



Clinical trial results:

A Phase III, Prospective, Multicenter, Randomized, Controlled Clinical Trial to Demonstrate the Efficacy and Safety of Liposomal Cyclosporine A (L-CsA) Inhalation Solution Delivered via the PARI Investigational eFlow® Device plus Standard of Care versus Standard of Care Alone in the Treatment of chronic lung allograft dysfunction / bronchiolitis obliterans syndrom in Patients post Single Lung Transplantation

Summary

EudraCT number	2018-003204-39
Trial protocol	FR DE GB ES BE
Global end of trial date	16 April 2024

Results information

Result version number	v1 (current)
This version publication date	29 October 2025
First version publication date	29 October 2025

Trial information

Trial identification

Sponsor protocol code	BOSTON 1
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03657342
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Zambon S.p.A.
Sponsor organisation address	Via Lillo del Duca 10, Bresso (Mi), Italy, 20091
Public contact	Sponsor Contact Point, Zambon SpA , Zambon SpA, +39 02 39 02 665241, clinicaltrials@zambongroup.com
Scientific contact	Sponsor Contact Point, Zambon SpA , Zambon SpA, +39 02 39 02 665241, clinicaltrials@zambongroup.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	16 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2024
Global end of trial reached?	Yes
Global end of trial date	16 April 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of this trial is to assess the efficacy and safety of aerosolized liposomal cyclosporine A (L-CsA) as add-on therapy to standard of care (SoC) as compared to SoC alone in single lung transplant recipients with chronic lung allograft dysfunction (CLAD)-bronchiolitis obliterans syndrome (BOS).

Protection of trial subjects:

The clinical study was performed in accordance with the principles that have their origin in the Declaration of Helsinki, and with local regulations.

The study was carried out in accordance with the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) notes for guidance on Good Clinical Practice (GCP).

Investigators ensured a close follow-up of safety signals, and that everything has been done to reduce the burden of study procedures (e.g. no painful procedures, etc.).

Background therapy:

Standard of Care (SoC) therapy: regardless of treatment allocation, all patients continued to receive their SoC regimen for maintenance of the lung allograft. Maintenance immunosuppressive therapy including tacrolimus, a second agent such as, but not limited to, MMF or azathioprine, and a systemic corticosteroid such as prednisone as third agent was administered according to institutional standards.

Evidence for comparator: -

Actual start date of recruitment	26 March 2019
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United States: 41
Country: Number of subjects enrolled	Israel: 6
Country: Number of subjects enrolled	Spain: 9
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Germany: 3
Worldwide total number of subjects	62
EEA total number of subjects	12

Notes:

Subjects enrolled per age group

In utero	0
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Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	48
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study randomized 62 patients globally from 26Mar2019 to 16Apr2024.

Pre-assignment

Screening details:

Of the 97 patients screened (up to 4 weeks screening period prior to Visit 1), 62 patients were enrolled, randomized, and treated.

Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

This was an open-label clinical trial. Clinical trial monitors, treating physicians, study nurses, study coordinators, and enrolled patients were not blinded to treatment assignment.

However, the pulmonary function technicians, respiratory therapists, or physiotherapists who conducted spirometry on-site were blinded to treatment assignment.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group A (L-CsA + SoC)

Arm description:

Liposomal Cyclosporine A 5 mg twice daily for 48 weeks + Standard of Care Therapy
L-CsA 5 mg/1.25 mL twice daily for 48 weeks; Standard of Care (as directed by treating physician)

Arm type	Experimental
Investigational medicinal product name	L-CsA
Investigational medicinal product code	
Other name	Liposomal Cyclosporine A
Pharmaceutical forms	Inhalation powder
Routes of administration	Inhalation use

Dosage and administration details:

5 mg L-CsA, powder for nebulization solution for inhalation use, administered with the nebulizer eFlow.
L-CsA 5 mg/1.25 mL was administered twice daily for 48 weeks.

More precisely, each patient received two L-CsA administrations per day, one in the morning and one in the evening. The inhalations were scheduled to be taken approximately 12 hours apart, e.g., at 8:00 a.m. and 8:00 p.m. each day.

Eligible patients should be on a maintenance regimen of immunosuppressive agents including tacrolimus, a second agent such as but not limited to MMF or azathioprine, and a systemic corticosteroid such as prednisone as third agent. The regimen must be stable within 4 weeks prior to randomization with respect to the therapeutic agents. Patients receiving azithromycin for prophylaxis or treatment of BOS, must be on a stable regimen for a least 4-weeks prior to randomization and will continue to receive azithromycin during the trial as deemed appropriate by the investigator.

Arm title	Group B (SoC alone)
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Arm description:

Standard of Care alone as directed by treating physician.

Arm type	Active comparator
Investigational medicinal product name	Standard of care
Investigational medicinal product code	
Other name	SoC
Pharmaceutical forms	Not assigned
Routes of administration	Oral use

Dosage and administration details:

In this active-comparator arm only the standard of care (SoC) is administered. SoC is a maintenance regimen of immunosuppressive agents. Eligible patients should be on a maintenance regimen of immunosuppressive agents including tacrolimus, a second agent such as but not limited to MMF or azathioprine, and a systemic corticosteroid such as prednisone as third agent. The regimen must be stable within 4 weeks prior to randomization with respect to the therapeutic agents. Patients receiving azithromycin for prophylaxis or treatment of BOS, must be on a stable regimen for a least 4-weeks prior to randomization and will continue to receive azithromycin during the trial as deemed appropriate by the investigator.

Number of subjects in period 1	Group A (L-CsA + SoC)	Group B (SoC alone)
Started	32	30
Completed	20	23
Not completed	12	7
Adverse event, serious fatal	6	3
Consent withdrawn by subject	4	4
Pt withdrawn by Sponsor due-to-use of Csa noallowe	1	-
PI withdrew pt due to unstable condition	1	-

Baseline characteristics

Reporting groups

Reporting group title	Group A (L-CsA + SoC)
Reporting group description: Liposomal Cyclosporine A 5 mg twice daily for 48 weeks + Standard of Care Therapy L-CsA 5 mg/1.25 mL twice daily for 48 weeks; Standard of Care (as directed by treating physician)	
Reporting group title	Group B (SoC alone)
Reporting group description: Standard of Care alone as directed by treating physician.	

Reporting group values	Group A (L-CsA + SoC)	Group B (SoC alone)	Total
Number of subjects	32	30	62
Age categorical			
Units: Subjects			
Adults (18-64 years)	9	5	14
From 65-84 years	23	25	48
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	66.9	69.3	
standard deviation	± 7.20	± 5.28	-
Gender categorical			
Units: Subjects			
Female	10	13	23
Male	22	17	39

Subject analysis sets

Subject analysis set title	Group A (L-CsA Treatment Plus SoC) (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group B (SoC alone) (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group A (L-CsA + SoC) (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized. All primary and secondary endpoints were performed using the FAS, unless otherwise specified.	
Subject analysis set title	Group B (SoC Alone) (FAS)

Subject analysis set type	Full analysis
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Subject analysis set description:

The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized. All primary and secondary endpoints were performed using the FAS, unless otherwise specified.

Reporting group values	Group A (L-CsA Treatment Plus SoC) (SAF)	Group B (SoC alone) (SAF)	Group A (L-CsA + SoC) (FAS)
Number of subjects	32	30	32
Age categorical Units: Subjects			
Adults (18-64 years)	9	5	9
From 65-84 years	23	25	23
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	66.9	69.3	66.9
standard deviation	± 7.20	± 5.28	± 7.20
Gender categorical Units: Subjects			
Female	10	13	10
Male	22	17	22

Reporting group values	Group B (SoC Alone) (FAS)		
Number of subjects	30		
Age categorical Units: Subjects			
Adults (18-64 years)	5		
From 65-84 years	25		
85 years and over	0		
Age continuous Units: years			
arithmetic mean	69.3		
standard deviation	± 5.28		
Gender categorical Units: Subjects			
Female	13		
Male	17		

End points

End points reporting groups

Reporting group title	Group A (L-CsA + SoC)
Reporting group description: Liposomal Cyclosporine A 5 mg twice daily for 48 weeks + Standard of Care Therapy L-CsA 5 mg/1.25 mL twice daily for 48 weeks; Standard of Care (as directed by treating physician)	
Reporting group title	Group B (SoC alone)
Reporting group description: Standard of Care alone as directed by treating physician.	
Subject analysis set title	Group A (L-CsA Treatment Plus SoC) (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group B (SoC alone) (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description: The SAF was defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. Independently of the treatment allocation at randomization, patients were analyzed according to the treatment they actually received. All safety and tolerability data were summarized and analyzed using the SAF.	
Subject analysis set title	Group A (L-CsA + SoC) (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized. All primary and secondary endpoints were performed using the FAS, unless otherwise specified.	
Subject analysis set title	Group B (SoC Alone) (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: The FAS was defined as all randomized patients. Patients were analyzed according to the treatment group to which they were randomized. All primary and secondary endpoints were performed using the FAS, unless otherwise specified.	

Primary: Mean change in FEV1 (L) from baseline to Week 48

End point title	Mean change in FEV1 (L) from baseline to Week 48
End point description: FEV1 is the Forced Expiratory Volume in One Second. For FEV1 were considered primary the data collected from the on site COMPACT study spirometer. Baseline is the mean of the best FEV1 obtained with the study spirometer at Screening Visit and the pre-randomization best FEV1 obtained at the Baseline Visit (V1). The primary efficacy analysis was carried out using a Linear Mixed Model (LMM) for repeated measures, using all observed available FEV1 measurements. In case of death or re-transplantation events, FEV1 was imputed as zero at each nominal day post event.	
End point type	Primary
End point timeframe: Week 48 (V9)	

End point values	Group A (L-CsA + SoC) (FAS)	Group B (SoC Alone) (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: L				
arithmetic mean (standard deviation)	-0.186 ($\pm$ 0.3093)	-0.090 ($\pm$ 0.2879)		

Statistical analyses

Statistical analysis title	L-CsA Treatment Plus SoC (FAS), SoC Alone (FAS)
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Statistical analysis description:

at V9.

Estimates are from a LMM for repeated measurements on the response variable change from baseline in FEV1 with factors for time splines, treatment, the interactions of time splines by treatment, baseline FEV1, the interactions of time splines with baseline FEV1, region, underlying indication for lung transplant (COPD vs all others), use of azithromycin at randomization, and time as random effect.

Comparison groups	Group A (L-CsA + SoC) (FAS) v Group B (SoC Alone) (FAS)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.731 ^[1]
Method	Mixed models analysis
Parameter estimate	Least Square Mean Difference
Point estimate	-0.095
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.405
upper limit	0.214

Notes:

[1] - 1-sided p value.

Secondary: Mean change in FEV1/FVC from baseline to Week 48

End point title	Mean change in FEV1/FVC from baseline to Week 48
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End point description:

Forced Expiratory Volume in One Second on Forced Vital Capacity. FEV1/FVC is a calculated ration used to diagnose obstructive and restrictive lung disease. It represents the proportion of a patient's vital capacity that he/she is able to expire in the first second of forced expiration to the full forced vital capacity.

End point type	Secondary
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End point timeframe:

Week 48 (V9)

End point values	Group A (L-CsA + SoC) (FAS)	Group B (SoC Alone) (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25	25		
Units: ratio				
least squares mean (standard error)	0.093 ($\pm$ 0.2353)	0.157 ($\pm$ 0.2433)		

Statistical analyses

Statistical analysis title	L-CsA Treatment Plus SoC (SAF), SoC Alone (SAF)
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Statistical analysis description:

At V9.

Estimates are - as for the primary outcome - from a LMM for repeated measurements on the response variable change from baseline in FEV1/FVC with factors for time splines, treatment, the interactions of time splines by treatment, baseline FEV1, the interactions of time splines with baseline FEV1, region, underlying indication for lung transplant (COPD vs all others), use of azithromycin at randomization, and time as random effect.

Comparison groups	Group A (L-CsA + SoC) (FAS) v Group B (SoC Alone) (FAS)
Number of subjects included in analysis	50
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8041 ^[2]
Method	Mixed models analysis
Parameter estimate	Least square mean difference
Point estimate	-0.064
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.212
upper limit	0.084

Notes:

[2] - 1-sided p value

Secondary: Time to Progression of BOS

End point title	Time to Progression of BOS
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End point description:

The progression of BOS is defined as the earliest of the following:

- Absolute decrease from baseline in FEV1 $\geq$ 10% or $\geq$ 200 mL and absolute decrease in FEV1/FVC of > 5% (if a patient had an event that met this criterion for progression of BOS, progression of BOS must have been confirmed by measurements that were taken with COMPACT spirometer at least 2 weeks apart) OR

- Worsening of BOS grade, OR

- Re-transplantation, OR

- Death from respiratory failure.

Rules for censoring progression of BOS are set. More than one type of event might correspond to the event of BOS progression (even those occurring on the same date). In case progression of BOS was defined by more than one criterion on different dates, the earliest event date was considered, i.e., the date closer to randomization was used as the progression date.

End point type	Secondary
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End point timeframe:

From date of randomization until the date of first documented progression of BOS, or date of retransplantation, or date of death from respiratory failure, whichever came first, assessed up to 48 weeks.

End point values	Group A (L-CsA + SoC) (FAS)	Group B (SoC Alone) (FAS)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	30		
Units: count of participants				
Absolute decrease from baseline in FEV1 $\geq 10\%$ or ≥ 2	2	1		
Worsening of BOS grade	1	2		
Re-transplantation	0	0		
Death from respiratory failure	1	0		
No. of patients in total with Progression of BOS	3	2		

Statistical analyses

Statistical analysis title	L-CsA Treatment Plus SoC (FAS), SoC Alone (FAS)
Comparison groups	Group A (L-CsA + SoC) (FAS) v Group B (SoC Alone) (FAS)
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1559 ^[3]
Method	Regression, Cox
Parameter estimate	adjusted hazard ratio
Point estimate	2.601
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.408
upper limit	16.585

Notes:

[3] - 1-sided p value. Adjusted Hazard Ratio calculated using Cox proportional hazards model with covariates of Treatment, Baseline FEV1, with Efron's method of tie handling.

Secondary: Number of Patients With Adverse Events (AE)

End point title	Number of Patients With Adverse Events (AE)
End point description:	
An AE is an untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine.	
End point type	Secondary
End point timeframe:	
Baseline through study completion (week 48)	

End point values	Group A (L-CsA Treatment Plus SoC) (SAF)	Group B (SoC alone) (SAF)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	32	30		
Units: count of patients				
No of patients with any AE	32	25		
No. of patients with any TEAE leading to discontin	8	2		
No. of patients with any TEAE leading to study dis	6	3		
No. of patients with any TEAE leading to death	6	3		
No. of patients with any TEAE of Grade 1 severity	22	22		
No. of patients with any TEAE of Grade 2 severity	14	12		
No. of patients with any TEAE of Grade 3 severity	15	8		
No. of patients with any study treatment-related T	11	0		
No. of patients with any serious TEAE	20	14		
No. of patients with any serious treatment-related	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Acute Tolerability of L-CsA: Change From Pre-dose to 1 hr and 4h Post-dose

End point title	Acute Tolerability of L-CsA: Change From Pre-dose to 1 hr and 4h Post-dose
End point description:	
Acute tolerability of IMP (L-CsA) during initial dosing was determined by measuring spirometry prior to administration of L-CsA as well as 1 hour and 4 hours after completion of IMP inhalation. A decline of $\geq 20\%$ in FEV1 associated with symptoms could have warranted IMP discontinuation. Parameters reflecting acute tolerability of IMP were: spirometry, cough, or dyspnea.	
End point type	Secondary
End point timeframe:	
Baseline through study completion Week 48	

End point values	Group A (L-CsA Treatment Plus SoC) (SAF)			
Subject group type	Subject analysis set			
Number of subjects analysed	29			
Units: Liters				
arithmetic mean (standard deviation)				
1 hr Post-dose	-0.022 ($\pm$ 0.0663)			

4 hr Post-dose	-0.019 ($\pm$ 0.0701)			
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Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Permanent assessment throughout the complete clinical trial period, from baseline (Week 0, Day 1, V1) till week 48 (V9)

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	23.1
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Reporting groups

Reporting group title	Group A (L-CsA + SoC) - SAF
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Reporting group description:

Liposomal Cyclosporine A 5 mg twice daily for 48 weeks + Standard of Care Therapy

L-CsA 5 mg/1.25 mL twice daily for 48 weeks; Standard of Care (as directed by treating physician)

Reporting group title	Group B (SoC alone) - SAF
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Reporting group description:

Standard of Care alone as directed by treating physician.

Serious adverse events	Group A (L-CsA + SoC) - SAF	Group B (SoC alone) - SAF	
Total subjects affected by serious adverse events			
subjects affected / exposed	20 / 32 (62.50%)	14 / 30 (46.67%)	
number of deaths (all causes)	6	3	
number of deaths resulting from adverse events	6	3	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Pancreatic carcinoma			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Small cell carcinoma			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Pelvic venous thrombosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Venous thrombosis limb			

subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza like illness			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple organ dysfunction syndrome			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Immune system disorders			
Lung transplant rejection			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory distress syndrome			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute respiratory failure			
subjects affected / exposed	4 / 32 (12.50%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Respiratory failure			

subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Dyspnoea			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Interstitial lung disease			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pleural effusion			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Productive cough			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Acute myocardial infarction			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure acute			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	3 / 32 (9.38%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Left ventricular failure			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular extrasystoles			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ventricular tachycardia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			

Presyncope			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Immune thrombocytopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	3 / 32 (9.38%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Gouty arthritis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar spinal stenosis			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			

subjects affected / exposed	7 / 32 (21.88%)	5 / 30 (16.67%)	
occurrences causally related to treatment / all	0 / 9	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 1	
COVID-19 pneumonia			
subjects affected / exposed	2 / 32 (6.25%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Clostridial sepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parainfluenzae virus infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia bacterial			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pneumococcal			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia pseudomonas			

subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia respiratory syncytial viral			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudomonal bacteraemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhinovirus infection			
subjects affected / exposed	0 / 32 (0.00%)	1 / 30 (3.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	2 / 32 (6.25%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Streptococcal sepsis			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral infection			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower Respiratory Tract Infection Bacterial			

subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Fluid overload			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 32 (3.13%)	0 / 30 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Group A (L-CsA + SoC) - SAF	Group B (SoC alone) - SAF	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 32 (87.50%)	17 / 30 (56.67%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 32 (6.25%)	4 / 30 (13.33%)	
occurrences (all)	2	4	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	4 / 32 (12.50%)	0 / 30 (0.00%)	
occurrences (all)	4	0	
Cough			
subjects affected / exposed	5 / 32 (15.63%)	2 / 30 (6.67%)	
occurrences (all)	5	2	
Dyspnoea			

subjects affected / exposed occurrences (all)	4 / 32 (12.50%) 7	4 / 30 (13.33%) 4	
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 32 (9.38%)	1 / 30 (3.33%)	
occurrences (all)	3	1	
COVID-19			
subjects affected / exposed	7 / 32 (21.88%)	5 / 30 (16.67%)	
occurrences (all)	9	5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2019	Amendment 1 has been issued to review the Eligibility Criteria, Treatment of Patients, Assessment of Efficacy and Safety, Visits Schedule and Statistical considerations. This amendment had considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
09 June 2020	Amendment 2 has been issued to add the COVID-19 related measures in order to ensure patient safety and efficacy data collection in case a given on-site visits cannot take place due to COVID-19 outbreak, including the possibility to perform remote visits, to carry out spirometry examination at patient home and the IMP re-supply at patient home. Furthermore the Eligibility Criteria have been reviewed. The amendment had considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
19 January 2021	Amendment 3 has been issued to include the Sponsorship change and to revise the Eligibility Criteria to ensure that the study population is aligned with the most recent criteria for CLAD-BOS (Chronic Lung Allograft Dysfunction - Bronchiolitis Obliterans Syndrome) stages. Furthermore Statistical sections have been modified according to the FDA Written Response Only discussions (type C meeting) and the EMA guidelines on clinical trial conducted during the COVID-19 contingency was added. This amendment had considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.
13 April 2023	Amendment 4 has been issued to accomplish with FDA recommendations received during last interactions (WRO) to continue BOSTON-1 and BOSTON-2 enrolment to achieve the originally planned total number of 220 patients for both clinical trials combined, to ensure the adequacy of the safety database and to implement the efforts to minimize missing data in both studies. Furthermore, this version includes the response to the FDA comments received on 15-February-2023 for the amendment to Study Protocol BOSTON-2 version 5.0 submitted on December 8, 2022, IND 078854 L-Cyclosporine A. This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union. The main changes are related to the Sample Size re-estimation to accomplish with the FDA recommendation.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

No limitations or caveats are applicable to this summary of results.
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Notes: