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A randomized controlled trial of liposomal cyclosporine A for inhalation in the prevention of bronchiolitis obliterans syndrome following lung transplantation

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Long-term survival after lung transplantation is limited by chronic allograft dysfunction. The aim of this study was to investigate the effect of locally augmented immunosuppression with liposomal cyclosporine A for inhalation (L-CsA-i) for the prevention of bronchiolitis obliterans syndrome (BOS). In a randomized, double-blind, placebo-controlled, multi-center Phase 3 study, 180 LT recipients in BOS grade 0 were planned to receive L-CsA-i or placebo in addition to triple-drug immunosuppression. L-CsA-i was administered twice daily via an Investigational eFlow nebulizer to recipients of single (SLT) and bilateral lung transplants (BLT) within 6–32 weeks posttransplant, and continued for 2 years. The primary endpoint was BOS-free survival. 130 patients were enrolled before the study was prematurely terminated for business reasons. Despite a 2-year actuarial difference in BOS-free survival of 14.1% in favor of L-CsA-i in the overall study population, the primary endpoint was not met ($p = .243$). The pre-defined per protocol analysis

Abbreviations: BLT, bilateral lung transplants; BOS, bronchiolitis obliterans syndrome; CLAD, chronic lung allograft dysfunction; CsA, Cyclosporine A; CsA-PG, CsA propylene glycol; FAS, full analysis set; L-CsA-i, liposomal cyclosporine A for inhalation (L-CsA-i); LT, Lung transplantation; PK, pharmacokinetics; PPS, per protocol set; SLT, single lung transplants.

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of SLT recipients (n = 24) resulted in a treatment difference of 58.2% (p = .053). No difference was observed in the BLT (n = 48) subpopulation (p = .973). L-CsA-i inhalation was well tolerated. Although this study failed to meet its primary endpoint, the results warrant additional investigation of L-CsA-i in lung transplant recipients.

KEYWORDS
bronchiolitis obliterans, clinical research/practice, clinical trial, immunosuppressant - calcineurin inhibitor: cyclosporine A (CsA), lung (allograft) function/dysfunction, lung transplantation/pulmonology

1 | INTRODUCTION

Lung transplantation (LT) is an established therapy for end-stage lung diseases. However, the long-term outcome is limited by the development of chronic lung allograft dysfunction (CLAD).[1,2] Pathologic changes in small airways manifested as bronchiolitis obliterans syndrome (BOS) are poorly understood but potentially preventable with locally administered high-dose immunosuppression.[3–6] While most solid transplants are inaccessible to localized immunotherapy, treatment via inhalation is a promising option in LT patients.

Cyclosporine A (CsA) aerosol inhalation has been shown to potentially reduce rejections and improve function.[7–9] Deposition of 5 mg CsA propylene glycol (CsA-PG) three times weekly was shown to deliver sufficient local immunosuppression.[10] However, CsA-PG is poorly tolerated and requires bronchodilator and local anesthetic drug premedication.[11] A pivotal study showed a significant difference in BOS-free and overall survival for inhaled CsA-PG therapy after 2 years.[12] However, this trial was hampered by intolerance of the CsA-PG formulation, long inhalation times, and a high discontinuation rate.

In this respect, the liposomal cyclosporine formulation for inhalation L-CsA-i (BREATH Therapeutics GmbH, Munich, Germany) offers an alternative with improved ease of administration. By using the handheld Investigational eFlow® nebulizer system (PARI Pharma GmbH, Graefelfing, Germany), high peripheral deposition and excellent tolerability without pre-medication can be achieved with short inhalation times.

Twice daily administration of L-CsA-i produced a lung dose equivalent to an aerosolized CsA-PG regimen previously shown to be effective. Inhalation time was less than 10 minutes (mean 9 ± 1 min) and inhalation of L-CsA-i was well tolerated.[13]

The objective of the present study was to assess the efficacy and safety of the addition of L-CsA-i to standard of care systemic immunosuppression for prevention of BOS in LT recipients.

2 | MATERIALS AND METHODS

2.1 | Study design

A Phase 3, multicenter, randomized, double-blind, placebo-controlled clinical trial of L-CsA-i for the prevention of BOS was performed. The study started as a Phase 2, explorative, 3-arm dose-finding study comparing high-dose L-CsA-i (10 or 20 mg per day for single lung transplant (SLT) or bilateral lung transplant (BLT) patients, respectively) versus low-dose L-CsA-i (5 or 10 mg per day for SLT or BLT patients, respectively) versus placebo for 2 years. During the early course of the study the design was amended to apply for a Phase 3 pivotal study concept, including sample size increment from 60 to 180 patients, omission of the low-dose L-CsA-i treatment arm, and 1:1 treatment randomization to high-dose L-CsA-i or placebo. The new sample size was powered with ß = 80% based on a 2-year event rate for BOS stage ≥1 of 25% and the expectation that L-CsA-i could lower the rate of BOS to 9%. Patients randomized to low dose L-CsA-i were moved to the high dose group. The study was carried out from 18 December 2009 until 12 July 2013, at which time it was terminated by the sponsor PARI Pharma GmbH, Germany. The study was conducted in 19 centers in 8 countries across Europe and Canada (ClinicalTrials.gov Identifier: NCT01334892, Eudra CT No: 2008-003800-73) and was approved by the central institutional ethics committee (Munich, Germany; registration number 143-09) and by institutional review boards at all participating sites. The study was terminated for business reasons and no futility analysis was performed.

2.2 | Administration of L-CsA-i and standard immunosuppression

Recipients ≥18 years of age were eligible. Patients were excluded if they underwent re-transplantation, had pneumonia, serum creatinine >265 µmol/L (>3 mg/dl), chronic dialysis or untreated bronchial stenosis, receiving mechanical ventilation or had BOS ≥1.

Participants had to receive a triple-drug regimen consisting of tacrolimus, prednisone, and mycophenolate mofetil within one week prior to the start of study medication. Study treatment had to begin within 6–32 weeks after LT. L-CsA-i or placebo was administered twice daily using PARI Pharma's Investigational eFlow® nebulizer system. The planned treatment duration was 96 weeks with 16 bimonthly study visits, and treatment compliance was recorded with the eFlow® Monitoring System.

2.3 | Pulmonary function test

Spirometry was performed twice monthly according to current American Thoracic Society/European Respiratory Society

spirometry guidelines.[14] The baseline lung function, equivalent to 100% FEV_1, was defined as the average of the two highest FEV_1 measurements from transplantation to randomization obtained at least three weeks apart without using a bronchodilator. BOS was defined as a persistent decrease ≥20% in FEV1 from baseline.

2.4 | Study endpoints and statistics

The primary endpoint was BOS-free survival and secondary efficacy endpoints were pulmonary function, incidence of BOS, acute cellular rejection, 6-minute walk test distance (6-MWD), and overall survival. The safety endpoints were treatment-emergent adverse events and evidence of infections. L-CsA-i and tacrolimus trough blood levels were measured and full L-CsA-i pharmacokinetics (PK) was assessed. It was prospectively determined that the per protocol set (PPS) population would be used as the basis for interpretation of the efficacy endpoints instead of the full analysis set (FAS) because adherence to inhalation is key for a successful therapy. The primary endpoint was analyzed by Kaplan–Meier analysis with stratification for SLT or BLT. Treatment group comparisons for continuous secondary outcomes were analyzed using analysis of covariance with treatment and SLT versus BLT as fixed factors and the baseline value of the outcome of interest at a covariate. Binary outcomes were analyzed using Cochran-Mantel-Haenszel tests stratified for SLT versus BLT. Missing values were not to be substituted and a 0.05 significance level was used.

3 | RESULTS

Due to the premature termination, 1:1 randomization was not achieved. In total, 130 patients were randomized to either the L-CsA-i group (74 patients) or to the placebo group (56 patients). However, no statistically significant differences regarding baseline clinical characteristics were detected (Table 1).

All 130 patients were included in the FAS population and analyzed for efficacy and safety. Outcome conclusions were made upon the analysis of the PPS population of 72 patients (L-CsA-i group: 34 patients; placebo group: 38 patients). The following prespecified criteria led to exclusion from the PPS population, with some patients fulfilling more than one criterion: intake of systemic cyclosporine (L-CsA-I 2), insufficient study treatment compliance ≤75% (L-CsA-I 34, placebo 18), randomization to low dose L-CsA-i during the Phase 2 period (L-CsA-I 17), and missing BOS assessment (L-CsA-I 1, placebo 1). There was no statistically significant difference between demographic characteristics of the FAS and PPS groups. The mean follow-up duration was 13.3 months in the L-CsA-i group (range: 8–742 days) and 13.4 months in the placebo group (range: 7–715 days, $p = .89$). The mean (±SD) compliance was 73.0% (±24.0%) in the L-CsA-i group and 77.3% (±22.0%) in the placebo group ($p = .43$). Use of azithromycin prior to the onset of BOS did not significantly differ between the L-CsA-i (54.4%) and placebo groups (49.2%; $p = .35$).

Of the 95 patients who discontinued early, the majority (n = 50, 52.6%) was discontinued due to early termination of the study. Figure 1 depicts patient disposition and a breakdown of the reasons for discontinuation or exclusion throughout the study flow.

TABLE 1 Study population (n = 130, full analysis set)

	L-CsA	Placebo	Overall
Total	74 (56.9)	56 (43.1)	130 (100.0)
Female	29 (39.2)	25 (44.6)	54 (41.5)
Type of procedure			
DLT	51 (68.9)	39 (69.6)	90 (69.2)
SLT	23 (31.1)	17 (30.4)	40 (30.8)
Age [years]	52.5 (21–69)	53.1 (25–68)	52.7 (21–69)
Body weight [kg]	65.0 (42–98)	67.5 (38–92)	66.1 (38–98)
Underlying diseases			
CODP / α-1-AT deficiency	35 (47.3)	26 (46.4)	61 (46.9)
Interstitial lung disease	16 (21.6)	14 (25.0)	30 (23.0)
Pulmonary hypertension	5 (6.8)	4 (7.1)	9 (6.9)
Cystic fibrosis	10 (13.5)	5 (8.9)	15 (11.6)
Others	8 (10.8)	7 (12.5)	15 (11.6)

Note: Data are presented as median (Q1-Q3) or number (percentage).

Abbreviations: COPD, chronic obstructive pulmonary disease; DLT, double lung transplant recipient; L-CsA, liposomal cyclosporine A; SLT, single lung transplant recipients; α-1-AT, alpha-1 antitrypsin deficiency.

3.1 | Efficacy analysis

The primary outcome result in the PPS population was based on the occurrence of BOS ≥ grade 1 alone. Overall, 29 (85.3%) patients in the L-CsA-i group and 28 (73.1%) patients in the placebo group survived BOS-free. The overall BOS-free survival was not significantly different in either the PPS ($p = .212$) or the FAS populations ($p = .243$) (Figure 2A,B). However, a numerical actuarial 2-year treatment difference of 19% in favor of L-CsA-i was found in the PPS. BOS events occurred earlier in the placebo group and this effect was more pronounced in SLT patients. Overall, 11 patients (91.7%) in the SLT L-CsA-i group and 7 patients (58.3%) in the SLT placebo group survived BOS-free in the PPS population with a trend for statistical significance ($p = .053$), thus favoring L-CsA-i treatment with an actuarial 2-year difference of 58% in the SLT group (Figure 3A,B). However, there was no concordant statistical signal in BLT patients ($p = .973$) (Figure 4A,B).

As diagnosis of BOS 0-p is a risk factor for the progression to BOS 1–3, the pre-defined endpoint "Development of BOS 1" was changed to "Development of BOS 0-p" in a post-hoc analysis of the composite endpoint for counterbalancing the shortened observation period. In the L-CsA-i group, 16/23 SLT patients (69.6%) and 7/17 SLT patients (41.2%) in the placebo group survived BOS 0-p-free (FAS; Kaplan–Meier survival analysis: $p = .078$; Figure S1). BOS 0-p free Kaplan–Meier survival analysis of the FAS and PPS populations are shown in Figure S2–S6. Deterioration of lung function to BOS 0-p started earlier in the placebo than in the L-CsA-i group.

After one year of study participation, placebo patients in the SLT group deteriorated in FEV_1 whereas L-CsA-i patients improved in comparison to baseline without the difference reaching statistical significance (PPS $p = .177$, FAS $p = .114$). Comparable improvements under L-CsA-i were not observed in BLT recipients in either analysis set. For the total study population, the difference in FEV_1 between the treatment groups after 12 months was also statistically not significant for the PPS ($p = .653$) and FAS populations ($p = .324$) even though in SLT recipients, FEV_1 remained continuously stable in the L-CsA-i group while a decrease was seen in the placebo group (Figure 5A for PPS). No difference was observed in the respective analyses of BLT recipients (Figure 5B for PPS). No differences in vital and total lung capacity was found between the groups as shown in the supplementary material of the manuscript (Figure S7–S10).

There was no statistically significant difference regarding the incidence of acute cellular rejection (FAS: L-CsA-i 3, 4.1%; placebo 2, 3.7%; Kaplan–Meier survival analysis: $p = .592$) or overall survival (FAS: L-CsA-i 71, 95.9%; placebo 55, 98.2%; Kaplan–Meier survival analysis: $p = .450$). In the FAS population, three patients in the L-CsA-i group (CMV pneumonia, B cell lymphoma, large intestine perforation) and one patient in the placebo group (lung allograft rejection) died. No significant differences regarding 6-MWD and dyspnea score were observed.

3.2 | Pharmacokinetics and safety analysis of adverse events

Pharmacokinetics analysis demonstrated that the highest C_{max} (50.7 ng/ml plasma CsA) was observed at a t_{max} of 30 min and a $t_{½}$ of 3 h after completion of L-CsA-i inhalation. There was no significant difference regarding mean baseline creatinine levels (baseline L–CsA-i: 95.9 ±35.5 μmol/l, baseline placebo: 112.6 ±46.3 μmol/l; $p = .095$) and mean change from baseline creatinine at the end of study (L-CsA-i: 20.0 ±33.2 μmol/l, placebo: 26.0 ±39.9 μmol/l; $p = .42$), respectively. As expected, analysis of tacrolimus trough levels revealed an incremental reduction throughout the study. However, no significant differences were detected, suggesting an overall comparable level of systemic immunosuppression.

The safety analyses revealed comparable numbers of AEs and SAEs in the L-CsA-i group (919 AEs/12.4 AEs per patient, 1.26 SAEs per patient) compared to the placebo group (605 AEs/10.8 AEs per patient, 1.41 SAEs per patient).

The most common reported AEs were diarrhoea (26.2%), nasopharyngitis (20.8%), cytomegalovirus infection (19.2%), cough (18.5%), oedema (17.7%), creatinine increase (16.2%), and leukopenia (16.9%). The most common SAEs were pneumonia (4.6%), lung transplant rejection (3.8%), and loss of FEV_1 (3.1%).

The most common infections were of viral origin, which were experienced by a total of 11.5% of patients with no significant statistical difference between the treatment groups. The second most frequently reported infections were of bacterial origin (9.2% of patients) and were experienced by a higher percentage of patients in the L-CsA-i group (13.5% of patients) compared to the placebo group (3.6% of patients) ($p = .085$). Fungal infection was observed in only 1/74 patient (1.4%) in the L-CsA-i group (Table 2).

4 | DISCUSSION

This Phase 3, international, multicenter, randomized, double-blind, placebo-controlled study investigated the efficacy and safety of L-CsA-i versus placebo as an additional therapy to standard of care immunosuppression in the prevention of BOS. The sponsor decided to terminate the study early not due to futility or safety concerns, but rather the need for an estimated 3.5 years of extended study duration associated with higher costs.

With respect to overall BOS-free survival as the primary outcome parameter, the result of this study was negative. However, a non-significant 2-year actuarial treatment difference in BOS-free survival of 14.1% in favor of L-CsA-i was observed in the full analysis population. This difference was primarily driven by the SLT subpopulation and is reflected by the course of FEV_1.

One possible explanation is that the definition of BOS stage 1 requires a drop of ≥20% from baseline FEV_1 which is usually reached earlier in SLT recipients due to the smaller lung volume achieved in comparison to BLT recipients.[15,16] Therefore, we

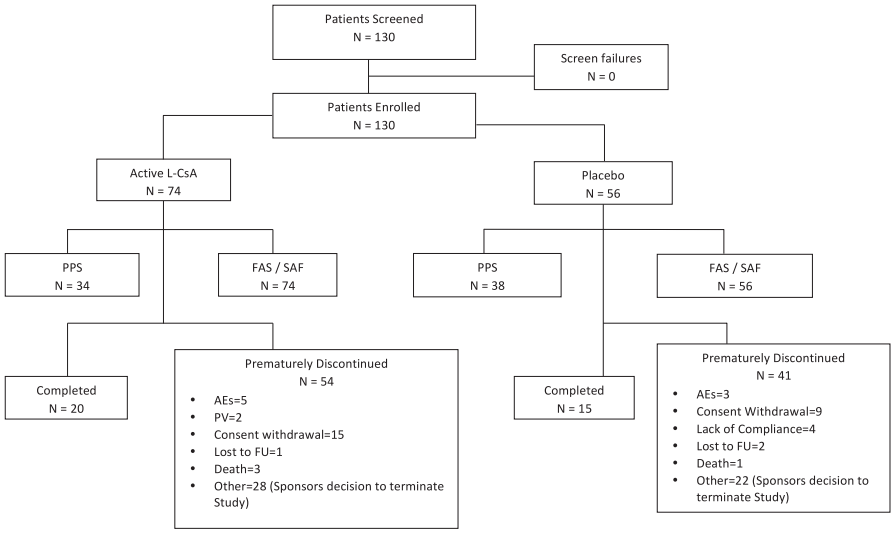

FIGURE 1 Patient disposition and reasons for discontinuation. FAS, full analysis set; FU, follow up; PPS, per protocol set; PV, protocol violation; SAF, safety analysis set

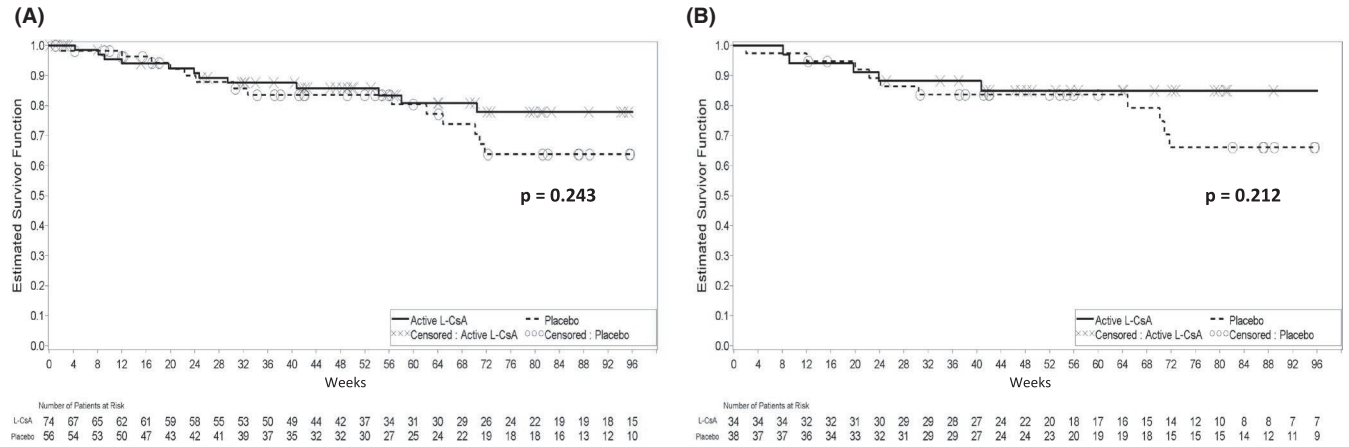

FIGURE 2 Estimated overall BOS-free survival by Kaplan–Meier curve: full analysis set (A) and per protocol analysis set (B). L-CsA, liposomal cyclosporine A

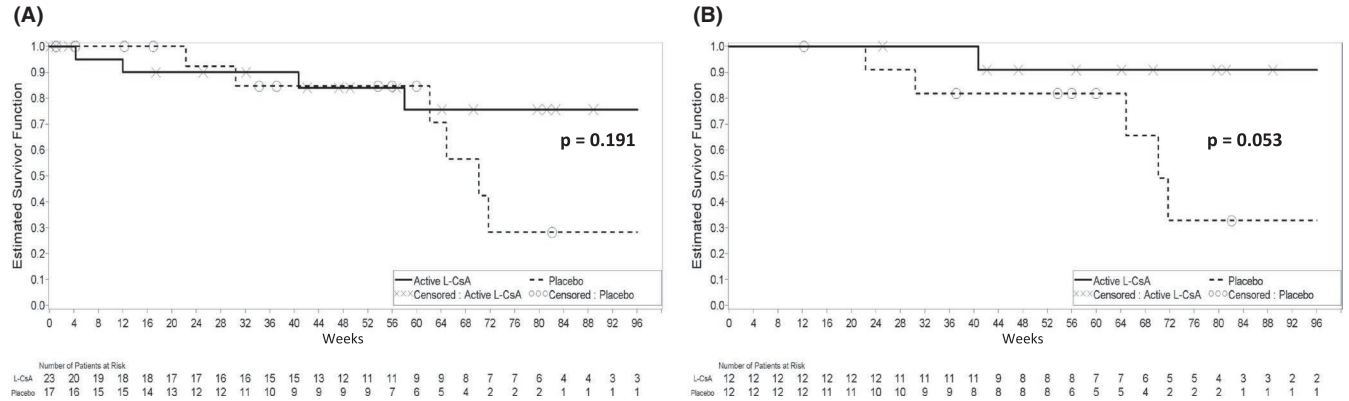

FIGURE 3 Estimated BOS-free survival for single lung transplant recipients by Kaplan–Meier curve: full analysis set (A) and per protocol analysis set (B). L-CsA, liposomal cyclosporine A

speculate that the follow-up period was too short to detect significant differences in BLT recipients, and thus in the overall study population. The majority of BLT patient had not reached their personal best FEV_1 at time of study termination. Hence, a post-hoc analysis on BOS 0-p-free survival was performed to correlate an earlier BOS stage within the limited observation period. In this analysis the actuarial 12-month group difference was 19% and the actuarial 18-month difference was 44% in favor of L-CsA-i. We speculate that more of the BOS 0-p patients in the placebo than in the L-CsA-i group would have progressed to BOS 1 in the

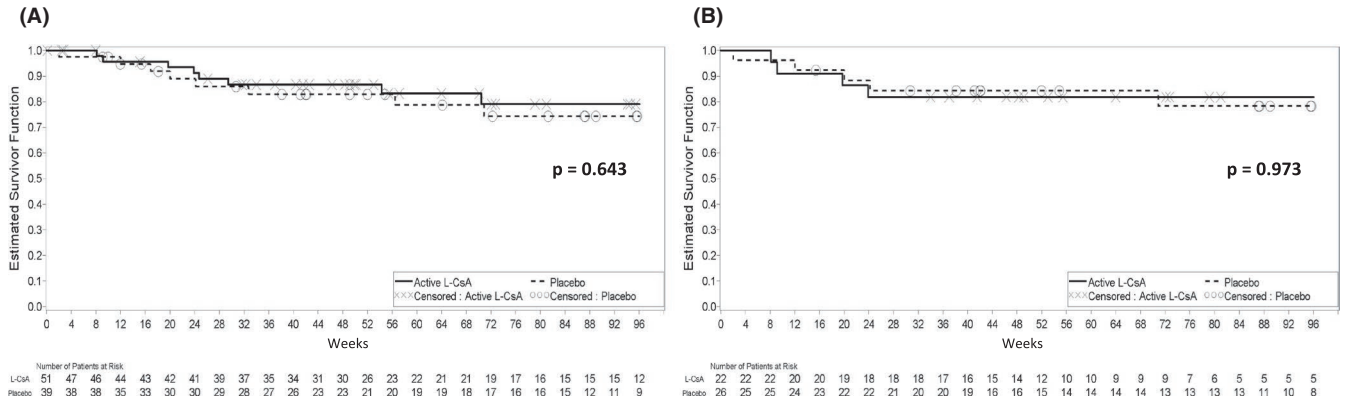

FIGURE 4 Estimated BOS-free survival for bilateral lung transplant recipients by Kaplan–Meier curve: full analysis set (A) and per protocol analysis set (B). L-CsA, liposomal cyclosporine A

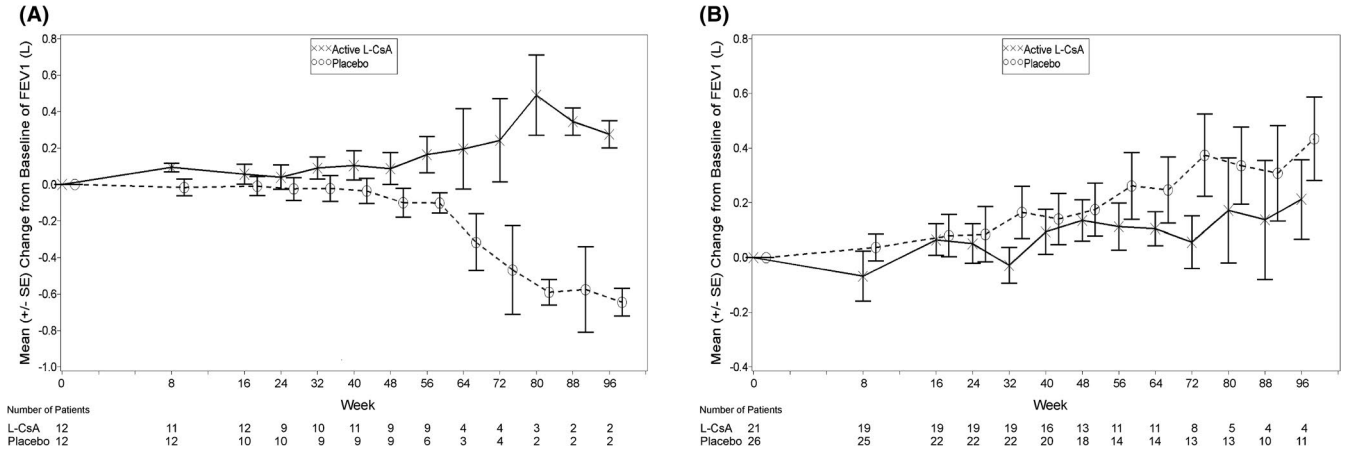

FIGURE 5 Changes from baseline of FEV1 single (A) and bilateral lung transplantation (B)—per protocol analysis. Mean ± SE changes of FEV1 (L) from baseline in single (A) and bilateral (B) lung transplantation, respectively, over the study period. FEV1, forced expiratory volume in 1 second; L-CsA, liposomal cyclosporine A; SE, standard error

TABLE 2 Summary of cumulative incidence of bacterial, viral, or fungal infection (safety analysis set)

	Active L-CsA group, *n* = 74			Placebo group, *n* = 56			Overall, *n* = 130		
	n	%	E	*n*	%	E	*n*	%	E
Any infection	18	24.3	25	9	16.1	9	27	20.8	34
Bacterial	10	13.5	11	2	3.6	2	12	9.2	13
Viral	8	10.8	13	7	12.5	7	15	11.5	20
Fungal	1	1.4	1	0	0	0	1	0.8	1

Abbreviation: L-CsA, liposomal cyclosporine A.

pre-specified observation period. Since the diagnosis of BOS following BLT is typically later compared to SLT, preventive effects of L-CsA-i might only emerge after an extended observation time. Based on the number of necessary events and the heterogeneity of CLAD, a follow-up time of three to five years may be required to produce definitive evidence for a positive treatment effect of L-CsA-I for the prevention of BOS.

However, in the CYCLIST Trial, PG-based cyclosporine inhalation failed to improve BOS-free and overall survival in comparison to standard of care in 284 patients during a mean post-transplant follow-up of 21.1 months.[17] Since this multi-center randomized controlled trial is only published in abstract form, it is difficult to draw substantial conclusions. Due to the lack of a placebo-control arm, there may have been a significant risk for variation in standard immunosuppression and overall post-transplant management, potentially resulting in a substantial bias. In addition, the deleterious effects of the PG formulation might have been in part responsible for the lack of a positive clinical signal in the CYCLIST trial.[17]

In contrast, in the current trial no significant differences in tacrolimus trough levels were observed throughout the study period, suggesting comparable use of CNI-based immunosuppression in both the L-CsA-i and placebo groups.

Interestingly, prophylactic azithromycin therapy has been demonstrated to improve CLAD-free survival and pulmonary function.[18] Our protocol did not specify the prophylactic use of azithromycin and a trial of azithromycin was not mandatory. However, there was no significant difference regarding the use of azithromycin, thus making a difference in azithromycin use unlikely to be responsible for the observed differences. There was no difference in the incidence of acute cellular rejections. Unfortunately, the incidence and severity lymphocytic bronchiolitis was not assessed in the study which however would have been of interest with regard to the side of action of L-CsA-i. Furthermore, assessment of donor-specific antibodies and subsequent antibody-mediated rejection was not part of the study protocol. At the time of study initiation the significance of different CLAD phenotypes was not established yet and therefore not assessed. However, no difference in vital and total lung capacity was found between the groups.

Inhalation of L-CsA-i appeared to be well tolerated with no relevant safety signal. However, the number of consent withdrawal was high in both groups. The preventive nature of the study in patients with good allograft function might have mitigated the willingness to participate in the study until the end. Furthermore, a numerically increased risk of respiratory infections due to locally augmented immunosuppression was observed, but statistically not significant. Notably, no additional risk of increased nephrotoxicity in L-CsA-i patients was detected. Trough levels of cyclosporine were low (~4–6 ng/mL) compared to recommended therapeutic levels (100–150 ng/mL) when applied systemically as the main immunosuppressive drug.

Taken together, our data demonstrate that preventive treatment with L-CsA-i in addition to standard immunosuppression was well tolerated and did not expose LT patients to additional risk. Furthermore, despite the limitations noted and the overall negative findings of the trial, our results provide evidence for a potentially improved outcome using L-CsA-i to prevent BOS after lung transplantation.

Although prevention of BOS should be the ultimate interest, investigation of L-CsA-i in the treatment of BOS on its early stage may generate reliable efficacy and safety data within a shorter period of time. Two separate Phase 3 trials for the treatment of BOS after SLT (NCT03657342) and BLT (NCT03656926) in the US and EU have been commenced in early 2019.

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DISCLOSURE

The authors of this manuscript have conflicts of interest to disclose as described by the *American Journal of Transplantation*. Claus Neurohr reports honoraria for consulting and advisory boards from Breath Therapeutics, a Zambon company, Italy and PARI GmbH, Germany. Romain Kessler reports grants from Breath Therapeutics, during the conduct of the study. Juergen Behr reports that he is PI of the ongoing phase 3 trials of inhaled liposomal cyclosporin A in lung transplant patients. Gerhard Boerner, Oliver Denk and Stefanie Prante are employees of Breath Therapeutics, a Zambon Group. The other authors have no conflicts of interest to disclose.

DATA AVAILABILITY STATEMENT

Data are available on request from the authors.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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