# Clinical Islet Transplant Consortium

# Statistical Analysis Plan for Protocol CIT-02

# Strategies to Improve Long Term Islet Graft Survival

## Version 1.0
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## Table of Contents

# 1 Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Clinical Islet Transplantation protocol CIT-02, "Strategies to Improve Long Term Islet Graft Survival".

This phase 2 study focuses on treating islets pre-transplant and subjects (during and post-transplant) with Lisofylline (LSF), an agent with a unique spectrum of anti-inflammatory, anti-apoptotic and $\beta$ cell enhancing properties, to improve $\beta$ cell function and viability, maximizing pre-transplant functional islet mass, islet engraftment and long-term function in subjects with type 1 diabetes.

The structure and content of this SAP provides sufficient detail to meet the requirements identified by the FDA and International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH): Guidance on Statistical Principles in Clinical Trials [1]. All work planned and reported for this SAP will follow internationally accepted guidelines, published by the American Statistical Association [2] and the Royal Statistical Society [3] for statistical practice.

The following documents were reviewed in preparation of this SAP:

- Clinical Research Protocol CIT-02.
- Case report forms (CRFs) for Protocol CIT-02.
- ICH Guidance on Statistical Principles for Clinical Trials.

The reader of this SAP is encouraged to also read the clinical protocol for details on the conduct of this study, the operational aspects of clinical assessments, and timing for completing assessments for a subject in this study.

Exploratory analyses not necessarily identified in this SAP may be performed to support the clinical development program. Any post-hoc, or unplanned, analyses not identified in this SAP that are performed will be clearly identified in the applicable clinical study report.

# 2 Study Design and Objectives

## 2.1 *Study Design*

This is a multi-center, single arm, open-label trial assessing the experimental treatment regimen as well as determining the proportion of subjects with insulin independence.

A larger phase 3 trial (Protocol CIT-07) in which subjects are treated with the standard islet transplant immunosuppression regimen is being conducted in parallel with Protocol CIT-02. Eligible subjects will be randomized to receive immunosuppression under either Protocol CIT-07 or this study (Protocol CIT-02) at the time a suitable islet preparation is available for transplantation. The randomization will provide a mechanism for balance between the two studies and to help ensure an objective selection of subjects.

## 2.2 *Study Objectives*

### 2.2.1 Primary Objective

The primary objective of this study is to estimate the proportion of subjects who are insulin independent at 75 ± 5 days following the first islet cell infusion among subjects treated with LSF.

### 2.2.2 Secondary Objectives

The secondary objectives of this study are to:

1. Increase the proportion of patients rendered insulin independent with a single (1-donor) islet transplant at 1 year by preservation of $\beta$-cell mass and enhancement of $\beta$-cell function.
2. Enhance the magnitude of glucose and non-glucose stimulated insulin responses of islet allografts.
3. Achieve long-term insulin independence by preventing the decline in $\beta$-cell function.

## 2.3 *Study Endpoints*

### 2.3.1 Primary Endpoint

The primary endpoint for the study is the proportion of insulin-independent subjects at day 75 ± 5 days following the first islet transplant.

The primary aim of the analysis is to estimate the true rate of this outcome in subjects analyzed by the intention-to-treat (ITT) principle. If the primary endpoint cannot be evaluated for an individual because of death, withdrawal of consent, or another reason, a failure (i.e. not insulin independent) will be imputed. However, if there is an evaluation done at a time longer than 75 days after transplant and before an additional islet transplant (a second or third transplant), the later evaluation will be used. All imputations of the primary endpoint will be reported with the primary analysis.

### 2.3.2 Secondary Endpoints

Because there is a large number of secondary endpoints, it is impractical to account for all multiple comparisons. Unadjusted p-values will be reported which allow others to apply any multiple comparison or false discovery rate approach they deem necessary to the p-values resulting from this study.

#### 2.3.2.1 Key Secondary Endpoints

There are two key secondary endpoints in this study. If a key secondary endpoint for a subject is not evaluable, a failure will be imputed. All imputations will be reported with the key secondary endpoint analyses.

1. The proportion of subjects with an HbA1c level < 7.0% and free of severe hypoglycemic events from Day 28 to Day 365, inclusive, after the first islet transplant.
2. The proportion of subjects with an HbA1c level < 7.0% and free of severe hypoglycemic events from Day 28 to Day 365, inclusive, after the last islet transplant.

#### 2.3.2.2 Additional Efficacy Endpoints

The following is a comprehensive list of the additional efficacy endpoints. In general, these efficacy endpoints are summarized for baseline (the most recent value prior to transplant), at 75 days and 365 days following the initial islet transplant, and again at 75 days, 365 days, and 730 days following the final islet transplant. Any variables that deviate from this schedule, as indicated by the schedule of events in the protocol, will be summarized accordingly. Imputations are not performed for missing values in the additional efficacy endpoints.

- Proportion of insulin-independent subjects
- Percent reduction in insulin requirements
- HbA1c
- Mean amplitude of glycemic excursions (MAGE)
- Glycemic lability index (LI)
- Ryan hypoglycemia severity (HYPO) score
- Clarke Score
- Basal (fasting) and 90-min glucose and c-peptide derived from the mixed-meal tolerance test (MMTT)
- C-peptide: (glucose X creatinine) ratio
- β-score
- Acute insulin response to glucose ($AIR_{glu}$), insulin sensitivity, and disposition index (DI) derived from the insulin-modified frequently-sampled IV glucose tolerance (FSIGT) test
- Glucose variability and hypoglycemia duration derived from the continuous glucose monitoring system® (CGMS)
- Quality of life (QOL) measures
- The proportion of subjects receiving a second islet transplant

- The proportion of subjects receiving a third islet transplant
- The number of severe hypoglycemic events

### 2.3.2.3 Safety Endpoints

The following safety endpoints will be reported:

- Safety, including incidence of post-transplant infections, malignancies, morbidity, and other AEs (e.g., increased body weight and hypertension) associated with conventional immunosuppression.
- Renal function as measured by serum creatinine, GFR, and other relevant laboratory parameters.
- Lipid profiles (triglycerides, total cholesterol, LDL cholesterol, HDL cholesterol) over time.

For the time periods from randomization until 365 days following the initial transplant and then from randomization until the end of follow-up, the following safety endpoints are assessed:

- The incidence and severity of AEs related to the islet transplant procedure including: bleeding (> 2 g/dL decrease in Hb concentration); segmental portal vein thrombosis; biliary puncture; wound complication (infection or subsequent hernia); and increased transaminase levels (> 5 times upper limit of normal [ULN]) (NOTE: These are AEs that are generally thought to be related to the islet transplant procedure. Actual relatedness is only captured for SAEs.)
- The incidence and severity of AEs related to the immunosuppression including: allergy; reduction in GFR; increase in urinary albumin excretion; addition or intensification of anti-hypertensive therapy; addition or intensification of anti-hyperlipidemic therapy; oral ulcers; lower extremity edema; gastrointestinal toxicity; neutropenia, anemia, or thrombocytopenia; viral, bacterial, or fungal infections; and benign or malignant neoplasms (NOTE: These are AEs that are generally thought to be related to immunosuppression. Actual relatedness is only captured for SAEs.)
- The incidence of a change in the immunosuppression drug regimen
- The incidence of immune sensitization defined by presence of anti-HLA antibodies absent prior to transplantation.

At 365 ± 14 days after the <u>first</u> islet transplant the following endpoint is assessed:

- The incidence of worsening retinopathy as assessed by change in retinal photography from pre-transplant.

## 2.4 *Sample Size Calculations*

The purpose of this pilot study is to estimate the true rate of insulin independence at 75 days. The selected sample size is 12 subjects. The point estimate of the true insulin independence rate will be the proportion of the 12 patients that achieve insulin independence. The precision of the estimate depends on the observed number of subjects achieving insulin independence. The following table displays the confidence intervals that would be computed for each possible outcome. If 6 of the 12 subjects achieve

insulin independence then the estimated rate will be 50% and a 95% confidence interval will be 0.21 to 0.79. That is, we are 95% confident that the true rate is at least 21% and no more than 79%. The confidence interval rules out any rate less than 21% or greater than 79%.

**Table 1: Sample Size Calculation**

| Number of Subjects Insulin Independent at 75 Days | Estimated Rate | Exact 95% Confidence Interval | |
|---|---|---|---|
| | | Lower Bound | Upper Bound |
| 0 | 0 | 0 | 0.26 |
| 1 | 0.08 | 0.002 | 0.38 |
| 2 | 0.17 | 0.20 | 0.48 |
| 3 | 0.25 | 0.05 | 0.57 |
| 4 | 0.33 | 0.10 | 0.65 |
| 5 | 0.42 | 0.15 | 0.72 |
| 6 | 0.50 | 0.21 | 0.79 |
| 7 | 0.58 | 0.28 | 0.85 |
| 8 | 0.67 | 0.35 | 0.90 |
| 9 | 0.75 | 0.43 | 0.94 |
| 10 | 0.83 | 0.52 | 0.98 |
| 11 | 0.92 | 0.62 | 0.998 |
| 12 | 1.0 | 0.74 | 1.00 |

# 3 General Analysis Definitions

## 3.1 *Study Period*

The study period of this trial is a 24-month follow-up visit after the final islet transplant. Subjects may undergo up to 3 transplants in the course of this study; the final transplant must occur not later than 8 months following the first transplant.

In the first period, individuals who meet the general inclusion criteria will be approached regarding participation in the study. After informed consent has been obtained, they will be formally enrolled into the study. Eligibility will be confirmed based on the results of the screening visit procedures detailed in the study Schedule of Events (Appendix 1 of the CIT-02 protocol). Enrolled subjects who meet the eligibility screening for the studies will be put on the waiting list for an islet transplant.

Once a compatible islet preparation becomes available, a subject's eligibility will be re-confirmed, and eligible subjects who are randomized to Protocol CIT-02 will begin immunosuppression therapy on Day 0 (Day 0 is defined as the day of transplant).

During the post-transplant follow-up period, subjects may receive up to two additional transplants. After receiving his/her initial islet transplant, if a subject does not meet the criteria for insulin independence described in the Study Definitions section of the CIT-02 protocol, but has either a basal or stimulated C-peptide level $\geq$ 0.3 ng/mL (0.1 nmol/L), s/he will be considered for a second islet transplant. A second islet transplant will be

considered after day 85, but before 8 months after the first islet transplant and when all required metabolic assessments are complete. If, after the second islet transplant, both basal and stimulated C-peptide levels remain <0.3 ng/mL (0.1 nmol/L), the recipient will be considered to have failed the endpoint, and immunosuppression will be managed as described in the protocol. A third islet transplant will be considered only if all the criteria described in Section 7.6.2 of the CIT-02 protocol are met. Islet transplant recipients who have completed 8 months of follow up after their first infusion will no longer be eligible for additional islet transplants under the CIT-02 protocol. The number of excluded subjects and the number of protocol violations will be noted throughout the duration of the study.

## 3.2 *Visit Windows*

The number of visits that occur before the first islet transplant will be determined by time on the waiting list and cannot be determined in advance. Screening tests and baseline measurements that are obtained during this period must be obtained within specified windows relative to the day of randomization, as described in Appendices 1 of the CIT-02 protocol. Following a transplant, up to 18 visits may be scheduled. The schedule of follow-up visits and their detailed activities are described in Appendix 1 and 2 of the CIT-02 protocol.

## 3.3 *Study Population*

The study population consists of individuals with T1D who meet the eligibility criteria for the trial described in Section 3 of the CIT-02 protocol. This section of the SAP describes three study populations. All efficacy analyses will be done on the Intent-to-Treat (ITT) population. Parallel analyses will be done on the per-protocol population. Safety analyses will focus on the safety population.

### 3.3.1 Intention to Treat Population

All efficacy and safety analyses will be based on a modified ITT principle: any subject in whom protocol-directed therapy (*e.g.*, immunosuppression) is initiated will be included in the ITT population. Subjects who are randomized but for whom a protocol-directed therapy is not initiated will be listed in the final study report but will not be included in the ITT population.

### 3.3.2 Per-Protocol Population

A per-protocol analysis will include all subjects who are randomized to Protocol CIT-02 and in whom the islet transplant procedure is initiated. The procedure will be considered initiated when the operator (*e.g.*, surgeon or interventional radiologist) has started the process of obtaining access to the portal vein (*i.e.*, entered the body with a needle or scalpel).

### 3.3.3 Safety Population

The safety population consists of any subject in whom protocol-directed therapy (*e.g.*, immunosuppression) is initiated. Subjects in this population might not receive an islet transplant.

## 3.4 *Treatment Assignment and Treatment Groups*

### 3.4.1 Treatment Assignment

Enrolled subjects who meet the eligibility criteria will be placed on a waiting list for a transplant. Once a compatible pancreas becomes available, the subject will be reevaluated to ensure that s/he satisfies all inclusion/exclusion criteria and therefore is still eligible for participation in the CIT-02 study. Subjects will enter into the CIT-02 study via randomization between this study and the phase 3 study, Protocol CIT-07. Note that this randomization is between protocols and not to treatment arms within a protocol. The randomization is being performed to avoid bias in the assignment of subjects to protocols. The treating center will be blinded to protocol assignments until the subject is ready for transplantation.

### 3.4.2 Treatment Groups

The treatment in Protocol CIT-02 is the islet transplant and the accompanying immunosuppressive regimen, which includes LSF. This is a single-arm, open-label trial, and all subjects assigned to this protocol receive identical study treatment.

### 3.4.3 Center Pooling Method

The analysis of the primary endpoint assumes no between-center variability with regard to the favorable outcome resulting from the treatment. The data from both centers will be pooled without any adjustment for centers. Descriptive statistics will be tabulated across and within centers for all endpoints.

## 3.5 *Subject Disposition*

The number of subjects enrolled and treated will be summarized and reported in the following categories:

a. The numbers of subjects who are screened - total and grouped by center.

b. The numbers of subjects who are excluded from study participation - total and grouped by center. The numbers will also be tabulated by the reason for exclusion.

c. The numbers of subjects who are enrolled (sign informed consent for screening) - total and grouped by center.

d. The numbers of subjects who are eligible for the transplant both after enrollment and before the transplant, grouped by center.

e. The numbers of subjects who are lost to follow-up, grouped by center and reason. (The rules for premature termination of study treatment are fully described in Section 5.7.2 of the CIT-02 protocol).

A list of all enrolled subjects (grouped by center) who are prematurely terminated from the study (withdraw consent or are lost to follow-up) will be provided. The list will give

subject identification, the specific reason for termination, immunosuppression regimen, and the duration of treatment before the termination.

### 3.6 *Major Protocol Deviations*

Major protocol deviations will be summarized by center and for the total study and grouped into the following categories:

1. Impacts the inclusion and/or exclusion criteria (PD1)
2. Involves consent violations (PD2)
3. Alters protocol-specified study therapy (PD3)
4. Impacts the ability of the Sponsor to evaluate the endpoints of the study (PD4)
5. Involves administration of prohibited medications (PD5)

Individual subjects with these protocol deviations will be listed with specifics regarding the deviation.

# 4 General Statistical Issues

## 4.1 *Analysis Software*

It is expected that the majority of analyses will be performed by SAS® Software (version 9.1 or later), R (version 2.5.1 or later), or S-Plus® (version 8 or later).

## 4.2 *Derived and Computed Variables*

It is expected that additional variables derived or computed from those listed in Section 2.3 will be required. The SAP will not be amended for additional variables. Any additional derived or computed variables will be identified and documented in the SAS programs that create the analysis files.

# 5 Demographic and Baseline Variables

Baseline data consists of demographic information and medical/physical assessments during the waiting period between enrollment and randomization. These data will be grouped into the following categories:

**Demographic Variables**

- Age
- Sex
- Race (White, Black, Hispanic, Asian, and other)

**Baseline Diabetes Control Variables**

- Insulin requirement
- HbA1c

- Fasting and post prandial plasma glucose
- Fasting and post prandial C-peptide
- Number of severe hypoglycemic events in the last year
- MAGE score
- LI
- Clarke Score
- HYPO Score
- β-score
- C-peptide/(glucose x creatinine) ratio

**Body Habitus variables**

- Body weight
- Height
- QOL Measures

## 5.1 *Statistical Analysis of Baseline Data*

Descriptive statistics for the baseline variables, collapsed over center, will be presented in summary tables.

Continuous variables will be summarized by mean, standard deviation, median and range. Categorical variables will be presented as enumerations and percentages. Because the number of subjects randomized in each center will be small, tests for statistically significant differences between centers will not be performed.

## 5.2 *Statistical Analysis of Use of Medication*

Concomitant medications will be coded according to the World Health Organization drug dictionary, and the number of subjects using each medication will be tabulated for each center. Results will be presented across centers and within centers.

## 5.3 *Statistical Analysis of Study Completion*

The number and percentage of subjects who complete the study, losses to follow-up, times to loss to follow-up, and reasons for loss to follow-up (*e.g.*, AEs) will be presented.

# 6 Efficacy Analyses

## 6.1 *Statistical Analyses of Primary Endpoint*

The primary endpoint for the study is the proportion of insulin-independent subjects at Day 75 (± 5 days) following the first islet transplant.

The primary analysis is designed to estimate the true rate of favorable outcomes at Day 75 in subjects in the ITT population pooled over both centers. The observed proportion of favorable outcomes out of the total number of subjects recruited will be used as the point estimate. A corresponding exact two-sided 95% confidence interval will be

constructed assuming an underlying binomial distribution for the target population as follows:

If $r$ out of N total enrolled subjects achieve the favorable outcome, the lower bound of the exact 95% confidence interval is given by $p \geq p_L$ where $p_L$ is the solution of the equation,

$$0.025 = \sum_{x=0}^{r} \binom{N}{x} p_L^x (1 - p_L)^{N-x}.$$

The upper bound of the exact 95% confidence interval is given by $p \leq p_U$ where $p_U$ is the solution of the equation,

$$0.025 = \sum_{x=r}^{N} \binom{N}{x} p_U^x (1 - p_U)^{N-x}.$$

This analysis will be conducted for the ITT population. The primary endpoint should be available for all treated subjects. Exception will be if a death occurs, if the subject withdraws consent to be followed, or if immunosuppression is begun but the subject never receives a transplant. In these cases, the endpoint will be classified as failure to achieve a favorable outcome. Should the endpoint not be evaluated for a particular individual for other reasons, a failure will be imputed unless an evaluation is done at a time later than 75 days after the first transplant but prior to a subsequent transplant, in which case the later value will be imputed. All imputations will be reported with the primary analysis.

There is no pre-defined minimum rate for efficacy in this study. Instead, an exact two-sided 95% confidence interval is reported.

## 6.2 *Statistical Analyses of Secondary Endpoints*

Except for the primary analyses, there are no explicit or implied hypotheses in the protocol. Changes in the secondary outcomes are of interest as they will relate to efficacy as measured by the primary outcome variable. All analyses are descriptive and are intended to document the changes in these important variables, but are not intended to be used explicitly for making a decision for the efficacy of islet transplantation in this population.

### 6.2.1 Statistical Analyses of Secondary Endpoints

As discussed in Section 2.3.2.2, the additional efficacy endpoints are generally summarized at baseline (the most recent value prior to transplant), at 75 days and 365 days following the initial islet transplant, and again at 75 days, 365 days, and 730 days following the final islet transplant. Any variables that deviate from this schedule, as indicated by the Schedule of Events (Appendix 1 of the CIT-02 protocol) will be summarized accordingly. Imputations are not performed for missing values in the additional efficacy endpoints. Continuous secondary endpoints will follow analysis

template 1 (AT1) below. Categorical secondary endpoints will follow analysis template 2 (AT2) below.

**Analysis Template 1 (AT1**): For continuous data, the mean, standard deviation, minimum and maximum for the endpoint under consideration will be reported across centers and within centers. A 95% confidence interval will be constructed for the mean at each appropriate time point using the usual large sample theory. For example, let $\bar{x}$ be the mean of the continuous variable and let $s^2$ be the corresponding sample variance. Then the 95% confidence interval shall be constructed as

$$\bar{x} \pm t_{0.025}^{n-1} \times \frac{s}{\sqrt{n}}$$

where $t$ is from the t-distribution with $n-1$ degrees of freedom and $n$ is the size of the sample collected for the endpoint at the timepoint of interest.

Two additional analyses will also be conducted. First, changes from baseline to each time point will be assessed via the Wilcoxon Signed-Rank Test. Second, the mean, standard deviation, minimum, and maximum change from 75 days to 365 days following the final islet transplant will be summarized as well. The latter will also be accompanied by a 95% confidence interval to be calculated in the same fashion as above, but with the mean of the individual changes, $\bar{d}$, and the corresponding sample variance of the individual changes, $s_d^2$, replacing the mean at any given time point, $\bar{x}$, and the associated sample variance, $s^2$.

**Analysis Template 2 (AT2):** For categorical variables, the proportion of subjects with the characteristic under consideration (*e.g.*, the proportion who are women) will be reported, pooled across centers. A corresponding exact two-sided 95% confidence interval will be constructed for the proportion at each time point. Calculation of the 95% confidence interval follows the same process described for the primary endpoint in Section 6.1 above. McNemar's test for paired binomial data will be used to assess changes from baseline to each time point.

# 7 Safety Analyses

Safety analyses will be conducted for the safety population. Summaries will be prepared for the targeted safety endpoints listed in the secondary endpoints and for all observed AEs organized by body system. The CIT consortium modified the National Cancer Institute (NCI) toxicity table to create a document relevant for trials of adult pancreatic islet transplantation. The resulting reference manual, "Terminology Criteria for Adverse Events (TCAE) In Trials of Adult Pancreatic Islet Transplantation" (*CIT-TCAE*), provides descriptive terminology and a grading (severity) scale which will be utilized for adverse event (AE) reporting.

Regular safety analyses will be prepared for the Data and Safety Monitoring Board (DSMB). These summaries will be used to monitor the overall safety profile of the study. These analyses will summarize all AE data that are available at the time of the DSMB meeting. Analyses will summarize AEs by MedDRA preferred term and body

system. Separate incidence summaries will be prepared for serious AEs, for non-serious AEs, and for all AEs combined. Separate tables will summarize severity and attribution for SAEs. Each SAE could be attributed to the investigational agent (allogeneic islets/transplant procedure), the immunosuppression, both, or neither. Identical safety summaries will be included in the final statistical report.

The protocol also describes targeted safety endpoints. The planned analyses for general safety outcomes and for these targeted safety endpoints are described in the following sections.

## 7.1 *Adverse Events*

An AE is any occurrence or worsening of an undesirable or unintended sign, symptom (including an abnormal laboratory finding), or disease that is temporally associated with the use of a medicinal product whether considered related to the medicinal product or not. An SAE is defined as any AE occurring at any dose that suggests a significant hazard, contraindication, side effect, or precaution. This includes but is not limited to any of the following events (21CFR§312.32):

- Death.
- A life-threatening event. A life-threatening event is any adverse therapy experience that, in the view of the investigator, places the patient or participant at immediate risk of death from the reaction as it occurred.
- Inpatient hospitalization or prolongation of existing hospitalization.
- Persistent or significant disability.
- Congenital anomaly or birth defect.
- An event that required intervention to prevent permanent impairment or damage. An important medical event that may not result in death, be life threatening, or require hospitalization may be considered an SAE when, based on appropriate medical judgment, it may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Other conditions specified in the protocol.

In addition, events that occur at a higher than expected frequency, as determined by appropriate medical judgment, may be considered SAEs.

AEs will be graded on a scale from 1 to 5 according to the following standards in the *CIT-TCAE* manual:

Grade 1 = Mild adverse event.
Grade 2 = Moderate adverse event.
Grade 3 = Severe and undesirable adverse event.
Grade 4 = Life-threatening or disabling adverse event.
Grade 5 = Death.

AEs not included in the *CIT-TCAE* listing will be recorded and graded 1 to 5 according to the General Grade Definition provided as in the table below:

**Table 1: General Severity Definition of Adverse Event**

| Grade | Description | Definition |
|---|---|---|
| Grade 1 | Mild | Transient or mild discomforts (<48 hours); no or minimal medical intervention/therapy required; hospitalization not necessary (non-prescription or single-use prescription therapy may be employed to relieve symptoms [*e.g.*, aspirin for simple headache, acetaminophen for post-surgical pain]). |
| Grade 2 | Moderate | Mild to moderate limitation in activity; some assistance may be needed; no or minimal intervention/therapy required; hospitalization possible. |
| Grade 3 | Severe | Marked limitation in activity; some assistance usually required; medical intervention/therapy required; hospitalization possible. |
| Grade 4 | Life-threatening | Extreme limitation in activity; significant assistance required; significant medical/therapy intervention required; hospitalization or hospice care probable. |
| Grade 5 | Death | Death. |

All AEs will be reported and graded whether they are or are not related to disease progression or treatment. The relationship of an SAE to islet transplantation, which includes the transplant procedure and/or the islet product, to the immunosuppression and/or infection prophylaxis, or to the secondary investigational agent will be defined by using the descriptors provided in Table 3.

**Table 2: Attribution of Adverse Event**

| Code | Description | Definition |
|---|---|---|
| UNRELATED CATEGORY | | |
| 1 | Unrelated | This adverse event is clearly not related to allogeneic islets, the islet transplant procedure, immunosuppression or infection prophylaxis, or secondary investigational agent. |
| RELATED CATEGORIES | | |
| 2 | Unlikely | The adverse event is doubtfully related to allogeneic islets, the islet transplant procedure, immunosuppression or infection prophylaxis, or secondary investigational agent. |
| 3 | Possible | The adverse event may be related to allogeneic islets, the islet transplant procedure, immunosuppression or infection prophylaxis, or secondary investigational agent. |
| 4 | Probable | The adverse event is likely related to allogeneic islets, the islet transplant procedure, immunosuppression or infection prophylaxis, or secondary investigational agent. |
| 5 | Definite | The adverse event is clearly related to allogeneic islets, the islet transplant procedure, immunosuppression or infection prophylaxis, or secondary investigational agent. |

The collecting and recording procedures for AEs are described in detail in Section 8.3 of CIT-02 protocol.

## 7.2 *Analysis of Secondary Endpoints for Safety Endpoints*

The secondary safety endpoints described in Section 4.1.2.2 of the CIT-02 protocol target AEs related to islet transplantation (transplant procedure and/or islet product) and the immunosuppression and/or infection prophylaxis.

The targeted AEs related to the islet transplantation include:

1. AE-IP-1: Bleeding (>2 g/dL decrease in hemoglobin concentration)
2. AE-IP-2: Segmental portal vein thrombosis
3. AE-IP-3: Biliary puncture
4. AE-IP-4: Wound complication (infection or subsequent hernia)
5. AE-IP-5: Increased transaminase levels (>5 times ULN)

The targeted AEs related to the immunosuppression or infection prophylaxis therapy or related to the secondary investigational agent include:

1. AE-IIP-1: Allergy
2. AE-IIP-2: Reduction in GFR
3. AE-IIP-3: Increase in urinary albumin excretion
4. AE-IIP-4: Addition or intensification of anti-hypertensive therapy
5. AE-IIP-5: Addition or intensification of anti-hyperlipidemic therapy
6. AE-IIP-6: Oral ulcers

7. AE-IIP-7: Lower extremity edema
8. AE-IIP-8: Gastrointestinal toxicity
9. AE-IIP-9: Neutropenia, Anemia, or Thrombocytopenia
10. AE-IIP-10: Viral, Bacterial, or Fungal Infections
11. AE-IIP-11: Benign or Malignant Neoplasms

Other safety endpoints include:

- Incidence of the change in the immunosuppression drug regimen
- Incidence of immune sensitization defined by the presence of anti-HLA antibodies absent prior to transplantation

### 7.2.1 Safety Analyses from Randomization through Day 365 Following First Transplant

From randomization through Day 365 following the initial islet transplant, the incidence rates for each type of AE, grouped by severity, will be reported. For each type of AE, the number of resolved events will be counted as well. The mean, median, standard deviation, and range for the number of days until the AE is resolved will be calculated. Moreover, we will also report SAEs categorized by attribution; that is, SAEs related to the islet transplant procedure, immunosuppression, or LSF.

The incidence rate of a change in immunosuppression regimen (if applicable) will be reported. The exact two-sided 95% confidence interval of the incidence rate will also be reported.

The incidence rate of immune sensitization, defined as detection of anti-HLA antibodies (if applicable), will be reported. The exact two-sided 95% confidence interval of the incidence rate will also be reported.

### 7.2.2 Safety Analyses from Randomization through All of Follow-up

The analyses described in Section 7.2.1 above will be performed again for the entire duration of the study.

### 7.2.3 Statistical Analysis of Adverse Events

AEs will be analyzed according to the body system described in the *CIT-TCAE* manual. Any event that appears in a body system will be categorized into one of the five severity grades according to the *CIT-TCAE* manual or the general definition of severity given in Table 2 and analyzed accordingly. For each event, we will analyze its incidence rate per 100 person-days. Suppose for each subject, the incidence of a particular event is a Poisson process with the homogeneous incidence rate $\lambda$. At the time of analysis, if a subject is only followed *r* days after the randomization, the incidence of this event is distributed according to the Poisson distribution with mean $r\lambda/100$. The maximum likelihood estimate of the incidence rate will be obtained based on data collected from the available subjects at the analysis time. The 95% confidence interval derived using the maximum likelihood estimator theory will be also reported.

# 8 Interim Analyses

The DSMB will be convened to review safety and efficacy data following National Institutes of Health (NIH) policy. When requested, formal interim analyses to assess safety and efficacy will be performed. Formal interim analyses will include distributions of endpoints, biomarkers, and AEs. Additional analyses may be requested by the DSMB.

## 8.1 *Interim Analyses for Early Stopping*

During the period when CIT is enrolling, CIT-02 will enroll at half the rate. CIT-02 will be continuously monitored with a futility analysis, and a recommendation for stopping new enrollment will be made if the accruing information indicates that the primary endpoint of CIT-02 is unlikely to be meaningfully higher than the historical rate of 15-20%; "meaningfully higher" is taken to be 50%.

As each CIT-02 endpoint is determined, an upper bound for the probability of a favorable CIT-02 primary endpoint will be calculated from an exact one-sided 95% confidence interval. A recommendation will be made to stop enrollment in CIT-02 if, and when, the upper bound is below 50%. Operationally, the following rule results:

**Stopping Rule**

- Stop at 5 subjects if there are no successes in first 5 subjects.
- Stop at 8 subjects if there is only 1 success in first 8 subjects.
- Stop at 11 subjects if there are 2 or fewer successes in first 11 subjects.
- Otherwise, complete enrollment to 12 subjects.

The rule ensures that, should 12 subjects be enrolled, there will be at least 3 successes out of 12 on the primary endpoint.

Should enrollment in CIT-02 be stopped, then long term follow-up data will continue to be collected until the end of the study.

An additional interim analysis will also be done for the DSMB at the time that CIT-07 enrollment is complete. In this analysis, all endpoints of CIT-02 are compared to corresponding endpoints of UM and UIC CIT-07 subjects. If the primary endpoint in CIT-02 has a significantly lower rate of favorable outcome using a one-sided test with a Type 1 error of 0.05, then a recommendation to stop enrollment in CIT-02 will be made.

**Table 3: Operating characteristics of stopping rule**

| Probability of Event | Probability Stop at 5 Subjects | Probability Stop at 8 Subjects | Probability Stop at 11 Subjects | Probability Reach 12 Subjects |
|---|---|---|---|---|
| 0.1 | 0.59049 | 0.23915 | 0.09685 | 0.07350 |
| 0.2 | 0.32768 | 0.20972 | 0.13421 | 0.32838 |
| 0.3 | 0.16807 | 0.12353 | 0.09079 | 0.61760 |
| 0.4 | 0.07776 | 0.05599 | 0.04031 | 0.82594 |
| 0.5 | 0.03125 | 0.01953 | 0.01220 | 0.93701 |
| 0.6 | 0.01024 | 0.00492 | 0.00235 | 0.98248 |
| 0.7 | 0.00243 | 0.00077 | 0.00024 | 0.99656 |
| 0.8 | 0.00032 | 0.00005 | 0.00001 | 0.99962 |
| 0.9 | 0.00001 | 0.00000 | 0.00000 | 0.99998 |

# References

1. US Federal Register, *International Conference on Harmonization; Guidance on Statistical Principles for Clinical Trials (E9). Department of Health and Human Services: Food and Drug Administration (Docket No. 97D-0174).* Federal Register, 1998. **Vol. 63**(No.179): p.p. 49583-49598.
2. ASA, *Ethical Guidelines for Statistical Practice.* Prepared by the Committee on Professional Ethics, 2016.
3. RSS, *The Royal Statistical Society: Code of Conduct.* 2014.
4. Goodman, L., *On Simultaneous Confidence Intervals for Multinomial Proportions.* Technometrics, 1965. **Vol. 7**(No. 2).
5. Kwong, K.-S., *On Sample Size and Quick Simultaneous Confidence Interval Estimations for Multinomial Proportions.* Journal of Computational and Graphical Statistics, 1998. **Vol. 7**(No. 2).