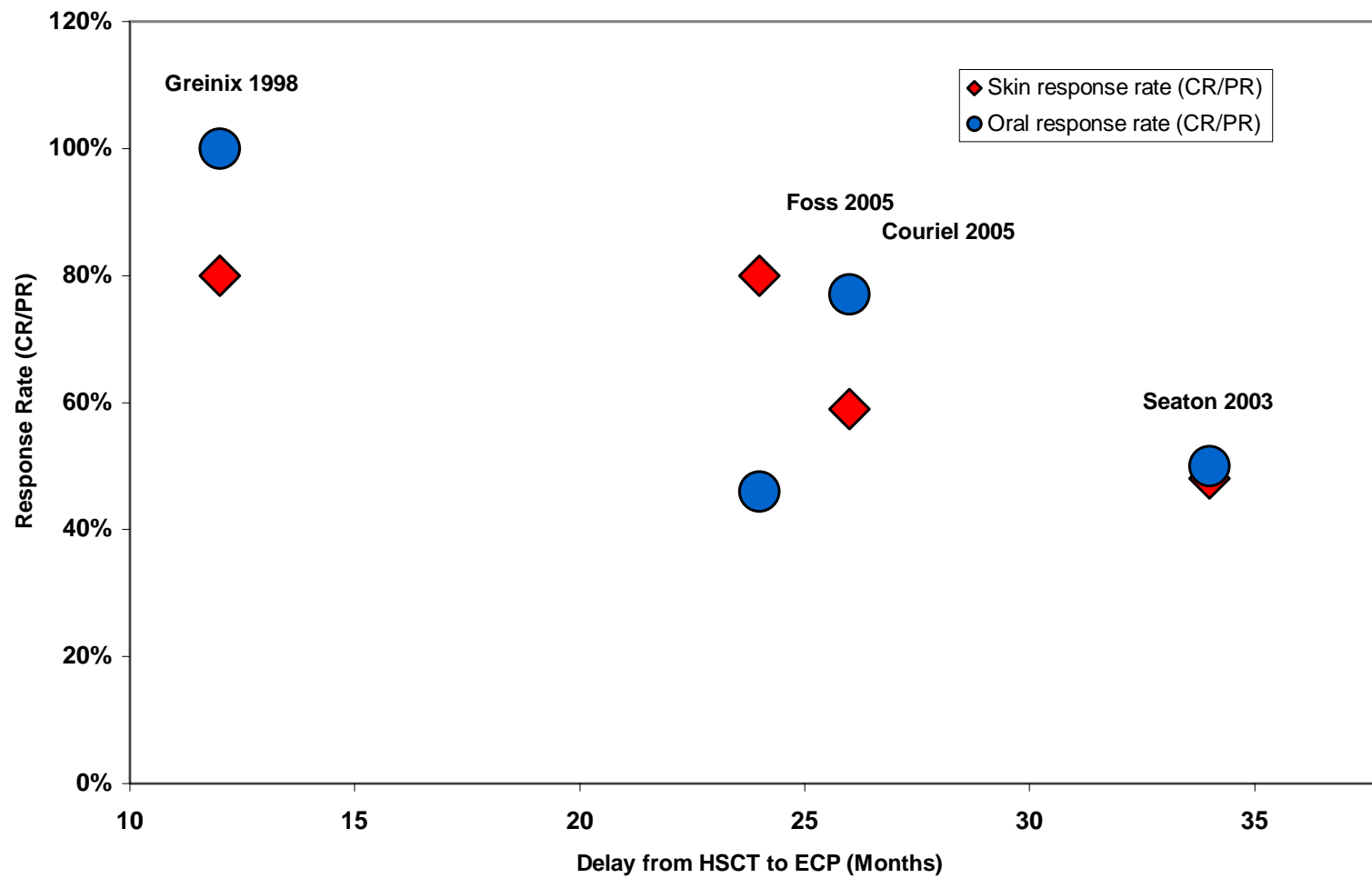
Numbers of cases were too small to identify any statistically significant difference or trend toward a higher or lower efficacy rate in any of these diagnostic subgroups. A total of just six cGVHD patients with underlying diagnoses which variously included ALL, aplastic anemia, sickle cell anemia and breast cancer were also included in this series.

Similarly, neither stratification on age (≤ 50 versus > 50 years) nor number of prior treatments (two versus three) revealed any significant differences or important trends in comparative CR/PR rates in the MD Anderson series:

<u>Age</u>	<u>N</u>	<u>CR/PR (%)</u>	<u>P</u>
≤ 50 years	48	27 (56%)	
> 50 years	15	10 (67%)	0.5
<u>Prior treatments</u>	<u>N</u>	<u>CR/PR (%)</u>	<u>P</u>
2 treatments	40	26 (65%)	
3 treatments	23	11 (48%)	0.2

There is no evidence or from other reported series to suggest that patients older than 65 years are significantly less responsive to ECP.

Skin and Oral cGVHD Response Rates in Relation to Delay from Stem Cell Transplant to Initiation of ECP



An examination of MD Anderson's CR/PR rates by type of chronic GVHD did suggest that patients with *de novo* cGVHD (no prior acute GVHD) may be more responsive to ECP therapy than patients with progressive disease ($P = 0.06$). However, the authors pointed out that, while the median delay from onset of cGVHD to ECP therapy was much longer for patients with *de novo* disease, this was possibly a reflection of less severe forms of disease in that group, likely translating into a delayed need for immediate intervention.

Treatment intensity. Another factor that could influence disease response rates, survival or time from treatment initiation to CR or PR, is the *intensity of ECP therapy*. Table 2 (attached) summarizes the ECP treatment algorithms used by each of the four centers whose case series are reviewed. Again, while treatment schedule is individualized, the MD Anderson protocol exposes patients to roughly twice the number of ECP treatments on average over the first two months of therapy than other centers. Comparative time-to-response data are not available, and multiple confounding factors described earlier preclude any meaningful analysis of treatment intensity on patient outcomes.

Treatment failures. Treatment failures comprise (1) patients who fail to respond with a CR or PR of extensive cGVHD disease involving one or multiple organs and (2) initial responders who subsequently progress despite continuing ECP therapy.

Of 43 patients who initially responded to ECP (in a total of 63 patients), 13 (32%) progressed after a median of 23 days (range 16-188 days). The remaining 30 patients maintained their responses for a median duration of 18 months. At six months following initiation of ECP, 28/44 patients who were alive continued to have a sustained response.

The median number of treatments in this patient series was 32 (range 1 to 359), which is very consistent with other reported series. The median number of treatments in non-responders was not reported in the MD Anderson study or, to our knowledge, in other case series.

Tapering or discontinuation of steroids and other immunosuppressive drugs

Drug therapy for cGVHD involves a balancing act for the specialist. Without aggressive treatment, the prognosis for patients with extensive cGVHD is dismal. But if control of cGVHD requires heavy or ongoing dosing with steroids and immunosuppressive agents, the risk of serious complications and mortality soars.

Clinical improvement secondary to ECP therapy permits the physician to taper or discontinue corticosteroids and other immunosuppressive drugs, and is itself widely reported as an important therapeutic benefit.

Below is a summary of steroid-sparing benefits documented in recent case ECP/cGVHD case series:

<i>Citation</i>	<i>Steroid sparing/discontinuation rate</i>
Couriel et al (2005)	22% cumulative discontinuation of steroids at one year after initiation of ECP therapy 10% discontinuation of all immunosuppressive therapy at one year after initiation of ECP therapy
Foss et al (2005)	52% tapered off corticosteroids 44% had discontinuation of at least one immunosuppressive medication
Apisarnthanarax (2003)	64% of patients achieved a steroid-sparing response, defined as $\geq 50\%$ steroid dose reduction

ECP mediates a steroid-sparing benefit in approximately one-half to two-thirds of patients. The ability of ECP to allow physicians to reduce anti-GVHD immunosuppressive medications may account, in part, for improved survival in ECP responders versus non-responders in several recent case series.²³

BlueCross BlueShield TEC Assessment

In November 2001, the BlueCross BlueShield Technology Evaluation Center published a technology assessment titled *Extracorporeal Photopheresis for Graft-Versus-Host Disease*. This assessment is attached (Appendix 4).

The Medical Advisory Board concluded that:

Extracorporeal photopheresis meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria as therapy for chronic graft-versus-host disease that is refractory to established therapy. Extracorporeal photopheresis does not meet the TEC criteria as therapy for acute GVHD or chronic GVHD that is either previously untreated or is responding to established therapies.

Most of the patient case series on which the TEC based its assessment have been followed by the larger case series presented in this NCD request. Nevertheless, the TEC determined that ECP applied for treatment-refractory cGVHD met all five criteria:

²³ Foss et al (2005).

1. *The technology must have final approval from the appropriate governmental regulatory body (reviewed earlier).*
2. *The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.* The TEC assessment evaluated six studies that reported outcomes in 112 patients with extensive cGVHD that were refractory to one or two lines of immunosuppressive therapy. “These reports provided sufficient evidence to permit conclusions on the health outcomes of ECP for treatment-refractory extensive chronic GVHD.”
3. *The technology must improve the net health outcomes; and*
4. *The technology must be as beneficial as any established alternatives.* The TEC summarized six studies documenting complete resolution and marked symptomatic improvements. “Adverse effects were consistently infrequent, mild, and transient in studies that added a sterile solution of 8-MOP (methoxsalen) directly to cell suspensions after leukapheresis.”

This evidence permits the conclusion that Extracorporeal photopheresis improves the net health outcome for patients with chronic GVHD that is refractory to standard immunosuppressive drug therapy, a disease for which no alternative therapies are available.”

5. *The improvement must be attainable outside the investigational setting.* The TEC concluded that these improvements in health outcome “are achievable outside the investigational setting at centers with experience using the FDA-approved device to treat patients with refractory GVHD and providing supportive care and symptom management to these patients.”

Currently, a total of 44 U.S. bone marrow and stem cell transplant centers are actively providing ECP therapy to patients with refractory cGVHD. These centers account for an estimated 80% of all U.S. allogeneic HSCT cases.

Current non-Medicare insurance coverage and payment patterns for ECP

An October 2004 national survey yielded responses from 42 of 44 active centers using ECP for drug-refractory or steroid-dependent cGVHD at that time. Findings from that survey are as follows:

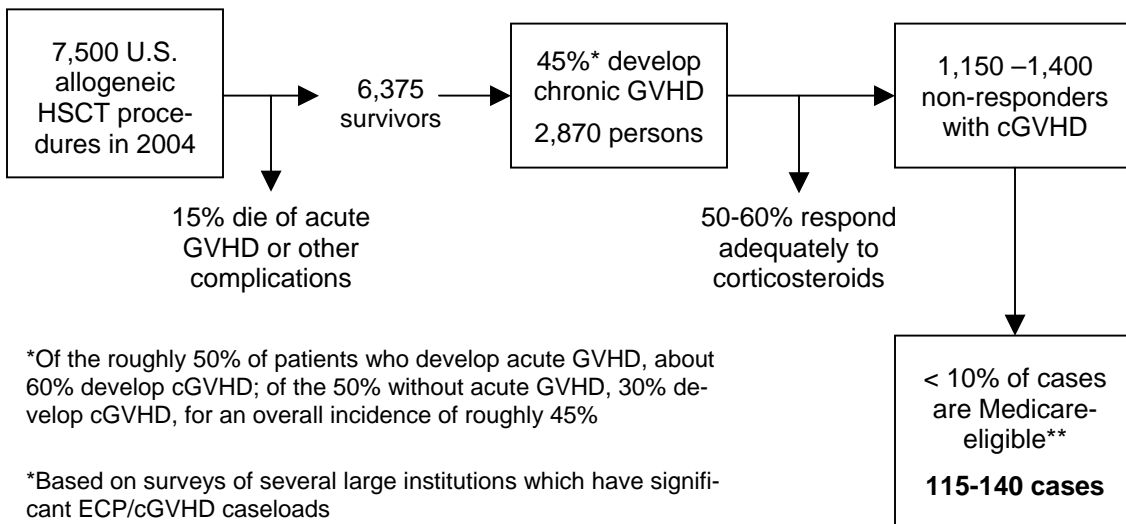
- 39 of 42 centers reported that all commercial insurers always cover and pay for ECP for this clinical use;
- 95 commercial insurers were identified which cover ECP for this clinical use (just three specific instances of non-coverage of individual patients were cited);

- 24 of 25 Blue Cross and Blue Shield Plans identified by surveyed centers cover ECP for cGVHD patients referred for treatment (one respondent identified a single plan – BCBS of Arkansas – which denied coverage for a specific patient; reason not known);
- Leading commercial insurers in addition to BCBS plans which cover ECP for cGVHD include Aetna, United Healthcare, CIGNA, Humana, HealthNet, Harvard Pilgrim Health Plan, Kaiser Permanente, Oxford Health Plan, Pacificare and Tufts Health Plan;

The Medicare cGVHD population

Patients undergoing allogeneic hematopoietic stem cell transplantation (HSCT) for treatment of a leukemia, lymphoma or other hematological disorder must endure the rigors of an intensive myeloablative regimen. While the qualifying age limit has increased in recent years with increasing use of nonmyeloablative regimens, a relatively small share of patients considered good candidates for HSCT are over age 65.

Based on the available literature and a 2005 survey we conducted of several larger institutional providers of ECP for treatment of cGVHD, *we estimate that the annual maximum U.S. target Medicare population is between 115 and 140 individuals.* As shown below, this represents 10% or fewer of the estimated 1,150 to 1,140 Americans with treatment-refractory cGVHD who are potential candidates for ECP:



The Medicare population includes both persons who are Medicare-eligible due to permanent disability status and because of eligibility on the basis of age.

Proposed coverage criteria and benefit categories for ECP

Proposed ECP coverage criteria. Specifically, we propose that qualifying Medicare-eligible patients must have documented extensive cGVHD which is refractory or resistant to conventional immunosuppressive drug therapy, or are corticosteroid-dependent and require dose reduction to abrogate or diminish the risk of infectious or other complications related to high-dose corticosteroid and other immunosuppressive drug therapy.

Proposed initial treatment course coverage limitation. Because treatment intensity can vary widely across centers and individual patients, Therakos proposes that any coverage limitation placed on an initial course of therapy be based on *a specified number of procedures*, as opposed to number of months of therapy. A consensus among several prominent transplant specialists is that patients who are responsive to ECP will generally achieve at least a partial remission in one or more affected organs with 20 ECP procedures.

A patient who has failed, after 20 ECP procedures over a two- to six-month period, to achieve partial or complete remission in at least one organ affected with extensive cGVHD, is very unlikely to attain a meaningful remission with further treatments.

According to several institutional ECP providers that routinely treat cGVHD cases, initial treatment series coverage by commercial insurers tends to follow one of three patterns: (1) approval of treatments for a three- to six-month period without regard to number of procedures during that period, (2) no limitation on period or number of treatments once authorized for coverage, and less frequently (3) coverage of a specified number of ECP treatments. Occasionally, coverage of up to one year is preauthorized as well.

Proposed benefit categories. Applicable benefit categories include (1) hospital outpatient services (2) hospital inpatient services, (3) physician services and (4) the physician-directed office or clinic services. Photopheresis is a covered therapy in both the hospital and physician-directed office or clinic settings.

Projected 2007 fiscal impact on the Medicare program

Well over 95% of ECP procedures for cGVHD are provided in hospital outpatient departments; this is anticipated to be the predominant site of service also for qualifying Medicare beneficiaries.

Using the following simplifying assumptions, Therakos estimates that the nominal fiscal impact of providing coverage for ECP in this population (not considering undefined off-

setting reductions in acute hospitalizations, symptomatic cGVHD disease management and drug cost savings) is \$4.4 million to \$5.4 million in 2007:

- 100% of the 115 to 140 potential candidates are treated with ECP;
- A median of about 30 treatments are provided (based on reported medians of 24 to 36 treatments) over a median four to six months;^{24, 25}
- The 2007 U.S. average payment rate for ECP (CPT 36522) is approximately \$1,600 (the 2006 U.S. average payment rate for APC 0112 is just under \$1,600);
- The Medicare responsibility is 80% of the APC 0112 payment rate.

To the extent that U.S. centers providing ECP are concentrated in higher-than-U.S.-average wage rate areas, the mean payment rate will be marginally higher. To the extent that actual share of the eligible population that actually receives ECP falls below 100%, the actual Medicare outlay will be lower.

²⁴ Seaton et al (2003)

²⁵ Couriel et al (2005)

Appendix 1

The Therakos UVAR[®] XTS extracorporeal photopheresis system:

Photopheresis technology	Procedure
UVAR[®] XTS Instrument (UVAR [®] Photopheresis System)	From patient's blood, a T cell-rich buffy coat and a small amount of plasma are isolated using centrifugation-based apheresis. Separated red blood cells and excess plasma are reinfused into the patient.
UVADEX[®] methoxsalen solution UVAR[®] XTS Procedural Kit UVAR[®] XTS Light Assembly (UVAR [®] Photopheresis System)	Concentrated methoxsalen solution (UVADEX) is added to the buffy coat fraction, which is then exposed to UVA light to activate the drug. UVADEX crosslinks DNA of T-lymphocytes, disrupting their metabolic/reproductive functions. The UVADEX [®] -treated T-lymphocytes and other buffy coat cells are reinfused into the circulation.

Appendix 2

FDA approval letters for the UVAR XTS system and the oral and UVADEX formulations of Methoxsalen

Appendix 3

Attach:

*Extracorporeal Photopheresis for Chronic GVHD:
Bibliography of published case reports/series, reviews and commentaries*

Appendix 4

*[attached is complete copy of BCBSA TEC Assessment:
Extracorporeal Photopheresis for Graft-Versus-Host Disease]*

Appendix 5

Maeda et al 2005 Mechanism of Action publication

Appendix 6

Additional 14 Journal publications review summaries



REFERENCE.doc

Appendix 7

Full bibliography of articles discussing the use of photopheresis in the treatment of graft vs. Host Disease.



"Therakos
bibliography 2006 as: