REGISTRY STUDY PROTOCOL:

Extracorporeal Photopheresis for the Management of Progressive Bronchiolitis Obliterans Syndrome in Medicare-Eligible Recipients of Lung Allografts (CAG-00324R2)

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1.0 BACKGROUND

Lung transplantation has become the treatment of choice for selected patients with end-stage lung disease. However, long-term survival after transplantation remains disappointing - the median survival according to the International Society for Heart and Lung Transplantation (ISHLT) Registry is approximately 5 years. Chronic rejection (bronchiolitis obliterans syn-

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[2] Project will be supported with an unrestricted grant from Therakos.

drome [BOS]) has emerged as the leading obstacle to better long-term outcomes and the leading cause of death beyond the first year after transplantation. The histologic hallmark of chronic rejection after lung transplantation is obliterative bronchiolitis (OB). This disorder is a fibroproliferative scarring process that involves the respiratory and membranous bronchioles, resulting in narrowing of the airway lumen and ultimately complete luminal obliteration. Physiologically and clinically, this luminal narrowing results in airflow limitation and breathlessness. Histologic confirmation of OB is difficult with bronchoscopically obtained lung biopsies because of the patchy distribution of the disorder and inadequate sampling of small airways with transbronchial lung biopsies. As a result, BOS is diagnosed and staged specifically in accordance with spirometry-measured changes in forced expiratory volume in one second (FEV_1), the clinical surrogate for obliterative bronchiolitis (Table 1):

Table 1. ISHLT definition of bronchiolitis obliterans syndrome (BOS) and its stages

Stage	*Definition*
BOS stage 0	FEV_1 > 90% & $FEF_{25-75\%}$ > 75% of baseline*
BOS stage 0-p	FEV_1 = 81% to 90% of baseline and/or $FEF_{25-75\%}$ ≤ 75% of baseline
BOS stage 1	FEV_1 = 66% to 80% of baseline
BOS stage 2	FEV_1 = 51% to 65% of baseline
BOS stage 3	FEV_1 ≤ 50% of baseline

*Baseline FEV1 is defined as the average of the two highest FEV_1 measurements obtained at least 3 weeks apart after transplantation.

As with COPD and other chronic obstructive pulmonary disease disorders, this progressive physiological impairment of lung function strongly correlates with survival in post-lung transplant patients with progressive BOS. In a large consecutive series of patients (n = 389) receiving a lung transplant between 1992 and 2004, both progression from BOS grade 1 to 2 and from BOS grade 2 to 3 were associated with a three-fold increase in mortality, with haz-

ard ratios of 3.1 (95% CI, 1.2 to 7.9) and 2.9 (95% CI, 1.6 to 5.3), respectively.[3] Investigators at Duke University Medical Center separately characterized the relationship between FEV_1 and mortality in a consecutive series of 51 post-lung transplant patients. In 51 lung allograft recipients admitted to the medical ICU over a two-year period, the ratio of last FEV_1 to best post-transplant FEV_1 was independently associated with hospital survival. Patients who died had a lower ratio of last FEV_1 to post-transplant best FEV_1 (FEV_1, 51.3 ± 21.9%, n = 14) compared to survivors (FEV_1 75.5 ± 20.4%, n = 30).[4]

In a recent examination of our own previously reported case series of 60 patients with progressive BOS who were treated with extracorporeal photopheresis (ECP),[5] we have independently established a strong association between FEV_1 and mortality. We compared baseline FEV_1 between survivors and non-survivors using non-parametric testing with two-sample Wilcoxon Rank-Sum testing due to unequal variances We found a highly significant difference in baseline FEV_1 between survivors and non-survivors at both 12 and 16 months following initiation of ECP therapy as summarized in Table 2 below:

Table 2. Baseline FEV_1 in survivors and non-survivors 12 and 16 months following initiation of extracorporeal photopheresis (ECP)

Months after initiation of ECP	*Baseline FEV_1 of survivors**	*Baseline FEV_1 of non-survivors**	*p-value*
12	1.57 ± 0.70 L	1.16 ± 0.47 L	0.013
16	1.69 ± 0.75 L	1.16 ± 0.72 L	0.002

*At 12 and 16 months, there were 39 and 30 survivors, respectively.

[3] Burton CM, Carlsen J, Mortensen J, et al. Long-term survival after lung transplantation depends on development and severity of bronchiolitis obliterans syndrome. *J Heart Lung Transplant* 2007 Jul:26(7):681-6.

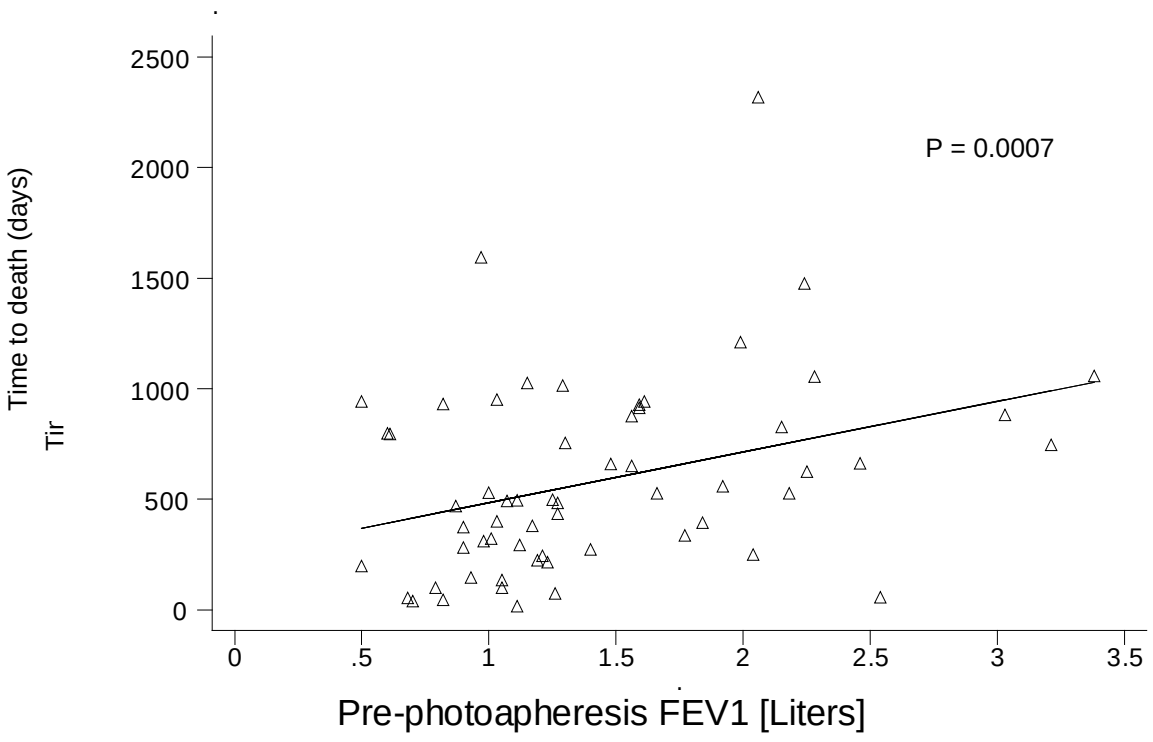
[4] Hadjiliadis D, Steele MP, Govert JA, et al. Outcome of lung transplant patients admitted to the medical ICU. *Chest* 2004;125:1040-5.

[5] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.

We additionally examined one-year survival in patients with an FEV_1 below the median baseline FEV_1 value (1.24 liters). Applying logistic regression analysis, patients with a baseline FEV_1 of less than 1.24 liters had an odds ratio of 5.7 for risk of mortality at 12 months following initiation of ECP, in relation to patients with a baseline FEV_1 greater than 1.24 liters.[6]

Applying univariate linear regression analysis, we observed a significant relationship between baseline FEV_1 (in liters) and time to death in our 60-patient treatment cohort. This relationship between survival and FEV_1 is graphically represented in Figure 1:

Figure 1. Relationship between baseline FEV_1 and time to death (based on 12-month mortality findings)



The management of BOS has been disappointing. The cornerstone of treatment has been intensifying the immunosuppressive regimen. The specific approach is variable from center to center, but typically includes optimizing the maintenance immunosuppressive regimen to

[6] Data and analysis on file (G.Despotis, E. Spitznagel, Washington University School of Medicine)

include tacrolimus and mycophenolate mofetil, high-dose steroids, and a course of anti-thymocyte globulin. Also, maintenance treatment with the macrolide antibiotic, azithromycin, can stabilize lung function in some cases. Nevertheless, the majority of patients does not respond to these interventions and has a progressive decline in lung function resulting in worsening functional status and quality of life and ultimately graft failure and death.

Extracorporeal photopheresis (ECP) has been used at some centers as a salvage treatment for progressive BOS with favorable clinical results in many cases. ECP involves separating the patient's blood into a leukocyte-enriched component (buffy coat) and a leukocyte-depleted component. The buffy coat is then photosensitized with 8-methoxypsoralen and treated with ultraviolet light within a photosensitization chamber, resulting in leukocyte apoptosis. Although the exact mechanism of action of ECP is unclear, reinfusion of this apoptotic leukocyte population into the patient's circulation is thought to result in alterations in antigen presenting cells, cytokine profiles, and the expansion of regulatory T cells. The immunomodulatory effect of ECP has been clearly shown to ameliorate cardiac allograft rejection; ECP is covered for treatment of heart transplant rejection in Medicare beneficiaries.

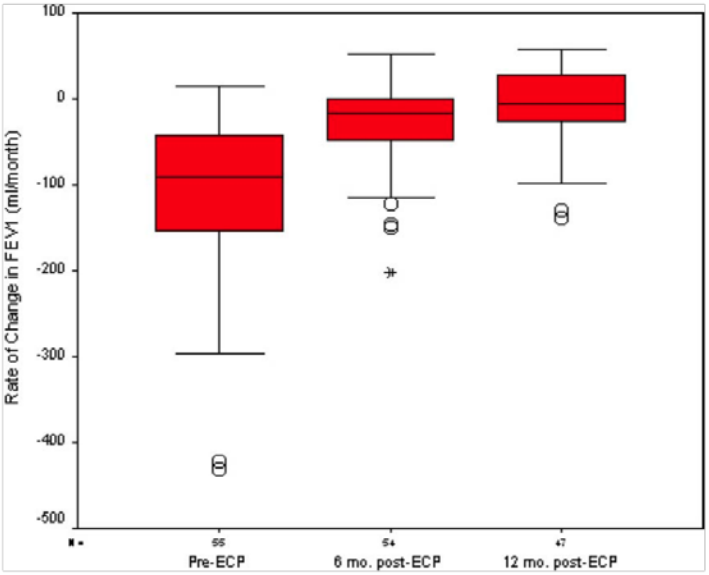
Multiple small case series have described a reduction or stabilization in the rate of decline in lung function after the initiation of ECP for progressive BOS.[7] In the largest case series, Morrell and colleagues reported the results of 60 lung transplant recipients treated with ECP for progressive BOS between 2000 and 2007.[8] Before the initiation of ECP, the mean rate of decline in FEV_1 was -116.0 ml/month. Patients received 24 ECP treatments over 6 months, and the slope of decline in FEV_1 decreased to -28.9 ml/month during the 6-months treatment pe-

[7] Reviewed in: Centers for Medicare and Medicaid Services. Final Decision Memorandum for Extracorporeal Photopheresis (CAG-00324R), April 30, 2012.

[8] Morrell MR, Despotis GJ, Lublin DM, et al. The efficacy of photopheresis for bronchiolitis obliterans syndrome after lung transplantation. *J Heart Lung Transplant* 2010 Apr;29(4):424-31.

riod; the mean difference in the rate of decline in FEV_1 before the initiation of ECP compared to after ECP was 87.1 ml/month (Figure 1; $p < 0.0001$). Further, 14 patients (25% of the overall group) experienced an improvement in lung function during the 6-month treatment period, by a mean of 120.6 ml compared to the pre-treatment rate of FEV_1 decline. In addition, the change in the rate of decline in FEV_1 for the entire cohort persisted over the ensuing 6 months after completion of the course of ECP; the mean rate of decline in FEV_1 over the 12 months after the initiation of ECP remained at -21.4 ml/month. The mean difference in the rate of decline over the 12-month post-ECP treatment period the 6-month period before ECP initiation was 94.6 ml/month (Figure 2; $p < 0.0001$).

Figure 2. Mean monthly rate of decline in FEV_1, pre-ECP and 6 and 12 months post-ECP



Ten of the 60 patients developed complications during treatment. Eight patients developed catheter-related blood stream infections, one patient developed transient hypotension requiring intravenous fluids during ECP, and one patient developed catheter-related partial thrombosis of the superior vena cava.

In a subgroup of 25 Medicare beneficiaries, the mean rate of decline in FEV_1 during the 6-month period before the initiation of ECP in the Medicare subgroup was -98.7 mL/month. The mean decrement in FEV_1 during this 6-month period was 594 mL. During the 6-month period after the initiation of ECP, the mean rate of decline decreased to -31.9 mL/month; see **Table 3** below. The mean decrement in FEV_1 during the 6 months after ECP initiation was 192 mL. The mean difference in the rate of decline of FEV_1 was 66.8 mL/month (95% confidence interval [CI], 22.0 – 111.4 mL/month; $p < 0.005$).

Table 3. Mean monthly rates of decline in FEV_1, pre-ECP and 6 months post-ECP

Group	6 months prior to ECP (mL)	6 months post-ECP (mL)	*p*-value	Mean difference (mL) (95% CI)
Medicare (n=25)	- 98.7	- 31.9	<0.005	66.8 (22.2 - 111.4)
Non-Medicare (n=31)	- 129.9	- 26.4	<0.0001	103.4 (62.1 - 144.8)
All Patients (n=56)	-116.0	- 28.9	<0.0001	87.1 (57.3 - 116.9)

The analysis was extended to 12 month after the initiation of ECP to evaluate the durability of the response; these findings are presented in **Table 4** below. In the Medicare sub-cohort, the mean rate of decline over the 12 months following initiation of ECP was -24.3 mL/month, and the mean decrement in FEV_1 during this 12-month period was 144 mL. The mean difference in the rate of decline between this 12-month period and the period before ECP was 74.4 mL (95% CI, 30.9 – 117.9 mL/month; $p = 0.002$).

Table 4. Mean monthly rates of decline in FEV_1, pre-ECP and 12 months post-ECP

Group	6 months prior to ECP (mL)	12 months post-ECP (mL)	*p*-value	Mean difference (mL) (95% CI)
Medicare (n=25)	- 98.7	-24.3	0.002	74.4 (30.9 - 117.9)
Non-Medicare (n=31)	- 129.9	-19.1	<0.0001	110.8 (73.0 - 148.7)
All Patients (n=56)	-116.0	-21.4	<0.0001	94.6 (66.5 - 122.6)

The results of this case series and other published reports provide compelling evidence that ECP is a potentially effective treatment for the management of progressive BOS after lung transplantation.

GENERAL CONSIDERATIONS RELATING TO CMS FINAL DECISION MEMO: EXTRACORPOREAL PHOTOPHERESIS (CAG-00324R)

On May 2, 2012, CMS issued a Decision Memo stating that ECP is covered for Medicare beneficiaries for the treatment of BOS following lung allograft transplantation only when the procedure is provided under a clinical research study that addresses one or more aspects of the following question:

> *Prospectively, do Medicare beneficiaries who have received lung allografts, developed BOS refractory to standard immunosuppressive therapy, and received ECP, experience improved patient-centered health outcomes as indicated by: (a) improved FEV_1, or decreased rate of decline of FEV_1; (b) improved survival after transplant; and/or (c) improved quality of life?*

In light of the compelling evidence that ECP is efficacious and because it is utilized as a salvage therapy – i.e. it is ordered when standard immunosuppressive drug therapy has failed to adequately slow progression of FEV_1 decline – it is highly unlikely that providers that cur-

rently order ECP for their BOS patients who have already failed optimized immunosuppressive drug therapy would be willing to randomize half of their patients to continue on their failed drug therapy.

What is not well understood at this time, however, is whether certain coexisting disease states or patient-related demographic, functional, treatment-related or diagnostic variables (e.g. extent or significance of the rate of pre-ECP FEV_1 decline) might prove to have predictive value in identifying subsets of BOS patients that are likely, or unlikely, to experience reduced rate of decline or stabilization in FEV_1 following ECP treatment. Therefore we propose a Registry study to enroll a large series of patients from multiple U.S. centers to (1) confirm that ECP significantly reduces the rate of FEV_1 decline in BOS patients refractory to standard immunosuppressive drug therapy, and (2) capture and assess specified patient demographic, treatment-related, diagnostic, functional and co-morbidity-related variables that may predict outcomes after ECP therapy.

2.0 STUDY OBJECTIVES AND DESIGN

The primary aims of this prospective cohort Registry study are to determine the efficacy and tolerability of ECP for the treatment of progressive BOS after lung transplantation in a large patient series. In compliance with the Centers for Medicare and Medicaid Services' (CMS) Coverage with Evidence Development (CED) decision, the study will collect specified demographic, comorbidity, treatment, and outcome data exclusively for Medicare beneficiaries treated with ECP for BOS. The design will be a prospective single-arm cohort study including at least ten (10) and no more than fifteen (15) participating centers. Patients will be enrolled from CMS-approved lung transplant centers and other ECP therapy providers with appropriate expertise that agree in writing to comply with the protocol, secure Institutional Review Board (IRB) approval and complete the case report forms.

This study protocol will be registered on ClinicalTrials.gov following approval by CMS. A waiver from IND requirements has been granted for this study by the U.S. Food and Drug Administration (Appendix 1). Study findings will be disseminated through publication in an appropriate peer-reviewed medical journal and through presentations at academic meetings.

3.0 PATIENT ELIGIBILITY AND ENROLLMENT

3.1 Subject Identification

At the participating clinical centers, potential subjects will be identified by physician investigators and co-investigators, other physicians, and study staff, and through review of relevant administrative databases that are maintained for routine clinical care purposes (e.g. lung transplantation division database, pulmonary function laboratory database, etc.), subject to local IRB approval. Patients may also be referred from external facilities.

3.2 Inclusion criteria (patients must meet <u>all</u> of these criteria):

- Adult age (at least 18 years old).
- Medicare-eligible status
- Lung transplant recipient (combined organ transplant recipients, e.g. heart-lung or liver-lung recipients, are eligible).
- Strong clinical suspicion for progressive BOS (defined as ongoing decline in FEV_1 despite at least one of the following treatments: azithromycin, high-dose steroid, anti-thymocyte globulin, total lymphoid irradiation, sirolimus, or everolimus).
- At minimum five recorded FEV_1 measurements obtained at intervals of at least one week apart, over the 6 months preceding study enrollment.

3.3 Exclusion criteria (subjects meeting <u>any one</u> of these criteria will be excluded):

- Current participation in another clinical treatment trial with an investigational agent.
- Any condition that may interfere with the subject's ability to perform pulmonary function testing.

- Known allergy or hypersensitivity to pharmacologic agents used during ECP
- Any condition that would significantly affect the participant's ability to adhere to the protocol, affect interpretation of the study results, or put the participant at unacceptable risk for study-related complications as judged by the referring clinician. This may include a) patients with a specific acute contraindication to receiving ECP due to any acute condition such as new or evolving myocardial infarction or central nervous system disorder, hemodynamic instability or hypovolemia, acute bleeding, respiratory distress; or b) patients with lupus erythematosus, porphyria cutanea tarda, erythropoietic protoporphyria, variegate porphyria, xeroderma pigmentosum, albinism, or other dermatologic or ocular condition that contraindicates the use of methoxsalen or markedly enhances photosensitivity in the investigator's judgment.
- Aphakia or absence of ocular lenses
- Pregnancy (positive pregnancy test - a urine or blood pregnancy test must be obtained within 1 week prior to enrollment in women of childbearing potential)

  .
- Inability to provide informed consent or to comply with study treatments or assessments (e.g. due to cognitive impairment or geographic distance)

3.4 Compliance with Federal Guidelines Pertaining to Study Eligibility

All participating study sites will be required to include, in their written protocols submitted to their Institutional Review Boards (IRBs) for approval, a clause stating that patient eligibility for enrollment will not be influenced in any way by gender, racial or ethnic status. As a condition of participation, sites will be required to affirm in writing that their partici-

pation in this research study will be conducted in compliance with all applicable federal regulations concerning the protection of human subjects found in 45 CFR Part 46.

3.5 Screening Procedures and Informed Consent

When a potential subject is identified, the investigator and/or an appropriately designated staff member will screen the medical history, laboratory studies, and past pulmonary function tests to confirm that the patient may be eligible. When a potentially eligible patient is identified, a member of the research team will contact the patient's physician to obtain permission to enroll the patient. If the patient's physician or a research team member believes that the patient is cognitively impaired or otherwise unable to provide informed consent, or if there is suspicion that the recent decline in lung function is due to an acute infection, the patient should not be invited to participate in the study. All subjects should be able to understand the nature of the research and their participation, show the ability to consider alternatives including the option of non-participation, and show the ability to make a reasoned choice. All subjects will be informed that a) they are being asked for permission to allow the study team to collect their medical information irrespective of whether they are treated with ECP in the study, and that b) to limit the use (and attendant risks) of ECP therapy to those patients who are most likely to benefit, their eligibility to receive ECP within the study will be determined by the study team's analysis of their pre-enrollment pulmonary function testing along with input from their physician.

The investigator or a designee should explain the study to the patient in a non-coercive manner and provide him/her with a Study Informed Consent Form to review, sign, and date. A copy should be provided to the patient and the original re-

tained by the study team. For subjects who are not fluent in English, the informed consent process should be conducted in the subject's native language, utilizing a qualified translator when appropriate. All patients must provide written informed consent per the local IRB's procedures before they are enrolled and registered. After written informed consent is obtained and assuming the patient meets all eligibility criteria, the investigator or a designee should enter the patient's information on the web-based eligibility form to formally request that the patient be enrolled. A physical examination,vital signs, urine or blood pregnancy test, and pulmonary function testing should be documented within 1 week prior to enrollment.

Patients for whom study eligibility and written informed consent are confirmed online by the site research team will be assigned a unique Case Number by the online registration system, at which time they will be considered enrolled in the study.

3.6 Treatment Arm Allocation

Patients will be electronically assigned to either the **ECP Treatment Arm** or to the **Observation Arm** of the study based upon the FEV_1 information entered by the site research team and the site physician's clinical judgment, as noted below. During the study, ECP Treatment Arm enrollees will receive protocol-based ECP therapy, whereas Observation Arm enrollees will not receive protocol-based ECP therapy unless crossed over subsequently (see below).

Once informed consent is obtained, site personnel will enter all available FEV_1 values for the preceding 6 months (of which one FEV_1 must have been obtained within the preceding 7 days) into a web-based treatment allocation form which will perform an automated calculation of FEV_1 slope via the linear relationship of FEV_1 versus time, and determine if the rate of

FEV_1 decline is statistically significant. Patients who have had a significant rate of decline within the preceding 6 months, defined as either a) for patients with $FEV_1 \geq 1200$ mL at the time of screening, a derived FEV_1 slope that is significantly lower (more negative) than -30 mL/month ($p < 0.05$); or b) for patients with $FEV_1 < 1200$ mL at the time of screening, a derived FEV_1 slope that is significantly lower (more negative) than -10 mL/month ($p < 0.05$), will be assigned to the ECP Treatment Arm. If a patient does not meet these criteria, he/she will be assigned to the Observation Arm. However, if progressive BOS is still suspected in a patient who does not meet these criteria, the site investigator may obtain up to 4 additional FEV_1 measurements (at intervals of no less than 7 days), and enter them into the web-based treatment allocation form. The patient can be enrolled subsequently into the ECP Treatment Arm if a) the rate and statistical significance of FEV_1 decline now meet the above criteria as confirmed by the web-based treatment allocation method using up to 4 additional FEV_1 measurements ; b) the site physician requests that the patient receive ECP therapy; and c) the site research team confirms online that the patient has not developed a new contraindication to the use of ECP therapy. If the relationship between FEV_1 and time still does not reach statistical significance after the 4 additional FEV_1 measurements but there is strong clinical suspicion for progressive BOS, the physician may still enroll the patient into the ECP Treatment Arm based on his/her clinical judgment ("clinical override"), provided that the rate of FEV_1 decline meets the above cut-off (-30 mL/month for patients with $FEV_1 \geq 1200$ mL or -10 mL/month for patients with $FEV_1 < 1200$ mL) and that the most recent FEV_1 was obtained within the preceding 7 days.

Patients who continue in the Observation Arm but who experience a decline in pulmonary function may be re-evaluated for potential crossover into the ECP Treatment Arm after 2 months, using the above process and criteria, as long as at least one additional FEV_1 value is available within the preceding 7 days and provided the patient has not developed a new con-

traindication to the use of ECP therapy. Patients who cross over into the ECP Treatment Arm will be followed for 1 year after the initiation of ECP.

3.7 Baseline and Pre-Treatment Assessments

Upon enrollment, each patient will be informed whether he/she has been allocated to the ECP Treatment Arm or to the Observation Arm (in which case he/she will not receive protocol-based ECP therapy but will be followed in the study to enable assessment of the FEV-1 based treatment allocation method

For all enrollees, patient demographics and co-morbidities should be entered on the case report form. The post-transplant baseline FEV_1 (as defined by the standard ISHLT definition), and all FEV_1 measurements captured within the 6 months prior to enrollment, should be entered on the case report form. The following laboratory and procedure related information will be recorded in the case report forms for each patient in the ECP Treatment Arm prior to each individual procedure or set of two scheduled procedures in any given week:

1. CBC with differential and the hemocytometer used for this measurement
2. the type of machine used (UVAR vs CELLEX) and confirmation that either five cycles or 1500 mL of plasma have been processed, respectively. If this did not occur, the reason why should be recorded
3. The type and dose of anticoagulant used for the procedure (e.g. citrate vs heparin)

Within the Washington University site only, buffy coat product specimens will be obtained in a subgroup of patients on as many as three separate occasions to measure CBC with differential prior to photoactivation.

Important: a physician investigator or co-investigator must provide a signed attestation that the patient meets all eligibility criteria before ECP or any other study-related invasive procedure (e.g. central venous catheter placement) is performed.

4.0 TREATMENT DESCRIPTION

4.1 Maintenance immunosuppressive therapy

Maintenance immunosuppressive regimens vary among transplant centers in the United States, but most patients are treated with triple-drug immunosuppression consisting of a calcineurin inhibitor (tacrolimus or cyclosporine A), a cell cycle inhibitor (mycophenolate mofetil or azathioprine), and prednisone. This research protocol does not require the use of a specific maintenance immunosuppressive regimen, and sites may choose specific regimens for patient-specific reasons. Similarly, infection prophylaxis protocols vary among centers, and participants may be treated according to local standard clinical practice. Patients may continue to receive their physician-prescribed treatments for other conditions. Women of childbearing potential in the ECP Treatment Arm will be instructed to use an effective contraception method during their time in the study, and will be instructed to notify the research team immediately if pregnancy occurs or if the contraceptive method fails in any manner.

4.2 Extracorporeal Photopheresis (ECP)

Patients in the ECP Treatment Arm should receive 24 ECP treatments over the 6-month period following enrollment, in accordance with the following schedule:

- 8 to 10 treatments over the first 30 days following treatment initiation;

- 8 to 10 treatments in the next 60 days (months 2 and 3);
- 6 treatments in the next 90 days (months 4 through 6) at a rate of 2 treatments per month.

Each treatment should be given on a separate day; treatments are scheduled more frequently early in the ECP treatment course to accelerate induction of the biological and clinical effects, and then are tapered over the remainder of the protocol. At the physician's discretion, additional ongoing maintenance ECP treatments may be ordered following completion of the 6-month treatment course; in some instances, based on pulmonary function testing and other findings, the physician may stop, continue or reinitiate maintenance treatments on an indefinite basis. All ECP procedures performed over the first 12 months from initiation of therapy will be captured on case report forms.

ECP treatments will be performed using either the Therakos UVAR XTS system or the Therakos CELLEX system. Procedures should be performed in compliance with the FDA-approved labeling for both of these systems (e.g. prerequisite criteria for minimum hematocrit; ≥28% for initial procedure).[*] The treatments should be performed using peripheral venous access whenever feasible (this is preferred, to avoid central venous catheter-related complications) or through a central venous catheter, per the institution's standard practice. A complete blood count with differential should be obtained before ECP is started (on the same day). At each treatment session, the patient should first be clinically assessed by the institution's clinical personnel to ensure that the patient is in suitable condition to undergo ECP that day. This assessment should include all the elements in the ECP Pre-Procedure Assessment Form in Appendix 3 - this Form should be completed for each ECP treatment session and filed in the patient's research binder at the site. If the pre-procedure assessment identifies any is-

[*] Therakos CELLEX Photopheresis System Operator's Manual and Therakos UVAR XTS Photopheresis System Operator's Manual.

sues of concern , a physician or other licensed practitioner (e.g. physician's assistant or nurse practioner) should assess the patient to determine if further clinical or laboratory investigations are required and ultimately to determine if ECP is safe to perform on that day. Alternative institutional policies for pre-procedure ECP assessment may be followed if reviewed and approved by the Washington University Principal Investigator. Treatments may be postponed or cancelled altogether at the treating physician's discretion if the patient develops a medical contraindication to ECP therapy; however, the reason must be documented. Patients should be monitored for complications in accordance with local standard practice and should be instructed to avoid sun exposure for 24-48 hours after each ECP treatment (ideally) and to wear hats, protective clothing, sunscreen, and UV-resistant sunglasses if sun exposure will occur within the first 24-48 hours after an ECP treatment.

5.0 STUDY OUTCOMES AND FOLLOW-UP

5.1 Primary endpoint: The primary endpoint of the study is change in the rate of FEV_1 decline assessed by comparing the average rate of FEV_1 decline over the 6 months prior to ECP against the average rate of FEV_1 decline over the 6 months following initiation of ECP.

5.2 Secondary endpoints: A) Average rate of FEV_1 decline over the 12 months following initiation of ECP; B) All-cause mortality at 12 months following initiation of ECP (observational only); and C) Proportion of patients with treatment-related serious adverse events. The above primary and secondary endpoints will be assessed in all ECP Treatment Arm enrollees who meet the pre-enrollment FEV-1-stratified slope cutoffs and statistical significance criteria specified in Section 3.6. Additional analyses will be performed to evaluate the validity of the study's FEV_1-based treatment allocation method using data from enrollees in both Arms who do not meet these criteria. SAEs will be captured and reported on all enrollees.

5.3 Pulmonary Function Testing

Spirometry should be routinely measured at all clinical centers by certified and trained technicians according to American Thoracic Society (ATS) guidelines. According to ISHLT criteria, baseline lung function is defined as the average of the two highest FEV_1 measurements obtained following transplantation, taken at least 3 weeks apart. This baseline is used as the reference value for the diagnosis and staging of BOS (Table 1 above). Additionally, participating sites will capture and report all FEV_1 measurements during the 6 months prior to enrollment, inclusive of an FEV_1 measurement on Day 0, where Day 0 is defined as the period within one week prior to, and on the date of, initiation of ECP. The five FEV1 measurements obtained in the six month period prior to enrollment should not be measured in an interval less than one week apart. These FEV_1 values obtained prior to initiation of ECP will be used to calculate an average pre-ECP rate of change in FEV_1 in mL/month as described below in the Data Analysis section.

In ECP Treatment Arm enrollees, the study will prospectively capture FEV_1 through spirometry during the course of ECP therapy and out to one year in accordance with the following schedule: Days 0, 30, 60, 90, 120, 150, 180, 240, 300 and 365. Spirometry from Day 0 through Day 120 may be performed within ±7 days to accommodate patient/provider scheduling needs, and generally will coincide with a scheduled ECP treatment. Spirometry from Day 150 through Day 365 may be performed within ±14 days to meet patient/provider scheduling needs. Observation Arm enrollees should be followed for the duration of the study's follow-up period, but may have the timing of pulmonary function testing determined by their local physicians. For Observation Arm enrollees, the results of all clinically-ordered pulmonary function tests should be collected and reported on the case report forms.

5.4 Subject Retention, Withdrawal, and Termination

To promote continued participation, study staff will provide telephone reminders to patients of study visits. Subjects will be encouraged to remain in the study until follow-up is complete but will be informed that they have the right to withdraw at any time without compromise to their care. Subjects will be terminated from the study if they die or elect to withdraw.

6.0 ADVERSE EVENT MONITORING AND REPORTING

6.1 Adverse Event (AE) Definition

An Adverse Event is defined as any untoward medical occurrence observed in a patient that develops or worsens from baseline status in association with a subject's participation in the research, whether considered research-related or not.

6.2 Serious Adverse Event (SAE) Definition

A Serious Adverse Event is any AE that results in death, a life-threatening adverse experience, a persistent or significant disability/incapacity, inpatient hospitalization or prolongation of existing hospitalization, evaluation in an emergency room or by an acute response team, pregnancy abortion, or a congenital anomaly, birth defect, or cancer in a neonate/infant born to a female subject. Medical events that do not strictly fulfill these criteria should be considered SAEs if they seriously jeopardize the subject or require aggressive medical or surgical intervention to prevent one of the above outcomes.

6.3 Pre-Existing Medical Conditions

A pre-existing medical condition is one that is present at the start of the study. Such conditions should ideally be reported in the baseline medical/surgical history. A pre-existing medical condition should be reported as an AE or SAE only if the frequency, severity, or character of the condition worsens significantly or unexpectedly during the study. Previously sched-

uled hospitalizations and hospitalizations needed for diagnostic or elective surgical procedures for the management of pre-existing conditions are not considered AEs.

6.4 Reporting of AE and SAE

Patients will be monitored and followed clinically according to each site's standard clinical practice. Sites should follow their local IRB's guidelines in terms of reporting AEs and SAEs to the local IRB. If an event is fatal or imminently life-threatening, the local IRB should be notified within 24 hours (Monday – Friday) of the research team's knowledge of the event. In addition, each SAE should be categorized by the site investigator as to whether it was related or possibly related to participation in the research study (meaning that there is a reasonable possibility that the AE may have been caused by ECP – SAEs determined to be solely caused by an underlying disease, disorder, or condition of the subject; or other circumstances unrelated to the research should be categorized as not related to participation in the research).

SAEs that a) are fatal or imminently life-threatening; b) are felt by the site investigator to be related or possibly related to the use of ECP, to methoxsalen, or to a central venous catheter that was placed for the purpose of performing ECP; or c) occur during or within six hours after an ECP procedure must be reported to the Data Coordinating Center (DCC) on the SAE Case Report Form, and source documentation provided, within 24 hours (Monday-Friday) of the site's awareness of the event. Each SAE that qualifies for reporting to the DCC should also be categorized by the site investigator as to whether it was unexpected (meaning that the SAE's occurrence is not consistent with the known or foreseeable risks associated with ECP or with the expected natural progression of any underlying disease, disorder, or condition of the subject and his/her predisposing risk factor profile for the SAE), or expected.

6.5 Expedited Review of ECP-Related, Fatal, or Life-Threatening SAE

At the DCC, each SAE report will be forwarded to the Principal Investigator or a physician designee. If additional details are needed to evaluate the event, this will be conveyed to the site investigator. For ongoing events, the Principal Investigator will communicate any suggestions relevant to the patient's care to the site investigator. Each reported SAE will be reviewed by the Data Safety Monitoring Board (DSMB); this will occur within 3 business days (Monday – Friday) for any SAE that is either a) categorized as related or possibly related to ECP; or b) fatal or imminently life-threatening. Any DSMB recommendations pertaining to the specific event, event categorization, or study site processes will be forwarded to the site investigator. Should an event be determined to qualify as an Unanticipated Problem, federal reporting guidelines will be followed. Stopping guidelines will be established in advance to guide the DSMB with respect to halting enrollment at either a specific center or at all participating study sites. If the DSMB stops enrollment, all site investigators will be notified. It will be the investigators' responsibility to notify their respective local IRBs.

7.0 STATISTICAL METHODS AND POWER CALCULATIONS

Based on a 95% power analysis and assuming a 5% loss to follow-up of enrolled patients, 160 patients who meet the pre-enrollment FEV-1-stratified slope cutoffs and statistical significance criteria specified in Section 3.6 will need to be enrolled in the ECP Treatment Arm to detect at least a 50% reduction in the rate of FEV_1 decline at one-year follow-up. Because we anticipate from our prior study that a maximum of 12% of enrolled patients will not meet these criteria, we plan to enroll up to 182 patients in total (including the Observation Arm). Once 160 patients have been entered into the ECP Treatment Arm (by new enrollment or crossover), further patients will not be enrolled or crossed over into the ECP Treatment Arm.

A 50% decrease in the rate of FEV_1 decline can importantly extend survival and improve the opportunity to receive a new lung allograft, as well as delay time to onset of severe physical limitations. Our power analysis was based on findings from our previously published 60 patient series. Specifically, we first calculated values that reflected the difference between pre-intervention and post-intervention FEV_1 slope values. The corresponding values for standard deviation of slope differences were adjusted for possible greater variability in the post-treatment period in this study. These values for derived slope differences (50% of 87 ml/month) and corresponding standard deviation values (150) were then used to calculate required enrollment using a treatment effect of 50% reduction of FEV_1 decline and using a power of 95%. This analysis, with 5% late loss, indicates a required enrollment of 160 patients who receive ECP and meet the FEV-1 criteria in Section 3.6.

Because this is a before-and-after Registry study in which enrolled subjects serve as their own controls, the heterogeneity of the study population will not influence overall study outcome. However, as described in the Data Collection, Analysis and Reporting section below, seven specific parameters for which there is a rational basis to potentially influence clinical outcome will be independently evaluated by univariate and multivariate linear and logistic regression analysis.

There are no restrictions in the study inclusion or exclusion criteria with respect to gender or minority status (e.g. race or ethnicity); thus enrollment will reflect the gender and racial/ethnic mix of patients enrolled in all participating study sites. In our previous single-center analysis of 60 patients, males and females were about equally represented (males: 53%; females: 47%); we anticipate roughly similar gender mix in this multicenter registry study. The small 160-subject enrollment sample effectively precludes a conclusive sub-analysis of any possible effect of race or ethnicity on clinical outcome; however, the hetero-

geneity should be diverse based on enrollment from multiple centers in several geographic areas within the United States.

It is difficult to project annual patient enrollment, in part because there are currently multiple barriers to ECP therapy for post-lung transplant BOS, most prominently the historical lack of Medicare coverage and payment. We expect that this Registry, with Medicare coverage and payment for qualifying patients, will expand utilization of ECP to include more centers and a higher proportion of the eligible patient population.

Based on experience over an 8-year period at Barnes-Jewish Hospital, approximately 13% of patients receiving a lung transplant eventually received ECP. Roughly one-half of post-transplant patients do not develop BOS, and a substantial proportion of those patients who do develop BOS die from complications of infection or other causes. To develop a projected enrollment over our proposed four-year study period, we apply the following assumptions:

- There will continue to be ~1,800 lung transplants performed yearly in the U.S.;
- Roughly 13% of post-transplant patients will eventually receive ECP treatment;
- Providers managing roughly 40% of U.S. lung transplants will refer their drug-refractory BOS for ECP (it is uncertain what share will actually do so); and
- Medicare beneficiaries are as likely to receive ECP therapy as non-Medicare patients and account for ~50% of qualifying candidates for ECP therapy.

Applying these assumptions, we estimate annual patient enrollment as follows:

1,800 transplants x 13% ECP tx rate x 40% participation rate x 50% Medicare = ~50 patients/year

To enroll 160 patients required to detect a 50% reduction in the rate of FEV_1 decline, enrollment may be required for approximately three years based on this 50-patient-per-year pro-

jection. An additional year will be required to complete one-year follow-up on the last patients enrolled. We estimate that a minimum of six months will be required to tabulate and analyze all data for submission to CMS for its review.

8.0 DATA COLLECTION, ANALYSIS, AND REPORTING

A Data Coordinating Center (DCC) will manage implementation of the study and provide biostatistical expertise for data capture, spreadsheet entry, and analysis. The DCC will develop case report forms (CRFs) to collect study-related data through a secure web-based data entry system. These case report forms will be approved by the study Steering Committee. Individual clinical sites will be responsible for electronic data entry, and the DCC will provide training and support for the use of the electronic data entry system.

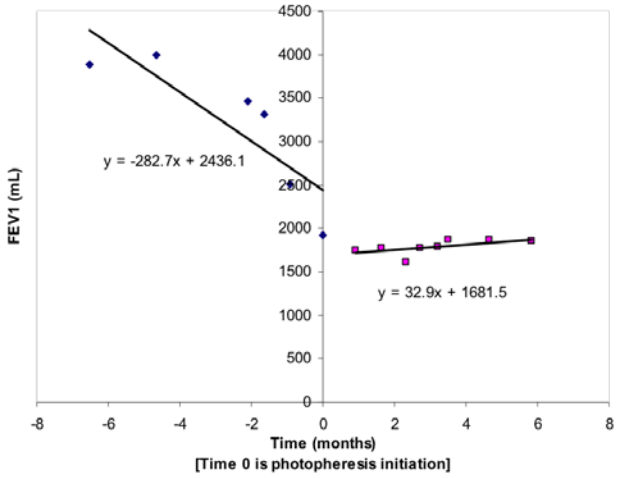
CRFs will be created as study-specific web forms linked to a central database. To minimize text entry errors, most of the data fields for each CRF only allow the user to select a radio button, check box, drop down menu, or electronically checked numeric data entry. To reduce missing data, CRFs will be constructed so they must be filled out completely before the system will allow submission. DCC staff will spot check incoming data to check for accuracy and completeness. A preliminary set of data fields for inclusion in Registry CRFs appear in Appendix 3 below.

Initial analyses will involve the use of descriptive statistics. To compare baseline characteristics between subgroups, we will use t-tests (or a non-parametric test) and chi-square (or Fisher's exact) tests. For comparisons among subgroups, we will use ANOVA or chi-square (or Fisher's exact) tests.

We will analyze the rate of change in FEV_1 using two methods. First, absolute values of all FEV_1 measurements obtained over the 6 months before the initiation of ECP will be collected

retrospectively at study enrollment, and absolute values of all FEV_1 measurements obtained over the 12 months after the initiation of ECP will be collected prospectively. A rate of change in FEV_1 will be obtained by plotting absolute FEV_1 measurements vs. time, and a linear regression line will be drawn through these data points (example in Figure 3 below). The rate of change in FEV_1 will be defined for each time period as the slope of this linear regression line, and the pre-ECP slope will be compared to the post-ECP slope for each patient using the paired t-test as recommended by the ISHLT consensus statement on BOS. In addition, changes in FEV_1 measurements in the different time periods (pre-ECP and post-ECP) will be analyzed using longitudinal mixed-effects models analysis of variance. We will use the Kaplan-Meier method to estimate survival and the log rank test to compare survival between subgroups.

Figure 3. Example of linear regression-based development of rates of FEV1 decline for the six-month period prior to and following initiation of ECP



Parametric (e.g. one-way or ANOVA analysis of variance), non-parametric (e,g, rank sum) and univariate and multivariate linear and logistic regression statistical methods will be used to characterize response and non-response and examine the potential association of one or more of several parameters with either response or non-response to ECP treatment. These parameters will include (1) Day 0 (pre-ECP) percent of post-transplant baseline FEV_1, (2) age, (3) race, (4) days from transplantation to initiation of ECP treatment, (5) individual use or non-use of calcineurin inhibitor, cell-cycle inhibitor, steroids, sirolimus or everolimus as components of maintenance immunosuppression, (6) history of gastroesophageal reflux disease (GERD) with and without active treatment and (7) single- or double-lung transplant status. All variables that are significant using univariate analyses will be included in multivariate analyses.

By nature this is a very heterogeneous population, in which declining pulmonary function may be influenced by numerous underlying demographic, co-morbidity and treatment-related factors. The very limited potential enrollment size for this study and the direct consequence of a very small qualifying post-lung transplant patient population with treatment-refractory BOS precludes the possibility of enrolling enough patients to assure that risk factors for pulmonary function decline are similar. Further, and equally importantly, a prospective randomized trial design is precluded for ethical reasons, given the consistent evidence of clinical benefit associated with ECP therapy in this patient population.

Quarterly interim status update reports will be submitted electronically by the study sponsor to CMS (Kimberly.Long@cms.hhs.gov) that contain the following information: (1) number screened, (2) number enrolled, (3) reason for non-enrollment, (4) number of dropouts and reason for dropout, (5) number with completed data collection, (6) progress of data analysis, (7) analysis file constructed (y/n), (8) descriptive analysis completed, (9) analyses to address

each hypothesis completed (y/n), (10) manuscript completed (y/n) and (11) manuscript sent to journal (date). Study data analysis will be initiated upon completion of enrollment and one year of treatment of all study subjects.

9.0 DATA CONFIDENTIALITY

The following precautions will be taken to ensure privacy of patient data:

1. The study will be conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA).
2. Personal identifiers will not be entered in the electronic database (this data will be stored in a secure location at the clinical center with restricted access), and will be removed from all patient material sent to the DCC (e.g. source documents). Data will be identified using unique Case Numbers that provide no subject information.
3. Clinical centers will require a complex password to gain access to web-based documents. Authentication (user credentials) and access privileges will be managed by DCC staff using proven, industry standard tools.
4. The DCC database will be password protected with strong encryption and will be hosted in a private cloud infrastructure managed by the DCC. The database server will be attached to a private network protected by a commercial grade firewall.
5. All attempts to access the DCC database will be logged.
6. All data-related practices will comply with Washington University policies and procedures for privacy and data security.
7. At the clinical centers, subject data will be kept in a locked office and on password-protected and firewall-protected computer systems, and will only be available to the research team. Different password-protected files will be created and will be linked using the patient's unique Case Number. Subject identifiers will be kept separate

from study data, with the identifier keys stored in separate files which only the site principal investigator and authorized personnel can access.

10.0 INVESTIGATOR TRAINING AND STUDY OVERSIGHT

Study personnel will have the appropriate qualifications related to education, training, and experience to perform study-related tasks. The study personnel will conduct the study in accordance with Good Clinical Practice (GCP) and local IRB guidelines. The protocol will require local IRB approval before its implementation. Clinical site personnel will obtain written informed consent from study participants before conducting study-related procedures. Site personnel are required to notify the Washington University Clinical Coordinating Center of any deviation from the IRB-approved protocol within 24 hours of their awareness.

The DSMB will consist of an independent group of three experts (comprising a pulmonologist with expertise in management of post-lung transplant BOS, a specialist with photopheresis procedural experience and a biostatistician) who will periodically review and evaluate the accumulated study data for participant safety, study conduct and progress, and make recommendations to the study Steering Committee regarding the continuation, modification, or termination of the study. The chairperson of the DSMB will also serve as the medical monitor for this project. Mandatory reviews of study data will be scheduled following enrollment and accrual of six months of ECP treatment data for (1) the first 50 and (2) the first 100 patients.

Study monitoring visits will be conducted by authorized representatives of the Principal Investigator to inspect study data, informed consent forms, and subjects' medical records. The clinical center investigator will permit authorized representatives of Washington University and federal and local health authorities to inspect relevant facilities and records.

11.0 STUDY TIMELINE

We expect to conduct this study over a minimum 4-year period that will include study start-up tasks, assembly of a DSMB, and central and local IRB approvals. We plan to enroll and treat patients over about 3 years, with 1 year follow-up on the last enrolled patient. At least 6 months of additional time will be necessary to complete data acquisition and analysis.

Appendix 1

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118030

ACKNOWLEDGE/EXEMPT IND

George J. Despotis, MD
Washington University School of Medicine
660 S. Euclid Avenue
Campus Box 8118
St. Louis, MO 63110-1093

Dear Dr. Despotis:

We acknowledge receipt of your Investigational New Drug Application (IND), submitted March 4, 2013, received March 5, 2013, under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for UVADEX (methoxsalen).

After reviewing the information contained in your submission, we have concluded that your study titled "Extracorporeal Photopheresis (ECP) for the Management of Progressive Bronchiolitis Obliterans Syndrome (BOS) in Medicare-Eligible Recipients of Lung Allografts" meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.

The IND regulations [21 CFR 312.2(b)] state that the clinical investigation of a drug product, including a biological product, that is lawfully marketed in the United States, is exempt from the requirements for an IND if all of the following apply:

1. The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for the drug.

2. The investigation is not intended to support a significant change in the advertising for a prescription drug product.

3. The investigation does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product.

4. The investigation is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50).

Reference ID: 3278962

5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective, nor may it be commercially distributed, for the purposes for which it is under investigation.

In addition, 21 CFR 312.2(b)(5) exempts from the IND requirements a clinical investigation that involves use of a placebo if the investigation does not otherwise require submission of an IND.

We remind you that exemption from the requirements for an IND does not in any way exempt you from complying with the requirements for informed consent under 21 CFR 50.20 or from initial and continuing Institutional Review Board review under 21 CFR Part 56. You are also responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) (42 U.S.C. §§ 282(i) and (j)), which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No. 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) (42 USC § 282(j)), which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices. Please note that, if in the future you submit an application under sections 505, 515, or 520(m) of the FDCA (21 USC §§ 355, 360(e), or 360(j)(m)), or under section 351 of the PHS Act (21 U.S.C. § 262), or you submit a report under section 510(k) of the FDCA (21 USC § 360(k)), the application or submission must be accompanied by a certification that all applicable requirements of section 402(j) of the PHS Act (42 USC § 282(j)) have been met. Where available, such certification must include the appropriate National Clinical Trial (NCT) control numbers (42 USC § 282(j)(5)(B)). Additional information regarding the certification is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information on registering your clinical trial(s) is available at the Protocol Registration System website (http://prsinfo.clinicaltrials.gov/).

For additional information, a searchable version of the IND regulations is available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm.

If you have any questions, call Judit Milstein, Chief, Project Management Staff at 301-796-0763,.

Sincerely,
{See appended electronic signature page}

Renata Albrecht
Director
Division of Transplant and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Reference ID: 3278962

Appendix 2

Data Fields for Inclusion in Registry Case Report Forms

DEMOGRAPHICS/MEDICAL HISTORY

1. Birth date
2. Gender
3. Race
4. Underlying lung disease necessitating lung transplantation
5. Date of lung transplantation
6. Operation performed (e.g. single, bilateral, heart-lung, etc.)
7. History of GERD (YES/NO)
8. Active treatment for GERD (YES/NO)
9. If being treated for GERD, what treatment? (Medical therapy, fundoplication)
10. DSA at ECP initiation? (YES/NO)

BOS DIAGNOSIS

1. Post-transplant baseline FEV_1 (per ISHLT definition)
2. Date of post-transplant baseline FEV_1 (per ISHLT definition)
3. BOS stage (0-p, 1, 2, 3) on Day 0
4. All FEV_1 measurements and their dates over the 6-month period prior to initiation of ECP (minimum of five (5) FEV_1 measurements required, which may include a measurement on or just prior to the date of the first ECP procedure)

PREVIOUS BOS TREATMENT

1. Steroid treatment (YES/NO)
2. Cytolytic therapy (i.e. anti-thymocyte globulin) (YES/NO)
3. Alemtuzumab (YES/NO)
4. Azithromycin (YES/NO)
5. Sirolimus or everolimus (YES/NO)

6. Methotrexate (YES/NO)

MAINTENANCE IMMUNOSUPPRESSION AT INITIATION OF ECP

1. Calcineurin inhibitor (tacrolimus, cyclosporine, or none)
2. Cell-cycle inhibitor (azathioprine, mycophenolate mofetil, or none)
3. Prednisone/other steroid drug (YES/NO) (IDENTIFY DOSAGE ON ECP TX DATES)
4. Sirolimus (YES/NO)
5. Everolimus (YES/NO)

CHANGES IN MAINTENANCE IMMUNOSUPPRESSION DURING ECP THERAPY

1. New drug initiated to specifically treat BOS (Identify drug)
2. Increase in dosage of maintenance immunosuppression drug (Identify drug); this does not include calcineurin inhibitor dose adjustments to target a therapeutic level
3. Change in dosage of prednisone/other steroid drug in the interval just preceding ECP tx date (YES/NO)

   If YES: (INCREASE: highest dosage) (DECREASE: lowest dosage)

PROSPECTIVE DATA COLLECTION

1. FEV_1 at days 0, 30, 60, 90, 120, 150, 180, 240, 300, & 365
2. Date of initiation of ECP therapy (Day 0)
3. Total number of ECP procedures performed at Day 180
4. Total number of ECP procedures performed at Day 365
5. Death (YES/NO)
6. Cause of death (consistent with UNOS registry)
7. Date of death

PREMATURE DISCONTINUATION OF ECP

1. Date of discontinuation of ECP
2. Reason for discontinuation of ECP

SERIOUS ADVERSE EVENTS

1. Description
2. Onset and stop dates
3. Outcome: resolved, resolved with sequelae, not resolved, fatal
4. Relevant medical history / co-existing diseases
5. Investigator causality assessment

APPENDIX 3 – ECP REGISTRY STUDY

ECP PRE-PROCEDURE ASSESSMENT FORM

SUBJECT IDENTIFICATION NUMBER

_____

Please check (✔) the appropriate box(es) (☉) and fill in the blank(s) as needed.

Date: : _____ Time: : _____	Procedure type: ☉ Photo Machine ☉ Cellex ☉ UVAR cycles _____ Procedure consent signed on:_____	Procedure #	Time Out Completed Initials:_____ Time:_____
Patient Gender: ☉Male ☉Female	Product #:	Location of procedure: Pheresis Center / Hospital Room Other:_____	

BASELINE ASSESSMENT Initials:

Patient Parameters	HT: _____ WT: _____lb/ _____kg HCT:_____ Date:_____ BMI:_____ Adjusted Body Wt:_____lb/_____kg Total Blood Volume: _____mL	Venous Access	Type: ☉ Central Line ☉ Port/IVAD Peripheral Other:_____ Location:_____ Date Placed:_____ Placement Verified by: ☉ Electronic Record ☉ Physician Dressing: ☉ Dry/Intact ☉ Changed CVC or IVAD abnormalities:_____ N/A Site: ☉ No Drainage ☉ No Redness
Neurologic	☉ Alert and Oriented x4 ☉ Confused ☉ Agitated ☉ Sedated ☉ Unresponsive ☉ Slurred speech ☉ New Memory Deficits ☉ New arm/leg weakness	Edema	☉ Absent ☉ Present: ☉ 1+ ☉ 2+ ☉ 3+ ☉ Location:_____
Respiratory	☉ Room Air ☉ Nasal Cannula ☉ O_2 ____L ☉ Unlabored/Regular ☉ SPO_2 ____% ☉ Labored ☉ Irregular ☉ Mechanical Assist ☉ Use of accessory muscles ☉ Inability to talk ☉ Wheezing (auscultation) ☉ Audible stridor Other: : _____	Cardio Pulmonary	VS: BP _____ RR _____ Temp _____ Pulse _____ ☉ Regular ☉ Irregular ☉ Denies any new symptoms ☉ Difficulty breathing / ☉ New or change in SOB at rest or with exertion ☉ Chest, arm, or jaw pain ☉ Recent lightheadedness, near syncope or syncope
Skin	☉ Warm ☉ Dry ☉ Cool ☉ Diaphoretic Color:_____	Activity	☉ Independent ☉ Wheelchair ☉ Bed rest ☉ Walker ☉ Cane
Injury or Fall	☉ None ☉ Yes Description of Incident:_____	Medications Changes	☉ Medication list reviewed ☉ Denies changes to current medication list ☉ Changes Updated
Diagnostic Procedures	Performed in the last week or scheduled for upcoming week : ☉ No ☉ Yes Describe:_____	Signs of Infection	☉ Denies any of the following: ☉ Fever ☉ Chills ☉ Night Sweats ☉ Diarrhea ☉ Persistent or Productive cough ☉ Painful urination
Pain	☉ Denies ☉ Present Quality: ☉ Dull ☉ Aching ☉ Stabbing ☉ Burning ☉ Throbbing Other:_____ ☉ Frequency:_____ ☉ Location:_____ ☉ Intensity:_____ 0-10 scale greater than or equal to 4 requires comment	Signs of Bleeding	☉ Denies ☉ Blood in stool, sputum or emesis ☉ Nose Bleeds ☉ Unexplained Bruising ☉ Petechiae ☉ Soft tissue hematomas Other:_____
		Hydration Status	☉ Denies any symptoms ☉ Poor PO intake ☉ Excessive Sweating ☉ Postural symptoms

Physician or Nurse Practitioner contacted: ☉ NO ☉ YES /Name:_____

Approval given to begin procedure: ☉ YES ☉ NO Reason for contact/comments: _____