Zambon SpA

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

Protocol: Z8000N01

Statistical Analysis Plan

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Abbreviations

AMR	Antibody-Mediated Rejection
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CLAD-BOS	Chronic Lung Allograft Dysfunction Bronchiolitis Obliterans Syndrome
eCRF	electronic Case Report Form
ENR	All Patients Enrolled Set
EU	European Union
FAS	Full Analysis Set
$FEF_{25-75\%}$	Forced Expiratory Flow Over the Middle one-half of the FVC
FEV_1	Forced Expiratory Volume in 1 Second
FVC	Forced Vital Capacity
KR	Kenward–Roger
LMM	Linear Mixed Model
LSM	Least Square Means
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
OS	Overall Survival
PT	Preferred Term
Q1	First Quartile
Q3	Third Quartile
RAS	Restrictive Allograft Syndrome
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SD	Standard Deviation
SOC	System Organ Class
TFL	Table, Figure, Listing
TLC	Total Lung Capacity
US	United States
WHO-DD	World Health Organization Drug Dictionary

1 Protocol Summary

Primary Objective	The primary objective of this study is to evaluate the forced expiratory volume in 1 second (FEV_1) trajectory of patients diagnosed with chronic lung allograft dysfunction bronchiolitis obliterans syndrome (CLAD-BOS).
Study Design	This is a retrospective, multinational, multicenter chart review study. The observational period for each patient will be from lung transplant date until last date of data available or death, whichever occurs earlier. 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 for a total of approximately 300 patients.
Primary Endpoint	Change in FEV_1 trajectory over time starting from the onset date through the end of post-diagnosis period.

Secondary Endpoints	• Demographics at transplant date
	• Clinical characteristics following the lung transplantation
	• Change in trajectories from the onset date through the end of post-diagnosis period for the following parameters:
	  ○ Forced vital capacity (FVC)
	  ○ FEV_1/FVC ratio
	  ○ Forced expiratory flow over the middle one-half of the FVC ($FEF_{25-75\%}$)
	• Overall survival (OS) from the onset date to death by any cause
	• The time to first CLAD-BOS progression from onset date
	• The cumulative incidence of CLAD-BOS progression events from onset date
	• The rate of hospitalizations due to respiratory failure starting from the onset date through the end of the post-diagnosis period.
	• The incidence rate of newly diagnosed cases of concomitant respiratory and non-respiratory diseases that occur starting from the onset date through the end of the post-diagnosis period.
	• Concomitant treatments and procedures for CLAD-BOS starting from the post-transplant date through the end of the post-diagnosis period

Follow-Up Schedule	• Pre-diagnosis period: The period of time from the lung transplant date up to, but not including the index date. • Index date: Date of CLAD-BOS clinician diagnosis. • Onset date: Date when the patient reaches for the first time a FEV_1 value ≤ 80% vs. personal best-FEV_1 (hereafter, 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. • 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.

2 Introduction

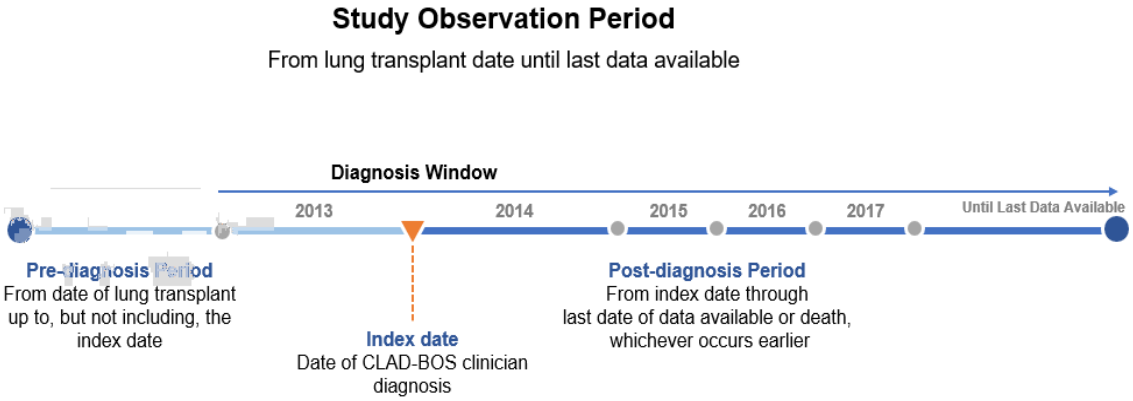
This Statistical Analysis Plan (SAP) addresses the planned analyses for the BOSTON EVOLUTION study based on the study protocol version 1.0 dated 05 March 2024. Specified analyses may be used for scientific presentations and/or manuscripts, and regulatory submissions. The analysis will be based on the data available up to the date of data abstraction. Mock shells for tables, figures, and listings (TFLs) are prepared along with the SAP text and included in a different document.

3 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 (Figure 1), 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.

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.

Figure 1. Study Design Schema



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

3.1 STUDY TIME PERIOD AND KEY DEFINITION

The observational period for each patient will include the following time periods:

CLAD-BOS diagnosis window

01 January 2013 through most recent data available.

Index date

Date of CLAD-BOS clinician diagnosis.

The closest spirometry assessment within ±1 month from the date of diagnosis will be considered for setting the spirometry parameters at diagnosis.

Personal best-FEV_1 date/value

The personal best-FEV_1 date is the first of the two post-transplant dates used to calculate patient's personal best FEV_1 value. For each patient, the personal best FEV_1 date/value:

- will set as identified in clinical records according to the physician's judgment, or
- will be derived from the data collected starting from the lung transplant date until the date of diagnoses (excluded).

To calculate the best post-transplant measurement(s), the 'personal best-FEV_1 value' form in the eCRF will be prioritized and only when no measurement are identified therein, the 'spirometry' form will be considered. The best-FEV_1 value post-transplant is defined as the mean of the first best FEV_1 and second best FEV_1 values post-transplant.

Note (applicable to identification of best-FEV_1 value post-transplant from the 'spirometry' form):

- The two best post-transplant measurements should have been taken before the date of diagnosis.
- To calculate the best FEV_1 value, at least one FEV_1 assessment per year (on average) must be conducted between the transplant and diagnosis.
- The two best post-transplant measurements should have been taken at least 3 weeks (i.e., > 21 days) apart.
- If a second assessment within this timeframe (> 21 days) is not available, assessments performed ≤ 21 days apart can be considered.
- If there is still no assessment meeting this requirement, then a single assessment can be used to define the best post-transplant measurement.
- In addition, once an onset date/value is defined, any subsequent values that exceed the initial best FEV_1 values (prior to CLAD-BOS onset) will not be considered.

- The derived best FEV_1 must be greater than the FEV_1 at diagnosis, otherwise it will be set as missing. Only applies when FEV_1 at diagnosis is not missing.

Onset date/value

Date when the patient reaches for the first time a FEV_1 value ≤ 80% vs. best-FEV_1, confirmed by a consecutive value ≤ 80% 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 best post-transplant FEV_1 date.

The onset value is defined as the first confirmed occurrence (after best post-transplant FEV_1 date) of a FEV_1 absolute value ≤ 80% vs. the best FEV_1 absolute value post-transplant.

Note:

- To validate the onset value, it must be confirmed by another consecutive FEV_1 value ≤ 80% vs. the best-FEV_1 value post-transplant occurring at least 3 months (i.e., > 91 days) apart.
- If the next FEV_1 value after 3 months is >80% vs. the best-FEV_1 value post-transplant, the onset value needs to be re-calculated using subsequent measurements.If the onset is not derivable (for any reason), then it will be set at diagnosis.

The data collected at the onset date will be considered as baseline for all endpoints with the exclusion of some secondary endpoints (specified in 4.2.1 and 4.2.2) for which the reference start date is the lung transplant date.

Other spirometry dates/values

For the other spirometry parameters (FVC, FEV_1/FVC, $FEF_{25-75\%}$) the best-post transplant and onset values will be those measured during the same spirometry assessment where the best post-transplant and onset FEV_1 values were measured.

Observation period

- 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 end of the observation period.

The observation period will extend until the earliest of the following events:

- date of death

- the last available date within the eCRF where the patient was known to be alive will be considered the date of last contact

4 Endpoint Analyses

4.1 PRIMARY ENDPOINT

The primary endpoint is defined as the change in FEV_1 trajectory over time starting from the onset date through the end of post-diagnosis period.

Onset and best-FEV_1 values will be programmatically derived as described in Section 8. If either the onset or the best FEV_1 value post-transplant cannot be derived, the patient will be excluded from the corresponding analysis.

4.1.1 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. Assuming a standard deviation (SD) of 700 mL for the FEV_1 from onset date (per BOSTON-1 and BOSTON-2 studies), the half-width of the 95% confidence interval (CI) would be a maximum of approximately 100 mL.

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

4.1.2 Primary Analysis

The primary analysis will be carried out using a linear mixed model (LMM) with random coefficients.

The dependent variable is the absolute change from onset of FEV_1 measurements through the end of post-diagnosis period (variable name in Statistical Analysis Software (SAS): `CHG`). As there are no mandated visits in this study, FEV_1 measurements may occur at various times during the observation period. A random coefficients model considering time from onset as continuous variable will be used.

The LMM model will include patient (USUBJID) and time in years (TIME) as random effects. The fixed effects will include time (months) from onset (TIME), FEV_1 onset value (BASE), TIME*BASE interaction, age class (< 55 years, ≥ 55 years; AGE_CL), region (EU, US; REGION), phenotype at CLAD-BOS onset (Obstructive FEV_1/FVC <0.7, Non-obstructive FEV_1/FVC >=0.7; PHEN_CL) use of azithromycin at CLAD-BOS onset (Yes, No; AZIFL). CLAD-BOS FEV_1/FVC phenotype and use of azithromycin at CLAD-BOS onset will be included in the analysis if the proportion of patients in either of the two categories falls within the range of 10% to 90%.

An unstructured covariance pattern will be used to estimate the variance–covariance. If the model leads to convergence issues in the estimation, the following model selection stages will be considered with additional flexibility incorporated should the need arise:

1. Include all covariates except “use of azithromycin at CLAD-BOS onset (Yes, No)” in the model, if convergence is reached, proceed with the analysis; otherwise

2. exclude “use of azithromycin at CLAD-BOS onset (Yes, No)” and “age class (< 55 years, ≥ 55 years”. If convergence is reached, proceed with the analysis; otherwise

3. exclude “use of azithromycin at CLAD-BOS onset (Yes, No)”, “age class (< 55 years, ≥ 55 years” and “region (EU, US)”. If convergence is reached, proceed with the analysis; otherwise

4. Change the covariance pattern to a heterogeneous Toeplitz structure on the full model, and proceed with steps 1 to 3 in case of persistent non-convergence issues. If convergence is reached, proceed with the analysis; otherwise

5. Repeat the process described in (4) with an auto regressive (1) structure, followed by a compound symmetry structure.

The model results will be summarized in terms of mean rate of decline (with SE) per year and corresponding 95% CIs along with estimates of FEV_1 at each year below the 75th percentile of time (in years) for the observations included in the model, e.g. if the 75th percentile for time is 4.5 years then estimates up to year 4 will be presented.. The Kenward–Roger (KR) method for calculating the denominator degrees of freedom will be used.

Normality assumption of the outcome (CHG) will be assessed through the Kolmogorov-Smirnov test, following the procedure:.

1) Perform a Kolmogorov-Smirnov test to statistically test the normality of the residuals on the raw data.

2) If the test is not significant, indicating normality, then the raw data will be used in the model. Otherwise if the test is significant, indicating non-normality, the Kolmogorov-Smirnov test will be undertaken on the log transformed data.

3) If the Kolmogorov-Smirnov test on the log transformed data is not significant, indicating normality, then the log transformed data will be used in the model. Otherwise,

4) If also the Kolmogorov-Smirnov test on the log transformed data is significant, indicating non-normality, then the data (raw or log transformed) with the smallest Kolmogorov-Smirnov test statistics (D) will be used in the model. Note, change in FEV_1 is expected to be close to normally distributed and not expected to be skewed. It is possible for the Kolmogorov-Smirnov test to indicate that the change in FEV_1 is not normal, especially due to the high number of observations. The LMM is robust to mild departures from normality.

If a log transformation is deemed appropriate, it will be applied to the data using the following algorithm:

$$\text{l_chg} = \log\left(CHG + |\min CHG\ values| + 1\right)$$

In cases where a log-transformed analysis is performed, the results and standard errors (SE) will be reported on the original scale. The p-values, however, will be derived from the log-transformed analysis. If log-transformed model will never converge, only the original model selection will be considered, and its p-value will be shown.

The example SAS code of the primary analysis is reported below:

```
PROC MIXED DATA= adxx;
  CLASS USUBJID AGE_CL REGION PHEN_CL AZIFL;
  MODEL <CHG or l_CHG>= TIME BASE TIME*BASE AGE_CL REGION PHEN_CL
AZIFL
  /solution DDFM = KR;
  RANDOM INT TIME / SUBJECT = USUBJID TYPE=UN;
 ESTIMATE "FEV1 yearly change" TIME 1 TIME*BASE <mean base>
  ESTIMATE "Change in FEV1 at xx " intercept 1 TIME <nominal
  timepoint> BASE <mean base> TIME*BASE %eval(<nominal
  timepoint>*<mean base>) / CL E;
RUN;
```

Descriptive statistics will be summarized in a different table for the absolute value and the change from onset at each analysis timepoint (defined in Section 5.7). Details regarding the statistical considerations for descriptive statistics are provided in Section 4.1. All FEV_1 results (either considered for the main analysis or not) will be listed.

4.1.3 Sensitivity Analysis

To investigate the impact of informative events preventing data collection, missing FEV_1 values at analysis timepoints following death or re-transplantation events will be imputed as zero herein. The statistical assessment will follow the same approach as described above for the primary analysis in Section 4.1.2.

4.2 SECONDARY ENDPOINTS

4.2.1 Demographics, medical history and CLAD-BOS characteristics

The following variables will be summarized as collected in the electronic case report form (eCRF) or as flagged, "[derived]", based on the derivation details provided in Section 8.

Demographics

- Age at lung transplantation (years) *[derived]*
- Age class at lung transplantation (<55 years, ≥55 years)
- Age at CLAD-BOS diagnosis (years) *[derived]*
- Age class at CLAD-BOS diagnosis (<55 years, ≥55 years)
- Sex (Female, Male)
- Ethnicity (Hispanic or Latino, Not Hispanic or Latino, Unknown)

- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other, Not to be collected per local regulation)
    - If Asian, specify (Asian Indian, Chinese, Japanese, Korean, Thai, Other Asian)

Lung transplant history

- Type of lung transplantation (Single, Bilateral)
- Reason for lung transplantation (Chronic obstructive pulmonary disease, Idiopathic pulmonary fibrosis, Cystic fibrosis and bronchiectasis for other causes, Pulmonary hypertension, Sarcoidosis, Lymphangioleiomyomatosis, Bronchoalveolar carcinoma, Other)
- Time from lung transplantation to CLAD-BOS onset (months) *[derived]*

Pre-transplant Medical History

Specified medical history reported terms will be coded to “Preferred Term” (PT) and associated primary “System Organ Class” (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version 27.0 or higher and will be summarized by SOC and PT. Conditions that are still ongoing at CLAD-BOS diagnosis (as indicated in the eCRF and/or with a stop date>CLAD-BOS diagnosis date) or for which the exact timing could not be established will be categorized as ongoing at CLAD-BOS diagnosis and will additionally be displayed separately.

Best Post-Transplant Spirometry Parameters

- FEV_1 (absolute) best post-transplant (liters) *[from eCRF or derived]*
- FEV_1 (predicted) best post-transplant (liters) *[from eCRF or derived]*
- FEV_1 (% predicted) best post-transplant (%) *[from eCRF or derived]*
- FVC (absolute) best post-transplant (liters) *[from eCRF or derived]*
- FVC (predicted) best post-transplant (liters) *[from eCRF or derived]*
- FVC (% predicted) best post-transplant (%) *[from eCRF or derived]*
- FEV_1/FVC (absolute) best post-transplant (liters) *[from eCRF or derived]*
- FEV_1/FVC (predicted) best post-transplant (liters) *[from eCRF or derived]*
- FEV_1/FVC (% predicted) best post-transplant (%) *[from eCRF or derived]*
- $FEF_{25-75\%}$ (absolute) best post-transplant (liters) *[from eCRF or derived]*
- $FEF_{25-75\%}$ (predicted) best post-transplant (liters) *[from eCRF or derived]*
- $FEF_{25-75\%}$ (% predicted) best post-transplant (%) *[from eCRF or derived]*

- Time from lung transplantation to best post-transplant spirometry (months) *[derived]*

CLAD-BOS characteristics

- CLAD-BOS grade at clinician diagnosis (CLAD 1, CLAD 2, CLAD 3, CLAD 4, Other, Not available)
- FEV_1 at CLAD-BOS onset (absolute) (liters)
- FEV_1 at CLAD-BOS onset vs. best post-transplant FEV_1 (%) *[derived]*
- Rate of decline from transplant to onset (continuous) *[derived]*
- FEV_1 at best post-transplant vs. predicted FEV_1 at best post-transplant *[derived]*
- Presence of Baseline Lung Allograft Dysfunction (BLAD) at best post-transplant FEV_1 (two consecutive FEV_1 predicted and FVC predicted <80% - present, FEV_1 predicted or FVC predicted ≥80% not present or not consecutive) *[derived]*
- FVC at CLAD-BOS onset (absolute) (liters)
- FVC at CLAD-BOS onset vs. best post-transplant FVC (%) *[derived]*
- FEV_1/FVC at CLAD-BOS onset (absolute)
- FEV_1/FVC at CLAD-BOS onset vs. best post-transplant FEV_1/FVC (%) *[derived]*
- FEV_1/FVC Phenotype at CLAD-BOS onset (Obstructive FEV_1/FVC <0.7, Non-obstructive FEV_1/FVC ≥0.7) *[derived]*
- $FEF_{25-75\%}$ at CLAD-BOS onset (absolute) (liters)
- $FEF_{25-75\%}$ at CLAD-BOS onset vs. best post-transplant $FEF_{25-75\%}$ (%) *[derived]*

4.2.1.1 Analysis

Demographics, pre-transplant medical history, transplantation details and CLAD-BOS characteristics at clinician diagnosis will be summarized with descriptive statistics (Section 5.1) and listed. 5.1

4.2.2 Clinical characteristics following lung transplantation

The following variables will be summarized as collected in the eCRF.

Acute rejection events

- Number of patients with any acute rejection following lung transplantation (0, 1, ≥2)

- Number of acute rejections following lung transplantation (continuous)
- Acute rejection treated (Yes, No, Unknown)
- Biopsy performed (Yes, No, Unknown)
  - If yes (Lung, Other)
- Acute rejection grading (0: None, A1: minimal, A2: mild, A3: moderate, A4: severe, Unknown)
- Number of patients with any airway inflammation following lung transplantation (0, 1, ≥2)
- Number of airway inflammation following lung transplantation (continuous)
- Airway inflammation grading (B0: none, 1R: low grade, 2R: high grade, X: upgradeable, Unknown)Number of patients with any chronic airway rejection – obliterative bronchiolitis following lung transplantation (0, 1, ≥2)
- Number of chronic airway rejection – obliterative bronchiolitis following lung transplantation (continuous)
- Chronic airway rejection – obliterative bronchiolitis grading (0 – absent, 1 – present, Unknown)
- Number of patients with any chronic vascular rejection following lung transplantation (0, 1, ≥2)
- Number of chronic vascular rejection following lung transplantation (continuous)
- Number of patients with chronic vascular rejection – accelerated graft vascular sclerosis
- Chronic vascular rejection – accelerated graft vascular sclerosis (- item present, + item absent or missing, Unknown)
- Clinical pulmonary antibody-mediated rejection (AMR) (Definite, Probable, Possible, Unknown) *[derived]*
- Sub-clinical pulmonary AMR (Definite, Probable, Possible, Unknown) *[derived]; derivation* from the following items:
  - Antibody-mediated rejection diagnosed (Yes, No, Unknown)
  - Allograft dysfunction (Present, Absent, Unknown, Missing)
  - Other causes excluded (Present, Absent, Unknown, Missing)
  - Lung histology (Present, Absent, Unknown, Missing)
  - Lung biopsy C4d (Present, Absent, Unknown, Missing)
  - Donor-specific antibodies (Present, Absent, Unknown, Missing)
- Donor-specific antibody taken (Yes, No, Unknown)
- Donor-specific antibody result (Negative, Positive, Unknown)

Plethysmography following lung transplantation

- Plethysmography performed (Yes, No, Unknown)
- Residual volume (liters)
- Functional residual capacity (liters)
- Total lung capacity (TLC) (liters)
- Was TLC used to define patient baseline (best post-transplant value) (Yes, No, Unknown)
- Present Presence of TLC >10% compared to baseline (best post-transplant value) (Yes, No, Unknown)
- Plethysmography results and patient's overall assessment compatible with CLAD-BOS phenotype (Yes, No, Unknown)
    - If No, which is the most likely alternative CLAD phenotype (RAS, Mixed, Undefined, Unclassifiable, Unknown)

CT-scan

- CT-scan performed (Yes, No, Unknown)
    - If yes, any CT opacities present (Yes, No, Unknown)
    - CT scan results and patient’s overall assessment compatible with CLAD-BOS phenotype (Yes, No, Unknown)

Signs, Symptoms or Other Clinical Findings

- Mobility (Yes, No, Unknown)
    - Number of occurrences (continuous)
    - Mobility results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)
- Self-care (Yes, No, Unknown)
    - Number of occurrences (continuous)
    - Self-care results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)
- Usual activities (Yes, No, Unknown)
    - Number of occurrences (continuous)
    - Usual activities results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)

- Pain (Yes, No, Unknown)
  - Number of occurrences (continuous)
  - Pain results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)
- Discomfort (Yes, No, Unknown)
  - Number of occurrences (continuous)
  - Discomfort results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)
- Anxiety (Yes, No, Unknown)
  - Number of occurrences (continuous)
  - Anxiety results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)
- Depression (Yes, No, Unknown)
  - Number of occurrences (continuous)
  - Depression results compared to previous evaluation (Sign/symptoms worsened, Sign/symptoms improved, Stable, Unknown)

4.2.2.1 Analysis

The clinical characteristics detailed in Section 4.2.2 along with the number of patients with any acute rejection, airway inflammation, chronic airway rejection, chronic vascular rejection and any signs/symptoms or other clinical findings will be summarized with descriptive statistics (see Section 5.1) and listed. 5.1

4.2.3 Trajectory of other relevant spirometry parameters

FVC, FEV_1/FVC and $FEF_{25-75\%}$parameters trajectories are defined as the change in the value trajectory over time starting from the onset date through the end of post-diagnosis period (see Section 8).

4.2.3.1 Analysis

The analysis of the other spirometry parameters trajectories will follow the same approach described in Section 4.1.2 for the primary endpoint.

4.2.3.2 Sensitivity Analysis

The sensitivity analysis will follow the same approach described in Section 4.1.3 for the primary endpoint.

4.2.4 Overall survival

The OS is defined as the time, in months, from CLAD-BOS onset to death by any cause (see Section 8) calculated after the imputation of partial dates (see Section 5.6):

- (Date of death by any cause or censor – onset date + 1) / 30.4375.

4.2.4.1 Analysis

The OS analysis will follow the approach described in Section 5.1 for time to event data.
Summaries will include the following:

- Deaths
  - Death from respiratory failure
- Censored patients: in the absence of death, the patient data will be censored at the last available date (i.e., the maximum date reported in the eCRF)
  - Alive at the data abstraction date
  - Unknown at the data abstraction date

4.2.4.2 Sensitivity Analysis

The sensitivity analysis will consider patients with an unknown status at the data abstraction date as deceased, with their last available date being considered the date of death.

4.2.5 Time to first CLAD-BOS progression

The time to first CLAD-BOS progression is defined as the time, in months, from CLAD-BOS onset to progression. (see Section 8) calculated after the imputation of partial dates (see Section 5.6):

- (Date of first CLAD-BOS progression or censor – onset date + 1) /30.4375.

4.2.5.1 Analysis

The analysis will follow the approach described in Section 5.1 for time to event data. The number and percentage of patients with the event and censored will be presented for each specific category:

- CLAD-BOS progression

- Absolute decrease from previously available spirometry assessment in FEV_1 ≥10% or ≥ 200 mL and absolute decrease in FEV_1/FVC of > 5%, with a confirmation spirometry assessment in a subsequent visit at least 3 weeks (i.e., > 21 days); where previously available spirometry assessment reflects either:
    a) The onset value for the first CLAD-BOS progression
    b) The value observed at the previous progression for the second and subsequent progressions
- Change in CLAD grade severity
- Re-transplantation
- Death from respiratory failure
- According to clinical judgment reporting CLAD-BOS progression in patient records
    - Reason not indicated in the physician's chart
    - Decrease in FEV_1
    - Change in CLAD grade severity
    - Re-transplantation
    - Death from respiratory failure
    - Other

o Censored patients
- Not progressed at the last spirometry evaluation
- Death from other reasons apart from respiratory failure

4.2.6 Cumulative incidence of CLAD-BOS progression

The cumulative number of CLAD-BOS progressions that occurred from CLAD-BOS onset to the end of the study period will be derived for each patient by adding up all the observed events.

4.2.6.1 Analysis

The CLAD-BOS progression rate will be estimated as described in Section 5.1 for the analysis of count data. Descriptive statistics (see Section 5.1) and model results will be displayed in the same table.

5.1

4.2.7 Hospitalizations due to respiratory failure

The cumulative number of hospitalizations due to respiratory failure occurred from CLAD-BOS onset to the end of the study period will be derived for each patient (based on the eCRF form) adding up all the observed occurrences. The reason for hospitalization will be validated from a medical team before the database lock in order that only the hospitalizations due to respiratory failure are summarized.

Hospitalization summary will include the status after discharge from hospital (Dead, Discharge home, Discharged to home health care, Discharged to nursing home care, Discharged to long term care, Other).

4.2.7.1 Analysis

The analysis will follow the procedure described in Section 5.1 for count data. Descriptive statistics (see Section 5.1) and model results will be displayed in the same table. All details regarding hospitalizations will be provided in a listing. 5.1

4.2.8 Concomitant respiratory and non-respiratory disease

Concomitant respiratory and non-respiratory disease (as indicated in the eCRF) will be coded to PT and associated primary SOC using MedDRA version 27.0 or higher. If the stop date of concomitant diseases is reported (or partially reported) before the CLAD-BOS diagnosis date, they will not be included in the summary table (but listed). If the exact timing cannot be established, they will be categorized as concomitant.

The list of concomitant disease collected per physician's will be validated by Zambon medical unit before database lock.

4.2.8.1 Analysis

The number and percentage of patients with any concomitant respiratory and non-respiratory diseases will be summarized overall and classified by SOC and PT. Data listings will display all collected concomitant respiratory, non-respiratory diseases and ADRs, along with their details.

4.2.9 Concomitant treatments and procedures for CLAD-BOS

Concomitant treatments and procedures following lung transplantation will be summarized as collected in the eCRF. If the stop date of concomitant treatments or the procedure date are

reported before the CLAD-BOS diagnosis date they will not be tabulated as concomitant, However, If the exact timing cannot be established, they will be categorized as concomitant.

Concomitant procedures and treatments for CLAD-BOS following lung transplantation

- Number of patients with any concomitant procedure for CLAD-BOS
  - Re-transplantation
  - Extracorporeal photopheresis
  - Other
- Number of patients with any concomitant treatment for CLAD-BOS
- Medication category (Antibiotic treatments, Immunosuppressants, Corticosteroids, Other)
- Treatment (ATC class) by medication category:
  - Antibiotic treatments: Azithromycin (J01FA10)
  - Immunosuppressants: Calcineurin inhibitors (L04AD) including Tacrolimus (L04AD02) and Cyclosporine (L04AD01), Mycophenolate (L04AA06), Azatriopine (L04AX01), Selective immunosuppressants not including Mycophenolate (L04AA), Tumor necrosis factor alpha (TNF-α) inhibitors (L04AB), Interleukin inhibitors (L04AC)
  - Corticosteroids: Glucocorticosteroids (H02AB)
- Number of concomitant treatments [continuous]
- Total daily dose (mg) for each category
  - Dose reported in (g) will be converted to (mg) as follows: mg = g / 1000
  - Dose reported in (ug) will be converted to (mg) as follows: mg = 1000 * ug
- Route (PO (By Mouth), IV (Intravenous), IM (Intramuscular), SL (Sublingual), SC (Subcutaneous), Intradermal, Transdermal, Topical, Rectal, Vaginal, Ocular / Ophthalmic, OTIC, Inhalation, Nasal, Intrathecal, Intra-Arterial, Other) Note: Only drugs received via the following routes will be summarized in a table, with all collected medications listed: PO (By Mouth), IV (Intravenous), IM (Intramuscular), SL (Sublingual), SC (Subcutaneous]
- Frequency (1 time per week, BD; Twice per day, Intermittent, BID; 2 times per day, PRN; As needed, QD; Once a day, QID; 4 times per day, TID; 3 times per day, Unknown, Other)

Concomitant treatments for CLAD-BOS following lung transplantation will be coded to Anatomical Therapeutic Chemical (ATC) classification level 1 (anatomical main group) and 2 (therapeutic

main group) and PT using the World Health Organization Drug Dictionary (WHO-DD) version (March 2024) or higher.

4.2.9.1 Analysis

Concomitant treatments and procedures for CLAD-BOS following lung transplantation will be summarized using descriptive statistics (see Section 5.1). 5.1The number of patients with concomitant treatments by ATC levels 1 and 2 and PT will be summarized in a separate table. Data listings will display all collected concomitant treatments and procedures, along with their details.

5 Analytics Methods

5.1 GENERAL STATISTICAL CONSIDERATIONS

Continuous data will be summarized with descriptive statistics including number of observations (n), mean, SD, median, first quartile (Q1), third quartile (Q3), minimum and maximum values. The minimum and maximum will be reported to the same number of decimal places as the raw data provided in the eCRF. The mean and median will be reported to 1 more decimal place than the raw data provided in the eCRF. The SD will be reported to 2 more decimal places than the raw data provided in the eCRF. If there are no observations, then not available abbreviation, 'NA', will be displayed with no other statistics. If there is only 1 observation, the SD will be displayed with 'NA'.

Categorical variables will be summarized with frequency counts and percentages (%).Whenever a missing response was allowed in the eCRF, the percentages will not include the missing category and will be calculated over the number of patients with available (non-missing) data and the count of missing observations will be provided. Percentages will be presented to 1 decimal place. Percentages equal to 100 will be presented as 100% and a '0' will be presented for zero frequencies.

For time-to-event variables, cumulative event-free survival times will be evaluated using the Kaplan-Meier method. A frequency table showing the number of events and censored patients by group will be presented, if relevant, along with the event-free rates at meaningful intervals as well as Q1, median and Q3 (and two-sided 95% CI). Kaplan-Meier graphs will be presented along with the number of patients-at-risk at specified timepoints. Unless otherwise specified, patients who are free from event will be censored at the last available date (i.e., the maximum date reported in the eCRF).

Count data (CLAD-BOS progression and hospitalization rates) per patient-year and 95% CIs will be estimated using negative binomial models (or Poisson models in case of estimation issues) including an offset for patient follow-up time. FEV_1 onset value (BASE), age class (< 55 years, ≥ 55 years) (AGE_CL), region (EU, US) (REGION), phenotype (FEV_1/FVC <0.7, FEV_1/FVC ≥0.7L) (PHEN_CL), and use of azithromycin at CLAD-BOS onset (Yes, No) (AZIFL) will be included as covariates in the model. CLAD-BOS FEV_1/FVC phenotype and use of azithromycin at CLAD-BOS onset will be included in the analysis if the proportion of patients in either of the two categories falls within the range of 10% to 90%.

SAS example code is provided below:

```
PROC GENMOD DATA= adxx;
 CLASS AGE_CL REGION PHEN_CL AZIFL;
 MODEL <AVAL for cumulative # of progressions/hospitalizations>=
 BASE AGE_CL REGION PHEN_CL AZIFL /dist= <NB or poisson> offset=
 log(TIMEy) link=log;
 ESTIMATE 'rate' intercept 1 BASE <mean base> / exp e;
 RUN;
```

Confidence intervals will be presented to one more decimal place than the raw data. All CIs will be for the 95% probability, unless otherwise specified.

In addition, the distribution of patients enrolled by country and the number and percentage of patients within each of the subgroups defined in Section 5.2 will be summarized

In addition, the duration of follow-up will be summarized along with the status at the data abstraction date:

- Patient status at data abstraction date (Unknown, Alive, Dead, Withdrawal of Informed Consent)
- If dead, primary cause of death (CLAD-BOS progression, Not related to CLAD-BOS progression, Unknown)
- If dead, investigator assessment, patient died from respiratory failure (Yes, No, Unknown)

Adverse drug reactions (related to Zambon products) as collected in the eCRF will be coded to PT and associated primary SOC using MedDRA version 27.0 or higher and will be documented in a dedicated listing.

5.2 SUBGROUPS

Initial consideration for the following subgroups (sample size permitting) will be implemented with summaries of primary endpoint for each subgroup and otherwise as noted in Table 1 below and as in alignment with the mock TFLs (see Section 9):

- Region (EU, US)
- Age class (<55 years, ≥55 years)
- Gender (Female, Male)
- Race (White, Black or African American, Asian, Other, Not to be collected per local regulation)
    - wherein "Other" incorporates race categories of: American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other
- FEV_1/FVC CLAD phenotype defined by FEV_1/FVC ratio (obstructive < 0.7, non-obstructive ≥ 0.7) at onset
- Rate of decline from transplant to onset (<Q1, ≥Q1-<median, ≥median-<Q3, ≥Q3)
- BLAD at best post-transplant (Yes, No)
- Azithromycin use at CLAD-BOS diagnosis (Yes, No)
- Type of transplant (single, bilateral)

Subgroup levels may be pooled to have an adequate number (≥10) of patients per strata to perform the analysis and/or alternative subgroups may be considered should the need arise. Decision on subgroup modifications will be made during the final data review meetings, before commencement of final analyses.

More specifically, it is expected that respective endpoint analyses will be summarized by subgroups noted in Table 1.

Table 1. Proposed Subgroups by Endpoint

Endpoint	Region	Age class	Gender	Race	Phenotype at CLAD-BOS onset	Rate of decline from transplant to onset	BLAD at best post-transplant	Azithromycin use at CLAD-BOS diagnosis	Type of transplant
Primary									
FEV_1 trajectory (not including the LMM)	X	X	X	X	X	X	X	X	X

Endpoint	Region	Age class	Gender	Race	Phenotype at CLAD-BOS onset	Rate of decline from transplant to onset	BLAD at best post-transplant	Azithromycin use at CLAD-BOS diagnosis	Type of transplant
Secondary									
Overall survival	X	X	X	X	X	X	X	X	X
Time to first CLAD-BOS progression					X	X	X	X	X
Cumulative incidence of CLAD-BOS progression					X	X	X	X	X

5.3 INTERIM ANALYSIS

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

5.4 TIMING OF ANALYSES

The final analysis will be conducted once the final datasets are extracted following the database lock.

5.5 ANALYSIS SETS

5.5.1 All Patients Enrolled Set (ENR)

The all patients enrolled set (ENR) will include all patients who were enrolled in the study and whose data were collected in the eCRF. This analysis set will be used for the patient disposition table as well as for generating listings.

5.5.2 Full Analysis Set (FAS)

The full analysis set (FAS) is defined as all enrolled patients who were confirmed to be included in the study (i.e., eCRF question: “Is the patient included in the study?” equal to YES) with an available onset FEV_1 value. Patients who do not meet the eligibility criteria but satisfy the above conditions will still be considered in the FAS. .This analysis set will be utilized for all the endpoint analyses in the study.

Note: A listing of inclusion/exclusion criteria will be provided for patients who did not meet all eligibility criteria.

5.6 MISSING DATA MANAGEMENT

In general, missing data will not be imputed and the data will be analyzed according to the complete case approach with missing counts reflected for categorical variables when relevant. The assumption of the LMM will be missing at random (MAR); however, imputation will also be performed per the sensitivity analysis for the spirometry trajectories sensitivity analyses (Sections 4.1.3 and 4.2.3.2).

However, partial dates will be imputed for missing day fields, with specific imputations for respective day fields (with broader imputation for last available date) provided in Table 2:

Table 2. Partial dates imputation

Partial date	Day imputed
Date of lung transplantation	01
Date of first (initial) CLAD-BOS diagnosis after lung transplantation	01 (imputed date must be subsequent to lung transplant and post-transplant best FEV_1 assessment date)
Pre-transplant medical history – Start date	- if the "Pre-transplant medical history – Start date" month is equal to the date of lung transplantation, the missing day field is imputed as the day before the date of lung transplantation, otherwise it will be imputed as 01 - If "Pre-transplant medical history – Stop date" is completed, and the month of "Pre-transplant medical history – Start date" is equal to stop date, the same day before the "Pre-transplant medical history – Stop date " is used. - If "Pre-transplant medical history – Stop date" is completed, and the month of "Pre-transplant medical history – Start date" is NOT equal to stop date, 01 is used as day imputation.
Pre-transplant medical history – Stop date	If the month is equal to the date of lung transplantation, the missing day field is imputed as the day before the date of lung transplantation, otherwise it will be imputed as 01
Date of spirometry assessment after CLAD-BOS diagnosis (spirometry related to second best-post transplant are excluded)	15
Onset date	15
First best-post transplant dates	15
Second best-post transplant dates	15; unless it results in being: o less than 21 days since first best post-transplant date, and if any day in the month results in exactly 21 days, impute that day to achieve a 21-day gap. OR o more than 91 days since the first best-post transplant date, and if any day in the month results in exactly 91 days, impute that day to achieve a 91-day gap.
Date of BOS progression (clinical judgment)	01 (imputed date must be subsequent to onset date)
Date of re-transplantation	01
Last date the patient was known to be alive' or 'Date of death'	If only day is missing: 01 If month and/or year is missing use the latest date recorded in the eCRF.
Stop date of medical conditions/ Stop date of concomitant treatment	if month of stop date is prior to diagnosis month (considering year), condition/treatment will not be considered ongoing/concomitant

Missing months and years will not be imputed unless a date can be inferred based on other reported information. Time-to-event and duration variables will be derived after partial date imputation. However, they will not be calculated if any of the source dates are missing. Dates will be provided per eCRF within listings; imputed dates will not be presented in the listings.

5.7 ANALYSIS WINDOWS

To allow for spirometry values assessments to be summarized at time intervals, analysis windows will be defined according to Table 3.

Table 3. Analysis windows

Nominal Study Week	Nominal Study Day	Time (days) from Onset date	Analysis Year
Onset/Baseline	1	0	-
W4	29	1-42	1
W8	57	43-70	1
W12	85	71-98	1
W16	113	99-140	1
W24	169	141-196	1
W32	225	197-252	1
W40	281	253-308	1
W48	337	309-378	1
W60 (W48+12 weeks)	337+84=421	379-462	2
W72 (W48+24 weeks)	421+84=505	463-546	2
W84 (W48+36 weeks)	505+84=589	547-630	2
W96 (W48+48 weeks)	589+84=673	631-714	2
W108 (W48+60 weeks)	673+84=757	715-798	3
W120 (W48+72 weeks)	757+84=841	799-882	3
W132 (W48+84 weeks)	841+84=925	883-1008	3
Following every 24 weeks until the last observation	+ 168	[x – 84] - [x + 83] (where x is the nominal study day)	… (assuming a year equal to 365.25 days)

**Nominal Study Day 1 is the day of CLAD-BOS onset.*

In case of multiple spirometry assessments within the same analysis window, the average of the non-missing measurements will be used. All data, along with their average, will be listed. Windowing will be applied to the data prior to any missing date imputation. If a missing day prevents from flagging a date as within a specified window and there is no other assessment

within that window, the corresponding spirometry data will be excluded from tabular summaries. However, this data will still be reflected in the listings without an imputed date.

5.8 MEASURES TO MINIMIZE BIAS

Selection bias

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).
- 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.

Immortal time bias

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.

Missing data

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.

To mitigate the occurrence of missing data:

- Whenever possible, "Unknown" fields will be included in the eCRF to quantify unavailable information in clinical records. Additionally, summary tables will identify the number of

patients with missing data per variable to gauge missingness, and percentages for categorical variables will exclude missing data counts.

- Sensitivity analysis will be conducted on OS to account for unknown patient status at the end of follow-up.
- Although imputation is kept to a minimum to most accurately portray the real-world data, imputation of some dates with missing day fields will be employed to facilitate derivations for summaries. However, for transparency this will be noted within tabular summaries and listings will retain the non-imputed values.

Informative censoring

Informative censoring may occur whenever a patient experiences death or re-transplantation and the FEV_1 trajectories are assessed using a MAR approach, like the one described in Section 4.1.2. To mitigate this, a sensitivity analysis will be conducted, imputing an FEV_1 value of 'zero' for the analysis timepoints following the intercurrent event.

Since the definition of progression of BOS includes all relevant intercurrent events as failures, drop-outs due to other reasons will be treated as non-informative censoring.

5.9 STATISTICAL SOFTWARE

The statistical analyses will be performed using SAS version 9.4 or higher (SAS Institute Inc., Cary, NC, US), in a secure and validated environment. All TFLs to be included in the report will be independently checked for consistency and integrity.

6 Bibliography

7 Revision History

Unique Identifier for this Version	Date of the Document Version	Author	Significant Changes from Previous Authorized Version
CCI			
Final v3.0	11 July 2025	CCI	

8 Appendix I. Key Variables Derivations

Variable	Derivation Details
Subgroups	
FEV_1/FVC phenotype at CLAD-BOS diagnosis defined by FEV_1/FVC ratio (obstructive < 0.7,non-obstructive ≥ 0.7).	Calculated as: FEV_1/FVC at onset date
Rate of decline from transplant to onset (<Q1, ≥Q1-<median, ≥median-<Q3, ≥Q3)	Calculated as: (CLAD-BOS onset FEV_1 – FEV_1 at best post-transplant) / (CLAD-BOS onset date – best post-transplant date (first value date) + 1). Then derive <Q1, ≥Q1-<median, ≥median-<Q3, ≥Q3 categories
BLAD at best post-transplant (Yes, No)	Calculated if absolute and predicted (from eCRF or derived) values for best-post transplant FEV_1 and FVC are available as: YES if: (FEV_1 at best post-transplant / predicted FEV_1 at best post-transplant)*100 <80% AND (FVC at best post-transplant / predicted FVC at best post-transplant)*100 <80% = 'Yes' Confirmed on two consecutive assessments >21 days apart Else 'No'
Azithromycin use at CLAD-BOS diagnosis (Yes, No)	Azithromycin use will be identified based on patients treated with ATC code (J01FA10) at the time of CLAD-BOS clinician diagnosis. The start and stop dates of azithromycin should include the CLAD-BOS clinician diagnosis date after partial date imputation. In cases where exact timing cannot be established, azithromycin use will be considered concomitant. In case of partial date stop date, if month is prior to diagnosis month (considering year), condition will be not considered present at diagnosis.
Key dates/values determination	
Value of FEV_1 at diagnosis *<Spirometry parameter (unit)>*	The closest FEV_1 value collected within ±1 month (±30.4375 days) from the date of diagnosis.
Date and value of best post-transplant *<Spirometry parameter (unit)>*	Date of best post-transplant is the date of the first best-post transplant FEV_1 measurement. This spirometry assessment date will be used as the reference timepoint of 'best post-transplant date' for all other spirometry parameters as well. The best post-transplant value is calculated as follows: *(<Spirometry parameter (unit)>* value at FEV_1 first best date + *<Spirometry parameter (unit)r>* value at FEV_1 second best date) / 2 Note: • The two best post-transplant measurements should have been taken before the date of diagnosis. • To calculate the best FEV_1 value, at least one assessment per year (on average) must be conducted between the transplant and diagnosis.

Variable	Derivation Details
	• The two best post-transplant measurements should have been taken at least 3 weeks (i.e., > 21 days) apart. • If a second assessment within this timeframe (> 21 days) is not available, assessments performed ≤ 21 days apart can be considered. • If there is still no assessment meeting this requirement, then a single assessment can be used to define the best post-transplant measurement. • The derived best FEV_1 must be greater than the FEV_1 at diagnosis , otherwise it will be set as missing.
Date of CLAD-BOS diagnosis (index date)	Date of first (initial) CLAD-BOS diagnosis after lung transplantation (Index Date). eCRF Form: CLAD-BOS clinician diagnosis.
Date of onset	Date of onset value is the date of the first occurrence of a FEV_1 value ≤80% vs. the best FEV_1 value post-transplant. This spirometry assessment date will be used as the reference timepoint of 'Onset' for all other spirometry parameters as well. Note: • To validate the onset value, it must be confirmed by another consecutive FEV_1 value ≤ 80% vs. the best-FEV_1 value post-transplant occurring at least 3 months (i.e., > 91 days) apart. • If the next FEV_1 value after 3 months is >80% vs. the best- FEV_1 value post-transplant, the onset value needs to be re-calculated using subsequent measurements. • If the onset is not derivable (for any reason), then it will be set to the diagnosis date. CLAD-BOS onset date/value must be confirmed programmatically in order for the patient to be included in the FAS and trajectory analyses performed
Onset value <*Spirometry parameter (unit)*>	FEV_1 value where: 100 - [(the best FEV_1 value post-transplant - FEV_1 value)/ the best FEV_1 value post-transplant]*100 with result ≤80% Note: • To validate the onset value, it must be confirmed by another consecutive FEV_1 value ≤ 80% vs. the best-FEV_1 value post-transplant occurring at least 3 months (i.e., > 91 days) apart. • If the next FEV_1 value after 3 months is >80% vs. the best- FEV_1 value post-transplant, the onset value needs to be re-calculated using subsequent measurements. • If the onset is not derivable (for any reason), then it will be set at diagnosis.
Predicted <*Spirometry parameter (unit)*>	*<Spirometry parameter (unit)> absolute / <Spirometry parameter (unit)> % predicted* Note: • Evaluate only when the predicted spirometry parameter is not reported in the eCRF. • Apply to all spirometry parameters, i.e. FEV_1, FVC, FEV_1/FVC, FEF25-75%
% Predicted <*Spirometry parameter (unit)*>	*<Spirometry parameter (unit)> absolute / <Spirometry parameter (unit)> predicted* Note: • Evaluate only when the % predicted spirometry parameter is not reported in the eCRF. • Apply to all spirometry parameters, i.e. FEV_1, FVC, FEV_1/FVC, FEF25-75%
Duration of follow-up	
Duration of follow-up (months)	('Last date the patient was known to be alive' or 'Date of death' "source: programmatic derivation" - Onset date "source: programmatic derivation"+ 1)/ 30.4375

Variable	Derivation Details
	The duration of follow-up (in years) will be used in the analysis of rates as an offset variable: Duration of follow-up (years) = Duration of follow-up (months)/12
Demographics, medical history and CLAD-BOS characteristics at diagnosis	
Age at lung transplantation (years)	[year part of (Date of lung transplantation "source: eCRF") – Year of birth "source: eCRF"]
Age at CLAD-BOS diagnosis (years)	[earliest year part of (a. Date of first (initial) CLAD-BOS diagnosis after lung transplantation (Index Date) "source: eCRF" b. Date of CLAD-BOS onset "source: programmatic derivation") – Year of birth "source: eCRF"]
Time from lung transplantation to CLAD-BOS onset (months)	- Onset date "source: programmatic derivation" - Date of lung transplantation "source: eCRF" + 1]/ 30.4375
Time from lung transplantation to best post-transplant spirometry (months)	(Date of first best-post-transplant FEV_1 "source: programmatic derivation" - Date of lung transplantation "source: eCRF" + 1)/ 30.4375
Time from CLAD-BOS onset to CLAD-BOS diagnosis (months)	(Date of first (initial) CLAD-BOS diagnosis after lung transplantation (Index Date) "source: eCRF" - Onset date "source: programmatic derivation" + 1)/ 30.4375
Clinical pulmonary antibody-mediated rejection	DEFINITE If allograft dysfunction, other causes excluded, lung histology, lung biopsy C4d and DSA are all five 'Present' PROBABLE If any combination of (allograft dysfunction, other causes excluded, lung histology, lung biopsy C4d and DSA) results in four 'Present' POSSIBLE If any combination of (allograft dysfunction, other causes excluded, lung histology, lung biopsy C4d and DSA) results in three 'Present' UNKNOWN otherwise.

<table>
<tr><th>Variable</th><th>Derivation Details</th></tr>
<tr><td></td><td>
<table>
<tr><th></th><th>Allograft dysfunction</th><th>Other causes excluded</th><th>Lung histology</th><th>Lung biopsy C4d</th><th>DSA</th></tr>
<tr><td>Definite</td><td>+</td><td>+</td><td>+</td><td>+</td><td>+</td></tr>
<tr><td>Probable</td><td>+</td><td>+</td><td>+</td><td>-</td><td>+</td></tr>
<tr><td>Probable</td><td>+</td><td>+</td><td>+</td><td>+</td><td>-</td></tr>
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<tr><td>Possible</td><td>+</td><td>-</td><td>-</td><td>+</td><td>+</td></tr>
</table>
DSA, donor-specific antibodies; +, item present; - item absent or missing
</td></tr>
<tr><td>Sub-clinical pulmonary antibody-mediated rejection</td><td>
DEFINITE
If lung histology, lung biopsy C4d and DSA are all three ‘Present’

PROBABLE
If any combination of (lung histology, lung biopsy C4d and DSA) results in two ‘Present’

POSSIBLE
If there’s only one item ‘Present’ among (lung histology, lung biopsy C4d and DSA)

UNKNOWN otherwise.

<table>
<tr><th></th><th>Lung histology</th><th>Lung biopsy C4d</th><th>DSA</th></tr>
<tr><td>Definite</td><td>+</td><td>+</td><td>+</td></tr>
<tr><td>Probable</td><td>+</td><td>-</td><td>+</td></tr>
<tr><td>Probable</td><td>-</td><td>+</td><td>+</td></tr>
<tr><td>Probable</td><td>+</td><td>+</td><td>-</td></tr>
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<tr><td>Possible</td><td>-</td><td>+</td><td>-</td></tr>
<tr><td>Possible</td><td>-</td><td>-</td><td>+</td></tr>
</table>
DSA, donor-specific antibodies; +, item present; - item absent or missing
</td></tr>
<tr><td colspan="2">Spirometry trajectories</td></tr>
<tr><td><Spirometry parameter (unit)> change from onset value</td><td>(<Spirometry parameter (unit)> at analysis timepoint <x> “source: programmatic derivation”
-
<Spirometry parameter (unit)> at onset “source: programmatic derivation”)

Note 1: Repeat for all post-onset analysis timepoints defined in Section 5.7
Note 2: This calculation applies to all spirometry parameters (FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$) and units</td></tr>
<tr><td><Spirometry parameter (unit)> change from onset value (%)</td><td>[(<Spirometry parameter (unit)> at analysis timepoint <x> “source: programmatic derivation”) - <Spirometry parameter (unit)> at onset date) “source: programmatic derivation” / <Spirometry parameter (unit)> at onset date “source: programmatic derivation”]*100

Note 1: Repeat for all post-onset analysis timepoints defined in Section 5.7
Note 2: This calculation applies to all spirometry parameters (FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$) and units</td></tr>
</table>

Variable	Derivation Details
<Spirometry parameter (unit)> change from previous progression value (absolute)	(*<Spirometry parameter (unit)>* at analysis timepoint <x> ("source: programmatic derivation" - *<Spirometry parameter (unit)>* at CLAD-BOS <first> progression "source: programmatic derivation") Note 1: Repeat for all post-onset analysis timepoints (Section 5.7 following the <first> CLAD-BOS progression defined in Section 4.2.5 Replace <first> with subsequent CLAD-BOS progression as they are observed. Note 2: This calculation applies to all spirometry parameters (FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$) and units
<Spirometry parameter (unit)> change from previous progression value (%)	(*<Spirometry parameter (unit)>* at analysis timepoint <x> "source: programmatic derivation" - *<Spirometry parameter (unit)>* at CLAD-BOS <first> progression "source: programmatic derivation" / *<Spirometry parameter (unit)>* at CLAD-BOS <first> progression "source: programmatic derivation"]*100 Note 1: Repeat for all post-onset analysis timepoints (Section 5.7) following the <first> CLAD-BOS progression defined in Section 4.2.5. Replace <first> with subsequent CLAD-BOS progression as they are observed. Note 2: This calculation applies to all spirometry parameters (FEV_1, FVC, FEV_1/FVC and $FEF_{25-75\%}$) and units
Overall survival	
Overall survival (months)	[Earliest of (a. [EVENT] Date of death "source: eCRF" b. [CENSOR, if a. did not occur] Last date the patient was known to be alive "source: programmatic derivation") - Date of CLAD-BOS onset "source: programmatic derivation"+ 1]/ 30.4375
Date of death	date taken from a. BOS progression due to 'Death from respiratory failure' "source: eCRF", OR b. Patient status at the end of study – date of death "source: eCRF"
Last date the patient was known to be alive	Max date of all patient's dates included in the eCRF not including: • The date of informed consent (if not given by the 'Patient') • The date of data abstraction
Time to first CLAD-BOS progression	
Time to first CLAD-BOS progression (months)	[Earliest of (a. [EVENT] Date of the first spirometry with: absolute decrease from previously available spirometry assessment in $FEV_1 \geq 10\%$ (or ≥ 200 mL) and absolute decrease in FEV1/FVC of > 5%, with a confirmation spirometry assessment in a subsequent visit at least 3 weeks (i.e., > 21 days) "source: programmatic derivation" . Where previously available spirometry assessment means: 1) The onset value for the first CLAD-BOS progression

Variable	Derivation Details
	2) The value observed at the previous progression for the second and subsequent progressions b. [EVENT] Change in CLAD grade severity "source: programmatic derivation" c. [EVENT] Date of re-transplantation "source: eCRF" d. [EVENT] Date of death from respiratory failure "source: eCRF" e. [EVENT] Clinical judgment of CLAD-BOS progression "source eCRF" f. [CENSOR, if a.-e. did not occur] with the earliest of (Last spirometry assessment date "source programmatic derivation" , Date of death from other reasons than respiratory failure "source eCRF") in case of Death not caused by respiratory failure BEFORE first spirometry evaluation g. [CENSOR, if a.-e. did not occur] Last spirometry assessment date "source programmatic derivation" in case of Death not caused by respiratory failure AFTER first spirometry evaluation) - Date of CLAD-BOS onset "source: programmatic derivation"+ 1]/ 30.4375
Absolute decrease from previously available spirometry assessment in FEV_1 ≥ 10% (or ≥ 200 mL) and absolute decrease in FEV_1/FVC of > 5%	Refer to: • <Spirometry parameter (unit)> change from previous timepoint value (absolute) • <Spirometry parameter (unit)> change from previous timepoint value (%)
Change in CLAD grade severity	Refer to: • *<Spirometry parameter (unit)> change from onset value (%) for FEV_1* *A change in CLAD severity occurs if FEV_1 change % is:* - *<=65% and* o *CLAD-BOS onset value [derived] was >65% OR* o CLAD-BOS grade at index [source: eCRF] was ='1' - *<=50% and* o *CLAD-BOS onset value [derived] was >50% OR* o CLAD-BOS grade at index [source: eCRF] was <='2' - *<=35% and* o *CLAD-BOS onset value [derived] was >35% OR* o CLAD-BOS grade at index [source: eCRF] was <='3'

Duration and time-to-event variables will be calculated after the imputation of partial dates.

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