Manuscript Supplement: A Randomized Trial of Inhaled Liposomal Cyclosporine for Bronchiolitis Obliterans Syndrome Post-Lung Transplantation

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Study Design

This manuscript entitled: "Inhaled Liposomal Cyclosporine Delays Progression of Bronchiolitis Obliterans Syndrome Following Allogeneic Lung Transplantation" has been defined by this study's IND protocol entitled *A Single Center, Randomized, Open-label, Controlled Pilot Study to Demonstrate Efficacy and Safety of the Addition of Liposomal Cyclosporine (L-CsA) Therapy versus Standard Therapy alone in the Treatment of Bronchiolitis Obliterans Syndrome: (BOS) Following Lung Transplantation*, approved to commence on November 2, 2011 (Principal Investigator Aldo T. Iacono; IND #11830).

This is the *first* trial using a liposomal formulation of aerosolized cyclosporine A for the treatment of chronic rejection in lung allograft recipients manifesting as BOS. In addition, this study is the *only* randomized, controlled, open-label study designed to test aerosolized cyclosporine as treatment for BOS. This Phase IIb using inhaled cyclosporine (L-CsA) plus standard of care immunosuppression vs standard of care immunosuppression alone (SOC) reported in the aforementioned manuscript, was designed having prespecified endpoints related to prevention of BOS progression, and conducted to enroll and treat patients with grade 1 and 2 BOS after single or double lung transplantation.

There are no approved immunosuppressive drug therapies that have ameliorated poor survival associated with chronic lung allograft dysfunction (CLAD). We hypothesize that inhaling the calcineurin inhibitor cyclosporine, the cornerstone of the oral maintenance immunosuppressive regimen, by depositing drug in inflamed airways directly, may logically ameliorate the inflammatory bronchiolar process. In this study, L-CsA was used in addition to standard of care immunosuppression consisting of triple drug therapy (SOC defined below) in both arms, with or

without L-CsA (i.e., L-CsA + SOC and SOC), assigned based on block randomization after having met all study inclusion and exclusion criteria. The prespecified endpoints in the protocol included the combined endpoints of BOS progression-free survival (FEV_1 stabilization, re-transplantation and death), BOS grade stabilization after randomization, and safety assessments.

The protocol and prespecified statistical analysis plans were submitted by the Principal Investigator, Aldo Iacono MD, and approved by the US Food and Drug administration on November 4, 2011 (IND #111830) and by the Institutional Review Board at the University of Maryland. A placebo-controlled study was not feasible as there is no constituently-matched placebo that meets regulatory guidance in the US.

Protocol

This was a single-center, randomized, controlled, open-label Phase IIb study for BOS treatment in recipients of a lung allograft with chronic lung allograft dysfunction, defined as grade 1 or 2 BOS. Patients were randomized to L-CsA and standard immunosuppression or standard immunosuppression alone (SOC), with a 24-week treatment period for L-CsA and a 24-week follow-up, totaling 48 weeks of follow-up in the L-CsA group. SOC cases were also followed for 48 weeks. There was potential for cross-over if SOC cases had met the efficacy endpoint outcome measure within the 48-week study interval, or rescue (crossover resumption of L-CsA) in those L-CsA cases that met the efficacy outcome measure defining BOS progression during their 24-week follow-up period while off of the study drug (L-CsA). The enrollment criteria for rescue and crossover were identical to inclusion and exclusion criteria and patients in the aforementioned categories were to initiate drug and continue treatments for 24 weeks.

Study Site

University of Maryland, 110 South Paca Street, 2nd Floor, Baltimore, MD, 21201, USA.

Study Approval

The protocol and informed consent form(s) for this study were approved by the Institutional Review Board (IRB) as defined by all local requirements at University of Maryland Medical Center.

Investigational Product

Liposomal Cyclosporine A (L-CsA) was supplied by PARI Pharma GmbH Lochhamer Schlag 21 82166 Graefelfing Germany. Liposomal Cyclosporine A (L-CsA) was dispensed in glass vials of 5 mg/1.25 mL (single lung recipients) and 10 mg/2.5 mL (double lung recipients) for inhalation using PARI Pharma's Investigational eFlow® Nebulizer System [3]. Inhalation was performed for 10-15 minutes twice daily through a mouthpiece during spontaneous respiration using the eFlow® Nebulizer System. At every visit, one inhalation cycle was monitored by the clinical trial center personnel.

Planned Number of Subjects

Thirty patients with diagnosed grade 1 or 2 BOS from years 2012-2015 (15 patients per arm) were planned to be enrolled in this study. Standard immunosuppression has been protocolled based on standardized immunosuppressive management at the University of Maryland for recipients of a lung allograft. A total of 21 patients were enrolled due to limitations of L-CsA manufacturing and moderate enrollment rates (Figure 1 Manuscript).

Objectives

This was the first randomized, controlled study completed using a novel liposomal formulation of cyclosporine (L-CsA) for treatment of BOS. A retrospective and a case-control study previously completed by the author using aerosol cyclosporine in an ethanol and propylene glycol-based vehicle for chronic rejection has shown functional and survival benefits [1,2].

This study was designed to assess the efficacy, tolerability, and safety of the addition of aerosolized L-CsA with standard of care (SOC) systemic immunosuppression as compared to SOC therapy alone for BOS management by assessing functional progression of chronic lung allograft dysfunction including changes in FEV_1 and FVC, death, and changes in the BOS grades from time to randomization and adverse events (AEs). Safety was monitored by peak flow assessments after L-CsA inhalation, AEs including infections, monthly assessments of creatinine and general laboratory data, and assessment of survival.

Eligibility Criteria

Inclusion Criteria

1. Age: 18 or older
2. Recipient of a single or double pulmonary allograft
3. BOS grade 1 or 2 [4]
4. Tacrolimus based immunosuppression
5. Capable of understanding the purposes and risks of the study, given written informed consent, agrees to comply with the study requirements and capable of aerosol inhalation

6. Women of childbearing potential must have a negative serum pregnancy test within 7 days prior to study entry
7. Stable to enable routine post-transplant bronchoscopy

Exclusion Criteria

1. Unresolved bacterial, viral or fungal infection
2. Mechanical ventilation
3. FEV_1 < 1 liter and/or FEV_1 < of 30% predicted [5]
4. Bronchiolitis obliterans syndrome grade III
5. Pregnant women or women who are unwilling to use appropriate birth control to avoid pregnancy
6. Breastfeeding women
7. Hypersensitivity to L-CsA or its respective ingredients
8. Serum creatinine value of > 2 fold upper normal value, dialysis or liver disease with a bilirubin > 2 fold upper normal value
9. Underlying disease thought to result in death within four months
10. Investigational drug use within 4 weeks prior to study entry
11. Psychiatric disorders or altered mental status precluding understanding of the informed consent process

12. A co-existing medical condition that in the Investigator's judgment will substantially increase the risk associated with the participation in the clinical trial
13. Significant bronchial strictures unresponsive to dilatation
14. Malignancy diagnosed within one year prior to screening (with the exception of skin cancers)

Treatment Regimen

All participants in both allocation arms (L-CsA + SOC group; SOC alone group) were managed according to the University of Maryland's standardized institutional protocol for clinical and basic immunosuppression management consisting of tacrolimus, sirolimus, prednisone, and mycophenolate mofetil, mycophenolic acid, and azathioprine or methotrexate. Patients were prospectively randomized by block randomization in a 1:1 ratio among the L-CsA + SOC and SOC alone control groups by block randomization stratified by transplant type, single or double, because of the known differences in survival between single and double lung transplants.

After screening and diagnosis of BOS, patients who provided written informed consent were randomized to one of the following treatments:

<u>Group A (L-CsA + SOC)</u>

- Single lung transplant recipients:

  L-CsA 5 mg/1.25 mL twice daily for 24 weeks, plus SOC conventional immunosuppression, including maintenance and augmented immunosuppression

- Double lung transplant recipients:

  L-CsA 10 mg/2.5 mL twice daily for 24 weeks, plus SOC conventional immunosuppression, including maintenance and augmented immunosuppression

Group B (SOC alone)

- Single or double lung transplant recipients:

  SOC conventional immunosuppression, including maintenance and augmented immunosuppression

Evaluation of Efficacy

We hypothesized that local delivery of L-CsA in higher concentrations is safer than increasing oral doses of systemic cyclosporine and tacrolimus, due to their systemic toxicities. The higher local drug dose should ameliorate better the small airway inflammatory response associated with bronchiolitis obliterans, thereby preventing further lung function deterioration.

Outcome analyses included clinical evidence for improvement of BOS by study drug. Since BOS is not curable by any conventional immunosuppressive treatments, the course of decline in FEV_1 is typically inexorable and results in severe infections, respiratory failure, graft loss or death. Therefore, a composite efficacy endpoint was selected for this study. FEV_1 was measured in a certified laboratory using ATS established criteria [5].

In order to evaluate the efficacy of L-CsA in preventing progression of chronic lung allograft dysfunction, lung transplant recipients with grade 1 or 2 BOS were randomized to L-CsA + SOC or SOC alone.

Efficacy Endpoints

A. Efficacy failure, defined as either a $\geq$ 20% decline from the initial randomization FEV_1 value (confirmed by 2 separate measurements of at least 3 weeks apart), or re-transplantation or death.

B. Change in BOS grade (grade 1-3) from baseline at randomization to study completion at 48 weeks.

Efficacy failure between each of the two investigational treatment regimens (5 mg and 10 mg L-CsA, for single and double lung allografts, respectively) and SOC control cases was assessed at study completion. For the efficacy endpoint, decline in FEV_1 was validated as related to BOS as opposed to concurrent illnesses and physiologic factors that would cause a decline in pulmonary function. An outcome committee adjudicated endpoint outcome events throughout the course of the study whenever necessary.

Other Exploratory Efficacy Endpoints

Exploratory efficacy endpoints included the following:

- To determine the effect of L-CsA on FVC at 48 weeks
- To determine the effect of L-CsA on FEV_1 and FEF_{25-75} at 48 weeks
- To determine whether allograft cytokines (measured at baseline prior to randomization and when clinically indicated by bronchoscopy and bronchoalveolar lavage [BAL] collection) are affected by L-CsA.

Pulmonary function tests, including FEV_1, FVC, and FEV_{25-75}, were performed in a certified laboratory by ATS standards at each clinic visit or when clinically indicated.

Evaluation of Safety

Safety-related objectives included the following:

- To determine tolerability of L-CsA (including individual patient compliance with known history of airway inflammation and BOS) and compliance and its influence on peak flow rates
- To determine the effect of L-CsA on infection rates and renal insufficiency
- To assess overall mortality in L-CsA cases compared to SOC alone.

A comparison of the safety profile between L-CsA + SOC and SOC was made. AEs were adjudicated for cause and severity by a safety and monitoring committee that reviewed blinded study results. Tacrolimus and sirolimus drug levels along with standard laboratory values were monitored at the time of each study visit.

Safety of L-CsA + SOC was assessed by comparison to SOC alone by the following parameters:

1. Acute tolerability of L-CsA during initial dosing
2. General toleration of L-CsA
3. Incidence and severity of AEs
4. Changes in clinical laboratory parameters
5. Changes in physical examinations

6. Infection rates
7. Maintenance doses of calcineurin inhibitors
8. Antimetabolite agents, and corticosteroids
9. Courses of immunosuppressants administered
10. Incidence of malignancies
11. Overall mortality

Treatment Response and L-CsA Rescue/Crossover

Response to L-CsA + SOC and Provision for L-CsA Rescue

If patients randomized to L-CsA + SOC met the efficacy endpoint while receiving L-CsA treatment during the first 24 weeks of the trial, L-CsA was *not* resumed. These patients were considered "treatment failures" with respect to the efficacy endpoint.

For patients who did not meet the efficacy endpoint, L-CsA + SOC was continued until the end of Week 24. These patients were considered "treatment successes" with respect to the efficacy endpoint.

The second 24-week period of the trial, while patients were off L-CsA but still receiving SOC, was used to assess the rate of recurrence of BOS progression. In the case of recurrence while off investigational L-CsA in treatment responders, a second course of L-CsA may have been offered to these patients provided they still met study eligibility criteria as defined in the protocol. The treatment duration of the second course of L-CsA was 24 weeks. Follow-up was according to the visit schedule as defined in the protocol.

Response to SOC Alone and Provision for Crossover to L-CsA

If patients randomized to SOC alone met the efficacy endpoint during the first 24 weeks of the trial, they were considered "treatment failures" with respect to the efficacy endpoint. Treatment with L-CsA may have been offered to these patients provided they still met study eligibility criteria as defined in the protocol

Adverse Events and Safety Monitoring

AEs reported by the patient or observed by the Investigator or hospital personnel were documented in the respective CRF including date and time of onset and resolution, serious or non-serious, treatment required, outcome, relationship to study drug, and if the AE caused withdrawal from the study. AEs were coded according to MedDRA 10.0. Results from clinical laboratory tests were recorded and analyzed for each patient. Abnormal reports were graded using the standard Common Toxicity Criteria (CTC), version 3.0. Each AE was classified by the Investigator as serious or non-serious by International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) standards.

BAL Cytokine Measurements

Each patient was evaluated before and after randomization for BAL cytokine expression including IL-1β, IL-2, IL-6, IL-8, IL-10, IL-17 and IFN-γ and TNF-α. BAL fluid was spun and BAL cell pellets were suspended in Triazol (2 cc) and frozen at −80 degrees C. BAL cells were isolated for cytokine measurements at the time of randomization before L-CsA administration and whenever an additional bronchoscopy was needed clinically due to decline in function or development of new respiratory symptoms, and at the end the study protocol. Cytokines were

quantitatively measured by the Cytokine Core Laboratory, University of Maryland, with a multiplex assay (Luminex 100™ system [Luminex Corporation] analyzed using the Bio-Plex Manager™ Software [Bio-Rad Laboratories]) [6].

Histopathology of Lung Allograft

Bronchoscopy (with biopsy and BAL) was performed at 3-4-month intervals for patients with respiratory symptoms and whenever rejection or lung infection was suspected.

Pharmacokinetics (PK)

The PK parameters were calculated using non-compartmental analysis and WINNONLIN version 5.0.1. The parameters calculated at Week 4 included: Maximum blood cyclosporine concentration (C_{max}), time to maximum plasma drug concentration (t_{max}), area under the curve (plasma drug concentration-time) from time zero to time t (AUC_{0-t}) where it is the last quantifiable result, area under the (blood drug concentration-time) curve from time zero to infinity (AUC_{0-inf}), and terminal half-life of drug in plasma ($t_{½}$). Pre-dose trough levels were summarized using data collected at each visit.

Trial Duration and L-CsA Administration

Patients randomized to L-CsA received L-CsA + SOC for 24 weeks, followed by SOC for 24 weeks, resulting in a total period of participation of 48 weeks unless patients met the efficacy endpoint. Patients randomized to SOC alone likewise had a total period of participation of 48 weeks unless they met the efficacy endpoint.

Peak flow values were monitored in each patient randomized to L-CsA before and then within the first 60 minutes after completion of study treatment for the first administration. These

patients were provided with a peak flow meter and peak flow was recorded after each treatment of L-CsA while at home during the initial 7 days of treatment. Patients were instructed on how to use the peak flow device. If a 20% decline or more in aforementioned values should have occurred, L-CsA was to be discontinued or the dose and frequency could have been reduced at the discretion of the Investigator. The latter events did not occur during the course of this trial.

Maintenance Immunosuppressive Regimen

Immunosuppressive therapy included tacrolimus, prednisone, mycophenolate mofetil or mycophenolic acid, azathioprine, and sirolimus or methotrexate and was adjusted at the discretion of the managing physician or surgeon throughout the course of the study. Immunosuppressive and prophylactic administration of pharmaceuticals was administered according to the institutional standards of the University of Maryland Medical Center by protocol. Dates of start and stop or change in dosage were recorded on the respective CRF. Dates of start and stop or change in dosage were recorded on the respective CRF.

<u>Baseline Immunosuppressive Regimens and Target Levels</u>

Systemic tacrolimus was dosed to achieve a target 12-hour trough level of 6-12 ng/mL. In patients with either a history of multiple episodes of acute rejection or apparent increased propensity for acute rejection, higher levels were targeted. Sirolimus was added in patients with high propensity for acute rejection with the target level being a combined sirolimus and tacrolimus of approximately 10 ng/mL. Systemic cyclosporine was not permitted.

Mycophenolate mofetil was given at a starting dose of 1 gm PO BID and switched to mycophenolic acid if gastrointestinal toxicity occurred. The doses were titrated or discontinued to adjust for individual risk for infection or rejection or individual risk or history of malignancy. Azathioprine was used as a substitute for mycophenolate mofetil at a dose of 2 mg/kg. Prednisone was started at 20 mg per day PO and the dose was adjusted.

Doses and immunosuppressants were adjusted based upon each individual patient's need at the clinician's discretion.

Evaluation of Rejection and Need for Augmented Immunosuppression

Potential lung allograft rejection was generally but not exclusively confirmed by biopsy. Treatment of rejection may have been initiated based on clinical assessment alone.

Acute Rejection

Acute rejection was defined by histopathology or by clinical methods. Histopathologically-defined acute rejection included having ISHLT grades 1-4. Clinical definitions were made with clinical signs and symptoms (new cough, shortness of breath, pulmonary infiltrates) or spirometry or signs of allograft dysfunction with or without histopathology evidence on biopsy after exclusion of infections. Treatment of acute rejection was with high dose methylprednisolone or a prednisone taper or increasing baseline immunosuppression levels or adding another immunosuppressant.

Chronic Rejection by Histology (BO)

- Grade B0 (No Airway Inflammation) [7]

- Grade B1R (Low-grade Small Airway Inflammation): Scanty mononuclear cells identified within the sub-mucosa of the bronchioles
- Grade B2R (High-grade Small Airway Inflammation): Presence of marked large activated intra-epithelial mononuclear cells and eosinophils and plasmacytoid cells; necrosis of the airway epithelium necrosis and metaplasia. Epithelial ulceration and exudate and neutrophils may be present.

Protocol-Specified Treatment Regimen for Chronic Rejection

1. Methylprednisolone (Solumedrol), 1 g IV QD x 3 days (generally given for first two proven rejection events), then consider alemtuzumab or thymoglobulin
2. Alemtuzumab (Campath), 30 mg IV x 1 day, or
3. Thymoglobulin (antithymocyte globulin [ATG]), 1.5 mg/kg IV x 3-5 days

Statistical Methods

Since this is the first study using L-CsA for BOS, much of the statistical plan focused on patient safety for planning of future controlled trials. Data were summarized for both the L-CsA + SOC treated patients and those who received SOC alone. Both treatment groups, independent of the type of transplantation, were analyzed in a pooled manner, followed by a stratified analysis comparing patients who received a single or a double lung transplant. Due to the current lack of availability of data required for the design of a confirmatory clinical trial, this Phase IIb trial was intended to yield sufficient data for a formal calculation of sample size and statistical hypotheses in a clinical investigation at a later phase of drug development (Phase III), which is to start in 2019.

Analyses of Patient Populations

Summary statistics were presented for continuous quantitative variables by way of n, mean, standard deviation (SD), median, minimum and maximum, and by way of group frequencies and percentages for categories of qualitative variables. Percentages were calculated using the total patients per treatment or sequence group.

Baseline Comparability Between Treatment Groups

Demographic data for age, height and weight were summarized using descriptive statistics. Categorical outcomes data were compared by Fisher's exact test. Group means were compared with the use of unpaired, two-tailed t-tests or Mann-Whitney tests. Subject randomization, and study drug assignment including dose of drug and dose change or discontinuation during the protocol, duration of treatment, subject disposition, and drug compliance were described. All analyses were based on the intent-to treat principle, i.e., all patients who are randomized and received the investigational drug L-CsA at least once have been included.

Progression of Bronchiolitis Obliterans Syndrome (BOS)

The BOS progression-free period is a combined endpoint defined by the length of time between resolution of the BOS episode (by L-CsA + SOC or SOC alone) by either prevention of a further decline in FEV_1 of ≥ 20% (or re-transplantation or death). The decline in FEV_1 meeting the endpoint was validated for concurrent illnesses other than rejection and measured at intervals of at least 3 weeks apart to confirm that defined decline. Other causes for the observed FEV_1 decline such as acute rejection, infection, stenosis or diffuse alveolar lung injury were excluded by bronchoscopic testing (biopsy and BAL) at the discretion of the Investigator. Bronchodilators

were not to be administered the day of FEV_1 testing. Patients in both arms who were free of progressive BOS were censored 48 weeks after study initiation at study closure.

This endpoint was compared between the L-CsA + SOC and SOC-alone groups by a log-rank test and stratified by transplant type (single lung vs double lung). Data were presented with 95% confidence intervals and hazard ratios. Estimates of progression of BOS progression-free survival between groups were determined by the method of Kaplan and Meier. A Cox Proportional Hazards model was used to assess FEV_1 at randomization and survival between groups. The diagnosis of progression of BOS for each subject was determined by an Outcomes Committee. For the other efficacy endpoints, a multivariate, linear, mixed-effects statistical model (PROC MIXED, SAS version 9.1.3; SAS Institute, Cary, NC) [8] was used to estimate FEV_1 % predicted trajectories for each group of patients, adjusted for confounding factors [7]. A mixed-effects model was also used to calculate differences in tacrolimus and sirolimus levels and analyze routine laboratory results between L-CsA + SOC and SOC alone. Another efficacy endpoint, changes in grades of BOS between groups after randomization was compared by ANOVA as were cytokine changes. As a prespecified safety analysis, overall survival was calculated between randomized groups and compared by the log-rank test. The grade of airway inflammation and acute rejection was evaluated descriptively between groups [8].

Overall Survival and Graft Survival

Graft survival as an indication of drug safety is provided below according to the IND plan for L-CsA. study. This is presented in addition to generalized patient survival in the manuscript.

Graft survival is an ideal measure of L-CsA safety and efficacy as opposed to re-transplant surgery as mode to maintain survival as there were four cases that required re-transplantation to maintain longevity. The Kaplan-Meier curve for graft survival as of September 2017 for L-CsA compared to SOC shows a median graft survival of 4.1 versus 2.7 years respectively (Figure below). In the L-CsA group, there were 6/11 treatment failures including 1 re-transplant; SOC had 10/10 treatment failures including 3 re-transplants, log-rank p-value = 0.01.

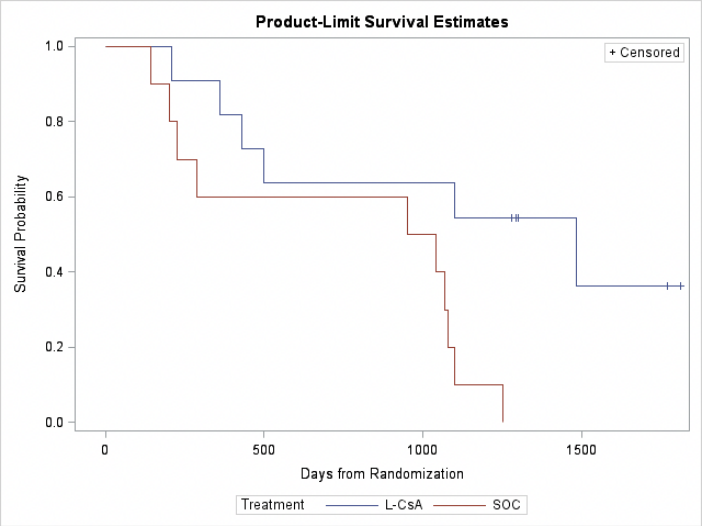

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Table 1: Maintenance and Augmented Immunosuppression during the Study Period

		Maintenance Immunosuppression							Augmented Immunosuppression Cycles	
Patient	**Study Arm**	**Tacrolimus**	**Sirolimus**	**Mycophenolate Mofetil**	**Mycophenolate Sodium**	**Azathioprine**	**Methotrexate**	**Prednisone**	**Pulse Steroids**	**ATG**
1	L-CsA	X				X		X		
4	L-CsA	X		X				X		
5	L-CsA	X	X		X			X		
7	L-CsA	X		X				X		
9	L-CsA	X	X	X		X		X	1	1
10	L-CsA	X		X		X		X		
14	L-CsA	X		X				X		
16	L-CsA	X	X	X				X	2	
18	L-CsA	X	X	X				X		
20	L-CsA	X	X	X				X		
21	L-CsA	X		X				X		
2	SOC	X	X					X		
3	SOC	X	X	X				X	1	
6	SOC	X		X				X		
8	SOC	X	X	X				X		
11	SOC	X	X					X	1	
12	SOC	X	X	X				X	1	
13	SOC	X	X	X				X		
15	SOC	X	X	X				X		1
17	SOC	X			X	X		X		
22	SOC	X					X			
Total	**L-CsA**	**11 (100%)**	**5 (45%)**	**9 (82%)**	**1 (9%)**	**3 (27%)**	**0 (0%)**	**11 (100%)**	**3 cycles**	**1 cycle**
Total	**SOC**	**10 (100%)**	**7 (70%)**	**6 (60%)**	**1 (10%)**	**1 (10%)**	**1 (10%)**	**9 (90%)**	**3 cycles**	**1 cycle**

L-CsA = randomized to L-CsA and standard of care immunosuppression; SOC = randomized to standard immunosuppression only.

Note: For augmented immunosuppression cycles, the mean days of administration post-randomization was 126 and 123 days for the L-CsA + SOC and SOC alone groups, respectively.

Table 2: Azithromycin Use by Treatment Group

Patient	Study Arm	Start (# of days pre-randomization)	End (# of days post-randomization)
1	L-CsA	NA	NA
4	L-CsA	NA	NA
5	L-CsA	−425	Through study completion
7	L-CsA	−493	Through study completion
9	L-CsA	−329	Through study completion
10	L-CsA	−716	Through study completion
14	L-CsA	NA	NA
16	L-CsA	NA	NA
18	L-CsA	NA	NA
20	L-CsA	−277	Through study completion
21	L-CsA	−348	252
2	SOC	NA	NA
3	SOC	−226	Through study completion
6	SOC	−175	Through study completion
8	SOC	NA	NA
11	SOC	−63	Through study completion
12	SOC	0	175
13	SOC	−621	Through study completion
15	SOC	−278	Through study completion
17	SOC	−383	Through study completion
22	SOC	NA	NA

L-CsA = randomized to L-CsA and standard of care immunosuppression; NA = not applicable; SOC = randomized to standard immunosuppression only.

Six patients (55%) in the L-CsA + SOC group and seven patients (70%) in the SOC alone group received azithromycin. Azithromycin was not initiated in any patient after the start of the study, and was stopped in two patients (1 L-CsA, 1 SOC) prior to study completion. Numbers above for start and stop days are relative to the date of randomization; negative numbers indicate days pre-randomization and positive numbers indicate days post-randomization.

Table 3: Compliance and Days of Treatment with L-CsA

Patient	Study Arm	Total Days of L-CsA Treatment
1	L-CsA	168
4	L-CsA	344 (168 study period + 176 re-therapy)
5	L-CsA	168
7	L-CsA	151
9	L-CsA	133
10	L-CsA	168
14	L-CsA	168
16	L-CsA	168
18	L-CsA	169
20	L-CsA	182
21	L-CsA	185
2	SOC	166 (crossover)
3	SOC	–
6	SOC	–
8	SOC	–
11	SOC	–
12	SOC	–
13	SOC	–
15	SOC	119 (crossover)
17	SOC	–
22	SOC	–

L-CsA = randomized to L-CsA and standard of care immunosuppression; ND = no data available; SOC = randomized to standard immunosuppression only.