CLINICAL STUDY REPORT

A Phase 3, Multicentre, Randomised, Double-Blind, Placebo Controlled Clinical Trial to Investigate the Efficacy and Safety of 10 or 20 mg/day Aerosolised Liposomal Ciclosporin A versus Aerosolised Placebo in the Prevention of Bronchiolitis Obliterans Syndrome in Lung Transplant Patients

Protocol No:	12011.201
Eudra CT No:	2008-003800-73
Study Product:	Aerosolised liposomal ciclosporin A (L-CsA)
Sponsor:	PARI Pharma GmbH
Contact Details:	Lochhamer Schlag 21 82166 Graefelfing Germany
Principal Investigators:	Prof. Jürgen Behr (17 Jul 2009 to 17 Nov 2010) and Dr. Claus Neurohr (17 Nov 2010 to 12 Jul 2013)
Contact Details:	Ludwig Maximilians Universität Klinikum Großhadern Transplantationszentrum Marchioninistraße 15, 81377 Munich
Indication Studied:	Bronchiolitis Obliterans Syndrome in Lung Transplant Patients
Development Phase:	Phase 3
Study Initiation Date:	18 Dec 2009 (first patient enrolled)
Date of Early Study Termination:	05 Jun 2013
Study Completion Date:	12 Jul 2013 (last patient completed)
Report Version:	Final Version 1.0
Report Issue Date:	20 Jan 2015
Good Clinical Practice (GCP) Statement:	This trial was conducted in accordance with the principles of GCP CPMP/ICH/135/95

2. SYNOPSIS

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Title of Study:

A Phase 3, multicentre, randomised, double-blind, placebo controlled clinical trial to investigate the efficacy and safety of 10 or 20 mg/day aerosolised liposomal ciclosporin A (L-CsA) versus aerosolised placebo in the prevention of bronchiolitis obliterans syndrome (BOS) in lung transplant (LT) patients

Principal Investigator:

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Study Centre(s):

Approximately 20 centres were planned in approximately 7 countries in Europe and the rest of the world.

Finally, the study was conducted in 19 centres in 8 countries across Europe and Canada.

However, only 11 of the 19 centres in 6 European countries enrolled patients.

Publication (Reference):

- Bauer B, Köhne K. Evaluation of experiments with adaptive interim analyses. Biometrics 1994; 50:1029-1041.
- Brannath W, Posch M, Bauer P. Recursive Combination Tests. J Am Statistical Association 2002; 97:236-244.
- Burckart GJ, Smaldone GC, Eldon MA, et al. Lung deposition and pharmacokinetics of cyclosporine after aerosolization in lung transplant patients. Pharmaceutical Research 2003; 20:252-256.
- Corcoran TE, Smaldone GC, Dauber JH, et al. Preservation of post-transplant lung function with aerosol cyclosporin. Eur Respir J 2004; 23:378-383.
- Corcoran TE. Inhaled delivery of aerosolized cyclosporine. Adv Drug Deliv Rev 2006; 58:1119-1127.
- Estenne M, Maurer JR, Boehler A, et al. Bronchiolitis obliterans syndrome 2001: an update of the diagnostic criteria. J Heart Lung Transplant 2002; 21:297-310.
- Hachem RR, Trulock EP. Bronchiolitis obliterans syndrome: pathogenesis and management. Semin Thorac Cardiovasc Surg 2004; 16:350-355.
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- Iacono A, Smaldone G, Keenan R et al. Dose Related Reversal of Acute Lung rejection by Aerosolized Ciclosporin. Am J Respir Crit Care Med 1997; 155:1690-1698.
- Iacono AT, Johnson BA, Grgurich WF, et al. A randomised trial of inhaled cyclosporine in lung-transplant recipients. N Engl J Med 2006; 354:141-150.
- Knoop C, Haverich A, Fischer S. Immunosuppressive therapy after human lung transplantation. Eur Respir J 2004; 23:159-171.

Phase of Development:

Phase 3

Studied Period (years):

Date of First Enrolment: 18 Dec 2009

Date of Last Completed: 12 Jul 2013

Objectives:

The objective of this study was to assess the efficacy and safety of the addition of aerosolised L-CsA to Standard of Care systemic immunosuppression as compared to aerosolised placebo plus Standard of Care therapy for prevention of BOS in LT recipients

Methodology:

This was a Phase 3, multicentre, randomised, double-blind, placebo-controlled clinical trial of aerosolised liposomal ciclosporin for the prevention of BOS in adult recipients of a pulmonary allograft (single or double).

The treatment was planned to commence within 6-32 weeks following lung transplantation.

The study drug was administered by inhalation twice daily (morning/evening, 12h apart), either 5 mg or 10 mg L-CsA, for single lung transplant (SLT) or double lung transplant (DLT) patients, respectively, in addition to Standard of Care systemic immunosuppression. Instead of L-CsA, placebo was administered to control patients following identical schedules. The treatment was to be given for 96 weeks (24 months), and 16 bi-monthly visits at the clinical trial centre were required. At every visit, one inhalation cycle was monitored by the clinical trial centre personnel. All participants regardless of treatment allocation received Standard of Care basic immunosuppression as a triple drug therapy (TDT) consisting of tacrolimus, prednisone, and mycophenolate mofetil (MMF).

Note: The study was originally planned and started as a Phase 2, randomised, explorative, 3-arm dose-finding study comparing high-dose L-CsA (10 or 20 mg per day for SLT or DLT patients) versus low-dose L-CsA (5 or 10 mg per day for SLT or DLT patients) versus placebo. A total of 60 patients (20 patients per arm) were expected to be enrolled. Following the recommendations of a Scientific Advice Meeting with European Medicinal Agency (EMA) (28 June 2010) the study design was changed from an explorative 3-arm dose-finding to a 2-arm pivotal Phase 2/3 design.

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The sample size was increased from 60 to 180 patients and the low-dose L-CsA arm was omitted and affected patients were shifted to receive high-dose L-CsA treatment in order to compare the dose of the assumed highest probability of success with placebo directly.

Duration of Treatment:

The total study duration was approximately 3 years and 7 months. Duration of patient treatment was two years maximum.

Number of Patients:

Planned:

Initially, 60 patients, 20 patients per 3 arms, were to be enrolled in a 1:1:1 ratio and were originally randomised to receive either high dose or low dose L-CsA or placebo. According to Protocol amendment 2 (including the increase in sample size to 180 patients), study participants were randomised to the high dose L-CsA or Placebo in a 1:1 ratio. Patients formerly randomised to low dose L-CsA were moved to the high dose L-CsA group.

However, the study was prematurely terminated at an enrolment status of 130 patients.

Analysed:

A total of 130 patients were eligible to participate in the study and were randomised to either the L-CsA group (74 patients) or to the Placebo group (56 patients).

Diagnosis and Main Criteria for Inclusion:

Male or female patients ≥18 years of age with an estimated life expectancy >6 months, who gave a written informed consent prior to any screening procedure and who met the following criteria were included in the study:

- Received a single lung, bilateral lung or heart/lung transplantation between 6 weeks and 32 weeks prior to first Investigational Medicinal Product (IMP) administration
- Capable of self-administration of medications
- Capable of understanding the purpose and risk of the clinical trial
- Received within one week prior to first IMP administration the following immunosuppressive agents and dosages for maintenance therapy:
    - Tacrolimus and
    - MMF 1 g to 3 g/day and
    - Prednisone or any other steroid therapy; tapered down within the first 3 months after transplantation
- Female patients of childbearing potential were to have a negative urine pregnancy test prior to first IMP administration. (For Canadian centres only: Female patients of childbearing potential must have a negative urine and serum pregnancy test prior to first

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IMP administration). Both, women and men, had to agree to use a medically acceptable method of contraception throughout the IMP treatment period and for 3 months after IMP discontinuation.

Investigational Medicinal Product:

Aerosolised L-CsA was supplied in glass vials of 1.25 ml/5 mg (SLT recipients) and 2.5 ml/10 mg (DLT recipients) using PARI Pharma's eFlow® vibrating membrane nebuliser device for inhalation.

Dose, Mode of Administration:

The study drug was administered twice daily by inhalation (morning/evening) for 96 weeks (24 months). The daily dose was 10 mg L-CsA in SLT patients and 20 mg L-CsA in DLT patients. At every visit, one inhalation cycle was to be monitored by the clinical trial centre personnel. The patient remained in the clinic for at least 2 h for observation after the first inhalation. Treatment compliance was to be verified with the eFlow® MS.

L-CsA Batch Number(s): 934611, 935608, 101902, 102406, 112201, 112301, 120803, 120807.

Reference Therapy:

Aerosolised placebo was supplied in glass vials of 1.25 ml (SLT recipients) and 2.5 ml (DLT recipients) using PARI Pharma's eFlow® vibrating membrane nebuliser device for inhalation.

Dose, Mode of Administration:

Placebo was administered twice daily by inhalation (morning/evening) for 96 weeks (24 months). At every visit, one inhalation cycle was to be monitored by the clinical trial centre personnel. The patient remained in the clinic for at least 2h for observation after the first inhalation. Treatment compliance was to be verified with the eFlow® MS.

Placebo Batch Number(s): 932601, 933601, 101705, 101805, 112003, 112102, 121002, 120903.

Criteria for Evaluation:

Efficacy:

The primary endpoint of this study was:

- BOS-free survival

The secondary efficacy endpoints of this study were:

- Pulmonary function at Baseline, 12, 18 and 24 months after first IMP administration:
  - Forced expiratory volume in one second (FEV_1)
  - Forced mid-expiratory flow (FEF_{25-75})
  - Vital capacity (VC)
  - Total lung capacity (TLC)
- Incidence of BOS at 12, 18 and 24 months after first IMP administration

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- Grading of BOS at 12, 18 and 24 months after first IMP administration
- Incidence of acute rejection grade A2 or higher at 12, 18 and 24 months after first IMP administration
- Walking distance from 6-minute walk test at 6, 12, and 24 months after first IMP administration
- Level of inflammatory markers, L-CsA and sucrose from bronchoalveolar lavage (BAL) from at least two visits during the clinical trial period
- Incidence of lung graft loss until 12, 18 and 24 months after first IMP administration
- Overall survival during the clinical trial period

Safety:

The safety endpoints of this study were the summaries of:

- Treatment-emergent adverse events (TEAEs)
- Incidence of invasive bacterial, viral or fungal infections 12, 18 and 24 months after first IMP administration
- Number of non-protocol procedures requiring overnight hospitalisations at 12, 18 and 24 months after first IMP administration
- Clinical laboratory
- Vital signs
- Physical examination
- L-CsA and tacrolimus trough blood levels at each visit and full L-CsA pharmacokinetic (PK) at Visit 1 and two additional days between Visits 2 and 16

Statistical Methods:

The primary endpoint, BOS-free survival, was analysed by means of Kaplan-Meier (KM) survival analysis with stratification by single or double lung transplantation. Patients terminating their participation in the trial at any time and for any reason without experiencing an endpoint event were censored.

A study wise type I error rate of α=0.025 (one-sided) was to be applied. The trial was performed with one adaptive Interim Analysis that included options for early acceptance (α_0=0.5) or rejection (α_1=0.0102) of the null hypothesis, should the data permit a statistical decision at that stage. If the hypotheses could already be decided upon, patient recruitment was to be stopped and the confirmatory part of the trial was to be terminated. Otherwise, the trial could be continued after an optional re-estimation of the sample size. After the second part of the trial, the conditions $p_1 \times p_2 \leq c_\alpha$ and $p_2 < \alpha_0$ (where p_1 and p_2 were the p-values determined for the first and second part of the trial, and $c_\alpha = 0.0038$) were to be met for null hypothesis rejection.

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Summary statistics were presented for continuous variables, by way of n, mean, standard deviation (SD), median, minimum and maximum and by way of group frequencies and percentages for categorical variables. Percentages were calculated using the total patients per treatment group. Statistical tests used a 0.05 significance level and were two-sided when applicable. Confidence intervals (CI) were at a 95% confidence level.

Statistical modelling was stratified by single and double lung transplant patients. Data were to be analysed by centre (centres contributing <5 patients were to be pooled) and after pooling data across centres. In addition, p-values were computed using analysis of variance (ANOVA) stratified by SLT vs. DLT or the Cochran-Mantel-Haenszel (CMH) tests stratified by SLT vs. DLT unless otherwise stated. Whilst for "Time to event" endpoint, survival analysis techniques were used (same as for primary endpoint). All data from all patients enrolled in the study were listed. No baseline testing was performed, but baseline values were included in modelling as appropriate.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Note: The primary endpoint is "BOS-free survival", which for the purpose of this study was defined as time to either development of BOS ≥stage 1 or re-transplantation or death. Censored data for primary endpoint refers to patients who neither had a "BOS event" nor a re-transplantation nor died.

Primary efficacy endpoint:

The primary outcome result in the PPS population was based on the occurrence of BOS ≥stage 1 alone. The other co-primary endpoints, re-transplantation and death, did not contribute to the outcome.

The KM plots indicated that the events occurred earlier in the Placebo group than in L-CsA group and this effect was more pronounced in the SLT patients. The overall BOS-free survival was not statistically significant in either the PPS population (p=0.212) or in the FAS population (p=0.243).

The log rank test comparing the L-CsA vs Placebo groups in the PPS population, approached statistical significance in SLT patients (p=0.053) favouring the L-CsA treatment, but was not statistically significant in DLT patients (p=0.973). The difference in results of the primary efficacy endpoint between the SLT and DLT patients were observed in the PPS population but were not apparent in the FAS population.

Due to the early termination of the study and consequently an extremely high proportion of censored data, the overall median time of BOS-free survival could not be assessed.

Occurrence of BOS 0-p:

The post-hoc BOS 0-p analyses showed a trend of a higher BOS 0-p free survival rate in favour of L-CsA. This difference between the treatment groups was apparent among SLT recipients in the PPS analysis population. The deterioration of lung functions to BOS 0-p started earlier in the Placebo than in the L-CsA groups. The incidence of BOS 0-p was approximately twice as high in

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the SLT recipients as in the DLT recipients. This treatment effect was considered clinically meaningful as patients with progressing deterioration of lung function determined as BOS 0-p are at high risk of further deterioration to BOS stage 1 and higher over time.

Secondary efficacy endpoints:

The mean changes of FEV_1 (L) from Baseline trended to increase over time in patients of both treatment groups, for both the PPS and FAS populations. The overall difference between the L-CsA and Placebo groups were comparable. Treatment differences became obvious when analysing SLT and DLT patients separately. After one year of study participation, Placebo patients in the SLT group deteriorated whereas L-CsA patients improved. The effect was more pronounced in the PPS population (p=0.089 at Month 24) than in the FAS population (p=0.123 at Month 24). This effect was not observed in the stratum of DLT recipients in both analysis sets. In general, the mean changes from Baseline of FEV_1 stabilised over time with a slight increasing slope.

The mean changes from maximum value of FEV_1 (L) trended to decrease over time in patients randomized to both treatment groups, for both the PPS and FAS populations. The decrease was most distinctive in the SLT patients of the PPS population. The overall difference between the L-CsA and Placebo groups showed statistical significance at the Visit 10 (12 months) for the PPS population (p=0.029) and FAS population (p=0.018). Again, the differences between L-CsA and Placebo treated patients became more prominent in the stratum of the SLT recipients (PPS and FAS) in which this parameter remained continuously stable over time in the L-CsA group whereas a sudden decrease was recorded in the Placebo group starting one year after commence of treatment. No difference could be recognised in the respective analyses of the DLT recipients.

The changes from Baseline of FEF_{25-75} (%) were negligible in both treatment groups and in both analyses sets, except for the L-CsA/FAS population in which a slight negative slope was observed.

Overall, the mean changes of VC (L) from Baseline were comparable between treatment groups and increased steadily over time. Only in the SLT subpopulation differences in favour of L-CsA treatment became apparent.

No trends in mean changes from Baseline of TLC (L) could be observed in any analysis.

BOS occurred earlier in patients randomised to receive Placebo than in patients randomised to receive L-CsA in both the PPS and FAS populations.

The incidence of acute rejection was comparable in patients in the L-CsA and Placebo groups in the PPS and FAS populations during the study. The difference between treatment groups was not statistically significant (p=0.953) in the PPS population nor in the FAS population (p=0.592).

None of the patients in the L-CsA group experienced a lung graft loss (failure) during the study. However, only one patient in the Placebo group lost his lung allograft before 12 months.

In the overall survival analysis of the PPS population, all patients in both treatment groups were alive until the end of their study participation, except one patient in the Placebo group. In the FAS population, three patients in the L-CsA group and one patient in the Placebo group deceased

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during their study participation.

The mean total walking distance (m) in the 6 min walk test was comparable in both treatment groups. It ranged from 442 to 509 m in the L-CsA group and from 428 to 491 m in the Placebo group of the PPS population. As expected, the walking distance was generally shorter in the SLT than in the DLT subpopulations.

No remarkable differences in mean SpO_2 (%) were found between the treatment groups or subsets. SpO_2 tended to increase slightly from Month 6 onwards in the L-CsA group as compared to the Placebo group.

The mean dyspnoea score was slightly higher at Month 24 as compared to Month 6 in both treatment groups with a tendency of higher scores in the Placebo group.

The mean fatigue score trended to be higher in the Placebo group than in the L-CsA group.

The majority of the inflammatory marker values in BAL samples were blow LLOQ and could be assessed only in a few patients and thus allowed no profound conclusions.

Pharmacokinetics:

The highest C_{max} (geometric mean) with 50.7 ng/ml CsA was observed at Visit 1 (Baseline). The L-CsA plasma t_{max} was approximately 30 min after completion of IMP inhalation at every visit and thus, suggesting a rapid absorption through inhalation. The $t_{1/2}$ was approximately 3h throughout the study visits.

These data show that CsA did not accumulate in systemic circulation by twice daily inhalation.

SAFETY RESULTS:

The most frequently reported AEs by system organ class (SOC) were 'Infections and infestations' observed in 80.8% of patients. Other frequently reported events by SOC were 'Gastrointestinal disorders' (57.7%) and 'Respiratory, thoracic and mediastinal disorders' (55.4%). The most common AEs by preferred term (PT) were diarrhoea (26.2%), nasopharyngitis (20.8%), cytomegalovirus infection (19.2%), cough (18.5%), oedema peripheral (17.7%), and blood creatinine increased (16.2%). The majority of the AEs were mild in severity (82.3%) and were not related to the study medication (92.3%).

The most common AEs leading to withdrawal included diarrhoea (3.1%) and nausea (2.3%). The most common ADRs were cough (9.2%), diarrhoea (6.2%), blood creatinine increased and oedema peripheral (5.4%), and blood urea increased (4.6%).

The frequency of AEs by SOC or PT was generally comparable between the treatment groups.

The majority of SAEs reported were not related to the study medication (41.9% in the L-CsA group, 42.9% in the Placebo group). Overall, the rate of SAEs per patient was astonishing low for this vulnerable population (1.26 for the L-CsA group and 1.36 for the Placebo group).

The most common SAEs reported were "Infections and infestations" (36.2%) followed by "Respiratory, thoracic and mediastinal disorders" (10.8%), and "Renal and urinary disorders" (7.7%). A higher percentage of patients in the L-CsA group than in the Placebo group reported

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serious "Infections and infestations" (41.9% vs 28.6%) or "Renal and urinary disorders" (9.5% vs 5.4%). The most common SAEs by PT were pneumonia (4.6% of patients), lung transplant rejection (3.8%), cytomegalovirus infection, bronchitis, pulmonary embolism, renal failure acute, anaemia and forced expiratory volume decreased (3.1%).

Generally, percentages of patients with these SAEs were low. However, a higher percentage was found in patients of the L-CsA group for bronchitis (4.1% in the L-CsA group and 1.8% in the Placebo group), renal failure acute (4.1% in the L-CsA group and 1.8% in the Placebo group) and anaemia (5.4% in the L-CsA group and 0.0% in the Placebo group).

Of the 9 SUSARs reported in eight patients, 6 SUSARSs were reported in 5 patients in the L-CsA group and 3 SUSARSs were reported in 3 patients in the Placebo group. The drug was withdrawn in six patients due to the SUSAR. The most commonly reported SUSAR was pneumonia in 4 patients.

Death was reported in a total of four patients (three patients in the L-CsA group and one patient in the Placebo group) during their participation in the study. For these four patients the reason for prematurely terminating the study was recorded as death. However another two patients (both in L-CsA group) died after they withdrew their consent and were excluded from the study. The reason for their premature discontinuation of study participation was withdrawal of consent. Hence, these two patients were not included in the BOS-free survival analysis.

The analysis of AEs, deaths and SAEs showed that these were mostly associated with pulmonary and immunological events. This was expected in a population of lung transplant and immunosuppressed patients. Neither laboratory values nor vital signs assessment showed any clinically relevant changes over time. Overall, the number of invasive infections was low.

The safety analyses of this study revealed a higher total number of AEs in the L-CsA (919 AEs/12.4 AEs per patient) than the Placebo group (605 AEs/10.8 AEs per patient). This observation is attributed to the fact that more patients were randomised to receive L-CsA. The number of SAEs per patient was rather low in both treatment groups with respect to the vulnerable patient population of this study (1.26 SAEs per patient in the L-CsA group and 1.54 SAEs per patient in the Placebo group).

Despite enhanced local immunosuppression, respiratory infectious events, including fungal infections, did not increase proportionally. This might be attributed to the generally advantageous impact of aerosol inhalation per se. Of special interest with respect to the L-CsA treatment is that no additional risk of an increased renal dysfunction (nephrotoxicity) for patients treated with L-CsA was detected. This observation is endorsed by the remarkably low CsA whole blood trough levels over the long-term use of L-CsA as evaluated in the PK analysis.

CONCLUSION:

- The patients in the PPS population were the basis for the interpretation of results regarding the primary endpoint and the BOS-relevant secondary efficacy endpoints because it was expected that only patients being compliant with the prophylactic therapy could take

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advantage of beneficial treatment effect of L-CsA inhalation.

- Overall, the BOS-free survival events occurred earlier in the Placebo group than in the L-CsA group. The major component of the composite endpoint was the occurrence of BOS. The fatal events occurred after the onset of BOS. Re-transplantations were not required at all.
- An actuarial 2-year treatment difference of 19% in favour of L-CsA was found in the PPS population (p=0.212). This outcome was primarily the result of the huge treatment difference observed in the subpopulation of SLT (actuarial 2-year difference=58%) which reached borderline statistical significance (p=0.053). Such difference is regarded as clinically relevant.
- The safety analyses of this study revealed a higher total number of AEs in the L-CsA (919 AEs/12.4 per patient) than the Placebo group (605 AEs/10.8 per patient). This observation is attributed to the fact that more patients were randomised to receive L-CsA.
- The number of SAEs per patient was rather low in both treatment groups with respect to the vulnerable patient population of this study (1.26 SAEs per patient in the L-CsA group and 1.54 SAEs per patient in the Placebo group).
- The patients treated with L-CsA were not exposed to an additional risk of increased renal dysfunction (nephrotoxicity) or fungal infections.
- Doses of twice daily either 5 mg or 10 mg L-CsA therapy for SLT and DLT, respectively, appeared to be well tolerated in LT patients.
- The treatment with L-CsA did not expose patients to an additional safety risk but provided strong evidence for improved outcome, at least in the SLT subpopulation.
- By balancing the outcome after SLT to the level achieved after DLT, L-CsA may contribute to counteract the general shortage of donor organs in indications which do not necessarily require DLT for medical reasons.
- Last but not least, it has to be clearly stated here that the study did not fail to meet its primary endpoint because of futility of the investigational treatment. The study had also not to be terminated because of safety issues. The only reason of premature termination was fiscal constraints of the Sponsor.

As currently, therapeutic alternatives to reduce the incidence of BOS following lung transplantation or satisfying therapeutic armaments to treat BOS are not available, the benefit/risk ratio for L-CsA prophylaxis is suggested to be positive, at least for SLT patients.

Date of the report: 20 Jan 2015