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STATISTICAL ANALYSIS PLAN

Protocol CLBS03-P01

NCT02691247

Protocol Title: A Prospective Randomized Placebo-Controlled Double Blind Clinical Trial to Evaluate the Safety and Efficacy of CLBS03 (Autologous *Ex Vivo* Expanded Polyclonal $CD4^+CD25^+CD127^{lo/-}FOXP3^+$ Regulatory T-cells [Tregs]) in Adolescents with Recent Onset Type 1 Diabetes Mellitus (T1DM)

Protocol Version # and Date: Version 7.0; 17-JAN-2017

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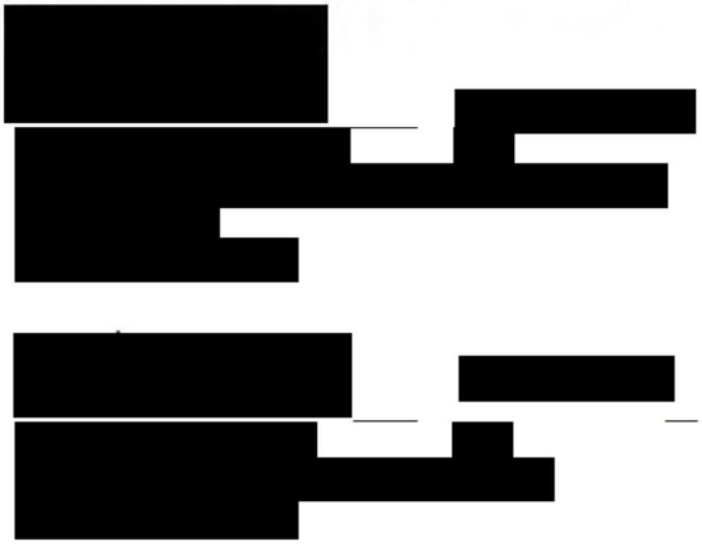
Approved By:



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LIST OF ABBREVIATIONS

Abbreviation/Term	Explanation
ADA	American Diabetes Association
AE	Adverse event
ANCOVA	Analysis of Covariance
AUC mean	From the mixed meal tolerance test, the time-weighted average concentration of C-peptide; the C-peptide AUC divided by the duration of the mixed meal test.
BMI	Body mass index
BW	Body weight
CGM	Continuous glucose monitoring
CMV	Cytomegalovirus
C-peptide	Insulin connecting peptide
CRF	Case report form
CSR	Clinical Study Report
DDI	Daily dose of insulin
DNA	Deoxyribonucleic acid
DSMB	Data and Safety Monitoring Board
EBV	Epstein-Barr virus
eCRF	Electronic case report form
HbA1c	Hemoglobin A1c
HCATS	Hitachi Chemical Advanced Therapeutics Solutions
HIV	Human immunodeficiency virus
HLA	Human leukocyte antigen
HTLV	Human T-lymphotropic virus
ICH	International Council on Harmonization
IP	Investigational product
ITT	Intent-to-treat
LS means	Least Squares Means
MedDRA®	Medical Dictionary for Regulatory Activities
mITT	Modified intent-to-treat
MMRM	Mixed model repeated measures
MMTT	Mixed meal tolerance test
PCR	Polymerase chain reaction
PCT	PCT, a Caladrius Company
PP	Per-protocol
PPD	Purified protein derivative

Abbreviation/Term	Explanation
RNA	Ribonucleic acid
SAE	Serious adverse event
SAP	Statistical analysis plan
SNPs	Single nucleotide polymorphism
T1DM	Type 1 diabetes mellitus
TB	Tuberculosis
TEAE	Treatment-emergent Adverse Events
Tregs	Regulatory T-cell
WHO	World Health Organization

1 INTRODUCTION

This document provides a detailed description of the statistical methods and procedures to be implemented during the analysis of Caladrius Bioscience's Protocol CLBS03-P01 (version 7.0 dated 17-Jan-2017).

[redacted]

This statistical analysis plan (SAP) focused on the study milestone Week 52 data analysis, as well as the final study closure data analysis. Any major differences between the statistical methods provided in the clinical study protocol and this SAP will be explained herein. If the data suggest and warrant it, deviations from this plan will be considered. However, any major changes and deviations from this SAP to the final data analysis must be substantiated by sound statistical rationale and fully documented in the clinical study report (CSR). This SAP is prepared in accordance with the ICH-E9 guidelines "Statistical Principles for Clinical Trials". A memorandum will be prepared to document the unblinding procedure and communication plan prior to conducting any interim analyses.

2 STUDY OBJECTIVES

2.1 Primary Objectives

The primary objective of this study is to assess the safety and potential efficacy of CLBS03 (either of the two doses [redacted] to modify the T1DM disease course, including preservation of β-cell function and improvements in measures of disease severity, as compared with placebo in adolescents with recent onset T1DM.

2.2 Secondary Objectives

The secondary objective is to assess the efficacy of CLBS03, including additional measures of T1DM severity, and to evaluate the effect of CLBS03 on the pathologic autoimmune response underlying T1DM and on the general immune responsiveness through 104 weeks.

2.3 Exploratory Objectives

[redacted]

[redacted]

3 STUDY OVERVIEW

3.1 Study Design

Study CLBS03–P01 is a double-blinded, multi-center, exploratory trial assessing a single infusion of one of 3 treatments: CLBS03 [redacted] and placebo. The study will include adolescent subjects (aged 8 to less than 18 years old at the time of randomization) with recent onset of T1DM.

[redacted]

A screening visit will be conducted to determine eligibility. Subjects who continue to be eligible will be randomized [redacted]

Approximately 111 subjects will be randomized to one of 3 treatment groups in a 1:1:1 ratio:

- [redacted]
- [redacted]

- Placebo

Randomization will be done centrally [redacted]

Safety, diabetes control, β-cell function, and immune function will be assessed over the course of the study. All subjects are expected to be on intensive diabetes management (refer to the Clinical Protocol **Section 9.6**) consistent with the American Diabetes Association (ADA) standard of care.

3.2 Study Procedures and Visit Structure

Table 1 below provides an overview of the clinical schedule of assessments and events. Schedule of exploratory biomarker assays is presented in Table 2. Visit windows are presented in Table 3 and Table 4 outlines the time points at which the blood samples were to be collected from the subject for MMTT-stimulated C-peptide/glucose measurement.

Table 1: Schedule of Study Assessments

[redacted]

[redacted]

[redacted]

[redacted]

Table 3: Visit Windows

	Visit Day(s)	Visit Windows
Visit 1: (screening)	day -79 to day -23	day -79 to day -23
Visit 2: (pretreatment)	-16 to -15	no window
Visit 3: (treatment)	0	no window
Visit 4[1]:	1	no window
Visit 5:	7	±1 day
Visit 6:	14	±3 days
Visits 7 and 8:	28 and 91	±7 days
Visits 9 through 13:	182, 273, 364, 546, and 728	±14 days

[1]Visit 4 was removed with protocol version 6.0.

Table 4: Sampling Time Points for MMTT-stimulated C-Peptide/Glucose Measurement

Time (minutes)	2-hour MMTT[1]	4-hour MMTT
–10	X	X
0	X	X
Participant drinks Boost®		
15	X	X
30	X	X
60	X	X
90	X	X
120	X	X
150		X
180		X
210		X
240		X

[1]4-hr MMTT data were requested by the Sponsor to "programmatically" cut out the 2-hr curve for data analysis, so basically all 4-hr MMTT visits should also have 2-hr MMTT data. Thus, 2-hr MMTT will be available for analysis at weeks 13,26,52,78, and 104.

3.3 Randomization Schedule and Blinding Procedures

This is a double-blind randomized trial. A randomization scheme of approximately double the intended sample number is produced in order to enable replacements. Subjects are to be allocated to CLBS03 [redacted] or placebo in a ratio of 1:1:1. The randomization was done centrally with stratification by median screening MMTT-stimulated C-peptide AUC mean value, using consecutive randomization number (subject identification code). The value used for stratification may be adjusted during the study so that a number near the evolving median is used. Subjects will be randomized once all screening procedure results are available and it's confirmed that the study eligibility requirements are met based on screening. Eligibility requirements will be confirmed at Visit 2 prior to [redacted].

The randomization list will be kept in a secure location until the end of the study (after the end of study database lock), unless required by the DSMB or in case of emergency unblinding for safety reasons.

4 STUDY ENDPOINTS

4.1 Primary Efficacy Endpoint

The primary study endpoint is the 4-hour MMTT-stimulated C-peptide AUC mean at 26 and 52 weeks.

4.2 Secondary Efficacy Endpoints

Secondary efficacy endpoints include the 2-hour MMTT-stimulated C-peptide AUC mean at 13, 26, 52, 78 and 104 weeks and the 4-hour MMTT-stimulated C-peptide AUC mean at 104 weeks.

Additional metabolic evaluations will include a comparison between the study treatment groups in:

- 4-hour MMTT-stimulated Glucose AUC mean at weeks 26, 52 and 104.
- 2-hour MMTT-stimulated Glucose AUC mean at weeks 13, 26, 52, 78 and 104.
- Daily dose of insulin use (DDI) as measured by U/kg BW at weeks 4, 13, 26, 39, 52, 78 and 104.
- Fasting blood glucose levels at weeks 13, 26, 52, 78 and 104 (based on MMTT).
- Post-prandial (including 2-hour post meal) blood glucose levels at weeks 13, 26, 52, 78 and 104 (based on MMTT).
- HbA1c at weeks 13, 26, 39, 52, 78 and 104.
- [redacted]

4.3 Safety Endpoints

The safety endpoints are:

- Treatment-emergent adverse events (TEAEs)
- SAEs
- [redacted]
- Clinical laboratory tests

- Physical examination findings
- Concomitant medications
- Vital signs

Proportion of subjects in which the infusion was prematurely stopped or paused because of adverse events will also be assessed for each treatment arm. Events of special interest (refer to the Clinical Protocol Section 11.3), clinical laboratory tests, physical examination findings, concomitant medications, and vital signs will be assessed.

5 ANALYSIS POPULATIONS

The following analysis population will be defined for study summaries and analyses. In general, data listings will be provided for all subjects in the Enrolled Population. The primary efficacy endpoint and the key secondary endpoints will be analyzed for the Modified Intent-to-Treat (mITT) Population. The safety data analyses will be based on the Safety Population. Subjects will be analyzed as treated for both the efficacy and safety data.

5.1 Enrolled Population

The Enrolled Population will comprise of all enrolled subjects. This includes all subjects who have passed the pre-screening and have been presented with Informed Consent forms. This population includes patients who have dropped out before the first dose has been administered. Listings will be provided for the Enrolled Population.

5.2 Modified Intent-to-Treat Population

The modified Intent-to-Treat (mITT) population will consist of all randomized subjects who received a study treatment and have at least one post-treatment assessment. Subjects will be assigned to a treatment group based on the actual number of Treg cells dosed and according to the table below. This population will be used for the primary efficacy analyses.

[redacted]	Treatment Group Assignment
[redacted]	[redacted]

5.3 Safety Population

The Safety Population will consist of all subjects who had blood collected for manufacturing of the investigational product. Subjects randomized to receive active treatment will be analyzed according to the actual number of Treg cells dosed and will be assigned to a treatment group as described in Section 5.2 for mITT. Subjects who got randomized, got blood collected for manufacturing of the investigational product, but never got dosed will be included in the safety population and will be shown as a separate group designated as 'Not treated'.

5.4 Per-Protocol Population

The Per-Protocol (PP) population will consist of all randomized subjects who receive the correct dose of the randomized study treatment and have at least one post-treatment assessment, have MMTT-stimulated C-peptide levels assessed at the Week 26 visit, and do not have any major protocol violations. This population will exclude subjects who receive less than the intended dose. The PP population will be used for subject demographics and as a supportive analysis for the primary and secondary efficacy analyses.

6 STUDY SUBJECTS

All data from the Safety Population will be provided in listings. Summary tables will be provided by treatment group for study level aggregate data.

6.1 Subject Disposition

Subject disposition information will be summarized by treatment group for the Safety Population. Counts and percentages of subjects who complete or withdraw early from the study further broken down by the reason for early withdrawal will be provided.

6.2 Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized descriptively for the Safety Population, mITT Population, and Per-Protocol Population.

Demographic and baseline characteristics include, but are not limited to: gender, age, race, ethnicity, body weight, height, body mass index (BMI), HbA1c, fasting glucose level, fasting C-peptide, and 4-hour MMTT-stimulated C-peptide AUC mean value.

6.3 Medical History

Medical history will be summarized descriptively (frequencies and percentages) by treatment group and by medical history code, coded with Medical Dictionary for Regulatory Activities

(MedDRA version 18.1) for the Safety Population. Body system and condition status will be summarized descriptively (frequencies and percentages).

Medical history will also be provided in listings at the subject-level for the Safety Population.

6.4 Treatment Compliance

The study medications are to be administered by the site personnel. Infusion date, start time, stop time, and reasons for not receiving the full dose are collected by the eCRFs on the infusion day. However, because volume of infusion administered and missed are not collected, therefore, the treatment compliance ratio will not be calculated.

6.5 Protocol Deviations

Protocol violations and deviations will be summarized with descriptive statistics by category. A listing of all events will also be included.

Protocol deviations include, but are not limited to, deviations from entry criteria, the MMTT procedure, the study medication intake/administration, study restrictions, etc.

6.6 Extent of Exposure

Number of subjects that received CLBS03 and placebo will be summarized by treatment group for the mITT Population. Additional descriptive statistics of the value of the Treg cells dose will be provided.

6.7 Concomitant Medications

The WHO Drug Dictionary (version March 2015) will be used to categorize verbatim descriptions of medications into the Anatomic Therapeutic Chemistry (ATC) classification system. Each verbatim name will be classified by anatomical main group (ATC level 1), therapeutic subgroup (ATC level 2), pharmacological subgroup (ATC level 3), chemical subgroup (ATC level 4), and trade name.

The number and percentage of subjects receiving concomitant, prior concomitant, and new concomitant medications will be summarized by treatment group and ATC classification (ATC level 2 and level 4) for the mITT population. Prior concomitant medications refer to medications that have a start date prior to receiving the first randomized study medication and continue to be taken on or after that. New concomitant medications refer to the medications that have been used on or after receiving the first randomized study medication. Prior concomitant and new concomitant medications constitute the concomitant medications.

Pre-treatment medications that start and stop prior to receiving the first randomized study medication will be excluded from the summary but be presented in the listing.

Prior and Concomitant Non-Drug Therapies will be provided in a listing.

7 STATISTICAL METHODS OF ANALYSIS

7.1 General Considerations

Analyses of primary and secondary efficacy endpoints will be performed with the mITT Population. Safety analyses will be performed with the Safety Population. All data collected during the study for Safety Population will be included in data listings.

7.1.1 Statistical Notation and Presentation

For descriptive statistical summary, mean, sample size (n), standard deviation (SD), standard error (SE), median, minimum (min), and maximum (max) will be calculated for continuous variables. For logarithm-transformed data, the geometric mean and standard error of the geometric mean will also be provided. For categorical variables, frequency and percentage in each category will be provided.

7.1.2 Definition of Baseline

In general, the study baseline is defined as the last observation obtained prior to the study treatment at Visit 3.

7.1.3 Handling of Multiple Observations or Out of Window Observations

For safety laboratory measurements, if multiple records were recorded for the same time point, (e.g., if the same blood sample was analyzed twice and recorded in the clinical database as two distinct records), the re-assayed data value (the repeated one) will be included in data summary and analysis. If a safety laboratory measurement was collected at an unscheduled visit (usually out of the visit window), such data will be evaluated for the incidence of abnormality and severity but will not be mapped to a scheduled visit for numeric descriptive summary.

All values, scheduled or unscheduled, will be presented in data listings.

7.1.4 Handling of Missing Data

No imputation will be done for missing clinical data.

In cases of incomplete dates for adverse events (AEs) or non-study medications, the missing component(s) will be assumed as the most conservative value(s) possible. For example, the imputation rule is to conservatively capture AEs with missing start dates as treatment-emergent AEs (TEAEs):

- If "day" is the only missing field, impute the "day" as the first randomized dose date if their "month" are the same; otherwise, the first day of the non-missing month.
- If "day" and "month" are the only missing fields, impute the "day" and "month" as the first randomized dose date if their "year" are the same; otherwise, January 1 of the non-missing year.
- If "day", "month", and "year" are all missing, to be conservative, the event will be assumed to occur on the same day as the first randomized dose date.

Non-study medications with missing or partial dates will be imputed similarly.

Date imputation will only be used for computational purposes; e.g., treatment-emergent status or identifying concomitant medications. Actual data values as they appear in the clinical database will be shown in the data listings.

7.2 Derivation of Efficacy Endpoints

[redacted] dose date to the first complete or partial remission using Kaplan-Meier estimates and curves.

7.3 Efficacy Analyses

7.3.1 Analyses of the Primary Efficacy Endpoints

The 4-hour MMTT-stimulated C-peptide AUC mean is defined as the area under the 4-hour MMTT-stimulated C-peptide concentration vs time curve divided by the actual time span the samples were collected during the target 4-hour period. If the actual time the samples were collected not recorded in the database, nominal time span will be used. The AUC will be

calculated using the trapezoidal rule. The 2-hour MMTT-stimulated C-peptide AUC mean is defined analogously. The unit for AUC mean is pmol/mL.

Per protocol study design, the 2-hour MMTT is scheduled at the Week 13 and Week 78 timepoint while the 4-hour MMTT is scheduled at the baseline and Week 26, Week 52, and Week 104 timepoints. To allow appropriate comparison across visits, the 2-hour MMTT-stimulated C-peptide AUC mean for baseline, Week 26, Week 52, and Week 104 timepoints will be calculated from the 4-hour data. The calculation method is described below:

2-hour MMTT-stimulated C-peptide AUC mean = area under MMTT-stimulated C-peptide concentration vs time curve from time 0 to the nominal time of 120 min as scheduled divided by time interval from 0 min to the actual minutes of the nominal 120 min scheduled time point. If the actual times are not available in the database, nominal times will be used.

Descriptive Statistics

The baseline value of 4-hour MMTT-stimulated C-peptide AUC mean is collected at screening (Visit 1). The change in 4-hour MMTT-stimulated C-peptide AUC mean from baseline to each of the post-baseline visits will be summarized descriptively by treatment group for the mITT Population. The 2-hour MMTT-stimulated C-peptide AUC mean will be summarized similarly.

[redacted]

[redacted]

7.3.2 Analysis of the Secondary Efficacy Endpoints

The 2-hour MMTT-stimulated C-peptide AUC means at 13, 26, 52, 78 and 104 weeks will be analyzed in a similar manner as described above for the analysis of the primary endpoints.

The 4-hour MMTT-stimulated C-peptide AUC mean at 104 weeks will be analyzed in a similar manner as described above for the analysis of the primary endpoints.

The 4-hour MMTT-stimulated Glucose AUC mean and 2-hour MMTT-stimulated Glucose AUC mean will be analyzed for the mITT Population in a similar manner as MMTT-stimulated C-peptide, however, no log-transformations will be performed prior to fitting the models.

The daily dose of insulin as measured by U/kg BW at weeks 4, 13, 26, 39, 52, 78 and 104 will be summarized and analyzed similarly as for the primary efficacy endpoints without the log-transformation.

The change from baseline in fasting plasma glucose and the 2-hour post-prandial glucose measured by MMTT at Weeks 13, 26, 52, 78, and 104 will be analyzed in a similar manner as for the analysis of the secondary endpoint of the 2-hour AUC mean C-peptide.

HbA1c will be summarized descriptively for Weeks 13, 26, 39, 52, 78, and 104.

7.4 Sensitivity Analysis for Primary Efficacy Endpoint

A sensitivity analysis for the primary efficacy endpoint would be treating dosage as a continuous variable instead of as the pre-defined categorical one ($< 10 \times 106$ cells/kg BW vs. $\geq 10 \times 106$ cells/kg BW). For visual examination, a scatter plot that present the dosage as a continuous variable versus the change in MMTT-stimulated C-peptide AUC Mean will be provided. A potential linear relationship may be explored. Other baseline characteristics may be explored using stepwise regression method, if needed.

The sensitivity analysis would be performed on the mITT Population.

7.5 Exploratory Endpoint Analyses

Descriptive statistical summaries will be provided all exploratory endpoints for mITT Population.

7.6 Safety Analyses

The analysis of safety data will be performed for the Safety Population unless otherwise stated. The primary safety and tolerability endpoints are the incidence of TEAEs.

7.6.1 Adverse Events

All reported terms (investigator descriptions) for AEs will be coded using the most recent version of the Medical Dictionary for Regulatory Activities (MedDRA, version 18.1). TEAEs are defined as those with onset or worsening on or after the randomized IP infusion. Blood collection-emergent adverse events are defined as those with onset or worsening on or after the blood collection for manufacturing the IP, and prior to the randomized IP infusion (if subjects received IP infusion). AEs occurring prior to receiving the randomized IP infusion are deemed non-TEAE. Blood collection-emergent AEs will be summarized by system organ classification and preferred term. Other non-TEAEs will not be summarized for incidence evaluation but will be provided in listings.

Number and percentage of subjects with TEAEs will be summarized by treatment group, system organ classification, and preferred term. TEAEs by severity will also be summarized.

Severe hypoglycemia, defined as an event requiring assistance of another person to actively administer carbohydrates, glucagon, or take other corrective actions, occurring from the time of treatment through the end of study. Severe hypoglycemic events will be listed.

TEAEs leading to discontinuation from the study, TEAEs related to randomized IP, TEAEs related to the large blood draw for manufacturing, TEAEs related to the infusion procedure, and serious TEAEs will be listed. TEAEs will be included in the listing of related events if the investigator's opinion is possibly or probably related. Events with missing causality will also be included in this listing. Deaths will be listed if any.

7.6.2 Clinical Laboratory Evaluations

All hematology, clinical chemistry, and urinalysis results will be listed by subject, visit, and treatment group including scheduled and unscheduled/repeat measurements (if any). Laboratory assessments that are outside of normal ranges and/or with potential clinical importance will be flagged in the listings.

The hematology assessments that are done at the local lab prior to infusion at the Treatment Visit will not be used in any calculations and therefore will not be reflected in any table, but they will be reviewed during the safety evaluation and will be included in the listings.

Baseline values, the values at post-baseline visits, and changes from the baseline values will be summarized descriptively for each of the quantitative laboratory assessments by treatment group. Shift tables of hematology, clinical chemistry, and urinalysis results will be generated to summarize the normal and abnormal (abnormal high and abnormal low) status changes from baseline to post-baseline visits. Tables that summarize the frequency and percentages of values outside the normal ranges for hematology, clinical chemistry, and urinalysis will be provided.

7.6.3 Vital Signs

Vital signs data will be summarized by visit.

7.6.4 Physical Examination

Physical examination data will be listed.

7.6.5 Other Safety Variables

All safety parameters that were not pre-specified will be listed.

[redacted]

9 SAMPLE SIZE AND POWER

The goal of this study, assuming that safety is acceptable, is to determine if there is sufficient evidence of clinically meaningful bioactivity to proceed with further development. Since there are no prior data in the current study population, sample size estimation was based on projected differences in the decreases in the 4-hour AUC mean MMTT-stimulated C-peptide in the control and active treatment groups at the Week 52 visit. [redacted]

[redacted]

10 STATISTICAL SOFTWARE

All statistical analyses will be performed using SAS® version 9.4.

11 REFERENCES

1. Lachin JM, McGee PL, Greenbaum CJ, Palmer J, Pescovitz MD, Gottlieb P and Skyler J. Sample size requirements for studies of treatment effects on beta-cell function in newly diagnosed type 1 diabetes. PLoS One. 2011;6:e26471.
2. Statistical Monitoring of Clinical Trials: A Unified Approach. Michael A. Proschan, K. K. Gordon Lan, Janet Turk Wittes, Springer, 2006.