

Pulminiq™ (cyclosporine, USP) Inhalation Solution (CyIS) Briefing Document for the Pulmonary Advisory Committee meeting June 6, 2005

I. INTRODUCTION

Lung transplantation provides patients with end-stage pulmonary disease a chance for improved quality of life and survival as reported in The Registry of the International Society of Heart and Lung Transplantation: Twenty-first Official Adult Lung and Heart-Lung Transplant Report – 2004 (Trulock EP *et al.* 2004). In the following paragraphs, we have summarized some of the highlights from this report, and invite you to read this reference for additional details.

The number of lung transplantations performed annually has increased from 400 lung transplantations in 1990 to approximately 800 in the US and 1,300 world-wide in 1995. After being relatively stable from 1995 to 1999, the annual number of lung transplants has grown by 17% from 1999 through 2002 and was approximately 1,100 in the US and more than 1,600 world-wide in 2002. Since 1994 the annual number of single lung transplantation has been nearly constant, while the number of double lung transplantation has increased 83% and exceeded the number of single lung transplantation in 2002 (single lung 794 versus double lung 861), the year more than 1600 lung transplants were reported to the International Society of Heart and Lung Transplantation (ISHLT) registry.

Another important trend has been the change in age distribution of adult recipients between 1985 to 1996 and 1997 to 2003. In the recent era, 50% of the recipients were in the 50 to 64 year-old category. This is characteristic of patients with advanced COPD and IPF, which together recently account for more than 50% of all lung transplants.

Survival rates for all lung transplant recipients from January 1990 through January 2002 were 84% at 3 months, 74% at 1 year, 58% at 3 years, 47% at 5 years, and 24% at 10 years. These survival rates are well below those reported for kidney, liver and heart transplantation. The incidence of acute rejection is greater, and chronic allograft dysfunction is more frequent and occurs at an earlier time-point in patients with lung transplants than other solid organ transplants. Although several immunosuppressive agents are used in managing patients after lung transplantation, none are FDA approved for this use. Given these factors, there is a clear need for treatments to improve outcomes in patients with lung transplantation.

The mortality rate is highest in the first year. One-year survival has improved over time and was 77% for the cohort transplanted in 1998-June 2002 compare to 67% for the cohort transplanted in 1988 to 1992. During the first year after transplantation the leading causes of death are infection, and acute graft failure. Acute rejection is a cause of death in only about 5% of the deaths in the first 30 days after transplantation, and declines rapidly thereafter. Chronic rejection (manifested clinically as bronchiolitis obliterans syndrome

or BOS and histologically as obliterative bronchiolitis or OB) is reported as a cause of death in less than 5% of the deaths during the first year after transplantation, but progressively increases thereafter to become a cause of death in about 30% of the deaths over the long term based on data from adult lung transplants between 1992 and 2003 (See Table 3. of Trulock EP *et al.* 2004). Note that infection also remains an important cause of death, particularly during the first year after transplantation (approximately 35%) and progressively declines thereafter as other causes of death emerge with more prolonged survival. From > 3 years to 5 years after transplantation, infection is still reported as the cause of death in about 20% of the deaths compared to 32% for chronic rejection.

Although survival rates for single and double lung transplant recipients appear comparable throughout most of the first year, thereafter, patients with single lung transplants have a worse prognosis than patients with double lung transplants, as seen in both transplant half life and conditional half life. The half life, meaning the time to 50% survival from time of transplantation, is 3.9 for patients with single lung transplants and 5.3 years for patients with double lung transplants. In addition, the conditional half life survival, meaning the time to 50% survival for those recipients surviving the first year after transplantation, is 6.2 years for patients with single lung transplants and 8.3 years for patients with double lung transplants. (Trulock EP *et al.* 2004, Figure 9). This may explain in part the increase in double lung transplantation compared to - single lung transplantation. The consequence of leaving a native lung *in situ* when performing single lung transplantation on risk for infection, and on results of pulmonary function tests (effect of hyperinflation in the remaining native lung) should be considered. Double and single lung transplant recipients differ in other ways, including their age distribution and indications for transplantations. This is why, in randomized, controlled clinical trials intended to evaluate comparative survival, when it is not possible to adjust for a number of these factors, consideration should still be given to stratifying randomization by type of transplant procedure. Stratification by single versus double lung transplantation may minimize the potential for bias.

Development of bronchiolitis obliterans (obliterative bronchiolitis, OB), a major contributor to chronic allograft dysfunction is the leading cause of morbidity and mortality in long-term survivors of lung transplantation, and remains the major limitation to long-term survival after lung transplantation. It is present in 60-70% of transplant recipients who survive 5 years. The median time to OB is approximately 18 months. Although the pathogenesis of OB is multifactorial and is not completely understood, chronic rejection resulting from alloimmune-dependent responses (acute rejection episodes) is considered to be the predominant cause of OB. While, non immune events such as viral infections, ischemia and acid reflux may also contribute to the development of OB, improvements in prevention of early and late acute rejection episodes in lung transplantation, represent potential approaches to prevention of OB and improvement of long term survival. (See Nueringer IP *et al.* 2005 and Sharples LD *et al.* 2002 for a more complete review and update on OB).

Bronchiolitis obliterans is characterized histologically by various degrees of submucosal fibrosis, with or without mononuclear infiltrate, involving the respiratory bronchioles,

which then results in complete or near-complete occlusion of the bronchiolar lumen. Clinically, small airway obstruction leads to the development of progressive airflow limitation. The disease has a variable course, meaning that some patients may experience rapid loss of lung function, and respiratory failure, while others may experience either slow progression or intermittent loss of function with long plateaus during which pulmonary function is stable. While the clinical course may be variable and fluctuate, the underlying chronic histological lesions are not considered reversible.

Histologic diagnosis of OB by bronchoscopy and transbronchial biopsy (TBB), even in patients with deteriorating lung function is very challenging. Lung biopsy specimens may be inadequate, unavailable, or may not be sufficiently sensitive for diagnosis. Routine surveillance bronchoscopies and TBB are timed to help monitor for acute rejection. Thus, TBB are performed more frequently early post transplantation, when acute rejection occurs more often. TBB may be performed less frequently after twelve months post transplantation when acute rejection becomes less common and chronic rejection becomes more common. While the sensitivity of TBB in making the diagnosis of OB is low, the specificity is high. However, TBB is not reliable in evaluating the extent or rate of progression of OB. Open-lung biopsies are much more sensitive in making the diagnosis of OB, but are not practical for the continued monitoring and documentation of OB in lung transplant recipients.

Because of the difficulties in documenting OB histologically, a committee sponsored by the International Society for Heart and Lung Transplantation (ISHLT) proposed in 1993 a clinical counterpart of OB, defined by pulmonary function changes rather than histology and called it bronchiolitis obliterans syndrome (BOS). (Estenne M et al. 2002). The BOS system has been adopted for more than a decade by transplant centers world wide as a descriptor of lung allograft dysfunction. While BOS is considered the most promising available surrogate marker for OB, and is also considered a predictor of ultimate endpoints of graft and patients survival, BOS has not yet been evaluated or validated in large, prospective clinical trials (Bowdish ME *et al.* 2004).

Monitoring for BOS relies on periodic evaluation of FEV1 post transplantation. The baseline values to which subsequent measures are compared, is defined as the average of the 2 highest (not necessarily consecutive) measurements obtained at least 3 weeks apart. Such measures must be made without the use of an inhaled bronchodilator preceding the study. The baseline should be recalculated using the highest values achieved, since spirometric values may increase with post-operative time. Thus, as more functional tests are performed, the definition of baseline, and hence of BOS stages, is expected to be more accurate.

Confounding factors in the diagnosis of BOS include, factors that affect the graft (infection and rejection, anastomotic complications, disease recurrence and aging), factors affecting the native lung (native lung hyperinflation in patients with emphysema who receive a single lung, infection, and disease progression in patients without emphysema) and other factors causing a restrictive ventilatory defect (increased body mass index, and respiratory muscle weakness, pleural effusions, rib fractures, chronic

post-operative pain, and pulmonary edema.) Please see Estenne M et al. 2004, for a more comprehensive discussion of BOS and an update of the diagnostic criteria.

Intravenous cyclosporine-A was approved by FDA for prevention of rejection in kidney, liver and heart transplantation in 1983. It has been and is used in lung transplantation but has not been FDA-approved for this indication. Other immunosuppressant agents have become commercially available and are being used in patients who have undergone lung transplantation; however, these agents have not been reviewed or approved by FDA for this indication.

Based on ISHLT registry data a variety of immunosuppressive agents are used, while no particular regimen appears to prevail. Induction therapy with polyclonal anti-lymphocyte/anti-thymocyte preparations or lately interleukin-2 receptor (IL-2R) antagonists is used in about 40% of de novo lung transplantations. Maintenance regimens with a calcineurin inhibitor plus a purine synthesis antagonist are used in approximately 80% of the recipients at both 1 and 5 years after transplantation, but no specific combination predominates over time (Trulock EP et al. 2004).

II. REGULATORY HISTORY OF AEROSOLIZED CYCLOSPORINE

This is an unconventional new drug application in a number of ways. While most new drugs are developed from the Investigational New Drug (IND) stage through the New Drug Application (NDA) stage by a commercial sponsor or pharmaceutical company, aerosolized cyclosporine was developed under a number of INDs sponsored by clinician investigators at the University of Pittsburgh Medical Center (UPMC). A summary of the studies conducted under INDs for aerosolized cyclosporine at the UPMC is included below:

Protocol	IND	Indication	# Patients	Start date	Stop date	Study design
001	XXXX7	OB	38	12/17/91	1/1/02	Open-label, historical controls
002	XXXX7	Refractory AR	75	6/16/93	1/1/02	Open-label, historical controls
003	XXXX4	Prophylaxis of Acute rejection	10	6/20/97	2/27/98	Pilot, Open label
003	XXXX4	Prophylaxis of Acute rejection	58	11/16/98	8/21/03	Randomized, double blind
004	XXXX7	Other/infection	3	4/3/95	11/4/96	Open-label
005	XXXX7	Other/Miscellaneous	2	3/6/96	7/17/96	Open-label
006	XXXX7	Pediatric	9	7/1/97	11/1/02	Open-label
007	XXXX7	Compassionate use	4	2/27/98	N/A	Open-label
008	XXXX7	Compassionate use	1	7/1/98	7/1/98	Open-label
009 *	XXXX7	Rescue Study: OB & Refractory AR	30*	9/1/02	Present	Open-label, historical controls

OB – obliterative bronchiolitis AR – Acute rejection CO - crossover

*Protocol 009 included 30 new enrolments and 24 cross over from protocols 001 and 002 for a total enrolment of 54 patients.

In the Table above, Protocol 3 (highlighted) consisted of a pilot open label study in 10 patients who received aerosolized cyclosporine, and was followed by a randomized, double blind study which enrolled 58 patients (56 patients included in the final report). [Note: The study was designed to enroll a total of 120 patients, but was terminated early.] Chiron obtained rights to the UPMC study and collected clinical data on the patients in Protocol 3 using retrospectively constructed case report forms to capture the data from source materials at UPMC. Study Report ACS001 included in this application was written after analysis of the data obtained from the original study conducted under UPMC Protocol 3.

Additional open-label, non-comparative safety data was collected from 70 subjects who were enrolled in open studies conducted at UPMC under the other protocols and INDS listed in the table above. Case report forms were retrospectively created by the Applicant to collect the data from original source materials at UPMC, and used to write Study report ACS002.

Thus, the NDA contains data from a single comparative study (ACS001), completed by investigators at a single institution, under the direction of one principal investigator. In this study 26 patients were randomized to aerosolized cyclosporine and 30 patients were randomized to placebo. The study failed to meet its primary objective of demonstrating a decrease in acute rejection with the use of cyclosporine inhaled solution (CyIS) in *de novo* lung transplant recipients, but is reported to demonstrate a survival advantage; mortality of 3/26 (12%) in the CyIS arm and 14/30 (47%) in the placebo arm. Safety information for aerosolized cyclosporine is based on data from the 26 patients in the randomized study (ACS001) 10 patients from the open-label portion of Protocol 3, and 70 patients from various open label, uncontrolled studies (compiled under study report ACS002). There is no second or corroborative controlled clinical study submitted in the NDA.

The Division accepted the new drug application (NDA) for review because rejection in lung transplantation represents a serious medical condition for which there are no FDA approved therapies, and because the study reported a statistically significant survival difference (Protocol 3, Study report ACS001). However, it was also recognized that the data would need to be reviewed in detail to determine whether they provide substantial evidence of safety and efficacy to support approval of this product for use in patients undergoing lung transplantation.

In addition, except for the 28-day preclinical inhalational toxicity study in rats, the 28-day preclinical inhalational toxicity study in dogs, and some additional clinical information from biopharmaceutical study reports, the rest of the information submitted in the NDA is from the published scientific literature.

Overall, therefore, this NDA represents a smaller than usual commercial application. For example, approvals of immunosuppressant products for the prevention of rejection in kidney transplantation have been based on substantial evidence of safety and efficacy from large, multi-center, randomized clinical trials, including a large safety database supporting the use of the proposed agent and regimen in the patient population. The other NDAs usually have included two trials in kidney or liver transplantation with approximately 200-300 per treatment arm for initial approval of a new molecular entity, and one or two large studies for subsequent indications in kidney, liver or heart transplantation. Complete study reports from preclinical studies, phase I studies, and other supportive clinical studies conducted by the applicant are also routinely part of such an application.

However, given that the incidence of lung transplantation is lower and the study results demonstrated a survival difference, the NDA was accepted for review.

Because the annual incidence of lung transplantation, like all other solid organ transplantation in the US, is less than 200,000 this product qualifies for Orphan Drug status. Pulminiq™ (cyclosporine USP) inhalation solution was granted orphan drug designation by FDA on November 19, 2003 for the prophylactic prevention and treatment of refractory acute rejection in patients requiring allogeneic lung transplantation (application #03-1801). The Office of Orphan Products Development (OOPD) subsequently authorized extension of the orphan drug designation to the indication they are seeking in this NDA. Orphan Drug designation does not diminish the statutory standards required for approval of a new drug product, substantial information of safety and efficacy from adequate and well controlled trials.

III. SUMMARY OF PRECLINICAL ACTIVITY AND SAFETY STUDIES

Activity in Animal Models

The Applicant has submitted some information from the published literature on the activity of aerosolized cyclosporine in short term (less than 7 days) animal models of lung transplantation. Aerosolized cyclosporine was shown to be effective in reducing graft rejection in rats and beagle dogs with orthotopic lung transplant. The activity of aerosolized cyclosporine was comparable to intramuscular administration of the drug. Such measurements were based on histological evidence of graft rejection for up to 6 days of transplant. Either ethanol or olive oil was used as vehicle to dissolve the cyclosporine in the solution for inhalation. Propylene glycol, the vehicle used in Pulminiq™ was not used as a vehicle in any of the studies. The effect on long term graft survival was not evaluated.

Pharmacology/toxicology background for Aerosolized Cyclosporine in Propylene Glycol

The preclinical support for administration of Cyclosporine inhalation solution (CyIS) in propylene glycol (PG) vehicle derives from two studies, a 28-day inhalation toxicity

study in rats and a 28-day inhalation toxicity study in dogs, both using PG as the vehicle, and historical data from published journal papers and chemical safety data for inhaled PG.

PG is generally recognized as safe, mainly through studies using oral and dermal exposure. The relatively low oral toxicity of PG is due to its metabolism to lactate. Information on the inhalation toxicity of PG is more limited. An occupational study reported acute (one minute) PG inhalation exposure produced upper airway irritation, cough and slight airway obstruction (Wieslander et al., *Occupational and Environmental Medicine* 58 (10) 649-655 (2001)). A single inhalation drug product, bitolterol mesylate for bronchodilation, used an unknown amount of PG in its vehicle. The most pertinent paper regarding PG inhalation toxicity (Suber et al., *Food Chemistry and Toxicology*, 27(9):573-83 (1989)) reported nasal hemorrhage in rats exposed to PG 6 hours per day for 3 months.

In the applicant's 28-day inhalation toxicity study in rats, pulmonary hemorrhage, edema and tracheal inflammation were related to the combined exposure to CyIS and PG, with incidence increasing with CyIS dose. Immunosuppression, characterized by decreased leukocytes and lymphocytes was observed in the high dose group. While dose levels were limited by the maximum tolerated dose, serum cyclosporine levels in the high dose group exceeded human exposure by 80-fold. The well-characterized cyclosporine toxicity, nephropathy, was observed at higher exposures.

The applicant's 28-day inhalation toxicity study in dogs demonstrated lung irritation as well, with alveolar and interstitial inflammation observed in all cyclosporine dose groups and the vehicle control. No sham control was used in this study, thus confounding separation of the extent of pulmonary toxicity due to CyIS versus that of the vehicle. Laryngeal inflammation with ulceration was seen in the mid dose group males. Inflammatory cell infiltrates (lymphocytes, plasma cells or monocytes) were seen in control and treated groups as well. No additional CyIS-related toxicity was observed. Dose levels in dogs were limited by the maximum feasible dose but serum cyclosporine levels in the high dose group exceeded human exposure by 2.5-fold.

The main toxicological issue for this application is lung inflammation due to PG. Induction of lung inflammation by PG in lung transplant recipients must be weighed against clinical efficacy of CyIS. The patient, while receiving CyIS with PG chronically (three times per week), is not exposed to PG daily as were experimental animals and may receive pretreatment (inhaled lidocaine) to alleviate discomfort.

IV. SUMMARY OF BIOPHARMACEUTICAL ISSUES

The description of the clinical pharmacokinetics of CyIS provided by Chiron in Section 3.2.3 of the briefing document was reviewed. The Clinical Pharmacology and Biopharmaceutics team concurs with the applicant's assessments of clinical pharmacokinetics of CyIS with the exception of the following points:

1. In the briefing document, the applicant discussed data from Reference #50 (Corcoran et al., Eur Resp J, 2004, Mar 23(3): 378-383). This reference was not provided with the NDA for our review and thus we are unable to concur with the applicant's assessment of the data from Reference #50. Similarly we are unable to concur with the data provided in Appendix 8.1, which includes Figures 8.1-1 to 8.1-4 because they pertain to Reference #50.

2. We do not concur with the applicant's statement on page 36 of 132 of the briefing document which states that, "Burckart et al estimated the terminal half-life (T1/2) of cyclosporine in lung tissue at about 40.7 hours following CyIS by inhalation. This contrasts to terminal elimination T1/2 measured in blood of 6.5 hours after IV or 8.4 hours after oral administration." Since Burckart measured only whole-blood cyclosporine concentrations and not directly tissue concentrations, the correct description of his findings should state that Burckart et al estimated the terminal half-life (T1/2) of cyclosporine in blood at about 40.7 hours following CyIS by inhalation. This contrasts to terminal elimination T1/2 measured in blood of 6.5 hours after IV or 8.4 hours after oral administration.

V. EFFICACY ISSUES

V.A CLINICAL EFFICACY ISSUES

We are in general agreement with the Applicant's description of the design and conduct of the study. This section is not intended to provide a comprehensive description and presentation of the data, results and analyses, but will describe clinical efficacy issues we wish to bring to your attention as you evaluate the data and analyses presented. As mentioned earlier above, Orphan Drug designation does not diminish the statutory standards required for approval of a new drug product, substantial information of safety and efficacy from adequate well controlled trials.

Study ACS001 was originally a phase II pilot study conducted at UPMC, designed to evaluate the effect of CyIS on the occurrence of acute rejection in *de novo* lung transplantation, its primary endpoint. The rationale was that prevention of acute rejection would have an impact on the leading cause of chronic rejection, and possibly benefit graft survival. Chronic rejection as measured by BOS and graft survival were secondary objectives. We are in agreement with the applicant that the study failed to demonstrate a treatment effect of CyIS on the occurrence of acute rejection, its intended primary objective. The intended enrollment of study ACS001 was 120 patients. However, the study was amended and terminated when the last of 56 randomized enrolled subjects (30 in the placebo group and 26 in the CyIS group) finished 2 years on study treatment. The observed difference in survival at the end of study was unexpected and warrants a thorough review of the study design, conduct, data collection and analyses.

The important question in this single-center study is whether one can determine that the observed survival difference is due to a treatment-effect, or other factors, such as chance,

imbalances across treatment groups in baseline donor/recipient characteristics, and/or conduct of the study.

V.A.1. Distribution of Baseline Donor/Recipient Characteristics

Randomization in Study ACS001 was not stratified by single versus double lung transplant, or other baseline donor/recipient characteristics known to influence long term survival. While this may not be a serious problem in a study originally intended to demonstrate a difference in rates of acute rejection episodes in allogeneic lung transplantation, it is a potential problem when evaluating patient survival. It is therefore important to compare baseline donor/recipient characteristics in the placebo group and aerosolized cyclosporine group. These baseline characteristics should also be considered in making the determination of whether the results of the study may be generalized to lung transplant recipients in the US.

Although stratified by period of enrollment and CMV donor/recipient mismatch, randomization was unsuccessful in evenly distributing across treatment groups baseline donor/recipients characteristics which would be expected to influence survival. Most noticeable are the imbalances in type of lung transplant (single lung or double lung), proportion of patients with an episode of grade 2 or more acute rejection prior to enrollment, or time in ICU after transplantation greater than 14 days, which favor the CyIS group over the placebo group. These imbalances would be expected to predict worse patient long term survival in the placebo group. Such imbalances also raise the concern that known as well as additional unknown covariates capable of influencing survival were not evenly distributed across treatment groups (Please see discussion of Statistical Efficacy Issues below).

Table 2: Baseline and Disease Characteristics

	CyIS (26)	Placebo (30)
Donor age > Patient age	4 (15%)	6 (20%)
CMV D+R- mismatch	5 (19%)	7 (23%)
Gender mismatch	7 (27%)	10 (33%)
Prior AR Grade 1	8 (31%)	6 (20%)
Prior AR Grade 2+	8 (31%)	13 (43%)
Single transplant	15 (58%)	24 (80%)
Double transplant	11 (42%)	6 (20%)
Time in ICU > 14 days	1 (4%)	4 (13%)
Time in ICU <10 days	25 (96%)	23 (77%)
Time in ICU > 7 days	3 (12%)	9 (30%)
Emphysema	9 (35%)	19 (63%)
Recipient renal dysfunction	1 (4%)	4 (13%)
Donor with inotropic support	13 (50%)	25 (83%)

V.A.2. Study Blind and Data Collection Issues

The ABCD code as part of the patient number exposed the treatment assignment to becoming unblinded. We share the Applicant's concerns that the study blind may not have been adequately preserved during the conduct of the study. Knowledge of treatment assignment could have influenced how patients were managed during the conduct of the study, as well as their continued willingness to participate in the study

The study did not benefit from the use of prospectively designed case report forms to guide and assure the consistent and reliable collection of all the relevant data across treatment groups, at the time the study was conducted. This is reflected in the amount of information available on FEV1 prior to enrollment and on the individual doses of concomitant systemic immunosuppressant treatments over time.

V.A.3. Dosing Issues

The protocol specified dosing QD for ten days while titrating up to maximum tolerated dose or up to 300mg CyIS per day. The protocol then specified dosing three times per week for 96 weeks at the dose achieved at ten days. However, there was a wide range of dosing practices and problems with compliance with the protocol-specified regimen. Thus, some patients included in the final analysis received only one dose while others received up to 321 doses of aerosolized cyclosporine. Eleven subjects (5 in the placebo group and 6 in the CyIS group) received less than 25 doses.

Table 3: Distribution of Number of Doses of Study Drug Administered in ACS001

Number of Doses –Quartiles	CyIS (n = 26)	Placebo (n=30)
Minimum	1	1
10%	2.4	7.5
25%	44.25	48.5
Median	260.5	227
75%	297	315
90%	320.3	320
Maximum	321	324
Mean	189.0	190.1
Standard Deviation	127.7	123.0

Although there is no significant difference in dosing between the groups, this in itself is surprising given the statistically significant mortality difference which would be expected to result in dosing imbalances between the groups. The lack of difference may be account for, at least in part, by the following:

- (a) During the first 24 months of study when patients were receiving aerosolized treatment, mortality was 3/26 (12%) in CyIS group and 7/30 (23%) in the placebo group; the other 7/30 (23%) of placebo patients died after 24 months, when dosing had been discontinued,
- (b) There were 3 CyIS patients and 2 placebo patients, who stopped therapy and were converted to "rescue" therapy,

(c) There were 6 CyIS patients and no placebo patients who withdrew consent, and presumably stopped receiving CyIS.

Such large deviations from protocol specified dosing schedules, and the large variation in doses received in the CyIS group make it difficult to establish a relationship between a specific treatment regimen and improved patient survival.

V.A.4. Causes of Death

The predominant causes of death were infection and sepsis. This is consistent with the information on causes of death over time post transplant from registry data.

Table 4: Primary Causes of Death in Study ACS001

	Placebo (n=30)	CIS (n=26)
All Deaths	14 (47%)	3 (12%)
Pneumonia	3	2
Sepsis	4	
Bronchiolitis Obliterans	2	
Pulmonary Embolism	1	
CHF	1	
Unknown	3	1

The contribution of associated morbidity conditions cannot be excluded but is difficult to quantify in this vulnerable population.

The need for additional immunosuppression to treat acute rejection is a potential risk factor for infection. However, acute rejection was common in both treatment groups, and there was no significant difference in proportion of subjects with one or more episode of acute rejection of grade 2 or higher (Placebo 22/30 or 73% versus CyIS 19/26 or 73%), or in the number of episodes across treatment groups.

There were significant differences in time to first episode of pneumonia and incidence of at least one episode of pneumonia (Placebo 24/30 or 80% versus CyIS 11/26 or 42%) which favored the cyclosporine arm and suggested that the placebo group was more susceptible to pulmonary infection. Examination of the Product-Limit Survival Fit – Survival Plot shows a cluster of episodes of pneumonia in the placebo group occurring very early after enrollment, which appears to account for most of the difference. One cannot reasonably exclude that this difference is due to pre-enrollment risk factors, which were unevenly distributed across treatment groups despite randomization. The presence of the native lung in single lung transplant recipients may be associated with a greater risk of infection. Such differences would be expected to influence patient survival analyses, because of the strong relation between pneumonia and death in this study.

V.A.5. Pulmonary Functions Tests and BOS/OB

While the sensitivity of TBB in making the diagnosis of OB is low, the specificity is high. However, TBB is not reliable in evaluating the extent or rate of progression of OB. Information on OB from TBB was only provided as present or not present in this application. There is essentially no information on the description of the actual histology, and it is not possible to determine whether these represent active OB with mononuclear cellular infiltration, nor is it possible to assess the extent or rate of progression of the OB over time. Analyses of OB-free survival should be interpreted with caution in this study as they appear driven by the unexpected survival difference.

Assessment of BOS was also performed in study ACS001. Monitoring for BOS relies on periodic evaluation of FEV1 post transplantation. The baseline value to which subsequent measures are compared is defined as the average of the 2 highest (not necessarily consecutive) measurements obtained at least 3 weeks apart. Such measures must be made without the use of an inhaled bronchodilator preceding the study. The baseline value should be recalculated using the highest values achieved, since spirometric values may increase with post-operative time. Thus, the definition of baseline, and hence of BOS stages, is expected to be more accurate as more functional tests are performed.

Information on FEV1 before enrollment is incomplete. Only 15 out of 26 patients in the aerosolized cyclosporine group and 17 out of 30 patients in the placebo control group have documented values of FEV1 pre-enrollment. It is not possible to ascertain whether these subjects are representative of the complete study population. The mean value for the placebo group is smaller than for the aerosolized cyclosporine group (1.37 L and 1.92 L, respectively). If these values were considered representative of the whole treatment groups, one would not be able to reliably exclude that the observed difference reflects other differences in baseline donor/recipient characteristics that were unevenly distributed across treatment groups, despite the randomization of treatment assignment, e.g. double lung vs single lung.

Analyses of FEV1 data that compare change in FEV1 from the 3 month determination or the maximum of 3 and 6 month determinations fail to demonstrate a treatment effect (See Section V.B.5

The lack of more complete information on FEV1 prior to enrollment in such a large proportion of study subjects, and the imbalance of certain baseline donor/recipient characteristics, including the proportion of single lung transplants, and the difficulty in assessing the effect of potential confounding factors, including but not limited to hyperinflation of the native lung in single lung transplant recipients or pneumonia, impair our overall ability to draw reliable conclusions from analyses of FEV1 data and BOS. Again, analyses of BOS free survival must also be interpreted with caution, as it appears to be driven by the observed survival difference.

V.A.6. Lack of Corroborative Evidence from another Controlled Clinical Trial.

There is no corroborative information from another controlled clinical trial in this application to help us confirm that the survival difference in study ACS001 is due to a treatment effect. Earlier clinical experience is limited to a number of small open-label uncontrolled studies in a variety of lung transplant patients.

V.B. STATISTICAL EFFICACY ISSUES

V.B.1 Single Center

As stated above, one double-blind, randomized, single-center, placebo-controlled Phase II comparative study is submitted by the Applicant to support the efficacy of cyclosporine for inhalation in the treatment of lung transplant patients. Given that this study was conducted at a single center and was led by a single investigator, it limits the generalizability of the study results, more so in light of the variation in the standard of care of this patient population across lung transplant centers in the US.

V.B.2 Blinding Issue

Patients were stratified by CMV status (D+/R- Mismatch or Match) and by enrollment window (7-21 days or 22-42 days) and were randomized to receive aerosolized cyclosporine or placebo vehicle in a 1:1 ratio. An ABCD code was added to the patient number to assist the pharmacy in preparing study medication. All patients with code A and D in their patient number were to receive placebo and all patients with code B and C were to receive aerosolized cyclosporine. Every patient was followed at least for 2 years until the study end date of 08/21/2003. There is concern that the ABCD code in the patient number may have revealed treatment assignments to the investigators. The presence or magnitude of the investigator bias resulting from this cannot be quantified but cannot be ruled out either.

During the course of the trial, the investigator removed 5 subjects from the randomized portion of the study early in order to provide these subjects with open-label CyIS in the UPMC rescue study. Typically, when patients are rescued in a randomized double-blind trial, the rescue medication used is different from the treatments used in the study. When one of the treatment arms is used by the investigator as rescue, it shows strong prior belief in the effectiveness of that treatment. This, together with the possibility that the investigators may have been aware of the treatment assignments makes concerns regarding investigator bias even more severe.

V.B.3 Data collection and Dosing Issues

The Case Report Forms (CRFs) and Data Analysis Plan (DAP) were generated by the applicant retrospectively. While it is important to recognize the objectivity of the survival endpoint, it is also just as important to note that the retrospective nature of the study, in terms of the CRFs and the DAP, makes it vulnerable to the introduction of bias. It is

difficult to unequivocally confirm (or deny) the presence of bias using the results of the study and this can rarely be achieved by means of statistical methods.

The following design characteristics and data collection methods may not affect the study's ability to detect a treatment difference, if any, in terms of acute rejection, but they preclude a rigorous assessment of secondary endpoints: patient survival, improvement in FEV1, occurrence of BOS and occurrence of OB.

- Randomization in Study ACS001 was not stratified by single versus double lung transplant, or other baseline donor/recipient characteristics known to influence long-term survival.
- The information on FEV1 is grossly incomplete including the lack of data on baseline FEV1 prior to enrollment for 43% of the patients.
- More than 66% of the patients in the study had one or more protocol violations or entry criteria violations reducing the per protocol population to only 19 subjects (10 in the placebo arm and 9 in the cyclosporine arm).
- The dosing schedule was not followed by most patients in the study. Only 7 cyclosporine patients completed (at least) 2 years of treatment (294 or more doses). Out of the remaining 19 patients in the cyclosporine arm, 3 died within 2 years and 16 (62%) patients discontinued at various times before completing protocol specified treatment. The following table gives descriptive data on the length of therapy and shows that the amount of therapy differed greatly among the patients.

Table 5: Number of patients receiving a certain number of doses

Number of Doses (length of therapy)	CyIS (n=26)	Placebo (n=30)
Less than 10 (less than 10 days)	3 (12%)	3 (10%)
Less than 25 (less than 6 weeks)	6 (24%)	5 (17%)
Less than 42 (less than 12 weeks (3 mo))	6 (24%)	6 (20%)
Less than 78 (less than 24 weeks (6 mo))	9 (35%)	8 (27%)
Less than 150 (less than 48 weeks (12 mo))	9 (35%)	11 (37%)
Less than 222 (less than 72 weeks (18 mo))	12 (46%)	15 (50%)
Less than 294 (less than 96 weeks (24 mo))	19 (73%)	21 (70%)
Completed treatment (at least 294 doses)	7 (27%)	9 (30%)

- The available biopsy data in the study shows no difference between the placebo and cyclosporine groups in terms of the number of biopsies performed and the timing of these biopsies, even when more patients on the cyclosporine arm were alive compared to the placebo arm. Moreover, these biopsy data are obtained from transbronchial biopsies done for acute rejection.

V.B.4 Imbalances in Treatment Arms

In a randomized study, it is impractical to stratify randomization with respect to each and every prognostic factor. Therefore, there is always a chance that one or more factors will not be balanced between the two arms. This chance (probability) increases as the number

of factors increases, and rapidly so in a small sample study such as ACS001 (Hsu, 1989; Pocock and Simon, 1975). However, it is necessary to guard as best as one can against imbalances with respect to those factors that are known to have clinically significant influence on the endpoint under evaluation. This study could not accomplish that since the study was not designed with the primary objective of evaluating survival or chronic rejection.

The following table presents descriptive data illustrating baseline imbalances (despite randomization) between the two treatment groups in terms of factors that are considered important for survival: single/double lung transplant, ICU stay for more than 10 days, Grade 2+ AR prior to dosing, donor history of inotropic support and emphysema.

Table 6: Important Baseline Factors that show imbalance

Baseline Characteristic	CyIS (n=26)	Placebo (n=30)
Single Lung Transplant	15 (58%)	24 (80%)
Double Lung Transplant	11 (42%)	6 (20%)
ICU stay > 10 days	1 (4%)	7 (23%)
Prior AR grade 2+	8 (31%)	13 (43%)
Donor with inotropic support	13 (50%)	25 (83%)
Emphysema	9 (35%)	19 (63%)

Due to the presence of baseline imbalances in factors that are considered to have an influence on long term survival, p-values obtained from any un-adjusted survival analysis (such as log-rank p-value) are not valid and not interpretable. Moreover, since there is imbalance with respect to several factors, statistical analyses which adjust for only one factor at a time (Applicant’s summary of efficacy on pages 15-19 in the briefing package) are not valid as the two groups are still not comparable due to imbalance with respect to the other factors. In this case, simultaneous adjustment for all the factors of importance is needed in the statistical analysis. However, there are sample-size limitations on this procedure. Due to the small sample size of study ACS001, simultaneous adjustment of all the factors in Table 6 would lead to the over-specification of the model (with possible multi-collinearity) and un-interpretable results. Thus, one should question the validity of any further statistical survival analyses, inferential or exploratory, performed on the data from this study including those presented by the Applicant. However, one can examine the data on survival (it being most objective and the ultimate endpoint) in the spirit of data-mining. This does not and should not lead to evidence based conclusions (positive or negative) about the treatment effect. It merely serves the purpose of evaluating the merit of possibility of future studies.

V.B.5 Post hoc Analyses

The statistical design of Study ACS001 was that of superiority of over placebo with 1:1 randomization. However, the sample size determination was not made based on statistical considerations.

In these types of designs, when the Applicant wishes to include a pre-specified secondary endpoint in the label, a prospectively stated plan for multiplicity adjustment (such as gate-keep strategy or co-primary endpoints) is followed. When no claim in the label is intended in terms of secondary endpoints, hypothesis testing for these secondary endpoints is not done with statistical rigor. These tests are only used as a supportive evidence of the treatment effect seen in the primary analysis. In this scenario, if the primary endpoint fails to reach statistical significance, the study is considered a failed study and further hypothesis testing conducted is considered exploratory and is used to plan future studies.

In Study ACS001, no statistical alpha adjustment for multiplicity was pre-specified since there was only one primary endpoint, namely the rate of acute rejection and there was no intention to label the product claiming survival difference or chronic rejection-free survival difference at the design stage. However, given that the endpoint was survival, it was important to consider this secondary endpoint, even in the absence of pre-specified multiplicity adjustment, provided that the study conduct and results were exceptionally clean and robust.

Almost all the statistical analyses the Applicant presented in the briefing document are based on the study end date (2 years of follow-up on the last patient). The Division requested that follow-up survival data up to 5 years after transplant be collected and provided by the Applicant. In the following, we present results, when appropriate, for the end of treatment (2 years), study end date (applicant's choice), and for the complete follow-up data (5 years).

We will first turn to exploratory analyses of secondary endpoints other than survival such as FEV1 and BOS for which the factors showing imbalance at baseline may not be as important with the exception of type (single/double) of lung transplant. We urge you to exercise caution when interpreting the nominal p-values reported here.

Lung Function: FEV1

The following table gives descriptive data on mean FEV1 over time. The number in parenthesis indicates the number of patients on whom the data at that time-point is available. Note that pre-enrollment data is missing on nearly 43% of the patients in the study.

|

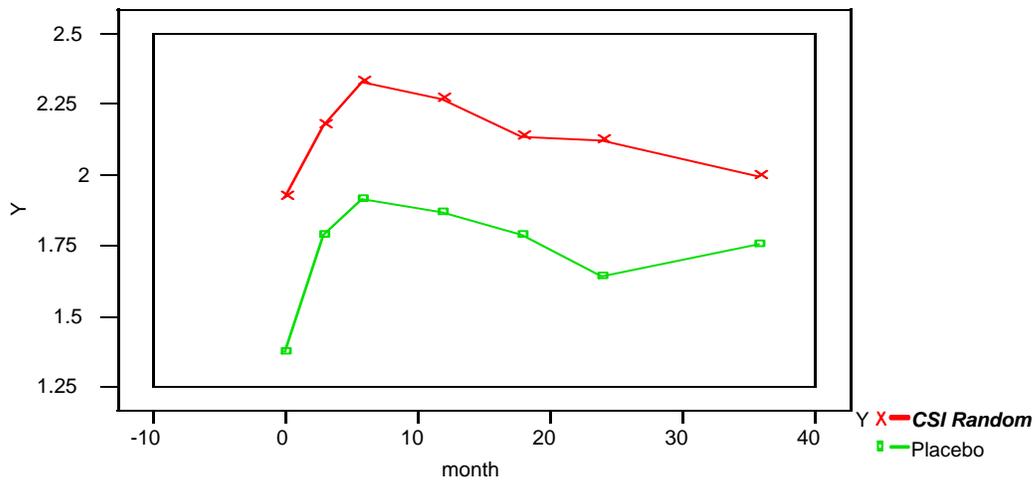
Table 7: Mean FEV 1 - descriptive raw data

Time point	CyIS (n=26)	Placebo (n=30)
Pre-enrollment	1.9233 (15)	1.3712 (17) *
3 months	2.175 (26)	1.7873 (26)
6 months	2.3264 (25)	1.9122 (27)
12 months	2.2688 (24)	1.8675 (24)
18 months	2.1355 (22)	1.7895 (22)
24 months	2.1235 (20)	1.6437 (19)
36 months	1.994 (10)	1.7543 (7)

* : There is a statistically significant (p-value of 0.0045) difference between CyIS and placebo arms in terms of mean FEV1 at pre-enrollment, presumably resulting from baseline imbalance with respect to type (single/double) of lung transplant.

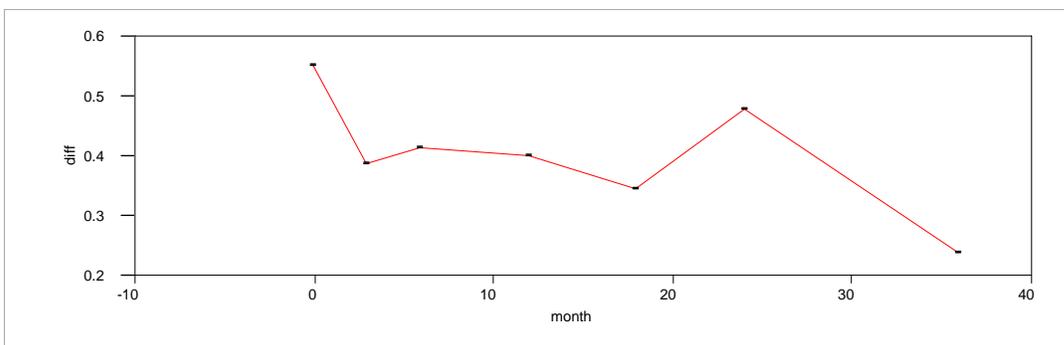
The following figure provides a graphical display of the numbers in Table 7.

Figure 1: Mean FEV1 over time



The following figure provides a graphical display of difference in mean FEV1 in CyIS and placebo arms over time.

Figure 2: Difference in Mean FEV1 between CyIS and Placebo



When a linear least squares model is used for fitting, the estimated slope of the line is -0.005, with a p-value (to test difference from zero) of 0.102. This analysis shows that the pre-enrollment difference in CyIS and placebo in mean FEV1 remains unchanged over time, that is, the change in lung function over time is not affected by the treatment.

In the following table, we provide the analyses of FEV1 data that compare change in FEV1 from the 3 month determination or from the maximum of 3 and 6 month determination. Both of these analyses fail to demonstrate a significant difference.

Table 8: Exploratory FEV1 Analyses

Analysis	CyIS	Placebo	p-value
Difference in FEV1 (final – baseline) when baseline is 3 mo data	Mean = -0.245	Mean = - 0.414	0.238
Difference in FEV1 (final – baseline) when baseline is max of 3 and 6 mo data	Mean = -0.4065	Mean = -0.4633	0.649

The Applicant has shown general agreement with our evaluation that the data from study ACS001 do not provide sufficient evidence that CyIS therapy results in improvement in FEV1 over placebo (page 79).

Lung Function: Time to BOS (death considered as censoring)

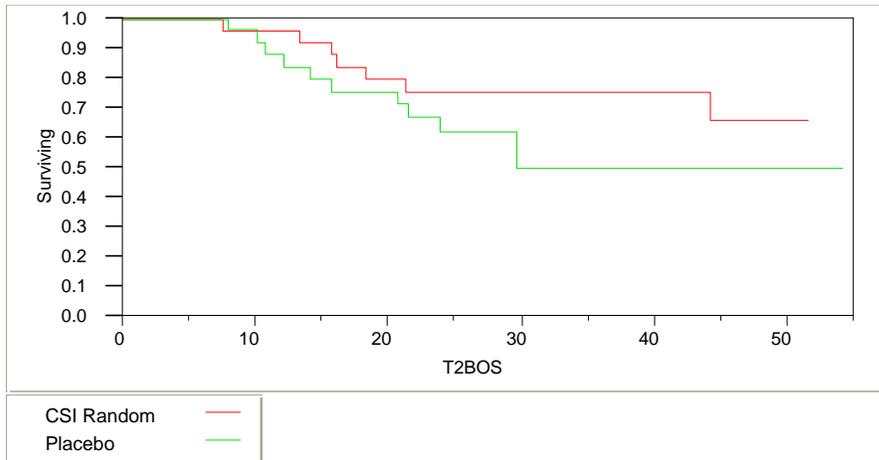
The following table gives descriptive data on incidence of BOS, the point estimate of the hazard ratio, its 95% confidence interval and p-value (to test the null hypothesis of hazard ratio of 1) obtained from the Cox model with censoring for deaths.

Table 9: Number of BOS, hazard ratios with confidence intervals and p-values

Analysis	CyIS	Placebo	Hazard Ratio	(95% CI) p-value
2 Years	6/26 (23%)	8/30 (27%)	0.687	(.226, 1.977) 0.485
End of Study	7/26 (27%)	11/30 (37%)	0.552	(.203, 1.406) 0.214

The following figure shows Kaplan- Meier plot of time to BOS censoring for deaths through the end of study, since information on BOS was collected only until that time point. The log-rank p-value in this analysis was 0.214.

Figure 3: Kaplan-Meier plot of Time to BOS censoring for deaths.



These analyses suggest that the data from study ACS001 do not provide sufficient evidence that CyIS therapy results in significant improvement in BOS over placebo.

Survival: Time to Death

We now turn our attention to survival analysis setting aside statistical rigor in the spirit of data mining. The graphs, point estimates, confidence intervals and p-values reported here merely serve the purpose of evaluating, in an exploratory way, how strong a signal of treatment effect, if any, is provided by the data to warrant further studies of this drug product.

The following table gives survival probability derived from the Kaplan-Meier plot at various time points for the placebo and cyclosporine arms.

Table 10: Estimated survival probability

Time point	12 months	24 months	36 months	48 months	60 months
Cyclosporine	96%	88%	88%	84%	77%
Placebo	83%	77%	60%	56%	45%

The following figures give Kaplan- Meier plots of time to death for the 2 years data, for the study end data and for the 5 years data. The log rank p-values are 0.229, 0.0075 and 0.0165, respectively.

Figure 4: Kaplan-Meier plot for Time to Death for the data at 2 years

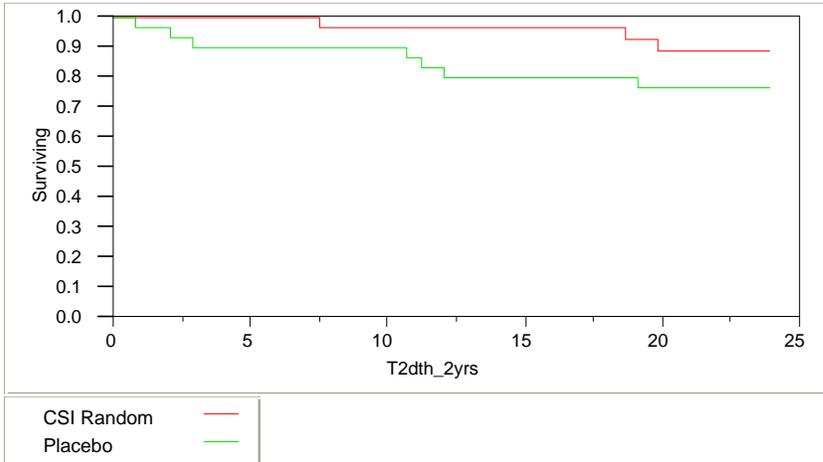


Figure 5 : Kaplan-Meier Plot for Time to Death for the data at the end of study

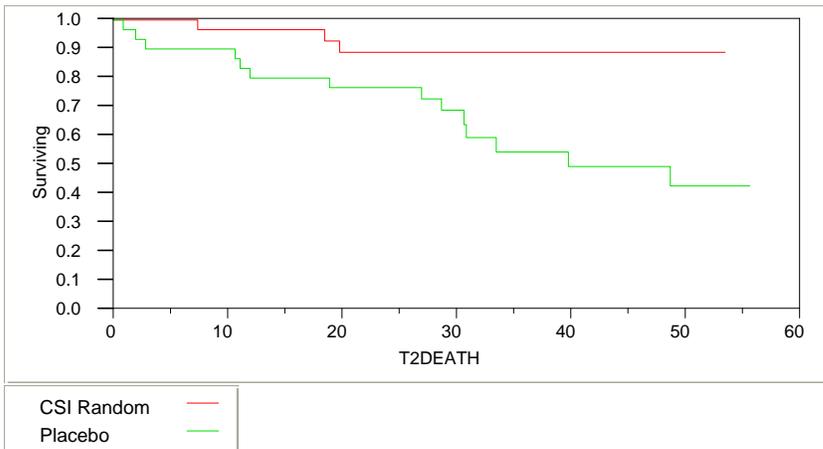
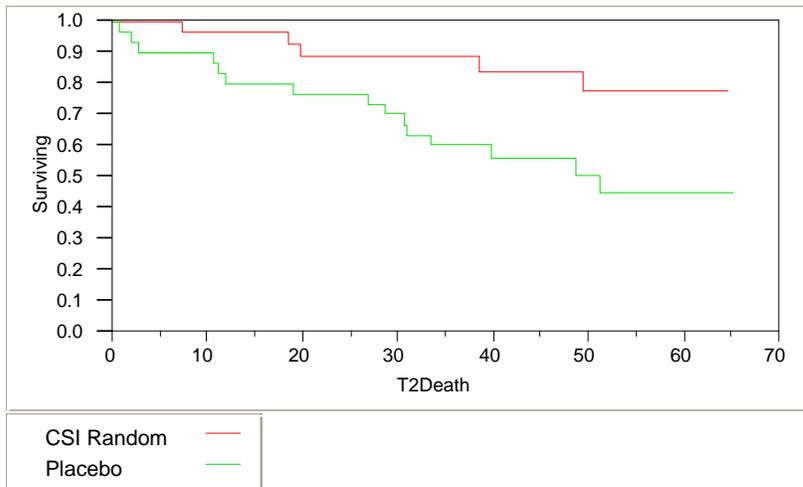


Figure 6: Kaplan-Meier Plot for Time to Death for the data at 5 years



It appears that a cluster of five patients in the placebo arm who died between 25 to 35 months after the transplant is driving the statistical significance in the study. Two of these 5 patients died of sepsis, 2 died because of unknown causes and 1 died due to pulmonary embolus. These 5 patients were mostly (4/5) single lung transplant patients, 80% (4/5) had primary diagnosis other than Emphysema, 80% (4/5) had at least 2 episodes of pneumonia, 80% (4/5) had prior acute rejection of grade 2+, 60% (3/5) had prolonged (20 days or more) ICU stay prior to dosing, 60% (3/5) had a donor with a history of inotropic support and all had FEV1 values of 1.5 or less at pre-enrollment. Clearly, these patients' characteristics are different from the majority of the patients in the cyclosporine arm and therefore one cannot make a determination of whether these patients would have survived if they were assigned to the cyclosporine arm.

As mentioned before, the above plots and the corresponding log-rank p-values are uninterpretable due to baseline differences in five major factors affecting long-term survival. An adjusted analysis using these factors as covariates in Cox's proportional hazards model is not appropriate as it may lead to over-specified model (given the small sample size of the study). We, once again, overlook this aspect and create the table given below. This table shows exploratory analysis of Cox regression model with treatment group and all five risk factors in Table 6 as covariates (for 2 years data, Study end data and 5 years data).

Table 11: Results of Cox Regression analysis

Covariates used in addition to treatment group: Listed in Table 6	Hazard ratio (CyIS/Placebo) for survival [95% Confidence interval] nominal p-value
2 years data	0.478 [0.091, 2.009] 0.321
Study End data	0.331 [0.070, 1.172] 0.089
5 Years data	0.461 [0.136, 1.361] 0.165

Another method that is used to adjust for baseline differences is based on propensity scores. Propensity score is defined as the conditional probability of receiving (the new) treatment given a collection of observed covariates and is estimated by modeling the distribution of treatment indicator variable given the observed covariates (logistic regression). Once estimated, we can use the propensity scores as a diagnostic tool to assess treatment comparability (which can be questionable in small studies such as ACS001 despite randomization). If the two treatment groups overlap well enough in terms of propensity scores, we can compare the two treatment groups adjusting for the propensity score thereby simultaneously balancing many covariates and thus reducing the bias. However, this method can only adjust for observed covariates and not the unobserved ones. Thus when data on important variables are not collected (given the retrospective nature of data collection in ACS001), this method is seriously flawed. We performed the propensity score analysis using the five major factors in Table 6 as covariates and the results obtained were similar to the ones in Table 11.

A sensitivity analysis of Time to Death

As mentioned before, there was a large variation in the number of doses received by the patients over the two year treatment period. Also, there were 8 patients (1 cyclosporine and 7 placebo) who were in ICU for more than 10 days after the transplant. Such prolonged ICU stay is considered to be an important factor affecting mortality in lung transplant patients. This brings into question whether or not one may reliably attribute statistically significant differences (in survival) to the assigned treatment. To assess, we conducted an unadjusted sensitivity analyses by excluding patients (4 cyclosporine, 9 placebo) who received less than 10 doses or who had more than 10 days of ICU stay before treatment. The results are given in the following table.

Table 12: Number of Deaths, hazard ratios with confidence intervals and p-values

Analysis	CyIS	Placebo	Hazard Ratio	(95% CI) p-value
2 Years	3/22	4/21	0.677	(0.133, 3.073) 0.608
End of Study	3/22	7/21	0.396	(0.085, 1.426) 0.160
5 Years	5/22	8/21	0.566	(0.171, 1.699) 0.312

This table suggests that data that may not be clinically relevant or meaningful is driving the statistical significance in this study.

The analyses of the data for occurrence of OB (with or without death considered as censoring) carry similar interpretations as that of survival analyses.

V.B.6 Summary

This randomized, double-blind clinical trial was designed as a small phase 2 study to show a treatment difference in terms of acute rejection. It failed to achieve that objective. Although the study uncovered a difference in survival between the two treatment arms in an exploratory post-hoc analysis, it suffers from five major weaknesses. First, the study was conducted at a single center and was led by a single investigator. This fact makes it difficult to generalize any results such a trial might produce. Second, the potential of the ABCD code (as part of the patient number) to break the study blind and the retrospective nature of the case report forms and the data analysis plan make the study vulnerable to the introduction of bias, as inadvertent as it may be. Detection of the presence of this type of bias is difficult, but its possibility lends to caution when interpreting the study results. Third, due to the small sample size, the study failed to benefit from randomization and the treatment arms were imbalanced with respect to several baseline factors that clinicians consider to influence patient survival. Statistical adjustments do not resolve the issue of comparability of the two treatment arms due to the presence of many factors and the small sample size. Fourth, the study failed to establish a treatment regimen and demonstrate its efficacy. Statistical analyses could neither answer the question of the amount of dose responsible for the survival difference observed in the two arms nor establish that the survival difference observed in the two arms is solely due to (a certain dose of) the treatment and not due to other factors. Finally, fifth, the study in which results for acute rejection, FEV1 and BOS fail to corroborate the observed unadjusted difference in survival and OB, raises questions of biological plausibility and reliability.

VI. CLINICAL SAFETY ISSUES

We agree with the Applicant that the systemic effects of cyclosporine in humans are well known, and that the amount of systemic exposure to cyclosporine (what is deposited in the lung appears to enter the blood stream before being eliminated), was not associated with a detectable increase in systemic toxicity. However, there is much more limited information on the adverse effects of aerosolized cyclosporine when it is administered by this new route with this particular vehicle, propylene glycol (PG). (Please see also the Pharmacology/toxicology background for Aerosolized Cyclosporine in Propylene Glycol, above.)

Evaluation of safety in this fragile population receiving systemic immunosuppression and numerous concomitant medications is complicated. Clinical safety data was collected retrospectively from source materials from one double-blind controlled study and a number of small open-label uncontrolled at UPMC. There were no prospectively designed case report forms to guide the systematic collection of safety data during the conduct of the study, including but not limited to the use of concomitant medications used to prevent or treat complications associated with the administration of study drug.

Comparative safety data is available on only 26 randomized subjects from Study ACS001 (or 36 subjects if one includes the first 10 non-randomized subjects from that study). As in the 28 pre-clinical animal studies, there was no sham treatment group, to help discern the contribution of inhaled PG to the respiratory tolerability and adverse events in both treatment groups. There was need for the use of premedication with bronchodilators and anesthetics to improve tolerability in both treatment groups. It is difficult to interpret the pattern of use of premedication over time, since after having their dose titrated on a daily basis over ten days to maximum tolerated dose of study drug (Placebo/PG or CyIS) not to exceed 300mg or its placebo equivalent, subjects were then administered three times per week for up to 24 months the dose they had previously tolerated. We have commented earlier on the variability of dosing and the wide range of number of doses administered over the study duration in both treatment groups. The proportion who completed 2-year dosing was 43% (13/30) in the placebo group, and 50% (13/26) in the CyIS group. Safety data was collected by the applicant in ACS001 beginning on the first day of administration of the study drug up through 90 days after the last dose administered (survival permitting) or August 21, 2003, whichever came first. We are in general agreement with the applicant's description of the safety data they were able to collect.

As described by the Applicant, there was evidence of more respiratory system adverse events in the CyIS group.

Adverse Event	Placebo (n = 30)	All CyIS (n = 36)
Acute Respiratory Failure	0	4 (11%)
Cough	8 (27%)	18 (50%)
Dyspnea Exacerbated	4 (13%)	11 (31%)
Hemoptysis	0	5 (14%)
Lung Consolidation	4 (13%)	11 (31%)
Pharyngitis	5 (17%)	14 (39%)
Respiratory Disorder NOS	0	7 (19%)
Respiratory Tract Irritation	1 (3%)	6 (17%)

From Chiron's PulminiQ™ Briefing Document Table 5.3.1-1

Although, a greater proportion of subjects in the placebo group (33% or 10/30) were reported to discontinue study drug due to an adverse event (other than death) than in the CyIS group (15% or 4/26), this comparison must be interpreted with caution. Six subjects in the CyIS group (23% or 6/26) were reported to have discontinued due to withdrawal of consent compared to none in the placebo group. Further examination of the individual case report forms reveal a number of respiratory adverse events associated with study

drug administration which could have influenced their continued willingness to participate in the study.

As described by the Applicant, additional non-comparative safety data was obtained in report ACS002 from a pool of 70 lung transplant recipients, representing a variety of transplant types, treated with CyIS from 7 open-label uncontrolled studies at UPMC, who were also receiving systemic tacrolimus-based immunosuppression. These represent experience with a wide range of dosing and duration of treatment, which is difficult to interpret.

Patients were generally administered a maximum tolerated which was individualized and depended on the characteristics of the patients and their response to premedication. No dose response relationship analysis was presented. Moreover, the data available in the study report and case report forms did not allow one to evaluate the temporal relationship between study drug administration and adverse events.

Overall, the safety database is smaller than usually expected in a commercial application. The acceptability of the safety information in this NDA must be weighed against the degree of certainty of the potential clinical benefit.

VII. DRAFT QUESTIONS

1.) Is there sufficient information to make the determination whether the observed survival difference in study ACS001 is due to study treatment or some other factor?

In your deliberations, please consider the statistical issues raised by this application, as well as the differences in baseline donor/recipient characteristics, and whether the product has demonstrated an effect on another endpoint that is pathophysiologically related to the mortality endpoint, including acute rejection, bronchiolitis obliterans syndrome, and histological bronchiolitis obliterans. Also consider whether the product has demonstrated a benefit on some other clinical endpoint?

If YES:

1.a.) Please discuss the generalizability of these results obtained from a single study at one institution to the treatment of lung transplantation recipients in the US?

If NO:

1.b.) What additional information would be needed to make this determination?

In your discussion please consider what additional clinical studies you would recommend be conducted. Do you have any specific recommendations regarding: patient population, drug dosing regimen and administration, efficacy endpoint(s)?

2.) Has the safety of the product been adequately characterized for its intended use?

In your deliberations, please consider the amount of pre-clinical and clinical information available on the administration of cyclosporine and the vehicle through this route, as well as the number of human subjects in this application exposed to the proposed recommended dosage.

If YES:

2.a.) For what population should the product be labeled?

2.b.) What information should be included on dosing regimen, dose preparation/administration, dosing intervals and duration?

2.c.) What information should be included in the labeling regarding expected benefit on acute rejection, BOS or OB?

If NO:

2.d.) What additional preclinical or clinical information would be needed?

VIII. REFERENCES (enclosed with Briefing Material)

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