STATISTICAL ANALYSIS PLAN

A Phase III, Prospective, Multicenter, Randomized, Controlled Clinical Trial to Demonstrate the Efficacy and Safety of Liposomal Cyclosporine A (L-CsA) Inhalation Solution Delivered via the [redacted] plus Standard of Care versus Standard of Care Alone in the Treatment of Chronic Lung Allograft Dysfunction / Bronchiolitis Obliterans Syndrome in Patients post Single Lung Transplantation

Protocol No: BT – L-CsA – 301 – SLT(BOSTON-1)

Statistical Analysis Plan Status: Final

Statistical Analysis Plan Version: 3.0

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SPONSOR

Zambon SpA

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INVESTIGATIONAL MEDICINAL PRODUCT

Liposomal Cyclosporine A (L-CsA)

CCI [redacted]

Developed by PPD

1 SIGNATORIES

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3 ABBREVIATIONS

AC	Adjudication Committee
AE	Adverse Event
AIC	Akaike Information Criterion
ALT	Alanine Aminotransferase
ANCOVA	Analysis of Covariance
AP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
ATC	Anatomical Therapeutic Code
BLAD	Baseline Lung Allograft Dysfunction
BOS	Bronchiolitis Obliterans Syndrome
BUN	Blood Urea Nitrogen
CLAD	Chronic Lung Allograft Dysfunction
CMV	Cytomegalovirus
CNI	Calcineurin Inhibitor
COPD	Chronic Obstructive Pulmonary Disease
COVID-19	Coronavirus Disease of 2019
CRF	Case report form
CSR	Clinical Study Report
DMC	Data Monitoring Committee
DRM	Data Review Meeting
EBV	Epstein Barr Virus
eCRF	Electronic Case Report Form
EoS	End of Study
EoT	End of Treatment
EQ-5D-5L	Euro QOL Health Questionnaire
FAS	Full Analysis Set
FDA	Food and Drug Administration
CCI	CCI
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
γ-GT	Gamma Glutamyl Transferase
IE	Intercurrent Event
IMP	Investigational Medicinal Product (study drug: L-CsA)
L	Liter

L-CsA	Liposomal Cyclosporine A Inhalation Solution
LMM	Linear Mixed Model
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MMF	Mycophenolate Mofetil
MNAR	Missing Not at Random
mTOR	Mammalian Target of Rapamycin
PD	Protocol Deviation
PPS	Per Protocol Set
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
[redacted]	[redacted]
SD	Standard Deviation
SLT	Single Lung Transplant
SoC	Standard of Care
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFL	Table, figure and listing
TNF-α	Tumor necrosis factor alpha
VAS	Visual Analogue Scale
WHO-DD	World Health Organization-Drug Dictionary
WRO	Written Response Only

4 VERSION HISTORY

Date	Version	Brief Description of Changes
28 July 2018	1.0	Initial Version drafted by Breath Therapeutics, this version was not signed.
03 September 2019	1.1	Signed draft version
14 September 2023	2.0	Necessary updates from the draft signed SAP v1.1 have been mentioned in the Study Protocol 5.0 (Amendment 4), dated 13 April 2023; these include enrollment with early termination resulting in the study being underpowered and the primary endpoint not being assessed for superiority, and therefore would only be descriptive in nature. There was also the removal of the planned interim analysis, and sensitivity analysis for the primary endpoint. [redacted] Furthermore, using the final Boston 2 SAP text v3.0 (dated 31st July 2023) to incorporate for all required consistency updates, as well as all other updates from the protocol amendment.
08 May 2024	3.0	Section 9.2.1 has been modified to clarify the definition of actual treatment in the SAF population.

		Additional explanations have been added in Section 12.1 to clarify the calculation of intervals between visits. The definition of BLAD has been fixed in section 11.3. CCI [redacted] Section 14.1.1 has been amended to consider a treatment composite strategy instead of a treatment policy one. Therefore, death and re-transplantation IE are included in the endpoint through an imputation of FEV1 as a treatment failure (FEV1 equal to zero). This applies also to 14.1.3, 14.2.1, 14.2.2, 14.3.1, and 14.4.6. In Section 14.2.1 a ranked ANCOVA has been planned in case of violation of normality assumption even after log-transformation of data. Clarifications in section 14.2.5.1, 14.3.2, 14.4.1, and 14.4.9 have been added to specify analysis, comparisons, and figures. It is clarified in section 14.3.2 that BOS progressions will be considered up to study end, even after treatment completion/discontinuation. It is specified in section 14.4.1 that in case of not enough responses for using logistic regression, then exact methods will be used for CI and test. Sensitivity analyses have added in sections 14.4.2 and 14.4.3. Additional subgroup analyses (by use of azithromycin at baseline and by BLAD disease at baseline) have been added in Section 14.5. The BLAD definition has been added in section 11.3. In section 15.2 more instructions for the analysis of Extent of Exposure have been added, while in Section 15.3.1 it has been added an analysis of infection rates by year and overall.

		Section 15.5.1 has been updated with the full list of Hematology and Biochemistry exams. Section 15.6 has been updated to include more PTs. Minor errors in the CCI have been fixed in section 17.

5 INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of specific planned analyses to be performed on the data to be collected from clinical trial BT – L-CsA – 301 – SLT (BOSTON-1). This SAP is based on the Clinical trial protocol version 5.0 (amendment 4.0), dated 13 April 2023.

Modifications to this SAP will be subject to detailed documentation relating to timing and rationale, with a focus on identifying and providing a rationale for changes. Any deviations from the SAP will be fully described in the integrated clinical study report (CSR).

The main purpose of this SAP is to pre-specify statistical analyses that relate to identified clinical trial objectives. Any supportive CCI analyses presented in the integrated CSR which are not described in the SAP will be noted as such.

6 TRIAL OBJECTIVES

The objective of this trial is to assess the efficacy and safety of add-on aerosolized Liposomal Cyclosporine A Inhalation Solution (L-CsA) to Standard of Care (SoC) therapy as compared to SoC therapy alone in the treatment of bronchiolitis obliterans syndrome (BOS) in single lung transplant (SLT) recipients.

7 INVESTIGATIONAL PLAN

7.1 Trial Design

This is a Phase III, prospective, multicenter, randomized, controlled clinical trial of L-CsA for the treatment of BOS in adults with clinically defined BOS (Chronic Lung Allograft Dysfunction (CLAD) – BOS phenotype) following SLT. Patients will receive either L-CsA (5 mg) via the CCI SoC treatment or SoC alone, for a period of 48 weeks. All patients will be eligible to continue in an open-label extension trial of L-CsA, BT – L-CsA – 303 – FU (BOSTON-3) following completion of BOSTON-1.

A total of 11 visits (Screening, V1 through V10) will be performed during the clinical trial. After informed consent has been obtained, a Screening Visit will be carried out in order to check general eligibility for participation. If a patient fails the screening process due to not meeting inclusion/exclusion criteria, a re-screening is allowed. At the Baseline Visit (V1, randomization visit), inclusion and exclusion criteria will be re-checked, and baseline serial spirometry will be performed. During the 48-week treatment period, visits are scheduled every 4-8 weeks (V2, …, V9). Visit 9 (End of Treatment, EoT) is scheduled to occur 48 weeks after Visit 1. If a patient has an event that meets one of the criteria for progression of BOS, progression of BOS must be

confirmed by measurements that are taken with CCI spirometer at least 2 weeks apart. Visit 10 (End of Study, EoS) is a safety follow-up visit performed 4 weeks after Visit 9/EoT only in patients not rolling over to the extension study (BOSTON-3) or if possible, in patients who decided to withdraw the consent during the study. For patients who will enroll to BOSTON-3, the EoT visit will be the EoS visit.

However, if one of the visits from Visit 2 to Visit 8 and discontinuation visits cannot be performed at site due to COVID-19, remote visits (e.g., by telephone) are possible.

7.2 Randomization and Stratification

At the Baseline visit (V1), after all inclusion and exclusion criteria have been fully evaluated, eligible patients will be randomized with equal probability to one of two treatment arms, a control arm (SoC alone) and an investigational arm (L-CsA plus SoC). The investigational medicinal product (IMP) is L-CsA. To assure balance between treatment arms with regard to key variables and potential confounders, stratification prior to randomization will be performed for the following variables:

- Screening FEV_1 ≥81% of personal best FEV_1 value post-transplant versus Screening FEV_1 between 80-51% of personal best FEV_1 value post-transplant
- Underlying indication for lung transplant: Chronic obstructive pulmonary disease (COPD) versus all other underlying diseases
- Region: North America versus all other countries together

Within each of the 8 strata, patients will be randomly assigned with equal probability (1:1) to either the investigational or control arm using a permuted blocks randomization. The randomization code, including specification of the block size, will be generated by a statistician not otherwise involved with the trial, using validated software. The unique randomization number and treatment assignment of each patient will be provided to the Investigator through the electronic Case Report Form (eCRF) after eligibility has been verified. The number assigned to a patient will be that patient's unique identifier throughout the clinical trial and cannot be re-assigned to another patient.

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

7.3 Primary Efficacy Endpoint

- Mean change in FEV_1 (L) from baseline to Week 48

FEV_1 data collected from the on site CCI spirometer will be considered primary, while the data collected with the CCI home spirometer will be used for supportive analyses.

CCI [redacted]

CCI [redacted]

7.6 Safety Endpoints

- Adverse events (AEs) (including infections and malignancies)
- Acute tolerability of IMP (L-CsA)
- Clinical laboratory variables
- Renal function
- Vitals signs
- Physical examinations

8 STATISTICAL CONSIDERATIONS

8.1 General Considerations and Descriptive Statistics

All report outputs will be produced using [redacted] version 9.2 or later, in a secure and validated environment. All tables, figures and data listings (TFLs) to be included in the report will be independently checked for consistency and integrity.

The data recorded in the eCRF will be summarized as appropriate, per treatment group and for the total group, using the following descriptive measures:

- All continuous variables will be summarized using descriptive statistics (i.e., n, mean, standard deviation (SD), median, Q1, Q3, minimum, and maximum).
- All categorical variables will be summarized by using frequency counts and percentages.
- Discrete ordinal or higher-level data will be summarized as continuous data, but a tabulation of categories may also be included, depending on the number of categories.
- 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 treatment group, will be presented along with the event-free rates (and two-sided 95% confidence). Kaplan-Meier graphs will be presented along with the number of patient-at-risk at exact time points. If different rules are not specified, patients who are free from event will be censored at the study termination.

For all measures analyzed descriptively (i.e., measures to characterize the treatment groups and their baseline status, efficacy, and safety outcomes), tabulations comparing the treatment groups will be prepared. For outcomes measured more than once, the analyses will include tabulations of the measured values by visit, as well as change from baseline. Where provided, all confidence intervals will be two-sided 95% intervals.

8.1.1 Baseline Definition

CCI baseline FEV_1: the FEV_1 value that is the mean of the best FEV_1 obtained with the CCI study spirometer at the Screening Visit and the pre-randomization best FEV_1 obtained at the Baseline Visit (V1) is referred to as "baseline FEV_1". If the value at Screening visit is missing, then the baseline FEV_1 will be the pre-randomization value from the Baseline Visit (V1). If the pre-randomization value at Baseline Visit (V1) is missing, then the baseline FEV_1 will be the value from the Screening Visit.

Other CCI baseline spirometry values: will be defined similarly as for Baseline FEV_1.

CCI baseline FEV_1: will be defined similarly as for CCI baseline FEV_1 but using the CCI home spirometer.

Baseline laboratory values: the last measurement obtained prior to or at the Baseline Visit at V1.

Other baseline measurements: unless otherwise specified, baseline refers to measurement obtained at the Baseline Visit at V1.

8.1.2 Treatment Definition

Treatment refers to add-on L-CsA to SoC therapy, as well as SoC therapy alone.

8.2 Sample Size Considerations

The initial sample size was based on the following considerations. Assuming a treatment group difference for mean FEV_1 change from baseline of 200 mL (0.2 L) and a standard deviation of 350 mL (0.35 L) at the end of treatment Week 48, an independent samples t-test with a one-sided type I error level of α=0.025 will have at least 80% power to reject the null hypothesis when the sample size in each treatment group is at least 50 patients. To compensate for a loss of power due to premature withdrawals, a total of 110 patients were initially planned to be randomized.

In accordance with the amended version of the protocol (version 5.0) and following Food and Drug Administration CCI [redacted].

It was anticipated that approximately 160-170 patients have been randomized in BOSTON-2 and approximately 60 patients in BOSTON-1. 169 patients were actually randomized in BOSTON-2 and 62 patients in BOSTON-1.

8.3 Interim Analysis

Due to premature stop of enrollment CCI [redacted] the originally pre-planned interim analysis for sample size re-estimation was deemed unnecessary and it will not be performed.

8.4 Data Monitoring Committee and Confidentiality of Results

An independent Data Monitoring Committee (DMC) will be established to monitor the safety of the IMP throughout the conduct of BOSTON-1 and BOSTON-2 studies. The DMC will monitor safety by evaluating the safety analysis generated by the unblinded independent statistician during the course of the clinical trial. Details of the safety analyses will be included in the DMC's Charter (from CCI [redacted]). The DMC will evaluate the treatment groups for possible trends

in AEs, determine whether the basic clinical trial assumptions remain valid, evaluate whether the overall integrity, scientific merit and conduct of the clinical trials remain acceptable, and make recommendations to the Sponsor.

The DMC will perform a comparison between the rate of observed COVID-19 cases, rate of patients' withdrawal, and rate of missing data among trial participants in both treatment arms.

Members of the DMC will be unblinded to the treatment group label, i.e., the DMC will know which group is L-CsA + Standard of Care and which group is Standard of Care alone. The DMC will evaluate all safety and acute tolerability parameters, to be detailed in the DMC charter.

Safety and acute tolerability parameters include AEs, acute tolerability of L-CsA, infections, malignancies, clinical laboratory data (white blood cell count with differential, red blood cell count, platelet count, alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase, gamma glutamyl transferase (γ-GT), blood urea nitrogen, serum bilirubin, serum creatinine), vital signs, physical examinations and FEV_1. The statistics provided will be merely descriptive.

Criteria for membership, responsibilities, meeting frequency, and identification of data listings, summaries and analyses to be provided to the DMC are detailed in the DMC charter.

Statistical analyses to be provided to DMC are planned in a specific DMC SAP.

8.5 Adjudication Committee

The adjudication committee (AC) – consisting of three independent physicians, with documented expertise in the clinical management of lung transplantation and diagnosis and treatment of BOS - will maintain the role of reviewing the BOS progression data in blind condition once each participating patient completes the study period, with the aim to ensure consistent and complete recording of data. If necessary, the AC may query the sites to ask for clarifications. In case there are discrepancies between the assessment of the AC and that of the investigator regarding BOS progression events, the CRO will notify the investigator. In all cases, the final decision as to whether or not specific event qualifies as BOS progression stands with the Investigator.

9 DEFINITIONS

9.1 Protocol Deviations

Major protocol deviations (PDs) are defined as those deviations from the clinical trial protocol for which there could be a significant influence on the assessment of the treatment efficacy. The impact of major protocol deviations on the efficacy results will be investigated by assessing the robustness of the clinical trial results and conclusions to the choice of analysis population, both

including and excluding data potentially affected by major protocol deviations. Please note that other study documents may refer to the major PDs as important PDs, and minor PDs as non-important PDs. The SAP and TFL shells will be using the terminology major and minor PDs. For the study, a PD List has been pre-specified. The PD list contains the list of all study PDs, the categorization, the criticality [Major (important) or Minor (non-important)], the potential impact on analysis populations. All the processes around the collection and the review of PDs are described in detail in the study PD Management Plan.

9.2 Analysis Data Sets

The term analysis data set is used to define the set of patients to be included in a class of analyses. The analysis data set is described in terms of the specific criteria for patient inclusion.

Eligibility for the analysis data sets will be determined in a blinded Data Review Meeting (DRM) held after closing, but before locking the database and then producing the final analysis. The blinded DRM will be used to determine if patients should be excluded from the Per-Protocol Set (PPS) in cases of significant and major protocol deviations that would interfere with the assessment of treatment efficacy. The protocol deviations and their impact are routinely collected and assessed during the conduct of the study.

9.2.1 Safety Analysis Set (SAF)

The SAF is defined as all randomized patients receiving SoC and/or at least one dose of L-CsA, independently of the treatment allocation at randomization. As per IE criteria, randomized patients should be already in SoC at enrollment, therefore it is expected that all randomized patients will enter the SAF population.

Independently of the treatment allocation at randomization, patients will be analyzed according to the treatment they actually received:

- L-CsA plus SoC group: for all randomized patients receiving at least one dose on IMP (L-CsA);
- SoC group: for all randomized patients not receiving any dose on IMP (L-CsA) but treated with SoC.

All data collected after baseline to the end of clinical trial participation will be included in the safety summaries.

All safety and tolerability data will be summarized and analyzed using the SAF.

9.2.2 Full Analysis Set (FAS)

The FAS is defined as all randomized patients. Patients will be analyzed according to the treatment group to which they were randomized. All primary, CCI endpoints will be performed using the FAS, unless otherwise specified.

9.2.3 Per Protocol Set (PPS)

The PPS is defined as all patients included in the FAS

- who complete randomized treatment as scheduled or who are withdrawn prematurely due to lack of efficacy or lack of tolerability of the clinical trial treatment, and
- for whom no major protocol deviations interfering with the assessment of treatment efficacy are observed.

For CCI the primary endpoint, the PPS may be used as a supplementary analysis to assess the impact of drop-outs and major protocol deviations on the results.

Lack of efficacy is defined by the withdrawn reason "Lack of efficacy" as collected in the End Of Study CRF form. Lack of tolerability is defined by the withdrawn reason "Adverse Event (Including SAE/Death)" as collected in the End Of Study CRF form.

9.3 Study Day and Time from Randomization

Study Day 1 is defined to be the day of the randomization visit (visit 1, week 0). Time from randomization (in days) for subsequent visits is defined to be visit date – date of randomization visit +1.

9.4 Visit Windows

Following randomization, the visits are scheduled every 4-8 weeks, but the actual times of the visits may deviate from the scheduled times. With spirometry data, consideration needs to be taken to remove the rejected spirometry assessments for analysis before applying the visit windowing.

To allow for any presentation that summarizes values by visit, visit windows will be defined according to the table below. Measurements (both scheduled and unscheduled) will be allocated to visits (and analyzed) as reported in **Table 1**.

Table 1: Visit windows.

Nominal Visit	V1	V2	V3	V4	V5	V6	V7	V8	V9/EoT	V10/EoS
Nominal Week	W0	W4	W8	W12	W16	W24	W32	W40	W48	W52
Nominal Day	1	29	57	85	113	169	225	281	337	365
Time (days) from Randomization***	0	1-42	43-70	71-98	99-140	141-196	197-252	253-308	*309-364 **309-385	*365-385

**Patients who do not consent or participate in BT – L-CsA – 303 – FU (BOSTON-3).*
***Patients who consented and participated in BT – L-CsA – 303 – FU (BOSTON-3), and will not have a V10 / EoS.*
**** Visit windows are based on [visit date – date of randomization visit] formula for time (days) from randomization.*

Data collected after 385 days or 364 days (as applicable, as per the table above) will not be used for analyses but will be included in the listings. If there are two or more measurements assigned to a nominal visit, only the one closest to the scheduled time of the visit will be used in the analysis, unless an additional measurement will be the last measurement during a patient's trial participation (e. g., in case of an unscheduled visit before premature withdrawal), which will always be included into the analysis.

In the case a scheduled visit is performed in the same date of an unscheduled visit, the scheduled visit assessments will be used; in the specific case of spirometries, if the spirometry data is accepted in the scheduled visit, the scheduled visit data will be used, otherwise (if the spirometry in the scheduled visit is rejected) if the spirometry data is accepted in the unscheduled visit, the unscheduled visit data will be used.

Finally, if a nominal visit has more than one accepted spirometry data assigned, and some of them are performed after IMP inhalation, then only the spirometries done before inhaling the IMP will be used for the visit window mapping rules described above. Instead, if all the accepted spirometries of the nominal visit are done after inhaling the IMP, then all of them will be considered for the above mapping rules. Spirometries collected at 1h and 4h post dose will be used only for safety evaluations and will only be presented in data listings.

Windowing will be applied to the data prior to any missing data imputation.

9.5 Handling of Missing Data

9.5.1 Handling of Missing Efficacy Data

If a patient prematurely discontinues clinical trial participation for any reason apart death, re-transplantation or withdrawal of consent, he/she will be encouraged to complete the follow-up. All observed available data will be used for the primary CCI [redacted] analyses. The assumption of the LMM (section 14.1) for missing data will be MAR. Since the definition of progression of BOS

includes all relevant intercurrent events (IEs) as failures, drop-outs due to other reasons will be treated as non-informative censoring (section 14.3.2).

9.5.2 Handling of Missing Safety Data

In general, missing clinical laboratory data, vital signs, and physical examination data will not be imputed. Unknown or partial medication and AE date imputations are given in the next section and to be used only for the assessment of prior/concomitant status for medications and treatment-emergent status for AEs.

9.5.3 Handling of Partial and Missing Dates

9.5.3.1 Partial and Missing Dates of Birth

Only the year is recorded for the Date of Birth, therefore there will not be any imputation.

9.5.3.2 Missing or Partial AE and Prior / Concomitant Medication Start and End Dates

Missing and/or incomplete dates for medications and AEs are imputed in a manner resulting in the earliest onset or the longest duration during the Treatment Period, whilst ensuring that the start date does not occur after the stop date.

For the derivation of the duration and cumulative of concomitant medication, if the medication is "Ongoing" then the medication end date will be imputed with the last visit date.

The stop date will not be imputed if the AE is "Ongoing". Technically, this will be done as follows:

- For a missing/incomplete start date/time, the earliest date/time of the following will be imputed:
  - The later date / time of: the earliest possible start date/time and the date/time of first dose of treatment (date/time of randomization).
  - The latest possible start date/time.
- For a missing/incomplete stop date/time, the later date/time of the following will be imputed:
  - The earlier date/time of: the latest possible stop date/time and the date/time of last dose of treatment (date/time of study completion or early termination).
  - The earliest possible stop date/time.
- Here, the earliest possible date/time is defined as:
  - The date/time itself if available.

- The date/time of the first day of the month at 00:00hrs, if month and year are available but the day/time is missing.
- The date/time of the first day of the year at 00:00hrs, if year is available but day/time and month are missing.
- 00:00hrs on the day of informed consent, if the date/time is completely missing.

- The latest possible date/time is defined as:
  - The date / time itself if available.
  - The date / time of the last day of the month at 23:59hrs, if month and year are available but the day / time is missing.
  - The date / time of the last day of the year at 23:59hrs, if year is available but day / time and month are missing.
  - 23:59hrs on the date of last known date on the study for the patient plus one year, if the date / time is completely missing.

10 DISPOSITION

The number of patients screened, failed screening (patients who did not meet all eligibility criteria and was not randomized)**,** enrolled (patients with informed consent and all eligibility criteria met or randomized), treated but not randomized, randomized (treated, and not treated with clinical trial treatment), completing clinical trial treatment (and reasons for not completing), and completing the clinical trial (and reason for not completing) will be presented in frequency tables by treatment group.

The number of patients in each analysis population (SAF, FAS, and PPS) will be summarized by treatment group. A by-patient listing of disposition will be provided.

All major protocol deviations will be presented as a frequency table by treatment group and in a by-patient listing for all randomized patients, which will include the category of the deviation, the deviation text, and whether the patient was excluded from PPS.

In addition, the counts on major COVID-19 related PDs will be provided, together with a by-patient listing for all COVID-19 related PDs.

In addition, a listing of the patients affected by Coronavirus Disease of 2019 (COVID-19) and their COVID-19 AE details will be provided for the FAS.

A table for the summary of stratification factors by treatment group for FAS and a separate listing of patients with mis-stratifications will be displayed.

11 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, AND DISEASE AND MEDICAL HISTORY

11.1 Demographic and Baseline Characteristics

All demographic, baseline characteristics, including azithromycin at randomization, and antibody-response data will be summarized by treatment group for SAF, FAS and PPS. For summary purposes, the most recent, non-missing result obtained on or prior to the baseline visit will be used.

Azithromycin at randomization will be derived by identifying azithromycin among medications collected in the study (generic name: azithromycin) using any of the following rules:

- azithromycin is ongoing at the date of randomization (regardless of start date)
- azithromycin start date is on the randomization date (regardless of end date)

By-patient listings will be provided for all demographic and baseline characteristics.

11.2 Disease and Medical History

Details of History of BOS diagnosis eCRF page [FVC (absolute), FVC - % of personal best post-transplant, FEV_1 (absolute), FEV_1 - % of personal best post-transplant, CCI (absolute), CCI - % of personal best post-transplant and FEV_1/FVC (ratio)], details of Historical Spirometry eCRF page [FVC (absolute), FEV_1 (absolute), CCI (absolute) and FEV_1/FVC (ratio)] as well as details related to each patient's lung transplant as recorded in the Lung Transplantation History eCRF page [type of underlying indication for lung transplant, time between lung transplantation and onset of BOS, donor gender, cytomegalovirus (CMV) status donor, CMV status recipient, Epstein Barr Virus (EBV)-status donor, EBV-status recipient, receive induction therapy, receive antiviral/antifungal/antibacterial therapy, cold ischemia duration for right and left lung] will be summarized by treatment group for SAF, FAS and PPS.

Disease history, including the details from the Risk Factors eCRF will be listed by FAS.

Time (days) between lung transplantation and onset of BOS is defined as the duration between date of lung transplantation and onset of initial BOS + 1.

All other significant medical conditions (including gastro-esophageal reflux disease) and procedures (including past surgeries) occurring before the informed consent form is signed will be recorded as medical history.

Medical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) [Version 23.1] and will be presented by Internationally Agreed order System Organ Class (SOC) and Preferred Term (PT) and total. The SOCs and PTs are to be sorted by SOC and descending PTs.

Medical history will be summarized by treatment group and overall for the SAF, FAS and PPS as follows:

- The number and percentage of patients with at least one medical history record will be presented.
- The number and percentage of patients with at least one medical history record within each primary SOC and PT will be presented. The summary will be sorted using the internationally agreed order for SOC and using descending order of overall numerical counts for PT. Where terms tie, these will be sorted alphabetically.

Medical history records will be listed by-patient and within-patient by medical history start date for the FAS.

11.3 Baseline Lung Allograft Dysfunction

Baseline Lung Allograft Dysfunction (BLAD) at time of personal best post-transplant FEV_1 (Yes, No) will be reported in the demographic table. BLAD patients are defined as patients with personal best post-transplant FEV_1/predicted FEV1*100 <80% [7]. The following formula for the calculation of predicted FEV1 will be used:

$$\text{Predicted } FEV_1 = b_0 + b_1 * \text{age} + b_2 * \text{age}^2 + b_3 * \text{height}^2$$

where the coefficients of the regression are reported in Table 2.

Table 2: Coefficients for FEV_1 Prediction

Sex	Ethnicity	Intercept (b_0)	Age (b_1)	Age^2 (b_2)	Ht (cm)^2 (b_3)
Male	Caucasian < 20 yr of age	−0.7453	−0.04106	0.004477	0.00014098
Male	Caucasian ⩾ 20 yr of age	0.5536	−0.01303	−0.000172	0.00014098
Male	African-American < 20 yr of age	−0.7048	−0.05711	0.004316	0.00013194
Male	African-American ⩾ 20 yr of age	0.3411	−0.02309	0	0.00013194
Male	Mexican-American < 20 yr of age	−0.8218	−0.04248	0.004291	0.00015104
Male	Mexican-American ⩾ 20 yr of age	0.6306	−0.02928	0	0.00015104
Female	Caucasian < 18 yr of age	−0.8710	0.06537	0	0.00011496
Female	Caucasian ⩾ 18 yr of age	0.4333	−0.00361	−0.000194	0.00011496
Female	African-American < 18 yr of age	−0.9630	0.05799	0	0.00010846
Female	African-American ⩾ 18 yr of age	0.3433	−0.01283	−0.000097	0.00010846
Female	Mexican-American < 18 yr of age	−0.9641	0.06490	0	0.00012154
Female	Mexican-American ⩾ 18 yr of age	0.4529	−0.01178	−0.000113	0.00012154

The age to be considered is at the time of personal best post-transplant FEV_1 (it has to be derived based on the date of personal best post-transplant FEV_1 versus the date of collection of Demographic information). Since only the year of birth is provided in the CRF, the age at the time of personal best post-transplant FEV_1 will be calculated considering the central day of the year for all patients (02/JUL/YEAR OF BIRTH).

Due to eCRF study design, ethnicity has not been recorded as required for Table 2, and as a result, the race field as recorded in the eCRF will be used for mapping as detailed below in Table 3.

Table 3: eCRF Race Classification

eCRF Term	Remapping
White	Caucasian
Black or African American	African-American
Asian	0.88% reduction will be used versus the Caucasian
Other	check "other, specify" to see additional race info. - If patients are defined as “white” or “black/African”, please use the corresponding classification. - If patients are defined as "latinos" , then use “Mexican-American”. - If patient is defined as “Arabian” then treat as the Asian category with the 0.88% reduction used versus the Caucasian. Otherwise consider them as "unknown"

For Asian or Other field with Arabian ethnicity, the calculation will be performed using the Caucasian coefficients of Table 2 (considering the corresponding sex, age, and height values) and then applying a correction factor of 0.88 [88]. For example, in case of an Asian male patient older than 20 years, the calculation will be:

Predicted $FEV_1 = 0.88 * (0.5536 - 0.01303 * age - 0.000172 * age^2 + 0.00014098 * height^2)$.

In case of other races (American Indian or Alaskan, Native, Native Hawaiian or Other, Pacific Islander), unknown, or unspecified ethnicities (including “multiracial”, “multicultural”, “mixed”, etc.), parameters calculated as average of the Caucasian, African-American, and Mexican-American parameters will be used, according to Table 4:

Table 4: Coefficients for FEV_1 Prediction for other/unspecified ethnicities.

Sex	Age class	Intercept (b_0)	Age (b_1)	Age^2 (b_2)	Ht (cm)^2 (b_3)
Male	< 20 yr of age	-0,7573	-0,04688	0,004361333	0,000141
Male	⩾ 20 yr of age	0,508433	-0,0218	-0,0000573	0,000141
Female	< 18 yr of age	-0,9327	0,062753	0	0,000115
Female	⩾ 18 yr of age	0,409833	-0,00941	-0,000134667	0,000115

12 Immunosuppressants

Immunosuppressants are collected in the Concomitant Medications CRF form.

As per CRF completion guidelines, immunosuppressants are to be collected using the same measurement unit i.e., mg. In those cases where it is not done, considerations will be taken on ongoing basis (at DRM at the latest) to convert units for each immunosuppressive agent to allow cumulative dose to be calculated. Immunosuppressant medications will be coded using the World Health Organization (WHO-DD) classification system and grouped by drug class and PT.

In order to identify immunosuppressants among concomitant medications, any of the following two rules will be applied.

1. Only the following routes are to be considered: oral, intramuscular, intravenous, and subcutaneous; the following codes are to be considered:
    - L04A Immunosuppressants:
        1. L04AA Selective immunosuppressants,
        2. L04AB Tumor necrosis factor alpha (TNF-α) inhibitors,
        3. L04AC Interleukin inhibitors,
        4. L04AD Calcineurin inhibitors,
        5. L04AX Other immunosuppressants;
    - H02AB Glucocorticoids (all);
2. L04AD02 Tacrolimus, and route = sublingual.

CCI [redacted]

12.1 Basic Immunosuppressants

As per protocol, regardless of treatment assignment, all clinical trial participants must be on a maintenance regimen of immunosuppressive agents including tacrolimus, a second agent such as but not limited to mycophenolate motfetil (MMF) or azathioprine, and a systemic corticosteroid such as prednisone as third agent. At each visit, the average maintenance doses of immunosuppressive agents will be recorded by the Investigator on the Concomitant Medication eCRF.

Basic immunosuppressants refer to maintenance regimen of immunosuppressive agents and include the following:

- Calcineurin inhibitors (Tacrolimus, Cyclosporine A);

- Antimetabolicte (Antimetabolite) agents (MMF, Azathioprine);
- mTOR inhibitor (Everolimus, Sirolimus);
- Selective costimulation blocker (Belatacept);
- Corticosteroids.

The total basic immunosuppression administered from the day of randomization will be evaluated.

Basic immunosuppressives will be coded by Anatomical Therapeutic Code (ATC) codes, and will be summarized by treatment group for SAF, FAS and PPS.

A p-value will be obtained from the Fisher's Exact test for the comparison of patients with any basic immunosuppressants from L-CsA plus SoC versus patients with any basic immunosuppressants from SoC alone, for each class of basic immunosuppressants listed above.

Descriptive statistics on cumulative doses for basic immunosuppressants will be provided:

- for the whole treatment period (from day of randomization to end of study)
- for each period between study visits (V1 to V2, V2 to V3, etc.)
- cumulatively for each period between study visits (V1 to V2, V1 to V3, V1 to V4, etc.),

where periods between study visits V_i to V_{i+1} (with i=2,3,4, etc) is defined as the interval starting from the first day post visit V_i and ending the last day of visit V_{i+1} (included). For V1 to V2 the date of V1 must be considered too.

Descriptive statistics will be calculated for each class of basic immunosuppressants listed above and overall. If a patient took more than one basic immunosuppressant related to the same class, then the total dose will be taken into consideration in the calculation.

P-values will be obtained from the Fisher's Exact test for the comparison of patients with any basic immunosuppressants, including each of basic immunosuppressant listed above from L-CsA plus SoC versus patients with any basic immunosuppressants from SoC alone at each time interval (V1 to V2, V1 to V3, …. ,V1 to V9).

Exposure to immunosuppressant medication details will be summarized similarly for each category of basic immunosuppressant, and overall for all.

This includes the calculation of the duration of intake (date of last basic immunosuppressant intake – date of first basic immunosuppressant intake + 1). The duration will be calculated by summing the duration of the associated treatments. The overlapping days will be counted only once.

The ratio between the cumulative dose and intake duration will be used to produce the dose per day. The overall dose per day per patient will then be displayed for each treatment group for each time interval along with the 95% confidence interval.

By-patient listings will be provided for all basic immunosuppressants for FAS.

12.2 Other Immunosuppressants

Other immunosuppressants refer to all the immunosuppressive therapies that are not classified as maintenance regimen as described in section 12.1 (but meet the conditions reported in section 12). Other immunosuppressive therapies will be coded by ATC codes, and will be summarized by treatment group for SAF, FAS and PPS.

All other immunosuppressants administered from the day of randomization will be evaluated. The number (%) of patients taking any other immunosuppressants will be provided overall and for each ATC code.

The same summary statistics for cumulative dose and for exposure as described in section 12.1 will be provided.

13 Prior and concomitant medications

Prior medications are those medications taken prior to randomization with a stop date and time prior to the randomization date/time (standard definition of prior/concomitant medications considers the first dose of study treatment but, as in this study SOC group won't have any first dose date, randomization date will be considered instead).

Concomitant medications are those medications with a start date and time on or after the randomization date/time, or those with a start date and time before the randomization date/time and either a stop date and time on or after the study randomization or are ongoing at the end of the study.

Prior and concomitant medications will be summarized by ATC codes and listed for FAS. Prior/concomitant medications will be coded using the WHO-DD classification system and grouped by drug class and PT.

14 EFFICACY

For each efficacy analysis, the adequacy of the model assumptions will be checked, and if it is found that these are inadequate then alternative approaches may be performed.

For all variables assumed to be normally distributed, the conditional studentized residuals from this model will be tested using the Shapiro-Wilk test. If the assumption of normality of these residuals is violated, then a log-transformed model will be fitted. The need for a possible log transformation of these variables will be investigated prior to unblinding by assessing the model

residuals without a treatment term. Where data are transformed for analysis, back transformation will be applied for the presentation of results. Presentation of the tables will be amended as needed for this, with the addition of an explanatory footnote.
Classification and imputation of missing data will be completed prior to any transformation of the data for analysis.

As a general remark for all efficacy endpoints based on spirometry data, values collected at 1h and 4h post dose will not be used for any efficacy analyses as they are collected only for safety evaluations.

It is important to note that due to the decrease in sample size (see section 8.2) the study will be underpowered for the assumed effect to assess the statistical hypothesis for the primary endpoint. The statistical modelling for the primary endpoint for the pre-specified covariates may lead to non-convergence of the models and selective covariates will have to be considered. Supplementary analyses for the primary endpoint, CCI will adopt simple statistical analyses. As a result, all analysis for this study will be descriptive in nature.

14.1 PRIMARY EFFICACY ANALYSIS

14.1.1 Analysis Population and Estimand

The primary endpoints will be analyzed using a "composite strategy" (International Conference on Harmonization (ICH) guideline E9 addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials). The estimand is defined by the following:

- Population: adult recipients of a single pulmonary allograft with clinically defined BOS, matching the inclusion and exclusion protocol criteria.
- Variable: FEV_1 data at Week 48 (visit 9) collected from the on site CCI spirometer (data collected with the CCI home spirometer will be used for supplementary analyses). Only accepted over-reader best FEV_1 data for the session from CCI will be used for analysis; data will not be re-derived.
- Intercurrent events: After IEs such as stopping treatment with L-CsA, augmentation of SoC therapy, etc., FEV1 measurements will still be collected and used in the analysis. In case of IEs preventing the use of FEV1 measurements, i.e. death and re-transplantation, the FEV1 will be imputed as treatment failure: FEV1 equal to zero for all visits subsequent the event. Rejected spirometries are those that did not meet the American Thoracic Society criteria; if rejected, then they would be re-done but there may be cases where they are rejected twice and resulting in missing data. Rejected spirometry is not an indicator of a better/worse outcome and can be assumed to be MAR.

- Population-level summary: difference in mean change from baseline in the FEV1 at week 48 between treatment groups.

14.1.2 Working Hypothesis

The alternative hypothesis (H_1) for this trial is that L-CsA plus SoC is superior to SoC alone in preserving FEV_1, i.e., under H_1 it is expected that patients treated with L-CsA plus SoC will exhibit a smaller mean FEV_1 decline between baseline and the end of Week 48 than those who receive SoC alone.

Due to the decrease in sample size (see section 8.2) then there will be an underpower to assess the statistical hypothesis, and instead the primary analysis will be descriptive in nature.

14.1.3 Analysis Model

The primary efficacy analysis will be carried out using a LMM for repeated measurements, using all observed available FEV_1 measurements. In case of death or re-transplantation events, FEV_1 will be imputed as zero at each nominal day post event.

The dependent variables are the absolute change from baseline of FEV_1 measurements at visit 2 (i.e., the first post-baseline visit) through visit 9 (Week 48). For the definition of baseline FEV_1 please refer to section 8.1.1.

A flexible and robust model will be chosen for the random part of the LMM according to a pre-specified stepwise procedure (see next section). The original protocol considered the fixed part of the LMM containing the following (except from the intercept): time cubic splines, treatment, the interactions of time splines by treatment, baseline FEV_1, the interactions of time splines with the baseline FEV_1, region (North America versus all other countries together), underlying indication for lung transplant (COPD versus all others), and use of azithromycin at randomization (i.e. Baseline, Visit 1). Due to the reduced sample size (see section 8.2), the covariates will be selected taking into account model convergence (as detailed below).

The primary efficacy parameter will be estimated from the model by the adjusted difference between treatment groups in mean FEV_1 change from baseline after 48 weeks. The p-value for the null hypothesis of no difference and a two-sided 95% confidence interval for the difference will be provided. The comparison between treatment groups at all the other visits (2-8) will also be presented.

A figure of observed mean change from baseline and standard errors at each visit, by treatment group will be presented. A figure with adjusted mean changes from baseline at each visit by treatment group derived from the LMM will be provided.

14.1.4 Specification of the Model

For valid inference on the primary efficacy parameter, the evolution of FEV_1 in both treatment groups should be modeled as a flexible function in time, without unnecessarily strong assumptions.

Therefore, time will be modeled assuming that the time evolution of FEV_1 is a smooth function of time. Cubic splines will be used with a large enough number of parameters to minimize the risk of misspecification. We will choose one knot at 182 days, i.e., halfway between the first (day 28) and the last scheduled measurement (337 days). So, it is assumed that the mean of FEV_1 is a third-degree polynomial at each of the two intervals, smoothly connected, equal at day 182 with equal first and second derivative. Thus, 4 parameters per group are used to model time. In total, as many as 12 parameters in the model will involve time, ensuring robust estimation of the time evolution of FEV_1. Denoting the covariates associated with the splines by $S_1=t$, $S_2=t^2$, $S_3=t^3$ and $S_4=\max(t-182,0)^3$, the treatment group by T (0=SoC; 1=L-CsA plus SoC), the day of the measurement by t and the baseline FEV_1 by X, the fixed part of the model will contain the following covariates:

Intercept, S_1, …, S_4, T, $T*S_1$,…, $T*S_4$, X, $X*S_1$,…, $X*S_4$, other covariates

The Kenward-Roger adjustment will be used for the denominator degrees of freedom needed for hypothesis tests and confidence intervals.

The other covariates are:

- underlying indication for lung transplant (COPD versus all others)
- Region (North America versus all other countries together)
- Use of azithromycin at randomization.

In case of collinearity or non-convergence, covariates will be dropped in the above order, starting with the last. With the final selection of covariates in the model in place, the random part of the LMM will then be selected by comparing the Akaike Information Criterion (AIC) of three models:

- model with random intercept and random time;
- model with random intercept, random time and random squared time;
- model with random intercept, random time, random squared time, and random cubic time.

The model with the lowest AIC will be adopted for the primary analysis.

The core excerpt of CCI code for the primary analysis is reported in section 17.1.

14.1.5 Specification of the Covariance Model

The model for the mean uses the actual times of the visits as a continuous variable instead of the scheduled visit times. Therefore, the covariance model will also use the actual visit times, using random effects. For valid inference, the model for the covariance should be correctly specified.

Thus, the preference will be for models with relatively many parameters in order to ensure robust estimation of the covariance, though this may lead to a loss of efficiency.

Therefore a model will be specified with four per patient random effects: intercept, t, t^2 , t^3, with an unstructured covariance matrix. This covariance model contains 11 parameters, ensuring sufficient robustness. In case the model does not converge, or the covariance matrix is not positive definite, we will drop terms from the highest order random effect.

14.2 Supplementary Analyses for the Primary Endpoint

Supplementary analyses can provide additional insights into the understanding of a treatment effect.

14.2.1 ANCOVA

The population-level summary for the variable will be altered. An analysis of covariance (ANCOVA) model will be performed on the changes from baseline in FEV_1 to Week 48, using the same stratification factors and the same covariates described for the LMM for the primary efficacy analysis (except for time factors). In case of death or re-transplantation events, FEV_1 will be imputed as zero at each nominal day post event.

In case of violation of the normality assumption even after log transformation (section 14), then rank transformation will be applied to normalize the data. The same ANCOVA model will be applied to the rank-transformed data.

14.2.2 T-test

The mean treatment difference in change from baseline up to Week 48 in FEV_1, standard deviation and 95% confidence interval will be presented. A two-sample t-test will be performed by treatment group at each visit using change from baseline in FEV_1.

In case of death or re-transplantation events, FEV_1 will be imputed as zero at each nominal day post event.

14.2.3 PPS

The analysis will be conducted as described for the primary endpoint but will be performed on the PPS.

14.2.4 CCI data

The endpoint for the estimand will be spirometry data stored on the CCI. The analysis will be conducted as described for the primary endpoint but on CCI data.

14.2.5 The impact of COVID-19

The COVID-19 pandemic has impacted the conduct of the study and might have impacted its results for different aspects including infections, quarantines, social distances [4], and other considerations linked to the different ways that each site has faced the pandemic. Date of COVID-19 outbreak was set at March 11, 2020 and different analyses will be performed to assess the impact of the COVID-19 pandemic to the study pre and post pandemic. In case evidence of an impact of pandemic on study endpoints should emerge, considerations on how the initial study assumptions have been altered must be done, and changes in the statistical criteria for final judgment should be applied.

14.2.5.1 Patients impacted by COVID-19 pandemic

The analysis of primary endpoint will be performed using the LMM described in the primary analysis with the inclusion of additional categorical covariates:

- A binary covariate representing if patients have been affected by COVID-19 during the treatment period:
  - Affected, if an AE of COVID-19 is reported in the eCRF AE page between randomization and date of study completion/premature discontinuation/withdrawal of informed consent in the EOS page.;
  - Not affected, if no AEs of COVID-19 are reported in the eCRF AE page between randomization and date of study completion/premature discontinuation/withdrawal of informed consent in the EOS page..
- A binary covariate representing if patients have been randomized before or after the COVID-19 pandemic outbreak:
  - Before, if date of randomization is before 11 March 2020;
  - After, if date of randomization is equal or after 11 March 2020.

FEV_1 data will be descriptively summarized by impact of COVID-19 (COVID-19 affected vs Not COVID-19 affected, and randomized before COVID-19 Pandemic Outbreak vs randomized after COVID-19 outbreak) at each visit, by treatment and overall. The treatment comparison for difference in mean change from baseline in the FEV_1 at week 48 will be carried out using t-tests as described in section 14.2.2, including both newly created binary covariates. This will also be performed for each of the subpopulations defined by the binary covariates above i.e. patients affected/not affected by COVID-19 during the treatment period and patients randomized before/after the COVID-19 pandemic outbreak.

Furthermore, it is of interest to categorize each visit for each patient to assign these before or after the COVID-19 pandemic outbreak. A summary table will be produced to descriptively display the effects of FEV_1 over time by taking each visit with respect to the COVID-19 outbreak pandemic

date into consideration. The treatment comparison for difference in mean change from baseline in the FEV_1 at week 48 will be analyzed similarly using the t-test as described in section 14.3 for both groups, visits before COVID-19 pandemic outbreak, visits after COVID-19 pandemic outbreak.

The observed mean change from baseline and standard errors of FEV_1 at each timepoint will be graphically reported by treatment and by impact of COVID-19 categorization. This will also be displayed by COVID-19 pandemic outbreak at each visit. Furthermore, a figure with adjusted mean changes from baseline at each visit by treatment group derived from the LMM with impact of COVID-19 will be provided.

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14.5 SUBGROUP ANALYSES

Analyses of primary CCI [redacted] endpoints will be performed on the following subgroups of patients:

- Age class (<55 years, ≥55 years),
- Gender (female, male, undifferentiated),
- Region (North America, all other countries together),
- Severity of disease, defined by:
  - % of baseline FEV_1 over personal best FEV_1 post-transplant (baseline FEV_1 >80%, >65–80%, >50–65%, and ≤50% of personal best FEV_1 post-transplant),
  - baseline FEV_1 % of predicted (<70%, ≥ 70%),
  - baseline FEV_1/FVC ratio (< 0.7, ≥ 0.7),
  - BLAD at time of personal best post-transplant FEV_1 (Yes, No);
- Race (American Indian or Alaskan Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, Other).

- Use of azithromycin at randomization (Yes/No)

Subgroup levels may be pooled to have an adequate number (≥ 10) of patients per strata to perform the analysis. Decision on pooling will be taken during the blinded DRM, before data base lock.

Within each subgroup level, descriptive analyses (section 8.1) will be performed on:

- FEV_1,
- FEV_1/FVC,
- Time to Progression of BOS.

FEV_1 and FEV_1/FVC change from baseline will be compared using a two-sample t-test (assuming unequal variances) or, if the required assumptions are not met, a two-sample Mann–Whitney U test.

Comparison of time to progression of BOS curves among treatments will be performed with the log-rank test.

15 SAFETY DATA

15.1 General Considerations

Summaries of safety data (e.g., AEs, laboratory data, vital signs) will be provided for the SAF. No inferential analyses are planned for safety endpoints.

15.2 Extent of Exposure

15.2.1 Exposure to L-CsA

Exposure to the investigational medicinal product (IMP), L-CsA will be confirmed based on the report of IMP vials returned and dosing recorded in the eCRF. IMP vials that were missing will not be included in the counts of returned (i.e. used) vials; this will also apply where vials are missing but the patients were considered to have taken the vials. A summary table will be prepared including the following details about administration of L-CsA:

- Descriptive statistics for the total vials planned. This is calculated as ([date of last dose – date of randomization + 1] x 2 vials);
- Descriptive statistics for the total actual dose (mg). This is calculated as total empty (used) vials multiplied by dose;
- Descriptive statistics for the duration of treatment in days and weeks. For each patient, the treatment duration will be calculated as the difference between the dates of last and first administration of L-CsA plus 1;

- Descriptive statistics for the duration of treatment in days and weeks, excluding the inhalation temporarily discontinued. For each patient, the treatment duration will be calculated as the difference between the dates of last and first administration of L-CsA plus 1, excluding the days of any inhalation temporarily discontinued. Derivation: (date of last dose – date of first dose + 1) - (stop date of inhalation temporarily discontinued– start date of inhalation temporarily discontinued +1).

Compliance of L-CsA using the drug accountability data is calculated as the total empty (used) vials returned divided by the total vials planned, and will be summarized on the FAS population. For the evaluation of compliance, all the planned vials up to the actual end of treatment for each patient will be considered in the calculation.

By-patient listings will present all IMP administration data.

15.2.2 Exposure to Study treatment (SoC or SoC+L-CsA)

SoC therapy period starts at randomization date and stops at date of study completion or early termination. L-CsA treatment period starts at date of first dose of L-CsA and stops at the date of last dose administered.

Descriptive statistics for the duration of any study treatment (SoC or SoC+L-CsA) in days and weeks will be provided. Since the SoC will cover the entire study period post-randomization, the study treatment duration (SoC or SoC+L-CsA) will be calculated as the difference between the date of study completion/early termination and randomization plus 1.

15.3 Adverse Events

All AEs occurring during the clinical trial, whether or not attributable to study treatment, will be documented in the eCRF. All AEs will be coded to SOCs and PTs using the MedDRA dictionary (version 23.1).

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset on or after the date of randomization.

The Investigator will assess the relationship (unrelated, possible, definite) of each AE to the clinical trial treatment assignment (L-CsA plus SoC or SoC alone). Treatment-related AEs are defined as events the Investigator considers to be possibly or definitely related to clinical trial treatment assignment.

All AEs reported in the eCRF will be presented in by-patient listings for the SAF.

The following summaries will be presented for AEs by treatment group and overall:

- Overview table including the number and percent of patients with
  - AEs;
  - TEAEs;
  - TEAEs leading to discontinuation of study treatment;
  - TEAEs leading study discontinuation;
  - TEAEs leading to death;
  - TEAEs by severity (Mild, Moderate, Severe);
  - Study treatment related TEAEs;
  - Serious TEAEs;
  - Serious study treatment related TEAE;
- TEAEs, grouped within SOC by decreasing frequency of PT;
- TEAEs by decreasing frequency of PT;
- TEAEs leading to discontinuation of study treatment, grouped within SOC by decreasing frequency of PT;
- TEAEs leading to study discontinuation, grouped within SOC by decreasing frequency of PT;
- TEAEs leading to death, grouped within SOC by decreasing frequency of PT;
- TEAEs by maximum severity, grouped within SOC by decreasing frequency of PT;
- TEAEs by relationship, grouped within SOC by decreasing frequency of PT;
- Serious TEAEs, grouped within SOC by decreasing frequency of PT;
- Related serious TEAEs, grouped within SOC by decreasing frequency of PT.

Patients who have multiple events coded to the same PT or within the same SOC will be counted only once in the patient counts for the corresponding summaries, but all events will be considered and listed. Table presentations will contain counts of patients, percentages of patients, and the number of events.

Any AE with missing relationship will be assumed related and summarized in the possible related category to clinical trial treatment assignment. Patients who experience the same event multiple times will be included in the most related category for summarization.

In summaries including severity, the following severity categories will be summarized: ‘Mild’, ‘Moderate’, ‘Severe’. Any AEs with missing severity will be assumed as ‘Severe’. Patients who experience the same event multiple times will be included in the most severe category.

AE summaries will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the L-CsA plus SoC column.

The following by-patient listings will be provided:

- AEs;
- TEAEs;
- TEAEs leading to discontinuation of study treatment;
- TEAEs leading to study discontinuation;
- TEAEs leading to death;
- Study treatment related TEAEs,
- Serious TEAEs.

These listings will include at least: center, patient identifier, treatment group, AEs (SOC, PT, and verbatim term), AE start date/time, AE end date/time, duration of AE, severity, seriousness, action taken, outcome and relationship.

15.3.1 Infections

All infections will be reported as AEs on the AE eCRF. The summaries described in this section will be provided for treatment-emergent infections (defined as for TEAEs). Treatment-emergent infections will be summarized on the basis of information reported on the AE eCRF.

For any infection, the following summaries will be presented by treatment group:

- Number (percent) of patients with at least one infection
- Number and % of infections per patient (0, 1, 2, …)
- Descriptive statistics for number of infections per patient

The number of infections per patient and per patient-years (cumulative follow-up of each patient) will be provided by year (e.g., 2019, 2020, 2021, etc.) and overall.

A by-patient listing summarizing information on infections will be provided on SAF set.

15.3.2 Malignancies

All malignancies must be confirmed by histopathology. Malignancies are documented as AEs, and will be coded by SOC and PT. The summaries described in this section will be provided for treatment-emergent malignancies (defined as for TEAEs). Malignancies will be identified through a blinded medical review of collected AEs. The result of the medical review will be a flag for the identification of malignancies added in an excel sheet, that will be imported for analysis.

A summary table by SOC and PT and by-patient listing summarizing information collection will be provided on SAF.

15.4 Acute Tolerability of IMP

At Visit 1, acute tolerability of IMP (L-CsA) during initial dosing will be determined by measuring:

- Spirometry (FEV_1, CCI , FVC) measured before and CCI .
- Spontaneous report of cough or dyspnea, recorded as AE in the appropriate eCRF.

Descriptive statistics of pre-dose (V1), post-dose (CCI) and change from pre-dose will be presented for each spirometry parameter on the SAF population.

In addition, the number and percent of patients experiencing a decline of CCI in FEV_1 will be presented.

The number and percent of patients experiencing new onset or worsening of TEAEs having the following PTs on the date of the first visit at which L-CsA is administered will be summarized:

- Cough;
- Dyspnea.

15.5 Clinical Laboratory Data

15.5.1 Hematology and Biochemistry

Clinical laboratory assessments will be performed at each visit by a certified local facility following the routine protocols at each site. As described in the clinical trial protocol (Section 13.1.5), the following clinical laboratory parameters will be reported in the eCRF:

Hematology

- White Blood Cell (WBC) count with differential,
- Red Blood Cell (RBC) count,
- Platelet count,
- Neutrophils,
- Lymphocytes,
- Monocytes,
- Eosinophils,
- Basophils,
- Neutrophils Absolute Count,
- Lymphocytes absolute counts,
- Eosinophils absolute count,
- Basophils absolute count,

- Monocyte absolute count.

Biochemistry

- Alkaline phosphatase (AP),
- Alanine aminotransferase (ALT),
- Aspartate aminotransferase (AST),
- Gamma Glutamyl Transferase (γ-GT),
- Blood urea nitrogen (BUN),
- Serum bilirubin,
- Serum creatinine,
- Sodium,
- Potassium,
- Chloride,
- Bicarbonate,
- Calcium,
- Magnesium.

Descriptive statistics of observed values and changes from baseline will be presented by visit and treatment group. The summaries described in this section will be presented relative to baseline, defined as the most recent, non-missing result on or before the date of randomization. No imputation for missing data will be performed.

All clinical laboratory data reported in the eCRF will be presented in by-patient listings.

15.5.2 Blood Sampling CNI/mTOR Inhibitors

A whole blood sample for the determination of blood sampling calcineurin inhibitor/mammalian target of rapamycin (CNI/mTOR) inhibitors, where for CNI, cyclosporine A and/or tacrolimus trough level will be collected at each visit. In patients allocated to L-CsA plus SoC, the sample should be collected 60 min before L-CsA inhalation. Blood samples will be evaluated by the local laboratories associated with each site. The summaries described in this section will be presented relative to baseline, defined as the most recent, non-missing result on or before the date of randomization. No imputation for missing data will be performed.

All CNI/mTOR data reported in the eCRF will be presented in by-patient listings. Descriptive statistics of observed values and changes from baseline will be presented by visit and treatment group.

15.5.3 Donor Specific Antibody Tests

Serum samples for donor specific antibody testing will be collected at Screening, and at Visits 4, 6, and 9. A by-patient listing of all results will be provided.

15.5.4 Pregnancy Tests

Serum samples from women of childbearing potential will be collected for pregnancy. A by-patient listing of all results will be provided.

15.6 Renal Function

In addition to the summarization of serum creatinine as described in previous section, renal dysfunction will be further listed and summarized by treatment group based upon the classification of AEs with the following PTs (see protocol section 13.1.5.4, Table 7 and SAP section 16):

- Blood Creatinine Increased,
- Renal Impairment,
- Renal Failure,
- Acute kidney injury,
- Azotaemia,
- Chronic kidney disease,
- Proteinuria,
- Renal disorder.

15.7 Vital Signs

Vital signs will be assessed at each visit. The following vital signs will be recorded:

- Systolic and diastolic blood pressure (sitting, after 5 minutes of rest);
- Heart rate (sitting, after 5 minutes of rest);
- Body temperature (the same method should be used for each patient and throughout the trial);
- Respiratory rate;
- Weight.

The summaries described in this section will be presented relative to baseline, defined as the most recent, non-missing result on or before the date of randomization. No imputation for missing data will be performed.

Descriptive statistics of observed values and for changes from baseline will be presented by visit and treatment group on SAF. Vital signs data reported in the eCRF will be presented in by-patient listings.

15.8 Physical Examination

A physical examination will be carried out at Screening and every subsequent visit.

The following body systems will be examined: body weight, cardiovascular, respiratory, nervous, gastrointestinal, hepatic, renal, dermatological, musculoskeletal, extremities, eyes, ears, nose, throat, and lymphatic. Patient height will be measured at Screening Visit only.

All physical examination data, including abnormal findings reported in the eCRF will only be presented in by-patient listing.

16 Changes from Planned Analyses

The following changes from protocol were made.

- The SAF population has been further detailed to better define the actual treatment received by patients.
- CCI [redacted].
- CCI [redacted]
- The protocol amendment version 5.0 Table 1 displaying the 2019 CLAD staging has been amended in this SAP. Table 6 shows the correct descriptions for the 2019 CLAD Staging as reported in Verleden et al., 2019 [3].
- CCI [redacted]
- In section 9.4 further details compared to protocol have been added for handling visits that have more than one accepted spirometry assigned, with some of them performed after IMP inhalation.
- The protocol amendment details the hypothesis to assess for superiority of the L-CsA plus SoC to SoC alone in preserving FEV1, i.e., under H1 it is expected that patients treated with L-CsA plus SoC will exhibit a smaller mean FEV1 decline between baseline and the end of Week 48 than those who receive SoC alone. However, due to the decrease in sample

size then the study will be underpowered to assess the statistical hypothesis, and therefore the primary analysis will be descriptive in nature. CCI [redacted]

- CCI [redacted]
- BOS Progressions will be evaluated up to last assessment, even after treatment discontinuation or completion.
- Additional PTs will be included in the definition of renal dysfunction. In addition to AEs listed in the protocol (Blood Creatinine Increased, Renal Impairment, and Renal Failure), the following AEs will be considered: Acute kidney injury, Azotaemia, Chronic kidney disease, Proteinuria, and Renal disorder.

17 CCI

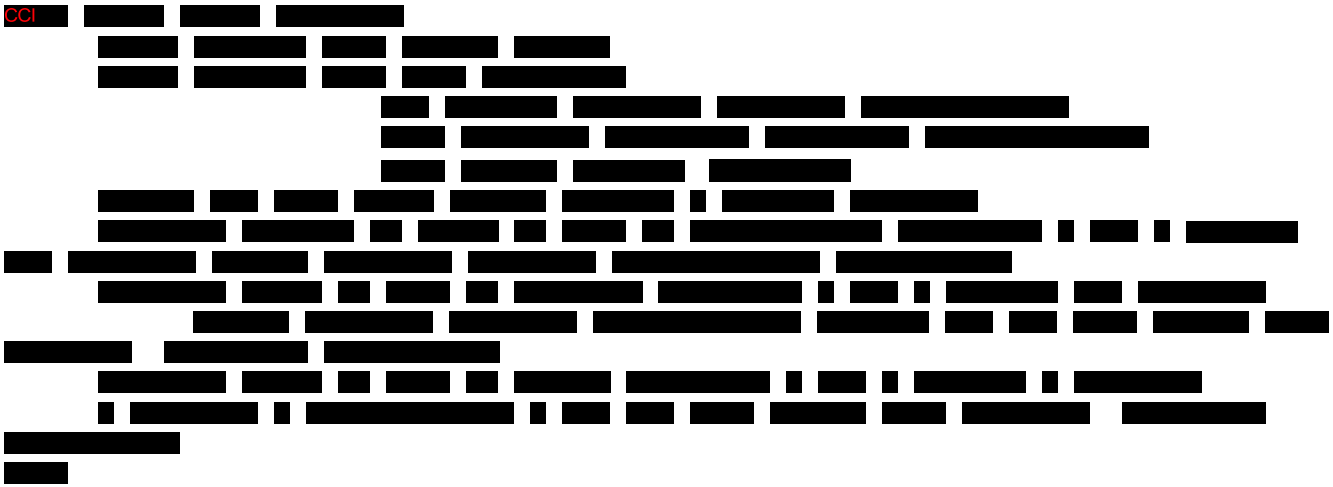
Please refer to Table 7 for details on names and content of the variables used in the CCI of this section.

Table 7: Variable names and descriptions.

Variable Name	Description
CCI	

17.1 Primary analysis

CCI



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19 APPENDICES

Not applicable