STATISTICAL ANALYSIS PLAN

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)

Version: 5.0

Date: 30 April 2021

Protocol Amendment No 4

SPONSOR

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INVESTIGATIONAL MEDICINAL PRODUCT

Liposomal Cyclosporine A (L-CsA)

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3 ABBREVIATIONS

AE	Adverse Event
allo-HSCT	Allogeneic Hematopoietic Stem Cell Transplantation
ATC	Anatomical Therapeutic Chemical Classification System
AUC_{0-4h}	Area Under the Curve, 0 – 4 hours after dosing
BDRM	Blind Data Review Meeting
bid	Bis in die, twice daily
BOS	Bronchiolitis Obliterans Syndrome
CGI	Clinical Global Impressions
cGvHD	Chronic Graft Versus Host Disease
C_{max}	Maximum Plasma Concentration
CsA	Cyclosporin A
CSR	Clinical Study Report
DMC	Data Monitoring Committee
eCRF	Electronic Case Report Form
EoS	End of Study
EoT	End of Treatment
FAS	Full Analysis Set
FEF_{25-75}	Forced Midexpiratory Flow
FEV_1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
IMP	Investigational Medicinal Product (study drug: L-CsA)
IPD	Important Protocol Deviation
L-CsA	Liposomal Cyclosporine A Inhalation Solution
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed Model of Repeated Measures
N-IPD	Non-Important Protocol Deviation
PD	Protocol Deviation
PK	Pharmacokinetics
PPS	Per Protocol Set
PT	Preferred Term
Q1	1st quartile
Q3	3rd quartile
SAE	Serious Adverse Event
SAF	Safety Analysis Set

SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SCT	Stem Cell Transplantation
SF-36	Short Form (36) Health Survey
SoC	Standard of Care
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TFLs	Tables, figures and listings
t_{max}	Time Between Dosing and Maximum Plasma Concentration
WHO	World Health Organization

4 VERSION HISTORY

Date	Version	Brief Description of Changes
25 FEB 2022	Final v1	No previous final version

5 INTRODUCTION

This Statistical Analysis Plan (SAP) provides details of planned analyses to be performed on the data to be collected from clinical trial BT – L-CsA – 201 – SCT (BOSTON-4). It is based on the Clinical Trial Protocol, version 5.0 of 30 April 2021 (including Protocol Amendment 4).

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

This SAP is not intended to pre-specify all possible analyses that may be performed after completion of the clinical trial. The main purpose of this SAP is to pre-specify statistical analyses that relate to identified clinical trial objectives. Any supportive or exploratory analyses presented in the integrated CSR which are not described in the SAP will be identified as such.

This SAP will be finalized before database lock or any unblinding for this study. The programming specifications including tables, figures and listings (TFLs) to support the analysis as described below will be presented as a separate document.

6 CHANGES TO STUDY PROTOCOL

The planned analysis will be performed according to the study protocol, its amendments and this statistical analysis plan. If there are contradictions between the study protocol or its amendments and this statistical analysis plan, the analysis will be performed according to this analysis plan. Any deviation from the planned analysis has to be described in the CSR.

The differences between study protocol and statistical analysis plan are summarized in the following table:

Change	**Clinical Study Protocol (CSP)**	**In the Statistical Analysis Plan Will be changed to:**
Wording in CSP	Major Protocol Deviation Minor Protocol Deviation	Important Protocol Deviation Non-Important Protocol Deviation

7 TRIAL OBJECTIVES

The primary objective of this study is to assess the tolerability and safety of two dose levels of aerosolized, liposomal cyclosporine A (L-CsA) in comparison to placebo, applied in addition to standard of care (SoC) therapy, for Bronchiolitis Obliterans Syndrome (BOS) in adult allogeneic hematopoietic stem cell transplantation (allo-HSCT) recipients. The secondary objectives are to assess the pharmacokinetics (PK) and exploratory efficacy and quality of life ratings of two dose

levels of aerosolized L-CsA in comparison to placebo in addition to SoC therapy in the same indication and patient population.

8 INVESTIGATIONAL PLAN

8.1 Trial Design

This is a Phase IIa, prospective, multicenter, randomized, single-blind, placebo-controlled clinical trial of L-CsA for the treatment of BOS in adults with confirmed BOS following allo-HSCT. Patients will receive either L-CsA 5 mg or L-CsA 10 mg or placebo via the CCI [redacted] System twice daily in addition to SoC treatment, for a period of 12 weeks (see Table 1).

A total of the following visits will be performed during the clinical trial:

- Screening
- Week 0 (Randomization/Baseline) [Visit 1]
- Week 2 [Visit 2]
- Week 4 [Visit 3]
- Week 8 [Visit 4]
- Week 12 (End of Treatment (EoT) [Visit 5]
- Week 14 (End of Study (EoS) [Visit 6]

After informed consent has been obtained, a Screening Visit will be carried out in order to determine the eligibility for randomized treatment. At the Baseline Visit (V1, randomization visit), inclusion and exclusion criteria will be re-confirmed and baseline spirometry performed. During the 12-week treatment period, interim visits are scheduled at weeks 2, 4, and 8 (V2 – V4). Visit 5 (End of Treatment, EoT) is scheduled to occur 12 weeks after Visit 1. Visit 6 (End of Study, EoS) is a safety follow-up visit performed 2 weeks after Visit 5/EoT.
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.

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.

Table 1 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 1 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 availability 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. of the protocol

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 12.1.1. of the protocol

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

8.2 Randomization and Stratification

At the Baseline visit (V1), 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.

No stratification will be performed.

8.3 Primary Endpoints

- Investigational medicinal product (IMP) tolerability and safety during the first 4 weeks of treatment. IMP tolerability will be assessed using the following outcomes:
    - Local Tolerability:
        - Cough
        - Wheezing
        - Bronchospasm
        - Throat irritation
        - Change in FEV_1
    - Overall Tolerability:
        - Clinical Global Impressions (CGI) scale
        - Investigator's tolerability assessment
    - Safety
        - Adverse events (AEs)
        - Serious adverse events (SAEs)
        - Clinical laboratory values
        - Vital signs
        - Physical examination

8.4 Secondary Endpoints

- IMP tolerability and safety during the first 12 weeks of treatment (using the outcomes listed in Section 8.3)
- CsA PK, using the following parameters:
    - 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}, $AUC_{0\text{-}4h}$
- Whole blood trough levels parameter (Cyclosporine A Concentration) at week 2, 4, 8, and 12

8.5 Exploratory Endpoints

The following measures of treatment efficacy will be analyzed as exploratory assessments:

- FEV1 % predicted, FEV1/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

For efficacy assessments determined at post-baseline visits, measured values as well as change from baseline will be analyzed.

8.6 Safety Endpoints

See Sections 8.3 and 8.4.

9 STATISTICAL CONSIDERATIONS

9.1 General Considerations and Descriptive Statistics

Analyses and outputs will be produced using SAS® software PPD, version 9.4 or later, or other suitable, commercially or publicly available statistical software, in a secure and validated environment. All tables, figures and data listings to be included in the report will be independently checked for consistency and integrity.

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

- All continuous assessments will be summarized using descriptive statistics (i.e., n, mean, standard deviation, median, Q1, Q3, minimum, and maximum).
- All categorical assessments will be summarized by using frequency counts and percentages.
- Discrete ordinal or higher-level data will be summarized as continuous data, but a tabulation of categories may also be included, depending on the number of categories.
- "Missing" category should be added for a categorical variable if there is at least one subject with missing data for that categorical variable unless the following evaluation requires otherwise.

For all measures analyzed, tabulations comparing the treatment groups will be prepared. For outcomes measured more than once, the analyses will include tabulations of the measured values

by visit, as well as change from baseline. Where provided, all confidence intervals will be two-sided 95% intervals.

All data recorded in the eCRF will be listed in subject data listings.

9.1.1 Imputation of Missing data

There will be no imputation of data for efficacy analysis. All data will be analyzed as they appear in the database. Missing data will be displayed in subject data listings and will be declared in tables as appropriate.

The following imputation rules will apply only for AE data:

- Imputed data should be flagged and properly footnoted as "imputed".
- AEs with unknown onset date/time will be counted as treatment emergent AEs (TEAEs).
- AEs/TEAEs with unknown end date/time will be counted as an ongoing AEs/TEAEs, unless ongoing was ticked on the CRF.
- TEAEs will be considered potentially IMP related if the investigator's rating of the causal relationship is anything other than 'not related' or missing.
- If for the calculation of a time period the full date format ddmmmyyyy is needed, missing entries will be imputed as follows:
  - Missing day in start date of a time period is imputed by the first day of the month;
  - Missing day in stop date of a time period is imputed by the last day of the month;
  - Missing month in start date of a time period is imputed by January of the year;
  - Missing month in stop date of a time period is imputed by December of the year;
  - Missing year is not imputed.

9.2 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 with 8 patients in each) are planned to be randomized.

9.2.1 Interim Analysis for Sample Size Re-estimation

Not applicable.

9.3 Type I Error Considerations

Not applicable.

9.4 Data Monitoring Committee and Confidentiality of Results

An independent Data Monitoring Committee (DMC) will be established to monitor the safety of the IMP throughout the conduct of the study. The statistical analysis to be prepared for the meetings of the DMC are described in a separate SAP.

10 DEFINITIONS

10.1 Protocol Deviations

According to the Protocol Deviation Management Plan, PDs are classified as either Important PDs (IPDs) or Non-important PDs (N-IPDs). IPDs are a subset of PDs that may significantly impact the completeness, accuracy, and/or reliability of the trial data or that may significantly affect a subject's rights, safety, or well-being. Additionally, PD related to Covid-19 will be classified.

IPDs for which a significant influence on the assessment of treatment efficacy cannot be excluded will lead to the exclusion of a subject from an efficacy analysis data set (see Section 10.2 below). The impact of PDs on the efficacy endpoint results will be investigated by assessing the robustness of the efficacy results and conclusions to the choice of analysis population, both including and excluding data potentially affected by such PDs (see Sections 10.2.2 and 10.2.3 below).

The relevant PDs have to be defined by a systematic data review prior to database closure. For this purpose, PDs that occurred during the study such as deviations of inclusion/exclusion criteria or forbidden concomitant medications or subject non-compliance will be assessed as ‘important’ or ‘non-important’ depending on their potential to interfere with the objectives of the study. Listings will be prepared to show the eligibility of all subjects. Comprehensive justification for the classification of a protocol deviation as “important” will be given in the integrated clinical study report.

Important protocol deviations and the assessment of analysis sets will be defined during the data review before data base closure. All definitions given in the Minutes of the Final Data Review will be taken into account in the analysis.

The list of protocol deviations will be reviewed by the sponsor and finalized before locking the database. The sponsor will identify important PDs which will lead to exclusion of subjects from PP population. Important PDs leading to the exclusion of patients from the analyses sets will be flagged in the protocol deviation listing.

10.2 Analysis Data Sets

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

Eligibility for the analysis data sets will be determined in a Blind Data Review Meeting (BDRM) held after closing the database but before unblinding the random code. To maintain the blinding of the meeting participants in this single-blind study, information on protocol deviation as well as any other subject data will be presented during the BDRM in a format that assures that the actual treatment assignment of the subjects will not be revealed.

Detailed justification for the classification of a protocol deviation as having an important influence on the assessment of treatment efficacy will be given in the BDRM minutes as well as in the integrated CSR.

10.2.1 Safety Analysis Set

The Safety Analysis Set (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. Patients will be analyzed according to the treatment they actually received.

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

10.2.2 Full Analysis Set

The Full Analysis Set (FAS) is defined as all randomized patients for whom a baseline and at least one post-baseline measurement of an efficacy outcome measure, i.e., for spirometry or quality of life measures (Section 8.5), is available. For spirometry measures, baseline will correspond to the assessment at randomization visit (Visit 1) prior to inhalation of IMP. Patients will be analyzed according to the treatment group to which they were randomized.

A BDRM will determine if patients should be excluded from the FAS in cases of significant protocol deviations that preclude an assessment of treatment efficacy (e.g., randomized patients not suffering from the condition under investigation). Any exclusion of patients from the FAS will require individual justification.

The primary analysis of all efficacy endpoints will be performed using the FAS.

10.2.3 Per Protocol Set

The Per Protocol Set (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 IPD leading to exclusion from PPS was identified during the data review meeting. The IPD criteria will be defined in the protocol deviation (PD) list and reviewed before database closure. The reviewed PD list will be included into the CSR.

Patients with one or more AE related to IMP will be discussed during the BDRM to decide if there is a lack of tolerability.

Patients with "AE (including SAE/Death)", "Investigator's withdrawal of subject in the best interest of the patient" or with free text "Lack of efficacy" as primary reason for non-completion of the study will be discussed during the BDRM to decide if there is a lack of efficacy.

For selected efficacy endpoints, the PPS may be used as a sensitivity analysis to assess the impact of important protocol deviations on the results.

Patients will be analyzed according to the treatment they were randomly assigned.

10.3 Definitions Related to Safety Data

10.3.1 Treatment-emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs with onset on or after the IMP intake or pre-existing and worsening after IMP intake.

10.3.2 Treatment-related Adverse Events

The Investigator will assess the relationship (unrelated, possible, definite) of each AE to the investigational treatment (L-CsA (10 mg bid or 5 mg bid) plus SoC or SoC alone). Treatment-related AEs are defined as events with any causal relationship other than 'not related' according to the assessment of the Investigator. Patients who experience the same event multiple times will be included in the most related category for summarization.

10.4 Study Day and Time from Randomization

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

11 DISPOSITION

The number of patients screened, who failed screening, randomized, treated with clinical trial treatment and completing the clinical trial (and reason for not completing) as scheduled will be presented in frequency tables by treatment group.

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

All important protocol deviations will be presented as a frequency table by treatment group. All protocol deviations will be presented in a by-patient listing, which will include the category of the deviation, the deviation text, if it was an important protocol deviation and if the PD led to the exclusion from FAS and/or PP.

A separate listing will be provided for covid-19 related protocol deviations.

12 BASELINE DEMOGRAPHICS AND DISEASE CHARACTERISTICS

All baseline demographic, anthropometric, medical data will be summarized by treatment group for the SAF, FAS, and PPS analysis populations. For summary purposes, the most recent, non-missing result obtained on or prior to the baseline visit will be used.

Prior and concomitant medication will be summarized and tabulated according to the 1st and 2nd levels of the WHO ATC system. The version will be provided in Data Management related document "DM-AD-089-Study-specific Dictionary Coding Conventions and Specifications". Non-IMP medication will be assessed as prior treatment when the start of the treatment lies before the baseline visit, and as concomitant medication for any treatment started or ongoing after baseline. The definition implies that medication started before the baseline visit but continued into the randomized treatment phase will be both prior and concomitant.

In case of incomplete information for start of non-IMP medication, the earliest possible date will be assumed for determining whether treatment is prior and/ or concomitant (e.g., '2019' will be assumed to indicate '01-Jan-2019'). For incomplete information on treatment end, the latest possible date will be assumed unless it lies in the future (e.g., '09-2017' will be assumed to indicate '30-Sep-2017'). Medication with an entirely missing start date will be assumed to be prior treatment. Similarly, medication with an entirely missing stop date will be assumed to be ongoing during randomized treatment.

Time from Transplantation to BOS Score 1 Diagnosis (days) will be summarized and is derived as: Date of BOS Score 1 Diagnosis – Date of Transplantation + 1.

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

13 PRIMARY ASSESSMENTS

The primary assessments will be measures of safety and local tolerability listed in Section 8.3 and covering the first 4 weeks of treatment, defined as data collected until Visit 3. AEs will be included into this analysis if their date of onset lies on or before Visit 3 or, in case of an incomplete or missing date of onset, if they could have started on or before Visit 3 in accordance with all available information, using the procedure for incomplete data information already described in Section 12 above.

Outcomes assessed during study visits will be included into the primary analysis up until Visit 3 scheduled to be performed at Week 4 after baseline, or until the EoT visit if it was performed on or before Visit 3.

All analyses described in this chapter will be performed on the SAF.

13.1 Analysis of Local Tolerability

In accordance with the study protocol, local tolerability events of interest (i.e., cough, wheezing, bronchospasm, throat irritation, and change in FEV_1) will be documented in the eCRF as AEs. During data analysis local tolerability events of interest thus have to be identified from the CRF form of AEs as follows:

- MedDRA (version 23.1) Preferred Terms (PTs):
  - Cough (MedDRA code 10011224)
  - Wheezing (MedDRA code 10047924)
  - Bronchospasm (MedDRA codes 10006482, 10072338)
  - Throat irritation (MedDRA code 10043521)
  - Change in FEV_1 (MedDRA codes 10016987, 10016989, 10016985)

  The version of the utilized dictionary will be presented either in the title or footnote of the provided tables and listings.
- The event must have newly appeared within 1 hour after the end of an IMP inhalation.
- They must have occurred within on or before Visit 3.
- Events meeting the criteria above will be selected independently of the causality assessment of the investigator.

For each local tolerability event, pairwise treatment group comparisons of the proportion of patients with at least one local tolerability event will be performed based on Wilson score 95% confidence intervals (Wilson, 1927).

Moreover, incidence densities of events per patient treatment day starting with the first IMP administration will be determined separately for each local tolerability event. 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 for the entire randomized treatment period up until Visit 3, and for entire randomized treatment period (as secondary assessment, please refer to section 8.4). Events will be assigned 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.

13.2 Analysis of Overall Tolerability

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. For CGI Items 1 and 2, a table of frequencies as well as a table of summary statistics will be produced, broken down by treatment group and visit. Item 3 will only be tabulated in frequency tables. The two dimensions of the item, 'Therapeutic effect' and 'Side effects', will be tabulated separately and overall.

For all CGI Items, a score of 0 ('Not assessed') will be treated as missing data and will thus be excluded from the computation of summary statistics. The scale does not support the computation of a summary (total) score.

A table of frequencies will be prepared for the Investigator's Tolerability Assessment at Visit 3.

Pairwise treatment group comparisons will be performed for CGI Items 1 and 2, for the dimensions of Item 3 assessed separately as well as for the Investigator's Tolerability Assessment using Wilcoxon-Mann-Whitney U-tests. Comparisons for CGI between treatment groups will be provided for Visit 3 and for Visit5/EOT.

13.3 Analysis of Safety

13.3.1 Adverse events (non-serious or serious)

AEs will be coded using the MedDRA. The version of the utilized dictionary will be presented either in the title or footnote of the provided tables and by-patient listings. 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. Events with an onset date before the date of the first IMP dose will be defined as Non-TEAE. Events with an onset date on or after the first IMP dose or pre-existing and worsening after IMP intake will be defined as TEAE.

For all TEAEs occurring during the first 4 weeks of treatment (on or before Visit 3), and separately for all TEAEs (i.e. events with onset at any time during randomized treatment, as secondary assessment, please refer to section 8.4), a summary containing the following counts and percentages of subjects will be presented by treatment group and overall:

- Overview table, including the number (percent) of patients with
  - Any TEAEs
  - Mild TEAEs
  - Moderate TEAE
  - Severe TEAEs,
  - Serious TEAEs
  - Treatment-related TEAEs,
  - Serious Treatment-related TEAEs,
  - COVID-19 related TEAEs;
  - TEAEs leading to discontinuation of study,
  - TEAEs leading to discontinuation of treatment,
  - TEAEs having an outcome of death.

AEs leading to discontinuation of study are identified as AEs whose CRF field in AE form "Study discontinued due to this (S)AE" is flagged as "Yes".
AEs leading to discontinuation of treatment are identified as AEs whose CRF field in AE form "Action taken" is flagged as "Treatment stopped".

Patients who have multiple events will be counted only once but all events will be considered as occurred.
Summaries (number of events as well as number and percentage of patients with any events of a particular type) of TEAEs will be provided by primary system organ class (SOC) and preferred term (PT) and will be ordered in terms of decreasing frequency for SOC, and PT within SOC, in the total column. Patients who have multiple events coding to the same PT or within the same SOC will be counted only once in the patient counts for the corresponding summaries, but all events will be considered and listed. Patients who experience the same event multiple times will be included in the most severe category where applicable.

Summaries of TEAEs by primary system organ class (SOC) and preferred term (PT) will be presented for all TEAEs occurring during the first 4 weeks of treatment (on or before Visit 3), and separately for all TEAEs (as secondary assessment-please refer to section 8.4).

Number of events and number (%) of patients experiencing TEAEs by maximum severity (mild, moderate, and severe), relationship to IMP, and action taken with regard to IMP will be summarized.

Number (%) of events and of patients with TEAEs leading to discontinuation of clinical trial participation as well as treatment discontinuation will also be summarized.

Tables will be provided also for TEAEs related to COVID-19 (as described in section 16.3), for related TEAEs, for serious TEAEs, for serious TEAEs by seriousness criteria, for serious TEAE by relationship and for serious -related TEAEs.

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 for TEAEs occurring on or before Visit 3, and for all TEAEs (as secondary assessment-please refer to section 8.4).

Incidence densities of events per patient day starting with the first IMP administration will be determined for all TEAEs. 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. Additionally, the overall of all incidence densities and the sum of the incidence densities during the first 4 weeks of treatment (on or before Visit 3) will be presented.

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.

13.3.2 Laboratory measures, vital signs, physical examination

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 for the following parameters:

Hematology (Basophils, Basophils/Leukocytes, Eosinophils, Eosinophils/Leukocytes, Lymphocytes, Lymphocytes/Leukocytes, Monocytes, Monocytes/Leukocytes, Neutrophils, Neutrophils/Leukocytes, Platelets, Erythrocytes, Leukocytes)

Chemistry (Alkaline Phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase, Bilirubin, Creatinine, Gamma Glutamyl Transferase, Urea Nitrogen)

Vital Signs (Systolic and diastolic blood pressure, Heart Rate, Body Temperature, Respiratory Rate.)

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 V3 and at EoT.

For physical examination results, tables of frequencies will be prepared, broken down by treatment group and visit.

13.4 Analysis Population

In this trial whose primary measures are safety and tolerability related outcomes, the applicable analysis population will be the SAF. See Sections 10.2.1 and 10.3 for further details.

13.5 Working Hypothesis

Not applicable.

13.6 Analysis Model

Not applicable.

13.7 Sensitivity Analyses for the Primary Endpoint

Not applicable.

14 SECONDARY ASSESSMENTS

14.1 Local and Overall Tolerability, and Safety

In the context of secondary assessments i.e. IMP tolerability and safety during the first 12 weeks of treatment, all analyses described in Section 13 will be performed for the entire randomized treatment period.

For all tabulations broken down by visit, no separate tabulations for primary and secondary assessments are required as the results for the period up until Visit 3 are a subset of those for the entire period of observation and can thus be taken from the same table.

All analyses will be carried out in the SAF set.

14.2 CsA Pharmacokinetics

PK analyses will be carried out using SAS® software, Version 9.4 or later. Descriptive statistics (N, arithmetic means, standard deviation, geometric means, geometric coefficient of variation, medians, minimum and maximum) will be presented for all PK parameters indicated in section 8.4 including Whole blood trough level parameter (Cyclosporine A Concentration) at Weeks 2, 4, 8, and 12, separately for each treatment group. A figure with overlaying individual pharmacokinetic concentration-time profiles will be presented for plasma concentrations after end of inhalation per treatment group.

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 with regards to $AUC_{0\text{-}4\ h}$ and C_{max}. This will include the computation of 95% confidence intervals for the between-group differences.

The statistical analysis will be performed as a valid case analysis including all patients of the FAS.

15 EXPLORATORY ASSESSMENTS

Exploratory analyses of efficacy will including accepted spirometry values performed as per protocol and be based on the FAS, and on the PPS analysis populations (as sensitivity analysis)

15.1 Spirometry Measures

For the spirometry measures (FEV1 % predicted, FEV1/FVC, FEV1 absolute, FVC absolute, FVC % predicted), the observed values and corresponding changes from baseline will be summarized using descriptive statistics by parameter and visit. Different methods of measuring will not distinguished in the descriptive statistics and the statistical model. Baseline spirometry measurement is the last post-bronchodilator assessment at randomization visit (Visit 1) prior to inhalation of IMP which is the following measurement in the eCRF: Before inhalation of IMP ("Before inhalation of 2-4 puffs of salbutamol" if "Before inhalation of IMP" is not available).

For each spirometry measure identified in Section 8.5, treatment group comparisons will be carried out using 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. Treatment group comparisons at each visit will be estimated by differences between the marginal (adjusted) means from the treatment x visit interaction, with accompanying p-values and 95% confidence intervals. The analyses will include pairwise treatment group comparisons for each post-baseline visit via contrasts.

For the covariance model of the MMRM analyses, an unstructured covariance matrix should preferably be used. If the model does not converge (e.g., due to the small sample size), a Heterogeneous Toeplitz matrix will be used and, if this model does not converge either, a compound symmetry matrix will be used. If all models fail to converge, patients treated with L-CsA 2 x 5 mg/day or 2 x 10 mg/day will be merged into one group that will be compared to placebo, and the models for the covariance matrix will be applied as before, starting with an unstructured matrix, until the model converges. If none of the models converge, treatment group

comparisons of change versus baseline will be performed for each visit using pairwise, independent samples t-tests on the observed data. Note that the covariance model to be used may be different for different spirometry parameters, depending on whether and when convergence is achieved.

Descriptive summary measures will be provided based on all observed values as well as based on the marginal means determined via MMRM analyses (if convergence can be achieved).

15.2 Short Form (36) Health Survey (SF-36)

The SF-36 is a multi-purpose, short-form health survey with 36 questions yielding 8 health domain scales and 2 psychometrically based physical and mental component summary measures.
The standard form of the SF-36 Version 1 will be used and the raw data (questions), the scoring of health domains and the summary scores will be provided in SAS Format to Biostats by Data Management. The calculation of the derived scores will be done by validated CCI [redacted] System.[1]

The 8 health domain scales are referred to as the 'Physical Functioning (PF)', 'Role- Physical (RP)', 'Bodily Pain (BP)', 'General Health (GH)', 'Vitality (VT)', 'Social Functioning (SF)', 'Role-Emotional (RE)', and 'Mental Health (MH)' scales. The two summary measures are referred to as the physical component score (PCS) and mental component score (MCS).

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 using 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. Treatment group comparisons in the change versus baseline at each visit will be estimated by differences between the marginal (adjusted) means from the treatment x visit interaction, with accompanying p-values and 95% confidence intervals.
Descriptive summary measures will be provided based on all observed values as well as based on the marginal means determined via MMRM analyses.

15.3 Corticosteroids and immunosuppressive drugs

Corticosteroid medications and immunosuppressive therapy will be identified through an ongoing medical review of the concomitant medications collected in the study, using an ad-hoc excel spreadsheet, including column "Immunosuppressant Yes/No" to flag corticosteroid medications

[1] CCI [redacted] CCI [redacted]

and immunosuppressive therapy. The process will be performed before database lock. This excel spreadsheet (approved by the sponsor and provided together with the database extract by data management) will be imported via SAS and included in SDTM datasets by the statistical programmer.
Summary with counts and frequencies of patients with corticosteroid medications and immunosuppressive therapy presented at Baseline will be presented for Safety Analysis Set per study arm and overall.
In addition, counts and frequencies of these patients will be presented for an increased, decreased or a stopped dose. This summary statistic will be repeated for patients started a new therapy after Baseline. An increase (or decrease) of a dose is defined as a change in the average daily dose. Increase (or decrease) of dosing will be discussed and confirmed during the BDRM with the physician.
A by-patient listing will present all different medications and doses per visit.

16 SAFETY DATA

16.1 General considerations

Except for the analysis of extent of exposure and COVID-19 related AEs, analysis of safety has already been covered in Sections 13 and 14 above.

16.2 Extent of exposure

Exposure to the IMP (L-CsA or placebo) will be confirmed based on the difference between the number of IMP vials/ampoules dispensed and the number of unused vials/ampoules returned, and dosing recorded in the eCRF (this implies that IMP vials/ampoules not returned will be considered as having been used). Summary tables will be prepared including the following details about administration of L-CsA or placebo:

- Descriptive statistics for the total number of doses received.
- Descriptive statistics for the duration of treatment in days. For each patient, the treatment duration will be calculated as the difference between the dates of last and first administration of L-CsA (or placebo) plus 1.
- Descriptive statistics for the number of exposure days. For each patient, the number of exposure days is the count of unique days on which the patient received at least one administration of L-CsA (or placebo).

A by-patient listing will present all IMP administration data. This listing will include at least: date and time of L-CsA (or placebo) administration and L-CsA (or placebo) dose changed (yes, no, not applicable). If L-CsA (or placebo) dose changed, dose adjustment date and time and the reason for deviation will be displayed as well.

Moreover, a table of treatment compliance will be produced for the investigational treatment based on the ratio between the amount of IMP actually administered and the prescribed amount across the period between baseline and EoT. Treatment compliance will be categorized as <50%, 50-79%, 80-120% as well as >120%. Besides using the safety analysis set, this table will also be produced using the Full Analysis Set and the Per Protocol set.

16.3 COVID-19 specific considerations

COVID-19 related AEs using COVID-19 (SMQ) available at https://www.meddra.org/COVID-19-terms-and-MedDRA will be reported as SAEs. All confirmed cases of COVID-19, occurring after the patient has provided informed consent will be summarized in a table and flagged in the AE subject data listing.

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” will be used.

In all cases, details of the patient's symptoms, treatment and any clinically relevant information, from the SAE CRF-form will be presented in a separate subject data listing.

17 REFERENCES

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