CONFIDENTIAL

CLINICAL TRIAL PROTOCOL

BOSTON-4: A Phase IIa Multi-Center, Randomized, Single-Blind Safety and Tolerability Study of inhaled Liposomal Cyclosporine A in Bronchiolitis Obliterans Syndrome Following Allogeneic Hematopoietic Stem Cell Transplantation

Protocol No: BT – L-CsA – 201 – SCT

(BOSTON-4)

EudraCT No.: 2019-000718-13

Version: 5.0

Date: 30 April 2021

Protocol Amendment No 4

SPONSOR

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

INVESTIGATIONAL MEDICINAL PRODUCT

Liposomal Cyclosporine A for inhalation (L-CsA)

1 SIGNATORIES

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Safety Reporting:

CCI

Central PK Laboratory:

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Document History Overview

DOCUMENT HISTORY	
Document	**Date**
Version 4.0 [Amendment 3]	30-Sep-2020
Version 3.0 [Amendment 2]	05-Sep-2019
Version 2.0 [Amendment 1]	26-Feb-2019
Original Protocol Version 1.0	30-Jan-2019

Protocol Acknowledgment / Confidentiality

BOSTON-4: A Phase IIa Multi-Center, Randomized, Single-Blind Safety and Tolerability Study of inhaled Liposomal Cyclosporine A in Bronchiolitis Obliterans Syndrome Following Allogeneic Hematopoietic Stem Cell Transplantation

(Protocol No.: BT – L-CsA – 201 – SCT)

By signing this Protocol, the Principal Investigator acknowledges and agrees:

The Protocol contains all necessary details for conducting the clinical trial. The Principal Investigator will conduct this clinical trial as detailed herein, in compliance with Good Clinical Practice (GCP) and the applicable regulatory requirements, and will make every reasonable effort to complete the clinical trial within the time designated.

The Protocol and all relevant information on the drug and device relating to nonclinical and clinical experience, which was furnished by the Sponsor, Zambon SpA, will be made available to all physicians, nurses and other personnel who participate in the conduct of this clinical trial. The Investigator will discuss this material with them to assure that they are fully informed regarding the Investigational Medicinal Product and the conduct of the clinical trial.

This document contains information that is privileged or confidential. As such, it may not be disclosed unless specific prior permission is granted in writing by the Sponsor or such disclosure is required by federal or other laws or regulations. Persons to whom any of this information is to be disclosed must first be informed that the information is confidential. These restrictions on disclosure will apply equally to all future information supplied, which is indicated as privileged or confidential.

Zambon SpA or its designee will have access to any source documents from which Case Report Form information may have been generated. The Case Report Forms and other data pertinent to this clinical trial are the sole property of Zambon SpA which may utilize the data in various ways, such as for submission to government regulatory authorities, or in publication of the results of the clinical trial.

The conduct and results of this clinical trial will be kept confidential. The results of this clinical trial may be published. Upon completion of the clinical trial it is the intention of the parties to prepare a joint publication regarding or describing the clinical trial and all the results there from and both parties shall co-operate in this regard.

I have read and agree to the protocol numbered BT – L-CsA – 201 – SCT. I am aware of my responsibilities as a Principal Investigator and agree to conduct this clinical trial according to international standards of Good Clinical Practice (International Council on Harmonisation guidelines), applicable government regulations, and Institutional research policies and procedures under the guidelines of International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), national regulations, and the protocol. I agree to appropriately direct and assist the staff under my control, who will be involved in the clinical trial.

Principal Investigator's Signature

Name & Title _____ _____

(Print) Date Signature

Center Name _____

(Print)

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3 ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
ATS	American Thoracic Society
AUC	Area Under the Curve
Bid	*Bis in die*, twice daily
BO	Bronchiolitis Obliterans
BOS	Bronchiolitis Obliterans Syndrome
BDRM	Blind Data Review Meeting
CGI	Clinical Global Impressions
CGvHD	Chronic Graft Versus Host Disease
C_{max}	Maximum concentration
CRO	Contract Research Organization
CsA	Cyclosporine A
CsA-PG	Cyclosporine A Propylene Glycol
CSR	Clinical Study Report
Dl	Deciliter
DLT	Double Lung Transplantation
DMC	Data Monitoring Committee
EC	Ethics Committee
eCRF	Electronic Case Report Form
EoS	End of Study
EoT	End of Treatment
ERS	European Respiratory Society
EU	European Union
EXP	Expiration date
FAS	Full Analysis Set
FEF_{25-75}	Forced Midexpiratory Flow
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
HSCT	Hematopoietic Stem Cell Transplantation
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IMP	Investigational Medicinal Product (L-CsA)

ISF	Investigator Site File
Kg	Kilogram
L	Liter
L-CsA	Liposomal Cyclosporine A
L-CsA CCI	[redacted] Nebulizer System
NHANESIII	Third National Health And Nutrition Examination Survey
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligram
µm	Micrometer
mL	Milliliter
MMRM	Mixed Model for Repeated Measures
mOsmol	Milli Osmoles of solute per litre of solution
N (n)	Number of patients
PCR	Polymerase Chain Reaction
PG	Propylene Glycol
Ph Eur	European Pharmacopeia
PI	Polydispersity Index
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred Term
Q1	Lower Quartile
Q3	Upper Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAF	Safety Analysis Set
SLT	Single Lung Transplantation
SmPC	Summary of Product Characteristics
SoC	Standard of Care
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
t_{max}	Time to reach the maximum concentration
ULN	Upper Limit of Normal
US	United States
USP	United States Pharmacopeia

4 PROTOCOL SYNOPSIS

Protocol Title:	BOSTON-4: A Phase IIa Multi-Center, Randomized, Single-Blind Safety and Tolerability Study of inhaled Liposomal Cyclosporine A in Bronchiolitis Obliterans Syndrome Following Allogeneic Hematopoietic Stem Cell Transplantation
Sponsor:	Zambon SpA Via Lillo del Duca 10, 20091 Bresso (MI) Italy
Protocol Number:	BT – L-CsA – 201 – SCT (BOSTON-4)
EUDRACT Number:	2019-000718-13
IND Number:	78,854
Investigational Medicinal Product:	Liposomal Cyclosporine A (L-CsA) Inhalation Solution 10 mg twice daily (bid) or Liposomal Cyclosporine A L-CsA Inhalation Solution 5 mg twice daily (bid) or Liposomal Placebo (0 mg L-CsA) Inhalation Solution twice daily (bid)
Protocol Phase:	Phase IIa
Protocol Date:	Version 5.0; 30 April 2021
Protocol Amendment	4
Clinical Trial Centers/Countries:	Up to 20 centers in Europe.
Planned Clinical Trial Period:	Duration of therapy: 12 weeks Total clinical trial duration per patient: up to 18 weeks
Planned Number of Patients:	24 patients randomized Randomization: 1:1:1 Patients will receive investigational treatment or placebo via the L-CsA specific [redacted] Nebulizer System (L-CsA CCI), in addition to standard of care (SoC) therapy.

	Treatment A: L-CsA 10 mg bid plus SoC (n=8) Treatment B: L-CsA 5 mg bid plus SoC (n=8) Treatment C: L-CsA 0 mg (placebo) bid plus SoC (n=8)
Objective:	The objectives of this study are to assess the tolerability, safety, pharmacokinetics (PK), exploratory efficacy and quality of life of two doses of aerosolized L-CsA vs placebo in addition to SoC therapy for the treatment of BOS in adult allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients.
Clinical Trial Design:	Phase IIa prospective, multi-center, single-blind, randomized clinical trial assessing two doses of inhaled L-CsA and placebo.
Eligibility Criteria:	***Inclusion Criteria:*** 1. Age ≥ 18 years 2. Patients must have undergone hematopoietic stem cell transplantation and have documented diagnosis of chronic Graft versus Host Disease (cGvHD), guided by the NIH consensus criteria. 3. Patients must have been diagnosed with BOS within >6 months and ≤3 years at Screening visit. 4. Spirometry test carried out at Screening visit must show: • A FEV_1 above 51% of predicted AND • A ≥ 10% decline in FEV_1 (L) within 2 years 5. Patient must be capable of understanding the purposes and risks of the study, has given written informed consent, and agrees to comply with the study requirements. 6. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to randomization and must agree to use one of the methods of contraception listed in Appendix II through their End of Study Visit.
	Exclusion Criteria: 1. Other acute or chronic restrictive or obstructive lung diseases, including but not limited to: active asthma (variable and recurring symptoms of airflow obstruction (reversible to beta-2 agonists) and bronchial hyper-responsiveness), chronic obstructive pulmonary disease, interstitial lung disease, or cryptogenic organizing pneumonia , neuromuscular weakness or diaphragmatic paralysis. 2. Any acute pulmonary bacterial, viral (as confirmed by multiplex PCR) or fungal infection not successfully resolved at least 4 weeks prior to the Screening Visit.

	3. Chronic renal dysfunction with serum creatinine ≥ 2.5 mg/dL. 4. Chronic hepatic dysfunction with serum total bilirubin > 5x upper limit of normal (ULN), transaminases > 5x ULN, or alkaline phosphatase > 5x ULN. 5. Evidence of clinical relapse of the primary malignancy, according to investigator's judgement, which warranted allogeneic bone marrow transplant. 6. Use of azithromycin within 4 weeks prior to Randomization (Visit 1). 7. Chronic oxygen use or use of non-invasive ventilation. 8. Active smokers (i.e. any kind of inhaled nicotine consumption). 9. Pregnant women or women who are unwilling to use appropriate birth control to avoid pregnancy over the course of the clinical trial (for details see Appendix II). 10. Women who are currently breastfeeding. 11. Known hypersensitivity to L-CsA or to cyclosporine A. 12. Patients with life-expectancy of less than 6 months. 13. Receipt of an investigational drug as part of a clinical trial within 4 weeks prior to the Screening Visit. Participation in registries, is allowed. 14. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary procedures. 15. Any co-existing medical condition that in the Investigator's judgment will substantially increase the risk associated with the patient's participation in the clinical trial. 16. Pre-scheduled hospitalizations, surgeries or interventions planned to be performed after obtaining Informed Consent for this study.
Investigational Medical Product:	The L-CsA/Liposomal Placebo is supplied in glass vials containing 10 mg or 5 mg of L-CsA or 0 mg L-CsA. The 10 mg L-CsA or placebo lyophilisate is reconstituted with 2.4 mL 0.25% NaCl and the 5mg L-CsA lyophilisate is reconstituted with 1.2 ml 0.25% NaCl to obtain a ready to use dispersion for inhalation via the L-CsA CCI .
Mode of Administration/ Dosing Schedule:	The investigational medicinal product (IMP) will be administered bid by inhalation (morning/evening). At every visit, one dose administered via inhalation will be monitored by the clinical trial center personnel. Nebulization time per inhalation dose is approximately 5-10 minutes for the 5 mg dose and 8-13 minutes for the 0 and 10 mg doses.
Treatment Regimen:	Regardless of treatment allocation, all participants will continue to receive their SoC regimen as prescribed by their treating physician. Patients will be randomized to one of the following treatment groups: ***Treatment A (L-CsA 10 mg treatment plus SoC):*** L-CsA 10 mg/2.5 mL bid for a maximum of 12 weeks plus

	SoC therapy ***Treatment B (L-CsA 5 mg treatment plus SoC):*** L-CsA 5 mg/1.25 mL bid for a maximum of 12 weeks plus SoC therapy ***Treatment C (0 mg L-CsA (placebo) plus SoC***): L-CsA 0 mg/2.5 mL bid for a maximum of 12 weeks plus SoC therapy
Endpoints:	***Primary assessment:*** IMP tolerability and safety during the first 4 weeks of treatment ***Secondary assessments:*** • IMP tolerability and safety during the first 12 weeks of treatment; • CsA PK ***Exploratory efficacy assessments:*** • FEV_1 % predicted at randomization compared to Week 2, Week 4, Week 8, and Week 12 • FEV_1/FVC at randomization compared to Week 2, Week 4, Week 8, and Week 12 • SF-36 Quality of Life Questionnaire at Baseline, Week 2, Week 4, Week 8, and Week 12 visits • Changes in the dose of corticosteroids and immunosuppressive therapy administered throughout trial duration ***IMP Tolerability Parameters:*** • ***Local Tolerability:*** ○ Cough ○ Wheezing ○ Bronchospasm ○ Throat irritation ○ Change in FEV_1 • ***Overall Tolerability:*** ○ Clinical Global Impressions (CGI) scale (on-site only) ○ Investigator's tolerability assessment at Visit 3 and Visit 5 ***Safety Parameters:*** • Adverse events (AEs) • Serious adverse events (SAEs) • Clinical laboratory values • Vital signs • Physical Examination

	Pharmacokinetic Parameters: • PK: (Week 0) at pre-dose; directly after end of inhalation; 15, 30, and 45 minutes, and 1, 1.5, 2, and 4 hours after end of inhalation: ○ C_{max} ○ t_{max} ○ AUC_{0-4h} • Whole blood trough levels (at Weeks 2, 4, 8, and 12)
Assessments	***Clinical Trial Plan:*** At total of 7 visits (Screening, Randomization (Week 0), Week 2, Week 4, Week 8, Week 12 (End of Treatment [EoT]) and Week 14 (End of Study [EoS]) will be performed during the clinical trial. AEs and concomitant medications will be recorded at all visits. **Screening:** After informed consent has been obtained. Screening Visit procedures will be carried out to check general eligibility for participation up to 4 weeks prior to randomization. Blood will be drawn for safety profiles. **Visit 1, Week 0 (Baseline Visit, Randomization):** Blood for baseline measures will be collected. Spirometry will be performed. A pregnancy test will be performed for all females of childbearing potential prior to randomization. A physical exam, including vital signs, will be performed. The CGI Questionnaire will be administered. The SF-36 Quality of Life Questionnaire will be administered. Patients will be randomized to study treatment and instructed on use of the L-CsA CCI . The first dose of IMP will be administered under observation and safety will be monitored. Spirometry will be repeated 1 hour ± 20 min after completion of the first dose of IMP. Blood will be drawn for safety profiles and PK data at pre-dose. PK samples will be obtained directly after end of first inhalation, at 15, 30, and 45 minutes, and 1, 1.5, 2, and 4 hours after end of inhalation. If no tolerability issues are observed, patients will be permitted to leave the clinic. Patients will receive the full IMP supply for the 12 weeks treatment period. The second dose of IMP and all subsequent doses should be inhaled approximately 12 hours after the first dose. **Visit 2, Week 2:** Spirometry will be obtained. Blood will be drawn for safety profiles and trough levels of CsA. A pregnancy test will be performed for all females of childbearing

	potential. A physical exam, including vital signs, will be performed. The CGI Questionnaire will be administered. The SF-36 Quality of Life Questionnaire will be administered. A dose of the IMP will be administered under observation. Patients will bring used and unused vials of the IMP for availability check. **Visit 3, Week 4:** During on-site visits, spirometry will be obtained. Blood will be drawn for safety profiles and trough levels of CsA. A pregnancy test will be performed for all females of childbearing potential. A physical exam, including vital signs, will be performed. The CGI Questionnaire will be administered. The SF-36 Quality of Life Questionnaire will be administered. An Investigator's Tolerability Assessment will be performed. A dose of the IMP will be administered under observation during on-site visits. Patients will bring used and unused vials of the IMP for availability check at on-site visits. **Visit 4, Week 8:** During on-site visits, spirometry will be obtained. Blood will be drawn for CsA trough level and safety parameters. A pregnancy test will be performed for all females of childbearing potential. A physical exam, including vital signs, will be performed. The CGI Questionnaire will be administered. The SF-36 Quality of Life Questionnaire will be administered. A dose of the IMP will be administered under observation during on-site visits. Patients will bring used and unused vials of the IMP for availability check at on-site visits. **Visit 5, Week 12 (EoT):** Spirometry will be obtained. Blood will be drawn for CsA trough level and safety parameters. A pregnancy test will be performed for all females of childbearing potential. A physical exam, including vital signs, will be performed. The CGI Questionnaire will be administered. The SF-36 Quality of Life Questionnaire will be administered. An Investigator´s tolerability assessment will be performed. Patients will return all used and unused vials of the IMP. Drug accountability will be performed. The L-CsA CCI will be returned.

	Visit 6, Week 14 (EoS): Blood will be drawn for safety parameters. A pregnancy test will be performed for all females of childbearing potential. A physical exam, including vital signs, will be performed. Safety and tolerability will be monitored by documentation of AEs throughout the study. Every effort will be made to have all planned and unscheduled visits at the study site. Mandatory on site visits are Screening and Visit 1, Visit 2 and Visit 5. However, if one of the visits V3, V4 and V6 cannot be performed at site due to COVID-19 , remote visits (e.g. by telephone) are possible. COVID-19 related Adverse Events will be reported as SAEs.
Data Monitoring Committee:	A Data Monitoring Committee (DMC) is established to monitor the safety of IMP. The DMC will monitor safety by evaluating the safety analyses generated by the independent statistician during the course of the clinical trial. Details of the safety analyses will be included in the DMC Charter. The DMC will evaluate treatment groups for possible trends in AEs, determine whether the basic protocol assumptions remain valid, evaluate whether the overall integrity, scientific merit and conduct of the clinical trial remain acceptable, and make recommendations to the Sponsor.
Statistical Considerations:	Exploratory statistical analyses will be performed using methods of descriptive data analysis. **Analysis of safety:** MedDRA coded, treatment emergent adverse events (TEAEs) will be tabulated at the Preferred Term (PT) and the System Organ Class (SOC) levels. Treatment group comparisons of the proportion of patients with TEAEs will be based on Wilson score confidence intervals. Pairwise group comparisons will be provided at the SOC level as well as for the events identified as local tolerability measures (cough, wheezing, bronchospasms, throat irritation, change in FEV_1), with separate analyses for all events with onset during the first 4 weeks of treatment and for events with onset at any time during randomized treatment. CGI scales will be analysed and compared between the treatment groups. **Analysis of efficacy:** Spirometric variables and SF-36 scales will be analyzed and compared between the treatment groups using mixed models for repeated measures (MMRM). **Pharmacokinetic measures:** The statistical analysis will be carried out based on a multiplicative model for $AUC_{0\text{-}4\ h}$ and C_{max} values, while t_{max} and trough levels will be evaluated on the basis of an

	additive model. Analyses of variance will be performed to compare the treatment groups. **Sample size determination:** The sample size for the study was established based on considerations of feasibility rather than on power calculations. A total of 24 patients (3 arms x 8 patients each) are planned to be randomized.

5 INTRODUCTION

5.1 Bronchiolitis Obliterans Syndrome

Bronchiolitis obliterans (BO) (also called obliterative bronchiolitis) is a progressive lung disease affecting the bronchioles. It is widely believed to be a sequela of injury or damage, and BO is usually diagnosed months to years following injury. Recognized forms of injury that predispose to the occurrence of BO include allograft rejection in lung transplantation, graft vs host disease in hematopoietic cell transplantation [Au 2011], respiratory infections, or environmental or chemical exposure [Aguilar 2016]. Lung allografts are particularly susceptible to BO as a result of acute rejection in addition to the other described risk factors [Meyer 2014]. BO is irreversible and leads to respiratory failure.

Although the pathogenesis of BO is not well understood, histopathologic findings of constrictive bronchiolitis, airway distortion, and subepithelial fibrosis are thought to be the result of post-injury inflammatory infiltrates leading to an abnormal cytokine response and subsequent accumulation of fibroblasts with fibroproliferation [Aguilar 2016].

The main histologic hallmark of BO is scarring with fibrosis of the airways. Because of difficulties with histologic diagnosis, the clinical manifestation of BO, bronchiolitis obliterans syndrome (BOS), was defined as irreversible airway obstruction, diagnosed by pulmonary function, in the absence of other causes. This diagnosis does not require histologic confirmation but is considered a reliable surrogate physiologic marker of the presence of BO [Estenne 2002].

In patients with BOS, the major findings on spirometry are a reduced forced expiratory volume in 1 second (FEV_1), a normal or slightly decreased forced vital capacity (FVC), and a reduced ratio of FEV_1 to FVC, with poor response to inhaled bronchodilators consistent with a fixed obstructive airway disease. Lung volumes indicate air trapping, with a normal total lung capacity and high residual volume. However, a subset of patients presents with a restrictive pattern characterized by a low FVC and a normal FEV_1/FVC ratio, or a mixed pattern of obstruction and restriction [Barker 2014].

5.1.1 BOS in Hematopoietic Stem Cell Transplant Recipients

Chronic graft-versus-host disease (cGvHD), which manifests clinically in the respiratory tract as BOS, is a common complication of hematopoietic stem cell transplantation (HSCT) [Aguilar 2016].

Diagnosis of BOS is difficult and relies on differential diagnosis to exclude other causes of lung function decline. Grading of BOS stages is regulated in a National Institutes of Health Consensus document [Jagasia et al. 2015]. Currently, there are no approved therapies for treatment of BOS

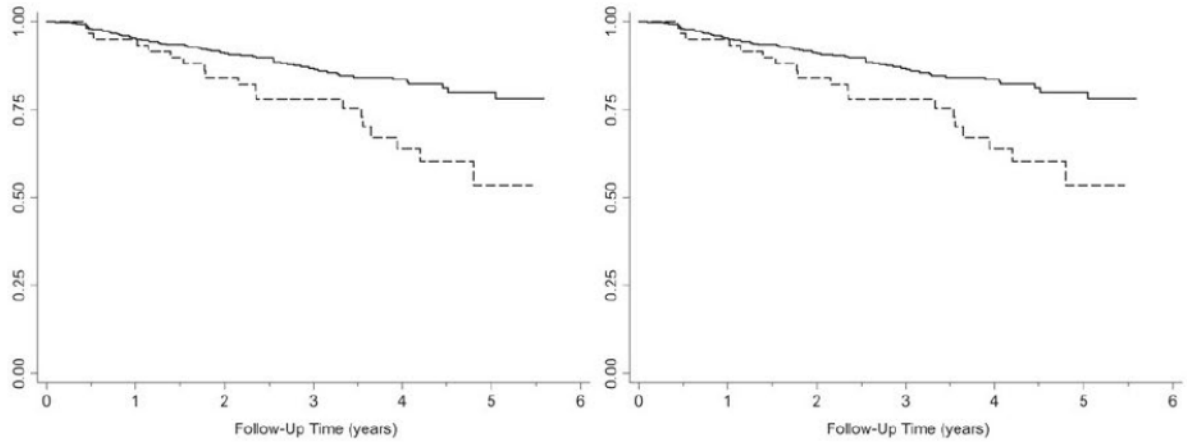
available. In the past, frequently used interventions included inhaled corticosteroids, pulsed systemic corticosteroids, azithromycin, montelukast, extracorporeal photopheresis and others. However, based on a study [Bergeron 2017] with azithromycin which showed an increase in relapse rates after long-term use of this substance, a Red Hand Letter in Europe and a Warning Letter of the Food and Drug Administration (FDA) was published to avoid long-term use of azithromycin for the treatment of BOS after HSCT.

Development of BOS after HSCT is a major cause of morbidity and mortality; treatment options are limited and have not been optimized by well-conducted clinical trials [Aguilar 2016]. In an analysis of patients who received allogeneic HSCT [Au et al. 2011], 5.5% of recipients developed BOS. The prevalence was 14% among patients with cGvHD [Au 2011]. BOS was diagnosed at a median of approximately 14 months post-transplantation. Sixty percent of patients diagnosed with BOS had no prior history of pulmonary disease. Diagnosis of BOS post-transplantation conferred a 1.6-fold increase in risk for mortality.

A Kaplan-Meier survival analysis showed a significant difference between patients who developed BOS and those who did not develop BOS (p = 0.002) (Figure 1). However, treatment with available therapeutic options (i.e., high-dose systemic corticosteroids, inhaled corticosteroids or azithromycin) remained without demonstrable benefit when compared to patient groups who did not receive these treatments.

Severe cases of BO after allogeneic hematopoietic stem cell transplantation may result in the need for lung transplantation.

Figure 1: Kaplan-Meier Estimates of Survival in Hematopoietic Stem Cell Transplant Recipients



Kaplan-Meier survival estimates of transplant-related mortality comparing BOS to non-BOS cases (p = 0.002). Noncases are denoted by a solid line, cases are shown as a dashed line.

Source: Modified from Au 2011.

The first studies of an inhaled immunosuppressive for BOS were conducted in patients with lung transplantation. These studies used cyclosporine in a formulation that contained propylene glycol (CsA-propylene glycol [CsA-PG]). In these studies, CsA-PG showed poor tolerability due to the hyperosmolality of the PG formulation and its propensity to cause airway inflammation. However, efficacy results from clinical trials evaluating prevention of BOS were promising [Iacono 1996; Iacono 2006].

With the goal of increasing tolerability as well as improving airway deposition, a liposomal formulation of CsA (L-CsA) was developed. L-CsA also was formulated specifically for use with the CCI Nebulizer System (L-CsA CCI) for optimal aerosol dynamics. Twice daily (bid) inhalation of L-CsA was well tolerated in a 2-year prevention study and a 6-month treatment study of BOS after lung transplant. There are over 1100 patient months of experience with L-CsA in lung transplant recipients with BOS. This study will be the first study to evaluate safety and tolerability of L-CsA in patients with BOS following allo-HSCT.

6 BACKGROUND INFORMATION

6.1 Investigational Medicinal Product

The Investigational Medicinal Product (IMP) is a drug/device combination consisting of L-CsA and the L-CsA CCI .

6.1.1 Drug Component

L-CsA consists of the active substance CsA and excipients as described in the Investigator's Brochure (IB). L-CsA is a lyophilisate for reconstitution with 0.25% saline. The formulation is developed for inhalation use and is therefore adjusted to a physiological tolerable value of pH 6.5 ± 0.3 and an osmolality of 430-550 mOsmol/kg in the reconstituted formulation.

The liposome size in the reconstituted formulation is in the range of 40-100 nm with a polydispersity index (PI) of not more than 0.50, which indicates the width of the size distribution. PI values above 0.5 indicate a broad distribution.

The doses of 0 mg and 10 mg L-CsA are reconstituted in a total volume of 2.5 mL. The 5 mg L-CsA dose is reconstituted in a total volume of 1.25 ml. The entire volume of the reconstituted solution is used per aerosol administration.

Additional information can be found in the IB.

6.1.2 Device Component

The L-CsA CCI (CCI) utilizes a new technology of nebulizing liquid drugs with a perforated vibrating membrane resulting in an aerosol with a low ballistic momentum and a high percentage of droplets in a respirable size range of 3-5 µm.

The L-CsA CCI to be used in this clinical trial is a modified version of the CC Nebulizer System for an optimized delivery of the investigational drug for the designated patient group. The configuration of the optimized L-CsA CCI has a high delivered dose, short nebulization time and inhibits contamination of the environment by using an exhalation filter. The device is CE-marked in Europe. The L-CsA CCI was used in the nonclinical and clinical trials of L-CsA.

Additional information can be found in the IB.

6.1.3 Nonclinical Data

For systemic administration of CsA, the nonclinical pharmacologic, pharmacokinetic (PK), and toxicity profiles of systemic CsA are well established [UK SmPC Ciclosporin A (Neoral®)].

For aerosolized administration of L-CsA, additional nonclinical studies have been conducted with L-CsA. Importantly, L-CsA inhibited T-cell proliferation in stimulated human peripheral blood mononuclear cells. Across 3 nonclinical toxicology studies in rats, aerosolized L-CsA given as 4-day, 6-week, and 26-week repeated applications of up to 2.6 mg/kg/day, no dose-limiting toxicity occurred. The no-observed-adverse-effect-level is considered to be 2.0 mg/kg/day via inhalation for chronic application based on the maximum dosage achieved in the 26-week inhalation study in rats.

Nonclinical and clinical data to date with L-CsA show negligible increase in serum levels of calcineurin inhibitors and do not show an increased risk of nephrotoxicity, respiratory infections, or malignancies.

Additional information can be found in the IB.

6.1.4 Clinical Experience

L-CsA has been evaluated in 3 clinical trials in adult patients who received a single-lung transplantation (SLT) or double-lung transplantation (DLT): (1) a Phase 1b study of the deposition and PK of aerosolized L-CsA in patients with lung transplantation (G035.011); (2) a Phase 3 study of the efficacy, safety, and PK of the addition of aerosolized L-CsA to standard of care (SoC) systemic immunosuppression therapy vs aerosolized placebo plus SoC therapy in the prevention of BOS following lung transplantation (12011.201; study was terminated early for business reasons); and (3) an investigator-initiated study of the efficacy, safety, and PK of the addition of aerosolized L-CsA to SoC systemic immunosuppression therapy vs SoC therapy alone in the treatment of BOS following lung transplantation (AI001). Collectively, these studies provided safety, efficacy, and PK data to support further evaluation in 2 Phase 3 studies of the efficacy and safety of the addition of aerosolized L-CsA to SoC systemic immunosuppression therapy vs SoC therapy alone for the treatment of BOS following SLT (BT – L-CsA – 301 – SLT) or double lung transplantation (BT – L-CsA – 302 – DLT). In particular:

- The Phase 1b lung deposition study (G035.011) showed that inhalation of 10 mg and 20 mg L-CsA via the L-CsA CCI would result in sufficient peripheral lung deposition of L-CsA (≥15 mg L-CsA/week) in lung transplant recipients. Aerosol application of 10 mg L-CsA was associated with an acceptable inhalation time of approximately 9 minutes.
- In the Phase 3 study investigating prevention of BOS (12011.201), the primary endpoint for prevention of BOS (BOS-free survival) was not met, although efficacy results may have been confounded by early termination of the trial due to business reasons.
- In the investigator-initiated study investigating treatment of BOS (AI001), the responder analysis of BOS progression-free survival based on Kaplan-Meier estimates revealed a treatment success rate of 81.8% in the L-CsA + SoC group (9 of 11 patients) and 50% in the control group (5 of 10 patients). FEV_1 slope analyses over time resulted in monthly decrements

of -0.008 L in the L-CsA + SoC group and -0.045 L in the control group. This difference translated into an annual preservation of FEV_1 of more than 400 mL in the L-CsA + SoC group, consistent with a meaningful slowing of the progression of the disease. The beneficial effect of L-CsA was also reflected in consistently positive trends favoring the L-CsA + SoC group in other lung function parameters, including forced midexpiratory flow (FEF_{25-75}), FVC, and FEV_1 % predicted. Five years after the start of Study AI001 (as of September 2017), 5 of 11 patients treated with L-CsA + SoC were alive, compared with 0 of 10 control patients who received SoC alone.

With respect to safety, inhaled L-CsA was generally well tolerated across all clinical trials. The overall analysis of adverse events (AEs), serious adverse events (SAEs), and deaths showed that these were mostly associated with pulmonary and immunological events, which are expected in a population of lung transplant and immunosuppressed patients and did not differ from the control arms. Neither laboratory values nor vital signs assessments showed any clinically relevant changes over time.

Nonclinical and clinical data to date with L-CsA do not show an increased risk of nephrotoxicity, respiratory infections, or malignancies.

Additional information can be found in the IB.

6.1.5 Summary of Known and Potential Risks and Benefits

Chronic GvHD, which manifests clinically in the respiratory tract as BOS, is a common complication of hematopoietic stem cell transplantation (HSCT) (Aguilar 2016; Bergeron 2013). Development of BOS after HSCT is a major cause of morbidity and mortality; beneficial treatment options are limited therapeutic interventions which have not been validated by well-conducted clinical trials (Aguilar 2016). With the diagnosis of BOS post-transplantation a 1.6-fold increase in risk for mortality is conferred.

Bronchiolitis obliterans (a diagnosis made by histopathology) and BOS (a diagnosis made clinically in high risk patients) is the same underlying disease regardless of the inciting injury. [Barker NEJM 2014]. Early efficacy studies have demonstrated a beneficial effect of L-CsA for the treatment of BOS in patients with BOS following lung transplantation.

This trial is the first to evaluate the safety, tolerability, exploratory efficacy and pharmacokinetics of L-CsA for the treatment of BOS in patients with BOS following allogeneic hematopoietic stem cell transplantation. The pharmacokinetic profile of L-CsA has been evaluated in 3 clinical trials in adult patients who received a single-lung transplantation (SLT) or double-lung transplantation (DLT). In the current trial for the first time the pharmacokinetic profile will be evaluated in patients with BOS following allogeneic HSCT to get information of the PK profile in this patient population and to support further evaluation in this indication.

Patients in clinical trials generally cannot expect to receive direct benefit from treatment during participation, as clinical trials are designed to provide information about the safety and effectiveness of an investigational medicine.

There are possible risks and discomforts associated with the blood draw for PK analysis. The general known risks including discomfort at the punction site of the blood draw can be bruising, bleeding, infection, and rarely, fainting or nerve damage.

L-CsA is contraindicated in persons with a history of allergy to cyclosporine or to any of the ingredients in the formulation.

Systemic formulations of cyclosporine are known to have contraindications related to St. John's Wort and medicines that are substrates of P-gp or organic anion-transporting polypeptide (OATP). Prior studies of L-CsA have demonstrated neglible serum levels and no accumulation over time of cyclosporine. No potential drug interactions during clinical studies have been reported. Drug-drug interactions are unlikely because the systemic cyclosporine exposure with L-CsA is much lower than for approved therapeutic doses of oral and IV cyclosporine.

Based on clinical experience to date with L-CsA, there are no special precautions for administration of L-CsA in clinical studies using the drug product and device component. Pharmacokinetic studies have shown that the systemic cyclosporine exposure with L-CsA is much lower than for approved therapeutic doses of oral and IV cyclosporine. Consult oral or IV cyclosporine prescribing information for various precautions associated with the higher systemic exposures that may occur after oral or IV dosing of cyclosporine.

Patients who are given L-CsA may also receive other inhaled medications. When L-CsA is administered concomitantly with other inhaled medicinal products, the order of inhalation should be as follows: inhaled bronchodilators, inhaled corticosteroids, inhaled antifungals/ antibiotics, and then inhaled L-CsA. L-CsA inhalation should occur at least 1 hour after administration of any other inhaled medications.

No event associated with overdose has been reported in any L-CsA clinical trial to date. As has been demonstrated through PK studies, systemic exposure is significantly low compared with the approved therapeutic doses of oral or IV cyclosporine.

COVID-19 considerations: At this time, it is unknown if specific patient populations are at higher risk of SARS-CoV-2 infection. Furthermore, the medical surveillance of transplanted patients is already based on specific precautions typical to all patients taking immunosuppressive agents. The medical value of this trial remains unchanged.

6.1.6 Justification of Therapy with Cyclosporine A and of Dose Regimen

Although multifactorial in etiology, most evidence suggests that BO is a host-dependent, immune mediated airway injury to bronchiolar cells. It has been postulated that the most important cause of chronic rejection of the lung allograft and BOS is T-lymphocyte activation by major histocompatibility alloantigens- or alloimmune-dependent mechanisms [Halloran 1997; Soubani & Uberti 2007]. Cyclosporine A was selected as the active substance for the development of a liposomal formulation because of its well-characterized mode of action and proven immunosuppressive potency.

The liposomal formulation of cyclosporine A (L-CsA) was developed with the intent of improving local tolerability, as shown in studies 12011.201 and AI001. Because lung function is significantly compromised in patients with BOS, an inhalation formulation that is tolerable and facilitates patient use is important for treatment compliance and assessment of safety and efficacy parameters of the IMP. The rationale for the selection of 5 mg and 10 mg bid doses of aerosolized L-CsA, is based on:

- Correlation of drug amount deposition and stabilization of lung function [Corcoran 2004] with CsA-PG
- Clinical trial deposition data from Corcoran [2006] in SLT and DLT patients (CsA-PG)
- Clinical trial deposition data from Behr [2009] in SLT and DLT patients (L-CsA)

During the clinical development of cyclosporine in its propylene glycol formulation, lung function in correlation with different amounts of CsA-PG deposited in the transplanted lung was recorded. A threshold of $\geq$ 5 mg CsA-PG peripheral dose per inhalation was determined to be required to result in a stabilization of lung function on the basis of FEV_1 measurements. Patients in this clinical trial inhaled CsA-PG three times per week. Hence, the minimal effective peripheral drug dose was calculated to be 15 mg/week.

The combination of the clinical data cited above on drug deposition behavior led to the calculation for the dosing regimens of L-CsA. It is estimated that a dose of L-CsA 5 mg bid will result in 2 mg
deposited in the peripheral airways per day, and 14 mg per week. It is estimated that a dose of L-CsA 10 mg bid will result in 4 mg deposited in the peripheral airways per day, and 28 mg per week.

The investigational dose of IMP is 10 mg bid via the L-CsA CCI This dose is modelled based on airway deposition and the surface area of adult lungs to achieve the target airway deposition. There are two exceptions to the proposed dose. One is patients who are the recipients of a single-lung transplantation. Scintography studies [Behr 2009] demonstrated a significant differential in topical deposition with the vast majority of the dose being distributed in the transplanted lung.

Thus, L-CsA 5 mg bid is being explored in this specific population. Analougously, children age 6-9 years have sufficiently lower bronchial airway surface area compared to adults with two functioning lungs and thus L-CsA 5 mg bid will be explored in future pediatric studies that include this age group.

To date, there is 1100 patients-months of tolerability data for L-CsA delivered to patients who are lung transplant recipients. It is anticipated that L-CsA 10 mg bid will be well tolerated in patients with native lungs affected by BOS as well. However, the current study will compare the tolerability of L-CsA 10 mg vs 5 mg bid in the target patient population.

6.1.7 Statement of Compliance

This study will be conducted in compliance with the protocol approved by the appropriate Ethics Committees (EC) and health authorities, according to International Committee on Harmonisation (ICH) and applicable Good Clinical Practice (GCP) standards, and in accordance with the ethical principles that have their origin in the Declaration of Helsinki (Fortaleza, 2013).

6.1.8 Population

Recipients of an allogeneic stem cell transplant, ≥ 18 years of age, with documented diagnosis of cGvHD in any organ other than the lung and confirmed diagnosis of BOS.

7 TRIAL OBJECTIVES AND PURPOSE

7.1 Trial Objectives

7.1.1 Primary Objective:

The primary objective of this study is to assess the tolerability and safety of two dose levels of aerosolized L-CsA vs placebo in addition to SoC therapy for BOS in adult allo-HSCT recipients.

7.1.2 Secondary Objectives:

The secondary objectives of this study are to assess PK and exploratory efficacy and quality of life of two dose levels of aerosolized L-CsA vs placebo in addition to SoC therapy for BOS in adult allo-HSCT recipients.

7.2 Purpose of the Trial

Currently, there is no approved medicinal product for the prevention or treatment of BOS after allogeneic stem cell transplant. All attempts for therapeutic intervention to alter the incidence or the progression of BOS are empirical and investigational. This circumstance explains the diversity and disharmony of therapeutic concepts in the HSCT community. There are SoC practices established to manage BOS that develops after allo-HSCT, but no therapeutic regimens have

conclusively demonstrated evidence of significant benefit in the prevention or treatment of BOS. Adequately designed and executed, randomized, controlled trials to assess efficacy and safety are needed to identify optimal therapies for established BOS.

The hypothesis that local delivery of CsA by aerosol inhalation will achieve higher intrapulmonary concentration than by systemic administration alone, with limited toxicity compared to similar systemic doses due to minimal absorption of drug into the blood circulation has been substantiated by the studies described in Section 6.1.4.

In particular, the investigator-initiated trial AI001 provided evidence of L-CsA's potential to delay progression of BOS when administered as add-on inhalation therapy as compared to SoC for systemic BOS therapy. In combination with the acceptable safety profile of L-CsA, observed in clinical trial 12011.201 when patients were treated for up to 2 years, L-CsA has the potential to provide superior efficacy over current best practice BOS therapy.

The purpose of this trial is to assess the safety and tolerability of L-CsA in patients with allo-HSCT as current understanding assumes identical pathophysiology of BOS after lung transplant and HSCT.

8 TRIAL DESIGN

8.1 Endpoints

8.1.1 Primary Assessment

IMP tolerability and safety during the first 4 weeks of treatment.

8.1.2 Secondary Assessments

IMP tolerability and safety during the first 12 weeks of treatment; CsA PK.

8.1.3 Exploratory Efficacy Assessment

- FEV_1 % predicted at randomization compared to Week 2, Week 4, Week 8, and Week 12
- FEV_1/FVC at randomization compared to Week 2, Week 4, Week 8, and Week 12
- SF-36 Quality of Life Questionnaire at Week 2, Week 4, Week 8, and Week 12
- Changes in the dose of corticosteroids and immunosuppressive therapy administered throughout trial duration

8.1.4 IMP Tolerability Parameters

- Local Tolerability:
  - Cough
  - Wheezing
  - Bronchospasm
  - Throat irritation
  - Change in FEV_1
- Overall Tolerability:
  - Clinical Global Impressions (CGI) scale
  - Investigator's tolerability assessment at Visit 3 and Visit 5

8.1.5 Safety Parameters

- AEs
- SAEs
- Clinical laboratory values
- Vital signs
- Physical Examination

8.1.6 Pharmacokinetic Parameters

- PK: (Week 0) at pre-dose; directly after end of inhalation; 15, 30, and 45 minutes, and 1, 1.5, 2, and 4 hours after end of inhalation:
  - C_{max}

- t_{max}
- AUC_{0-4h}

- Whole blood trough levels (at Weeks 2, 4, 8, and 12)

8.2 Trial Design

This is a Phase II prospective, multi-center, single-blind, randomized clinical trial evaluating safety and tolerability in in adult recipients of an allo-HSCT with BOS. Twenty-four patients are planned for enrollment. The clinical trial will be conducted in up to 20 centers in Europe. Patients will be randomly allocated 1:1:1 to receive either L-CsA (10 mg bid or 5 mg bid) plus SoC or 0 mg L-CsA (placebo) plus SoC. IMP will be administered for up to 12 weeks.

8.3 Stratification and Randomization

At the baseline visit (see Section 13.2.2), after all inclusion and exclusion criteria have been fully evaluated, eligible patients will be assigned to one of the three treatment groups at a ratio of 1:1:1 by means of block randomization. Randomization will be performed by a statistician otherwise not involved with the trial, using validated random number generator software. The randomization code of each patient will be provided to the Investigator after compliance with all eligibility criteria has been confirmed, through the electronic Case Report Form (eCRF) into which the generated random code list will be uploaded. Each patient will be assigned a number as part of the randomization process. The number assigned to a patient will become that patient's unique treatment number throughout the clinical trial and cannot be re-assigned to another patient.

No stratification will be performed.

8.3.1 Blinding

This is a single-blind trial. Due to the different appearance of the three tested strengths of IMP, a full blinding of the study was not possible. Only the randomized study patients will be blinded to study treatment assignment. For details of the blinding of the Data Monitoring Committee members, see Section 12.2.

8.3.2 Investigational Medicinal Product: Treatment, Dosage and Administration

8.3.2.1 Formulation of L-CsA

The composition of the L-CsA formulation is shown in Table 1. It is a lyophilisate intended for reconstitution with 0.25% NaCl. The formulation is developed for inhalation use and adjusted to physiological tolerable values of pH (6.5 $\pm$ 0.3) and osmolality 430-550 mOsmol/kg).

Table 1: Qualitative Composition of the IMP

Ingredient	Function	Quality
Cyclosporine A	Active ingredient	Ph Eur[1]
Lipoid S100	Carrier	non compendial
Polysorbate 80	Surfactant	Ph Eur
Disodium hydrogen phosphate dodecahydrate	Buffer	Ph Eur
Sodium dihydrogen phosphate dihydrate	Buffer	Ph Eur
Disodium edetate dihydrate	Stabilizer	Ph Eur
Sucrose	Lyoprotectant	Ph Eur
Water	Dispersion medium	Ph Eur/USP[2]

1: European Pharmacopeia
2: United States Pharmacopeia

The particle size of the liposomes is in the range of 40-100 nm with a PI of not more than 0.50, which indicates the width of the size distribution. Values of polydispersity index above 0.5 indicate a broad distribution. For colloidal disperse systems a PI of 0.20 to 0.50 is appropriate.

The IMP (L-CsA) and 0.25% NaCl for reconstitution will be supplied by the IMP depot on behalf of the sponsor:

PPD

Germany

8.3.2.2 Treatment and Dosage

After Screening, patients complying with all inclusion and exclusion criteria (see Sections 9.1 and 9.2) will be randomized to one of the following treatments:

Treatment A (L-CsA 10 mg treatment plus SoC):
L-CsA 10 mg/2.5 mL bid for a maximum of 12 weeks
plus
SoC therapy

Treatment B (L-CsA 5 mg treatment plus SoC):
L-CsA 5 mg/1.25 mL bid for a maximum of 12 weeks
plus
SoC therapy

Treatment C (L-CsA 0 mg (Placebo) plus SoC):
L-CsA 0 mg/2.5 mL bid for a maximum of 12 weeks
plus
SoC therapy

8.3.2.3 Administration of IMP

In clinical trials 12011.201 and clinical trial AI 001 totaling > 1100 patient months of exposure, L-CsA was well tolerated. Patients will be educated regarding use of the L-CsA CCI and administration of the first dose will be observed. At subsequent study visits, it will be requested that the patient self-administer a dose of IMP while observed by study personnel.

Each patient will receive two IMP administrations per day, one in the morning and one in the evening. The inhalations are scheduled to be taken approximately 12 hours (but not less than 6 hours) apart, e.g., at 8:00 a.m. and 8:00 p.m. each day. Instructions for administration should be followed as described in the Instructions For Use.

Handling of IMP Inhalation:

Each patient will open a glass vial by lifting up the plastic disk/cap, lifting up the metal flap to remove the metal ring, metal cap, and the rubber stopper. The plastic ampoule containing 1.2 ml or 2.4 mL of the 0.25% NaCl as solvent will be opened by twisting the head part several times in one direction. The NaCl solution will be squeezed into the glass vial containing the whitish lyophilisate cake. The glass vial will be re-closed with the rubber stopper and swirled gently without spilling any liquid for a minimum of 1 minute and up to 5 minutes, until the visible particles are completely dissolved. Shaking of the vial must be avoided to prevent foaming of the reconstituted solution.

Next, the reconstituted IMP should be poured into the L-CsA CCI chamber. The nebulizer should be kept horizontal during operation. During inhalation, the patient should sit in an upright position and inhale and exhale deeply through the mouthpiece of the nebulizer without interruption until nebulization shuts off automatically. The solution is for single use only, and no remaining solution should be left in the glass vial. All other clinical trial materials, including unused IMP, must be brought back to the clinical trial center at each scheduled visit for drug and device accountability. After completion of the inhalation, the patient should remove all excess IMP in the mouth and pharynx by rinsing and gargling with water and subsequently discharging the solution.

Interruption of IMP Inhalation:

If a patient needs to temporarily interrupt IMP inhalation (e.g., due to coughing), the patient should turn off the device and turn it back on when ready to resume inhalation.

IMP maybe temporarily discontinued as deemed necessary by the investigator (see Section 9.3.1) and will be documented in the eCRF.

8.4 Investigational Medicinal Product Packaging, Labeling and Storage

8.4.1 Packaging and Labeling of IMP

Packaging

The IMP will be provided as 0 mg and 10 mg L-CsA lyophilisate in glass vials type I with grey rubber stoppers and an aluminum cap with a yellow plastic disk and stored in an outer packaging box consisting of 60 vials with the L-CsA/placebo and 70 plastic ampoules containing 2.4 mL 0.25% NaCl for reconstitution. The 5 mg L-CsA lyophilisate will be supplied in glass vials type I with grey rubber stoppers and an aluminum cap with a green plastic disk and stored in an outer packaging box consisting of 60 vials with the L-CsA and 70 plastic ampoules containing 1.2 mL 0.25% NaCl for reconstitution.

The IMP will be labelled in compliance with Good Manufacturing Practice (GMP) specifications according to applicable regulations.

8.4.2 Storage

The unopened IMP must be kept in a secure, locked, temperature-controlled location with access to authorized staff only. IMP should be stored not above 25 °C protected from light.

8.4.3 Inhalation Device Packaging

The Investigational CCI Nebulizer System consists of the following two packages:

1) Controller Kit

The controller kit will be provided at randomization visit and includes

- 1x eTrack Controller
- 1x Nebulizer Handset including connection cord, an AC power supply and 4 “AA” batteries
- 1x Easycare cleaning aid
- 1x Carrying bag
- 1x Instructions For Use
- 2x Aerosol Heads

2) CCI in combination with L-CsA Kit below

Monthly Supply –At Each following Clinic Visit

- CCI

8.5 Stopping Rules and Discontinuation Criteria

8.5.1 Patient Level

Regular termination of clinical trial participation:

The investigational treatment will be terminated after 12 weeks (End of Treatment [EoT]). The treatment period will be followed by a 2-week follow-up period (End of Study [EoS]). Any patients with ongoing AEs and SAEs will be followed-up until recovery or stabilization of the AE/SAE.

Premature termination of clinical trial participation:

- Patients may discontinue participation in the clinical trial at any time by revoking their informed consent.
- The Investigator may withdraw a patient at any time if it is in the best interest of the patient based upon clinical assessments.
- Patient is lost to follow-up
- Pregnancy (the patient will be followed via the sponsor's safety department)
- Termination of the clinical trial as a whole by Zambon SpA as defined in section 8.5.3.

If the participant fails to return for clinical follow-up, the patient will be contacted by telephone or a letter will be sent requesting a clinic visit (EoS), and the reason for non-compliance will be documented. The final visit will encompass the assessments listed under EoS Visit (Visit 6; Section 13.2.5). Additionally, used and unused IMP and inhalation device will be retrieved, if applicable. Zambon SpA will be notified that the patient has terminated clinical trial participation.

8.5.2 Center Level

Regular termination of clinical trial centers:

All centers will be closed after patients have completed clinical trial participation and the database has been locked.

Premature termination of a clinical trial center:

The sponsor may close a center for the following reasons:

- In case of repeated and continuous violations of GCP and applicable regulations
- Inaccurate or incomplete data collection
- Falsification of records
- Failure to adhere to the protocol
- Organizational or structural changes in the center which challenge the requirements or qualification for clinical trial participation (e.g., change of investigator, shift of center activities)

In case a center is closed for any of the reasons above, efforts will be made to ensure the safety and data reliability of ongoing patients until clinical trial completion.

8.5.3 Clinical Trial Level

Regular termination of the clinical trial:

The clinical trial will be considered complete after the pre-defined number of patients have been randomized and completed their clinical trial participation. The last visit of the last patient is the defined end of the study.

Premature termination of the clinical trial:

- Serious safety concerns that indicate a potential health hazard caused by treatment with the IMP (termination due to safety issues)
- The clinical trial may be discontinued at any time for reasons such as but not limited to medical futility and administrative reasons, upon the discretion of Zambon SpA.

In this case, an abbreviated clinical study report will be reported to Competent Authorities and Ethics Committees according to applicable regulatory requirements. The Investigator must notify his/her EC of clinical trial closure.

8.6 Investigational Medicinal Product: Supply and Accountability

Each Investigator is responsible for ensuring that deliveries of IMP vials and boxes, L-CsA CCI and other clinical trial materials are correctly received and recorded, that these are handled and stored safely in a locked and temperature controlled storage place with access for authorised study staff only and that they are used in accordance with this protocol. In addition, the Investigator will monitor each patient's treatment compliance by counting the used/unused drug vials at each visit.

For the purpose of this trial patients will be regarded as compliant if no more than 45 vials of IMP over the entire treatment period of 12 weeks are returned as unused – this corresponds to approximately 75% treatment compliance. The reason for non-compliance shall be documented according on the respective eCRF.

Unused IMP vials, ampoules, boxes, and L-CsA CCI must be returned or destroyed on-site after accountability has been completed and destruction is approved by Zambon SpA. A list of IMP, L-CsA CCI, and other materials received, used, returned, or destroyed must be prepared, completed and signed by the Investigator; any discrepancies must be accounted for.

COVID-19 specific consideration: the patients will be supplied during V1 with the full amount of study medication needed, to cover the total treatment period of 12 weeks. Patient has to bring all study medication back to the site at EoT Visit V5 for Drug Accountability.

9 SELECTION AND WITHDRAWAL OF PATIENTS

9.1 Patient Inclusion Criteria

1. Age ≥ 18 years
2. Patients must have undergone hematopoietic stem cell transplantation and have documented diagnosis of chronic Graft versus Host Disease (cGvHD) guided by the NIH consensus criteria.
3. Patients must have been diagnosed with BOS within >6 months and ≤3 years at Screening visit.
4. Spirometry test carried out at Screening visit must show:
   A FEV_1 above 51% of predicted
   AND
   A ≥ 10% decline in FEV_1 (L) within 2 years
5. Patient must be capable of understanding the purposes and risks of the study, has given written informed consent, and agrees to comply with the study requirements.
6. Women of childbearing potential must have a negative serum or urine pregnancy test within 7 days prior to randomization and must agree to use one of the methods of contraception listed in Appendix II through their End of Study Visit.

9.2 Patient Exclusion Criteria

1. Other acute or chronic restrictive or obstructive lung diseases, including but not limited to: Patients with clinically active asthma (variable and recurring symptoms of airflow obstruction and bronchial hyper-responsiveness), chronic obstructive pulmonary disease, interstitial lung disease, or cryptogenic organizing pneumonia or other causes of restrictive lung disease such as neuromuscular weakness or diaphragmatic paralysis.
2. Any acute pulmonary bacterial, viral (as confirmed by multiplex PCR) or fungal infection not successfully resolved at least 4 weeks prior to the Screening Visit.
3. Chronic renal dysfunction with serum creatinine ≥ 2.5 mg/dL.
4. Chronic hepatic dysfunction with serum total bilirubin > 5x upper limit of normal (ULN), transaminases > 5x ULN, or alkaline phosphatase > 5x ULN.
5. Evidence of clinical relapse of the primary malignancy, according to investigator's judgement, which warranted allogeneic bone marrow transplant.
6. Use of azithromycin within 4 weeks prior to Randomization (Visit 1).
7. Chronic oxygen use or use of non-invasive ventilation.
8. Active smokers (i.e. any kind of inhaled nicotine consumption).
9. Pregnant women or women who are unwilling to use appropriate birth control to avoid pregnancy over the course of the clinical trial (for details see Appendix II).
10. Women who are currently breastfeeding.
11. Known hypersensitivity to L-CsA or to cyclosporine A.
12. Patients with life-expectancy of less than 6 months.
13. Receipt of an investigational drug as part of a clinical trial within 4 weeks prior to the Screening Visit. Participation in registries, , is allowed

14. Psychiatric disorders or altered mental status precluding understanding of the informed consent process and/or completion of the necessary procedures.
15. Any co-existing medical condition that in the Investigator's judgment will substantially increase the risk associated with the patient's participation in the clinical trial.
16. Pre-scheduled hospitalizations, surgeries or interventions planned to be performed after obtaining Informed Consent for this study.

9.3 Patient Withdrawal Criteria

In the event of patient withdrawal, the Investigator must complete the appropriate end of study form in the eCRF as soon as possible after withdrawal, stating the reason and date of withdrawal. An automated e-mail alert will be generated by the eCRF system and will be sent to the Clinical Research Organization (CRO).

9.3.1 Procedures of Patient Withdrawal and IMP discontinuation

Withdrawal:

The patient is free to withdraw from the clinical trial for any reason and at any time without giving a reason for doing so and without penalty or prejudice. The Investigator is also free to terminate a patient's involvement in the clinical trial at any time if the patient's clinical condition warrants it. In case of early withdrawal, the patient will be encouraged to perform a final visit. The final visit will encompass the assessments listed under EoS Visit (Section 13.2.5).

Additionally, used and unused IMP and inhalation device will be retrieved, if applicable. Zambon SpA will be notified by the Investigator via entry in and notification by the eCRF that the patient has terminated clinical trial participation.

IMP discontinuation

The Investigator or patient is free to discontinue regular intake of IMP, if the clinical condition of the patient or other serious reasons warrant it. Reasons for discontinuation of IMP may include (but are not limited to) the following:

- Significant respiratory infection requiring therapy
- Respiratory failure from any cause
- Mechanical ventilation

If 10 or more consecutive doses of IMP are missed, regardless of reason, then IMP will be considered as discontinued and should not be resumed. If IMP inhalation is discontinued, the patient will be asked to return for clinical trial visits according to the visit schedule defined in the protocol but shall not receive IMP.

Stopping criteria are outlined in detail in Section 8.5.1.

9.3.2 Type and Timing of Data Collection for Patient Withdrawal and IMP discontinuation

All cases of patient withdrawal or discontinuation of IMP will be recorded on the applicable eCRF pages by the Investigator including date and reason.

Patients who are discontinued should have the final clinical trial visit procedures performed within 1 month after stopping IMP, if possible. For details of the procedures, please refer to Section 13.2.5, Visit 6/End of Study.

9.3.3 Replacement of Withdrawn Patients

Patients withdrawn before randomization will be regarded as screen failures. A sufficient number of patients will be screened until the pre-defined number of randomized patients has been reached. Randomized patients will not be replaced. However, patients prematurely withdrawn from treatment should be encouraged to continue to participate in the clinical trial until the scheduled end. The eligibility of prematurely withdrawn patients for the different analysis populations will be determined in a blind data review meeting with consideration of the definition of these analysis populations provided in Section 14.1.

9.3.4 Follow-up of Withdrawn Patients

All patients withdrawn from IMP should be followed for AEs and SAEs for a further 4 weeks from the time of withdrawal. In case of patient consent withdrawal, the patient will be encouraged to complete an EoS Visit (Section 13.2.5).

10 TREATMENT OF PATIENTS

Patients will receive L-CsA (either 10 mg, 5 mg or 0 mg bid) in addition to SoC as prescribed by the treating physician and as described in Section 8.3.2. L-CsA will be administered as 10 mg/2.5 mL, 5 mg/1.25 mL, or 0 mg/2.5 mL inhalation via the L-CsA CCI for up to 12 weeks.

Any changes in SoC treatment will be documented in the eCRF.

10.1 Concurrent Treatment or Medication

All participants will maintain their usual care throughout the course of the study. SoC includes prophylaxis against common opportunistic infections, immunosuppression, and any other chronic medication. All concurrent treatment or medications given within 30 days prior to Randomization until EoS (Visit 6) will be recorded in the eCRF, this also includes vaccination for SARS-CoV-2.

10.1.1 Prophylaxis and Therapy of Infections

All patients will receive standard infectious disease prophylaxis and therapy consisting of appropriately targeted antibiotics, antivirals and/or antifungals according to institutional standards. Dates of start and stop or change in dosage will be recorded on the respective eCRF.

10.1.2 Immunosuppression

Immunosuppressive therapy is permitted and will be performed to centers' standard regimen.

The use of different formulations of aerosolized Cyclosporine A other than L-CsA is strictly prohibited during the complete clinical trial period. Systemic administration of CsA is permissible if medically necessary at the decretion of the investigator.

10.1.3 Treatment for BOS

The following medications will be permitted:

- Inhaled corticosteroids are allowed and patients should be on a stable dose for 4 weeks prior to randomization and throughout the study.
- For all other inhaled medications please refer to Section 10.1.4.
- Systemic corticosteroid treatment for BOS (or cGVHD) will be permitted, but a pulse dose has to be completed prior to screening.
- Extracorporeal photophoresis (ECP) for treatment of BOS is permitted within 4 weeks prior to randomization.
- Montelukast will be permitted, but patients should be on a stable dose for 4 weeks prior to randomization and throughout the study.

10.1.4 Other Medication

All inhaled medications, except investigational inhaled medications, are permissible during the trial.

Patients on bronchodilators should be on a stable dose 4 weeks prior to randomization and throughout the study. All other inhaled medication should be administered after spirometry in the following order: inhaled corticosteroids, inhaled antifungals/antibiotics, and then inhaled IMP. For details with regard to spirometry measurements, please refer to Section 11.1.1.

10.1.5 Prohibited Medication

Azithromycin will not be permitted. In the event a patient has used chronic azithromycin, it must be discontinued for at least 4 weeks prior to randomization.

Zafirlukast will not be permitted.

Treatments with other Investigational Medicinal Products (IMPs) or previous therapies within four weeks or five times half-life of the drug, whichever is longer, is prohibited prior to study screening and during the study.

11 ASSESSMENT OF EFFICACY

11.1 Methods and Timing of Efficacy Assessments and Analyses

11.1.1 Spirometry

Each clinical trial site will use their own spirometry equipment. Sites will ensure that spirometry equipment is calibrated before first spirometry measurement at each study visit. Spirometry will be measured according to current American Thoracic Society (ATS)/European Respiratory Society (ERS) spirometry guidelines at each visit [Miller 2005a; Miller 2005b; Wanger 2005; Pellegrino 2005]. Three acceptable maneuvers will be obtained and the largest value for FVC and FEV_1 will be recorded, even if they come from different maneuvers The FEV_1/FVC ratio will be calculated from the recorded best FEV_1 and FVC. FEV_1, FVC, absolute values will be recorded in the eCRFs.

Historical values documented in the patient file will be used for the calculation of decline ≥10% predicted FEV_1 over 24 months as requested in the Inclusion criteria.

It is well known that spirometry relies on the cooperation between the patient and examiner and that the results obtained will depend on technical as well as personal factors. Therefore, all efforts will be undertaken to have a particular patient assessed by the same examiner. To reduce the variability of the results, the method should be standardized as much as possible.

Within-maneuver acceptability criteria:

Individual spirograms are acceptable if:

- They are free from artefacts:
  - Cough during the first second of exhalation
  - Glottis closure that influences the measurement
  - Early termination or cut-off
  - Effort that is not maximal throughout
  - Leak
  - Obstructed mouthpiece
- They have good starts:
  - Extrapolated volume < 5% of FVC or 0.15 L, whichever is greater
- They show satisfactory exhalation:
  - Duration of ≥ 6 seconds or a plateau in the volume-time curve or if the patient cannot or should not continue to exhale

Between-maneuver acceptability criteria:

After three acceptable spirograms have been obtained, apply the following test:

- The two largest values of FVC must be within 0.150 L of each other

- The two largest values of FEV_1 must be within 0.150 L of each other

If both of these criteria are met, the test session may be concluded.

If both of these criteria are not met, continue testing until:

- Both of the criteria are met with analysis of additional acceptable spirograms
  or
- A total of eight tests have been performed (optional)
  or
- The patient cannot or should not continue

The three best values out of the performed maneuvers will be recored in the eCRF.

Timing of spirometry measures is provided in Section 10.1.4. Timing of spirometry measures in relation to administration of IMP is provided in Section 13.2.

11.1.2 SF-36 Quality of Life Questionnaire

The SF-36 Version 1.0 is a standardized, short form measure of generic health status, designed for self-administration. It takes 5-10 minutes for the patient to complete the questions. Patients will be asked to complete the questionnaire at Visits 1 (Baseline), 2, 3, 4, 5, and results will be entered into the eCRFs by the site staff.

12 ASSESSMENT OF SAFETY

12.1 Safety Parameters

Safety assessments at every visit include AE reporting, physical examination, CGI assessment, vital signs and clinical laboratory parameters (performed at the local labs in each study site).

L-CsA pharmacokinetic measurements at Visits 1 to 5 are analyzed at the Central Laboratory ACC GmbH in Germany, and also listed in this section, although they will not be available for immediate safety assessment by the DMC or Investigator.

COVID-19 specific consideration: In case the planned on-site visit cannot be performed due to COVID-19 restrictions, the PI or the Sub-Investigator and/or an appropriately qualified site study team member must call the patient. A remote visit must be performed to assess any potential adverse events (AEs) and to confirm the patient's status and well-being (see also Section 13.2.7).

12.1.1 Definitions

Adverse Event (AE)

An AE is any untoward medical occurrence in a patient after administration of a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH Guidelines for Good Clinical Practice E6(R2), 9 November 2016).

This includes worsening of a pre-existing condition or increase in frequency of a pre-existing condition. An AE is considered serious if it meets any of the serious criteria listed below. To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious", which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a patient's life or functioning. Seriousness (not severity) serves a guide for defining regulatory reporting obligations.

The official definition also extends to AEs occurring during the off-treatment follow-up period.

Each patient will be closely observed and questioned for AEs throughout the clinical trial period with non-leading questions (e.g., how do you feel?). The patients will be instructed to report to the clinical trial staff immediately any symptoms and/or signs which occur between the scheduled observation times.

All AEs reported by the patient or observed by the Investigator or hospital personnel will be documented in the respective eCRF. The following information regarding each AE will be obtained: date and time of onset and resolution (duration), serious or non-serious (as defined below), severity, treatment required, outcome, relationship to certain medication, and if the AE caused withdrawal from the clinical trial.

In addition to the Investigator's own description of the AE, each AE event will be coded by data management according to the Medical Dictionary for Regulatory Activities (MedDRA) code list. The verbatim term will be recorded in the eCRF.

Abnormal laboratory test results will be reported as AEs if they are indicative of a clinical condition that meets the criteria for an AE.

Adverse Drug Reaction (ADR)

Adverse drug reactions (ADRs) are all noxious and unintended responses to a medicinal product related to any dose that a causal relationship between the medicinal product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out. An unexpected ADR is any adverse reaction not identified in nature, frequency, or intensity listed in the referrent safety section of the current IB.

Serious Adverse Event (SAE)

Each AE is to be classified by the Investigator as SERIOUS or NON-SERIOUS.

The International Conference on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use defines an SAE as any AE occurring at any dose that results in any of the following outcomes:

- Death
- A life-threatening event (immediate risk of death at the time of the event)
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant disability/incapacity
- A congenital anomaly/birth defect
- Other important medical event (Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.)

12.1.2 Relationship to Clinical Trial Treatment Assignment

All AEs will be evaluated by the Investigator for potential relationship to the clinical trial treatment assignment (L-CsA or placebo) in the following categories:

- **Unrelated**: An AE with a known cause other than the use of IMP (no reasonable relationship).
- **Possible**: An AE that might be due to the use of the IMP. An alternative explanation, e.g., concomitant drug(s), concomitant disease(s), is inconclusive. The relationship in time is reasonable; therefore the causal relationship cannot be excluded (reasonable relationship).
- **Definite**: An AE that follows a reasonable temporal sequence from administration of the IMP; that follows a known or expected response pattern to the suspected clinical trial treatment assignment (reasonable relationship).

In the absence of information on causality provided by the reporting investigator, the sponsor will consult the investigator and encourage him/her to give an opinion on this event. The causality assessment given by the investigator will not be downgraded by the sponsor. If the sponsor disagrees with the investigator's causality assessment, the opinion of both the investigator and the sponsor will be provided.

12.1.3 Maximum Intensity

All AEs will be graded according to the following:

- **Mild**: Event requiring no special treatment and generally does not interfere with usual activities.
- **Moderate**: Event that impairs usual activities but may be ameliorated by simple therapeutic maneuvers.
- **Severe***: Event which impairs usual activities and requires intervention.

* There is a distinction between a severe AE and an SAE; a severe reaction is not an SAE unless it meets one of the criteria for serious events (see Section 12.1.1).

12.1.4 Serious Adverse Event (SAE) Reporting

Any SAE occurring

- between the first clinical trial procedure after obtaining informed consent and within 2 weeks after the completion of the EoT Visit, whether or not considered related to the clinical trial treatment assignment.

  or
- at any time after completion of the last follow-up and coming to the attention of the Investigator, if it is judged as related to the patient's participation in the clinical trial

must be reported to the Sponsor's Drug Safety (CCI) IMMEDIATELY, but within 24 hours upon knowledge, as follows:

- Document the event in the eCRF within 24 hours of discovery
- Submit the SAE report by Fax or e-mail to a list of predefined recipients
- Follow-up the SAE until the outcome is determined, providing periodic updates in the eCRF
- Provide any additional information if requested

Contacts of the Sponsor's Drug Safety are as follows:

CCI Belgium	**Fax:** CCI **Phone:** CCI **E-Mail:** CCI

12.1.4.1 Timelines for Suspected Unexpected Serious Adverse Reaction (SUSAR) reporting to Competent Authorities and ECs

All suspected unexpected serious adverse reactions (SUSARs) will be reported by the Sponsor to the Competent Authorities and to the ECs concerned as soon as possible, but within a maximum of 15 days (fatal or life-threatening SUSARs within a maximum of 7 days) of first knowledge.

Relevant follow-up information of fatal or life-threatening SUSARs will be communicated subsequently within an additional 8 days.

12.1.4.2 Other Events to be treated as Serious Adverse Events

Exposure to drug during pregnancy/lactation:

In principle, pregnancy and the lactation period are exclusion criteria. In the event of a pregnancy occurring during the course of the clinical trial, the patient must be withdrawn from all IMP treatment immediately and permanently. The Sponsor must be notified without delay by completing the Pregancy Form A and the patient followed during the entire course of the pregnancy and postpartum period. Prenatal and neonatal outcomes must be recorded even if they are completely normal and without AEs. The pregnancy reporting timelines are the same as described for SAE reporting procedure in section 12.1.4.

If any clinical trial patient becomes pregnant during the clinical trial period, the Investigator must contact Zambon SpA as the Sponsor of the clinical trial or its designee to discuss the management of the patient.

Adverse Device Effect

In principle, serious advers events caused by a device issue should be reported as SAEs as described above.

Other device deficiencies and malfunctions not associated with the adverse event should be reported via the CCI Complaint Form, provided in the IMP manual.

COVID-19 specific considerations:

All confirmed cases of COVID-19, occurring after the patient has provided informed consent and until 4 weeks after the EoT visit, must be reported as SAE and reported to CCI within 24 hours upon knowledge.

The seriousness criterion for COVID-19 hospitalized patients should be "hospitalization"; if the patient was not admitted to a hospital or the event is not resulting in prolonged hospitalization, the seriousness criterion "medically significant" should be used.

In all cases, details of the patient's symptoms, treatment and any clinically relevant information, should be entered in the SAE forms, as appropriate.

12.1.4.3 Investigational Medicinal Product (IMP) Overdosing

An overdose is a deliberate or inadvertent administration of a treatment at a dose higher than specified in the protocol. For the purposes of this clinical trial, any dose of aerosolized IMP administered to a patient that exceeds the dose foreseen in the protocol by more than 50% over 4 weeks should be reported as an overdose. Any occurrence of overdose are to be reported throught the SAE procedures described above.

12.1.4.4 Events not regarded as Adverse Events/Serious Adverse Events

The following events will be not regarded as AEs/SAEs:

- Not applicable

12.1.4.5 Duration of Follow-up after Adverse Events

All AEs should be followed until they are resolved or until a stable clinical endpoint is reached. The occurrence of AEs and SAEs will be monitored until 2 weeks after the EoT visit.

12.1.5 Tolerability of IMP

Local tolerability findings will be recorded as AEs in the appropriate eCRF.

The patient will be observed for local tolerability findings for 1 hour after inhalation at each on-site study visit.

Local tolerability events are:

- Cough
- Wheezing
- Bronchospasm

- Throat irritation
- Change in FEV_1

In addition, these events will be solicited actively before IMP inhalation at each study visit (except EoS) by questioning the patient whether he/she has experienced any of the events in-between the study visits. If applicable, an AE report form will be completed.

Overall tolerability assessment by the investigator includes:

- CGI questionnaire (Guy 1976)
- Investigator's tolerability assessments at Visit 3 and Visit 5, assessed by means of a five-point verbal rating scale with the response options 'very good', 'good', 'satisfactory', 'moderate', and 'poor'

12.1.6 Clinical Laboratory

Laboratory assessments will be performed following the routine protocols at each on-site visit by the local laboratory at each site.

The following clinical laboratory parameters have to be documented:

- White blood cell count with differential
- Red blood cell count
- Platelet count
- Alkaline phosphatase
- Alanine aminotransferase
- Aspartate aminotransferase
- Gamma glutamyl transferase
- Blood urea nitrogen
- Serum bilirubin
- Serum creatinine

Laboratory assessments listed above will be performed at a local facility, checked and interpreted by the investigator and entered into the appropriate section of the eCRF. The Normal Laboratory Ranges of each local laboratory will be used for the the assessment of clinical significance.

12.1.6.1 Pregnancy Test

Serum or urine samples from women of childbearing potential will be collected for pregnancy tests at Screening, and on-site Visits 1, 2, 3, 4, 5, and 6. Positive results will be recorded in the eCRF and appropriate actions will be taken.

12.1.6.2 Pharmacokinetic Parameters

Whole blood samples for determination of cyclosporine A will be collected at Visit 1 pre-dose, directly after end of inhalation; and 15, 30, and 45 minutes (+/- 5 minutes), and 1, 1.5, 2, and 4

hours (+/- 15 minutes) after end of inhalation for determination of C_{max}, t_{max}, and AUC_{0-4h}. PK analysis will be performed in a central laboratory (CCI [redacted]).

All sites will be provided with specific Laboratory Kits for collecting the PK blood samples.
Blood should be collected into the respective pre-labelled K2-EDTA Tubes and should be stored at -20°C immediately after collection until shipment to the central laboratory.
Instruction on handling, processing, storage and shipment are in detailed described in the Laboratory Manual for Pharmacokinetic Blood Sampling.

12.1.6.3 Cyclosporine A Whole Blood Trough Levels

A whole blood sample for the determination of cyclosporine A trough level will be collected at Visit 2 to Visit 5 at each on-site visit. The sample should be collected 15 minutes before inhalation The trough levels of CsA at visit 2 to 5 will be analysis will be performed in a central laboratory (CCI [redacted]).

All sites will be provided with specific Laboratory Kits for collecting the PK blood samples.
Blood should be collected into the respective pre-labelled K2-EDTA Tubes and should be stored at -20°C immediately after collection until shipment to the central laboratory.
Instruction on handling, processing, storage and shipment are in detailed described in the Laboratory Manual for Pharmacokinetic Blood Sampling.

12.1.7 Vital Signs

Vital signs will be assessed at each on-site visit.

The following vital signs will be recorded:

- Systolic and diastolic blood pressure (sitting, after minimum 5 minutes of rest),
- pulse rate (sitting, after minimum 5 minutes of rest),
- body temperature (the same method should be used for each patient and throughout the clinical trial),
- respiratory rate.

12.1.8 Physical Examinations

A physical examination will be carried out at the Screening Visit and at every subsequent on-site visit. The following body systems will be examined: body weight and height (at Screening visit only), cardiovascular, respiratory, nervous, gastrointestinal, hepatic, renal, dermatological, musculoskeletal, extremities, eyes, ears, nose, throat, and lymphatic.

Abnormal findings will be summarized for each patient and will be documented as AE.

12.1.9 Clinical Global Impression (CGI)

The CGI is a 3-item observer-rated scale that measures illness severity, global improvement or change and therapeutic response. A modified version of the CGI will be used in this trial to assess "illness" instead of "mental" illness. Investigators will complete the questionnaire at Visits 1 (Baseline), 2, 3, 4, 5, and results will be entered into the eCRFs by the site staff. A CGI can only be assessed during an on-site visit and not be assessed remotely.

12.2 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC) will be established to monitor the safety of IMP throughout study BT – L-CsA – 201 – SCT. The DMC, represented by four members in total, three expert physicians in the field of BOS and one non-medical expert, will monitor safety by evaluating the safety analyses prepared by the independent DMC statiscian during the course of the clinical trial. Details of the composition, meeting frequence and safety analyses will be included in the DMC's Charter.

The DMC will evaluate 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 trial remain acceptable, and make recommendations to Sponsor.

Members of the DMC will be unblinded.

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

DMC recommendations may include advice regarding continuation, modification, suspension or discontinuation of the trial based on safety (but not on efficacy) reasons. However, the final decision for trial continuation, modification, suspension or discontinuation rests solely with the Sponsor

13 VISIT SCHEDULE

All clinical trial visits, investigations and activities are listed in the Clinical Trial Schedule of Activities below. Further details on the methodology of these investigations and activities are described in detail in Section 11 and Section 12. The investigator will adhere to the visit and procedure schedule as closely as possible.

All patients assigned to a randomization number will be followed according to the protocol unless consent for follow-up is withdrawn. The Sponsor must be notified of all deviations from the protocol visit schedule or evaluations, and these visits/evaluations, if applicable, must be rescheduled or performed at the closest possible time to the original schedule.

Proper patient understanding and competency of the L-CsA CCI use will be ensured in an individual training by the responsible clinic personnel. The patient will be administering the drug independently under supervision to verify patient competency with the equipment and drug tolerability.

For emergency and other unscheduled visits to a medical facility other than the clinical trial site, medical records of the visit should be obtained by the Investigator.

If a patient prematurely discontinues clinical trial participation for any reason, e.g., the patient withdraws consent for further participation in the clinical trial, the evaluation listed under "End of Study Visit (EoS)" (Visit 6) should be completed prior to discontinuation whenever possible (the reason for premature withdrawal should always be documented).

Schedule of Activities

Clinical Trial Period	**Screening**	**Treatment**						**Follow-Up**
Visit Number	-	**V 1**	**V 2**	**V 3**	**V 4**	**V 5 / EOT**	**Remote Visits**	**V 6 / EoS**
Week & Window	**W -4 to W 0**	**W 0 Day 1**	**W 2 ± 3 Days**	**W 4 ± 3 Days**	**W 8 ± 7 Days**	**W 12 ± 7 Days**	V3, V4 and V6 can be performed remotely	**W 14 ± 3 Days**
Informed Consent[1]	X							
Demographics/Medical History	X	-						
Inclusion/Exclusion criteria	X							
Serum/Urine Pregnancy Test	X	X	X	X	X	X		X
Physical Examination[2]	X	X	X	X	X	X		X
Vital signs[3]	X	X	X	X	X	X		X
Clinical Laboratory Tests[4]	X	X	X	X	X	X		X
PK Blood Sampling[5]		X	X	X	X	X		
Spirometry[7]	X	X[6]	X[6]	X[6]	X[6]	X[6]		
Randomization		X						
SF-36		X	X	X	X	X	X[8]	
CGI Questionnaire		X	X	X	X	X		
Investigator's Tolerability Assessment				X		X		
Local IMP Tolerability		X	X	X	X	X		
IMP Administration		Twice daily administration					X	
Concomitant Medication	X	X	X	X	X	X	X	X
Adverse Events	Permanent assessment throughout the complete clinical trial period							
Drug Accountability/IMP availabilty check			X	X	X	X	X	

[1] Conduct prior to any screening activities.

[2] Including body weight and height (at Screening visit only), cardiovascular, respiratory, nervous, gastrointestinal, hepatic, renal, dermatological, musculoskeletal, extremities, eyes, ears, nose, throat, and lymphatic.

[3] Including systolic and diastolic blood pressure (sitting, after minimum 5 minutes of rest), pulse rate (sitting, after min. 5 minutes of rest), body temperature (the same method should be used for each patient and throughout the clinical trial), and respiratory rate.

[4] According to Section 12.1.6.

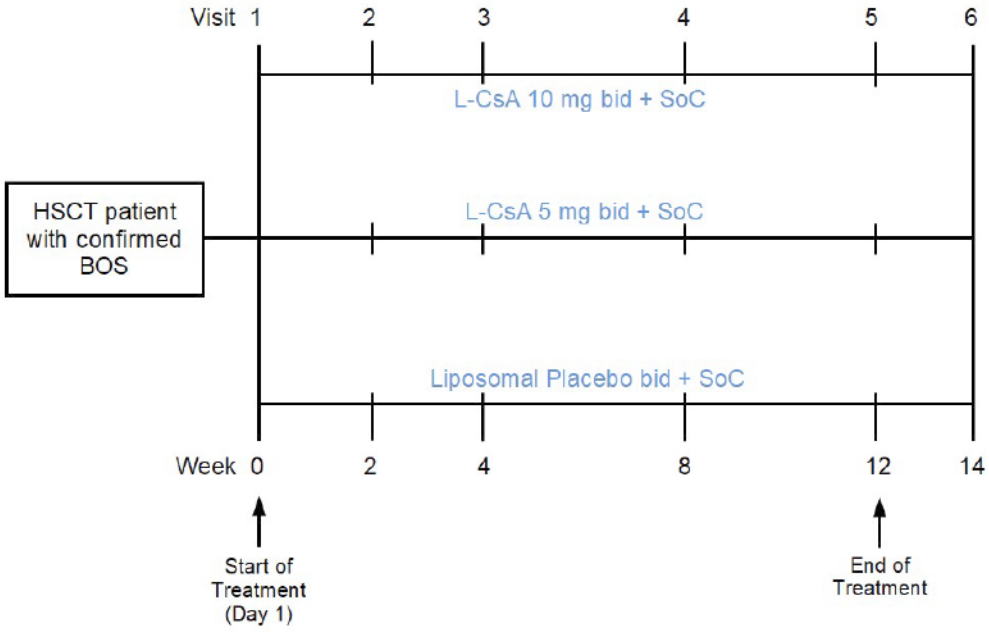
[5] Day 1 blood samples at pre-dose, directly after end of inhalation, 15, 30, 45 min (+/- 5 minutes), and 1, 1.5, 2, 4 h (+/- 15 minutes), after end of inhalation. Other visits are a trough (pre-dose – 15 min before inhalation) sample only.

[6] According to Section 11.1 1.

[7] Spirometry results at screening visit are required to confirm BOS diagnosis. The assessment is allowed to be peformed +/-2 days from screening visit date (but has to be performed after informed consent was given by the patient).

[8] applicable for remote Visits 3 and 4 only

13.1 Clinical Trial Flow Chart



13.2 Visits

13.2.1 Screening

Eligible patients who express interest in participating in the trial must sign an EC approved informed consent form (ICF) prior to initiation of any clinical trial activities. Patients who fulfill all of the inclusion criteria and none of the exclusion criteria may be enrolled into the clinical trial.

Documentation of the patient's consent and eligibility must be completed by the Investigator or his/her designee. All patients who fail the screening activities will be documented in the screening failure log. Re-screening of patients can be considered.

The following screening activities will be performed during the screening visit (up to 4 weeks prior to Visit 1):

- **Informed Consent:** Obtain informed consent prior to performing any clinical trial activities.
- **Demographics:** Year of birth, gender, ethnic group.
- **Medical History:** Details related to each patient's allo-HSCT will be recorded and will include: underlying condition (reason for HSCT), date, type of transplantation, donor demographics, donor/recipient human leukocyte antigen status, donor/recipient cytomegalovirus status, donor/recipient Epstein Barr virus status. All other significant medical conditions and procedures (including past surgeries, documentation of cGvHD in another organ) occurring before the ICF is signed will be recorded as medical history
- **Diagnosis of BOS:** Historical spirometry values documented in the patient file will be used for the calculation of decline ≥10% predicted in FEV_1 over 24 months as requested in the Inclusion criteria. Date of first diagnosis of BOS will be documented.
- **Inclusion/Exclusion Criteria:** Evaluate eligibility for the clinical trial per the inclusion/exclusion criteria.
- **Serum/Urine Pregnancy Test:** Will be obtained in women of childbearing potential unless there is documented infertility.
- **Physical Examination:** Body weight and height (at Screening only), cardiovascular, respiratory, nervous, gastrointestinal, hepatic, renal, dermatological, musculoskeletal, extremities, eyes, ears, nose, and throat, and lymphatic.
- **Vital Signs:** Blood pressure, pulse rate, body temperature, respiratory rate.
- **Clinical Laboratory Tests:** All parameters listed in Section 12.1.6 of the protocol, to be performed in the local laboratory at the site.
- **Spirometry:** FEV_1, FVC, FEV_1/FVC according to ATS/ERS standards.
- **Concomitant Mediations/Therapies:** Name of drug, dosage, start date, stop date, indication
- **AEs**

13.2.2 Visit 1 / Baseline Visit / Randomization

Baseline Prior to Start of Treatment

- Verify Informed Consent was obtained
- Verify Demographics/Medical History
- Repeat Urine/Serum Pregnancy Test (Urine samples can be collected at the Randomization Visit in order to obtain results quickly while the patient is in the clinic and not delay randomization)
- Physical examination
- Vital signs
- Clinical laboratory tests
- PK blood sample pre-dose
- Spirometry
- Randomization
- Concomitant medications/therapies
- AEs
- CGI (Item 1 only)
- SF-36 questionnaire

Start of Treatment

Following activities will be performed:

- Train patient on L-CsA CCI use, drug storage, and inhalation technique
- IMP Administration. Supervise first inhalation for proper use of the nebulizer and for tolerability issues.
- Verify patient is familiar with drug administration and use of nebulizer device
- Emphasize importance of adherence to IMP
- Emphasize importance of adherence to usual medications as taken prior to participating in the trial
- Spirometry: (1 hour ± 20 minutes after completion of dosing with IMP)
- PK blood samples directly after end of inhalation, 15, 30, and 45 minutes (+/- 5 min), and 1, 1.5, 2, and 4 hours (+/- 15 min.) after end of inhalation
- Local IMP tolerability

Prior to release from clinic, study drug and the nebulizer system for home use will be dispensed to each patient. Patient will receive full IMP supply for the 12 weeks treatment period.

13.2.3 Visit 2 through Visit 5 / EoT

- Physical examination
- Vital signs
- Clinical laboratory tests
- Cyclosporine A whole blood trough levels (blood sample pre-dose)
- Urine/Serum pregnancy test
- Spirometry
- IMP Administration
- Concomitant medications/therapies
- AEs
- CGI (Items 1-3)
- SF-36 questionnaire
- Local IMP tolerability
- Drug Accountability by vial count (Visit 5 only)
- Check IMP supplies of patient

13.2.4 Visit 3 and Visit 5

- In addition to the assessments described in section 13.2.3. the clinical investigator will perform an Investigator's Tolerability Assessment assessed by means of a five-point verbal rating scale with the response options 'very good', 'good', 'satisfactory', 'moderate', and 'poor'.

13.2.5 Visit 6 / End of Study (EoS)

- Physical examination
- Vital signs
- Clinical laboratory tests
- Urine/Serum pregnancy test
- Concomitant medications/therapies
- AEs

13.2.6 Unscheduled Visits

Whenever medically warranted, the Investigator may ask the patient to appear or the patient may elect to appear at the clinic for an unscheduled visit. All medical measures performed during an

unscheduled visits (see assessment listed in Section 13.2.3) shall be documented in the respective eCRF.

13.2.7 **Remote Visits**

If patients cannot attend clinic visits due to COVID-19 restrictions, Visit 3, Visit 4 and Visit 6 may be performed as remote visits. For remote visits, the clinical trial personnel will telephone the patient and guide them through the assessments that are required for remote visits (details see Table of Contents Section 13) and

- capture any potential adverse events (AEs) and to confirm the patient's status and wellbeing.
- capture any changes in concomitant medication
- check IMP availabilty with patient over the phone/video as far as possible to ensure adherence to the treatment.
- remind the patient of IMP inhalation
- ensure completion of SF-36 questionnaire

The PI or Sub-Investigator must confirm if, in their opinion, the patient is stable and suitable for prolonged home-treatment, and that patient is in agreement to continuing home-treatment until their next on-site study visit can occur.

All medical measures performed as appropriate shall be documented in the eCRF.

14 STATISTICS

This section presents an overview of the planned analyses. Final analyses are not limited to the summaries described herein. The Statistical Analysis Plan (SAP) will provide a detailed description of the planned statistical analyses and data summaries, and will be finalized before database lock or any unblinding for this study. If circumstances arise during the clinical trial that make these analyses inappropriate or if improved methods become available, the SAP may be revised. If discrepancies exist between the text of the statistical analysis as planned in the protocol and the final SAP, the final SAP will define the planned analysis of record. Reasons for such discrepancies will be described in the final Clinical Study Report (CSR).

This is a Phase IIa, prospective, multicenter, randomized, placebo-controlled trial with a fixed sample size design.

All analyses will be exploratory, and hence any p-values will be interpreted descriptively without adjustment.

Data will be listed by patient and treatment group.

14.1 Analysis Data Sets

The following analysis data sets will be analyzed:

Safety Analysis Set (SAF Set)

The SAF is defined as all randomized patients who have received a partial dose of IMP at least once. All data collected after baseline to the end of clinical trial participation will be included in the safety summaries.

Full Analysis Set (FAS)

The FAS is defined as all randomized patients for whom at least one post-baseline measurement of an efficacy outcome measure is available, i.e. for spirometry or quality of life measures is available.

A Blind Data Review Meeting (BDRM) will be used to determine if patients should be excluded from the FAS in cases of significant, major protocol deviations that preclude an assessment of treatment efficacy (e.g., randomized patients not suffering from the condition under investigation).

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 was identified during the data review meeting. The major protocol deviation criteria will be defined in the protocol deviation list and reviewed before database closure. The reviewed protocol deviation list will be included into in the clinical study report as appendix. .

Eligibility for the analysis data sets will be determined in a BDRM held after closing the database before unblinding. Protocol deviations will be classified as 'major' when a significant influence on the assessment of treatment efficacy cannot be excluded. Comprehensive justification for the classification of a protocol deviation as 'major' will be given in the BDRM minutes as well as in the integrated CSR. Any exclusion of patients from the FAS will require individual justification.

Any data pertaining to safety and tolerability will be analyzed in the SAF. The analysis of treatment efficacy will be performed in the FAS. An additional efficacy analysis in the PPS will be provided as a sensitivity analysis. For safety outcomes patients will be analysed according to the treatment actually received. For efficacy measures patients will be analysed as randomized.

14.2 Statistical and Analytical Methods

14.2.1 Descriptive Statistics

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

- All continuous assessments will be summarized using descriptive statistics (i.e., N, mean, standard deviation, median, lower quartile (Q1), upper quartile (Q3), minimum, and maximum).
- All categorical assessments will be summarized by time point, as applicable, using frequency counts and percentages.
- Discrete ordinal or metric data will be summarized as continuous data, but a tabulation of categories may be included additionally depending on the number of categories.

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 an analysis of change from baseline. Where provided, all confidence intervals will be two-sided 95% confidence intervals.

14.2.2 Characterization and Baseline Comparability of Treatment Groups

The number and percentage of patients who complete and discontinue the clinical trial as well as reasons for early discontinuation will be presented.

Descriptive statistics will be presented for demographic, anthropometric, and medical data.

14.2.3 Analysis of Safety

Safety outcomes are listed in Section 12.1. All safety measures will be compared descriptively between the treatment groups in accordance with the concept of descriptive data analysis in the SAF population.

14.2.3.1 Extent of Exposure

Exposure to IMP will be confirmed based on the report of IMP vials returned and dosing recorded in the eCRF.

14.2.3.2 Adverse Events

AEs will be coded using the MedDRA. Events will be identified as treatment-emergent (TEAE) and non-treatment-emergent (Non-TEAE) on the basis of the date of onset relative to the date of the first IMP dose.

Separate analyses will be presented for all TEAEs, for potentially IMP related TEAEs, for all serious TEAEs, and for serious, potentially treatment related TEAEs. TEAEs will be considered potentially IMP related if the investigator's rating of the causal relationship is anything other than 'not related' or missing.

Summaries (number and percentage of events as well as of patients with any events of a particular type) of TEAEs (by system organ class [SOC] and preferred term [PT]) will be provided. Number (%) of patients experiencing TEAEs by severity, relationship to IMP, seriousness, and action taken with regard to IMP will be summarized. Number (%) of patients with TEAEs leading to discontinuation of clinical trial participation will also be summarized.

Treatment group comparisons of the proportion of patients with TEAEs will be based on Wilson score confidence intervals [Wilson, 1927]. Pairwise comparisons between all treatment groups will be provided at the SOC level as well as for the events identified as local tolerability measures in Section 12.1.5. For the latter, separate analyses will be presented for all events with onset during the first 4 weeks of treatment and for events with onset at any time during randomized treatment.

Incidence densities of events per patient day starting with the first IMP administration will be determined for all TEAEs as well as separately for each of the events identified as local tolerability measures in Section 12.1.5. In accordance with the visit schedule, incidence densities will be provided for the periods between every two adjacent visits starting with the first IMP administration as well as for the entire randomized treatment period. Events will be assignet to their period of onset.

In addition to the pairwise treatment group comparisons, all analyses specified above in this section will also be performed for the comparison between all patients treated with L-CsA (2 x 5 mg/day or 2 x 10 mg/day) and those treated with placebo in order to increase the chance of identifying TEAEs potentially related to L-CsA.

14.2.3.3 Measures of Overall Tolerability

For the measures of over-all tolerability identified in Section 12.1.5, descriptive statistics will be presented by visit (see Section 14.2.1). Pairwise treatment group comparisons will be performed for applicable visits using exact Wilcoxon-Mann-Whitney U-tests.

14.2.3.4 Laboratory and Other Safety Evaluations

For clinical safety laboratory test results and vital signs, the numeric values and corresponding changes from baseline will be summarized using descriptive statistics by parameter and time point. In addition to the tables showing the distribution parameters, laboratory measures will be presented in 'shift tables' that show the position of all patients relative to the applicable reference range at clinical trial entry, broken down by the position at clinical trial exit.

14.2.4 Analyses of Efficacy

Analyses of efficacy will be based on the FAS and on the PPS analysts populations.

Scoring of the eight scales and two summary scores of the SF-36 will be performed according to the instructions provided for the Australian Longitudinal Study on Woman's Health.).

For the spirometry measures identified in Section 11.1.1 as well as for the scales and summary scores of the SF-36, the numeric values and corresponding changes from baseline will be summarized using descriptive statistics by parameter and time point.

The analysis will be carried out with a mixed model for repeated measures (MMRM), using all available measurements of the outcome of interest. The dependent variables will be the absolute change from baseline of the outcome of interest at the visits scheduled for Weeks 2 through 12, using fixed effects for treatment, visit, and the treatment x visit interaction and the baseline value as a fixed effect covariate. Ttreatment group comparisons at each visit will be estimated by differences between the marginal (adjusted) means from the treatment x visit interaction, weith accompanying p-valies and 95% confidence intervals. Further details of the analysis will be described in detail in the SAP.

Descriptive summary measures will be provided based on all observed values as well as based on the marginal means determined via MMRM analyses.

14.2.5 Pharmacokinetic Variables

The statistical analysis will be performed as a valid case analysis including all patients of the FAS. No subgroup analysis is planned.

Descriptive statistics will be used by the CCI [redacted] (N, arithmetic means, standard deviation, geometric means, geometric coefficient of variation, medians, minimum and maximum) and will be presented for all PK parameters indicated in Section 8.1.6, separately for each treatment by using the CCI [redacted].

The plasma concentration levels in the CCI are measured using a validated LC-MS / MS method. The procedure for validation and the acceptance limits are based on the requirements of the EMA Guideline (Guideline on bioanalytical method validation (EMEA / CHMP / EWP / 192217/2009 Rev. 1 Corr. 2 **), July 2011).

The statistical analysis will be carried out on a log scale for $AUC_{0\text{-}4\,h}$ and C_{max}-values, while t_{max} and trough levels will be evaluated on a linear scale. Analyses of variance will be performed to compare the treatment groups.

14.3 Interim Analysis

Not applicable.

14.4 Missing Data

No missing data imputation will be performed. For efficacy outcomes, time courses will be modeled via MMRM (see Section 14.2.4).

14.5 Sample Size Considerations

This is a Phase IIa study in a rare indication with very limited availability of eligible patients and a purely descriptive statistical concept. Accordingly, the sample size for the study was established based on considerations of feasibility rather than on power calculations.

A total of 24 patients (3 arms x 8 patients each) are planned to be randomized.

15 DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

Source data is all information, original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents. Examples of these original documents and data records include but are not limited to: hospital records, clinical and office charts, laboratory notes, memoranda, patients' diaries or questionnaires or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilms or magnetic media, X-rays, patient files, and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical trial. The eCRF is not considered to be source data.

Case report forms, all copies of test results, and clinical trial-related regulatory documents (e.g., Informed Consents, EC favourable opinion /correspondence) must be available always for regulatory agency inspection and review by the Sponsor or its designee. During the periodic site monitoring visits, the source documents will be verified against data entered onto the eCRF to assure that all data is accurately and completely reflected on the patient's eCRF.

16 QUALITY CONTROL AND QUALITY ASSURANCE

This clinical trial will be monitored by the Sponsor or its designee according to ICH GCP guidelines. A site visit will be held prior to initiation of patient enrollment. The protocol, eCRFs, IMP supplies, and relevant procedures will be explained in detail at the Site Initiation Visit. Subsequent to patient enrollment, a site monitor from the Sponsor or its designee will review the eCRFs and source documents to ensure that the clinical trial is conducted according to the protocol and ICH GCP guidelines.

To ensure compliance with ICH GCP guidelines and all applicable regulatory requirements, the Sponsor or its designee may conduct quality assurance audits. Any potential serious GCP non-compliance will be promptly reported to sponsor by the CRO and Health Authorities and Ethics Commitees, as applicable.

17 ETHICS COMMITTEE (EC)

The protocol and ICF(s) for this clinical trial must have received a favourable opinion by an appropriately constituted Ethics Committee (EC) as defined by local requirements. A list of the EC voting members, their titles or occupation, and their institutional affiliations (if available and allowable under EU law) and/or the EC general assurance number, if applicable, must be submitted to the Sponsor or its designee to be archived in the Trial Master File.

Any documents that the EC may need to fulfill its responsibilities, such as protocol amendments, and information concerning patient recruitment, payment or compensation procedures, or information from Zambon SpA will be submitted to the EC. The EC's written favourable opinion of the protocol and the ICF/patient information leaflet will be in the possession of the Investigator before the clinical trial is initiated. The EC's favourable opinion statement will be transmitted by the Investigator to Zambon SpA or its designee prior to shipment of IMP supplies to the site. This favourable opinion must refer to the clinical trial by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written EC favourable opinion except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the clinical trial. Such modifications will be submitted to the EC and written verification that the modification was submitted should be obtained.

The EC must be informed by the Investigator of informed consent changes or revisions of other documents originally submitted for review; serious and/or unexpected AEs occurring during the clinical trial; new information that may adversely affect the safety of the patients or the conduct of the clinical trial; an annual update and/or request for review and opinion; and when the clinical trial has been completed.

The Investigator will ensure that the conduct of the clinical trial conforms to the Declaration of Helsinki (current revision) and with applicable national laws and regulations for clinical research. Before starting this clinical trial, the protocol will be submitted to each center's Ethics Committee for evaluation at each site. As required, the clinical trial will not start before the EC has given favourable opinion.

Periodic status reports and SAEs must be submitted to the EC according to the EC reporting requirements. The EC must also be notified of completion of the clinical trial and a final report must be submitted to the EC in accordance with the EC reporting requirements. The Investigator must maintain an accurate and complete record of all communication, reports and submissions to the EC.

18 PATIENT INFORMED CONSENT

Patients will be required to sign a statement of informed consent that meets the requirements of European and local regulations, ICH E6 (R2) guidelines, and the EC of the center. The medical record will include a statement that written informed consent was obtained before the patient was enrolled in the clinical trial and the date written consent was obtained.

Members of the treating team will review the nature of the clinical trial, its purpose, the procedures involved, the expected duration, the potential risks and benefits and alternative therapies including best supportive care. Patients must be informed that participation in the clinical trial is voluntary, he/she may withdraw from the clinical trial at any time and withdrawal from the trial will not affect his/her subsequent medical treatment or relationship with the treating physician. Financial costs that will or may be incurred as a result of participation in the trial, as well as the efforts to maintain patient confidentiality will also be discussed.

This consent must be witnessed and dated and retained by the Investigator as part of the clinical trial records. A copy of the ICF must be given to the patient. If the patient signed the informed consent more than 30 days prior to the date of randomization, it should be documented that consent has not been rescinded. Alternatively, the site should follow the EC's requirement for re-consenting a patient.

A copy of the EC approved consent form must be submitted to Zambon SpA or its designee prior to shipment of IMP supplies to the Investigator. Each patient's signed informed consent must be kept on file by the Investigator for regulatory authority and Sponsor inspection at any time.

The Declaration of Helsinki, as amended (version of Fortaleza, Brazil, 2013), recommendations guiding doctors in clinical research should be followed by the Investigator.

19 HEALTH AUTHORITIES

The protocol and any related documentation including all subsequent changes (substantial amendments) of these documents will be submitted for approval to the regulatory authorities in compliance with applicable European regulations.

Non-substantial amendments will be submitted according to local regulatory requirements for notification.

Any premature termination of the clinical trial will be submitted within 15 days, and regular end of the study will be notified as well.

20 DATA HANDLING AND RECORD KEEPING

20.1 Confidentiality

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a coded number and initials only. All clinical trial records will be kept at each center in a locked file cabinet. Clinical information will not be released without written permission of the patient, except as necessary for monitoring or inspections by the authorities or a designee of the Sponsor as described in the informed consent form.

The Investigator must assure that the privacy of the patients, including their personal identity and all personal medical information, will be maintained at all times. In eCRFs and other documents patients will not be identified by their names, but by an identification code (e.g., by an arbitrary, unique patient number).

The Investigator agrees that all information received from Zambon SpA including but not limited to this protocol, eCRF, and any other clinical trial information, remain the sole and exclusive property of Zambon SpA during the conduct of the clinical trial and thereafter. This information is not to be disclosed to any third party (except employees or agents directly involved in the conduct of the trial or as required by law) without prior written consent from Zambon SpA. The Investigator further agrees to take all reasonable precautions to prevent the disclosure by any employee or agent of the investigative site to any third party or otherwise into the public domain.

With reference to EU Regulation no.679/2016 of European Parliament and of the Council of 27 April 2016, the General Data Protection Regulation (GDPR), and other local law provisions the data protection roles within the study are the following:

- the sponsor and the investigational center are autonomous data controllers, and will process the personal and study data of the participants exclusively for study related purposes and for pharmacovigilance purposes.
- The CRO will process the participant's data on behalf of the sponsor and will be appointed as a data processor by the sponsor. The CRO may avail itself of subcontractors, who will be appointed as sub processors as well, pursuant to art. 28 of GDPR.
- The principal investigators will process the data as a data processor, on behalf of the study center.

As concerns the data protection information/notice, participants must be informed properly about all the data protection elements provided by art. 13 and 14 of GDPR. Investigator or his/her representative will give to the participant a proper data protection information notice compliant with GDPR, and will consequently ask to the participant a data protection consent, together with the study informed consent. According to the provisions of the GDPR, the level of disclosure in the informed consent must also be explained to the participant. The participant must be informed

that his/her medical records may be examined by Auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.

As regards the organizational and security measures adopted, the operations of collection, storage, circulation of biological samples as well as all the data processing operations regarding the study data are performed in compliance with GDPR. The investigator or his/her representative will assign to the participants a unique identifier. Investigator will be the only one who can match the participant's identity with the data referred to the study. Any participant records or datasets that are transferred to the sponsor will contain the identifier code only; participant names or any other information which would make the participant identifiable will not be transferred to the sponsor.

20.2 Completion of Electronic Case Report Forms

An eCRF will be used in this clinical trial. Staff authorized to enter or modify data on the eCRF will be assigned an appropriate user role:

- study coordinators or nurses may enter, modify, or delete data and may enter, modify, or delete responses to queries;
- investigators may perform the same activities as study coordinators. Moreover, they may authorize data by entering an electronic signature.

Any data entries, modifications, and deletions will be recorded in an automated audit trail together with a time stamp and the identification code of the person performing the entry / modification / deletion.

To access the eCRF authorized users will receive a unique user name and password that will also be required for data authorization (investigators only). These credentials are strictly personal and confidential and must not be shared with anyone.

Investigators will be provided with detailed eCRF Completion Guidelines that will identify the required data points to be collected, how to document them and when these data should be documented. Appropriate training in electronic data capture and support will be provided.

It is the responsibility of the Investigator to maintain adequate and accurate eCRFs to record (according to the eCRF Completion Guidelines) all observations and other data pertinent to the clinical trial obtained during scheduled or unscheduled visits. All eCRFs should be fully completed to ensure accurate data interpretation.

All eCRF entries should be made within a maximum of 5 days of a visit by a designated and trained member of the site staff. The Investigator must ensure the accuracy, completeness legibility and timeliness of data reported in the eCRF and all required reports. Any change or correction to an eCRF must be documented as instructed and explained (if necessary) in the clinic notes, this applies to both written and electronic changes. The patient's medical source documents must support any changes made.

Data reported in the eCRF that are derived from source documents should be consistent with the source documents or the discrepancies should be explained.

The investigator must review and electronically sign the completed eCRF casebook to verify its accuracy.

The main objective is to obtain those data required by the protocol in a complete, accurate, legible, and timely fashion. These data in the eCRF should be consistent with the relevant source documents.

The eCRFs and the corresponding electronic database shall be processed, evaluated, and stored in anonymous form in accordance with the data-protection regulations.

These data recorded in the course of this clinical trial may periodically be remotely reviewed and compared to the electronic database. The computerized handling of these data after receipt of the eCRFs may generate additional requests via electronic queries to which the Investigator is obliged to respond by confirming or modifying these data questioned. These requests with their responses will be appended to the eCRFs held by the Investigator and Sponsor.

In the case of missing data/remarks, the entry spaces provided for in the eCRF should be cancelled out to avoid unnecessary follow-up inquiries. The eCRFs are regulatory documents and must be suitable for electronic submission to authorities.

The Investigator must keep a separate patient identification list showing code numbers, names, and dates of birth to allow unambiguous identification of each patient included in the clinical trial. A note will be made in the hospital medical records that the patient is participating in a clinical trial. The eCRF will be completed appropriately.

20.3 Source Data and Patient Files

The Investigator has to keep a paper or electronic patient file for every patient participating in the clinical trial. In this patient file, the available demographic and medical information of a patient has to be documented, in particular the following: name, date of birth, sex, height, weight, patient history, concomitant diseases and concomitant medication (including changes during the clinical trial), statement of entry into the clinical trial, trial identification, patient number, the date of informed consent, all visit dates, pre-defined performed examinations and clinical findings, observed AEs (if applicable) and reason for withdrawal from clinical trial treatment or from the trial (if applicable). It should be possible to verify the inclusion and exclusion criteria for the clinical trial from the available data in this file. It must be possible to identify each patient by using this patient file.

Additionally, any other documents with source data, especially original printouts of data that were generated by technical equipment have to be filed. This may include laboratory value listings, electrocardiogram recordings, X-rays, computed tomography scans, etc. (if applicable). All these

documents have to bear at least the patient identification and the printing date printed by the recording device to indicate to which patient and to which procedure the document belongs. The medical evaluation of such records should be documented as necessary and signed/dated by the Investigator.

Printouts of computerized patient files must be signed and dated by the Investigator, and kept as a source document.

20.4 Investigator File and Archiving

The Sponsor will provide, and the investigator will maintain an Investigator Site File (ISF) containing all essential documents for the clinical trial. The ISF will contain each patient's eCRF pdf after the database has been locked. The investigator should maintain a record of the location(s) of their respective essential documents including source documents. The storage system used during the trial and for archiving (irrespective of the type of media used) should provide for document identification, version history, search and retrieval.

Essential documents are subject to audit and inspection at all times and will be archived according to applicable regulatory requirements.

20.5 Monitoring, Quality Assurance, and Inspection by Authorities

This clinical trial is to be conducted in accordance with ICH E6 (R2) and applicable European regulations. Monitoring and auditing of the trial will be the responsibility of the Sponsor or a designee authorized by the Sponsor.

To ensure compliance with ICH GCP guidelines and all applicable regulatory requirements, the Sponsor or its designee may conduct quality assurance audits. Regulatory agencies may also conduct a regulatory inspection of this clinical trial. Such audits or inspections can occur at any time during or after completion of the clinical trial. If audits or inspections occur, the Investigator and the institution agree to allow the auditor/inspector direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the auditor/inspector to discuss findings and any relevant issues.

20.6 Data Management and Data Control

The Sponsor will be responsible for the processing and quality control of the data. Data management and filing will be carried out as described in the contracted CRO's Standard Operating Procedures for clinical trials.

Prior and concurrent medications within 30 days of randomization will be listed. Prior/concurrent medications will be coded using the World Health Organization Drug Dictionary classification

system and grouped by drug class and preferred term. AEs and current medical conditions for concomitant medications will be coded using MedDRA.

The eCRF data and patient data listings will be archived by the Sponsor for the lifetime of the product. No clinical trial document should be destroyed without prior written agreement between the Sponsor and the Investigator. Should the Investigator wish to assign the clinical trial records to another party or move them to another location, advance written notice should be given to the Sponsor.

21 FINANCING AND INSURANCE

A separate financial agreement (Clinical Investigators' Agreement) will be made between each Investigator and the Sponsor before the IMP is delivered. The Sponsor will ensure financing of the complete clinical trial.

The clinical trial is covered under a Sponsor group combined liability insurance policy. The certificate of insurance and an information leaflet containing essential information about the insurance coverage will be provided upon request.

22 PUBLICATIONS

After conclusion of the clinical trial, an integrated clinical and statistical study report will be prepared by the Sponsor or designee. The first publication of the clinical trial will comprise of data from the entire clinical trial population enrolled at all sites. Any publications of the results, either in part or in total (abstracts in journals or newspapers, oral presentations, etc.) by Investigators or their representatives will require pre-submission review by the Sponsor. The Sponsor is entitled to delay publication in order to obtain patent protection. For more details regarding publications, refer to the clinical trial agreement/Investigator trial agreement.

The results of the clinical trial will be published and/or presented in scientific meetings in a timely manner. Any formal publication of clinical trial results will be a collaborative effort between the Sponsor and the Investigator(s). All manuscripts and abstracts will be reviewed and approved in writing by the Sponsor prior to submission.

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

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24 APPENDIX I – CORE INFORMED CONSENT FORM

The informed consent form must be adapted to local requirements but must contain at least the following points:

- That the trial involves research.
- The purpose of the trial.
- The trial treatment(s) and the probability for random assignment to each treatment.
- The trial procedures to be followed, including all invasive procedures.
- The patient's responsibilities.
- Those aspects of the trial that are experimental.
- The reasonably foreseeable risks or inconveniences to the patient and, when applicable, to an embryo, fetus, or nursing infant.
- The reasonably expected benefits. When there is no intended clinical benefit to the patient, the patient should be made aware of this.
- The alternative procedure(s) or course(s) of treatment that may be available to the patient, and their important potential benefits and risks.
- The compensation and/or treatment available to the patient in the event of trial related patient injury.
- The anticipated prorated payment, if any, to the patient for participating in the trial.
- The anticipated expenses, if any, to the patient for participating in the trial.
- That the patient's participation in the trial is voluntary and that the patient may refuse to participate or withdraw from the trial, at any time, without penalty or loss of benefits to which the patient is otherwise entitled.
- That the monitor(s), the auditor(s), the EC, and the regulatory authority(ies) will be granted direct access to the patient's original medical records for verification of clinical trial procedures and/or data, without violating the confidentiality of the patient, to the extent permitted by the applicable laws and regulations and that, by signing a written informed consent form, the patient or the patient's legally acceptable representative is authorizing such access.
- That records identifying the patient will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available. If the results of the trial are published, the patient's identity will remain confidential.
- That the patient or the patient's legally acceptable representative will be informed in a timely

manner if information becomes available that may be relevant to the patient's willingness to continue participation in the trial.

- The person(s) to contact for further information regarding the trial and the rights of trial patients, and whom to contact in the event of trial-related injury.
- The foreseeable circumstances and/or reasons under which the patient's participation in the trial may be terminated.
- The expected duration of the patient's participation in the trial.
- The approximate number of patients involved in the trial.
- Information regarding the trial can be found on clinicaltrials.gov.

25 APPENDIX II – ACCEPTABLE METHODS OF CONTRACEPTION

A woman is considered of childbearing potential, i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. The status of post-menopausal is defined as no menses for 12 months without an alternative medical cause and/or the age of 60 years.

According to the Clinical Trial Facilitation Group (CTFG) dated 21/Sep/2020, the following methods are allowed for contraception during the clinical trial with a failure rate of less than 1%:

- combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation [1]:
    - oral
    - intravaginal
    - transdermal
- progestogen-only hormonal contraception associated with inhibition of ovulation [1]:
    - oral
    - injectable
    - implantable [2]
- intrauterine device (IUD) [2]
- intrauterine hormone-releasing system (IUS) [2]
- bilateral tubal occlusion [2]
- vasectomised partner [2,3]
- sexual abstinence [4]

From results of previous clinical trials with aerosolized L-CsA potential interactions between the IMP and hormonal contraceptives have not been investigated. It is recognized that hormonal contraceptives can increase serum levels of systemically dosed cyclosporine, but cyclosporine does not alter the efficacy of hormonal contraceptives. Subjects in the trial will be monitored for systemic cyclosporine levels.

[1] Hormonal contraception may be susceptible to interaction with the IMP, which may reduce the efficacy of the contraception method

[2] Contraception methods that in the context of this guidance are considered to have low user dependency.

[3] Vasectomised partner is a highly effective birth control method provided that partner is the sole sexual partner of the WOCBP trial participant and that the vasectomised partner has received medical assessment of the surgical success.

[4] In the context of this guidance sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study treatments. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject.