Clinical Islet Transplant Consortium

Statistical Analysis Plan for CIT-03

Peritransplant Deoxyspergualin in Islet Transplantation in Type 1 Diabetes

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Glossary of Abbreviations

AE	adverse event
AIR_{glu}	acute insulin response to glucose
BMI	body mass index
CGMS	Continuous Glucose Monitoring System®
CIT	Clinical Islet Transplantation
DDS	Diabetes Distress Scale
DI	disposition index
DSMB	Data Safety Monitoring Board
EQ-5D	European Quality of Life
FSIGT	frequently-sampled intravenous glucose tolerance
GFR	glomerular filtration rate
HbA1c	glycosylated hemoglobin
HFS	Hypoglycemia Fear Scale
HLA	histocompatability antigen
ITT	intent to treat
LI	lability index
MAGE	mean amplitude of glycemic excursions
MMTT	mixed-meal tolerance test
NCI	National Cancer Institute
NIH	National Institutes of Health
OHS	Overall Health Status

QOL	quality of life
SAE	serious adverse event
SAP	statistical analysis plan
SI	insulin sensitivity
SMC	Summary Mental Component
SPC	Summary Physical Component
T1D	Type 1 Diabetes
TCAE	Terminology Criteria for Adverse Events
ULN	upper limit of normal

Preface

This Statistical Analysis Plan (SAP) describes the planned analysis and reporting for Clinical Islet Transplantation protocol CIT-03, "Peritransplant deoxyspergualin in islet transplantation in type 1 diabetes".

This phase 2 study is being completed to assess the safety and efficacy of deoxyspergualin (DSG) on post-transplant islet function for treatment of diabetes in a sample of subjects with long-standing type 1 diabetes (T1D) that is refractory to intense insulin therapy.

The structure and content of this SAP provide 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-03.
- Case report forms (CRFs) for Protocol CIT-03.
- ICH Guidance on Statistical Principles for Clinical Trials.

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

The planned analyses identified in this SAP will be included in regulatory submissions and/or future manuscripts. Also, 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 performed will be clearly identified in the respective clinical study report.

1 Study Design and Objectives

1.1 Study Design

This is a multi-center, single arm, open-label trial assessing the safety and efficacy of DSG on post-transplant islet function in subjects with long-standing T1D that is refractory to intensive insulin therapy.

1.2 Study Objectives

1.2.1 Primary Objective

The primary objective of this protocol is to assess the safety and efficacy of an immunosuppressive regimen consisting of ATG (1st transplant only), basiliximab

(subsequent transplants only), etanercept, DSG, sirolimus, and low-dose tacrolimus on post-transplant islet function in subjects with T1D

1.2.2 Secondary Objectives

The secondary objective of this study it to improve mechanistic understanding of determinants of success and failure of islet transplants in T1D.

Additional secondary objectives of this study will assess whether successful islet transplantation leads to improved quality of life and improved metabolic control.

1.2.3 Primary Endpoint

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

Islet transplant recipients will be considered insulin-independent with full islet graft function if they are able to titrate off insulin therapy for at least 1 week and all of the following criteria are met:

- One HBA1c level, one fasting serum glucose level, and a Mixed Meal Tolerance Test are documented within the visit window (e.g. 70-80 days at Day 75) and 7 consecutive days of blood sugar and insulin readings are documented within +/- 7 days of the visit window(e.g. 63-87 days at Day 75);
- HbA1c < 7.0% or a ≥2.5% decrease from baseline;
- Fasting capillary glucose level should not exceed 140 mg/dL (7.8 mmol/L) more than three times in the 7 consecutive days (fasting is defined as 1st blood sugar reading of the day not noted as post-prandial or bedtime);
- Post-prandial serum glucose ≤ 180 mg/dL (10.0 mmol/L) at 90 minutes during the MMTT;
- Fasting serum glucose level ≤126 mg/dL (7.0 mmol/L); if the fasting serum glucose level is >126 mg/dL (7.0 mmol/L), it must be confirmed in an additional one out of two measurements;
- At least one MMTT fasting or stimulated c-peptide ≥ 0.5ng/ml.

1.2.4 Secondary Endpoints

The key secondary endpoint is the proportion of subjects with an HbA1c < 7.0% AND free of severe hypoglycemic events from Day 28 to Day 365, inclusive, after the first islet transplant.

> A severe hypoglycemic event is defined as an event with one of the following symptoms: memory loss; confusion; uncontrollable behavior; irrational behavior; unusual difficulty in awakening; suspected seizure; seizure; loss of consciousness; or visual symptoms, in which the subject was unable to treat him/herself and which was associated with either a blood glucose level <54 mg/dL [3.0 mmol/L] or prompt recovery after oral carbohydrate, IV glucose, or glucagon administration.

The other secondary endpoint is the proportion of subjects with an HbA1c < 7.0% AND free of severe hypoglycemic events from Day 28 to Day 365, inclusive, after the final islet transplant.

Secondary endpoints have been categorized by study investigators into efficacy endpoints and safety endpoints. Secondary endpoints are measured at 75 ± 5 days after the initial and final transplant, at 365 ± 14 days after the initial and final transplant, and at 730 ± 14 after the final transplant. Endpoints are listed below, and corresponding details may be found in section 4.1 of the CIT-03 protocol. Quality of life (QOL) measures fall under the category of Efficacy Secondary Endpoints but will be addressed in a separate section.

1.2.4.1 Secondary Efficacy Endpoints

At 75 ± 5 days following the <u>first</u> islet transplant and following the final islet transplant:

- The percent reduction in insulin requirements
- HbA1c
- MAGE
- LI
- Ryan hypoglycemia severity (HYPO) score
- Basal (fasting) and 90-min glucose and C-peptide derived from the mixed-meal tolerance test (MMTT)
- β-score
- C-peptide: (glucose·creatinine) ratio
- Acute insulin response to glucose (AIR_{glu}), insulin sensitivity, and disposition index (DI) derived from the insulin-modified frequently-sampled IV glucose tolerance (FSIGT)
- Glucose variability and hypoglycemia duration derived from the CGMS®
- QOL measures

At 365 ± 14 days following the <u>initial</u> transplant, the following endpoint will be assessed:

- The proportion of subjects with an HbA1c <7.0% at Day 365 AND free of severe hypoglycemic events from Day 28 to Day 365 inclusive

At 365 ± 14 days following the final transplant, the following endpoint will be assessed:

- The proportion of subjects with an HbA1c <7.0% at Day 365 AND free of severe hypoglycemic events from Day 28 to Day 365 inclusive

At 365 ± 14 days following the initial and final islet transplant(s) the following endpoints will be assessed:

- The percent reduction in insulin requirements
- HbA1c
- MAGE
- LI
- Clarke score
- HYPO score
- Basal (fasting) and 90-min glucose and C-peptide (MMTT)
- β-score
- C-peptide: (glucose·X creatinine) ratio
- Glucose variability and hypoglycemia duration derived from the CGMS®
- AIRglu, insulin sensitivity, and DI derived from the insulin-modified FSIGT
- QOL measures
- The proportion of subjects receiving a second islet transplant
- The proportion of subjects receiving a third islet transplant
- Rate of favorable outcome at each center preparing islets (rate of subjects with an Hb1Ac <7.0% and free of severe hypoglycemic events)

Secondary efficacy endpoints measured at 365 ± 14 days following the final islet transplant will include the change in the above measures from the results obtained at 75 ± 5 days following the final islet transplant.

At two years (730 ± 14 days) following the final islet transplant:

- The percent change from baseline insulin requirements
- The number of severe hypoglycemic events from 28 days to two years
- HbA1c
- Clarke score
- Basal (fasting) and 90-min glucose and c-peptide (MMTT)
- β-score
- C-peptide: (glucose·creatinine) ratio
- CGMS
- QOL

1.2.4.2 Secondary Safety Endpoints

- 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

At 75 ± 5 days following each transplant and 365 ± 14 days following the first and final islet transplant(s), the following safety endpoint will be evaluated:

- 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])
- 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

- The incidence of immune sensitization defined by presence of anti-HLA antibodies absent prior to transplantation

At 365 ± 14 days following the initial islet transplant, the following safety endpoint will be evaluated:

- The incidence of worsening retinopathy as assessed by change in retinal photography

1.3 Sample Size Calculations

The purpose of this study is to estimate the true rate of insulin independence at 75 days. Since there is no formal hypothesis test associated with the primary endpoint, no power calculations were performed. Study investigators selected a sample size of 20 subjects.

2 General Analysis Defintions

2.1 Study Period

The trial consists of three periods: (1) the pre-transplant period, which includes screening, enrollment, and wait list time; (2) the period that includes the islet transplant procedure(s); and (3) follow-up visits through 24 months following the final transplant. The study period of this trial is a 24-month follow-up after the final islet transplant. Subjects may undergo up to 3 transplants in the course of this study; the final transplant can occur no later than 12 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 procedure detailed in Appendix 1 of the CIT-03 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 will begin immunosuppression therapy on Day -2 (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 an initial islet transplant, if a subject does not meet the criteria for insulin independence described in the Study Definitions of the CIT-03 protocol, but has either a basal or stimulated C-peptide level $\geq$ 0.3 ng/mL (0.1 nmol/L), the subject will be considered for a second islet transplant in the interim between the 75± 5 days / metabolic assessment visit and 8 months post-initial transplant. 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 7.5 of the CIT-03 protocol are met. Islet transplant recipients who have completed 12 months of follow up after their first infusion will no longer be eligible for additional islet transplants under the CIT-03 protocol. The number of excluded subjects and the number of protocol violations will be noted throughout the duration of the study.

2.2 Visit Windows

The number of visits that occur before the first islet transplant will be determined by time spent 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 Appendix 1 of the CIT-03 protocol. The schedule of follow-up visits and their detailed activities are described in Appendix 1 of the CIT-03 protocol

2.3 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-03 protocol. This section of the SAP describes three study populations. All efficacy analyses will be done on the Intention-to-Treat (ITT) population. Parallel analyses will be done on the per-protocol population. Safety analyses will focus on the safety population.

2.3.1 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 protocol directed

therapy is not initiated will be listed in the final study report but will not be included in the ITT population.

2.3.2 Per-Protocol Population

A per-protocol analysis will include all subjects who are randomized to CIT-03 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).

2.3.3 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.

2.4 Treatment Assignment and Treatment Groups

2.4.1 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 the CIT-03 study. Subjects will enter into the CIT-03 protocol via randomization between the CIT-03 study and the phase 3 study, 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.

2.4.2 Treatment Groups

The treatment in CIT-03 is the islet transplant and treatment with DSG in the peri-transplant period. This is a single-arm, open-label trial, and everyone assigned to this protocol receives the same study treatment.

2.4.3 Center Pooling Method

The analysis of the primary endpoint and secondary efficacy endpoints assumes no between-center variability. The data from all centers will be pooled without any adjustment for centers. Descriptive statistics for the primary and all secondary endpoints will be tabulated across and within center for all endpoints.

In Section 9 of the study protocol it is noted that comparisons of endpoints obtained in this study to the corresponding endpoints in the CIT07 study will be performed. These analyses will account for potential center specific effects. Detail regarding these analyses is described in Section 5.2.4.

2.5 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 the 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-03 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.

2.6 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)

The template of summary tables for the protocol deviations is provided in Appendix 1. Individual subjects with these protocol deviations will be listed with specifics on the deviation.

3 General Issues for Statistical Analyses

3.1 Analysis Software

It is expected that the majority of analyses will be performed using SAS® Software (version 9.3 or later), or R (version 2.5.1 or later).

3.2 Derived and Computed Variables

It is expected that additional variables derived or computed from those listed in SAP Section 1.2 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.

4 Demographic and Baseline Characteristics

Baseline data collected for all enrolled patients 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
- Number of severe hypoglycemic events
- Ryan HYPO score
- Glycemic Lability index
- Serum creatinine
- Fasting serum glucose level
- C-peptide
- Neurologic exam
- Basal C-peptide
- Mixed meal test
- β-score
- CPGCR
- Clarke score
- MAGE
- Insulin modified FSIGT
- CGMS

Body Habitus variables

- Body weight
- Height

4.1 Statistical Analysis of Baseline Data

Descriptive statistics, collapsing over center, for the baseline variables will be presented in a summary table. From this table, marginal descriptive statistics for centers will also be tabulated and presented.

Continuous variables will be summarized by mean, standard deviation, median and range. Categorical data will be presented as enumerations and percentages. The templates for these tables are shown in Appendix 2. Because the number of patients randomized in each center will be small, tests for statistically significant differences between centers will not be performed.

Baseline variables will be analyzed according to one of three analytic templates described in the following section.

4.2 Statistical Analysis Templates for Baseline Data

Analysis Template 1 (AT1): For continuous variables, the mean, median, standard deviation, minimum and maximum of the variable under consideration will be reported across center and within center. The 95% confidence interval for the mean will also be reported. In cases where the normality assumption used to estimate the confidence interval is questionable a transformation that achieves normality may be considered.

Analysis Template 2 (AT2): For categorical variables the proportions will be reported within and across center. Where appropriate an exact 95% confidence interval based on the binomial distribution will be reported.

4.3 Statistical analysis of Demographic Variables

The following listing shows the analysis template that will be used to analyze each demographic variable:

Demographic Variable	Analysis Template
Age	AT1
Sex	AT2
Race	AT2

4.4 Statistical Analysis of Diabetes Control Variables

The following listing shows the analysis template that will be used to analyze each diabetes control variable.

Diabetes Control Variable	Analysis Template
Insulin requirement	AT1
HbA1c	AT1
Number of severe hypoglycemic events	AT1
Ryan HYPO score	AT1
Glycemic Lability index	AT1
Serum creatinine	AT1
Fasting serum glucose level	AT1
C-peptide	AT1
Basal C-peptide	AT1
Mixed meal test	AT1
β-score	AT1
CPGCR	AT1
MAGE	AT1
Insulin modified FSIGT	AT1
CGMS	AT1

4.5 Statistical Analysis of Body Habitus Variables

Body habitus variables include height, weight, and body mass index (BMI). BMI is computed as the ratio of weight in kilograms to the square of height in meters. These three variables are continuous and will be analyzed using AT1.

4.6 Statistical Analysis of Medical History Variables

Medical history variables include the existence of current signs and symptoms of clinical significance by body system and the use of any concomitant medication. The number of subjects with previous symptoms will be tabulated for both centers by body system. Results will be presented across centers and within centers. Results will be reported using the template provided in Appendix 3.

4.7 Statistical Analysis of Use of Medication

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

4.8 Statistical Analysis of Study Completion

The number and percentage of subjects who complete the study, losses to follow-up, times to lost to follow-up, and reasons for loss to follow-up will be presented. Statistical presentation of study completion may be further summarized by demographic variables for each participating center. This descriptive analysis will be summarized in a template given in Appendix 5.

5 Efficacy Analyses

5.1 Statistical Analysis of Primary Endpoint

HbA1c is the standard measure of glucose control and is used in all major studies as an endpoint for glycemic control. It has been valuable as a risk predictor of diabetes complications. However, since HbA1c is an integrated average, it does not provide information about the range of glucose values a subject experiences. This limitation is a rationale for also including hypoglycemic event occurrence as part of the primary endpoint and various glycemic excursion measures as secondary endpoints.

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

The primary analysis is designed to estimate the true rate of favorable outcomes at one year in subjects in the ITT population pooled over all centers. The observed proportion of favorable outcomes out of 20 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 20 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,

$$0.025 = \sum_{x=0}^{r} \binom{20}{x} p_L^x \left(1 - p_L\right)^{20-x}.$$

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,

$$0.025 = \sum_{x=r}^{20} \binom{20}{x} p_U^x \left(1 - p_U\right)^{20-x}.$$

This analysis will be conducted for the ITT population. The primary endpoint should be available for all treated subjects. An 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 longer than 75 days after the first transplant, in which case, that later value will be imputed. All imputations will be reported with the primary analysis. The rates and the exact 95% confidence intervals for complete data and imputed data will be compared to ascertain the sensitivity of the imputation.

The following table displays the confidence intervals that would be computed for each possible outcome. For example, if 10 of the 20 subjects achieve insulin independence, then the estimated rate will be 0.5, and a 95% confidence interval will be 0.272 to 0.729. That is, we are 95% confident that the true rate is at least 27.2% and no more than 72.9%. The confidence interval rules out any rate less than 27.2% or greater than 72.9%.

Table 1: Exact 95% confidence intervals for all possible outcomes of primary endpoint

Number of Subjects out of 20 Insulin Independent at 75 Days	Estimated Rate	Exact 95% Confidence Interval Lower Bound	Exact 95% Confidence Interval Upper Bound
0	0.00	0.000	0.069
1	0.05	0.001	0.249
2	0.10	0.012	0.317
3	0.15	0.032	0.379
4	0.20	0.057	0.437
5	0.25	0.087	0.492
6	0.30	0.119	0.543
7	0.35	0.154	0.593
8	0.40	0.191	0.640
9	0.45	0.230	0.685
10	0.50	0.272	0.729
11	0.55	0.315	0.770
12	0.60	0.360	0.809
13	0.65	0.408	0.847
14	0.70	0.457	0.882
15	0.75	0.509	0.914
16	0.80	0.563	0.943
17	0.85	0.621	0.968
18	0.90	0.683	0.988
19	0.95	0.751	0.999
20	1.00	0.831	1.000

5.2 Statistical Analyses of Efficacy Secondary Endpoints

Except for the primary analyses, there are no explicit or implied hypotheses in the protocol. 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.

5.2.1 Statistical Analysis Secondary Endpoints Collected at 75 ± 5 Days Post Initial and Final Transplant

Statistical analysis of secondary endpoints at 75 ± 5 days following the first and subsequent transplant(s) will be based on the analysis templates described in Section 4.2.

Analysis Template 1 at 75 days (AT1 at 75 days): For continuous data, the mean, standard deviation, minimum and maximum for the endpoint under consideration will be reported across center and within center. A 95% confidence interval will also be reported for the mean at 75 days. In cases where the normality assumption used to estimate the confidence interval is questionable a transformation that achieves normality may be considered.

Analysis Template 2 at 75 days (AT2 at 75 days): For categorical variables, proportions will be reported within and across center. A corresponding exact two-sided 95% confidence interval will be constructed assuming an underlying binomial distribution for the target population as follows as described in Analysis Template 2 in SAP Section 4.2.

The following listing shows the analysis template that will be used to analyze each secondary endpoint collected at 75 ± 5 days following the first and subsequent transplant(s).

Secondary Endpoint	Analysis Template
Insulin requirement	AT1 at 75 days
HbA1c	AT1 at 75 days
Number of severe hypoglycemic events	AT2 at 75 days
Ryan HYPO score	AT1 at 75 days
Glycemic Lability index	AT1 at 75 days
Serum creatinine	AT1 at 75 days
Fasting serum glucose level	AT1 at 75 days
C-peptide	AT1 at 75 days
Basal C-peptide	AT1 at 75 days
Mixed meal test	AT1 at 75 days
β-score	AT1 at 75 days
CPGCR	AT1 at 75 days
MAGE	AT1 at 75 days
Insulin modified FSIGT	AT1 at 75 days
CGMS	AT1 at 75 days

5.2.2 Statistical Analysis of Efficacy Secondary Endpoints Collected at 365 ± 14 Days Post Initial Transplant

At 365 ± 14 days following the initial transplant, the following endpoints are collected:

- The proportion of subjects with an HbA1c <7.0% at Day 365 AND free of severe hypoglycemic events from Day 28 to Day 365 inclusive
- The proportion of subjects receiving a second islet transplant
- The proportion of subjects receiving a third islet transplant

All endpoints listed here are categorical variables with two levels and will be analyzed using statistical analysis template, AT2 at 75 days, described in SAP Section 5.2.1.

5.2.3 Statistical Analysis of Secondary Endpoints Collected at 365 ± 14 Days Post Initial and Final Transplant

Statistical analysis of secondary endpoints at 365 ± 14 days following the first and subsequent transplant(s) will based on the analysis templates described in SAP Section 5.2.1.

Analysis Template 1 at 365 days (AT1 at 365 days): For continuous data, the mean, standard deviation, minimum and maximum will be reported across center and within center. A 95% confidence interval for the mean at day 365 will be reported. In cases where the normality assumption used to estimate the confidence interval is questionable a transformation that achieves normality may be considered.

For endpoints measured at day 365 post final transplant, the mean change from day 75 post final transplant will also be reported. A 95% confidence interval for the mean difference will also be reported.

Analysis Template 2 at 365 days (AT2 at 365 days): For categorical variables, proportions will be reported within and across center. A corresponding exact two-sided 95% confidence interval will be constructed assuming an underlying binomial distribution for the target population as follows as described in Analysis Template 2 in SAP Section 4.2.

For endpoints measured at day 365 post final transplant, the difference in proportion from day 75 post final transplant will also be reported. A 95% confidence interval for the change in proportion will also be reported.

The following listing shows the analysis template that will be used to analyze each secondary endpoint collected at 365 $\pm$ 14 days following the first and final transplant.

Secondary Endpoint	Analysis Template
Proportion of insulin-independent subjects	AT2 at 365 days
Percent reduction in insulin requiremennts	AT1 at 365 days
HbA1c	AT1 at 365 days
MAGE	AT1 at 365 days
LI	AT1 at 365 days
Clarke score	AT1 at 365 days
Hypo score	AT1 at 365 days
Basal (fasting) and 90-min glucose and C-peptide (MMTT)	AT1 at 365 days
B-score	AT1 at 365 days
C-peptide: (glucose.X creatinine) ratio	AT1 at 365 days
AIRglu, insulin sensitivity and DI dervived from insulin modified FSIGT	AT1 at 365 days
QOL measures	AT1 at 365 days

5.2.4 Comparison of Endpoints between CIT-03 and CIT-07

Additional secondary analyses will compare the primary and secondary endpoints in this study to the corresponding endpoints in the CIT-07 Phase 3 study. These comparisons are of interest because subjects enrolled under the CIT-03 protocol receive DSG as part of the transplantation process, whereas those enrolled in CIT-07 do not. Therefore, the comparison of secondary endpoints between the two protocols is a comparison between subjects treated with DSG and those not treated with DSG.

5.2.5 Statistical Analysis for Comparison of Endpoints between CIT03 and CIT07

Comparison of primary endpoint:
Fisher's exact test will be used to compare the rates of insulin independence at 75 days after the first transplant between the two studies by testing the null hypothesis, $p_{CIT03} = p_{CIT07}$, against the two-sided alternative, $p_{CIT03} \neq p_{CIT07}$, where p_{CIT03} is the proportion of insulin independent subjects at 75 days in CIT-03 and p_{CIT07} is the proportion of insulin independent subjects at 75 days in CIT-07. The null hypothesis will be rejected in favor of the alternative if the exact p-value is less than 0.05. Should the null hypothesis be rejected, it will be concluded that $p_{CIT03} > p_{CIT07}$ if the observed proportion of insulin independent subjects in CIT-03 is *larger* than that of CIT-07 subjects; it will be concluded that $p_{CIT03} < p_{CIT07}$ if the observed proportion of insulin independent subjects in CIT03 is *smaller* than that of CIT-07 subjects.

The point estimate of $p_{CIT03} - p_{CIT07}$ will also be reported and estimated as the difference in the observed proportions of insulin independent subjects in CIT-03 and CIT-07. A corresponding 95% exact unconditional confidence interval for the difference will also be calculated.

Comparisons of secondary endpoints:
Secondary endpoints will be compared between CIT-03 and CIT-07. Analyses will be conducted using one of two statistical analysis templates described here.

Analysis Template 1 for Comparisons (AT1 for comparison):
For categorical variables with two levels, the proportion of patients with the characteristic under consideration (*e.g.*, proportion who are insulin independent) will be reported within and across center according to study protocol (DSG or non-DSG). Differences in proportion between the DSG group and the non-DSG group will be analyzed using a generalized linear mixed effects model with random effects and a logit link function.

The model that will be fit is stated here:

$$\mathbf{logit(p_{ij}) = \beta_0 + \beta_1 * DSG_{ij} + \gamma_j}$$

where:

$\mathbf{p}_{ij}$ is the probability of outcome for the i^{th} patient in the j^{th} center.

$\mathbf{DSG_{ij}}$ = 1 if the i^{th} patient in the j^{th} hospital was treated using DSG
0 otherwise

$\boldsymbol{\gamma_j}$ is a center specific random effect

A generalized linear mixed effect model is used because the inclusion of a center specific random effect, γ, accounts for the likely correlation between subjects within a center and also allows the DSG effect to vary across center. The center specific random effect, γ, is assumed to be distributed according to a normal distribution with mean zero and variance, σ^2. Adaptive Gaussian quadrature will be used in conjunction with the method of marginal likelihood to fit the model[6]. If convergence cannot be attained using Gaussian quadrature, then the method of restricted pseudo-likelihood will be used to estimate model parameters[7].

A Wald test will be used to test the null hypothesis that β_1 is equal to zero against the two-sided alternative that it is not. If the null hypothesis is rejected at significance level 0.05 then the DSG group differs statistically from the non-DSG group. A statistically significant positive estimate implies the probability of outcome in the DSG group is larger than the probability of outcome in the non-DSG group.

Parameter estimates are obtained on the link function scale, in this case, the logit scale, so the difference in expected odds of event between the DSG group and the non-DSG group is the inverse of the link function or $\exp(\beta_1)$. The odds of favorable outcome for DSG patients relative to non-DSG patients will be estimated by $\exp(\beta_1)$. The results of the Wald test, $\exp(\beta_1)$ and the corresponding 95% confidence interval will be reported.

Analysis Template 2 for Comparisons (AT2 for comparison):
For continuous secondary endpoints, the mean, standard deviation, minimum and maximum of the variable under consideration will be reported within center and across center according to study protocol (DSG or non-DSG). Differences in mean between the DSG and non-DSG group will be analyzed using linear mixed effect models.

The model that will be fit is stated here:

$$\mathbf{y_{ij} = \beta_0 + \beta_1 * DSG_{ij} + \gamma_j + \varepsilon_{ij}}$$

where:

$\mathbf{y}_{ij}$ is the outcome for the i^{th} patient in the j^{th} center.

$\mathbf{DSG_{ij}}$ = 1 if the i^{th} patient in the j^{th} hospital was treated using DSG
0 otherwise

$\boldsymbol{\gamma_j}$ is a center specific random effect

$\boldsymbol{\varepsilon_{ij}}$ is a patient specific random error term

A linear mixed effects model is used because the inclusion of a center specific random effect, γ, accounts for the likely correlation between subjects within a center and also allows the DSG effect to vary across center. The center-specific random effect, γ, is assumed to be distributed according to a normal distribution with mean zero and variance, σ_C^2. The patient specific random error term, ε, is assumed to be distributed according to a normal distribution with mean zero and variance, σ^2. Adaptive Gaussian quadrature will be used in conjunction with the method of marginal likelihood to fit the model. If convergence cannot be attained using Gaussian quadrature, then the method of restricted pseudo-likelihood will be used to estimate model parameters.

A Wald test will be used to test the null hypothesis that β_1 is equal to zero against the two-sided alternative that it is not. If the null hypothesis is rejected at significance level 0.05, then the DSG group differs statistically from the non-DSG group.

The expected difference between the DSG group and the non-DSG group is β_1. A statistically significant positive estimate implies the mean outcome in the DSG group is larger than the mean of the non-DSG group and the difference is β_1. A statistically significant negative estimate implies the mean outcome in the DSG group is smaller than the mean in the non-DSG group and the difference is $-\beta_1$. If the null hypothesis is not rejected, then there is no statistical difference between the DSG and non-DSG groups. The corresponding 95% confidence interval will be reported.

5.2.6 Statistical Analysis for comparison of CIT-03 and CIT-07 endpoints

The following listing shows the analysis template that will be used to compare endpoints between CIT-03 and CIT-07.

Secondary Endpoint	Analysis Template
Insulin requirement	AT1 for comparison
HbA1c	AT1 for comparison
Number of severe hypoglycemic events	AT2 for comparison
Ryan HYPO score	AT1 for comparison
Glycemic Lability index	AT1 for comparison
Serum creatinine	AT1 for comparison
Fasting serum glucose level	AT1 for comparison
C-peptide	AT1 for comparison
Basal C-peptide	AT1 for comparison
Mixed meal test	AT1 for comparison
β-score	AT1 for comparison
CPGCR	AT1 for comparison
MAGE	AT1 for comparison
Insulin modified FSIGT	AT1 for comparison
CGMS	AT1 for comparison

5.3 Quality of Life Measures

Generic and disease-specific measures will be used to assess QOL. Questionnaires will be completed at enrollment and every 3 months during the screening period, then at day 75 and months 6 and 12 following transplant. QOL measures will be analyzed using the ITT population.

5.3.1 Generic Quality of Life Measures

Two measures will be used for generic QOL:

- SF-36
- EQ-5D

5.3.2 Disease-Specific Quality of Life Measures

Two measures will be used for disease-specific QOL:

- Diabetes Distress Scale
- Hypoglycemic Fear Survey

5.3.3 Statistical Analysis of Quality of Life Measures

All QOL measures are continuous variables and will be analyzed using analysis templates previously described. QOL measures at 75 ± 5 days following the first transplant will be analyzed using template AT1 at 75 days (SAP Section 5.2.1). The measurement performed during the screening period that is closest to the transplant will be used as the baseline QOL measurement.

Statistical analysis of QOL measures at 365 ± 14 days following the first transplant be analyzed using template AT1 at 365 days (SAP Section 5.2.3). The measurement performed during the screening period that is closest to the transplant will be used as the baseline QOL measurement.

6 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," 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 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 term and body system. Separate incidence summaries will be prepared for serious AEs, for nonserious AEs and for all AEs combined. Separate tables will summarize severity and attribution. Each AE can be

attributed to the investigational agent (allogeneic islets), 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 few sections.

6.1 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 2: 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 AE to islet transplantation, which includes the transplant procedure and/or the islet product, or to the immunosuppression and/or infection prophylaxis will be defined by using the descriptors provided in Table 3.

Table 3: 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; the secondary investigational agent (DSG); immunosuppression or infection prophylaxis.
RELATED CATEGORIES		
2	Unlikely	The adverse event is doubtfully related to allogeneic islets; the islet transplant procedure; the secondary investigational agent (DSG); immunosuppression or infection prophylaxis.
3	Possible	The adverse event may be related to allogeneic islets; the islet transplant procedure; the secondary investigational agent (DSG); immunosuppression or infection prophylaxis.
4	Probable	The adverse event is likely related to allogeneic islets; the islet transplant procedure; the secondary investigational agent (DSG); immunosuppression or infection prophylaxis.
5	Definite	The adverse event is clearly related to allogeneic islets; the islet transplant procedure; the secondary investigational agent (DSG); immunosuppression or infection prophylaxis.

The collecting and recording procedures for AEs are described in detail in Section 8.2 of CIT-03 protocol.

6.2 Analysis of Secondary Safety Endpoints

The safety secondary endpoints in SAP Section 1.2.4.2 study 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-IIP-1: Bleeding (>2 g/dL decrease in hemoglobin concentration)
2. AE-IIP-2: Segmental portal vein thrombosis
3. AE-IIP-3: Biliary puncture
4. AE-IIP-4: Wound complication (infection or subsequent hernia)
5. AE-IIP-5: Increased transaminase levels (>5 times ULN)

The targeted AEs related to the immunosuppression and infection prophylaxis therapy include:

1. AE-IP-1: Allergy
2. AE-IP-2: Reduction in GFR
3. AE-IP-3: Increase in urinary albumin excretion
4. AE-IP-4: Addition or intensification of anti-hypertensive therapy
5. AE-IP-5: Addition or intensification of anti-hyperlipidemic therapy
6. AE-IP-6: Oral ulcers
7. AE-IP-7: Lower extremity edema
8. AE-IP-8: Gastrointestinal toxicity
9. AE-IP-9: Neutropenia, Anemia, or Thrombocytopenia
10. AE-IP-10: Viral, Bacterial, or Fungal Infections
11. AE-IP-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
- The incidence of worsening retinopathy as assessed by change in retinal photography

6.2.1 Safety Analyses at 75 ± 5 Days Following Each Transplant

At 75±5 days following each islet transplant (up to three transplants per subject are possible), 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. The results will be summarized in the table provided in SAP Appendix 6. Moreover, we will also report AEs categorized by attribution that is, AEs related to the islet transplant procedure or to immunosuppression; the report format is shown in SAP Appendix 7.

For second and third islet transplants, immunosuppression is modified by using Daclizumab (Zenapax®) instead of Thymoglobulin® for induction. For subjects who receive more than one islet transplant, we will compare the incidence rate at 75±5 days following the initial and final islet transplant for all AEs related to the islet transplant procedure and to immunosuppression one at a time using the McNemar's matched-pair test. The claim of a difference in incidence rate will be made if the p-value is less than 0.05. If the incidence is rare in certain severity categories for an AE, we will compare the incidence rate regardless the severity to accommodate the validity of the test.

The incidence rate of immune sensitization, defined as detection of anti-HLA antibodies at 75 ± 5 days following the initial and final islet transplant, (if applicable) will be reported. The exact two-sided 95% confidence interval of the incidence rate will also be reported.

These same analyses will be performed again at 365 ± 14 days following each transplant.

6.2.2 Safety Analyses at 365 ± 14 Days Following Each Transplant

The analyses described in the previous section will be performed again at 365 ± 14 days following each transplant.

6.2.3 Safety Analyses at 365 ± 14 Days Following the First Transplant

The incidence of worsening retinopathy will be analyzed at 365 ± 14 days following the first transplant as described in SAP section 6.2.1.

6.2.4 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 λ. 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. The results will be summarized in the table provided in SAP Appendix 8. Moreover, we will also list all the individuals who have ever had an incident of any of the AEs listed in Appendix 9 since their randomization.

7 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.

7.1 Interim Analyses for Early Stopping

The following provides information on a potential strategy for stopping when there is evidence that the insulin independence rate is too low. This strategy is based on ruling out rates below which clinicians would recommend that treatment with DSG was likely to achieve an unacceptably low rate of insulin independence at 75 days. The following table describes boundaries for selected minimal rates of insulin independence. These recommendations are based on calculate 95% exact binomial confidence intervals for the true rate and recommending stopping if the upper bound of the computed confidence interval does not contain the minimal rate.

For example, if 50% is the targeted minimal rate, then the rule would recommend stopping enrollment if any of the following occurred: 0 successes in the first 5 subjects entered, no more than 1 success in the first 7 subjects, no more than 2 successes in the first 9 subjects, no more than 3 success in the first 11 subjects, no more than 4 success in the first 16 subjects, or no more than 5 successes in the first 19 subjects. Note that these confidence intervals were not adjusted for the multiplicity of the calculated confidence intervals.

Table 4: Stopping rules for selected minimal rates of insulin independence

	Minimal Rate of Insulin Independence			
Level	50%	40%	30%	20%
1	0 in first 5	0 in first 6	0 in first 10	0 in first 14
2	1 in first 7	1 in first 10	1 in first 14	
3	2 in first 9	2 in first 14	2 in first 19	
4	3 in first 11	3 in first 17		
5	4 in first 16			
6	5 in first 19			

The investigators have suggested that there would be a concern if the rate of insulin independence were less than 30%. We plan to use the rule that uses 30% as the targeted minimal rate. The rule would recommend stopping enrollment if any of the following occurred: 0 successes in the first 10 subjects, no more than 1 success in the first 14 subjects or no more than 2 successes in the first 19 subjects.

8 References

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4. Goodman L. On Simultaneous Confidence Intervals for Multinomial Proportions. *Technometrics* Vol. 7, No. 2: 1965.

5. Kwong K-S. On Sample Size and Quick Simultaneous Confidence Interval Estimation for Multinomial Proportions. *Computational and Graphical Statistics* Vol. 7, No. 2: 1998.

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Appendix 1: Protocol Deviations

	Number of Protocol Deviations					
Centers	**PD1**	**PD2**	**PD3**	**PD4**	**PD5**	**Total**
University of Minnesota						
University of California, San Francisco						
Northwestern University						

Appendix 2: Descriptive Statistics of Baseline Data

	Center						
	Univ of Alberta	**Univ of Miami**	**Univ of Minnesota**	**Univ Of Pennsylvania**	**Emory Univ**	**Northwestern Univ**	**Total**
Demographic Variables							
n mean s.d. median range							
Sex: n (%) 1. male 2. female 3. total							
Race: n (%) 1. White 2. Black 3. Hispanic 4. Asian 5. Other							
Disease Factors							
Insulin Req. n mean s.d. median range							
HbA1c n mean s.d. median range							
# of Severe Hypo. n mean s.d. median range							
MAGE n mean s.d. median range							
LI n mean							

s.d. median range							
Clarke Score n mean s.d. median range							
HYPO score n mean s.d. median range							
β-score n mean s.d. median range							
C-peptide glucose Creatinine Ratio n mean s.d. median range							
Physical Conditions							
Body Weight n mean s.d. median range							
Height n mean s.d. median range							
QOL 1. SPC n mean s.d. median range 2. SMC n mean s.d. median range							

3. OHS n mean s.d. median range 4. DDS n mean s.d. median range 5. HFS n mean s.d. median range							

Appendix 3: Summary of Medical History

	Center		
	Minnesota	***UCSF***	***Northwestern***
Body System A Symptom 1 N (%) Symptom 2 N (%) ⋮			
Body System B Symptom 1 N (%) Symptom 2 N (%) ⋮			
⋮			

Appendix 4: Summary Table for Medication Use

	Withdrew		**Insulin Independence at 75 ± 5 days**	
	Yes N (%)	No N (%)	Yes N (%)	No N (%)
University of Minnesota				
Medication 1				
Medication 2				
Medication 3				
⋮				
UCSF				
Medication 1				
Medication 2				
Medication 3				
⋮				
Northwestern University				
Medication 1				
Medication 2				
Medication 3				
⋮				
Total				
Medication 1				
Medication 2				
Medication 3				
⋮				

Appendix 5: Summary Table for Study Completion

	University of Minnesota			UCSF			Northwestern University		
	Age	**Sex**	**Race**	**Age**	**Sex**	**Race**	**Age**	**Sex**	**Race**
Completion of Study N (%)									
Lost to follow-up N (%)									
Time to Lost to Follow-up Mean S.D Max Min									
Reasons for Loss to Follow-up 1. AE1: N (%) 2. AE2: N (%) 3. AE3: N (%) ⋮									

Appendix 6: Summary Table of Adverse Events Related to Islet Transplant and Immunosuppression Therapy

	Degrees of Event Severity					
Events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
AE related to the islet transplantation (islet product or islet transplant procedure):						
AE-IIP-1 Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IIP-2** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IIP-3** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IIP-4** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IIP-5** Number (%) Resolved? Number (%) mean s.d. median min-max						
AE related to the immunosuppresion and/or infection prophylaxis:						
AE-IP-1 Number (%) Resolved? Number (%) mean						

s.d. median min-max **AE-IP-2** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-3** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-4** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-5** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-6** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-7** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-8** Number (%) Resolved?						

Number (%) mean s.d. median min-max **AE-IP-9** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-10** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-11** Number (%) Resolved? Number (%) mean s.d. median min-max						
AE related to DSG						
AE-IP-1 Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-2** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-3** Number (%) Resolved? Number (%) mean s.d. median min-max						

AE-IP-4 Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-5** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-6** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-7** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-8** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-9** Number (%) Resolved? Number (%) mean s.d. median min-max **AE-IP-10** Number (%) Resolved? Number (%) mean s.d.						

median min-max **AE-IP-11** Number (%) Resolved? Number (%) mean s.d. median min-max						

Appendix 7: Number of Adverse Events with Patient Identification Grouped by Severity and Attribution

	Degrees of Event Severity					
Events	**Grade 1**	**Grade 2**	**Grade 3**	**Grade 4**	**Grade 5**	**Total**
AE related to the islet transplantation (islet product or islet transplant procedure):						
AE-IIP-1 incidences	6 (12.5%) C11+ C12 C22 C34 C63 C66					
AE-IIP-2 incidences						
AE-IIP-3 incidences						
AE-IIP-4 incidences						
AE-IIP-5 incidences						
AE related to the immunosuppression and/or infection prophylaxis:						
AE-IP-1 incidences						
AE-IP-2 incidences						
AE-IP-3 incidences						
AE-IP-4 incidences						
AE-IP-5 incidences						
AE-IP-6						

incidences **AE-IP-7** incidences **AE-IP-8** incidences **AE-IP-9** incidences **AE-IP-10** incidences **AE-IP-11** incidences						
AE related to DSG						
AE-IP-1 incidences **AE-IP-2** incidences **AE-IP-3** incidences **AE-IP-4** incidences **AE-IP-5** incidences **AE-IP-6** incidences **AE-IP-7** incidences **AE-IP-8** incidences **AE-IP-9** incidences **AE-IP-10**						

incidences **AE-IP-11** incidences						

+ : Patient's identification, for example C11 stands for the incidence occurring on patient number 1 at Center #1

Appendix 8: Table for Adverse Events at Month since Randomization

	AE related to the islet transplantation (islet product or islet transplant procedure), the secondary investigation agent (DSG) or immunosuppression and/or infection prophylaxis			AE **not** related to the islet transplantation (islet product or islet transplant procedure), the secondary investigation agent (DSG) or immunosuppression and/or infection prophylaxis		
All Adverse Events	**# of incidences**	**The incidence rate per 100 person-days (λ)**	**The 95 % confidence interval of λ based on MLE theory**	**# of incidences**	**The incidence rate per 100 person-days (λ)**	**The 95 % confidence interval of λ based on MLE theory**
Body System A **1. Grade 5** Event 1 Event 2 ⋮ **2. Grade 4** Event 1 Event 2 ⋮ **3. Grade 3** Event 1 Event 2 ⋮ **4. Grade 2** Event 1 Event 2 ⋮ **5. Grade 1** Event 1 Event 2 ⋮						
Body System B **1. Grade 5** Event 1 Event 2 ⋮ **2. Grade 4** Event 1 Event 2 ⋮ **3. Grade 3** Event 1 Event 2						

⋮ **4. Grade 2** Event 1 Event 2 ⋮ **5. Grade 1** Event 1 Event 2 ⋮						
Body System C **1. Grade 5** Event 1 Event 2 ⋮ **2. Grade 4** Event 1 Event 2 ⋮ **3. Grade 3** Event 1 Event 2 ⋮ **4. Grade 2** Event 1 Event 2 ⋮ **5. Grade 1** Event 1 Event 2 ⋮						
⋮						

Appendix 9: Table for Identification of Adverse Events at Month since Randomization

	AE related to the islet transplantation (islet product or islet transplant procedure), the secondary investigation agent (DSG) or immunosuppression and/or infection prophylaxis		AE **not** related to the islet transplantation (islet product or islet transplant procedure), the secondary investigation agent (DSG) or immunosuppression and/or infection prophylaxis	
All Adverse Events	**Identification of incidences**	**Number and percentage of patients who have had the incidence**	**Identification of incidences**	**Number and percentage of patients who have had the incidence**
Body System A **1. Grade 5** Event 1 Event 2 ⋮ **2. Grade 4** Event 1 Event 2 ⋮ **3. Grade 3** Event 1 Event 2 ⋮ **4. Grade 2** Event 1 Event 2 ⋮ **5. Grade 1** Event 1 Event 2 ⋮	C111 C112 C113* C221 C231 C232 C331 C421 C461	6 (12.5%)		
Body System B **1. Grade 5** Event 1 Event 2 ⋮ **2. Grade 4**				

Event 1 Event 2 ⋮ **3. Grade 3** Event 1 Event 2 ⋮ **4. Grade 2** Event 1 Event 2 ⋮ **5. Grade 1** Event 1 Event 2 ⋮				
Body System C **1. Grade 5** Event 1 Event 2 ⋮ **2. Grade 4** Event 1 Event 2 ⋮ **3. Grade 3** Event 1 Event 2 ⋮ **4. Grade 2** Event 1 Event 2 ⋮ **5. Grade 3** Event 1 Event 2 ⋮				
⋮				