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Observational Study Protocol

Title	A Retrospective Chart Review Study of Patients With Chronic Lung Allograft Dysfunction-Bronchiolitis Obliterans Syndrome (CLAD-BOS) Post Lung Transplantation
Short Title	BOSTON EVOLUTION
Protocol version identifier	Z8000N01, Version 1.0
Date of last version of the protocol	Not applicable
Active substance	Not applicable
Medicinal product	Not applicable
Product reference	Not applicable
Procedure number	Not applicable
Research question and objectives	The primary objective of this study is to evaluate the forced expiratory volume in 1 second (FEV_1) trajectory of patients diagnosed with CLAD-BOS. The demographics, clinical characteristics, trajectory of other relevant spirometry parameters, overall survival, CLAD-BOS progression, rate of hospitalization due to respiratory failure, incidence of concomitant disease, and the use of treatments and procedures for CLAD-BOS will also be evaluated in this study.
Country/region of study	United States and European Union region
Sponsor	Zambon SpA Via Lillo del Duca, 10 Bresso (MI) 20091 Italy

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2. LIST OF ABBREVIATIONS

AE	adverse event
BO	bronchiolitis obliterans
BOS	bronchiolitis obliterans syndrome
CFR	Code of Federal Regulations
CI	confidence interval
CLAD	chronic lung allograft dysfunction
CRO	contract research organization
CSR	Clinical Study Report
eCRF	electronic Case Report Form
EDC	electronic data capture
EU	European Union
$FEF_{25-75\%}$	forced mid-expiratory flow
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GCP	Good Clinical Practices
GDPR	General Data Protection Regulation
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LMM	Linear Mixed Model
MAR	missing at random
OS	overall survival
PII	personally identifiable information
RAS	restrictive allograft syndrome
SAP	Statistical Analysis Plan
US	United States

3. RESPONSIBLE PARTIES

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CONTRACT RESEARCH ORGANIZATION:

CCI

Investigator's Agreement

I have read the attached protocol entitled "A Retrospective Chart Review Study of Patients With Chronic Lung Allograft Dysfunction-Bronchiolitis Obliterans Syndrome (CLAD-BOS) Post Lung Transplantation", dated 05 March 2024, and agree to abide by all provisions set forth therein.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Zambon SpA.

Name and Title_____ _____

(Print) Date Signature

Center Name and Address_____

(Print)

4. SYNOPSIS

Title

A Retrospective Chart Review Study of Patients With Chronic Lung Allograft Dysfunction-Bronchiolitis Obliterans Syndrome (CLAD-BOS) Post Lung Transplantation

Short Study Title: BOSTON EVOLUTION

Date: 05 March 2024, Version 1.0

Sponsor: Zambon SpA, Via Lillo del Duca, 10, Bresso (MI) 20091, Italy

Background and Rationale

Lung transplantation is the ultimate treatment option for patients with advanced lung disease or irreversible pulmonary failure. Although refinements and advancements in surgical techniques, lung preservation, immunosuppressive regimen, management of ischemia/reperfusion injury and infections, as well as post-transplant patient care have resulted in improved outcomes, acute and chronic pulmonary allograft rejection continues to be the major obstacle for satisfactory long-term results. Acute rejection after lung transplantation exceeds the incidence and severity compared with other solid organ transplantations. Chronic lung allograft dysfunction (CLAD), and in particular bronchiolitis obliterans syndrome (BOS), which is the most frequent CLAD phenotype, is the leading cause of death beyond the first year after lung transplantation. Whereas the development of BOS is rare within the first year after lung transplantation, approximately half of patients develop CLAD-BOS within 5 years of transplantation.

The aim of this study is to describe the forced expiratory volume in 1 second (FEV_1) decline and natural disease evolution in patients affected by CLAD-BOS after lung transplantation and receiving an immunosuppressive therapy as standard of care. CCI [redacted]

Research Question and Objectives

The primary objective of this study is to evaluate the FEV_1 trajectory of patients diagnosed with CLAD-BOS.

The secondary objectives of this study are as follows:

1. To describe demographics of patients diagnosed with CLAD-BOS
2. To describe clinical characteristics following lung transplantation for patients diagnosed with CLAD-BOS
3. To evaluate the trajectory of other relevant spirometry parameters (i.e., forced vital capacity [FVC], FEV_1/FVC, forced mid-expiratory flow [$FEF_{25-75\%}$])

4. To evaluate the overall survival (OS) of patients diagnosed with CLAD-BOS
5. To evaluate the time to first CLAD-BOS progression
6. To evaluate the cumulative incidence of CLAD-BOS progression
7. To evaluate the rate of hospitalization due to respiratory failure after CLAD-BOS onset
8. To evaluate the incidence of concomitant respiratory disease
9. To evaluate the incidence of concomitant non-respiratory disease
10. To describe the use of concomitant treatments and procedures for CLAD-BOS.

Study Design

This is a retrospective, multinational, multicenter chart review study of adult patients with clinically diagnosed CLAD-BOS after lung transplantation. All data will be retrospectively collected from patient records starting from lung transplantation date through last date of available data, and as such, no interventions will be applied as part of this study. There will be no protocol-mandated patient assessments or follow-up visits. Patient's written consent will be obtained in accordance with local ethics and regulatory requirements, unless it is deemed by local authorities that it is possible to collect data without an informed consent for retrospective studies (i.e., Informed Consent Form waiver).

The observational period for each patient will be from lung transplant date until last date of data available or death, whichever occurs earlier and will include the following time periods:

- Diagnosis window: 01 January 2013 through most recent data available.
- Index date: Date of CLAD-BOS clinician diagnosis.
- Personal best-FEV_1 date: Date in which the patient reaches his/her personal best, post-transplant FEV_1 value, defined as the mean of the 2 best post-transplant FEV_1 measurements taken at least 3 weeks apart. For each patient, the personal best-FEV_1 will be derived from the data collected starting from the lung transplant date or identified in clinical records according to physician judgment.
- Onset date: Date when the patient reaches for the first time a FEV_1 value $\leq 80\%$ vs best-FEV_1, confirmed in a subsequent visit occurring at least 3 months apart. For each patient, the onset date will be derived from the data collected starting from the lung transplant date.
- Pre-diagnosis period: The period of time from the lung transplant date up to, but not including, the index date.
- Post-diagnosis period: The period of time from, and including, the index date through the last date of data available or death, whichever occurs earlier.

Study Population

The study population will include adult patients aged ≥ 18 years who are recipients of a lung transplant and diagnosed with CLAD-BOS following transplantation. It is anticipated that the

study will be conducted and patients approximately equally enrolled in the United States (US), and European Union region, across approximately 6 study sites.

To be eligible for the study, patients must meet all of the following inclusion criteria:

1. Adult patients ≥ 18 years of age on the date of CLAD-BOS diagnosis
2. Patients with a CLAD-BOS clinician diagnosis from as early as 01 January 2013
3. Patients with CLAD-BOS clinician diagnosis made at least 12 months after lung transplant
4. Patients received at least basic maintenance regimen of immunosuppressive agents including tacrolimus, a second agent such as but not limited to mycophenolate mofetil or azathioprine (or other anti-proliferative agent), and a systemic corticosteroid such as prednisone as third agent for at least 1 month before the index date. As long as the basic maintenance regimen is maintained for the abovementioned period, patients will still be considered eligible for the study even if they are receiving other immunosuppressive agents in addition to the basic maintenance regimen.

Patients who meet any of the following exclusion criteria will not be eligible for the study:

1. Patients with severe concomitant disease at the time of index date, which according to physician's judgment, can interfere with CLAD-BOS progression and mortality (e.g., malignancies, severe chronic diseases)
2. Patients who have been exposed to any investigational medical products in the 4 weeks prior to index date or during the post-diagnosis period
3. Patients with confirmed other CLAD phenotype (e.g., restrictive allograft syndrome) according to physician's judgment.

Outcomes

Table 1. Primary Objective and Primary Outcome Measure

Objective	Outcome Measure
To evaluate the FEV_1 trajectory of patients diagnosed with CLAD-BOS	Change in FEV_1 trajectory over time starting from the onset date through the end of post-diagnosis period. Personal best-FEV_1 value is defined as the mean of the 2 best post-transplant FEV_1 measurements taken at least 3 weeks apart. The personal best-FEV_1 will be derived from the data collected starting from the lung transplant date or identified in clinical records according to physician judgment.

CLAD-BOS = chronic lung allograft dysfunction-bronchiolitis obliterans syndrome; FEV_1 = forced expiratory volume in 1 second

Table 2. Secondary Objectives and Secondary Outcome Measures

Objectives	Outcome Measures
To describe demographics of patients diagnosed with CLAD-BOS	Demographics at transplant date will include: • Age in years • Sex (men and women) • Race • Pre-transplant medical history • Date and type of lung transplant (i.e., single or bilateral) • Reason for transplantation (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis)
To describe clinical characteristics following lung transplantation for patients diagnosed with CLAD-BOS	Clinical characteristics following the lung transplantation will include: • Acute rejection events • Donor-specific antibodies • Total lung capacity (plethysmography) • Presence of lung opacities (e.g., as documented from computed tomography scans) • Sign/symptoms or other clinical records related to mobility, self-care, usual activities, pain/discomfort, anxiety/depression
To evaluate the trajectory of other relevant spirometry parameters (i.e., FVC, FEV_1/FVC, $FEF_{25-75\%}$)	Trajectories will be evaluated starting from the onset date through the end of the post-diagnosis period. Spirometry values will include (absolute value, percent value, and percent predicted, where available): • FVC • FEV_1/FVC ratio • $FEF_{25-75\%}$
To evaluate the OS of patients diagnosed with CLAD-BOS	The OS will be calculated as the time from the onset date to death by any cause. The cause of death will be documented. Patients with unknown vital status at the time of data abstraction will have their status imputed or censored.
To evaluate the time to first CLAD-BOS progression	The time to first CLAD-BOS progression will be calculated as the time from onset date to CLAD-BOS progression defined as the earliest of any of the following events: • Absolute decrease from previously available spirometry assessment in $FEV_1 \geq 10\%$ or ≥ 200 mL and absolute decrease in FEV_1/FVC of $> 5\%$, that must be confirmed by another spirometer evaluation performed at least 2 weeks apart, OR • Change in CLAD grade severity, OR • Re-transplantation, OR • Death from respiratory failure, OR • According to clinical judgment reporting CLAD-BOS progression in patient records.

Objectives	Outcome Measures
	Patients with no CLAD-BOS progression at the time of data abstraction will be censored at the last date of data available.
To evaluate the cumulative incidence of CLAD-BOS progression	The cumulative incidence of CLAD-BOS progression events will be calculated from the onset date through the end of the post-diagnosis period. The CLAD-BOS progression is defined by 1 of the following events: • Absolute decrease from previously available spirometry assessment in $FEV_1 \geq 10\%$ or ≥ 200 mL and absolute decrease in FEV_1/FVC of $> 5\%$, that must be confirmed by another spirometer evaluation performed at least 2 weeks apart, OR • Change in CLAD grade severity, OR • Re-transplantation, OR • Death from respiratory failure, OR • According to clinical judgment reporting CLAD-BOS progression in patient records.
To evaluate the rate of hospitalization due to respiratory failure after CLAD-BOS onset	The rate of hospitalizations due to respiratory failure starting from the onset date through the end of the post-diagnosis period. The cause of hospitalization will be documented.
To evaluate the incidence of concomitant respiratory disease	The incidence rate of newly diagnosed cases of concomitant respiratory diseases that occur starting from the onset date through the end of the post-diagnosis period.
To evaluate the incidence of concomitant non-respiratory disease	The incidence rate of newly diagnosed cases of concomitant non-respiratory diseases that occur starting from the onset date through the end of the post-diagnosis period.
To describe the use of concomitant treatments and procedures for CLAD-BOS	Concomitant treatments and procedures for CLAD-BOS starting from the post-transplant date through the end of the post-diagnosis period: • Antibiotic treatments (e.g., azithromycin) • Immunosuppressants • Extracorporeal photopheresis • Corticosteroids • Other

CLAD-BOS = chronic lung allograft dysfunction-bronchiolitis obliterans syndrome, $FEF_{25-75\%}$ = forced expiratory flow, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, OS = overall survival
FVC refers to the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. FEV_1/FVC ratio is the ratio of the forced expiratory volume in the first 1 second to the FVC of the lungs. $FEF_{25-75\%}$ refers to forced expiratory flow over the middle one-half of the FVC; the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled.

Data Sources

The study data sources will consist of medical records (including electronic and/or paper) and patient notes for the study patients. All source data will be abstracted from the medical records and patient notes and entered into the validated electronic data capture system, CCI [redacted] hosted by CCI [redacted]

Electronic medical records used in the creation/capture of electronic clinical data and to the control of other processes with the potential to affect patient protection and reliability of study data shall be validated according to guidelines on computerized systems and electronic data in clinical trials in order for the data to adequately support robust results and good decision making.

Sample Size

Approximately 300 patients will be enrolled to achieve at least 200 patients providing at least 5 years of data post-CLAD-BOS onset (based on an estimated 5-year survival rate of 70% of the patients).

The sample size will provide adequate precision to estimate the FEV_1 trajectory and sufficient outcomes data. CCI [redacted]

Patient medical records will be reviewed for eligibility starting with the patients diagnosed with CLAD-BOS starting from 01 January 2013 and moving in chronological order to the next diagnosed patients until the target sample size of eligible patients is reached.

A quota will be applied to ensure that 80% of the total study population enrolled are recipients of a bilateral lung transplant.

Statistical Analysis

Descriptive summary statistics for continuous variables will include the number of patients, mean, standard deviation, median, interquartile range, and range. Descriptive summary statistics for categorical variables will include frequency counts and percentages. Confidence intervals around mean or proportion will be presented where applicable.

The trajectories of FEV_1 and other longitudinal parameters will be characterized using a Linear Mixed Model for repeated measurements, using all observed available FEV_1 measurements up to the last date of data available.

Overall survival and time to first CLAD-BOS progression will be assessed using Kaplan-Meier methods. Rates at yearly intervals will be reported along with the estimated medians and the corresponding CIs, whenever estimable. Kaplan-Meier curves will be presented along with the number of patients at risk at exact time points. Incidence rates will be evaluated using negative binomial or Poisson (in case of lack of convergence) regression, including an offset for patient follow-up time. Estimations will be provided along with their 95% CIs.

Subgroup analyses of main outcomes will be performed by age class, gender, race, region, and severity of disease. Statistical details and potential new subgroup definitions will be reported in the Statistical Analysis Plan (SAP).

The SAP will be issued before starting the collection of data with more technical and detailed elaboration of the principal features of statistical analyses.

Additional post-hoc analyses may be produced to further explore data according to the results obtained. Any deviations from the original SAP (including unplanned analyses) will be documented in the Clinical Study Report.

5. MILESTONES

Milestone	Planned date
Start of data collection	May 2024
End of data collection	December 2024
Clinical Study Report	April 2025

6. BACKGROUND AND RATIONALE

6.1. Background

Lung transplantation is the ultimate treatment option for patients with advanced lung disease or irreversible pulmonary failure. Although refinements and advancements in surgical techniques, lung preservation, immunosuppressive regimen, management of ischemia/reperfusion injury and infections, as well as post-transplant patient care have resulted in improved outcomes, acute and chronic pulmonary allograft rejection continues to be the major obstacle for satisfactory long-term results. Acute rejection after lung transplantation exceeds the incidence and severity compared with other solid organ transplantations. Chronic lung allograft dysfunction (CLAD), and in particular bronchiolitis obliterans syndrome (BOS), which is the most frequent CLAD phenotype, is the leading cause of death beyond the first year after lung transplantation. Whereas the development of BOS is rare within the first year after lung transplantation, approximately half of patients develop CLAD-BOS within 5 years of transplantation.[1]

The main histologic hallmark of BOS is scarring with fibrosis of the airway. However, this process is patchy, making the sensitivity of transbronchial biopsy for detection of bronchiolitis obliterans (BO) highly dependent on adequacy of sampling and skill of histologic interpretation. Therefore, the clinical manifestation of BOS is defined as irreversible airway obstruction, diagnosed by pulmonary function, in the absence of other causes. This diagnosis does not require histologic confirmation but is considered a reliable surrogate physiologic marker of the presence of BO. In its most common presentation, BO is characterized by the pathophysiological features of respiratory obstruction. The major findings on spirometry are a reduced forced expiratory volume in 1 second (FEV_1), a normal or slightly decreased forced vital capacity (FVC) (i.e., the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible), and a reduced ratio of FEV_1 to FVC, with poor response to inhaled bronchodilators. Lung volumes indicate air trapping, with a normal total lung capacity and high residual volume. However, a subset of patients present with a restrictive pattern characterized by a low FVC and a normal FEV_1/FVC ratio, or a mixed pattern of obstruction and restriction.[2] Bronchiolitis obliterans syndrome is often a diagnosis of exclusion and other causes of allograft dysfunction, including restrictive allograft syndrome (RAS), acute rejection, and acute infection, need to be excluded before the diagnosis of BOS is made.[3]

The 2002 BOS grading system for Grades 0 through 3 (Table 1) is solely based on FEV_1 and/or forced mid-expiratory flow ($FEF_{25-75\%}$) rate. The $FEF_{25-75\%}$ refers to the forced expiratory flow

over the middle one-half of the FVC; the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled. The 2002 BOS grading system is a useful surrogate marker for BO: it is easy to measure by standardized spirometry and is reproducible; it becomes abnormal prior to histologic confirmation[4]; and it displays high sensitivity and specificity when assessed against biopsy- and autopsy-confirmed BO.[5] The 2002 definition has been updated in the 2019 International Society for Heart and Lung Transplantation consensus statement[3], which now references BOS as CLAD-BOS phenotype. In the following table, "baseline" or personal best is defined as the patient's personal best FEV_1 following transplant.

Table 1. Bronchiolitis Obliterans Syndrome Classification

Original Classification (1993)		2002 Classification		2019 ISHLT Classification	
		BOS 0	FEV_1 > 90% of baseline and $FEF_{25-75\%}$ > 75% of baseline		
BOS 0	FEV_1 80% or more of baseline	BOS 0-p	FEV_1 81% to 90% of baseline and/or $FEF_{25-75\%} \leq$ 75% of baseline	CLAD 0	FEV_1 > 80% of baseline
BOS 1	FEV_1 66% to 80% of baseline	BOS 1	FEV_1 66% to 80% of baseline	CLAD 1	FEV_1 > 65-80% of baseline
BOS 2	FEV_1 51% to 65% of baseline	BOS 2	FEV_1 51% to 65% of baseline	CLAD 2	FEV_1 > 50-65% of baseline
BOS 3	FEV_1 50% or less of baseline	BOS 3	FEV_1 50% or less of baseline	CLAD 3	FEV_1 > 35-50% of baseline
				CLAD 4	$FEV_1 \leq$ 35% of baseline

BOS = bronchiolitis obliterans syndrome; CLAD = chronic lung allograft dysfunction; $FEF_{25-75\%}$ = forced mid-expiratory flow rate; FEV_1 = forced expiratory volume in 1 second; ISHLT = International Society for Heart and Lung Transplantation.[3,6]
Note: Baseline is defined as the patient's personal best FEV_1 following transplant.

Bronchiolitis obliterans syndrome represents the major determinant of long-term graft and patient survival following lung transplantation. While BOS has been recognized for decades, it has increased more substantially as the number of lung transplantations has increased as an acceptable treatment for lung failure. To reduce the rate of rejection (acute as well as chronic forms), immunosuppressive regimens are employed. Although the immunosuppressive protocols vary from center to center, conventional maintenance therapy consists principally of triple drug therapy comprising a calcineurin inhibitor (cyclosporine A or tacrolimus), an antiproliferative agent (mycophenolate mofetil, azathioprine, sirolimus, or everolimus), and corticosteroids. Historically, cyclosporine A and azathioprine were used along with prednisone, but additional agents have become available, including tacrolimus, mycophenolate, and mammalian target of rapamycin inhibitors like sirolimus and everolimus. Often when BOS is diagnosed in a lung transplant recipient, immunosuppression is augmented but no augmentation therapy has been demonstrated to impact BO reliably. Additional systemic immunosuppression comes with the added burden of additional end-organ toxicity and tolerability issues. Development of BOS is the major confounding factor of long-term success following lung transplantation. Bronchiolitis obliterans syndrome is reported as the main cause of death beyond the first post-transplant year over the last 3 decades.[7]

6.2. Rationale

The aim of this study is to describe the FEV_1 decline and natural disease evolution in patients affected by CLAD-BOS after lung transplantation and receiving an immunosuppressive therapy as standard of care. CCI [redacted] The use of such historical real-world data as a benchmark can be particularly useful for characterizing the natural history of the disease and clinical outcomes for a disease that is not only rare but also has insufficient informative data about its natural history (e.g., severe unmet need, scarcity of available patients).[8,9,10]

7. RESEARCH QUESTIONS AND OBJECTIVES

7.1. Primary Objective

The primary objective of this study is to evaluate the FEV_1 trajectory of patients diagnosed with CLAD-BOS.

7.2. Secondary Objectives

The secondary objectives of this study are as follows:

1. To describe demographics of patients diagnosed with CLAD-BOS
2. To describe clinical characteristics following lung transplantation for patients diagnosed with CLAD-BOS
3. To evaluate the trajectory of other relevant spirometry parameters (i.e., FVC, FEV1/FVC, $FEF_{25-75\%}$)
4. To evaluate the overall survival (OS) of patients diagnosed with CLAD-BOS
5. To evaluate the time to first CLAD-BOS progression
6. To evaluate the cumulative incidence of CLAD-BOS progression
7. To evaluate the rate of hospitalization due to respiratory failure after CLAD-BOS onset
8. To evaluate the incidence of concomitant respiratory disease
9. To evaluate the incidence of concomitant non-respiratory disease
10. To describe the use of concomitant treatments and procedures for CLAD-BOS.

8. RESEARCH METHODS

8.1. Study Design

This is a retrospective, multinational, multicenter chart review study of adult patients with clinically diagnosed CLAD-BOS after lung transplantation. All data will be retrospectively collected from patient records starting from lung transplantation date through last date of available data, and as such, no interventions will be applied as part of this study. There will be

no protocol-mandated patient assessments or follow-up visits. Patient written consent will be obtained, in accordance with local ethics and regulatory requirements unless it is deemed by local authorities that it is possible to collect data without an informed consent for retrospective studies (i.e., Informed Consent Form [ICF] waiver).

8.1.1. Setting

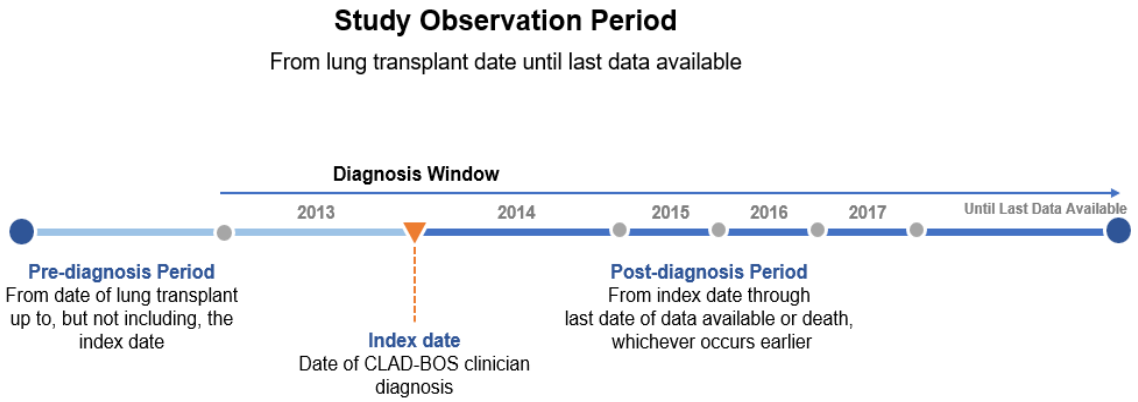
The study will be conducted and patients approximately equally enrolled in the United States (US) and European Union (EU) region, across approximately 6 study sites.

8.1.2. Study Time Period

The observational period for each patient will be from lung transplant date until last date of data available or death, whichever occurs earlier and will include the following time periods (see Figure 1):

- Diagnosis window: 01 January 2013 through most recent data available.
- Index date: Date of CLAD-BOS clinician diagnosis.
- Personal best-FEV_1 date: Date in which the patient reaches his/her personal best, post-transplant, FEV_1 value, defined as the mean of the 2 best post-transplant FEV_1 measurements taken at least 3 weeks apart.[3] For each patient, the personal best-FEV_1 will be derived from the data collected starting from the lung transplant date or identified in clinical records according to physician judgment.
- Onset date: Date when the patient reaches for the first time a FEV_1 value $\leq$ 80% vs best-FEV_1, confirmed in a subsequent visit occurring at least 3 months apart.[3] For each patient, the onset date will be derived from the data collected starting from the lung transplant date.
- Pre-diagnosis period: The period of time from the lung transplant date up to, but not including, the index date.
- Post-diagnosis period: The period of time from and including the index date through the last date of data available or death, whichever occurs earlier.

Figure 1. Study Design Schema



CLAD-BOS = chronic lung allograft dysfunction-bronchiolitis obliterans syndrome

8.1.3. Study Population

The study population will include adult patients aged ≥ 18 years who are recipients of a lung transplant and diagnosed with CLAD-BOS following transplantation.

8.1.3.1. Inclusion Criteria

To be eligible for the study, patients must meet all of the following inclusion criteria:

1. Adult patients ≥ 18 years of age on the date of CLAD-BOS diagnosis
2. Patients with a CLAD-BOS clinician diagnosis from as early as 01 January 2013
3. Patients with CLAD-BOS clinician diagnosis made at least 12 months after lung transplant
4. Patients received at least basic maintenance regimen of immunosuppressive agents including tacrolimus, a second agent such as but not limited to mycophenolate mofetil or azathioprine (or other anti-proliferative agent), and a systemic corticosteroid such as prednisone as third agent for at least 1 month before the index date. As long as the basic maintenance regimen is maintained for the above-mentioned period, patients will still be considered eligible for the study even if they are receiving other immunosuppressive agents in addition to the basic maintenance regimen.

8.1.3.2. Exclusion Criteria

Patients who meet any of the following exclusion criteria will not be eligible for the study:

1. Patients with severe concomitant disease at the time of index date which, according to physician's judgment, can interfere with CLAD-BOS progression and mortality (e.g., malignancies, severe chronic diseases)
2. Patients who have been exposed to any investigational medical products in the 4 weeks prior to index date or during the post-diagnosis period
3. Patients with confirmed other CLAD phenotype (e.g., CLAD-RAS) according to physician's judgment.

8.1.4. Outcomes

8.1.4.1. Primary Outcome

Table 2. Primary Objective and Primary Outcome Measure

Objective	Outcome Measure
To evaluate the FEV_1 trajectory of patients diagnosed with CLAD-BOS	Change in FEV_1 trajectory over time starting from the onset date through the end of post-diagnosis period. Personal best-FEV_1 value is defined as the mean of the 2 best post-transplant FEV_1 measurements taken at least 3 weeks apart.[3] The personal best-FEV_1 will be derived from the data collected starting from the lung transplant date or identified in clinical records according to physician judgment.

CLAD-BOS = chronic lung allograft dysfunction-bronchiolitis obliterans syndrome; FEV_1 = forced expiratory volume in 1 second

8.1.4.2. Secondary Outcomes

Table 3. Secondary Objectives and Secondary Outcome Measures

Objectives	Outcome Measures
To describe demographics of patients diagnosed with CLAD-BOS	Demographics at transplant date will include: • Age in years • Sex (men and women) • Race • Pre-transplant medical history • Date and type of lung transplant (i.e., single or bilateral) • Reason for transplantation (e.g., chronic obstructive pulmonary disease, idiopathic pulmonary fibrosis)
To describe clinical characteristics following lung transplantation for patients diagnosed with CLAD-BOS	Clinical characteristics following the lung transplantation will include: • Acute rejection events • Donor-specific antibodies • Total lung capacity (plethysmography) • Presence of lung opacities (e.g., as documented from computed tomography scans) • Sign/symptoms or other clinical records related to mobility, self-care, usual activities, pain/discomfort, anxiety/depression
To evaluate the trajectory of other relevant spirometry parameters (i.e., FVC, FEV_1/FVC, $FEF_{25-75\%}$)	Trajectories will be evaluated starting from the onset date through the end of the post-diagnosis period. Spirometry values will include (absolute value; percent value and percent predicted, where available): • FVC • FEV_1/FVC ratio • $FEF_{25-75\%}$

Objectives	Outcome Measures
To evaluate the OS of patients diagnosed with CLAD-BOS	The OS will be calculated as the time from the onset date to death by any cause. The cause of death will be documented. Patients with unknown vital status at the time of data abstraction will have their status imputed or censored.
To evaluate the time to first CLAD-BOS progression	The time to first CLAD-BOS progression will be calculated as the time from onset date to CLAD-BOS progression defined as the earliest of any of the following events: • Absolute decrease from previously available spirometry assessment in $FEV_1 \geq 10\%$ or ≥ 200 mL and absolute decrease in FEV_1/FVC of $> 5\%$ that must be confirmed by another spirometer evaluation performed at least 2 weeks apart, OR • Change in CLAD grade severity[3], OR • Re-transplantation, OR • Death from respiratory failure, OR • According to clinical judgment reporting CLAD-BOS progression in patient records. Patients with no CLAD-BOS progression at the time of data abstraction will be censored at the last date of data available.
To evaluate the cumulative incidence of CLAD-BOS progression	The cumulative incidence of CLAD-BOS progression events will be calculated from the onset date through the end of the post-diagnosis period. The CLAD-BOS progression is defined by 1 of the following events: • Absolute decrease from previously available spirometry assessment in $FEV_1 \geq 10\%$ or ≥ 200 mL and absolute decrease in FEV_1/FVC of $> 5\%$, that must be confirmed by another spirometer evaluation performed at least 2 weeks apart, OR • Change in CLAD grade severity[3], OR • Re-transplantation, OR • Death from respiratory failure, OR • According to clinical judgment reporting CLAD-BOS progression in patient records.
To evaluate the rate of hospitalization due to respiratory failure after CLAD-BOS onset	The rate of hospitalizations due to respiratory failure starting from the onset date through the end of the post-diagnosis period. The cause of hospitalization will be documented.
To evaluate the incidence of concomitant respiratory disease	The incidence rate of newly diagnosed cases of concomitant respiratory diseases that occur starting from the onset date through the end of the post-diagnosis period.
To evaluate the incidence of concomitant non-respiratory disease	The incidence rate of newly diagnosed cases of concomitant non-respiratory diseases that occur starting from the onset date through the end of the post-diagnosis period.
To describe the use of concomitant treatments and procedures for CLAD-BOS	Concomitant treatments and procedures for CLAD-BOS starting from the post-transplant date through the end of the post-diagnosis period: • Antibiotic treatments (e.g., azithromycin) • Immunosuppressants

Objectives	Outcome Measures
	• Extracorporeal photopheresis • Corticosteroids • Other

CLAD-BOS = chronic lung allograft dysfunction-bronchiolitis obliterans syndrome, $FEF_{25-75\%}$ = forced expiratory flow, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, OS = overall survival
FVC refers to the amount of air that can be forcibly exhaled from the lungs after taking the deepest breath possible. FEV_1/FVC ratio is the ratio of the forced expiratory volume in the first 1 second to the FVC of the lungs. $FEF_{25-75\%}$ refers to forced expiratory flow over the middle one-half of the FVC; the average flow from the point at which 25% of the FVC has been exhaled to the point at which 75% of the FVC has been exhaled.

Data to be collected and their timings are provided in the data collection schedule in Annex 2.

8.2. Data Sources

The study data sources will consist of medical records (including electronic and/or paper) and patient notes for the study patients. All source data will be abstracted from the medical records and patient notes and entered into the validated electronic data capture (EDC) system, CCI CCI hosted by CCI

Electronic medical records used in the creation/capture of electronic clinical data and to the control of other processes with the potential to affect patient protection and reliability of study data shall be validated according to guidelines on computerized systems and electronic data in clinical trials in order for the data to adequately support robust results and good decision making. Original source records shall comply with Attributable, Legible, Contemporaneous, Original, Accurate (ALCOA)+ principles.

Sponsor retains all data, programs and outputs generated for the study. At study close, data are uploaded from the CCI database and stored in accordance with sponsor's standard operating procedures.

The participating sites will maintain the following study documents (Site Study File): the identification log of all participating patients, original medical records, source worksheets, all original signed and dated ICFs according to local regulations, regulatory and ethics approvals, electronic copy of electronic Case Report Forms (eCRFs) including queries and audit trails, contract arrangements to allow evaluations or audits from regulatory authorities, the sponsor or its designees. These documents will be kept for all patients for a period of time specified by local regulations or specified in the Clinical Study Site Agreement between the investigator and the sponsor. No records are to be destroyed without sponsor approval and to be transferred to another location without notification to the sponsor.

The contract research organization (CRO) and sponsor will maintain study documents in electronic Trial Master File (based on CCI application) available in the event of inspection.

8.3. Sampling

Patient medical records will be reviewed for eligibility starting with the patients diagnosed with CLAD-BOS starting from 01 January 2013 and moving in chronological order to the next diagnosed patients until the target sample size of eligible patients is reached.

A quota will be applied to ensure that 80% of the total study population enrolled are recipients of a bilateral lung transplant.

8.4. Sample Size

Approximately 300 patients will be enrolled to achieve at least 200 patients providing at least 5 years of data post-CLAD-BOS onset (based on an estimated 5-year survival rate of 70% of the patients).

The sample size will provide adequate precision to estimate the FEV_1 trajectory and sufficient outcomes data. CCI [redacted]

8.5. Data Management

Each patient will be assigned a unique identification number at the time of the ICF signature or first data abstraction. This unique identification number will be used to link data to subsequent chart reviews (patient data will be pseudo anonymized). The data will be abstracted by study site staff from patient medical records into a web-based validated EDC system. The EDC system will include eCRFs which will be designed to capture the outcomes of interest.

Only authorized and trained staff of each study site will enter the data in the eCRF and resolve queries.

The qualified designee for data entry will ensure that:

- data entry is performed in a timely manner
- data entry is complete and accurate
- all eCRF data are verifiable in the source documentation
- queries are resolved and documented in a timely manner
- all completed eCRFs will be validated with electronic signature by the investigator (changes to data previously submitted will require a new electronic signature to acknowledge/approve the changes) and before any interim analysis.

The data management team of the CRO will review the data entered into the eCRFs by investigational site staff for completeness in parallel to source data verification by the assigned monitors on the study sites for accuracy (details will be provided in the Clinical Monitoring Plan). Queries are sent to the investigational sites using an electronic data query. Designated investigator site staff are required to respond to the query and confirm or correct the data.

The Monitor of the CRO is responsible for verifying the accuracy of patient data during site visits and issue queries for inconsistencies versus source documents. Monitoring details describing strategy, methods, responsibilities, and monitoring techniques (central, remote, or on-site monitoring) will be provided in the Clinical Monitoring Plan.

The investigator by signing the eCRF confirms that all recorded data are true and accurate.

Concomitant medications entered into the database will be coded using the World Health Organization Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events (AEs) will be coded using the Medical Dictionary for Regulatory Activities terminology. More details will be provided in the Data Management Plan.

After these actions have been completed and the database has been declared to be complete and accurate, it will be locked. Any changes to the database after that time can only be made by joint written agreement between the Zambon SpA Regulatory Affairs & Drug safety and the Global Chief Medical Officer and R&D Head.

8.6. Data Analysis

An overview of the analyses to be undertaken for this study is provided below. Further details of the analyses will be described in the Statistical Analysis Plan (SAP). The SAP will be issued before starting the collection of data with more technical and detailed elaboration of the principal features of statistical analyses.

8.6.1. Statistical Methods – General Aspects

This section describes the statistical analysis as foreseen at the time of planning the study. Changes, additions, and further details about the analyses will be described in the SAP. After finalization of the SAP, any additional analyses or changes to analyses that may be required will be disclosed in the Clinical Study Report (CSR).

Descriptive summary statistics for continuous variables will include the number of patients, mean, standard deviation, median, interquartile range, and range. Descriptive summary statistics for categorical variables will include frequency counts and percentages. Confidence intervals around mean or proportion will be presented where applicable.

The trajectories of FEV_1 and other longitudinal parameters will be characterized using a Linear Mixed Model (LMM) for repeated measurements, using all observed available FEV_1 measurements up to the last date of data available.

Overall survival and time to first CLAD-BOS progression will be assessed using Kaplan-Meier methods. Rates at yearly intervals will be reported along with the estimated medians and the corresponding CIs, whenever estimable. Kaplan-Meier curves will be presented along with the number of patients at risk at exact time points. For OS, patients with unknown vital status at the time of data abstraction will have their status imputed or censored. For time to CLAD-BOS progression, if the patient dies for reasons different from respiratory failure, is lost to follow-up, or the study ends before the event of interest is observed, the patient will be censored.

Incidence rates will be evaluated using negative binomial or Poisson (in case of lack of convergence) regression, including an offset for patient follow-up time. Estimations will be provided along with their 95% CIs.

Analyses will be performed using statistical analysis software (SAS), Version 9.4 or higher (SAS Institute, Cary, North Carolina).

8.6.1.1. Missing Data

Data will be analyzed for observed data only, without imputation of missing values, unless otherwise stated. Derivations with missing data for 1 or more source variables will be set to missing. Outcomes will be assessed with a LMM for repeated measurements, which does not explicitly impute the missing values, but does assume data are missing at random (MAR) and follows the trend within group. Sensitivity analyses to the MAR assumption may be performed using different approaches. Details will be provided in the SAP.

In order to mitigate against missing data, the eCRF system will use a combination of required data fields, queries (automated and manual), data range checks, and edit checks for missing or partial data fields. Missing data will generally not be imputed. The "Unknown/Not available" response option will be presented within the eCRF, and data will be summarized accordingly in the analysis tables.

8.6.1.2. Adjustment for Multiple Comparisons

Due to the descriptive nature of the study, adjustment for multiple comparisons will not be performed.

8.6.1.3. Subgroup Analyses

Subgroup analyses of main outcomes will be performed by age class, gender, race, region, and severity of disease. Statistical details and potential new subgroup definitions will be reported in the SAP.

8.6.1.4. Interim and Final Analyses

Intermediate analyses may be conducted before the ending of collection of all data, once a sufficient number of patients and variables are enrolled and collected. Intermediate analyses will not influence the subsequent collection of data and will be performed according to pre-planned analyses in the SAP.

Additional post-hoc analyses may be conducted to further explore the data based on the results obtained. Any deviations from the original SAP, including unplanned analyses, will be documented in the CSR. The final analysis will be conducted once the final datasets are extracted following the database lock.

8.7. Quality Control and Quality Assurance

Data quality in regard to data management and monitoring will be ensured as noted in Section 8.5.

The study site(s) may also be subject to quality assurance audits by Zambon SpA or designated representatives.

It is important that the investigators and their relevant personnel are available for possible audits or inspections. The investigator must permit study-related monitoring, audits, Institutional Review Board (IRB)/Independent Ethics Committee (IEC) review, and regulatory agency inspections and provide direct access to source data documents and all study documents

including ICFs where access by the above parties is permitted by patient's explicit consent except for those cases where ICF cannot be obtained or waived (e.g., dead patients).

8.8. Limitations of the Research Methods

The major strengths of this study include the collection of real-world data on the natural disease evolution in patients affected by CLAD-BOS after lung transplantation.

This is a retrospective, descriptive study and therefore subject to bias related to the sample selection and temporal measurement of outcomes.

The known limitations of this study are described below:

- Patients included in the study may ultimately only represent a sample of the entire population of patients with CLAD-BOS following lung transplantation, in that the medical records will be obtained only from study sites which are willing to participate in the study, from eligible patients in whom clinical and symptomatic outcomes were available and documented. Therefore, the findings may not be representative of the overall population of patients diagnosed with CLAD-BOS after lung transplantation.
- Selection bias is possible if the study population is not a representative of the target population (i.e., the eligible patient population), which will hence limit applicability of the results. A chief source of the bias is through the choice of study sites. It will be minimized by:
    - Enrolling all consenting (unless ICF waiver is permitted) eligible patients consecutively. Starting from 01 January 2013, all the patients available in each study site's database will be screened in a chronological order and when a patient's diagnosis of CLAD-BOS is confirmed, that patient will be consented for enrollment (regardless the length of follow-up).
    - Where ICF is required per local requirement, allowing for the collection of the reasons for refusal and basic information (based on the ethics) among those who declined to give consent. Although the possibility of collecting such information may be limited, such information (if collected) can be considered when interpreting the results.
    - The use of stratified analyses should be considered to account for potential behavioral changes of the study site staff after the initiation of the study as this might introduce bias between the data collected before and after the start of the study. Stratified analyses can account for the possibility of less documentation being available in data collected before the study start at each study site.
    - For very severe cases, death may occur before the minimum required time after lung transplant (12 months). This may introduce selection bias, but this definition aligns with the study's target population, which consists of patients who survived and were diagnosed with CLAD-BOS at least 1 year after lung transplant.
- All data captured in the study will be limited to information available in the medical records; while patient notes are often the most complete and robust source of retrospective patient data, they are limited to what was recorded at the time of the

encounter. Patient notes may have data gaps and/or variance in the way information is recorded between study sites and countries.

- Information bias is common in this kind of observational study due to the variability of data abstraction and missing data elements among study sites. It will be minimized by the use of a standard measurement instrument such as eCRF, data entry manual/training materials, and provision of appropriate training of the study site staff who will be entering the data. This will be ensured through training and monitoring for this study and minimizing missing data.
- Given that the diagnosis of CLAD-BOS is determined by physicians and OS is defined from the onset date, which will be programmatically derived, there is a chance that the CLAD-BOS diagnosis may occur earlier or, conversely, later than the onset date. This situation introduces the potential for an immortal time bias. However, such instances should be limited both in terms of the number of patients impacted and the duration from CLAD-BOS onset to physician diagnosis, thus not substantially compromising the validity of the results.

8.9. Other Aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Study Termination

This is a retrospective, observational study based on medical chart review data collection; therefore, the event to terminate the study to protect human patients is null.

9.2. Risk to Patients

This retrospective study will analyze de-identified data; therefore, the risk to patients is minimal. No efforts will be made by the sponsor, CRO, and/or study sites to re-identify patients after data have been abstracted into the EDC platform. Monitors will verify patient data with personally identifiable information (PII) on-site for study purpose only and they are bound to confidentiality and trained on General Data Protection Regulation (GDPR) or Health Insurance Portability and Accountability Act (HIPAA) in the US.

9.3. Personally Identifiable Information

All parties will ensure protection of PII in agreement with GDPR and HIPAA and will not include names on any sponsor forms, reports, publications, or in any other disclosures. In case of data transfer, the sponsor and CRO will maintain high standards of confidentiality and protection of PII. The PII such as name, full date of birth, social security number, street address, and email address will not be collected in the study.

De-identified study data will be maintained on a secure server hosted by CCI Data Center. Any study results presented in medical journals or scientific meetings will be summarized. No individual patient data will be presented.

9.4. Ethical Conduct of the Study

The observational study will be performed as far as applicable in accordance with ethical principles that are consistent with the Declaration of Helsinki, International Council for Harmonisation-Good Clinical Practices (ICH-GCP), in compliance with Good Pharmacoepidemiology Practices (GPP), and the applicable legislation on observational studies.

The investigator will perform the observational study in accordance with the regulations and guidelines governing medical practice and ethics in the country of the observational study and in accordance with currently acceptable techniques and expertise.

The study procedures outlined in this protocol will be conducted in accordance with the Code of Federal Regulations (CFR) governing Protection of Human Subjects (21 CFR 50), Financial Disclosure by Clinical Investigators (21 CFR 54), Institutional Review Boards (21 CFR 56), as appropriate. In the EU, local ethical regulations will be followed.

In accordance with the US CFR Title 21 Section 56 (21 CFR 56), or the local EU requirements for observational studies, the protocol and the ICF (where applicable) will be reviewed and approved by the IRB or IEC or given a favorable opinion in writing and Health Authority notified where required. The sponsor will supply relevant material for the protocol's review and approval by the IRB/IEC. Verification of the IRB/IEC's unconditional approval of the protocol and the written ICF (where applicable) will be transmitted to the sponsor/CRO/investigator.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval/favorable opinion except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the observational study. Such protocol amendment will be submitted to the IRB/IEC and written verification that the amendment was submitted should be obtained.

In case of non-substantial protocol amendments which do not require IRB/IEC and/or Health Authority's approval, the reasoning should be documented, referenced with applicable laws and regulations (if any), and signed by the responsible managers.

The IRB/IEC will be informed of subsequent protocol amendments. Approval for protocol amendments will be transmitted in writing to the sponsor/CRO/investigator. If requested, the investigator will permit audits by the IRB/IEC and regulatory inspections by providing direct access to source data/documents.

9.5. Informed Consent

The ICF will be collected according to local regulations and requirements, if applicable for this type of study.

As this is a retrospective, observational study based on medical chart review data collection, informed consent may not be applicable in some countries depending on local regulations (i.e., ICF waiver).

For countries where informed consent is required from patients, an ICF in local language will be provided by sponsor/CRO to the participating study sites following IRB/IEC approval before protocol-specific data are collected.

If required per local regulations for the collection of anonymized data from patients' medical records, and unless a consent waiver is granted by IRB/IEC, the investigator at each study site will ensure the patient or the legally authorized representative is given full and adequate oral and written information about the nature, purpose, possible risks, and benefits of the study. Patients must also be notified that they are free to withdraw from the study at any time. The patients and the legally authorized representative should be given the opportunity to ask questions and allowed time to consider the information provided. In accordance with 21 CFR 50, the ICF is to be signed and personally dated by the patient or legally authorized representative and by the person who conducted the informed consent discussion. The acquisition of informed consent is to be documented in the patient's medical records. The original signed ICF is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the patient or legally authorized representative. If a potential patient is illiterate or visually impaired and does not have a legally authorized representative, the investigator must provide an impartial witness to read the ICF to the patient and must allow for questions. Thereafter, both the patient and the witness must sign the ICF to attest that informed consent was freely given and understood.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

For the secondary data collection in this study, reporting of AEs within the database is limited to all serious adverse drug reactions, adverse drug reactions, and AEs of special interest (e.g., exposure during pregnancy or lactation, abuse, misuse, extravasation, medication error, overdose, lack of efficacy, unexpected beneficial effect, and occupational exposure), if such an event is clearly identified in the patient's medical record, only if it is related to Zambon products approved in the participating country. The data captured in the medical record will constitute all clinical information known regarding these AEs and no follow-up will be conducted.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

After conclusion of this study, a CSR will be prepared by the sponsor or designee. The first publication of the clinical study will comprise of data from the entire clinical study population enrolled at all study sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by investigators or their representatives will require pre-submission review by the sponsor. For more details regarding publications, refer to the Clinical Study Agreement/Investigator Study Agreement.

The results of the clinical study will be published and/or presented in scientific meetings in a timely manner. Any formal publication of clinical study results will be a collaborative effort between the sponsor and the investigator(s). All manuscripts and abstracts will be reviewed and approved in writing by the sponsor prior to submission. Any formal publication, including abstracts, posters, and manuscripts that may be considered will follow guidelines established by the International Committee of Medical Journal Editors Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals.[11]

Policies regarding the publication of the clinical study results are defined in the Clinical Investigator's Agreement.

The data that serves as the external control arm will be made available to the relevant agencies, including the medical journal(s) involved.

12. REFERENCES

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ANNEX 1. ADDITIONAL DOCUMENTS

Not applicable.

ANNEX 2. DATA COLLECTION SCHEDULE

	Study Observation Period		
Data to be collected	**Pre-diagnosis Period[a]**	**Index Date**	**Post-diagnosis Period[b]**
Lung transplantation date	X		
CLAD-BOS diagnosis		X	
Informed consent/notification (where applicable)	X		
Inclusion/exclusion criteria	X		
Enrollment	X		
Demographics	X		
Pre-transplant medical history	X		
Date and type of lung transplant (i.e., single or bilateral)	X		
Reason for transplantation	X		
Acute rejection events	← Permanently throughout the complete study period →		
Donor-specific antibody assay	← Permanently throughout the complete study period →		
Plethysmography	← Permanently throughout the complete study period →		
Computed tomography scans (presence of pulmonary opacities)	← Permanently throughout the complete study period →		
Sign/symptoms or other clinical records related to mobility, self-care, usual activities, pain/discomfort, anxiety/depression	← Permanently throughout the complete study period →		
FEV_1	← Permanently throughout the complete study period →		
FVC	← Permanently throughout the complete study period →		
$FEF_{25-75\%}$	← Permanently throughout the complete study period →		
CLAD-BOS progression evaluation[c]	← Permanently throughout the complete study period →		
Hospitalization due to respiratory failure	← Permanently throughout the complete study period →		
Concomitant respiratory and non-respiratory diseases	← Permanently throughout the complete study period →		

	Study Observation Period		
Data to be collected	**Pre-diagnosis Period[a]**	**Index Date**	**Post-diagnosis Period[b]**
Concomitant treatments and procedures for CLAD-BOS[d]	← Permanently throughout the complete study period →		
Death due to any cause	← Permanently throughout the complete study period →		

CLAD-BOS = chronic lung allograft dysfunction-bronchiolitis obliterans syndrome, FEV_1 = forced expiratory volume in 1 second, $FEF_{25-75\%}$ = forced mid-expiratory flow, FVC = forced vital capacity

[a] Pre-diagnosis period is the time from the lung transplant date up to but not including the index date.

[b] Post-diagnosis period is the time from and including the index date through the last date of data available or death, whichever occurs earlier.

[c] CLAD-BOS progression evaluation according to clinical judgment reported in patient records will be collected.

[d] Concomitant treatments and procedures for CLAD-BOS may include antibiotic treatments (e.g., azithromycin), immunosuppressants, extracorporeal photopheresis, corticosteroids, and other.

ANNEX 3. AMENDMENTS AND HISTORY OF CHANGES

Protocol Version and date	Reason for Changes
1.0, 05 March 2024	Not Applicable