Fifth Annual Report

Prepared by:

CITR Coordinating Center
The EMMES Corporation
Rockville, MD

Sponsored by:
National Institute of Diabetes & Digestive & Kidney Diseases
National Institutes of Health
Bethesda, MD

September 15, 2008

NOTICE:

The CITR Annual Report details data received as of April 1, 2008 for all islet transplant recipients registered by December 31, 2007.

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

September 15, 2008

M E M O R A N D U M

TO: CITR Collaborators, Islet Transplant Centers, Diabetes Research Community, and Interested Public

FROM: Michael Appel, PhD
Director, Islet Biology and Transplantation Research Program
NIDDK

Bernhard Hering, MD
CITR Medical Director, SAC Chair

SUBJECT: 2008 CITR Annual Report

Funded by the National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) with supplemental funding from the Juvenile Diabetes Research Foundation (JDRF), the Collaborative Islet Transplant Registry (CITR) serves the mission to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America, Europe and Australia.

We are pleased to present this fifth Annual Report (2008) including data from the great majority of islet transplant programs in North America active since 1999 and two European programs that joined CITR in 2006 and 2007. We also are privileged to have the collaboration of the United Network for Organ Sharing and the Islet Cell Resource Centers, with whom we have ongoing data sharing agreements. The US Food and Drug Administration and the National Institute of Allergy and Infectious Disease (NIAID) lend continuing support and advice.

The report has been prepared by staff of The EMMES Corporation under the leadership of the CITR Publications and Presentations Committee chaired by Dr. Rodolfo Alejandro, and CITR Coordinating Center Principal Investigator, Ms. Franca Benedicty Barton.

We thank everyone who has contributed data and collaborated in the development of the CITR Registry and the production of this Annual Report, including the islet recipients who voluntarily consent to the submission of their information. We look forward to their continued participation, along with that of all centers and organizations active in the islet transplant community of North America, Europe and Australia.

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Scientific Summary

BACKGROUND AND PURPOSE

Islets are clusters of insulin-producing cells located in the pancreas. In patients with Type 1 diabetes mellitus (T1DM), all islets are destroyed by an autoimmune attack and patients need to inject insulin every day to stay alive. The total prevalence of diagnosed insulin dependent diabetes mellitus (IDDM) in the United States (US) (all ages, 2005) is approximately 1,400,000-2,800,000 people (http://diabetes.niddk.nih.gov/dm/pubs/statistics). In patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. T1DM patients with severe hypoglycemia may be eligible for an alternative procedure using insulin-producing cells (islets of Langerhans) extracted from a deceased donor pancreas which, in the US, is an experimental procedure. A small subset of these allogenic islet recipients have previously received a kidney transplant for end-stage renal disease and were already receiving long-term immunosuppression therapy at the time of their islet transplant. Yet another group of islet recipients are those whose own islets are reinfused after removal of their pancreas due to a medical indication. These autologous recipients are summarized in a supplemental report. For all three types of recipients, islets are implanted typically via the portal vein in the liver, where the islets produce insulin as needed by the recipient.

To accumulate and compile the data from all completed and ongoing studies between 1999 and the present, the National Institute of Diabetes & Digestive & Kidney Diseases funded the Collaborative Islet Transplant Registry (CITR) for data collection from North American programs. The Juvenile Diabetes Research Foundation (JDRF) has granted additional funding to include the participation of selected European and Australian centers. The mission of CITR is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants. Each year the Registry provides a comprehensive overview of the cumulative data to date since 1999. This fifth report, published in 2008, summarizes information on patients who received one or more islet cell transplants between 1999 and 2007 inclusive. CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

In the United States, islet transplantation is an experimental procedure that is regulated by the Food and Drug Administration (FDA). Thirty-one medical institutions in the US and Canada are currently or were previously active in islet transplantation since 1999.

Detailed data are included from two JDRF-sponsored European centers whose participation began in 2006 and 2007. For most of the analyses, these European data are pooled with the US and Canadian data for the basic descriptions of recipient characteristics, donor, organ and islet characteristics and safety and efficacy outcomes. Descriptions of funding sources and North American transplant activity exclude European data. No center-specific data are presented in any CITR reports.

Individual transplant units initiate their own independent research protocols to advance the field of islet transplantation. It is the goal of these studies to help determine if improvement in the glycemic control and/or reversal of insulin dependency can be achieved, to assess the long-term function of successful islet transplants and risks of associated immunosuppressive medication, and if the natural history of diabetes complications is altered. Each center publishes the results of their studies and

provides information regarding their open and recruiting protocols through their own means and/or at the National Library of Medicine's developed website www.clinicaltrials.gov.

PATIENTS AND METHODS

Patients typically eligible for islet transplantation are those who have T1DM for more than five years, are between 18 and 65 years of age, and have very poor diabetes control including severe hypoglycemia. Poor diabetes control can manifest as frequent episodes of critically low blood sugar levels (severe hypoglycemic episodes and insulin reactions) requiring the assistance of another person, wide swings of blood sugar levels (blood glucose liability), or consistently high HbA_{1c} levels(>8%).

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators for scientific evaluations and for reports to the multiple agencies and entities required by US Food and Drug Administration (FDA) regulated trials or according to the requirements of the respective nation. In US centers, demographic information is collected in CITR only once, at the time of the islet transplant recipient's registration. For each islet/beta cell infusion, information is collected on the pancreas donor(s), islet processing and testing of all pancreata used for the infusion procedure, and recipient status from screening through the early and long-term transplant period.

Follow-up data are abstracted at Day 30, Month 6 and Month 12 post first infusion procedure for four main indicators (severe hypoglycemic episodes, hemoglobin A1C, fasting blood glucose and C-peptide), and daily for insulin status. Detailed follow-up data are abstracted at Month 6, Month 12, and annually post infusion. At each new infusion, a new follow-up schedule is established to abstract data at six-month and annual anniversaries of the last infusion. There is also data abstraction on event-driven data including reportable adverse events, recipient's vital status, non-islet transplant and follow-up, islet graft dysfunction, loss to follow-up, and transfer of the recipient to another islet transplant center. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center (citr@emmes.com), or viewed at the CITR Website (www.citregistry.org).

CITR utilizes the Coordinating Center's (The EMMES Corporation, Rockville, MD) web-based data entry and management systems to capture data on recipients and donors. Donor and islet processing data are also obtained through data sharing agreements with the United Network for Organ Sharing (UNOS) and the Administrative and Bioinformatics Coordinating Center (ABCC) of the Islet Cell Resource Centers (ICR), respectively. Pooled together from all protocols, these data characterize and follow general trends in safety and efficacy for recipients of islet transplantation. Outcomes can be related to recipient characteristics, donor information, islet procurement, processing and product characteristics, transplant techniques, and treatment protocols.

All grade 3, 4 and 5 adverse events, according to the Terminology Criteria for Adverse Events (TCAE) of the Clinical Islet Transplantation Consortium (CIT), and all serious adverse events (regardless of grade) are reported to CITR. Respective CITR Principal Investigators currently determine the relationship of the adverse event to the immunosuppression therapy and to the islet infusion procedure at the time adverse event forms are completed.

The Registry data exists because of the voluntary participation of the transplanting centers, with written informed consent by the islet recipients. While the Registry likely represents the most comprehensive collection of the human islet transplantation experience since 1999, there may exist uncontrollable biases and imbalances including selective reporting and differences in clinical care and decision-making. Even with the diligent efforts of the participating centers, the total number of cases

and outcomes remains relatively small. Hence, the aggregate results should be interpreted cautiously.

The data are continuously reviewed by the CITR Coordinating Center for quality assurance, errors and data outliers. For this report, data queries were identified and the database updated by the islet transplant centers. The database was closed for analysis on April 1, 2008 for data on recipients that were registered in CITR as of December 31, 2007.

The 2008 CITR Annual Report presents descriptive summary information on all islet allograft recipients, procedures, donors and islet preparations included in the database as of the cut-off date, either aggregately or by islet-alone (IA) or islet-after-kidney (IAK) recipients. Descriptive statistics include distribution summary statistics such as mean and standard deviation or standard error, median and interquartile range (IQR), or distributions/bar charts for categorical variables. Box and whisker plots show the mean as a star, median as a central line, the IQR as the box, and $\pm$1.5xIQR as the whiskers; outliers beyond the whiskers are plotted as individual points. Extreme outliers may be excluded from the graph to avoid overall distortion but are footnoted.

Primary outcomes are: achievement of insulin independence; maintenance/loss of insulin independence; HbA_{1c} level; severe hypoglycemia; hypoglycemia status; C-peptide level; islet graft dysfunction or loss; and combinations of these. These are analyzed variously as time-to-event (Kaplan-Meier) estimates or frequency distributions of categorical status such as insulin independent, insulin dependent with detectable C-peptide or absence of graft function (three mutually exclusive and exhaustive states). Events are analyzed by post first infusion censored at re-infusion, complete islet failure or last follow-up (whichever occurs first), and also post last infusion up to last follow-up. Increasing levels of missing data accrue with longer follow-up times. A small number of patients have no follow-up to determine their status regarding these events. They are accounted for but may be excluded from selected analyses.

Analysis of the effect of various factors on the primary outcomes has begun and will continue as the Registry grows and the data are more completely reported. Explanatory factors include pre-infusion recipient, donor, procurement and final product characteristics, as well as time-dependent factors such as re-infusion and the occurrence of other events and subsequent interventions, which present competing risks. Methods to handle the issues of competing risks are being applied to the analyses and include censoring for one event—such as achievement of insulin independence—based on the timing of another event such as complete graft loss. Analyses are presented for events occurring after single infusion up to re-infusion, current follow-up or complete graft loss, contrasted to analyses conducted on outcomes after the recipient's last infusion regardless of the total number of infusions the recipient has received.

Secondary endpoints include: measures of primary complications of diabetes such as fasting and stress glucose and C-peptide levels, and HbA_{1c} levels; measures of metabolic function such as the mixed meal test, oral glucose tolerance test, mean amplitude of glycemic excursion (MAGE), and others administered according to local protocols; measures of secondary complications of diabetes including nephropathy, neuropathy, and retinopathy among others; measures of kidney and liver function, lipid and blood pressure stasis and concomitant medications; and adverse events reporting.

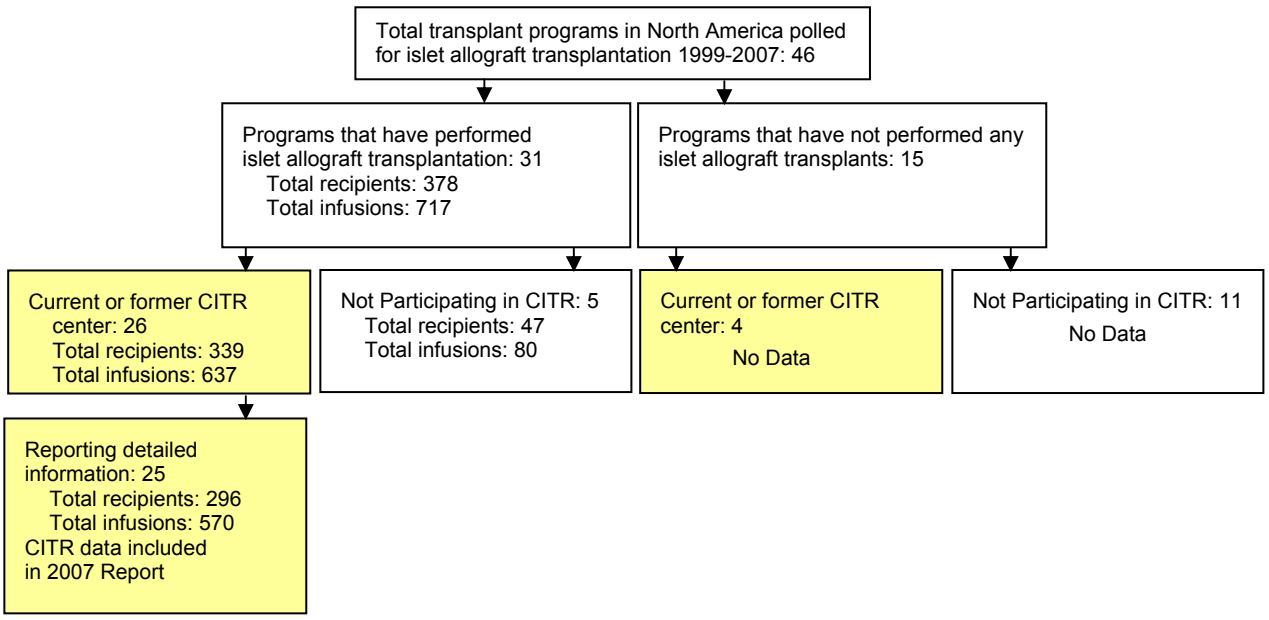
RESULTS

Islet Allograft Transplantation Activity 1999-2007. All 46 North American medical institutions with an identified islet transplant program between 1999 and 2007 responded to a general questionnaire. Thirty-one of the 46 reported performing at least one islet allograft transplant. Exhibit A displays the

activity of North American islet transplant centers for 1999-2007, including the total number of recipients and infusions, and according to the centers' participation in CITR.

Exhibit A

North American Islet Allograft Transplant Centers, Recipients and Infusions
Total Performed and Total Reported to CITR 1999-2007



Exhibits B1 and B2 display the data collected from the 31 active islet transplant programs in North America from 1999 through 2007. To the knowledge of the Registry, this table is inclusive of all human-to-human islet transplant programs in North America.

Exhibit B-1

Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
All North American Islet Transplant Centers 1999-2007

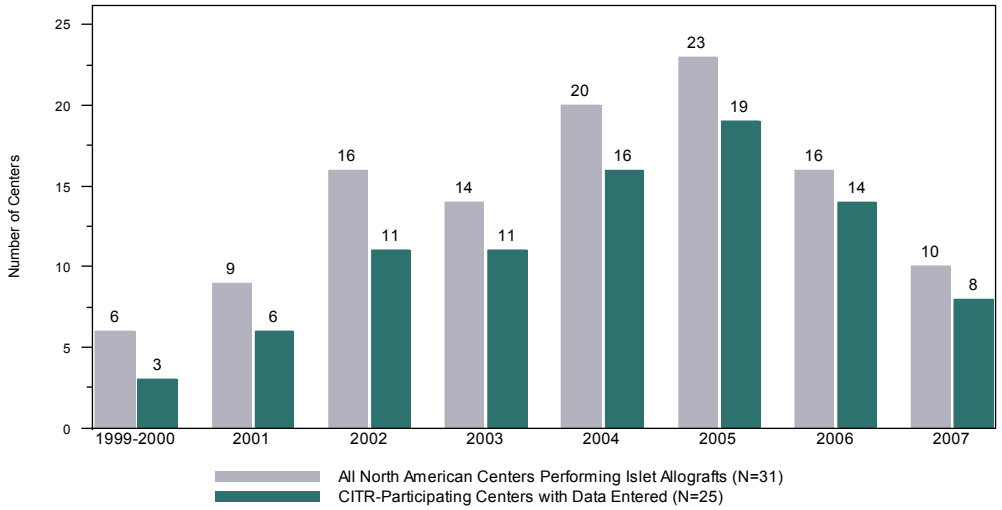
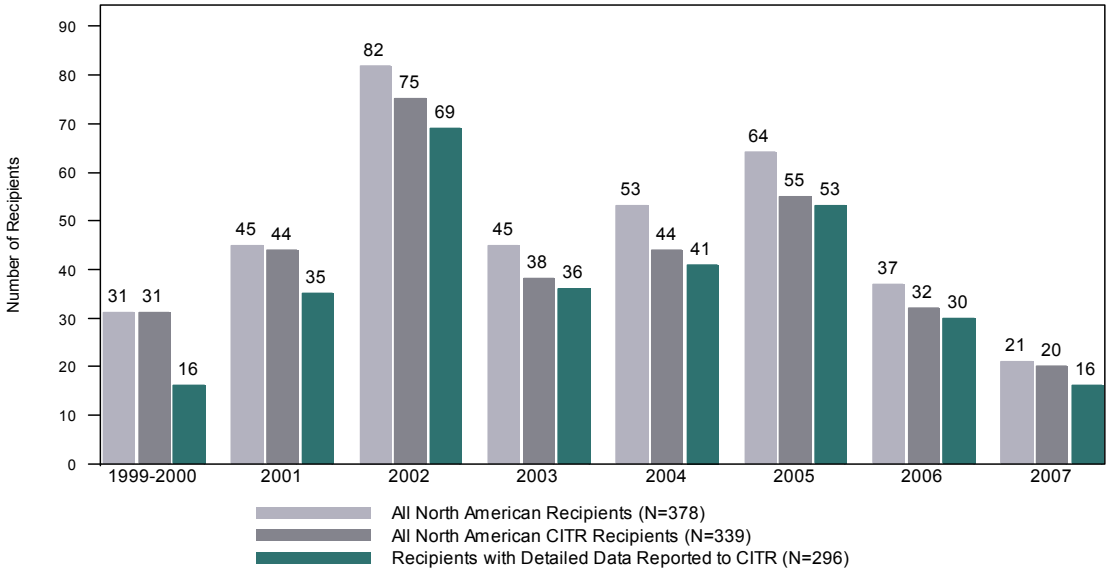


Exhibit B-2

Total Number of Islet Transplant Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion
All North American Islet Transplant Centers 1999-2007



Two European centers joined the Registry in 2006 and 2007 and contributed data for this report. Pooling the reported data from the North American and European centers, the Registry comprises

325 allograft recipients with detailed data reported as of the data cut-off, and 649 infusion procedures derived from a total of 712 donors. Eighty-four of the recipients (26%) received a single islet infusion, 164 (50%) received two, 71 (22%) received three, and six (2%) received a total of four islet infusions. On average, recipients received a total of 837,308 (SD 377,481) total islet equivalents (IEQs), or 12,942 IEQs/kilogram body weight (SD 5,974).

Of the total 325 North American and European recipients included in this report, 279 (86%) were recipients without a previous kidney transplant who received one or more islet-alone infusions (IA), while 46 recipients (14%) had previously received a kidney transplant (IAK).

Recipient Characteristics. The mean age of islet allograft transplant recipients in CITR is 44 Years (range 19 to 67) and the mean duration of diabetes is 29 Years (range 2 to 54). The mean weight of the participant is 66 kg (range 35 to 98) and the mean body mass index (BMI) is 23.6 kg/m^2 (range 15 to 32). About 65% of the participants are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 36% of the 325 allograft islet transplant participants were on an insulin pump prior to their first infusion and 97% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, 92% of the participants had a basal C-peptide <0.5 ng/mL and 83% had a HbA_{1c} >6.5%. The mean daily insulin requirement of participants prior to their first infusion procedure was 37 units (SD 13.5) and the subset on intensive insulin therapy had received intensive therapy for a mean of 16.3 Years (SD 14.0). The mean fasting blood glucose for all participants was 174 mg/dL (SD 93), mean HbA_{1c} was 7.7% (SD 1.3), and the mean basal C-peptide was 0.1 ng/mL (SD 0.2).

Compared to recipients of a single infusion, recipients of three infusions were younger, on the waitlist for less time, had a higher HbA_{1c} and had a lower PRA percentage.

Donor Information. There were no living donors. The mean age of donors was 43 Years (range 1 to 75) and the mean body mass index was 29 kg/m^2 (range 3 to 69). The mean time from cross clamp to pancreas recovery was 39 minutes (SD 20) while the mean cold ischemia time was 7.3 hours (range 1 to 27). Approximately 59% of the donors were male, 11% were Hispanic and 89% were white. Fifty-five percent of the donors had a cerebrovascular/stroke as cause of death while 31% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 20% had a history of alcohol dependency.

Thirty-three percent of the donors received a transfusion during hospitalization, while only 6% received a transfusion intraoperatively. Sixty percent of the donors received steroids, 39% of the donors received insulin and 96% received at least one vasopressor during the donor's terminal hospitalization. There was a report of one donor testing positive for anti-HBC and this donor was used for a hepatitis B immunized recipient. Another donor tested positive for RPR-VDRL. The mean serum creatinine of the donors was 1.2 mg/dL.

Pancreas Procurement. In 64% of the pancreas procurement procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team, while 90% of the processing procedures took place at the same institution as the islet transplant center. The median duration of cold ischemia was 7 hours (range 1 to 27). UW, Two Layer and UW followed by Two Layer were the most common methods used for pancreas preservation.

Liberase HI was the collagenase type used during most islet processing (86%) followed by Blendzyme (7%) and NB1 (6%). All of the pancreata processed used a density gradient for islet

purification. When cultured, defined as six or more hours in a specially prepared nutrient medium, the mean culture time was 26 hours (range 6 to 96). Of the 712 islet preparations reported to CITR, thirteen final preparations showed a positive aerobic culture, six showed a positive anaerobic culture, five showed a positive fungal culture, and one tested positive for mycoplasma.

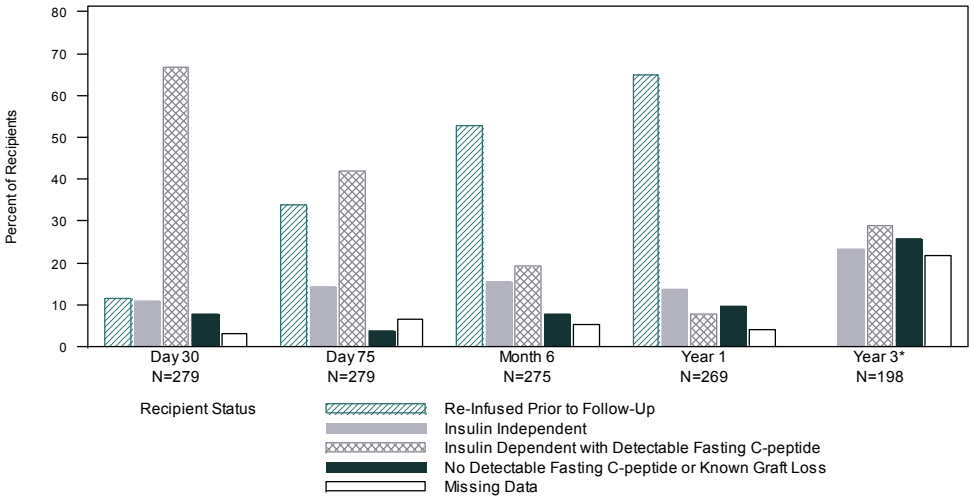
Immunosuppression Therapy. The majority (59%) of the islet transplant alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus only immunosuppression regimen. Daclizumab was used for induction alone in 65% of IA first infusions, and in combination with other antibodies in another 12% of first infusions. Anti-thymocyte globulin was given alone or in combination in 12% of first infusions.

Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 11% by Day 30, 34% by Day 75, 53% by Month 6, and 65% by Year 1 (Exhibit C-1). The proportion that is insulin independent without re-infusion remains fairly constant at 10-15% throughout the first year. An additional 8-12% of all IA recipients retain detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 279 IA recipients, 71% are expected at three years post first infusion, at which time, regardless of the total number of infusions received, about 23% are insulin independent, 29% are insulin dependent with detectable C-peptide, 26% have no detectable C-peptide, and 22% have missing data (required but not yet reported).

Analyzed from last infusion (Exhibit C-2), where re-infusion is not an issue, the percentage of all IA recipients that are insulin independent declines steadily from 54% at Month 6 to 22% at Year 3. The proportion with loss of islet function (reported graft failure or no detectable C-peptide) increases steadily from 10% at Month 6 to 34% at Year 3. A stable 23-26% retains graft function with exogenous insulin over the three years; the percentage of missing data increases over time. These trends of increasing prevalence of graft loss and decreasing prevalence of insulin independence over time post last infusion prevail regardless of the total number of infusions given, although the rates differ somewhat among the three groups (data not shown).

Exhibit C-1
Prevalence of Insulin Status and Detectable Fasting C-Peptide

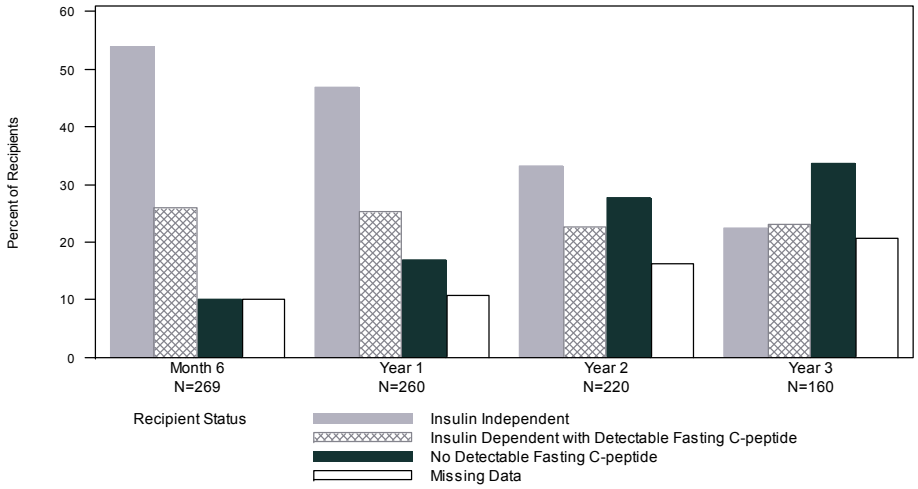
Post First Infusion
Islet Alone Recipients



*Year 3 status regardless of re-infusion

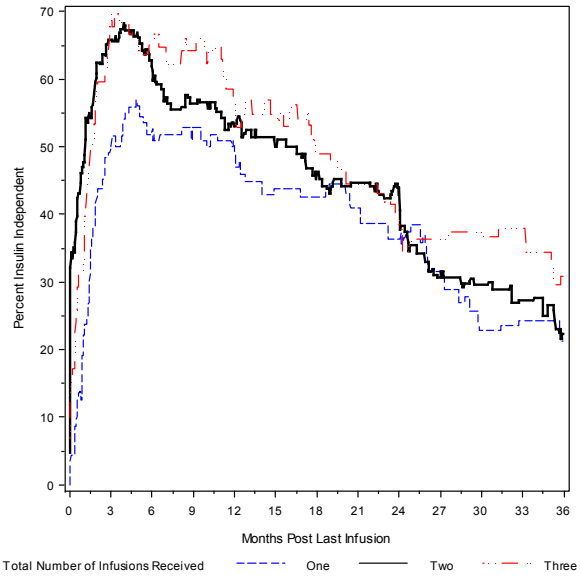
Exhibit C-2
Prevalence of Insulin Status and Detectable Fasting C-Peptide

Post Last Infusion
Islet Alone Recipients



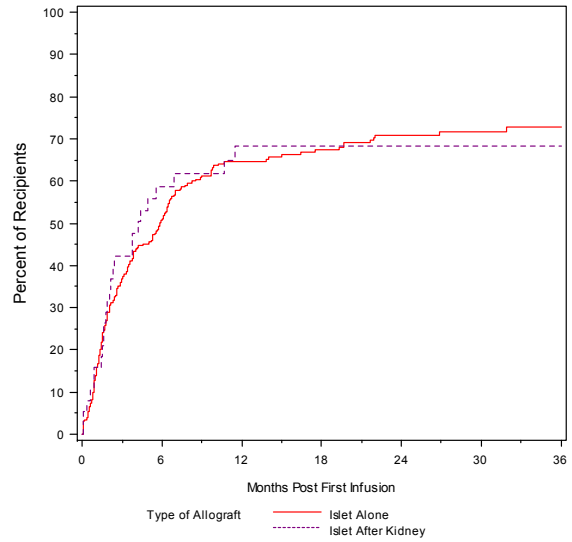
Focusing only on the insulin independence status (available from daily diaries with increasing missing data over time), the prevalence of insulin independence from last infusion declines from 65% at Month 4 to about 24% at Year 3 post last infusion (Exhibit D). Two or three infusions boost the prevalence of insulin independence in the first year to a peak of about 69%, with a subsequent decline to levels that are comparable to those with a single infusion.

Exhibit D
Prevalence of Insulin Independence Post Last Infusion
by Total Number of Infusions Received
Islet Alone Recipients



As incidence or cumulative rates of ever achieving insulin independence after islet transplantation, 64% of the IA and IAK recipients combined to achieve insulin independence in the first year post first infusion (not censored at re-infusion or graft loss), and by Year 2 this increases to 70% (Exhibit E).

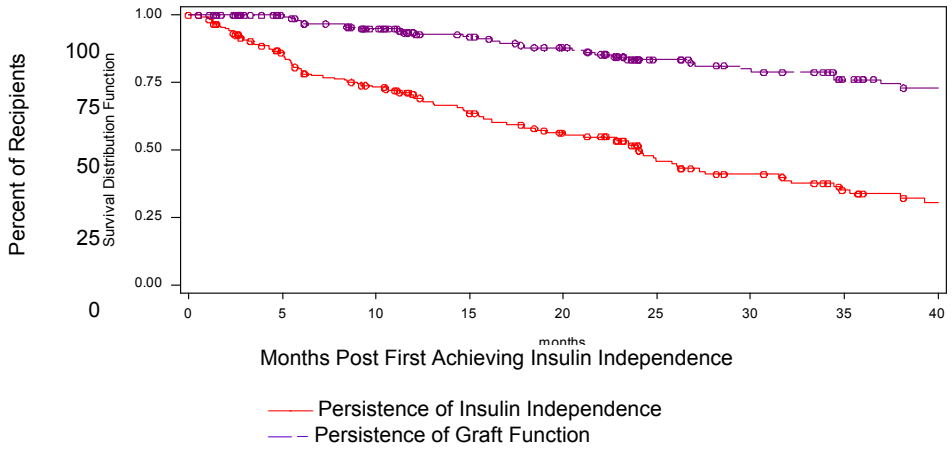
Exhibit E
Achievement of Insulin Independence After Islet Transplantation
Not Censored at Re-Infusion or Graft Loss



The proportion of recipients attaining insulin independence quickly post each re-infusion is much higher for second and third infusion than for first infusion (data not shown).

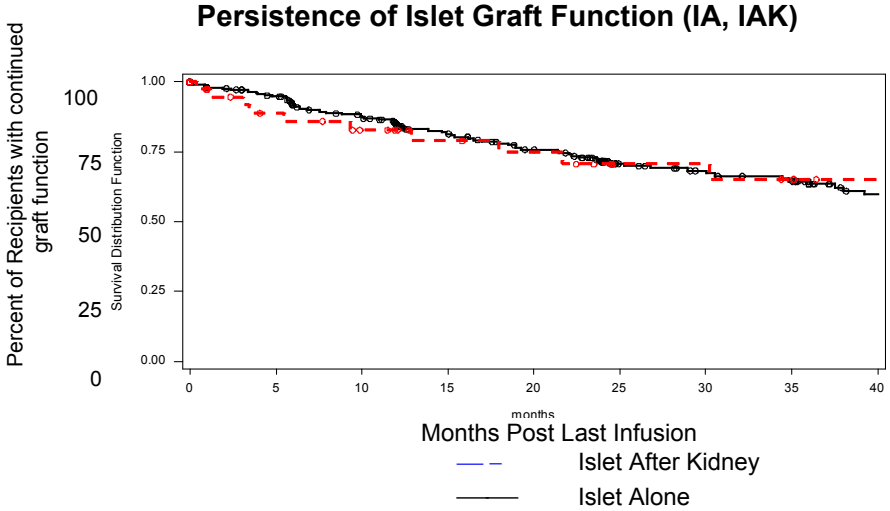
Over time there is a decrease in the sustainability of insulin independence (Exhibit F). For islet alone participants who ever achieved insulin independence, 71% have retained this status one year after achieving it and this decreases to 52% at two years.

Exhibit F
Persistence of Insulin Independence and Persistence of Graft Function
Islet Alone Recipients Achieving Insulin Independence
Not Censored at Re-Infusion



Similarly, graft function is lost over time. Viewed as Kaplan-Meier survival estimates (Exhibit G), 64% of IA recipients retained function by Year 3 post last infusion. Long-term graft function is more likely in recipients who achieve insulin independence at some time during their one to several islet infusions (data not shown).

Exhibit G
Persistence of Islet Graft Function (IA, IAK)



C-peptide levels are substantially increased by islet transplantation. The percent of IA recipients with C-peptide >0.5 ng/mL increases from 8% pre-infusion to 47% at Month 6 and 43% at Year 1 post first

infusion (censored at re-infusion, Exhibit H-1), with 32% retaining this level of function at Year 3 post last infusion (Exhibit H-2).

Exhibit H-1
C-peptide ≥ 0.5 ng/mL

Post First Infusion

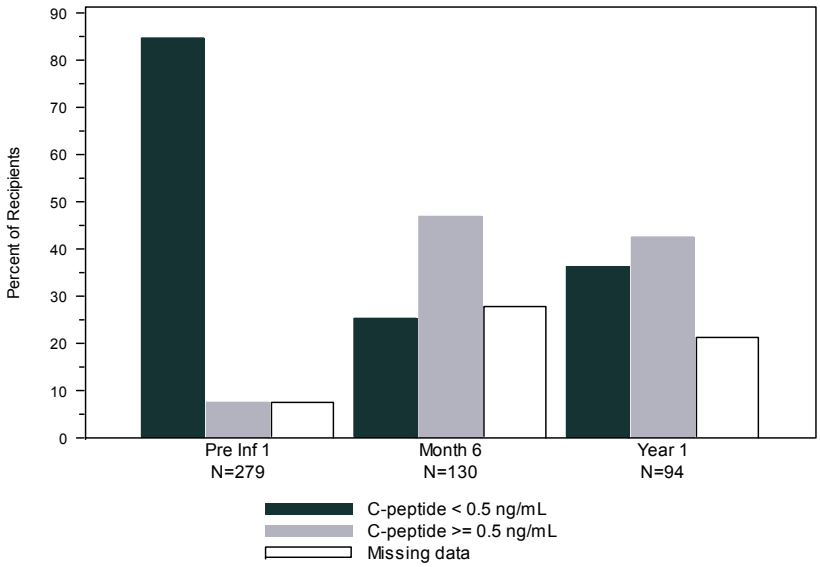
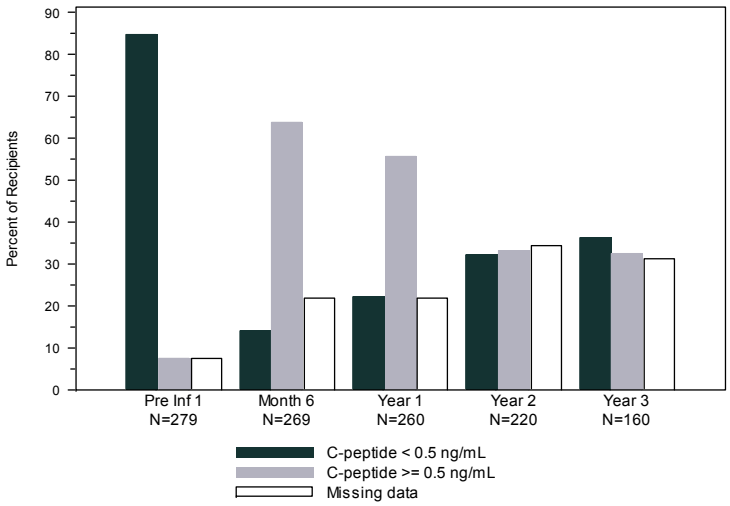


Exhibit H-2
C-peptide ≥ 0.5 ng/mL

Post Last Infusion



Severe Hypoglycemia and HbA_{1c}. The prevalence of severe hypoglycemic events decreases dramatically following islet transplantation. Islet transplants also substantially improve HbA_{1c} levels. Taken as a composite outcome (Exhibit I), the percent of IA recipients with HbA_{1c} <6.5% and absence of severe hypoglycemic episodes increases from 2% pre-infusion to 47-69% at Year 1 post last

infusion. In this range, the lower estimate represents the case where all missing data are counted as not achieving the outcome whereas the upper estimate assumes all missing data for recipients with confirmed or unknown graft function do achieve the outcome. All participants that experienced a severe hypoglycemic event during follow-up were on exogenous insulin at the time of the event. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit J).

Exhibit I
Composite Outcome (Hypoglycemia and HbA_{1c}) Post Last Infusion
Islet Alone Recipients

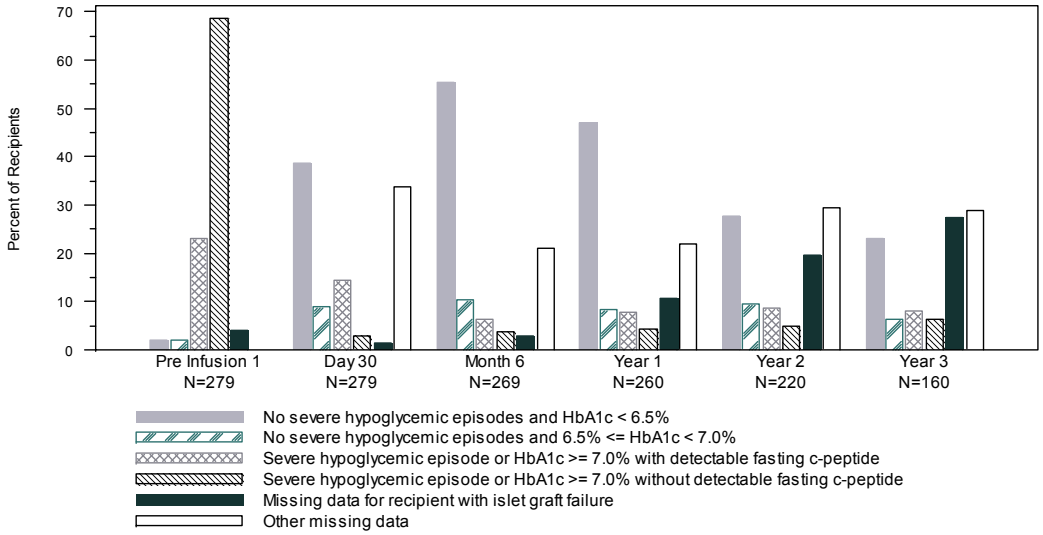
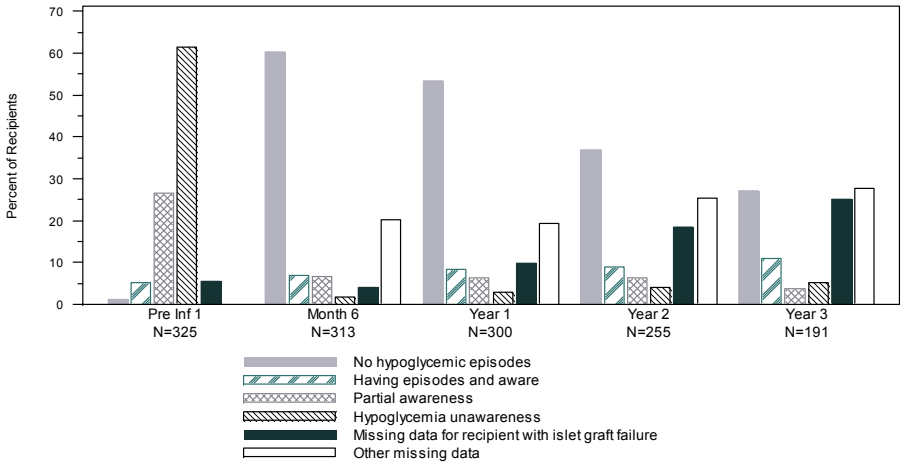


Exhibit J
Hypoglycemia Status
All Allograft Recipients

Post Last Infusion



Factors of Primary Outcomes. Multivariate Cox regression models were used to investigate the effect of pre-infusion and cumulative infusion factors on primary outcomes of islet transplantation post

last infusion. Hazard ratios (HR) less than one indicate a lower risk of the event with higher levels of the factor. Binary factors are coded 0=absent and 1=present.

The final multivariate model for insulin independence post last infusion is:

Variable	**HR**	**p**
Baseline HbA_{1c} (%)	0.878	0.0541
Donor(s) Hispanic (0=N 1=Y)	0.543	0.0444
Processing/infusion center (0-Unrelated 1-Related	4.074	0.0058
Islet size (0-small 1-large)	1.719	0.0031
Daclizumab (0-N 1-Y)	1.951	0.0183

Baseline HBA_{1c} is substantially correlated with baseline weight, baseline BMI, baseline daily insulin, fasting glucose, and number of daily injections. Any of these measures of initial control suffices to explain its influence on achieving insulin independence: the better the control, the more likely to achieve insulin independence. Larger islet size (estimated by IEQs/total particles at time of islet counting, here cumulated over all infusions) favors achieving insulin independence. Hispanicity is correlated with receiving insulin, steroids and various HLA markers: these predict less success. Processing centers related to the transplant center favor the endpoint. Daclizumab is favorable. Variables that cannot be excluded as significantly associated with this outcome are donors given steroids, HLA factors and islet beta cell counts. Again here, there is substantial imbalance between most immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of those immunosuppressant therapies in a multivariate model. Their univariate effects cannot be dismissed. Daclizumab is stable in this model and seems to be unfavorable for insulin independence.

Loss of insulin independence lacks sufficient events to permit multivariate modeling of factors.

The final model for complete islet failure post last infusion is:

Variable	**HR**	**P**
Recipient age (years)	0.523	<0.001
Processing/infusion center (0-Unrelated 1-Related)	0.329	0.003
Viability > 87% (0=N 1=Y)	0.317	0.012
Etanercept	0.352	0.016
Calcineurin inhibitor	0.120	<0.001

Older recipient age predicts lower risk of losing the graft. Related processing and infusion centers substantially reduce the chances of losing the last graft. Higher islet viability reduces risk of islet loss. Etanercept and calcineurin inhibitors seem favorable for persistent function.

There are significant correlations among the factors investigated for association with the primary outcomes that influence how the multivariate models operate.

Metabolic Measures. The choice of which metabolic tests to perform varies from center to center.

Overall, fasting plasma glucose values and HbA_{1c} substantially decrease over time, while basal C-peptide values substantially increase. This trend is seen both overall and by total number of infusions. These results are affected by the recipients' transient insulin status and whether or not they ever achieved insulin independence

Concomitant Medications. Prior to the first infusion, 41% of the recipients were on at least one anti-hypertensive medication and 32% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to 52% and 61%, respectively.

Elevated Laboratory Tests. Reports of two times or greater than the upper limit of normal (ULN) at any of the specified follow-up time points (pre-subsequent infusion, 6 months, 1 year, 2 years and 3 years post infusion) were minimal for ALT (5%), AST (4%), alkaline phosphatase (10%) and for total bilirubin (1%). There were no reports at this level for total cholesterol and 10 reports (4%) for triglycerides. There were 46 reports (16%), of a participant with an increase in their serum creatinine of greater than 0.5 mg/dL above their baseline level. Actual incidence of elevated labs might be higher if CITR reported time points were more frequent.

Adverse Events. Sixty-four percent of the islet alone recipients experienced at least one adverse event in Year 1 post first infusion, while 46% experienced one or more serious adverse events in this same period. Of the 509 adverse events reported in Year 1 post first infusion for islet alone recipients, 35% were related to the immunosuppression therapy and 33% were related to the infusion procedure. Of the 252 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 28% were related to the immunosuppression therapy and 41% were related to the islet infusion procedure. Overall, a total of 440 serious adverse events were reported to the Registry as of datafile closure, with 37% of them classified as life threatening and 51% requiring an inpatient hospitalization. Sixty-five percent (286 of 440) of serious adverse events occurred in the first year following the participants' first infusion procedure. Over 27% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 26% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator. Approximately 87% of the serious adverse events resolved with no residual effects. Most of the reported serious adverse events were categorized as investigations (18%), gastrointestinal disorders (18%) and blood and lymphatic system disorders (14%) as classified by the MedDRA classifications system.

The most common serious adverse events within the first year following an islet allograft infusion are: elevated liver function tests (9% of all allograft recipients) and neutropenia (9%), followed by procedural hemorrhage (6%), abdominal pain (4%), and pneumonia (3%). Anemia, diarrhea, hypoglycemia, portal vein thrombosis, vomiting, cholecytitis, and lymphopenia occur less frequently (2% each).

Neoplasms have been diagnosed in 14 allograft recipients over the reported period of follow-up (1999-2007). None of the neoplasms were reported by the investigator as related to the islet infusion procedure. Four were reported to be related to the immune suppression medication (basal cell carcinoma, squamous cell carcinoma, ovarian cysts and papillary thyroid cancer). The most frequent type of neoplasm was squamous cell carcinoma (N=6). Ten recipients continued their islet transplant immunosupression regimen, two withdrew voluntarily, and two have missing follow-up.

Reported Deaths. There have been seven reports of death to the Registry for islet allograft recipients: a viral meningitis attributed death possibly related to the immunosuppressant therapy occurring more than three years following the person's second islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post the person's third infusion, a stroke more than two years post the person's second infusion, another stroke more than three years post the person's only infusion, and three deaths due to unknown causes.

CONCLUSIONS

The number of centers performing clinical islet cell allograft transplants and the total number of islet cell transplants have steadily declined since 2005. However, with the anticipated start of the new Clinical Islet Transplantation (CIT) Consortium protocols in 2008, the number of new islet cell recipients is expected to rise. Islet transplantation continues to show short-term benefits of insulin independence, normal or near normal HbA_{1c} levels, sustained marked decrease in severe hypoglycemic episodes and a return of hypoglycemia awareness. Long-term primary efficacy and safety of immunosuppression as well as effects on secondary complications are less well understood and are the focus of ongoing research. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are older recipients in better glycemic control; more IEQ's infused and larger islet size yield higher levels of good outcomes; the effects of most of the immunosupression regimens cannot be definitively assessed in this uncontrolled setting; and the role of specialized, remote processing islet centers requires better understanding.

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Detailed Methods and Definitions

Background and Purpose

Funded by the National Institute of Diabetes & Digestive & Kidney Diseases with a supplemental grant from the Juvenile Diabetes Research Foundation International, the Collaborative Islet Transplant Registry (CITR) expedites progress and promotes safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America, Europe, and Australia. Each year the Registry reports on the cumulative data to date since 1999. This fifth report, published in 2008, summarizes information on patients who received one or more islet cell transplants between 1999 and 2007. All CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

History

CITR opened participation to North American centers early in the fall of 2002. The first Annual Report (2004) contained information on 86 islet transplant recipients, 173 deceased donors and 158 islet infusion procedures from twelve islet transplant centers. The second Annual Report (2005) summarized information on 138 islet transplant recipients, 256 deceased donors and 266 islet infusion procedures. The third Annual Report (2006) summarized information on 227 islet transplant recipients, 469 deceased donors and 429 islet infusion procedures. The fourth Annual Report (2007) summarized information on 292 islet transplant recipients, 634 deceased donors and 579 islet infusion procedures. This Annual Report (2008) summarizes information on 325 islet transplant recipients, 712 deceased donors, and 649 islet infusion procedures. This represents a 11% increase in the number of recipients, 12% increase in the number of donors, and a 12% increase in the number of infusion procedures that are reported in this Annual Report compared to last year's Report.

The focus of this report is data collection on all islet allograft transplants. Although islet autografts are conducted (over 300 procedures so far in North America) for other indications (pancreatitis), centers may voluntarily report these data also to the Registry. As of December 31, 2007, a total of 164 autologous islet transplant recipients were registered in CITR. Efforts are underway to collect complete autograft information in the Registry, both prior to and going forward from December 31, 2007.

Data Sources

CITR implements web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry and obtain donor, organ procurement, and islet processing data through data sharing agreements with respective organizations (the United Network for Organ Sharing and the Islet Cell Resource Centers). These data characterize and follow trends in safety and efficacy for recipients of islet transplantation, including donor information, islet processing, transplant techniques, and treatment protocols. Data reported to the Registry is abstracted from data that is routinely collected by investigators for scientific evaluations and for reports to the multiple agencies and entities required by US Food and Drug Administration (FDA) regulated trials or according to the requirements of the respective nation. In US centers, demographic information is collected in CITR only once, at the time of the islet transplant recipient's registration. For each islet/beta cell infusion,

information is collected on the pancreas donor(s), islet processing and testing of all pancreata used for the infusion procedure, and recipient status from screening through the early transplant period.

Follow-up data are abstracted at Day 30, Month 6, and Month 12 post first infusion procedure for four main indicators (severe hypoglycemic episodes, hemoglobin A1C, fasting blood glucose and C-peptide). Detailed follow-up data is abstracted at Month 6, Year 1, and annually post infusion. At each new infusion, a new follow-up schedule is established to abstract data at six-month and annual anniversaries of the last infusion. There is also event driven data abstraction on adverse events, recipient's vital status, non-islet transplant and follow-up, islet graft dysfunction, loss to follow-up, and transfer of the recipient to another islet transplant center. A copy of the CITR data collection forms may be viewed at the CITR Website (www.citregistry.org).

CITR also collects basic survey information from all islet allograft transplant centers in North America, regardless of their participation with CITR. Forty-six islet transplant programs were sent a questionnaire requesting the number of islet transplant infusions performed at their islet transplant center as well as the number of recipients. All 46 programs responded and 31 of the 46 programs had been active during 1999-2007, transplanting at least one patient. The remaining programs (N=15) had not transplanted yet, or were in the process of starting their islet transplant program.

The following table displays the number of islet transplant recipients and total infusions performed at the 31 active islet allograft transplant programs in North America for 1999-2007. To the knowledge of the Registry, this table is inclusive of all human islet allograft transplant programs in North America.

All Active Islet Transplant Programs in North America (N=31)	Number of Human Islet Allograft Procedures Conducted	Number of Patients Receiving Their First Allograft
Total	717	378
1999	18	10
2000	32	21
2001	65	45
2002	142	82
2003	106	45
2004	110	53
2005	124	64
2006	78	37
2007	42	21

In summary, this report includes data on 78% (296/378) of all islet allograft recipients in North America and 79% (570/717) of all islet allograft procedures conducted.

Study Endpoints

The primary endpoints presented in this report are:

- Insulin independence
- HbA_{1c} level <6.5, 6.5-<7.0 or >=7.0%
- C-peptide ≥0.5 ng/mL
- Insulin independence and C-peptide >0.5 ng/mL
- Severe hypoglycemia
- Complete islet graft failure

Secondary endpoints include:

- Average daily insulin and percent of baseline insulin
- Fasting plasma glucose, C-peptide and HbA_{1c} levels
- Laboratory indicators of primary complications of diabetes and major organ function
- Metabolic testing
- Secondary complications of diabetes

These are variously described by prevalence bar charts (frequency distributions) pre-infusion and post first and last infusion, accounting for all participants expected at each time point. For prevalence bar charts (e.g. Exhibits 5-1 to 5-3, etc.), all recipients expected at each follow-up time point based on the dates of their infusions and the report cut-off date are included in the analysis. Bar charts are intended to display prevalence and generally sum to 100% at each time point. Incidence and persistence are analyzed by Kaplan-Meier time-to-event or survival estimates and by Cox proportional hazards regression using relevant baseline factors as explanatory covariates.

Insulin use is available daily post each infusion as well as at pre-specified study time points, so the daily "bar charts" are shown as stepped line graphs (Exhibits 5-4 and 5-5). Cumulative incidence may be shown as bar charts such as in Exhibit 5-10 or as Kaplan-Meier curves such as Exhibit 5-11. These two types of displays show similar observed rates in slightly different ways.

Insulin status is collected from the day of the participant's first infusion procedure and throughout follow-up. Any changes in insulin status from going on insulin to coming off insulin are recorded. A change from insulin dependence to independence by definition requires at least 14 consecutive days of no insulin use. A change from insulin independence to insulin dependence by definition requires a minimum of 14 consecutive days of insulin use. Average daily insulin use is recorded for periods of insulin use before and after any re-infusion procedures, changes in islet graft function, and all CITR follow-up visits.

Complete islet failure (CIF) is a reportable event. However, C-peptide data was used to impute CIF: any recipient with fasting C-peptide less than local detectable levels at their last scheduled follow-up and with stimulated c-peptide less than 0.3 ng/mL (or less than local detectable levels) was imputed as a complete islet failure for this report.

Boxplots are used in the report to summarize data. The "star" (★) in the boxplot represents the mean value while the lower line of the box represents the 25th percentile, the upper line of the box represents the 75th percentile and the middle line in the box represents the median (50th percentile).

Statistical significance of analyses, not adjusted for repeated testing, is shown for a number of the Exhibits. These are provided to the reader for their own interpretation. Conclusions should recognize that the significance levels control for random variance, but not systematic biases in the data nor multiple testing. It may be that statistical significance of the analyses in subsequent reports based on

a greater sample size will vary from this year's report. However, these analyses do provide insight and direction for future questions and analyses.

Statistical Modeling

The Cox regressions represent a first attempt to comprehensively assess factors that may be predictive of the primary outcomes. Univariate models are used to analyze effects first. Any factor with an association at a nominal significance level of $p<0.10$ was included in a multivariate model. Multivariate modeling was performed first in a step-down manner, and then manually replicated by stepping up to check for stability of the model. Two or more factors significantly associated with an outcome at $p<0.10$ but also strongly correlated with each other (Pearson $r>0.4$), were stepped into the multivariate model individually to test their effect. Of such correlated factors, the one with the greater effect was retained in the final model. The results of these models should be viewed as preliminary due to the small number of events, the relatively large number of factors, the effect of outliers and highly skewed distributions for many of the factors, and the associations among the factors.

The CITR data are analyzed to characterize the possible outcomes or states that an individual can experience following islet cell transplantation. Such analyses may help elucidate both biological factors affecting outcomes and clinically meaningful predictors of achievement and durability of success. Figure 1 presents one view of the possible states following the first of one to several infusions: individuals can have immediate islet cell failure (primary non function), or they can enter either the insulin dependent or insulin independent states. An individual may change from one state to another before re-infusion: if insulin independence is achieved, it might be lost; other than primary non-function, islet failure can subsequently occur; finally, a subsequent infusion can be performed. Time-to-event models can be used to investigate the effect of pre-infusion patient, donor and islet characteristics on these outcomes after first infusion.

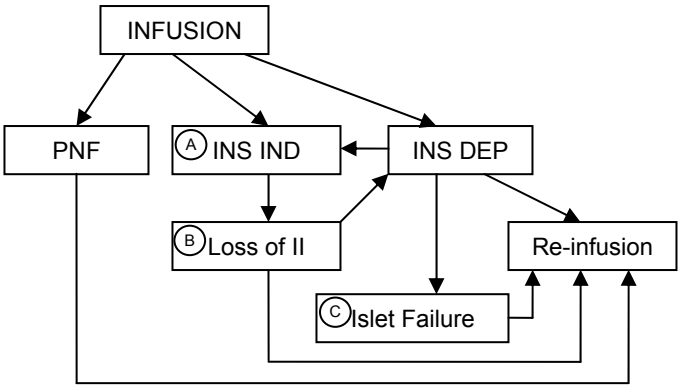


Figure 1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent)

In Exhibit 5-22, we present proportional hazard regression analyses of factors affecting transition to insulin independence (univariate results in 5-22 column A and multivariate results in Panel D) and loss of the insulin independent state (5-22 column B). Because the insulin dependent state is substantially the complement of the independent state, it is not modeled separately. Because of low event numbers, primary non-function is not analyzed. The absorbing state of death has occurred too infrequently to be analyzed separately; further follow-up and/or a larger sample size will be required

before its inclusion would be meaningful. Initial analysis of the transition to the islet failure state is provided (5-22 column C). This will be further analyzed in subsequent reports with more extensive follow-up. There are multiple paths leading to reinfusion; factors affecting this decision include site treatment plans which may not depend on the individual's paths or outcome states. Thus, no analysis of this outcome state is attempted.

Following reinfusion, the outcomes path could be extended to depict the identical outcome states following the second and subsequent infusions. Rather than attempting to examine outcomes after each infusion, we consider the experience following a series of infusions as described in Figure 2.

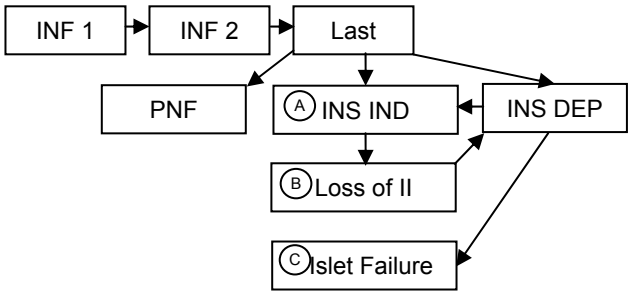


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent)

We call these analyses "post last infusion," defined as all infusions performed over no more than 18 months, with at least 6 months follow-up available post last infusion and excluding primary non-function. Only those recipients meeting this definition are included in this analysis. In this view, the outcomes after each infusion are regarded as intermediary steps with focused consideration of the outcome states post last infusion. Exhibit 5-23 details univariate analyses of the insulin independence, loss of insulin independence and islet failure states. Multivariate results are presented in 5-23 Panel D.

Definitions

Several key terms used by CITR in the Annual Report exhibits are listed below with their respective CITR definitions:

Abnormal tests: Liver function and lipid tests were analyzed as ≥ 1 times the upper limit of normal (ULN) and at ≥ 2 times the ULN. The ULN (Stedman's Medical Dictionary, 26th edition, Williams & Williams) for each of the tests are defined as the following:

ALT (alanine aminotransferase): *56 IU/L*

AST (asparate aminotransferase): *40 IU/L*

Alkaline phosphatase: *90 IU/L*

Total bilirubin:	*1.3 mg/dL*
Total cholesterol:	*240 mg/dL*
Triglycerides:	*150 mg/dL*

Adverse Event: Grade 3-5 as classified by the Clinical Islet Transplantation Consortium (CIT), Terminology Criteria for Adverse Events (TCAE), Version 4.0. Adverse event relationships to the infusion procedure and to the immunosuppression regimen are determined by the local CITR Investigator.

Cell volume: Total volume of islet cells in a preparation. Either packed cell volume or settled cell volume may be reported depending on the methods used by the transplant center.

Complete islet graft failure: Reported by transplant centers when a recipient no longer has detectable C-peptide. However, C-peptide data at scheduled follow-up was used to correct for missing or tardy reports: any recipient with fasting C-peptide less than local detectable levels and stimulated C-peptide less than 0.3 ng/mL (or less than local detectable levels) at their last scheduled follow-up were imputed as a complete islet graft failure for this report.

Detectible C-peptide: A C-peptide level greater than or equal to the local laboratory's lower limit of detectability, which may vary in numerical value from one center to another.

Duration of cold ischemia: Duration of time from when the pancreas was placed in cold preservation solution until the heating up of the organ to start the digestion process.

Hazard Ratios: In Cox proportional hazards regression, hazard ratios less than 1.0 indicate a reduced risk of the outcome with higher levels of the predictor, and HR greater than 1.0 indicate increased risk of the outcome with higher levels of the predictor. Binary factors are coded 0=no/absent and 1=yes/present.

Hypoglycemia status: Hypoglycemia status at baseline and during follow-up visits is determined by choosing one of the following categories that best describes the participant:

No occurrence: Participant was not diagnosed with hypoglycemia and/or signs and symptoms did not occur.

Having episodes and aware: Participant experiences episodes and has autonomic warning symptoms.

Partial awareness: Participant has a decreased magnitude of autonomic symptoms or an elevated threshold for autonomic symptoms at low glucose levels.

Unawareness: Participant has a lack of autonomic warning symptoms at a glucose level of < 54 mg/dL.

Insulin dependence: Insulin administered for a period of 14 or more consecutive days.

Insulin independence: Free from insulin use for 14 or more consecutive days.

Islet after kidney recipient (IAK): A recipient of an islet cell transplant with a prior history of kidney transplantation.

Islet alone recipient (IA): A recipient of an islet transplant with no prior history of kidney transplantation.

Islet equivalent count (IEQ): Number of islets in a preparation adjusted for size of the islet. One IEQ is equal to a single islet of 150 µm in diameter.

Islet function: Fasting C-peptide detectable by local assay or stimulated C-peptide greater than 0.3 ng/mL.

Islet graft dysfunction:

> In *insulin independent recipients* (after completion of induction immunotherapy), islet graft dysfunction is defined as when the recipient displays, with no evidence of infection or drug toxicity, 3 blood glucose readings 2 hours or longer post prandial over 180 mg/dL in any 1-week period OR 3 pre-prandial blood glucose readings over 140 mg/dL in any 1-week period.
>
> In *insulin dependent recipients* (after completion of induction immunotherapy), islet graft dysfunction will be suspected if the recipient displays, with no evidence of infection or drug toxicity, a 50% increase in insulin requirements (with a minimum increase of 5 units per day) OR an increase of 10 units per day over a 1-2 week period.

Islet particle count: Number of islets in a preparation without any adjustment for the size of the islet.

Loss of insulin independence: Time from attainment of insulin independence to the first day insulin was required for 14 or more consecutive days.

Lost to follow-up: Site has submitted form denoting recipient as having discontinued follow-up voluntarily or without reason.

Missing: Form not submitted on time or item left blank. Clinical site is still required to report a valid value or designate that the answer is unknown.

Outcome of islet graft dysfunction: If a complete dysfunction was not experienced (islet graft failure), there may be:

> *Partial recovery:* Recovery achieved but not to the functional level (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.
>
> *Full recovery*: Recipient was able to obtain the same level of functioning (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

PRA: Panel Reactive Antibody. Sensitization is reported as the percent PRA, which is the percentage of cells tested that were killed by the patient's serum.

Serious Adverse Event: Any adverse event involving death, life threatening event, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant

disability/incapacity, congenital anomaly/birth defect, or required intervention to prevent permanent damage, regardless of the TCAE grading. Serious adverse event relationships to the infusion procedure and to the immunosuppression regimen are determined by the local CITR Investigator.

Severe hypoglycemia: Having hypoglycemic events requiring the assistance of another person to diagnose symptoms or administer treatment. Prior to the first infusion, this is defined as the number of episodes in one year prior to infusion. At follow-up, it is defined as the number of episodes during the follow-up period (0 to 30 days post infusion, 30 days to 6 months post infusion, 6 to 12 months post infusion, or at yearly intervals thereafter).

Unknown: The value or response to a form item is not available from the medical record, the recipient, or from any other source data. Distinguished from "missing" which means not answered/left blank.

Data contained in this report must be interpreted cautiously. Even with the combined efforts of the participating centers, the total number of reports is still small. As with any registry, a number of potential biases may exist. First, not all active islet transplant centers in North America have submitted data to CITR (25/31; 77%). Second, not all of the islet transplant recipients or all of the infusion procedures have been reported. Third, some information may be reported selectively based on the center's protocol or other local decisions.

This report presents islet alone (IA) and islet-after-kidney (IAK) allogenic islet transplant results side-by-side in most exhibits. Chapter 1 summarizes the reported human islet transplant activity from 1999 through 2007. Chapter 2 through 7 present recipient and donor characteristics, pancreas procurements and islet processing summaries, data on immunosuppression and other medications, graft function, primary endpoints, markers of islet function and diabetic control, laboratory data addressing safety and adverse events. Chapter 8 summarizes the Registry data quality review.

No center-specific information is present in this report.

Data Quality Assurance

CITR adheres to strict quality control and assurance procedures. All data submitted are reviewed through several quality review processes. Islet transplant recipient data for this report reflect data entered by the islet transplant centers on participants from January 1, 1999 through December 31, 2007. These data were reviewed by the Coordinating Center for quality assurance, errors and data outliers. Any missing follow-up information on these participants were identified and conveyed back to the center for verification and correction. Any questions concerning specific data elements were also sent to the islet transplant centers for review and correction, if necessary. All islet transplant centers were provided ample time for completing any identified data discrepancies. The database was then updated and closed for analysis on April 1, 2008 based on the 325 recipients that had been registered for CITR at the December 31, 2007 participant registration closure date.

All participating North American islet transplant centers and the data they submit to the Registry are monitored and audited by the Registry's Coordinating Center. The schedule for monitoring includes an initial visit to the islet transplant center after the first three participants are submitted to the Registry, and then after every 10 participants are entered or at the discretion of the Coordinating Center if less than 10 new participants have been registered. Monitoring reports, with suggestions for improvement, data discrepancies, and all action items are sent both to the islet transplant center and CITR's sponsor, NIDDK.

Chapter 1
Islet Transplant Activity

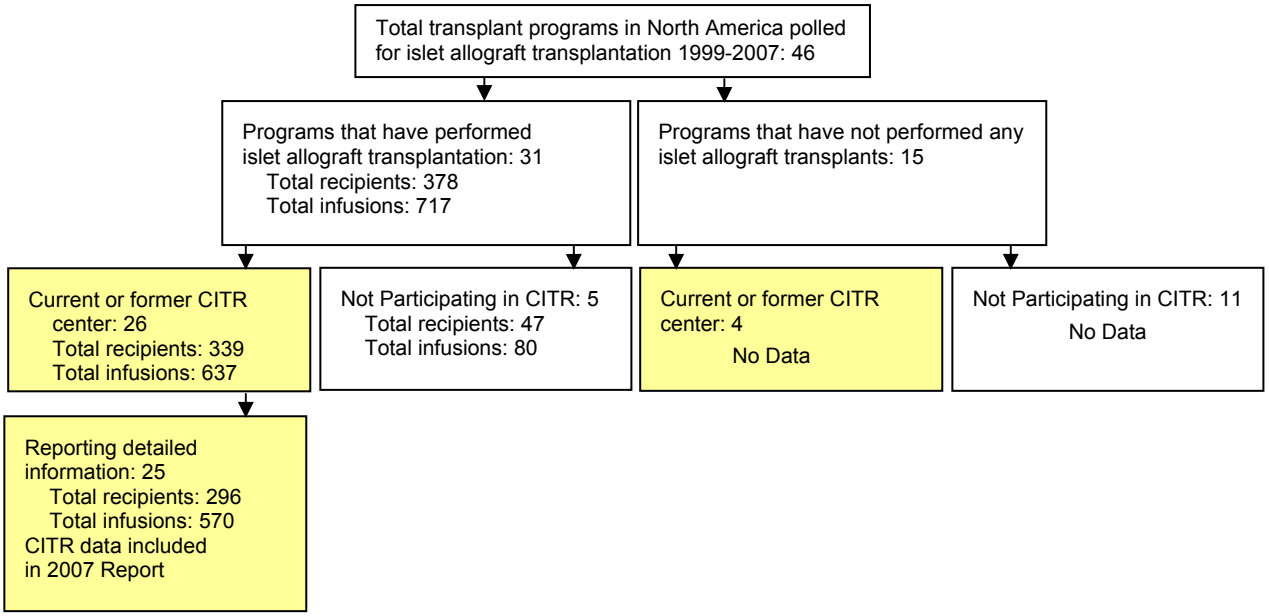
Islet Transplant Activity

As of December 31, 2007, 34 North American and European islet transplant centers were current or former contributors to the Collaborative Islet Transplant Registry (CITR). Of these centers, 27 have submitted detailed data on 325 islet alone (IA) or islet after kidney (IAK) allograft recipients to the Registry. Exhibit 1-1 displays the locations of all current and former CITR-participating North American centers. A listing of CITR-participating centers and their staff is found in Appendix A.

Overall, there has been a steady increase in the number of islet transplant programs joining CITR and contributing information since the inception of the Registry. There has been an 11% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 12% increase in the total number of islet allograft infusion procedures reported.

Exhibit 1-2 displays the number of North American centers contributing to this report compared to those that were conducting allograft transplants during the same time period. For example, 8 of the 10 (80%) active North American islet transplant programs in 2007 contributed information to the Registry.

CITR distributed a questionnaire to 46 North American centers to capture information on the number of islet infusions conducted. The graphic below illustrates the results of the questionnaire by CITR participation status.



Exhibits 1-3 and 1-4 compare the total number of North American allograft recipients and allograft infusions contained in this year's Annual Report to the overall number of allograft recipients and allograft infusions performed in all of North America. Overall, 296 of 378 allograft recipients (78%)

and 570 of 717 (79%) allograft infusions performed in North America are included in this year's Annual Report.

Two European centers have contributed detailed data to the Registry. A third European center has registered recipients with the Registry, but has not yet reported detailed data.

A summary of the total 649 North American and European islet allograft infusions entered in the Registry by year of infusion is included in Exhibit 1-5. These 649 infusions derived from 712 total donors; 589 were single donor preparations and 60 were multiple donor preparations. There was a large number of first islet infusions reported by the CITR centers in 2002 (N=69) as well as a large number of second islet infusions in 2002 (N=45). In other years, first infusion reports range from 18-60 recipients.

Eighty-four recipients (26%) have received a single islet infusion at the time of this report, 164 (50%) received a total of two infusions, 71 (22%) received three infusions, and six recipients (2%) received a total of four islet infusions (Exhibit 1-6).

Of the 325 islet allograft recipients presented in this report, 279 (86%) are islet alone recipients, and 46 (14%) are islet after kidney recipients (Exhibit 1-8). Three islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

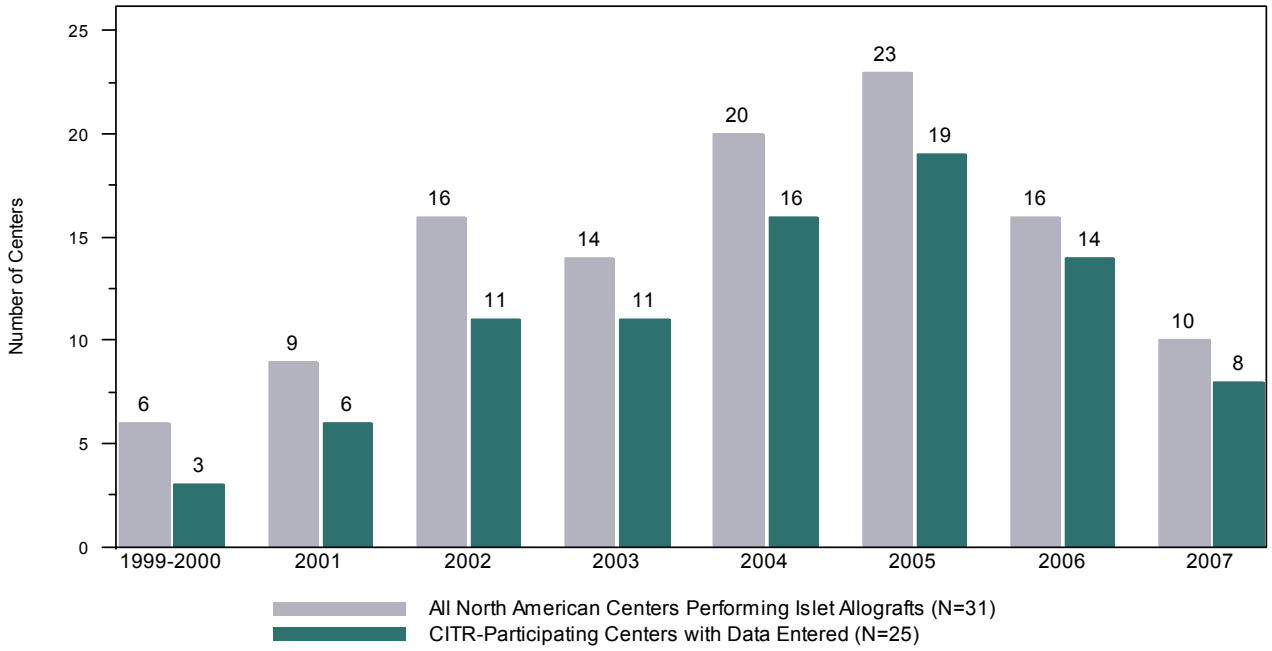
One hundred seventy of 339 North American autograft recipients have been reported to the Registry. Detailed data for these recipients is being collected. When complete data are available, a supplemental Annual Report will present analyses for autologous islet transplants.

Exhibit 1 – 1
Islet Transplant Centers Reporting Data to CITR:
Participating North American Centers 1999-2007

A - CITR Centers with at least one islet allograft infusion procedure conducted in 2007
C - CITR Centers with no islet allograft infusions in 2007
D - CITR Coordinating Center

For more information on North American islet transplant programs, please visit the CITR Website at www.CITRegistry.org.

Exhibit 1 – 2
Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
All North American Islet Transplant Centers 1999-2007

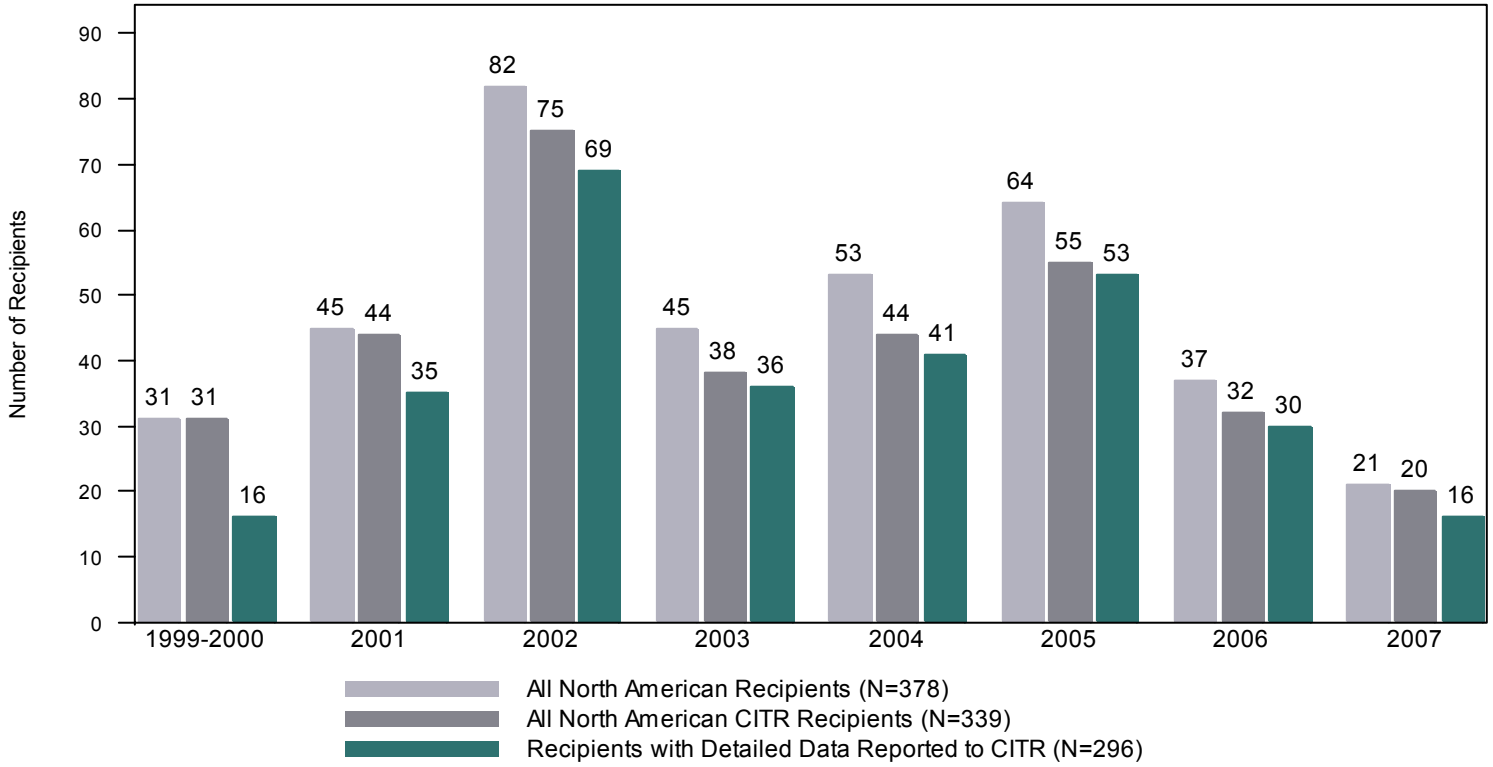


CITR distributes an Islet Transplant Summary (ITS) questionnaire to all known islet transplant programs in North America regardless of their participation in the Registry. The questionnaire captures information on the number of patients who received one or more islet infusions. Of 46 North American islet transplant programs polled, all 46 have provided information through 2007.

"All North American Centers Performing Islet Allografts" represents the number of programs that have reported performing at least one islet infusion procedure in the specified year. "CITR-Participating Centers with Data Entered" represents the number of islet transplant programs in the specified year that have contributed data for the analyses included in this Annual Report. Four islet transplant programs participating in CITR have not yet conducted an islet allograft transplant and data from one CITR-participating center was excluded due to incompleteness.

Since last year's report, one additional North American center has contributed data for islet transplants performed.

Exhibit 1 – 3
Total Number of Islet Transplant Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR By Year of First Islet Allograft Infusion
All North American Islet Transplant Centers 1999-2007

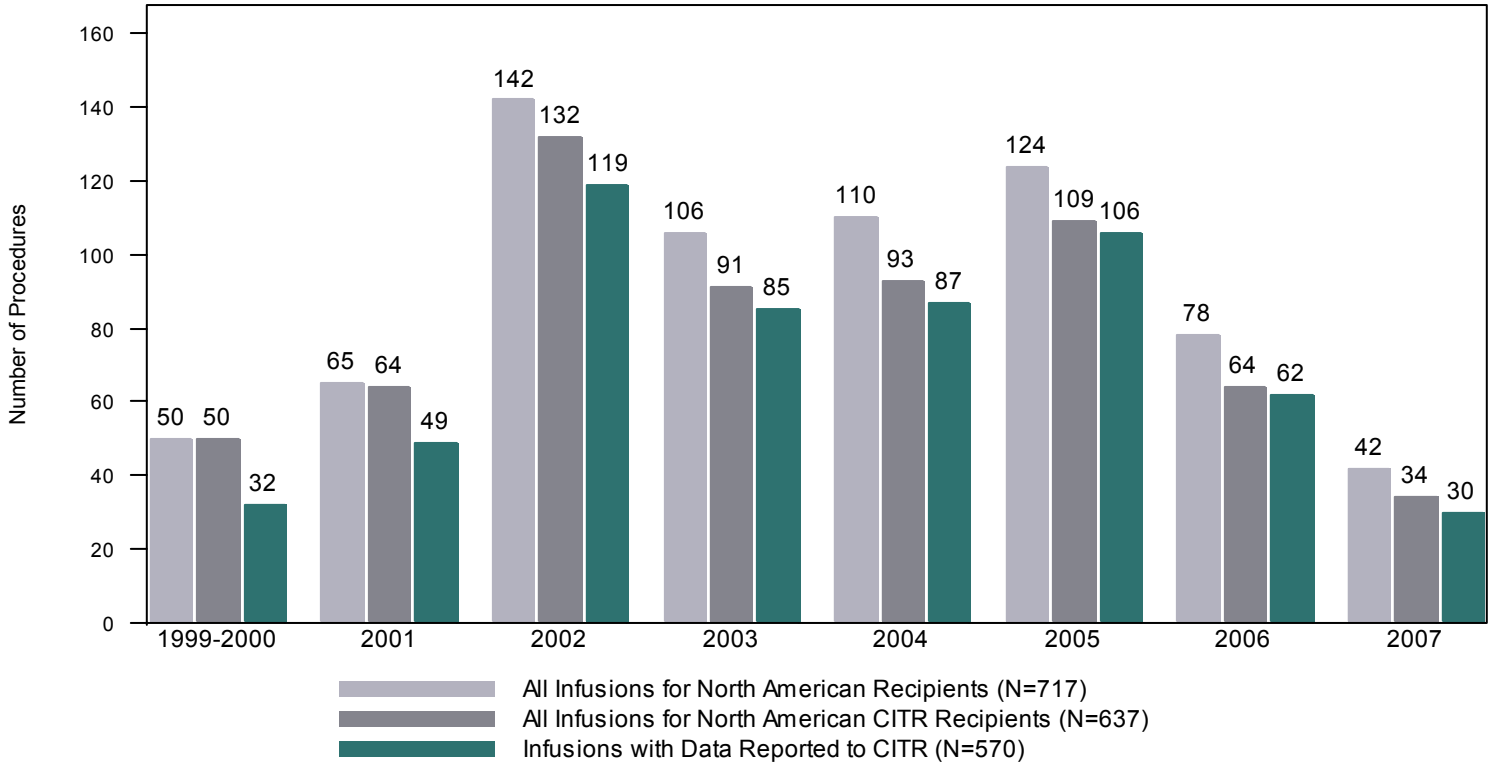


The Islet Transplant Summary (ITS) questionnaire is completed by all North American islet transplant programs regardless of their participation in the Registry. Of 46 North American islet transplant programs polled, all have provided this information through 2007.

From 1999-2007, 378 patients with Type 1 diabetes mellitus have received at least one islet allograft infusion procedure in North America. Of those 378 patients, 339 (90%) received their allograft from a CITR participating center. CITR-participating centers have reported detailed data on 296 of these recipients, representing 78% of all 378 human-to-human islet allograft recipients in North America from 1999-2007.

Since last year's report, North American centers have contributed data on 12 allograft recipients transplanted in 2003-2006 not previously reported.

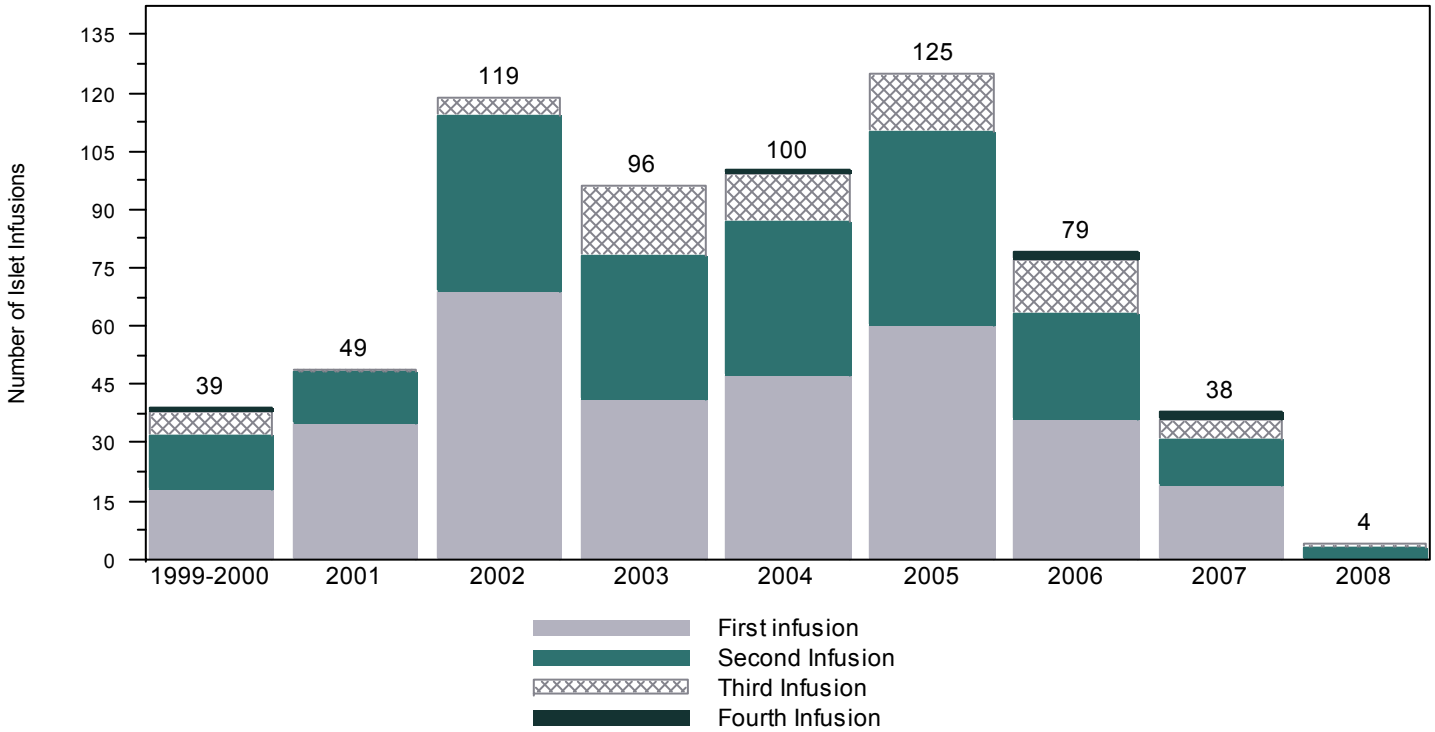
Exhibit 1 – 4
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR: CITR-Participating North American Islet Transplant Centers 1999-2007



From 1999-2007, 378 patients with Type 1 diabetes mellitus have received a total of 717 allograft infusion procedures. CITR-participating North American islet transplant centers have performed 637 of those 717 (89%) procedures. The Registry has received detailed data on 570 allograft infusion procedures performed at CITR-participating North American islet transplant centers, representing 79% of all 717 human-to-human islet allograft infusions performed in North America from 1999-2007.

Since last year's report, North American centers have reported an additional 28 allograft infusions not previously reported.

Exhibit 1 – 5
Total Number (N=649) of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number: CITR-Participating North American and International Centers, 1999-2007



Infusion procedure number is defined as the sequence number of all the infusion procedures received by the recipient.

For example, in 2001, 35 participants received their first infusion, 13 received their second, while one person received their third infusion. If a participant received their first islet infusion between 1999 and 2007 and a subsequent infusion between January and March of 2008, data for the subsequent infusion is also included in the graph.

Exhibit 1 – 6
Total Number (N=649) of Islet Allograft Infusion Procedures Per Recipient:
CITR-Participating North American and International Centers, 1999-2007

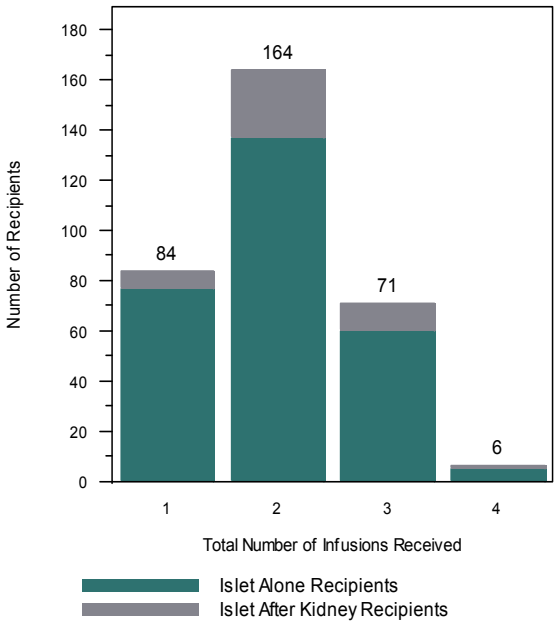


Exhibit 1 – 7
Total Number (N=712) of Deceased Donors per Islet Allograft Infusion Procedure:
CITR-Participating North American and International Centers, 1999-2007

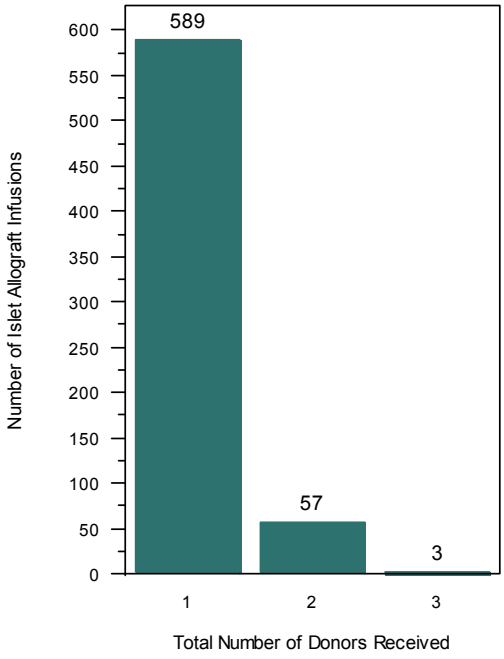
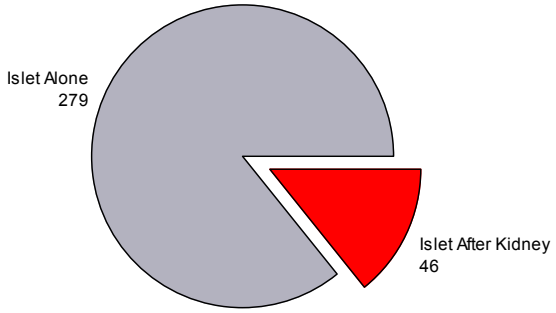


Exhibit 1 – 8
Islet Alone and Islet After Kidney Recipients:
CITR-Participating North American and International Centers, 1999-2007



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Chapter 2
Recipient and Donor Characteristics

Recipient and Donor Characteristics

Islet Alone Recipient Information

The mean age of the islet alone transplant recipient is 43 years (range 19 to 67) and the mean duration of diabetes is 28 years (range 2 to 54). The mean weight of the recipient is 67 kg (range 35 to 98) and the mean body mass index (BMI) is 24 kg/m^2 (range 15 to 32). Females comprise 66% of the recipients. There is limited racial and ethnic diversity (Exhibit 2-1).

At the time of their first infusion, 22% of the recipients were unemployed or underemployed due to their disease. The majority of funding for islet cell transplants at participating US centers was provided by the NIH, JDRF, and institutional contributions (Exhibit 2-2).

The vast majority of the islet transplant recipients were on an insulin pump or were taking three or more insulin injections per day (Exhibit 2-4). At baseline, 8% of the participants had a basal C-peptide $\geq$ 0.5 ng/mL and 69% had an $HbA_{1c} \geq 7.0\%$ (Exhibit 2-4). The mean daily insulin requirement prior to their first infusion procedure was 37 units (SD 13) and the 97% on intensive insulin therapy had received intensive therapy for a mean of 19 years (SD 13) (Exhibit 2-3). At pre-transplant mean fasting plasma glucose for all recipients was 173 mg/dL (SD 91), mean HbA_{1c} was 7.7% (SD 1.3), and mean basal C-peptide was 0.1 ng/mL (SD 0.2).

Serology tests indicated that four participants (3 IA, 1 IAK) tested positive for hepatitis B core antibodies, one participant tested positive for hepatitis B surface antigen, and three participants (all IAK) tested positive for CMV IgM (Exhibit 2-5).

Exhibits 2-6 and 2-7 describe participant baseline characteristics prior to first infusion by the total number of infusions received. In comparison, participants who received a total of three infusions were younger, on the waitlist for less time, had a higher HbA_{1c} and lower PRA percentages than those participants who had one or two infusion procedures.

Donor Information

All 712 islet preparations were derived from deceased donors. The mean age of donors was 43 years (range 1 to 75) and the mean body mass index was 29 kg/m^2 (SD 7). Approximately 59% of the donors were male, 11% were Hispanic and the majority was white. Fifty-five percent of the donors had a cerebrovascular/stroke as cause of death while 31% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 20% had a history of alcohol dependency. The mean time from cross clamp to pancreas recovery was 39 minutes (SD 20) while the mean cold ischemia time was 7.3 hours (SD 3.4) (Exhibit 2-11).

About 33% of the donors received a transfusion during hospitalization; 6% received a transfusion intraoperatively. About 39% of the donors received insulin during their hospitalization and 96% of the donors received at least one vasopressor during the donor's terminal hospitalization (Exhibit 2-12).

Donor serology is presented in Exhibit 2-13. There was a report of one donor testing positive for Anti HBC and this donor was used for a hepatitis B immunized recipient. Another donor tested positive for RPR-VDRL.

Donor laboratory data are presented in Exhibit 2-14. The mean serum creatinine of the donors is 1.2 mg/dL, total bilirubin 0.9 mg/dL, AST 75 IU/L, ALT 59 IU/L, serum lipase 73 IU/L and serum amylase 167 IU/L.

Exhibit 2 – 1
Recipient Demographics

	Islet Alone			Islet After Kidney		
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
Age (yrs)	279	43.8	0.6	46	46.0	1.0
	N	**%**		**N**	**%**	
Gender						
Female	183	65.6		28	60.9	
Male	96	34.4		18	39.1	
Ethnicity						
Non Hispanic or Latino	179	64.2		46	100.0	
Hispanic or Latino	5	1.8		-	0.0	
Unknown*	95	34.1		-	0.0	
Race						
American Indian or Alaska Native	2	0.7		-	0.0	
Asian	-	0.0		-	0.0	
Black or African American	-	0.0		1	2.2	
Indian Sub-Continent	-	0.0		-	0.0	
Mideast or Arabian	-	0.0		-	0.0	
Native Hawaiian or Other Pacific Islander	-	0.0		-	0.0	
White	184	65.9		45	97.8	
Unknown*	104	37.3		1	2.2	
Employment status						
Working full time	151	54.1		16	34.8	
Working part time by choice	16	5.7		3	6.5	
Working part time due to disease	19	6.8		2	4.3	
Working part time, reason unknown	2	0.7		-	0.0	
Not working by choice	13	4.7		2	4.3	
Not working due to disease	36	12.9		17	37.0	
Not working, unable to find employment	2	0.7		-	0.0	
Not working, reason unknown	2	0.7		3	6.5	
Student	2	0.7		-	0.0	
Retired	15	5.4		-	0.0	
Employment status unknown	13	4.7		2	4.3	
Missing	8	2.9		1	2.2	

* Race and ethnicity are not collected or reported outside of the United States.

Exhibit 2 – 2
Transplant Recipient Primary Funding Information
CITR-Participating US Centers

	Islet Alone		Islet After Kidney	
	N	%	N	%
Payment for Organ Acquisition				
US/State Government Agency	73	43.5	8	25.0
Non-Government Research Grant	42	25.0	20	62.5
Institutional Contribution	40	23.8	1	3.1
Missing	13	7.7	3	9.4
Payment for Islet Processing				
US/State Government Agency	65	38.7	8	25.0
Non-Government Research Grant	48	28.6	20	62.5
Institutional Contribution	42	25.0	1	3.1
Missing	13	7.7	3	9.4
Payment for transplant				
US/State Government Agency	51	30.4	8	25.0
Non-Government Research Grant	41	24.4	17	53.1
Institutional Contribution	62	36.9	1	3.1
Other*	1	0.6	3	9.4
Missing	13	7.7	3	9.4
Payment for Induction Medication				
US/State Government Agency	44	26.2	7	21.9
Non-Government Research Grant	53	31.5	19	59.4
Institutional Contribution	56	33.3	-	-
Other*	2	1.2	3	9.4
Missing	13	7.7	3	9.4

*Other includes payment by the transplant recipient, Medicare and donations.

Exhibit 2 – 3
Recipient Characteristics at First Infusion

	Islet Alone		Islet After Kidney	
	N	**%**	**N**	**%**
Total	279	100.0	46	100.0
Diabetes Type				
Type 1 Diabetes	278	99.6	46	100.0
Pancreatectomy Induced	1	0.4	-	-

	Islet Alone			Islet After Kidney		
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
Duration of Diabetes (yrs)	279	28.1	0.7	46	33.5	1.1
Weight (kg)	268	66.9	0.7	44	61.4	1.4
Body Mass Index (kg/m2)	265	23.8	0.2	43	22.5	0.4
Daily insulin requirement prior to infusion (units)	267	37.3	0.8	43	36.3	2.0
Duration of intensive therapy among those on intensive therapy (yrs)	176	18.9	1.0	1	10.0	-
Avg daily insulin / kg recipient body weight	262	0.6	<0.1	42	0.6	<0.1
Number of days on wait list	268	287.4	18.8	41	252.4	47.3
Fasting plasma glucose (mg/dL)	256	173.2	5.7	41	176.4	17.3
Basal C-Peptide (ng/mL)	258	0.1	<0.1	39	<0.1	<0.1
HbA_{1c} (%)	258	7.7	0.1	42	7.9	0.2
Most recent PRA (%)	247	3.1	0.7	36	0.5	0.3
Peak PRA (%)	226	4.3	0.9	31	5.1	3.2

Exhibit 2 – 4
Recipient Diabetes Characteristics at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	279	100.0	46	100.0
Use of insulin pump				
Yes	104	37.3	9	19.6
No	167	59.9	34	73.9
Missing	8	2.9	3	6.5
Number of injections per day				
N/A-on pump	104	37.3	9	19.6
1-2*	7	2.5	1	2.2
3-5	149	53.4	26	56.5
6 or more	4	1.4	2	4.3
Unknown	6	2.2	5	10.9
Missing	9	3.2	3	6.5
Use of insulin pump or 3 or more injections per day				
Yes	257	92.1	37	80.4
No	7	2.5	1	2.2
Missing	15	5.4	8	17.4
Basal C-peptide ≥ 0.5 ng/mL				
Yes**	20	7.2	3	6.5
No	238	85.3	36	78.3
Unknown	10	3.6	5	10.9
Missing	11	3.9	2	4.3
HbA_{1c}				
<6.5%	47	16.8	4	8.7
6.5% - 7.0%	32	11.5	8	17.4
≥ 7.0%	179	64.2	30	65.2
Unknown	11	3.9	3	6.5
Missing	10	3.6	1	2.2
Hypoglycemia Status				
No Occurrence	0	0.0	3	6.5
Having Episodes and Aware	11	3.9	6	13.0
Partial Awareness	76	27.2	10	21.7
Unawareness	181	64.9	20	43.5
Unknown	2	0.7	3	6.5
Missing	9	3.2	4	8.7

*Six of eight participants administering two injections per day with a mean average daily insulin use of 41 units. Two participants administering one injection per day with average daily insulin use of 33 units. Seven of eight participants had experienced severe hypoglycemic episodes in the year prior to transplant.
**Recipients with positive fasting C-peptide verified correct by center. Recipients lacked C-peptide response to stimulation test. All recipients received their islet infusion prior to 2004.

Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics at First Infusion

	Islet Alone		Islet After Kidney	
	N	**%**	**N**	**%**
Pre transplant autoantibody - GAD 65				
Positive	58	20.8	7	15.2
Negative	107	38.4	16	34.8
Unknown	101	36.2	19	41.3
Missing	13	4.7	4	8.7
Pre transplant autoantibody - IA-2				
Positive	39	14.0	1	2.2
Negative	77	27.6	18	39.1
Unknown	150	53.8	22	47.8
Missing	13	4.7	5	10.9
Pre transplant autoantibody - Insulin				
Positive	100	35.8	11	23.9
Negative	21	7.5	10	21.7
Unknown	145	52.0	21	45.7
Missing	13	4.7	4	8.7
Total number of positive autoantibodies				
None	39	14.0	9	19.6
One	92	33.0	9	19.6
Two	42	15.1	5	10.9
All Three	7	2.5	-	0.0
Unknown	86	30.8	19	41.3
Missing	13	4.7	4	8.7

Exhibit 2 – 5
Recipient Infectious Disease Testing at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	279	100.0	46	100.0
HIV				
Positive	-	0.0	-	0.0
Negative	264	94.6	39	84.8
Not Done/Unknown/Missing	15	5.4	7	15.2
CMV IgG				
Positive	107	38.4	20	43.5
Negative	144	51.6	23	50.0
Not Done/Unknown/Missing	28	10.0	3	6.5
CMV IgM				
Positive	0	0.0	3	6.5
Negative	138	49.5	22	47.8
Not Done/Unknown/Missing	141	50.5	21	45.7
HepB core antibody				
Positive	3	1.1	1	2.2
Negative	206	73.8	29	63.0
Not Done/Unknown/Missing	70	25.1	16	34.8
HepB surface antigen				
Positive	1	0.4	-	0.0
Negative	256	91.8	42	91.3
Not Done/Unknown/Missing	22	7.9	4	8.7
HepC antibody				
Positive	-	0.0	-	0.0
Negative	252	90.3	43	93.5
Not Done/Unknown/Missing	27	9.7	3	6.5
EBV IgG				
Positive	223	79.9	40	87.0
Negative	25	9.0	2	4.3
Not Done/Unknown/Missing	31	11.1	4	8.7
EBV IgM				
Positive	30	10.8	7	15.2
Negative	105	37.6	24	52.2
Not Done/Unknown/Missing	144	51.6	15	32.6

Exhibit 2 – 6
Recipient Characteristics at First Infusion by Total Number of Infusions Received

	Islet Alone									Islet After Kidney								
	Total Number of Infusions Received									Total Number of Infusions Received								
	One Infusion			Two Infusions			≥ Three Infusions			One Infusion			Two Infusions			≥ Three Infusions		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Age (yrs)	77	44.1	1.1	137	44.8	0.9	65	41.2	1.0	7	47.8	3.0	27	46.4	1.3	12	44.3	1.7
Duration of Diabetes (yrs)	77	29.2	1.3	137	28.2	0.9	65	26.7	1.4	7	35.6	3.7	27	33.9	1.4	12	31.3	1.5
Weight (kg)	77	64.8	1.2	134	67.5	0.9	57	68.5	1.4	6	58.9	3.6	27	59.7	2.0	11	67.0	2.0
Body Mass Index (kg/m2)	76	23.8	0.3	133	23.8	0.2	56	23.9	0.3	6	21.5	0.7	27	22.3	0.6	10	23.3	0.6
Daily insulin requirement (units)	75	32.9	1.3	133	38.3	1.1	59	40.5	2.0	7	38.1	4.7	27	35.1	2.7	9	38.1	4.5
Average daily insulin / kg recipient body weight	75	0.5	0.0	132	0.6	0.0	55	0.6	<0.1	6	0.7	0.1	27	0.6	<0.1	9	0.6	0.1
Duration of intensive insulin therapy (yrs)	48	19.6	2.3	96	19.3	1.3	32	16.9	2.1	0	-	-	1	10.0	-	0	-	-
Number of days on wait list for first infusion	74	297.5	33.5	133	336.1	29.8	61	169.1	25.9	6	168.7	94.9	27	297.2	64.1	8	164.1	78.5
Fasting plasma glucose (mg/dL)	76	162.6	9.6	122	177.3	8.4	58	178.5	12.5	6	198.8	46.8	27	158.0	16.6	8	221.8	59.8
Basal C-peptide (ng/mL)	74	0.1	0.0	126	0.1	0.0	58	0.1	<0.1	6	0.0	<0.1	24	0.1	<0.1	9	0.0	<0.1
HbA_{1c} (%)	73	7.4	0.1	126	7.6	0.1	59	8.0	0.2	6	7.8	0.7	27	8.1	0.2	9	7.1	0.3
Most recent PRA (%)	71	4.6	1.9	121	3.2	0.9	55	1.1	0.5	7	0.0	<0.1	24	0.7	0.4	5	0.0	<0.1
Peak PRA (%)	67	6.1	2.3	111	4.0	1.1	48	2.5	0.9	6	0.3	0.3	20	7.8	5.0	5	0.0	<0.1

Exhibit 2 – 7
Recipient Demographics and Characteristics at First Infusion
by Total Number of Infusions Received

	Islet Alone						Islet After Kidney					
	Total Number of Infusions Received						Total Number of Infusions Received					
	One Infusion		Two Infusions		≥ Three Infusions		One Infusion		Two Infusions		≥ Three Infusions	
	N	%	N	%	N	%	N	%	N	%	N	%
Recipient Gender												
Male	16	20.8	52	38.0	28	43.1	3	42.9	6	22.2	9	75.0
Female	61	79.2	85	62.0	37	56.9	4	57.1	21	77.8	3	25.0
Pre transplant autoantibody - GAD 65												
Positive	13	16.9	32	23.4	13	20.0	1	14.3	5	18.5	1	8.3
Negative	27	35.1	58	42.3	22	33.8	2	28.6	9	33.3	5	41.7
Unknown	33	42.9	43	31.4	25	38.5	4	57.1	12	44.4	3	25.0
Missing	4	5.2	4	2.9	5	7.7	-	-	1	3.7	3	25.0
Pre transplant autoantibody - IA-2												
Positive	13	16.9	14	10.2	12	18.5	-	-	1	3.7	-	-
Negative	19	24.7	37	27.0	21	32.3	2	28.6	11	40.7	5	41.7
Unknown	41	53.2	82	59.9	27	41.5	4	57.1	14	51.9	4	33.3
Missing	4	5.2	4	2.9	5	7.7	1	14.3	1	3.7	3	25.0
Pre transplant autoantibody - Insulin												
Positive	19	24.7	61	44.5	20	30.8	3	42.9	6	22.2	2	16.7
Negative	5	6.5	13	9.5	3	4.6	-	-	7	25.9	3	25.0
Unknown	49	63.6	59	43.1	37	56.9	4	57.1	13	48.1	4	33.3
Missing	4	5.2	4	2.9	5	7.7	-	-	1	3.7	3	25.0
Total number of positive autoantibodies												
None	9	11.7	17	12.4	13	20.0	-	-	5	18.5	4	33.3
One	23	29.9	52	38.0	17	26.2	2	28.6	6	22.2	1	8.3
Two	8	10.4	26	19.0	8	12.3	1	14.3	3	11.1	1	8.3
All Three	2	2.6	1	0.7	4	6.2	-	-	-	-	-	-
Unknown	31	40.3	37	27.0	18	27.7	4	57.1	12	44.4	3	25.0
Missing	4	5.2	4	2.9	5	7.7	-	-	1	3.7	3	25.0

Exhibit 2 – 8
Recipient Laboratory Values at First Infusion

	Islet Alone			Islet After Kidney		
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
HbA_{1c} (%)	258	7.7	0.1	42	7.9	0.2
ALT (U/L)	256	22.1	0.7	42	28.6	2.1
AST (U/L)	269	24.5	0.5	43	32.1	2.6
Alkaline phosphatase (U/L)	264	74.4	2.0	41	127.3	15.7
Total bilirubin (mg/dL)	265	0.6	<0.1	42	0.5	<0.1
Total cholesterol (mg/dL)	263	169.8	1.8	41	185.3	5.9
HDL (mg/dL)	260	64.0	1.0	36	67.5	3.6
LDL (mg/dL)	260	92.9	1.5	36	98.3	4.4
Triglycerides (mg/dL)	263	67.9	2.4	41	95.5	6.1
Serum creatinine (mg/dL)	271	0.9	<0.1	44	1.3	0.1
Calculated creatinine clearance (mL/min/1.73m^2)	222	103.1	1.9	28	79.8	6.1
Basal C-peptide (ng/mL)	258	0.1	<0.1	39	0.0	<0.1

Exhibit 2 – 9
Donor Demographics
All Allograft Donors

	N	Mean	SD
Age (yrs)	690*	43.5	12.4
	N		**%**
Total	712		100.0
Gender			
Male	400		56.2
Female	283		39.7
Unknown	10		1.4
Missing	19		2.7
Ethnicity			
Hispanic	49		6.9
Non Hispanic	390		54.8
Unknown**	254		35.7
Missing	19		2.7
Race			
American Indian or Alaska Native	-		0.0
Asian	3		0.4
Black or African American	50		7.0
Indian Sub-Continent	2		0.3
Mideast or Arabian	-		0.0
Native Hawaiian or Other Pacific Islander	-		0.0
White	424		59.6
Unknown**	214		30.1
Missing	19		2.7

*Age was missing for 22 donors.
**Race and ethnicity are not collected or reported outside of the United States.

Exhibit 2 – 10
Donor Characteristics
All Allograft Donors

	N	Mean	SD
Weight (kg)	684	87.7	21.3
Height (m)	676	1.7	0.1
Body Mass Index(kg/m^2)	676	29.3	6.7
	N	**%**	
Total	712	100.0	
Donor ABO blood group			
A	217	30.5	
A_1	39	5.5	
A_1B	1	0.1	
A_2	1	0.1	
AB	11	1.5	
B	40	5.6	
O	382	53.7	
Missing	21	2.9	
History of hypertension			
Yes	218	30.6	
No	415	58.3	
Unknown	59	8.3	
Missing	20	2.8	
Hypertension duration			
0-5 years	83	38.1	
6-10 years	18	8.3	
>10 years	34	15.6	
Unknown	83	38.1	
Hypertension control-Diet			
Yes	25	11.5	
No	50	22.9	
Unknown	143	65.6	
Hypertension control-Diuretics			
Yes	24	11.0	
No	72	33.0	
Unknown	122	56.0	

Exhibit 2 – 10 *(continued)*
Donor Characteristics
All Allograft Donors

	N	%
Hypertension control-Other medications		
Yes	108	49.5
No	40	18.3
Unknown	70	32.1
History of alcohol dependency		
Yes	118	16.6
No	485	68.1
Unknown	87	12.2
Missing	22	3.1
Alcohol use in past 6 months		
Yes	63	53.4
No	23	19.5
Unknown	32	27.1
History of diabetes		
Yes	-	0.0
No	679	95.4
Unknown	13	1.8
Missing	20	2.8

Exhibit 2 – 11
Characteristics of Organ Procurement and Donor Cause of Death
All Allograft Donors

	N	Mean	SD
Time from admission to brain death (hrs)	489	49.8	66.0
Duration of cardiac arrest where cardiovascular death (mins)	63	16.1	12.6
Time from cross clamp to pancreas recovery (mins)	458	38.9	20.1
Cold ischemia time (hrs)	665	7.3	3.4
	N		**%**
Total	712		100.0
Cause of death			
Anoxia/cardiac arrest	31		4.4
CNS tumor	7		1.0
Cerebrovascular/stroke	375		52.7
Head trauma	210		29.5
Other	55		7.7
Missing	19		2.7
Unknown	15		2.1
Mechanism of death			
Asphyxiation	9		1.3
Blunt injury	100		14.0
Cardiovascular	25		3.5
Death from natural causes	4		0.6
Drowning	3		0.4
Drug intoxication	8		1.1
Gunshot wound	45		6.3
Intracranial hemorrhage/stroke	452		63.5
Seizure	3		0.4
None of the above	12		1.7
Unknown	31		4.4
Missing	20		2.8

Exhibit 2 – 12
Treatments Given to Donor During Hospitalization
All Allograft Donors

	N	%
Total	712	100.0
Vasopressors used*		
Epinephrine hydrochloride	45	6.3
Dobutamine hydrochloride	30	4.2
Dopamine hydrochloride	371	52.1
Norephinephrine bitartrate	282	39.6
Phenylephrine hydrochloride	172	24.2
Pitressin/DDAVP	249	35.0
Total number of vasopressors used		
None	24	3.4
One	217	30.5
Two	275	38.6
Three	131	18.4
Four	23	3.2
Five	1	0.1
Unknown	4	0.6
Missing	37	5.2

* Multiple agents could be used, hence categories sum to >100%.

Exhibit 2-12 *(continued)*
Treatments Given to Donor During Hospitalization
All Allograft Donors

	N	%
Total	712	100.0
Transfusions given to donor during hospitalization		
0 units	420	59.0
0-5 units	151	21.2
6-10 units	38	5.3
>10 units	22	3.1
Unknown	54	7.6
Missing	27	3.8
Transfusions given to donor intraoperatively		
0 units	529	74.3
0-5 units	27	3.8
6-10 units	6	0.8
>10 units	2	0.3
Unknown	120	16.9
Missing	28	3.9
Steroids given to donor during hospitalization		
Yes	275	38.6
No	187	26.3
Unknown	228	32.0
Missing	22	3.1
Insulin given to donor during hospitalization		
Yes	245	34.4
No	382	53.7
Unknown	71	10.0
Missing	14	2.0

Exhibit 2 – 13
Donor Serology
All Allograft Donors

	N	%
Total	712	100.0
Anti HIV I/II		
Positive	-	0.0
Negative	689	96.8
Not Done/Unknown/Missing	23	3.2
Anti HTLV I/II		
Positive	-	0.0
Negative	668	93.8
Not Done/Unknown/Missing	44	6.2
RPR VDRL		
Positive	1	0.1
Negative	635	89.2
Not Done/Unknown/Missing	76	10.7
Anti CMV		
Positive	378	53.1
Negative	302	42.4
Not Done/Unknown/Missing	32	4.5
HBsAg		
Positive	-	0.0
Negative	682	95.8
Not Done/Unknown/Missing	30	4.2
Anti HBC		
*Positive	1	0.1
Negative	677	95.1
Not Done/Unknown/Missing	34	4.8
Anti HCV		
Positive	-	0.0
Negative	679	95.4
Not Done/Unknown/Missing	33	4.6

*Verified by center as correct. Donor was used for a hepatitis B immunized recipient.

Exhibit 2 – 14
Donor Laboratory Data
All Allograft Donors

	N	Mean	SD
Serum creatinine (mg/dL)	585	1.2	0.8
BUN (mg/dL)	476	15.2	8.5
Total bilirubin (mg/dL)	484	0.9	0.8
AST (IU/L)	509	75.5	214.9
ALT (IU/L)	507	59.4	172.7
Serum lipase (IU/L)	550	72.8	119.5
Serum amylase (IU/L)	577	166.8	333.2
Minimum pre-insulin blood glucose (mg/dL)	623	126.1	39.1
Maximum blood glucose (mg/dL)	583	239.0	91.8

Exhibit 2 – 15
Organ Crossmatch Results
All Allograft Donors

	N	%
Crossmatch for T-Cell		
Positive	2	0.3
Negative	398	55.9
Unknown	275	38.6
Missing	37	5.2
Crossmatch for B-Cell		
Positive	14	2.0
Negative	348	48.9
Unknown	312	43.8
Missing	38	5.3

Chapter 3
Pancreas Procurement, Islet Processing, and Infusion Characteristics

Pancreas Procurement, Islet Processing, and Infusion Characteristics

Summarized in this chapter are pancreas procurement, islet processing, and transplant surgery data reported to the Registry. Only pancreata used for clinical islet transplantation are included in this report. Exhibits in this section include data for all pancreata processed for islet cell allografts or all islet allograft infusions where applicable.

In about 64% of the procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team (Exhibit 3-1), while 90% of the processing procedures took place at the same institution as the islet transplant center. UW and Two Layer were the most common methods used for pancreas preservation (Exhibit 3-1). Other preservation solutions used in conjunction or in absence of UW and/or PFC included HTK, P Phase 2, Eurocollins, Celsoir, IGL-1 and SCOT solutions. The median duration of cold ischemia was 7 hours (range 1 to 27) (Exhibit 3-2).

Liberase HI was the collagenase type used for most islet processing (86%) followed by Blendzyme (7%) and NB1 (6%). All of the pancreata processed used a density gradient for islet purification. Forty-nine percent of islets were placed in culture, defined as six or more hours in any specially prepared nutrient medium. When cultured, the median culture time was 26 hours (range 6.0 to 96.0) (Exhibit 3-2). Of the 634 preparations reported to CITR, thirteen final preparations showed a positive aerobic culture (2.1%), six showed a positive anaerobic culture (1.3%), five showed a positive fungal culture (0.8%), and one preparation tested positive for mycoplasma (0.2%).

Exhibit 3-5 shows the islet cell characteristics by pancreas preservation method. Significant univariate correlations of islet product characteristics with donor, recovery, and processing characteristics are located in Exhibits 3-6 and 3-7. These results are described more thoroughly in a focus analysis currently in development. The results require further characterization with multivariate methods to confirm the observed trends.

Islet Infusion Information

Exhibit 3-4 summarizes the core infusion procedure characteristics overall and Exhibit 3-8 by the infusion number. The mean number of islet equivalents infused was lower for the second infusion compared to the first infusion. On average, if a participant received a second infusion, they received this infusion 23 weeks following their first infusion, while those receiving a third infusion received this infusion 60 weeks after their initial one and 48 weeks after their second infusion.

Portal pressures did not differ by infusion sequence (Exhibits 3-9 through 3-11). Change from pre-infusion to closure averaged 2-3 mmHg for all infusions.

Exhibit 3 – 1
Pancreas Procurement and Islet Processing

	N	%	% of Known
Total	712	100.0	100.0
Pancreas procurement team			
Unrelated to processing/infusion team	405	56.9	63.6
Related to processing/infusion team	232	32.6	36.4
Unknown	29	4.1	
Missing	46	6.7	
Islet processing/testing center			
Same location as infusion center	599	84.1	90.2
Other location than infusion center	65	9.1	9.8
Missing	48	6.7	
Pancreas preservation			
UW	382	53.7	56.0
Two Layer	215	30.2	31.5
UW followed by Two Layer	25	3.5	3.7
Neither UW nor Two Layer	60	8.4	8.8
Missing	30	4.2	
Other preservation solutions used*			
HTK	65	9.1	9.5
P Phase 2	13	1.8	1.9
Eurocollins	12	1.7	1.8
Celsior	3	0.4	0.4
IGL-1	2	0.3	0.3
SCOT	1	0.1	0.1

*Other preservation solutions used in conjunction with UW, Two Layer, both or neither.
"Two Layer" is defined as any Two Layer solution and includes Two Layer solutions of UW and PFC (N=232) as well as HTK and PFC (N=7) and SCOT and PFC (N=1).

Exhibit 3 – 1 *(continued)*
Pancreas Procurement and Islet Processing

	N	%	% of Known
Collagenase Type			
Liberase HI	593	83.3	86.4
Blendzyme	51	7.2	7.4
NB1	42	5.9	6.1
Collagenase P	4	0.6	0.6
Unknown	4	0.6	
Missing	22	3.1	
Islet purification			
Density gradient	665	93.4	100.0
Unknown	3	0.4	
Missing	44	6.2	
Islet pretreatment			
None	352	49.4	51.0
Culture**	338	47.5	49.0
Missing	22	3.1	

**Culture is defined as ≥ 6 hrs spent in a specially prepared nutrient medium.

Exhibit 3 – 1 *(continued)*
Pancreas Procurement and Islet Processing

	N	%	% of Known
Gram stain			
Positive	0	0.0	0.0
No organism seen	577	81.0	100.0
Unknown	121	17.0	
Missing	14	2.0	
Aerobic culture			
Positive	13	1.8	2.1
No Growth	614	86.2	97.9
Unknown	61	8.6	
Not Done	3	0.4	
Missing	21	2.9	
Anaerobic culture			
Positive	6	0.8	1.3
No Growth	467	65.6	98.7
Unknown	144	20.2	
Not Done	74	10.4	
Missing	21	2.9	
Fungal Culture			
Positive	5	0.7	0.8
No Growth	628	88.2	99.2
Unknown	53	7.4	
Not Done	6	0.8	
Missing	20	2.8	
Mycoplasma			
Positive	1	0.1	0.2
Negative	450	63.2	99.8
Unknown	46	6.5	
Not Done	197	27.7	
Missing	18	2.5	

Islet microbiology results represent the final culture results of the preparation.

Exhibit 3 – 2
Cold Ischemia Information

	N	Mean	SD	Median	Min	Max
Time from cross clamp to pancreas recovery (mins)	458	38.9	20.1	37.5	0.0	127.0
Duration of cold ischemia (hrs)	665	7.3	3.4	6.9	1.0	27.0
Time from brain death to pancreas recovery (hrs)	433	20.7	11.3	18.0	0.3	91.0
Culture time (hrs)	338	29.3	17.1	26.0	6.0	95.8

Time of brain death is defined as the physician-confirmed time documented in the medical chart. Time of cross clamp is defined as the time of aorta cross-clamp prior to organ retrieval. Duration of cold ischemia is defined as the time from pancreas placement in cold preservation solution to the heating up of the organ at the start of the digestion process. Culture is defined as ≥ 6 hrs spent in a specially prepared nutrient medium. Islet preparations placed in a nutrient medium for less than six hours (N=57) are not defined as "cultured."

Exhibit 3 – 3
Islet Equivalents and Timing of Count

	Total Islet Equivalents					
	N	Mean	SD	Median	Min	Max
Islet equivalents (IEQ) measured at:						
Post digestion	10	642,947	302,148	630,088	260,463	1,122,400
Post purification (Pre culture)	379	399,886	159,583	374,767	84,615	991,550
Post culture	294	377,944	141,024	373,320	54,453	1,014,000

This Exhibit represents the total Islet Equivalents (IEQs) measured from each individual pancreas at specified times of the count (eg., Post Digestion). Multiple pancreata are sometimes used for a single infusion procedure and will account for some of the counts in this Exhibit to be <100,000 IEQs.

Exhibit 3 – 4
Islet Product Characterization

	N	Mean	SD	Median	Min	Max
Total cell volume (mL)	666	3.5	2.1	3.0	0.5	16.0
Islet particle count	556	359,489.7	150,493.0	342,592.0	86,750.0	996,000.0
Embedded islets (%)	390	15.1	19.0	8.0	0.0	95.0*
Islet equivalents	697	393,531.0	158,985.5	373,550.0	54,453.0	1,122,400.0
Islet equivalents/kg donor weight	680	4,647.0	2,071.2	4,351.9	716.1	27,010.6
Beta cells ($x10^6$)	234	263.9	216.0	196.0	4.0*	975.0
Beta cells ($x10^6$) / kg donor weight	224	3.4	2.8	2.6	0.0	20.3
Insulin content (µgrams)	285	3,255.6	2,151.4	2,890.0	22.0	9,914.0
DNA content (µgrams)**	282	7,451.4	8,213.1	4,997.0	83.0*	55,111.0
Endotoxin units	569	28.1	55.2	5.0	0.0	540.6*
Endotoxin units/kg donor weight	554	0.3	0.6	0.1	0.0	6.6
Islet purity: Dithizone positive cells (%)	489	63.4	17.5	63.0	10.0	100.0*
Islet potency: Stimulation index	580	3.2	3.2	2.2	0.1	28.8
Islet Viability (%)						
Fluorescein Diacetate/Propidium Iodide	276	93.0	5.6	94.0	65.0	100.0*
Syto Green 13	165	86.9	7.1	88.0	63.0	99.0
Trypan Blue	113	92.9	5.1	95.0	72.0	100.0*
Fluorescein Diacetate/Ethidium Bromide	24	90.2	7.3	90.0	80.0	100.0
Syto Green/Ethidium Bromide	14	91.3	3.1	91.0	86.0	96.0

*Values verified by center as correct.
**Method of measurement unspecified.

Stimulation index is calculated as the glucose-stimulated insulin release at high glucose divided by the glucose-stimulated insulin release at low glucose.

Exhibit 3 – 5
Differences in Islet Characteristics by Pancreas Preservation Method
Univariate Analysis

	Pancreas Preservation Method						Statistically Significant at $p < 0.05$
	UW Only			Two Layer Only			
	N	Mean	SE	N	Mean	SE	
Total cell volume (mL)	339	3.6	0.1	192	3.4	0.1	
Islet particle count	300	368,132.8	8,331.3	152	340,167.8	11,811.5	
Embedded islets (%)	213	14.2	1.3	93	17.1	2.3	
Islet equivalents	361	395,258.9	7,691.5	195	371,732.5	11,011.4	
Islet equivalents/kg donor weight	350	4,768.3	114.8	193	4,289.2	121.5	✓
Beta cells ($x10^6$)	135	233.9	18.1	70	301.2	26.8	✓
Beta cells ($x10^6$)/kg donor weight	126	3.2	0.2	69	3.7	0.4	
Insulin content (µgrams)	170	3,338.1	172.2	83	3,287.6	215.1	
DNA content (µgrams)*	168	6,124.0	453.8	87	10,940.3	1,229.2	✓
Endotoxin units	280	30.6	3.6	170	26.0	3.8	
Endotoxin units/kg donor weight	271	0.4	<0.1	169	0.3	<0.1	
Islet purity: Dithizone positive cells (%)	234	63.4	1.2	149	62.2	1.4	
Islet potency: Stimulation index	313	3.2	0.2	167	2.9	0.2	

*Method of measurement unspecified.

Exhibit 3 – 6
Significant Relationships between Islet Outcomes and Categorical Predictors
Univariate Analysis

Donor, Procurement or Islet Processing (Independent) Variables	Islet Outcomes (Dependent variables)				
	Beta cells (X10E6)*				
	N	Q1	Median	Q3	p
Insulin given					
No	132	73	182	335	
Yes	70	156	295	453	<0.001
	Beta cells (X10E6)*				
Steroids given					
No	45	119	187	342	
Yes	38	169	276	423	0.06**
	Beta cells (X10E6)*				
Density gradient type					
Discontinuous	12	140	187	370	
Continuous	199	110	217	397	
Continuous with rescue gradient	11	13	96	187	0.01
	Islet equivalents				
Density gradient type					
Discontinuous	50	249,178	328,519	429,467	
Continuous	514	291,040	375,648	452,164	
Continuous with rescue gradient	58	313,325	390,556	536,735	0.007
	Insulin content (micrograms)				
Donor ABO blood group					
A	97	1,266	2,544	4,075	
B	13	2,024	2,204	3,757	
O	158	1,893	3,245	4,841	0.047
	Insulin content (micrograms)				
Steroids given					
No	70	1,704	3,382	5,396	
Yes	55	932	2,054	3,656	
Yes	337	89	94	96	0.004*

*Method of measurement unspecified.
* *Giving steroids may improve beta cells but reduce insulin content.

Exhibit 3 – 7
Univariate Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

Spearman Correlation Coefficients
Prob > |r| under H0: Rho=0
Number of Observations

		Total Cell Volume	Embedded Islets	Islet Particle Count	Islet Equivalents	IEQs/kg donor	Endotoxin Units/kg donor	Beta Cells/kg donor	Total Beta Cells
Donor Age	r	-0.12726	**-0.21313**	0.06383	-0.06039	-0.00343	-0.01009	-0.09314	-0.11295
	p	0.0012	**<.0001**	0.1396	0.1168	0.9294	0.8145	0.1667	0.0910
	N	646	**378**	537	676	668	543	222	225
Donor Weight in kgs	r	0.11361	0.01672	0.18969	**0.34134**	**-0.25806**	0.04622	**-0.20349**	0.04655
	p	0.0040	0.7485	<.0001	**<.0001**	**<.0001**	0.2818	**0.0023**	0.4892
	N	640	370	531	**670**	**670**	544	**223**	223
Donor Height in cms	r	0.07611	-0.02154	0.18019	0.14263	-0.09967	-0.04562	**-0.20336**	-0.10217
	p	0.0558	0.6830	<.0001	0.0002	0.0103	0.2904	**0.0024**	0.1309
	N	632	362	524	662	662	539	**220**	220
Donor Body Surface Area	r	0.12004	0.01656	**0.20403**	**0.33304**	**-0.24735**	0.02866	**-0.23847**	0.00172
	p	0.0025	0.7535	**<.0001**	**<.0001**	**<.0001**	0.5067	**0.0004**	0.9798
	N	632	362	**524**	**662**	**662**	539	**220**	220
Donor Body Mass Index (kg/m2)	r	0.07152	0.03182	0.11841	**0.29522**	**-0.21580**	0.06063	-0.10420	0.10391
	p	0.0724	0.5462	0.0067	**<.0001**	**<.0001**	0.1598	0.1233	0.1244
	N	632	362	524	**662**	**662**	539	220	220
Donor Min Pre-insulin Blood Glucose level	r	0.01915	0.05587	-0.03712	-0.07361	-0.04558	0.02860	-0.11344	-0.16136
	p	0.6426	0.3094	0.4166	0.0688	0.2642	0.5289	0.1071	0.0187
	N	590	333	481	612	602	487	203	212
Donor Maximum Blood Glucose level	r	-0.00619	0.05489	0.01413	0.09012	0.07906	0.17153	-0.04346	-0.04073
	p	0.8852	0.3483	0.7674	0.0313	0.0611	0.0002	0.5770	0.5926
	N	547	294	441	571	562	475	167	175
Donor HbA_{1c}	r	0.17261	0.28293	0.07781	0.11214	-0.01022	0.03012	-0.04318	0.05394
	p	0.0583	0.0852	0.4235	0.2169	0.9107	0.7504	0.7808	0.7280
	N	121	38	108	123	123	114	44	44
Donor Serum Creatinine	r	0.06550	0.06652	0.10245	0.19479	0.03609	-0.00213	-0.00511	0.05670
	p	0.1278	0.2734	0.0327	<.0001	0.3893	0.9624	0.9510	0.4952
	N	542	273	435	572	571	490	147	147
Donor BUN	r	0.08139	0.01036	0.04412	0.12257	0.04029	-0.06159	-0.02961	-0.02591
	p	0.0907	0.8942	0.4272	0.0083	0.3871	0.2208	0.7805	0.8074
	N	433	167	326	463	463	397	91	91
Donor Total bilirubin	r	0.05437	0.05598	0.04701	0.11085	-0.02091	0.07873	0.15988	0.19692
	p	0.2546	0.4593	0.3918	0.0161	0.6508	0.1132	0.1279	0.0599
	N	441	177	334	471	471	406	92	92
Donor AST	r	0.04635	0.01028	-0.08407	-0.03694	0.01230	0.00001	0.00877	-0.00132
	p	0.3181	0.8851	0.1118	0.4117	0.7849	0.9998	0.9332	0.9899
	N	466	200	359	496	495	429	94	94
Donor ALT	r	0.01738	-0.03268	-0.03502	0.03420	0.04726	-0.01484	0.05297	0.05205
	p	0.7089	0.6477	0.5095	0.4482	0.2950	0.7601	0.6102	0.6164
	N	464	198	357	494	493	426	95	95
Donor Serum Lipase	r	0.03697	-0.02403	0.01554	0.03860	0.05649	-0.01805	-0.04453	-0.03756
	p	0.4047	0.6916	0.7546	0.3711	0.1912	0.7009	0.5835	0.6426
	N	510	275	407	539	537	455	154	155

The rank correlation coefficient (r) measures the strength of a rank relationship between two variables. Donor weight, BMI and BSA are mutually correlated; any of them impacts particle count and IEQs recovered. IEQs/kg donor and Beta cells/kg donor are then necessarily inversely correlated with the predictors of weight, BMI and BSA.

Exhibit 3 – 7 *(continued)*
Univariate Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations									
`		**Total Cell Volume**	**Embedded Islets**	**Islet Particle Count**	**Islet Equivalents**	**IEQs/kg donor**	**Endotoxin Units/kg donor**	**Beta Cells/kg donor**	**Total Beta Cells**
Donor Serum Amylase	r p N	0.02186 0.6142 534	0.00626 0.9179 273	-0.04428 0.3608 428	-0.10706 0.0110 564	-0.06327 0.1341 562	-0.09842 0.0324 473	-0.04094 0.6201 149	-0.07878 0.3379 150
Time from cross clamp to pancreas recovery (mins)	r p N	-0.01518 0.7567 419	-0.08127 0.2216 228	0.01345 0.8055 338	-0.17980 0.0001 445	-0.17615 0.0002 445	-0.12450 0.0176 363	-0.06999 0.3838 157	-0.05032 0.5314 157
Time from brain death to pancreas recovery (hrs)	r p N	-0.04513 0.3698 397	-0.02571 0.7071 216	0.08473 0.1335 315	0.15756 0.0012 420	0.05213 0.2865 420	0.05634 0.2967 345	0.09699 0.2442 146	0.15088 0.0691 146
Duration of cardiac arrest where cardiovascular death (mins)	r p N	0.04420 0.7486 55	0.00928 0.9553 39	0.01701 0.9107 46	0.09526 0.4652 61	-0.06701 0.6079 61	-0.07290 0.6341 45	0.07163 0.7453 23	0.14305 0.5150 23
Pre-Treatment (0=None 1=Culture)	r p N	-0.07191 0.0655 657	0.00564 0.9122 385	-0.15491 0.0003 548	-0.13782 0.0003 687	-0.14756 0.0001 670	**-0.24552** **<.0001** **544**	**0.35894** **<.0001** **223**	**0.42445** **<.0001** **233**
Culture time (hrs)	r p N	-0.17996 0.0011 328	-0.01555 0.8275 199	0.01715 0.7736 284	0.08409 0.1234 337	0.04758 0.3882 331	**0.34084** **<.0001** **284**	0.01230 0.9049 97	0.04140 0.6872 97

Culturing islets, vs. not culturing them, reduces endotoxin and increases Beta cells.
Longer culture time, when cultured, increases endotoxin but lessens other effects on islet characteristics.

Exhibit 3 – 7 *(continued)*
Univariate Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations								
		Insulin Content	**DNA Content**	**Total Endotoxin Units**	**Viability (%)**	**Stimulation Index**	**Average Islet Size**	**Islet Size Category (0=Small 1=Large)**
Donor Age	r p N	0.00260 0.9656 277	-0.14599 0.0162 271	-0.01696 0.6921 548	-0.07609 0.0601 611	-0.06189 0.1436 560	-0.13838 0.0013 535	-0.12783 0.0031 535
Donor Weight in kgs	r p N	0.04223 0.4855 275	-0.05273 0.3882 270	0.14306 0.0008 544	0.11715 0.0038 608	0.06002 0.1572 557	0.16373 0.0002 529	0.15526 0.0003 529
Donor Height in cms	r p N	0.10614 0.0806 272	-0.01754 0.7755 267	-0.00685 0.8739 539	0.08948 0.0281 602	0.06991 0.1005 553	-0.02046 0.6409 522	0.00135 0.9755 522
Donor Body Surface Area	r p N	0.07022 0.2484 272	-0.04454 0.4687 267	0.12464 0.0038 539	0.11797 0.0037 602	0.07234 0.0892 553	0.14423 0.0010 522	0.13606 0.0018 522
Donor Body Mass Index (kg/m2)	r p N	0.01715 0.7783 272	-0.05517 0.3692 267	0.14453 0.0008 539	0.08394 0.0395 602	0.04513 0.2894 553	0.18784 <.0001 522	0.16201 0.0002 522
Donor Min Pre-insulin Blood Glucose level	r p N	0.05471 0.3805 259	-0.00782 0.9013 254	0.02037 0.6512 495	-0.09683 0.0224 556	0.04818 0.2686 529	-0.02982 0.5142 481	-0.02202 0.6300 481
Donor Maximum Blood Glucose level	r p N	-0.05916 0.3814 221	-0.07716 0.2566 218	0.16439 0.0003 483	0.08390 0.0509 542	-0.00184 0.9677 487	0.08542 0.0731 441	0.06326 0.1848 441
Donor HbA_{1c}	r p N	0.11053 0.4005 60	0.00515 0.9683 62	0.07113 0.4520 114	0.03084 0.7338 124	-0.23732 0.0125 110	0.06026 0.5356 108	0.00548 0.9551 108
Donor Serum creatinine	r p N	0.03396 0.6374 195	0.08885 0.2241 189	0.02833 0.5312 491	0.08618 0.0432 551	0.06047 0.1926 466	0.14285 0.0029 433	0.15833 0.0009 433
Donor BUN	r p N	0.05656 0.5179 133	-0.01513 0.8659 127	-0.04532 0.3678 397	0.02211 0.6403 449	0.12323 0.0174 372	0.09512 0.0874 324	0.12190 0.0282 324
Donor Total bilirubin	r p N	**0.23781** **0.0058** **133**	-0.00697 0.9378 128	0.10051 0.0430 406	0.05824 0.2140 457	0.12998 0.0115 377	0.06764 0.2190 332	0.06794 0.2169 332
Donor AST	r p N	0.05119 0.5525 137	0.06454 0.4639 131	0.00281 0.9536 430	-0.02859 0.5311 482	0.01347 0.7887 398	0.03823 0.4715 357	-0.01119 0.8331 357
Donor ALT	r p N	0.07933 0.3515 140	-0.07701 0.3765 134	-0.00486 0.9202 427	-0.02533 0.5799 480	0.07440 0.1395 396	0.06156 0.2473 355	0.04461 0.4021 355
Donor Serum Lipase	r p N	0.07163 0.3197 195	-0.00741 0.9187 192	-0.02014 0.6680 456	0.02612 0.5596 501	0.06420 0.1764 445	0.08440 0.0898 405	0.05009 0.3146 405

Exhibit 3 – 7 *(continued)*
Univariate Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations								
		Insulin Content	**DNA Content**	**Total Endotoxin Units**	**Viability (%)**	**Stimulation Index**	**Average Islet Size**	**Islet Size Category (0=Small 1=Large)**
Donor Serum Amylase	r p N	0.00177 0.9805 195	-0.00183 0.9799 191	-0.10465 0.0227 474	0.01606 0.7111 534	0.04416 0.3457 458	-0.08303 0.0870 426	-0.07537 0.1203 426
Time from cross clamp to pancreas recovery (mins)	r p N	-0.04424 0.5444 190	0.00596 0.9364 182	-0.13032 0.0130 363	-0.12691 0.0099 412	0.04517 0.3889 366	-0.13693 0.0119 337	-0.09922 0.0689 337
Time from brain death to pancreas recovery (hrs)	r p N	-0.12711 0.0918 177	-0.09733 0.2067 170	0.06796 0.2079 345	0.07943 0.1188 387	0.13925 0.0092 349	0.05599 0.3219 315	0.04818 0.3941 315
Duration of cardiac arrest where cardiovascular death (mins)	r p N	-0.11974 0.5773 24	0.34234 0.0805 27	-0.00634 0.9671 45	0.12357 0.3687 55	0.08608 0.5360 54	0.08057 0.5946 46	0.16715 0.2669 46
Pre-Treatment (0=None 1=Culture)	r p N	-0.05280 0.3754 284	0.18018 0.0025 280	**-0.23483** **<.0001** **559**	-0.16223 <.0001 623	0.00637 0.8793 571	0.02249 0.6000 546	0.03545 0.4084 546
Culture time (hrs)	r p N	-0.17816 0.0496 122	0.06717 0.4661 120	**0.31661** **<.0001** **290**	0.18353 0.0008 331	0.11322 0.0580 281	0.10539 0.0762 284	0.03796 0.5240 284

Exhibit 3 – 8
Islet Product and Infusion Characteristics by Infusion Sequence

	Islet Alone								
	Infusion 1			Infusion 2			Infusion 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Islet Equivalents Infused	270	446,261.8	149,621.3	183	413,385.2	153,512.8	61	416,116.7	175,139.9
Islet Equivalents Infused / kg recipient body weight	263	6,803.4	2,510.5	175	6,408.3	2,491.2	56	6,435.3	3,058.4
Embedded islets (%)	173	14.5	17.8	129	15.2	17.9	36	17.0	19.7
Cell volume (mL)	257	4.2	2.2	179	3.7	1.9	60	3.5	1.8
Time since first infusion (weeks)	0	-	-	202	24.7	36.1	65	61.5	68.4
Time since second infusion (weeks)	0	-	-	0	-	-	65	49.5	66.8
	Islet after Kidney								
	Infusion 1			**Infusion 2**			**Infusion 3**		
	N	**Mean**	**SD**	**N**	**Mean**	**SD**	**N**	**Mean**	**SD**
Islet Equivalents Infused	42	468,836.6	155,167.4	30	377,921.3	120,227.5	8	311,606.0	127,679.1
Islet Equivalents Infused / kg recipient body weight	40	7,810.8	2,761.7	28	6,446.6	2,519.5	6	4,439.3	1,670.5
Embedded islets (%)	10	17.4	18.3	9	7.2	10.0	1	10.0	-
Cell volume (mL)	31	4.3	2.4	26	4.2	2.6	7	4.3	1.4
Time since first infusion (weeks)	0	-	-	39	16.8	24.8	12	51.3	72.9
Time since second infusion (weeks)	0	-	-	0	-	-	12	40.0	70.3

Exhibit 3 – 9
Pre Infusion Portal Pressure by Infusion Sequence

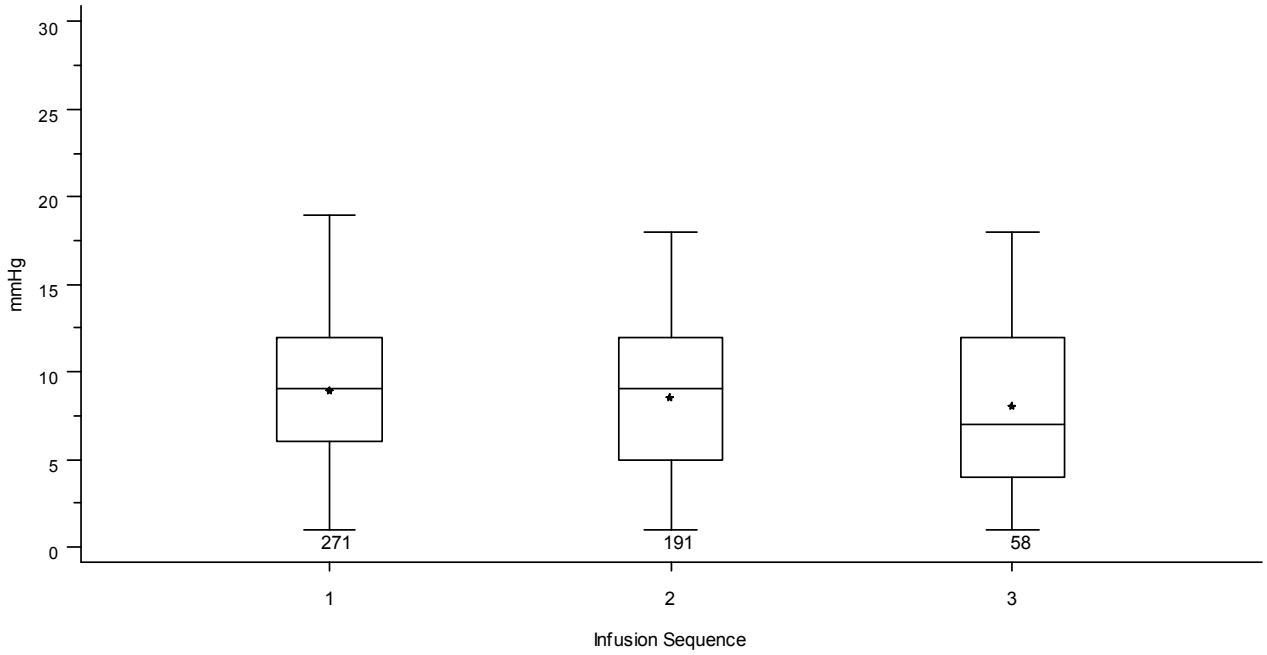


Exhibit 3 – 10
Peak Portal Pressure by Infusion Sequence

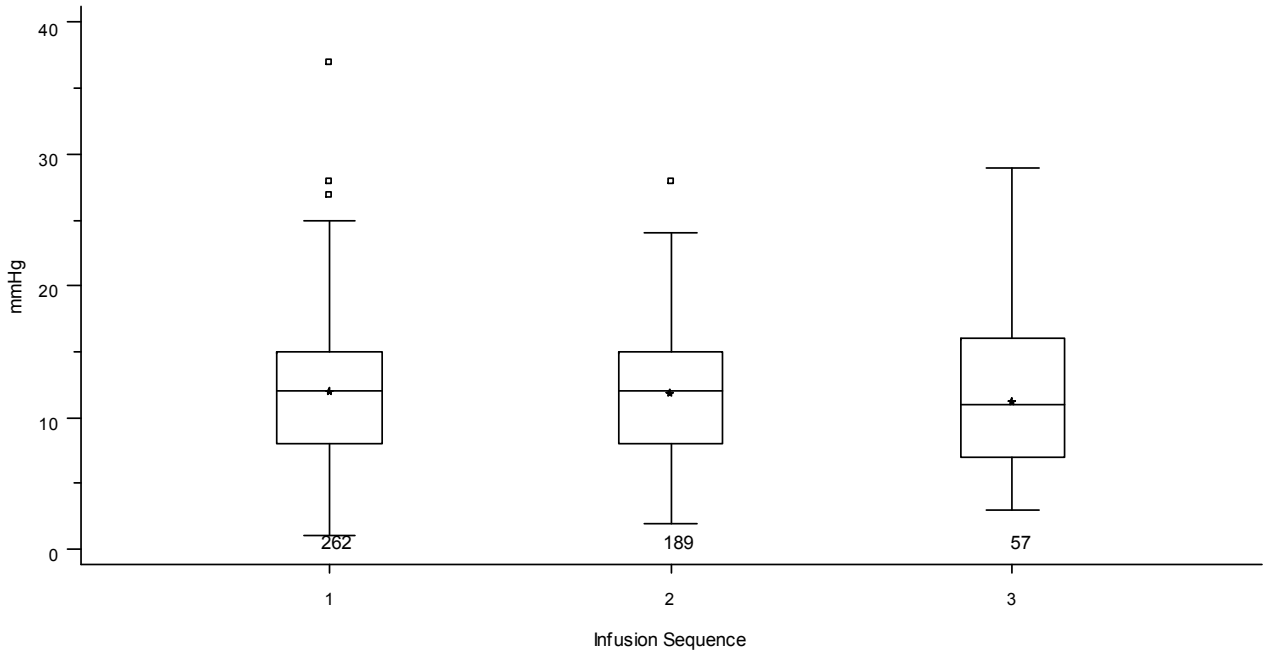


Exhibit 3 – 11
Closure Portal Pressure by Infusion Sequence

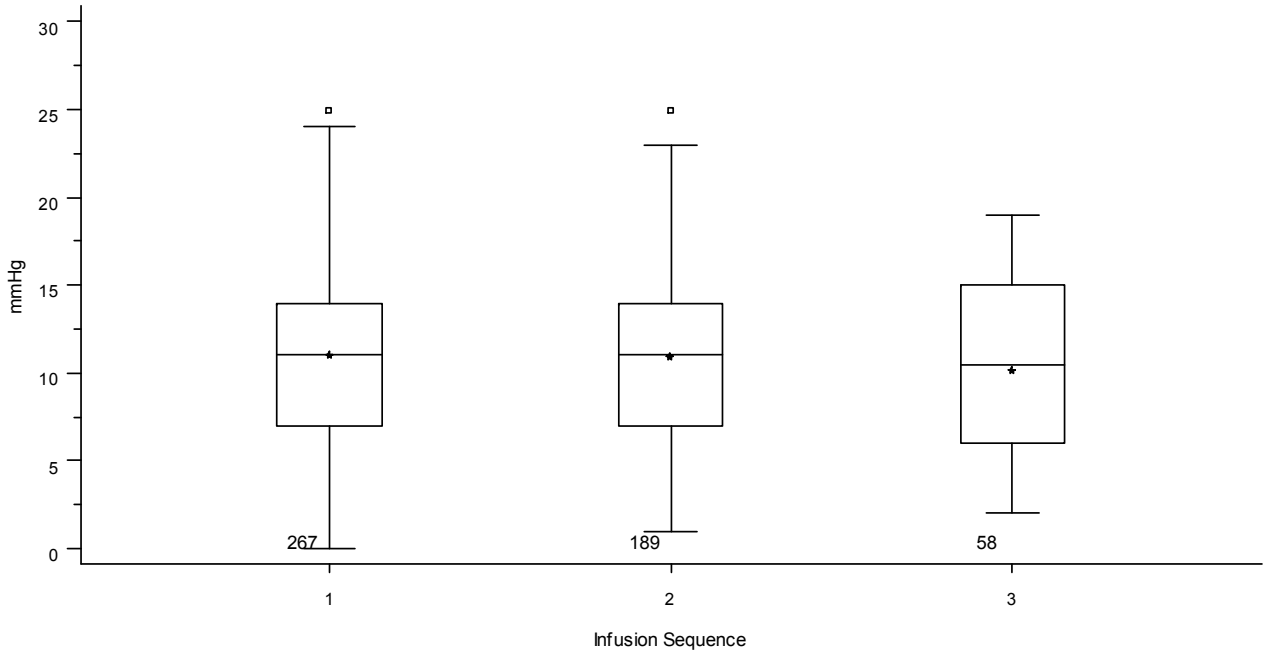


Exhibit 3 – 12
Change from Pre Infusion to Closure Portal Pressure by Infusion Sequence

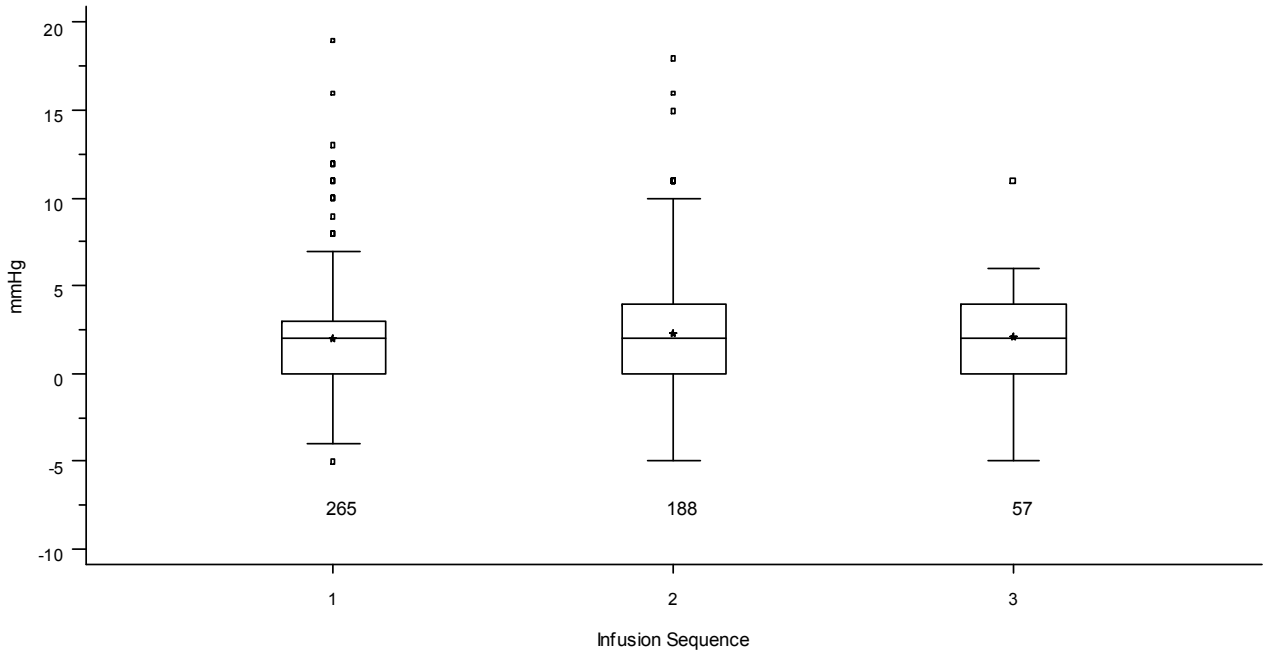


Exhibit 3 – 13
Change from Pre Infusion to Peak Portal Pressure by Infusion Sequence

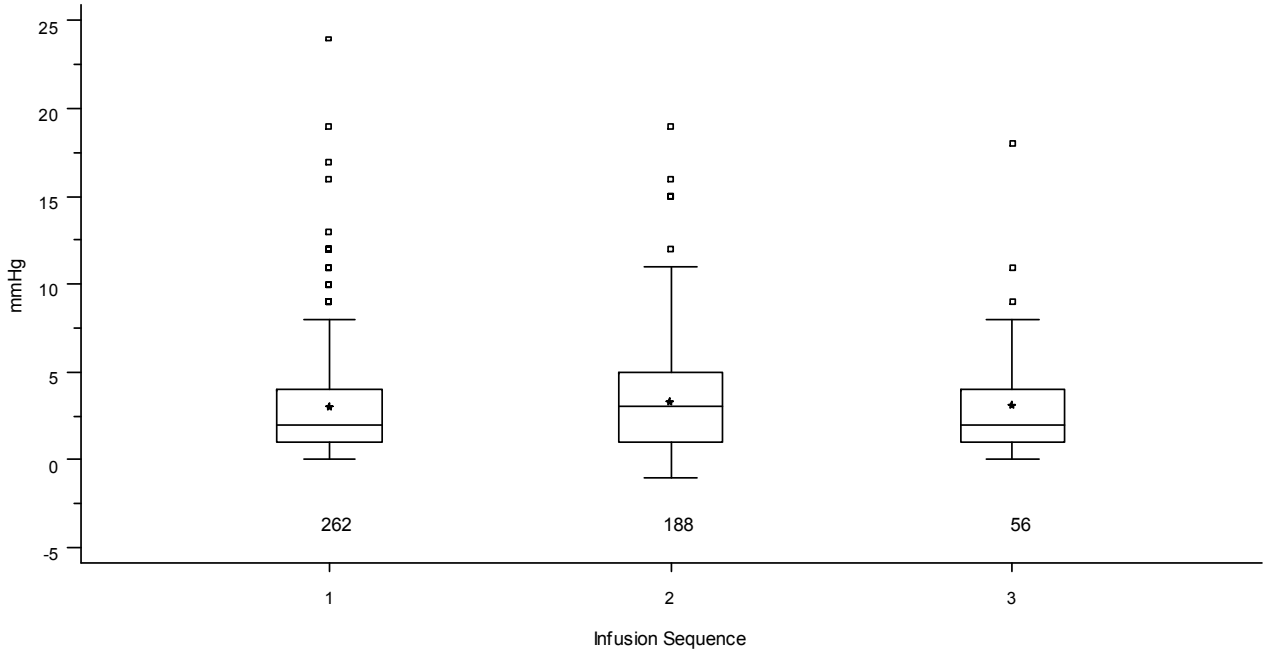
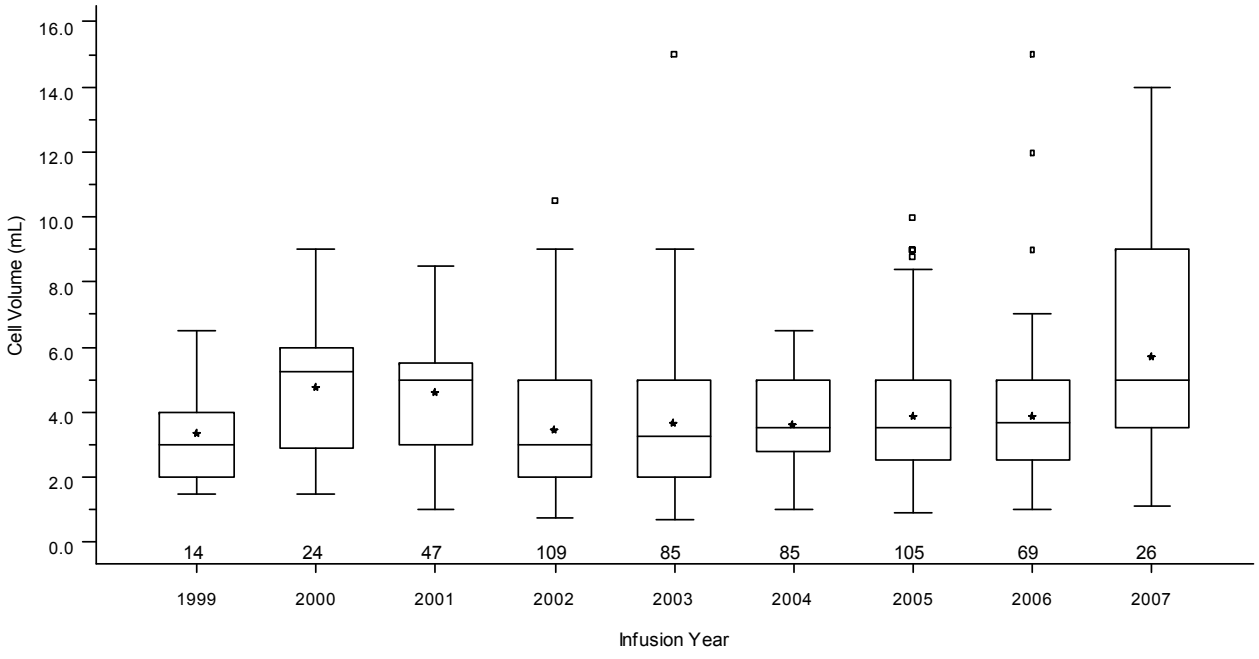
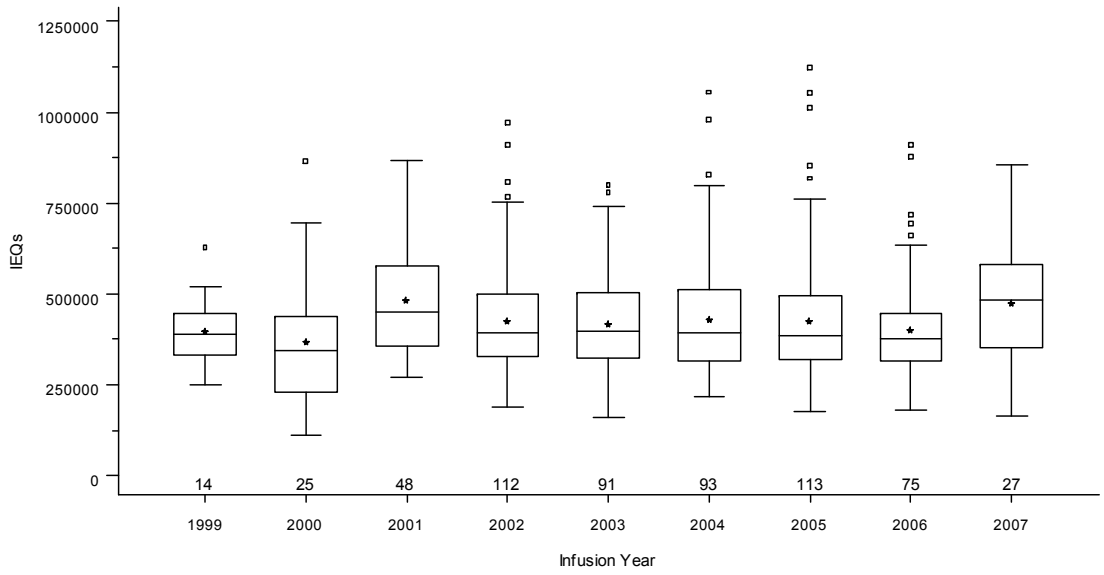


Exhibit 3 – 14
Cell Volume Infused per Infusion by Infusion Year



This graph represents both settled and packed cell volumes depending on center procedure. Higher volumes typically represent unpacked cells.

Exhibit 3 – 15
IEQs Infused per Infusion by Infusion Year



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Chapter 4
Immunosuppression and Other Medications

Immunosuppression and Other Medications

Immunosuppressive, anti-hypertensive, and lipid lowering medications, as well as a summary of the administration of adjunctive therapies used by the islet transplant recipients are included in this chapter of the report. The majority of the islet transplant alone (IA) recipients at the time of first infusion were given a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen alone (59%). A number of other immunosuppression regimens (N=25) were used and are listed in Exhibit 4-1.

A summary of antibodies used for the participant's first infusion is displayed in Exhibit 4-2. Daclizumab was the sole T-cell antibody used in 65% of first infusions for IA recipients. Dosing for the immunosuppressive medications at induction (dosing by mg/day and the mean total dose) are located in Exhibits 4-3 and 4-4. Maintenance therapy regimens and dosing information are located in Exhibits 4-5 and 4-6. Sirolimus and Tacrolimus trough levels at Day 30 for each infusion (1, 2, and 3), as well as trough levels at Month 6, Year 1, Year 2, and Year 3 post last infusion are presented as boxplots in Exhibits 4-7 and 4-8.

Prior to the first infusion, 41% of the recipients were on at least one anti-hypertensive medication (Exhibits 4-9 and 4-10) and 32% were on a lipid lowering medication (Exhibits 4-11 and 4-12). By Year 1 post last infusion, these rates increased to 52% and 61%, respectively. Percentages are based on participants with complete medication information. For adjunctive therapies, at the time of their first infusion (Exhibit 4-13), 99% of recipients used an antibiotic, 88% used antivirals, and 78% used vitamin supplements. The most common adjunctive therapies used during follow-up (Exhibit 4-14) included vitamin supplements (18% at Month 6 and 16% at Year 1) and Pentoxifylline (13% at Month 6).

Exhibit 4 – 1
Immunosuppression Regimen at Time of First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	279	100.0	46	100.0
Daclizumab + Sirolimus + Tacrolimus	155	55.6	22	47.8
Daclizumab + Sirolimus + Tacrolimus + MMF	3	1.1	2	4.3
Daclizumab + Sirolimus + Tacrolimus + Prednisone	-	0.0	2	4.3
Daclizumab + Sirolimus + Tacrolimus + MMF + Prednisone	-	0.0	1	2.2
Daclizumab + Sirolimus + Tacrolimus + Azathiopine + Prednisone	-	0.0	1	2.2
Daclizumab + Tacrolimus + MMF	-	0.30	1	2.2
Daclizumab + Tacrolimus + MMF + Prednisone	-	0.0	4	8.7
Daclizumab + Infliximab + Sirolimus + Tacrolimus	18	6.5	2	4.3
Daclizumab + Etanercept + Sirolimus + Tacrolimus	9	3.2	1	2.2
Daclizumab + Etanercept + Sirolimus + Tacrolimus + MMF	-	0.0	1	2.2
Daclizumab + Etanercept + Sirolimus + Tacrolimus + MMF + Methylprednisolone	-	0.0	1	2.2
Daclizumab + 15-deoxyspergualin + Sirolimus + Tacrolimus	5	1.8	-	0.0
Daclizumab + Neoral Cyclosporine + MMF	-	0.0	1	2.2
Daclizumab + Efalizumab + Tacrolimus + MMF	1	0.4	-	0.0
Basiliximab + Sirolimus + Tacrolimus	1	0.4	-	0.0
Basiliximab + Etanercept + Sirolimus + Tacrolimus	11	3.9	-	0.0
Basiliximab + Etanercept + MMF + Mycophenolic Acid + Generic Cyclosporine	-	0.0	1	2.2
Anti-Thymocyte Globulin + Daclizumab + Sirolimus + Tacrolimus	4	1.4	-	0.0
Anti-Thymocyte Globulin + Daclizumab + Sirolimus + MMF	1	0.4	-	0.0
Anti-Thymocyte Globulin + Daclizumab + Etanercept + Sirolimus + Tacrolimus	1	0.4	-	0.0
Anti-Thymocyte Globulin + Daclizumab + Etanercept + Sirolimus + Tacrolimus + MMF + Methylprednisolone	7	2.5	-	0.0

(continued on following page)

Exhibit 4 – 1 *(continued)*
Immunosuppression Regimen at Time of First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Anti-Thymocyte Globulin + Tacrolimus + MMF	1	0.4	-	0.0
Anti-Thymocyte Globulin + Sirolimus + MMF + Methylprednisolone	3	1.1	-	0.0
Anti-Thymocyte Globulin + MMF + Neoral Cyclosporine + Prednisone	-	0.0	1	2.2
Anti-Thymocyte Globulin + Intravenous Immunoglobulin + Sirolimus + Tacrolimus	1	0.4	-	0.0
Anti-Thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus	2	0.7	-	0.0
Anti-Thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus + MMF + Methylprednisolone	-	0.0	1	2.2
Anti-Thymocyte Globulin + Etanercept + Tacrolimus + MMF	1	0.4	-	0.0
Anti-Thymocyte Globulin + Etanercept + Tacrolimus + MMF + Prednisone	-	0.0	1	2.2
Anti-Thymocyte Globulin + Etanercept + Neoral Cyclosporine + Everolimus	1	0.4	-	0.0
Anti-Thymocyte Globulin + Etanercept + Neoral Cyclosporine + Methylprednisolone + Everolimus	5	1.8	-	0.0
Anti-Thymocyte Globulin + Efalizumab + Sirolimus + Methylprednisolone	5	1.8	-	0.0
Alemtuzumab + Sirolimus + Tacrolimus	8	2.9	-	0.0
Alemtuzumab + Tacrolimus + MMF	6	2.2	-	0.0
Alemtuzumab + Etanercept + Sirolimus + Tacrolimus	5	1.8	-	0.0
Alemtuzumab + Infliximab + Sirolimus + Tacrolimus	1	0.4	-	0.0
hOKT3γ-1 (Ala-Ala) + Sirolimus + Tacrolimus	6	2.2	-	0.0
hOKT3γ-1 (Ala-Ala)+ Etanercept + Sirolimus + Tacrolimus	2	0.7	-	0.0
Missing Information on Immunosuppression	16	5.7	3	6.5

Exhibit 4 – 2
Antibodies Used Peri First Infusion for Induction Therapy

	Allograft Type			
	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	263	100.0	43	100.0
Daclizumab Alone	163	62.0	34	79.1
Daclizumab + Anti-Thymocyte Globulin	5	1.9	-	0.0
Daclizumab + Anti-Thymocyte Globulin + Etanercept	8	3.0	-	0.0
Daclizumab + Infliximab	18	6.8	2	4.7
Daclizumab + Etanercept	9	3.4	3	7.0
Daclizumab + Efalizumab	1	0.4	-	0.0
Alemtuzumab Alone	14	5.3	-	0.0
Alemtuzumab + Etanercept	5	1.9	-	0.0
Alemtuzumab + Infliximab	1	0.4	-	0.0
Anti-Thymocyte Globulin Alone	5	1.9	1	2.3
Anti-Thymocyte Globulin + Etanercept	9	3.4	2	4.7
Anti-Thymocyte Globulin + Efalizumab	5	1.9	-	0.0
Basiliximab Alone	1	0.4	0	0.0
Basiliximab + Etanercept	11	4.2	1	2.3
hOKT3γ-1(Ala-Ala) Alone	8	3.0	-	0.0

Exhibit 4 – 3
Antibody Dosing at Time of Infusion by Infusion Sequence

	Islet Alone									Islet After Kidney								
	Infusion 1			Infusion 2			Infusion 3			Infusion 1			Infusion 2			Infusion 3		
	N	Total Dose Mean	SD	N	Total Dose Mean	SD	N	Total Dose Mean	SD	N	Total Dose Mean	SD	N	Total Dose Mean	SD	N	Total Dose Mean	SD
Daclizumab (mg/kg)	161	3.7	1.7	115	4.1	2.1	44	3.9	1.9	35	3.6	2.3	27	3.6	2.4	4	5.2	3.1
Basiliximab (mg)	11	38.2	6.0	5	88.0	107.3	0	-	-	1	20.0	-	1	20.0	-	1	20.0	-
Infliximab (mg/kg)	14	8.0	2.4	4	10.0	0.0	1	10.0	-	2	10.0	0.0	1	10.0	-	0	-	-
Etanercept (mg)	43	127.9	25.1	25	131.0	27.3	10	122.5	34.3	6	120.8	48.5	4	143.8	12.5	0	-	-
Anti-Thymocyte Globulin (mg/kg)	19	5.5	1.0	0	-	-	0	-	-	2	5.3	0.8	0	-	-	0	-	-
Alemtuzumab (mg)	8	35.0	7.6	3	40.0	0.0	0	-	-	0	-	-	0	-	-	0	-	-
hOKT3γ-1 (Ala-Ala) (mg/kg)	8	0.7	0.1	0	-	-	0	-	-	0	-	-	0	-	-	0	-	-

Exhibit 4 – 4
Immunosuppression Dosing (mg/day) at Time of Infusion by Infusion Sequence

	Islet Alone									Islet After Kidney								
	Infusion 1			Infusion 2			Infusion 3			Infusion 1			Infusion 2			Infusion 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	243	11.0	3.3	165	7.7	3.0	51	7.9	3.2	30	5.5	2.8	26	6.8	2.4	6	6.8	1.7
Tacrolimus (mg/day)	243	2.5	1.8	171	3.9	2.0	55	4.5	2.0	35	3.4	1.8	30	4.1	1.8	8	5.1	1.6
MMF (mg/day)	23	1315.2	699.9	15	1248.0	576.7	11	1340.9	726.9	13	976.2	549.5	7	1392.9	643.2	3	1500.0	866.0
Prednisone (mg/day)	0	-	-	0	-	-	0	-	-	10	32.8	77.1	8	39.8	85.9	3	20.0	18.0
Methylprednisolone (mg/day)	20	140.2	93.3	0	-	-	0	-	-	2	51.0	69.3	0	-	-	0	-	-
Generic Cyclosporine (mg/day)	0	-	-	0	-	-	0	-	-	1	125.0	-	0	-	-	0	-	-
Neoral Cyclosporine (mg/day)	6	216.7	66.5	4	437.5	189.8	0	-	-	2	287.5	123.7	1	200.0	-	2	287.5	123.7
15-deoxyspergualin (mg/day)	5	117.6	9.5	4	111.0	14.3	2	107.0	9.9	0	-	-	0	-	-	0	-	-
Everolimus (mg/day)	6	3.0	0.0	4	2.3	0.5	0	-	-	0	-	-	0	-	-	0	-	-
Mycophenolic Acid (mg/day)	0	-	-	1	1440.0	-	1	1440.0	-	1	500.0	-	1	720.0	-	1	360.0	-

Exhibit 4 – 5
Immunosuppression Therapy Use at Specified Times Post Last Infusion
Allograft Recipients without Reported Graft Failure at the Time of Follow-Up

	Islet Alone								Islet After Kidney							
	Follow-Up								Follow-Up							
	6 Months		1 Year		2 Years		3 Years		6 Months		1 Year		2 Years		3 Years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	248	100.0	225	100.0	166	100.0	108	100.0	39	100.0	33	100.0	26	100.0	22	100.0
Daclizumab + Sirolimus + Tacrolimus	14	5.6	10	4.4	3	1.8	-	0.0	2	5.1	2	6.1	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus + MMF	-	0.0	-	0.0	-	0.0	-	0.0	1	2.6	-	0.0	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	1	2.6	1	3.0	-	0.0	-	0.0
Daclizumab + Sirolimus + MMF	1	0.4	-	0.0	1	0.6	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Tacrolimus + MMF	-	0.0	2	0.9	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus + MMF + Methylprednisolone	-	0.0	-	0.0	-	0.0	-	0.0	1	2.6	-	0.0	-	0.0	-	0.0
Daclizumab + Tacrolimus + Mycophenolic Acid	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Anti-thymocyte Globulin + Sirolimus + MMF	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Anti-thymocyte Globulin + Sirolimus + Tacrolimus	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Efalizumab + Sirolimus + MMF	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Efalizumab + Tacrolimus + MMF	1	0.4	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Tacrolimus	125	50.4	111	49.3	65	39.2	34	31.5	17	43.6	13	39.4	12	46.2	8	36.4
Sirolimus + Tacrolimus + MMF	15	6.0	12	5.3	9	5.4	8	7.4	-	0.0	1	3.0	1	3.8	-	0.0
Sirolimus + Tacrolimus + Mycophenolic Acid	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Tacrolimus + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	3	7.7	2	6.1	1	3.8	2	9.1
Sirolimus + Tacrolimus + Other Steroid	-	0.0	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0

(*Continued on next page*)

Exhibit 4 – 5 *(continued)*
Immunosuppression Therapy Use at Specified Times Post Last Infusion
Allograft Recipients without Reported Graft Failure at the Time of Follow-Up

	Islet Alone								Islet After Kidney							
	Follow-Up								Follow-Up							
	6 Months		1 Year		2 Years		3 Years		6 Months		1 Year		2 Years		3 Years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sirolimus	-	0.0	-	0.0	1	0.6	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + MMF	8	3.2	9	4.0	3	1.8	4	3.7	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Mycophenolic Acid	1	0.4	1	0.4	1	0.6	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Neoral Cyclosporine + MMF	-	0.0	-	0.0	-	0.0	1	0.9	-	0.0	-	0.0	-	0.0	-	0.0
Azathioprine + Sirolimus + Prednisone	-	0.0	1	0.4	1	0.6	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus	1	0.4	-	0.0	2	1.2	1	0.9	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus + MMF	19	7.7	19	8.4	14	8.4	12	11.1	1	2.6	2	6.1	3	11.5	2	9.1
Tacrolimus + Mycophenolic Acid	1	0.4	3	1.3	3	1.8	1	0.9	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	1	2.6	2	6.1	-	0.0	-	0.0
Tacrolimus + MMF + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	3	7.7	2	6.1	2	7.7	-	0.0
Mycophenolic Acid + Neoral Cyclosporine	1	0.4	2	0.9	1	0.6	1	0.9	-	0.0	-	0.0	-	0.0	-	0.0
Mycophenolic Acid + Neoral Cyclosporine + Everolimus	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Neoral Cyclosporine + MMF	-	0.0	-	0.0	3	1.8	1	0.9	-	0.0	-	0.0	-	0.0	-	0.0
Neoral Cyclosporine + Everolimus	4	1.6	3	1.3	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Neoral Cyclosporine + MMF + Everolimus	-	0.0	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Neoral Cyclosporine + MMF + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	3.0	-	0.0	1	4.5
Generic Cyclosporine + Mycophenolic Acid	-	0.0	-	0.0	1	0.6	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Generic Cyclosporine + MMF + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	3.8	-	0.0
No Immunosupressant Medications Taken	5	2.0	2	0.9	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	4.5
Missing Information on Immunosuppression	46	18.5	47	20.9	58	34.9	45	41.7	9	23.1	7	21.2	6	23.1	8	36.4

*Majority of unknown information due to unsubmitted follow-up forms to the Registry as of the datafile closure.

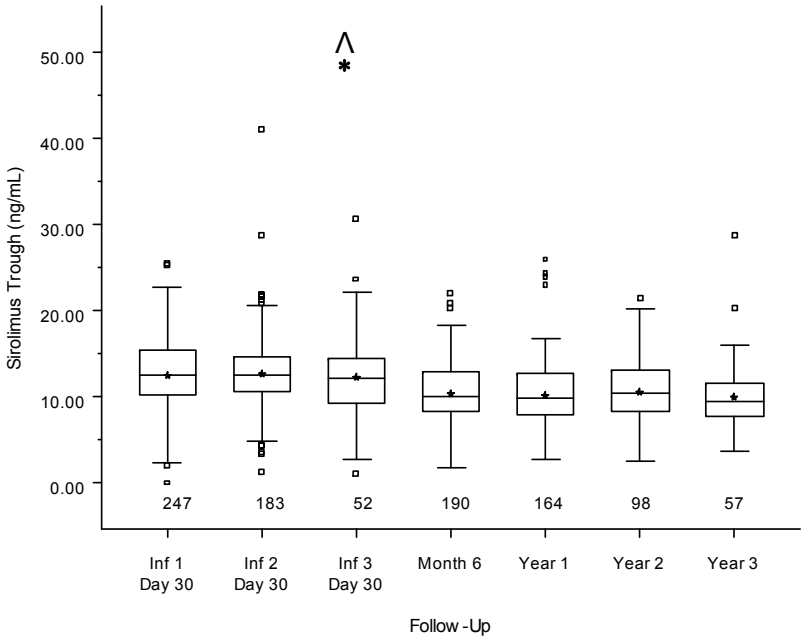
Exhibit 4 – 6
Immunosuppression Dosing Post Last Infusion

	Islet Alone														
	Follow-Up														
	Day 30			Month 6			Year 1			Year 2			Year 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	223	7.8	3.4	173	6.9	4.4	148	6.4	2.9	89	5.8	2.5	51	4.9	2.2
Tacrolimus (mg/day)	226	4.0	2.0	189	3.8	1.9	164	3.6	1.9	104	3.5	1.9	61	3.3	1.6
Neoral Cyclosporine (mg/day)	6	295.8	158.4	6	341.7	100.8	6	267.7	99.8	4	250.0	61.2	3	283.3	28.9
Generic Cyclosporine (mg/day)	0	-	-	0	-	-	0	-	-	1	375.0	-	0	-	-
MMF (mg/day)	37	1222.2	757.0	50	1406.8	604.0	45	1418.0	532.3	34	1469.2	676.2	27	1614.1	725.9
Prednisone (mg/day)	0	-	-	0	-	-	1	10.0	-	1	7.5	-	0	-	-
Everolimus (mg/day)	6	3.3	1.5	5	3.7	1.8	4	5.1	1.9	0	-	-	0	-	-
Daclizumab (mg/kg)	0	-	-	13	1.3	1.2	10	1.0	0.0	3	1.0	0.0	0	-	-
Anti-thymocyte Globulin (mg/kg)	0	-	-	1	7.5	-	0	-	-	0	-	-	0	-	-
Mycophenolic acid (mg/day)	2	1260.0	254.6	6	1380.0	353.9	7	1440.0	180.0	6	1350.0	355.5	2	1320.0	169.7
Efalizumab (mg/day)	5	62.7	14.3	1	63.0	-	1	64.0	-	0	-	-	0	-	-
Azathioprine (mg/day)	0	-	-	0	-	-	1	75.0	-	1	75.0	-	0	-	-

Exhibit 4 – 6 *(continued)*
Immunosuppression Dosing Post Last Infusion

	Islet After Kidney														
	Follow-Up														
	Day 30			Month 6			Year 1			Year 2			Year 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	27	6.8	2.7	24	6.0	2.3	19	4.8	1.6	16	3.7	1.8	10	3.8	1.3
Tacrolimus (mg/day)	32	3.9	1.5	28	3.6	1.5	26	3.8	1.5	20	3.6	1.6	14	3.4	1.4
Neoral Cyclosporine (mg/day)	2	250.0	70.7	2	250.0	70.7	3	250.0	50.0	2	175.0	106.1	3	233.3	28.9
Generic Cyclosporine (mg/day)	1	300.0	-	1	200.0	-	0	-	-	1	250.0	-	0	-	-
MMF (mg/day)	11	1113.6	563.1	8	1218.8	618.7	9	1222.2	565.2	10	968.0	568.8	7	1071.4	607.5
Prednisone (mg/day)	8	10.6	12.4	10	5.6	3.5	9	5.3	2.0	5	6.0	2.2	4	5.0	0.0
Methylprednisolone (mg/day)	1	4.0	-	1	4.0	-	0	-	-	0	-	-	0	-	-
Daclizumab (mg/kg)	0	-	-	4	1.0	0.0	3	1.0	0.0	0	-	-	0	-	-
Mycophenolic acid (mg/day)	1	720.0	-	0	-	-	0	-	-	0	-	-	0	-	-

Exhibit 4 – 7
Sirolimus Trough Level (ng/mL) Post Last Infusion
All Allograft Recipients



*Value of 61.8 ng/mL at Inf 3 Day 30 excluded from display.
Verified correct by center, attributed to the participant taking Sirolimus shortly before sampling.

Exhibit 4 – 8
Tacrolimus Trough Level (ng/mL) Post Last Infusion
All Allograft Recipients

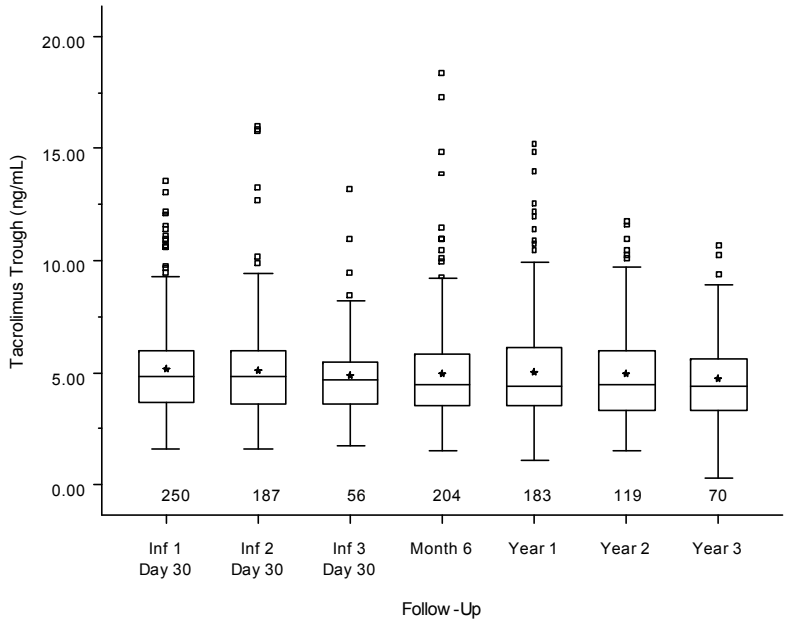


Exhibit 4 – 9
Anti-Hypertensive Medications Pre Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up Post Last Infusion									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	% of known	N	% of known	N	% of known	N	% of known	N	% of known
Total	314	100.0	245	100.0	218	100.0	145	100.0	88	100.0
No Anti-Hypertensive Medications Taken	185	58.9	133	54.3	105	48.2	63	43.4	41	46.6
ACE Inhibitors	100	31.8	85	34.7	85	39.0	55	37.9	33	37.5
Alpha Adrenergic Blockers	-	0.0	3	1.2	4	1.8	2	1.4	0	0.0
Angiotensin II Receptor Blockers	22	7.0	16	6.5	22	10.1	17	11.7	6	6.8
Beta Adrenergic Blockers	19	6.1	14	5.7	13	6.0	12	8.3	8	9.1
Calcium Channel Blockers	19	6.1	16	6.5	17	7.8	13	9.0	9	10.2
Centrally Acting Agents	2	0.6	1	0.4	1	0.5	1	0.7	2	2.3
Diuretics	12	3.8	21	8.6	28	12.8	16	11.0	11	12.5
Vasodilators	3	1.0	1	0.4	1	0.5	1	0.7	2	2.3

Exhibit 4 – 10
Total Number of Anti-Hypertensive Medications
Pre Infusion and Post Last Infusion
All Allograft Recipients

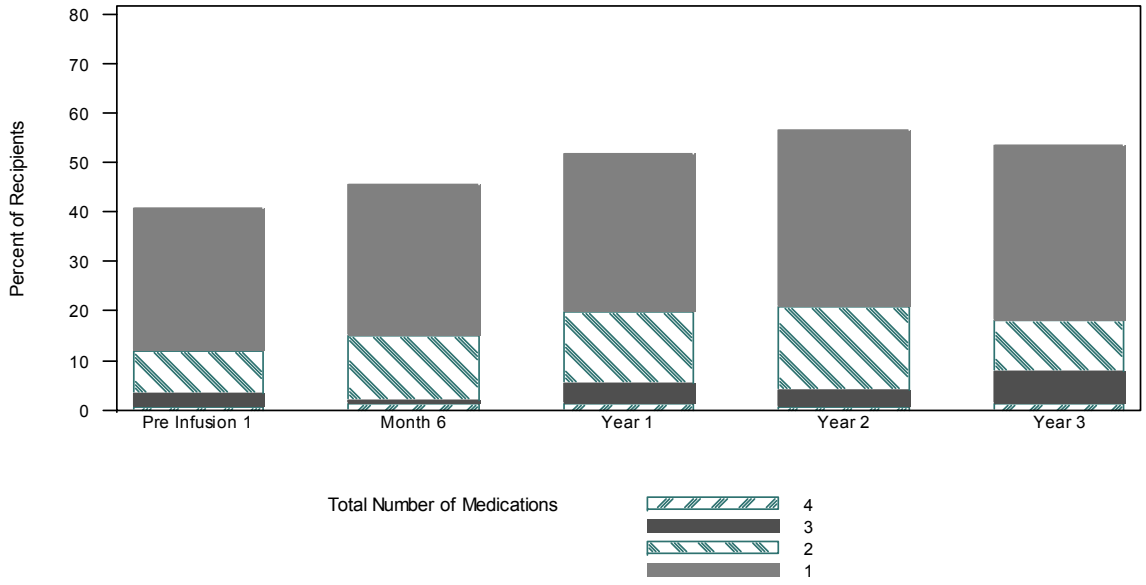


Exhibit 4 – 11
Lipid Lowering Medications Pre Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up Post Last Infusion									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	% of known	N	% of known	N	% of known	N	% of known	N	% of known
Total	315	100.0	247	100.0	217	100.0	145	100.0	89	100.0
No Lipid Lowering Medications Taken	214	67.9	116	47.0	85	39.2	48	33.1	33	37.1
Bile Acid Sequestrants	3	1.0	3	1.2	1	0.5	1	0.7	-	0.0
Cholesterol Absorption Inhibitors	9	2.9	8	3.2	8	3.7	9	6.2	2	2.2
Fibric Acid Derivatives	1	0.3	1	0.4	2	0.9	-	0.0	-	0.0
HMG CoA Reductase Inhibitors	97	30.8	122	49.4	119	54.8	86	59.3	53	59.6
Nicotinic Acid	1	0.3	7	2.8	5	2.3	6	4.1	-	0.0

Exhibit 4 – 12
Total Number of Lipid Lowering Medications
Pre Infusion and Post Last Infusion
All Allograft Recipients

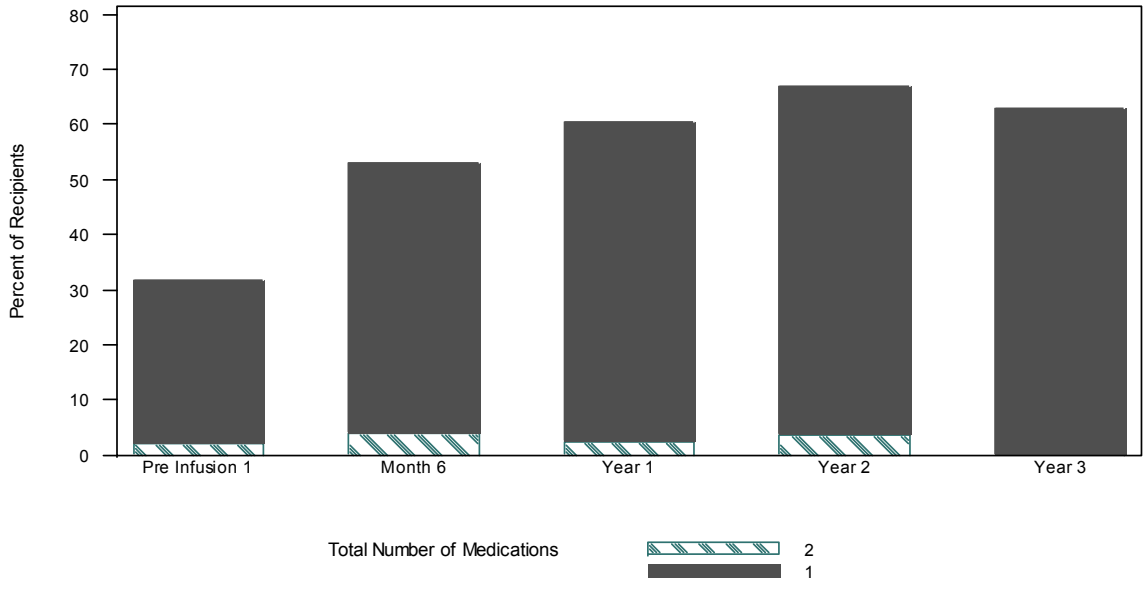


Exhibit 4 – 13
Adjunctive Therapy Used at Time of First Infusion
All Allograft Recipients

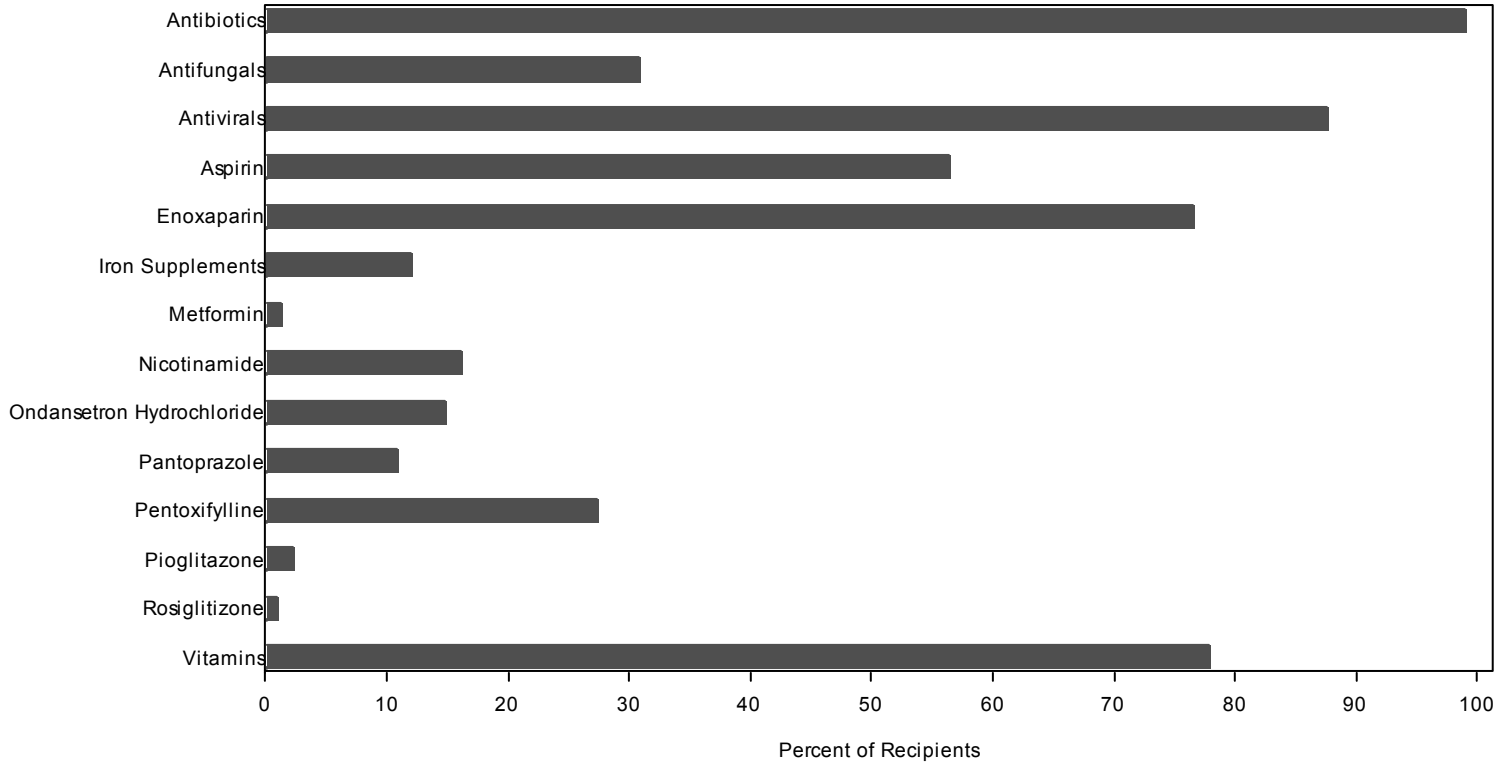


Exhibit 4 – 14
Adjunctive Therapy Post Last Infusion
All Allograft Recipients

	Follow Up Visit							
	Month 6		Year 1		Year 2		Year 3	
	N	% of known	N	% of known	N	% of known	N	% of known
Total	246	100.0	217	100.0	150	100.0	92	100.0
Pentoxifylline	31	12.6	1	0.5	-	0.0	-	0.0
Metformin	11	4.5	7	3.2	6	4.0	4	4.3
Exenatide	7	2.8	8	3.7	4	2.7	5	5.4
Rosiglitazone	4	1.6	5	2.3	3	2.0	3	3.3
Pioglitazone	2	0.8	1	0.5	1	0.7	-	0.0
Acarbose	3	1.2	2	0.9	1	0.7	-	0.0
Repaglinide	3	1.2	1	0.5	3	2.0	4	4.3
Sitagliptin	1	0.4	1	0.5	-	0.0	-	0.0
Gliclazide	-	0.0	-	0.0	-	0.0	1	1.1
Chromium picolinate	2	0.8	1	0.5	1	0.7	-	0.0
Iron	5	2.0	7	3.2	6	4.0	-	0.0
Vitamins	44	17.9	35	16.1	9	6.0	-	0.0

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Chapter 5
Graft Function

Graft Function

Chapter 5 summarizes results on graft function for the 325 allogeneic islet transplant alone or islet after kidney participants reported to the Registry.

Insulin Independence and Graft Function

After the first infusion (Exhibit 5-1), increasing proportions of islet-alone (IA) recipients are re-infused: 11% by Day 30, 34% by Day 75, 53% by Month 6, and 65% by Year 1. The proportion that is insulin independent without re-infusion remains fairly constant at 10-15% throughout the first year. An additional 8-12% retains detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 279 IA recipients, 71% are expected at three-years post first infusion, at which time, regardless of the total number of infusions received, about 23% are insulin independent, 29% are insulin dependent with detectable C-peptide, 26% have no detectable C-peptide and 22% have missing data (required but not yet reported).

Analyzed from last infusion (Exhibit 5-2), the percentage of all IA recipients that is insulin independent declines steadily from 54% at Month 6 to 22% at Year 3. The proportion with loss of islet function (reported graft failure or no detectable C-peptide) increases steadily from 10% at Month 6 to 34% at Year 3 (Exhibit 5-2). A stable 23-26% retains graft function with exogenous insulin over the three years; the percentage of missing data increases over time. These trends of increasing prevalence of graft loss and decreasing prevalence of insulin independence over time post last infusion prevail regardless of the total number of infusions given (Exhibit 5-3), although the rates differ somewhat among the three groups.

Focusing only on the insulin independence status (available from daily diaries with increasing missing data over time), the prevalence of insulin independence from last infusion declines from 65% at Month 4 to about 24% at Year 3 post last infusion (Exhibit 5-4). Two or three infusions (Exhibit 5-5) boost the prevalence of insulin independence in the first year to a peak of about 69%, with a subsequent decline to levels that are comparable to those with a single infusion. The area under the curve of these prevalence diagrams is an indication of the proportion of total person-time of insulin independence experienced by these 279 IA recipients.

Cumulative event rates of achieving insulin independence after first infusion regardless of the number of infusions given is an indicator of the rate of engraftment under the real-time conditions of competing events including graft loss, islet resource availability, and myriad biologic factors, some of which are characterized in the CITR data and some are not. It is notable that the cumulative rate of achievement of insulin independence (Exhibit 5-13) follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Overall, 72% of all recipients achieved insulin independence, for both IA and IAK recipients, and follow very similar cumulative event rates. The median time to achievement of insulin independence is 5-6 months after first infusion. Multiple infusions increase the likelihood of achieving insulin independence (Exhibit 5-13, Panels B-D). After achievement, 71% of IA recipients retain insulin independence by one year later, and this decreases to 52% at two years (Exhibit 5-14, solid line).

However, a substantial proportion of those achieving insulin independence retain graft function with lowered exogenous insulin requirements: 76% still have graft function at Year 3 (Exhibit 5-14, dashed line). Three infusions appear to increase the likelihood of retaining insulin independence (Exhibit 5-15), but the numbers at long-term follow-up are small.

HbA_{1c}

HbA_{1c} levels are improved substantially by islet transplantation. The percent of IA recipients with HbA_{1c} < 7.0% increases from 28% pre-infusion to 59-82% at Month 6 and 55-78% at Year 1 post first infusion, censored at re-infusion (Exhibit 5-6). In these percentile ranges, the lower estimate represents the case where all missing data are counted as $HbA_{1c} \geq 7.0\%$ whereas the upper estimate assumes all missing data for recipients with confirmed or unknown graft function have HbA_{1c} levels < 7.0%. Post last infusion; these rates are 68-88% at Month 6 and 36-64% at Year 3. Notably, the percent with measured values ≥ 7% remains fairly constant at about 10% throughout follow-up. Based on available measurements, Exhibit 5-25 shows substantial downward shifts in the overall distribution, with means and medians stabilizing at <6.5% in Years 1-3 post last infusion.

C-peptide

C-peptide levels are substantially increased by islet transplantation. The percent of IA recipients with C-peptide >0.5 ng/mL increases from 8% pre-infusion to 47% at Month 6 and 43% at Year 1 post first infusion (censored at re-infusion, Exhibit 5-7), with 32% retaining this level of function at Year 3 post last infusion.

Severe Hypoglycemic Events

There continues to be a striking decrease in the prevalence of severe hypoglycemic events that occur both post first and post last infusion procedure. Severe hypoglycemia prevalence is reduced from 81-85% pre-infusion to less than 3-10% throughout the first year post last infusion, and to 8-35% at three years post last infusion (Exhibit 5-8 C). In these percentile ranges, the lower estimate represents the case where all missing data are recipients who do not experience severe hypoglycemic episodes whereas the upper estimate assumes all missing data for recipients with islet graft failure are recipients who do experience severe hypoglycemic episodes. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit 5-9). All participants that experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.

Composite Outcome: Severe Hypoglycemia and HbA_{1c}

Taken as a composite outcome, the percent of IA recipients with HbA_{1c} <6.5% and absence of severe hypoglycemic episodes increases from 2% pre-infusion to 47-69% at Year 1 post last infusion. In this range, the lower estimate represents the case where all missing data are counted as not achieving the outcome whereas the upper estimate assumes all missing data for recipients with confirmed or unknown graft function do achieve the outcome.

Changes in Islet Graft Function

Graft loss, whether measured by C-peptide levels, or reported by the site, increases steadily over time. At Year 3 post last infusion, 34% of IA recipients lost graft function (Exhibit 5-10). Viewed as Kaplan-Meier estimates (Exhibit 5-11), 36% of IA recipients lost graft function by Year 3 post last infusion. Long-term graft function is more likely in recipients who achieve insulin independence at any time during their one to several islet infusions (Exhibit 5-12). While this result is subject to bias from post-hoc stratification, it is confirmed by Cox regression with achievement of insulin independence as a time-dependent covariate ($p<0.001$).

Changes in Insulin Dosing

Average daily insulin used and reduction in insulin from baseline are shown as box-plots pre-infusion and at Month 6, and annually post last infusion, and according to ever achieving insulin independence (Exhibits 5-17 to 5-21). Average daily insulin reduction reached and remained at 50% of pre-infusion requirements for those taking insulin throughout the three years post last infusion.

Factors of Primary Outcomes

Factors of insulin independence and complete islet failure, post first and post last infusion are presented in Exhibits 5-22 and 5-23, where they are fully described.

Metabolic Measures

The choice of which metabolic tests to perform varies from center to center.

Overall, fasting plasma glucose values (Exhibit 5-24) and HbA_{1c} (Exhibit 5-25) decrease over time, while basal C-peptide values (Exhibit 5-26) increase. This trend is seen both overall and by total number of infusions (Exhibits 5-27 to 5-35). C-peptide levels in those who ever achieve insulin independence are substantially higher than in those who do not (Exhibits 5-40 and 5-41). There is a substantially higher proportion of recipients with fasting glucose <126 mg/dL and HbA_{1c} <6.5% when the recipient is concurrently insulin independent than not (Exhibits 5-48 and 5-50).

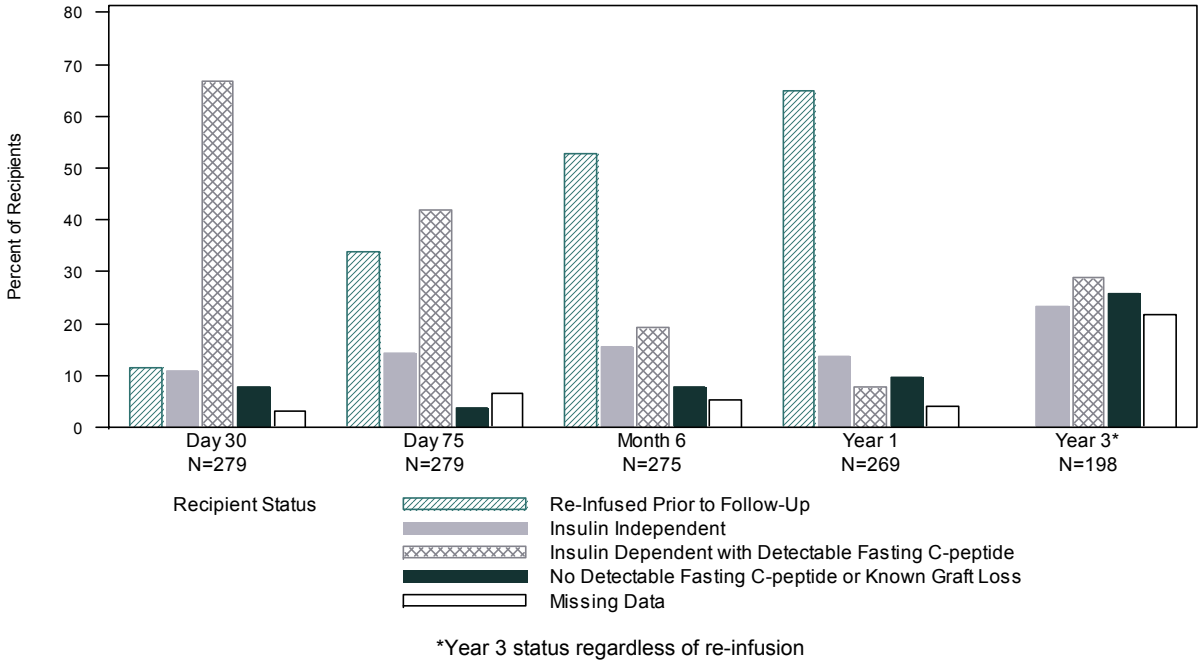
A complete set of laboratory values are summarized by infusion sequence in Exhibit 5-51. Additional metabolic test summaries are located in Exhibits 5-52 and 5-53.

Diabetes Related Secondary Complications

Exhibits 5-54 and 5-55 display diabetes related secondary complications experienced by the recipients prior to their first infusion procedure and post their last infusion procedure. At 2-3 years post infusion, there are high rates of missing data. It is the goal of the Registry to continue to track the occurrence of these complications across time to determine any trends.

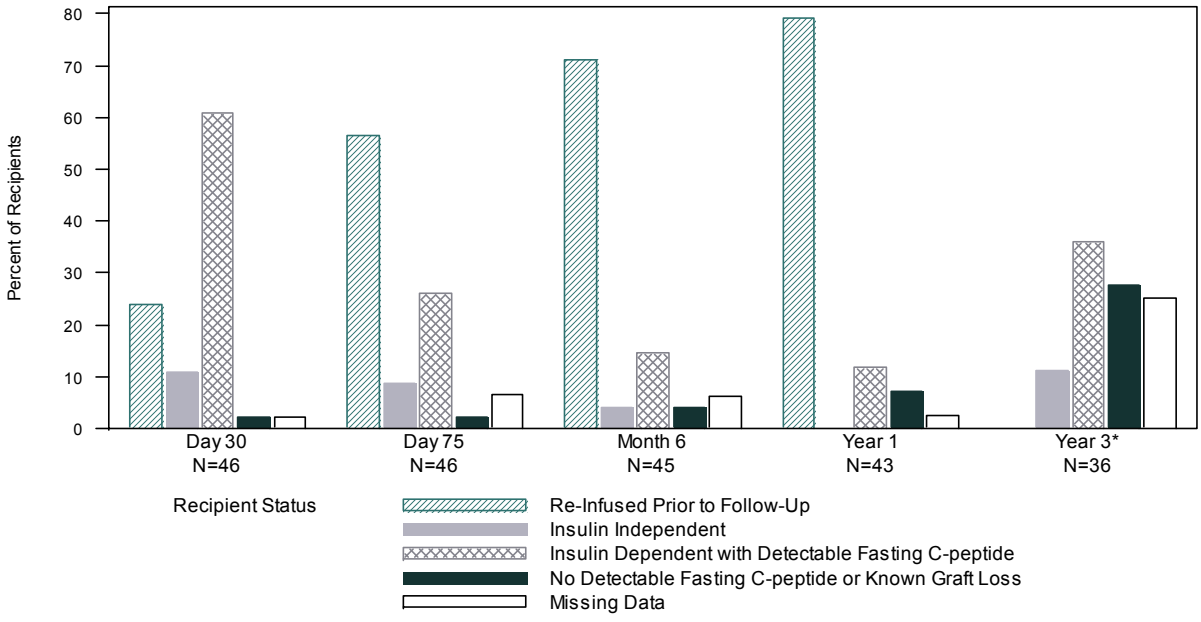
Exhibit 5 – 1
Insulin Independence, Insulin Dependence, Absence of Fasting C-peptide, or Re-Infusion Post First Infusion

A. Islet Alone Recipients



*Year 3 status regardless of re-infusion

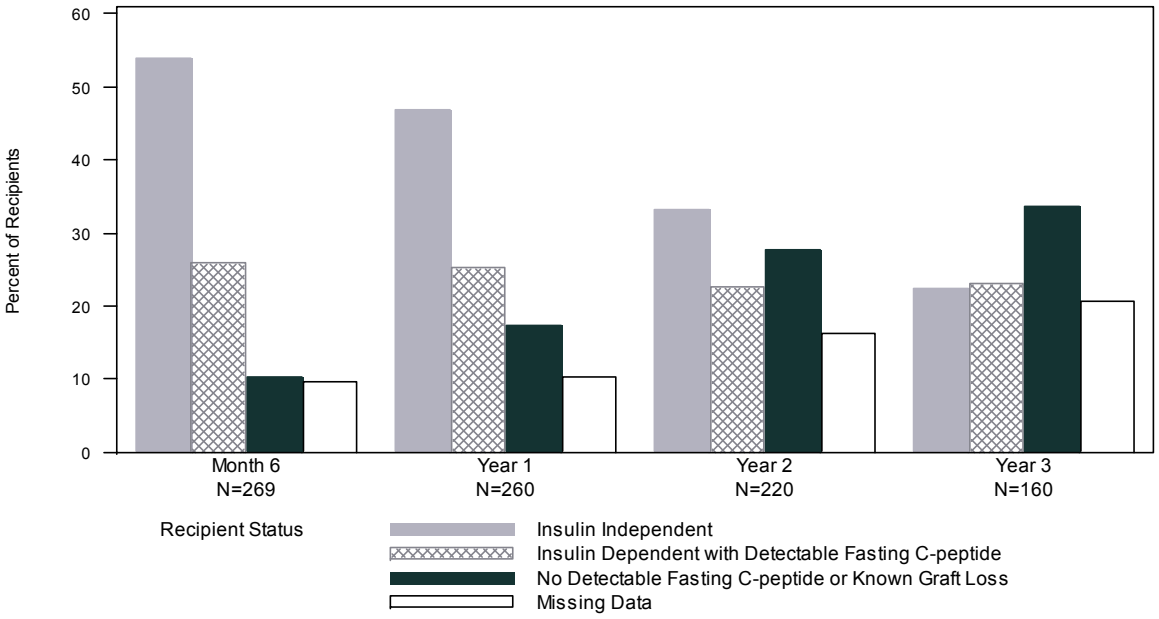
B. Islet After Kidney Recipients



*Year 3 status regardless of re-infusion

Exhibit 5 – 2
Insulin Independence, Insulin Dependence or Absence of Fasting C-peptide Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

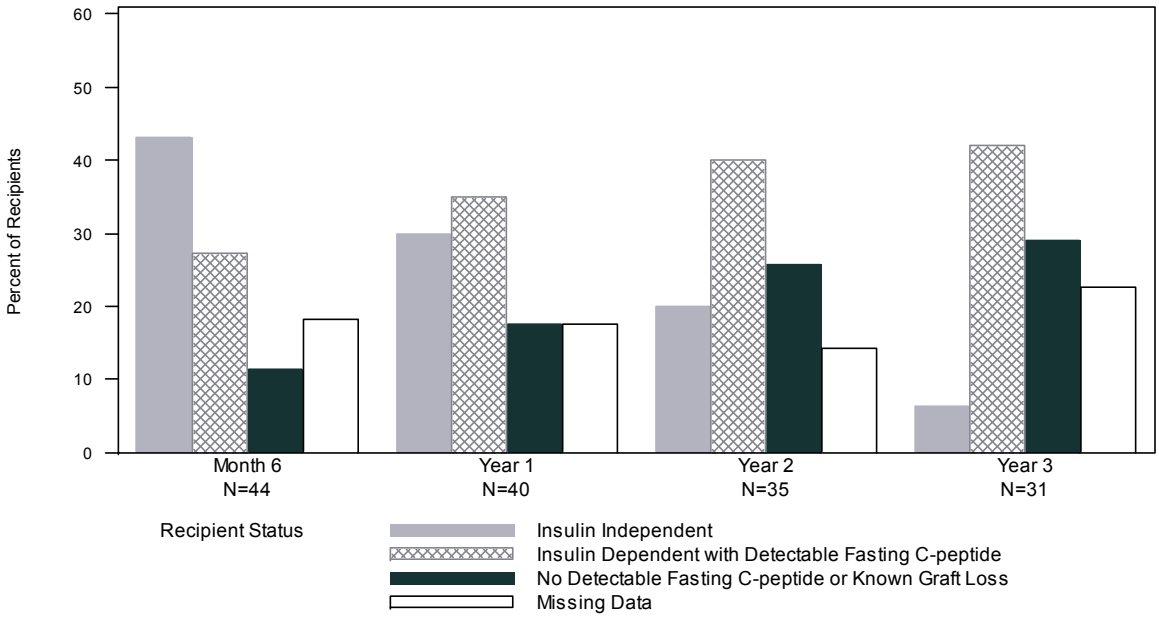
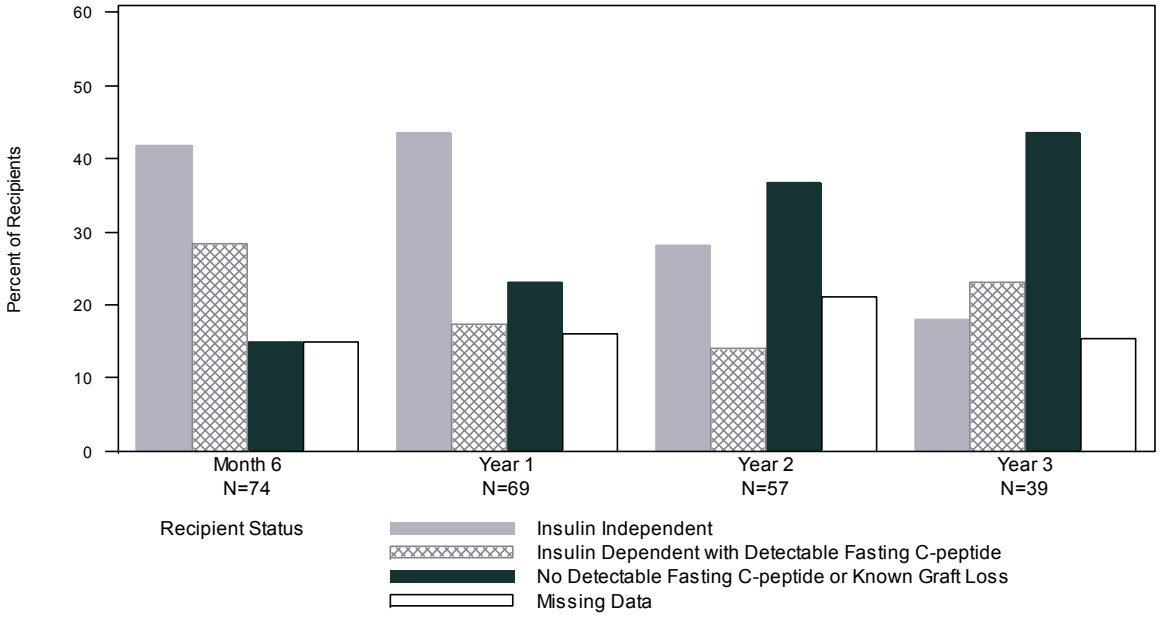


Exhibit 5 – 3
Insulin Independence, Insulin Dependence, or Absence of Fasting C-peptide Post Last Infusion by Total Number of Infusions Received
Islet Alone Recipients

A. Recipients of 1 Infusion



B. Recipients of 2 Infusions

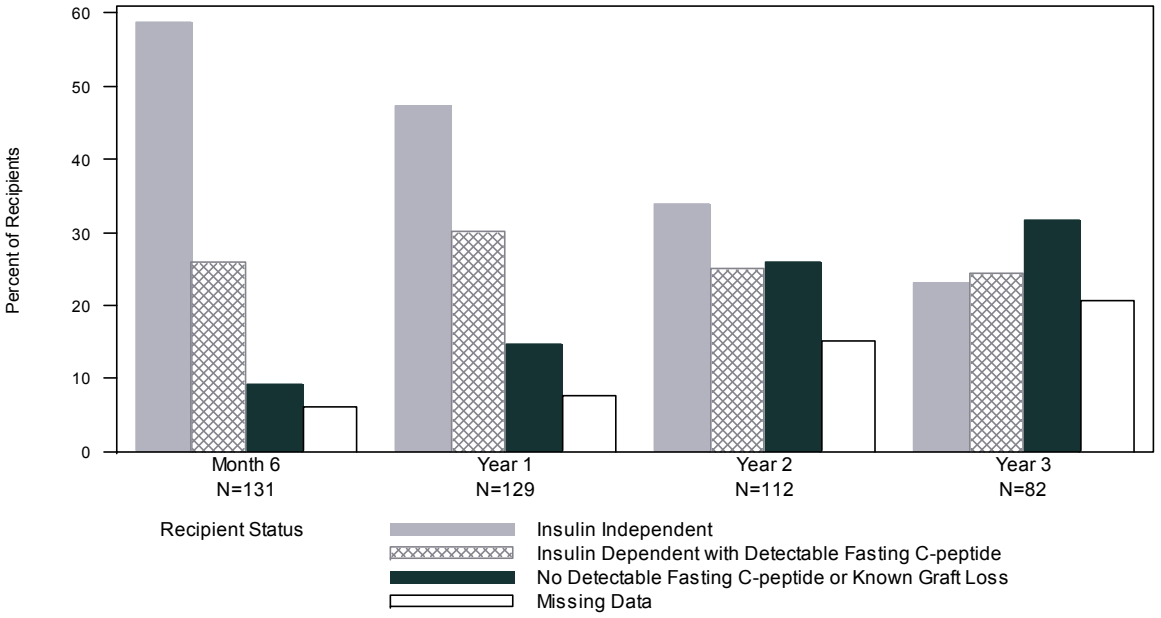


Exhibit 5 – 3 *(continued)*
Insulin Independence, Insulin Dependence, or Absence of Fasting C-peptide Post Last Infusion by Total Number of Infusions Received Islet Alone Recipients

C. Recipients of 3 Infusions

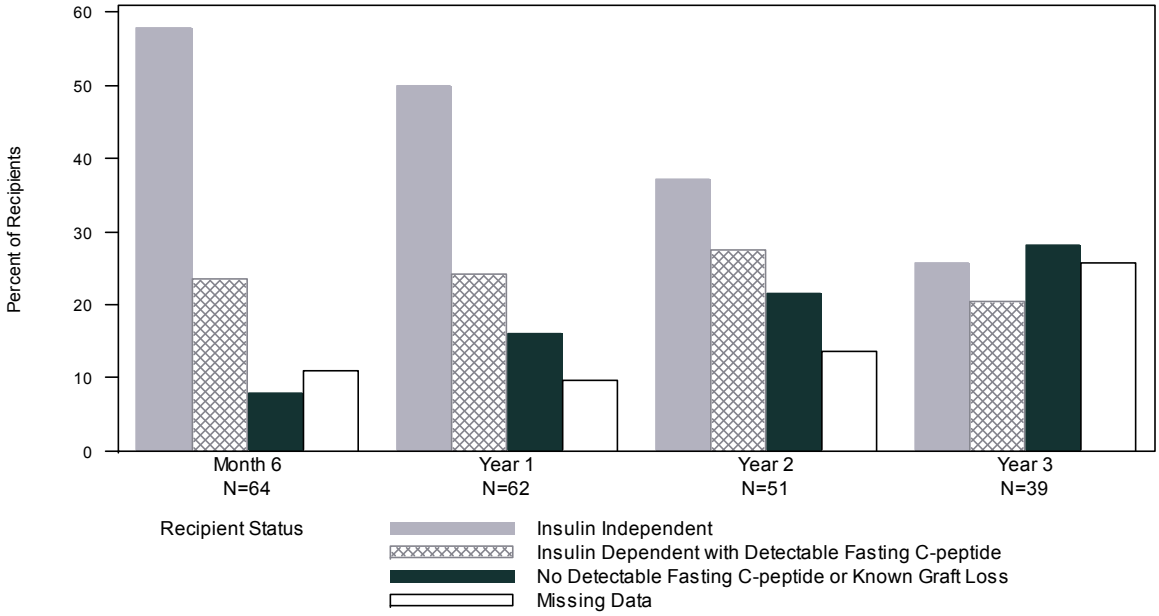
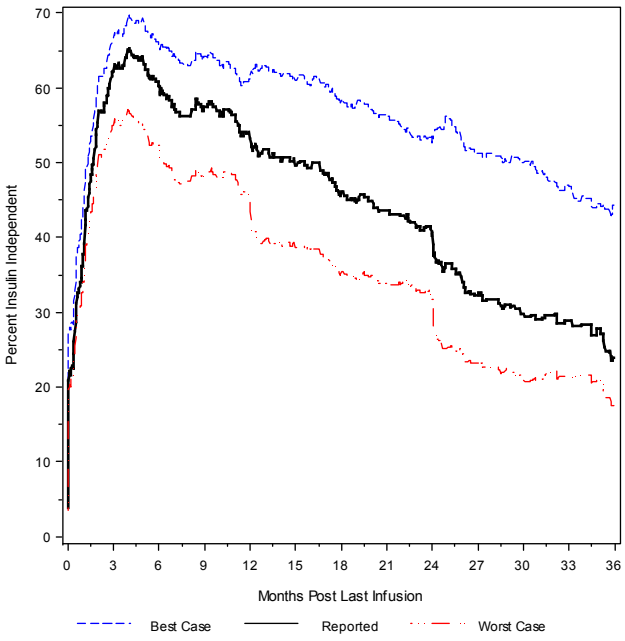


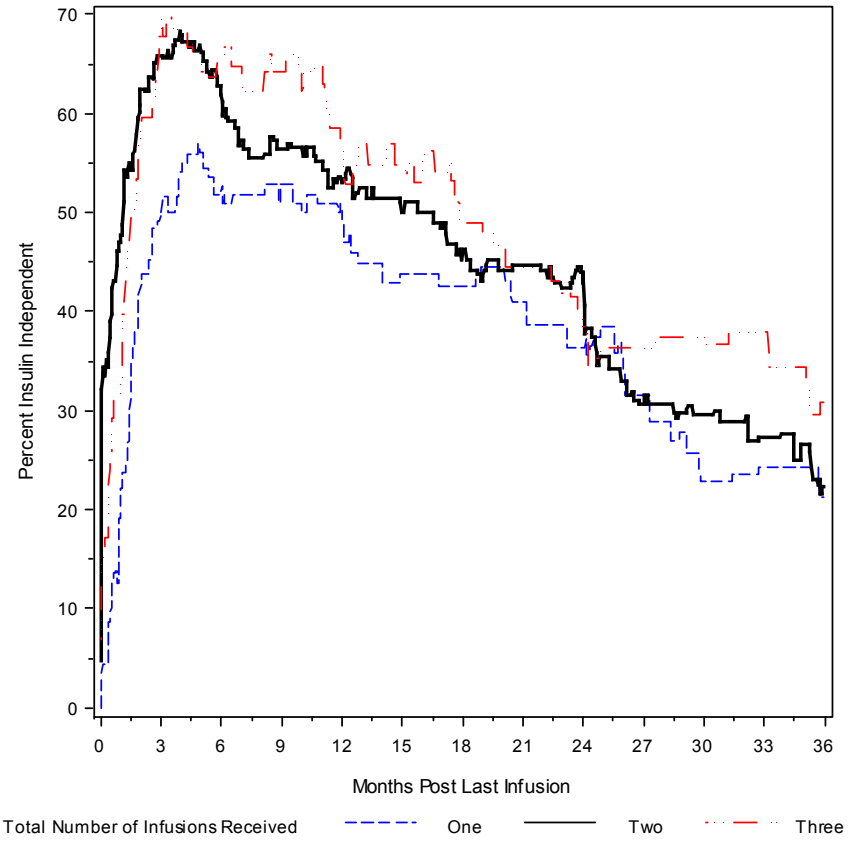
Exhibit 5 – 4
Prevalence of Insulin Independence Post Last Infusion
Islet Alone Recipients



Month	0	6	12	18	24	30	36
N Expected	279	269	260	245	220	194	160

"Prevalence" is the percentage of recipients that are known to be insulin independent at the given time points post last infusion, out of the number with data. Known graft loss is imputed as insulin dependent. "Best Case" is the representation where missing data are classified as insulin independent. "Worst Case" is the representation where missing data are classified as insulin dependent.

Exhibit 5 – 5
Prevalence of Insulin Independence Post Last Infusion
By Total Number of Infusions Received
Islet Alone Recipients



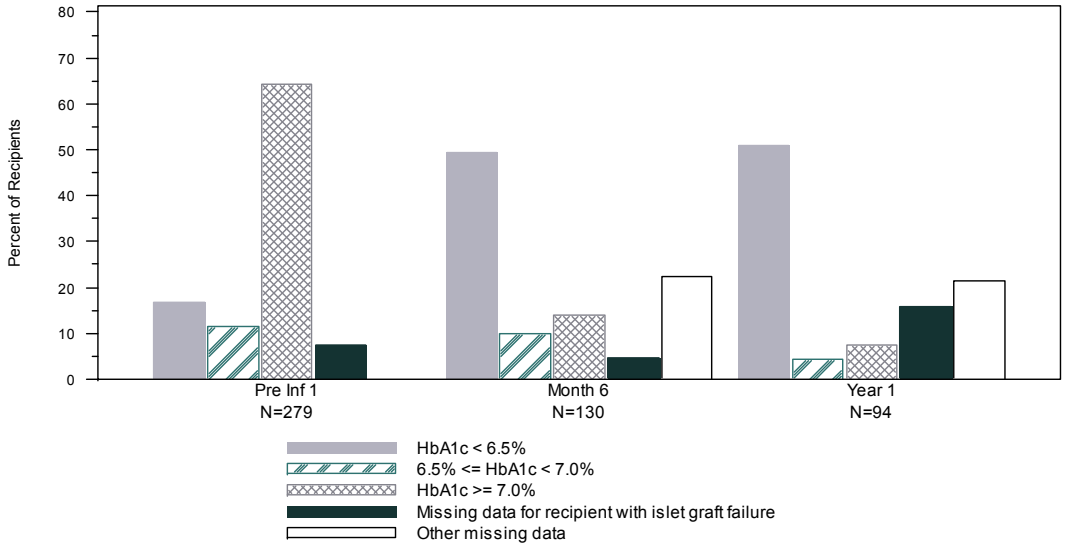
Month	0	6	12	18	24	30	36
N 1 Infusion	77	56	52	47	44	35	33
N 2 Infusions	125	121	111	95	91	71	58
N 3 Infusions	58	55	51	47	39	32	26

This Exhibit summarizes the percent of recipients that are insulin independent by time post their last infusion procedure. At Month 4, 69% of participants who received more than one islet infusion were insulin independent, while 54% with one infusion were insulin independent. By Year 2, these rates drop to 43% for those with two infusions, 38% with three or four infusions, and 36% for those with one infusion.

Exhibit 5 – 6
HbA_{1c}

A. Post First Infusion (Censored at Re-Infusion before Visit)

Islet Alone Recipients



Islet After Kidney Recipients

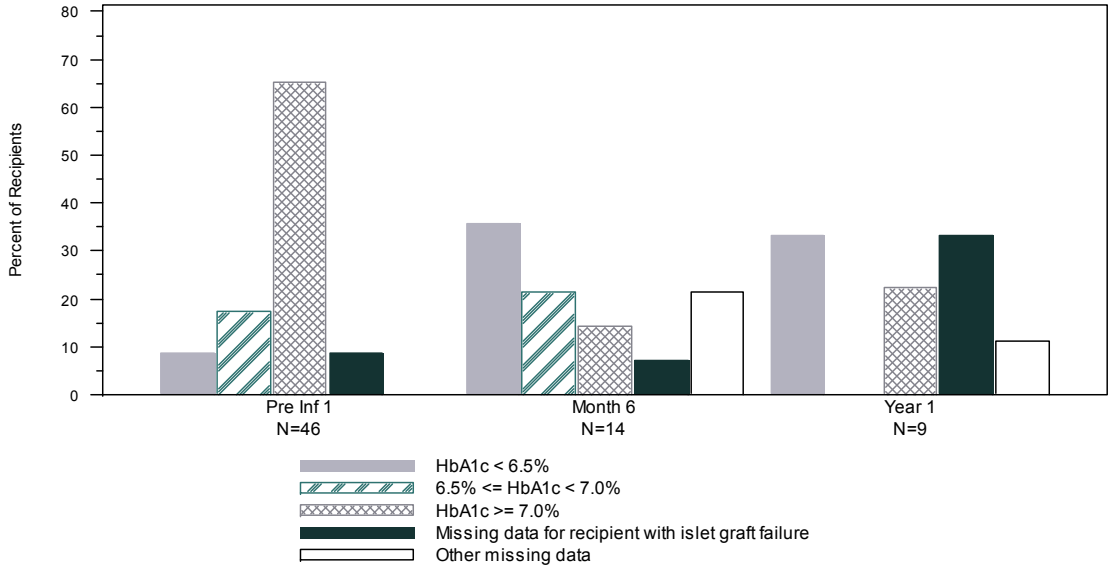
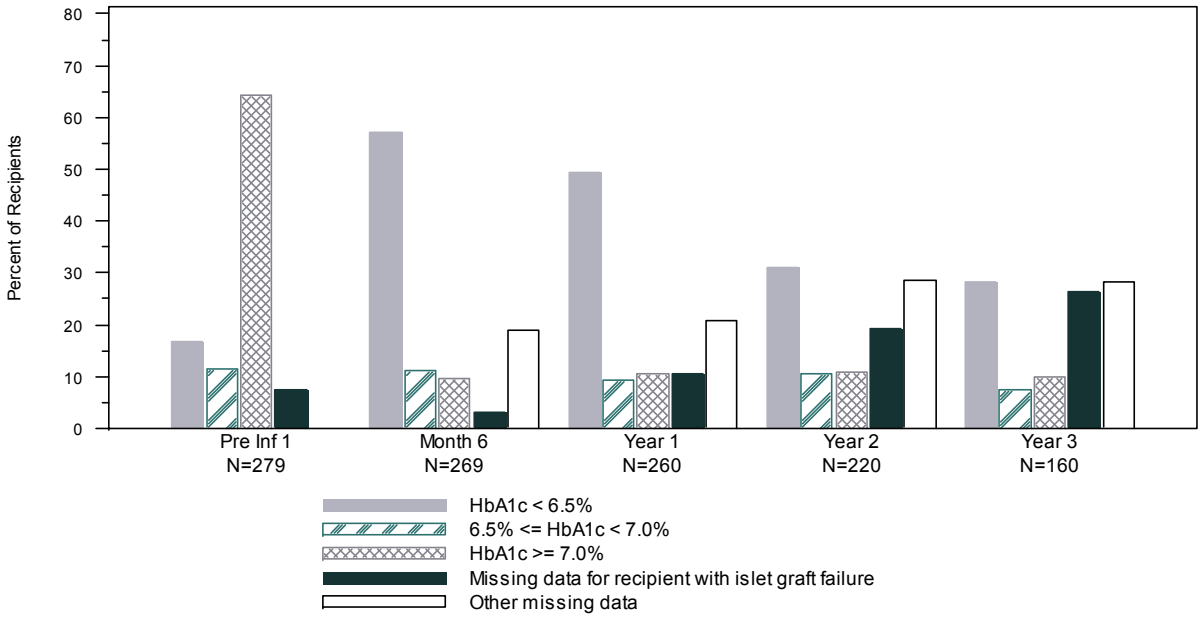


Exhibit 5 – 6 *(continued)*
HbA_{1c}

B. Post Last Infusion

Islet Alone Recipients



Islet After Kidney Recipients

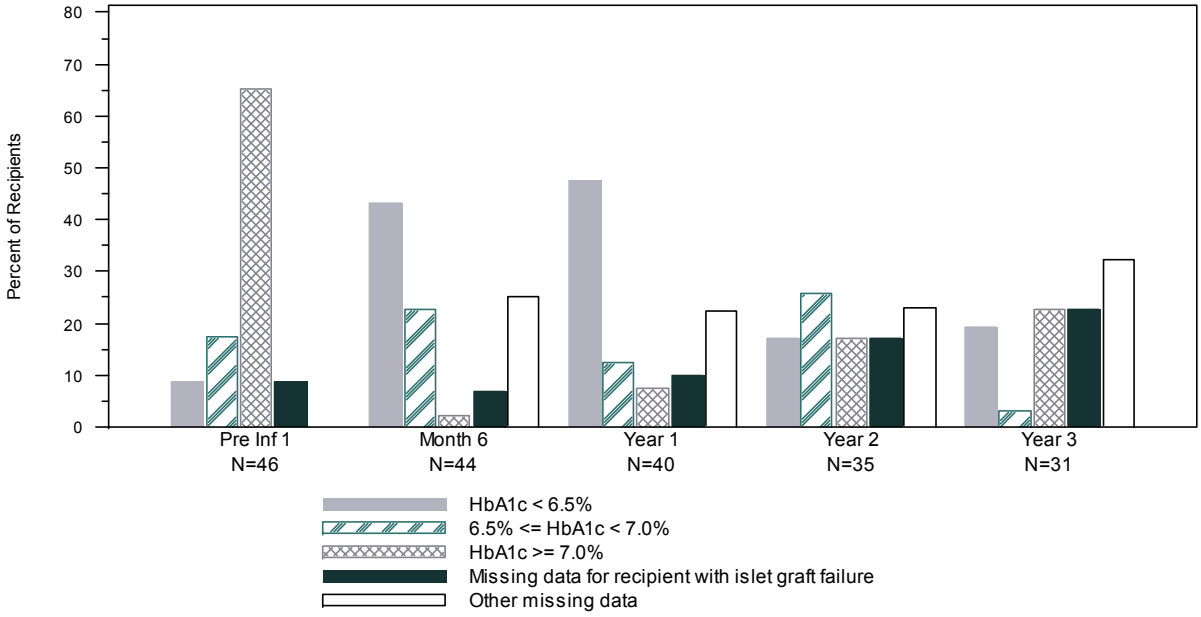
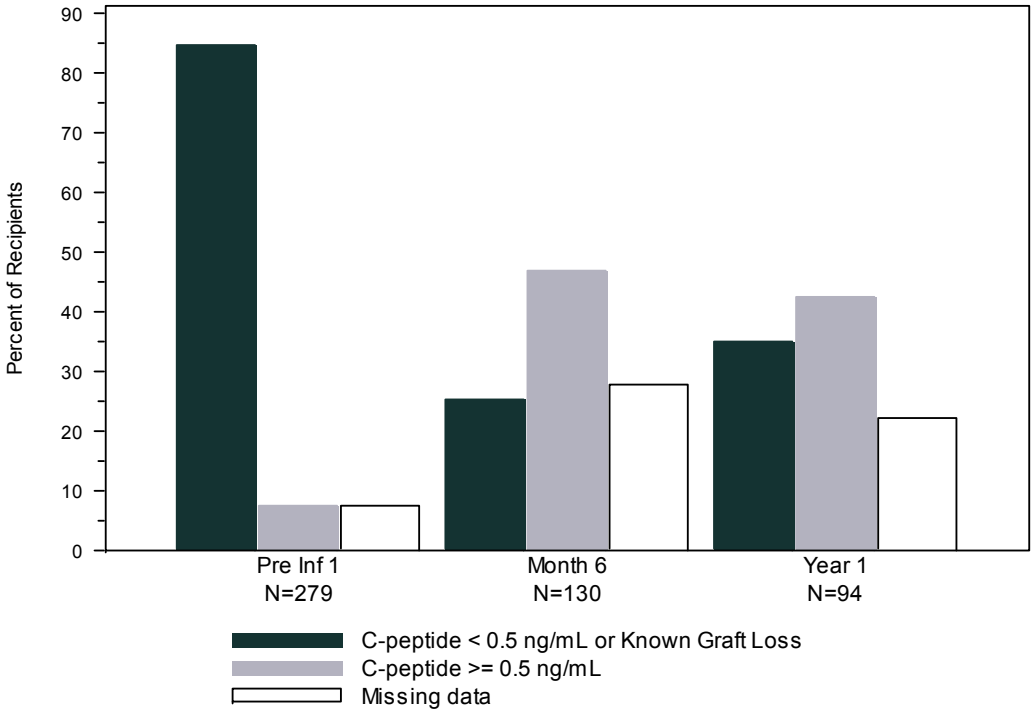


Exhibit 5 – 7
C-peptide ≥ 0.5 ng/mL

A. Post First Infusion (Censored at Re-Infusion before Visit)

Islet Alone Recipients



Islet After Kidney Recipients

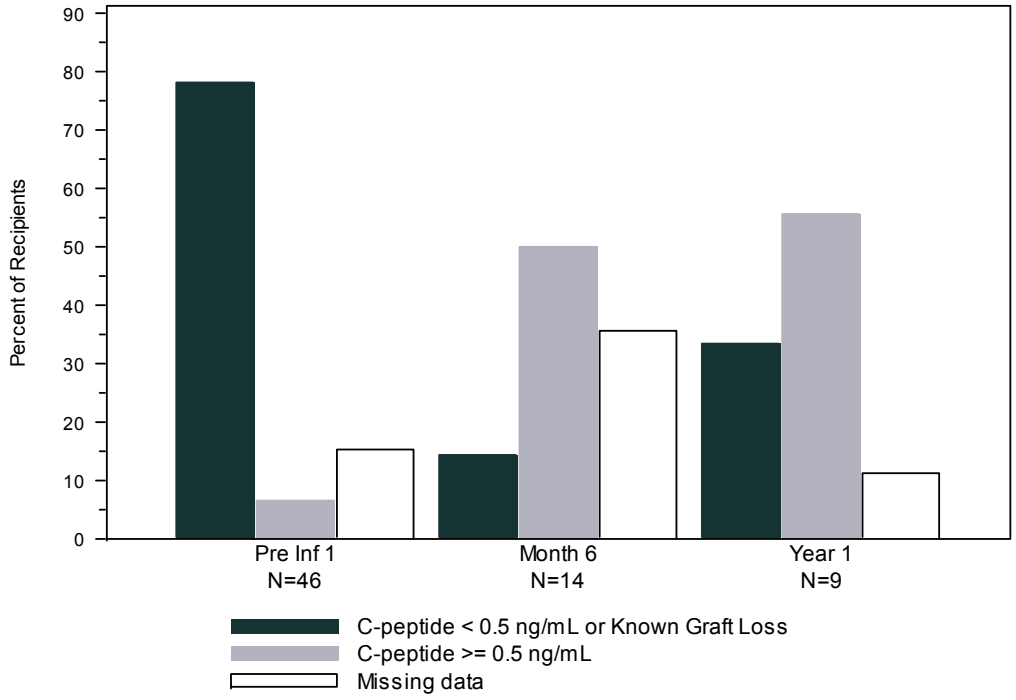
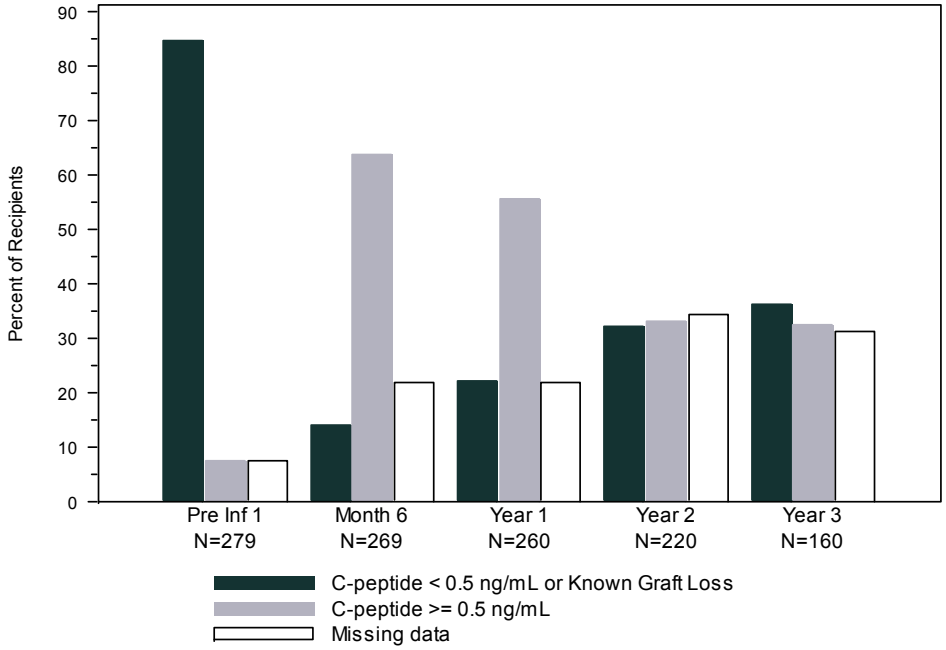


Exhibit 5 – 7 *(continued)*
C-peptide ≥ 0.5 ng/mL

B. Post Last Infusion

Islet Alone Recipients



Islet After Kidney Recipients

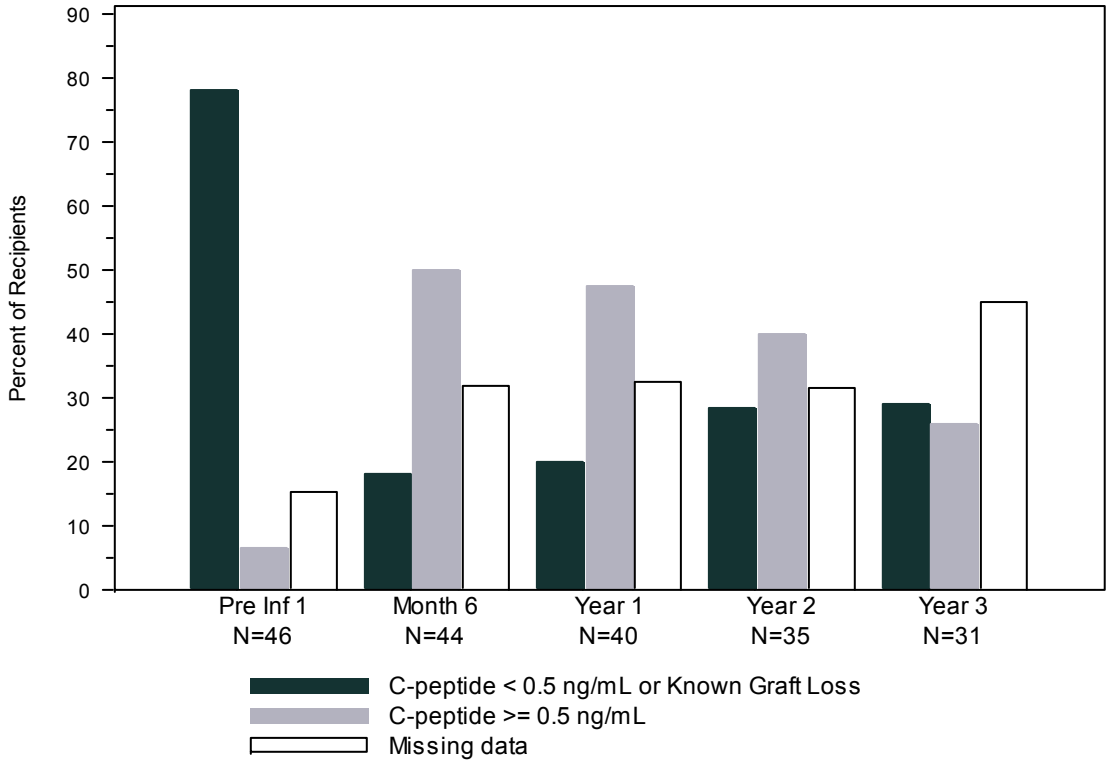
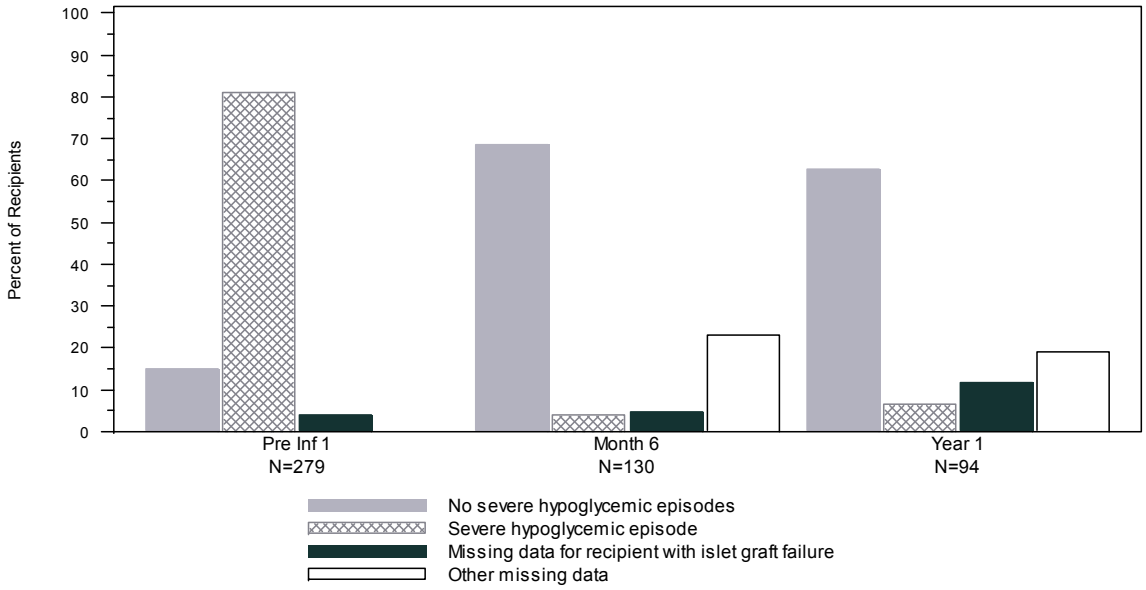


Exhibit 5 – 8
Severe Hypoglycemia

A. Post First Infusion (Censored at Re-Infusion before Visit)
Islet Alone Recipients



B. Post First Infusion (Censored at Re-Infusion before Visit)
Islet After Kidney Recipients

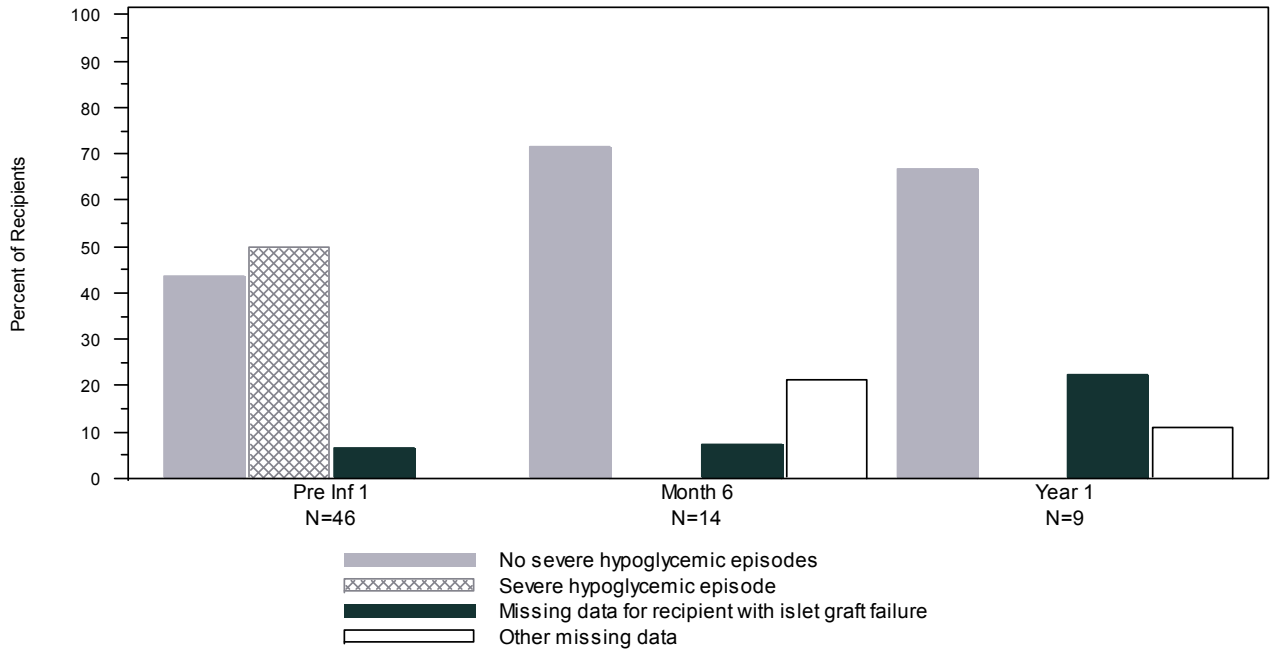
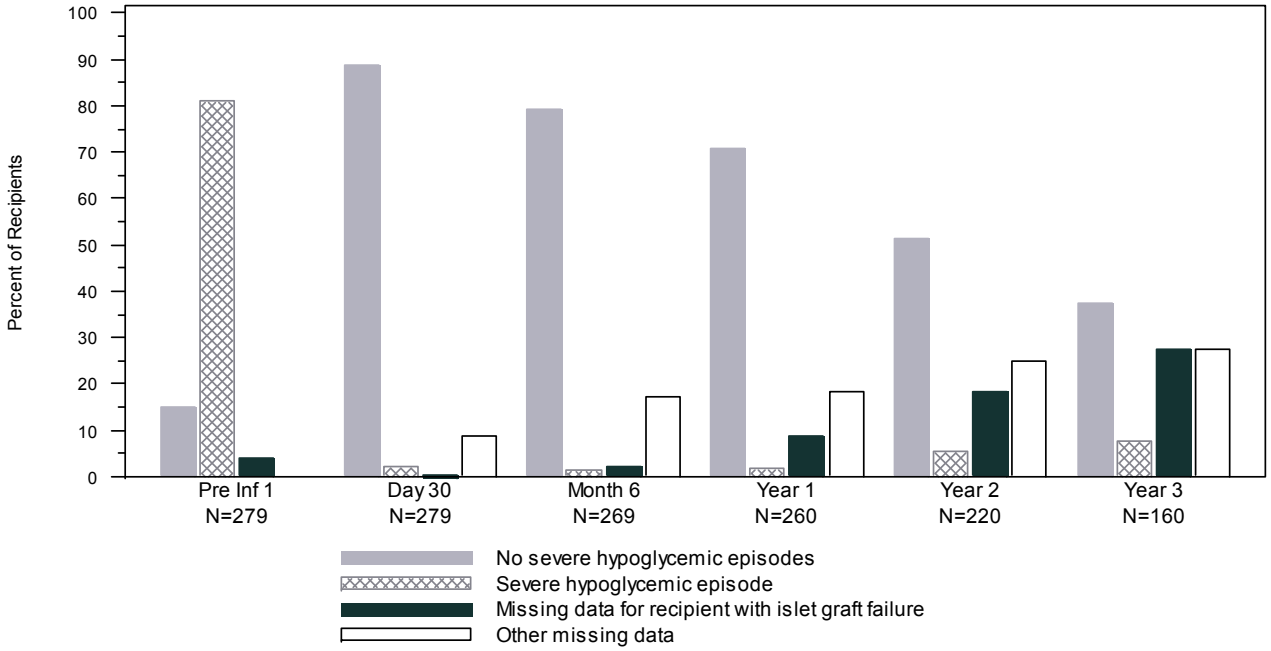


Exhibit 5 – 8 *(continued)*
Severe Hypoglycemia

C. Post Last Infusion
Islet Alone Recipients



D. Post Last Infusion
Islet After Kidney Recipients

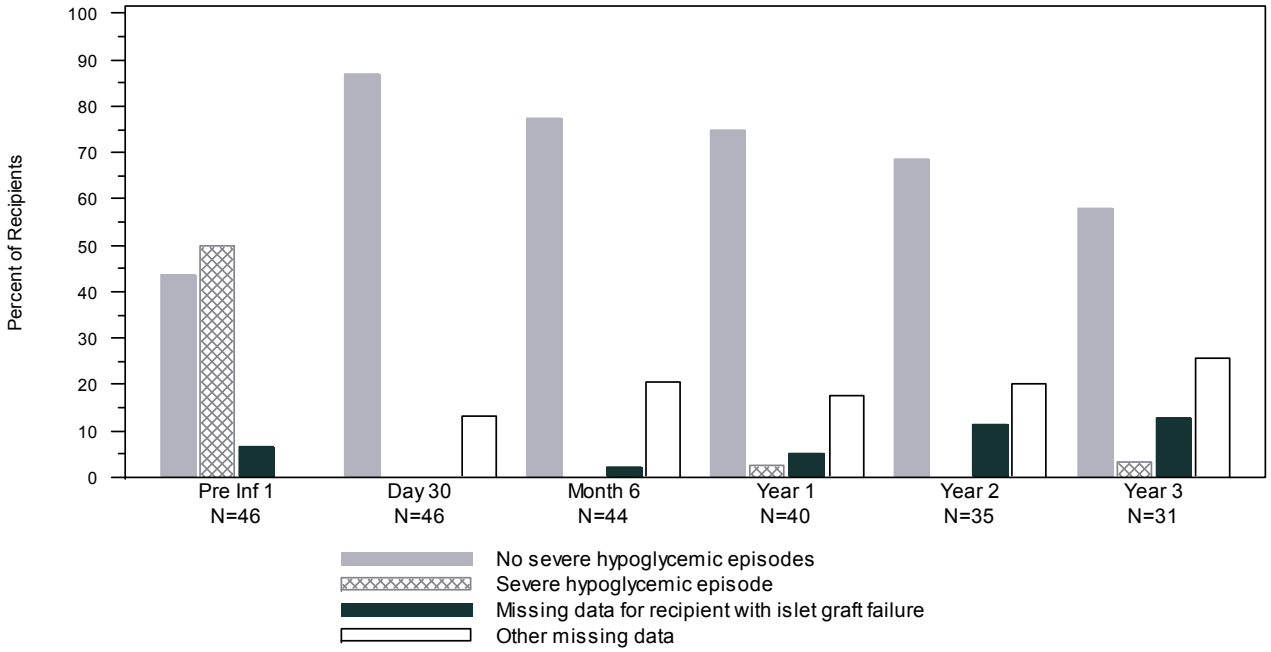
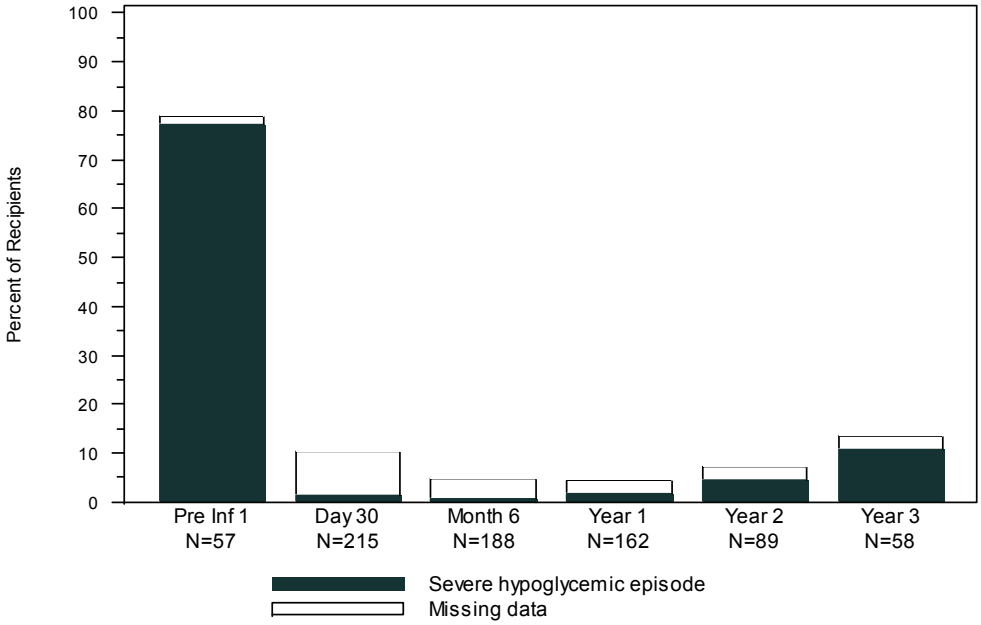


Exhibit 5 – 8 *(continued)*
Severe Hypoglycemia

E. Post Last Infusion
Islet Alone Recipients with Detectable Fasting C-peptide

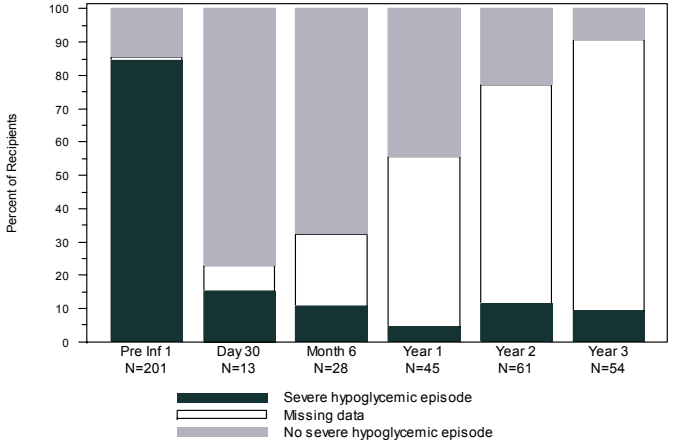


All those experiencing hypoglycemic episodes were on insulin at the time of the episode with a mean daily insulin dose of 23 units/day

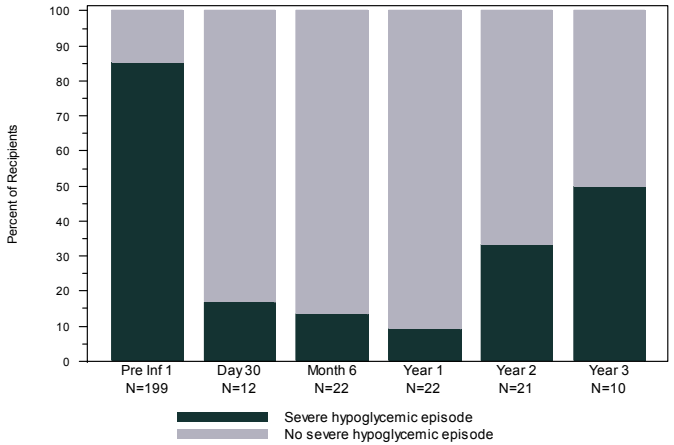
.

Exhibit 5-8 *(continued)*
Severe Hypoglycemia

F1. Post Last Infusion
All Islet Alone Recipients with
No Detectable Fasting C-peptide or Known Graft Loss



F2. Post Last Infusion
Subset of F1: Islet Alone Recipients with
No Detectable Fasting C-peptide or Known Graft Loss and
Known Information on Occurrence of Severe Hypoglycemic Episodes



This exhibit relates occurrence of severe hypoglycemia episodes with loss of islet function. Panel F1 shows missing data while Panel F2 excludes them. If data are missing at random (i.e., not due to severe hypoglycemic episodes), F2 shows increasing loss of protection against severe hypoglycemic episodes following islet graft loss, but also substantial levels of protection relative to pre-infusion.

Exhibit 5 – 9
Hypoglycemia Status Pre First Infusion and Post Last Infusion
All Allograft Recipients

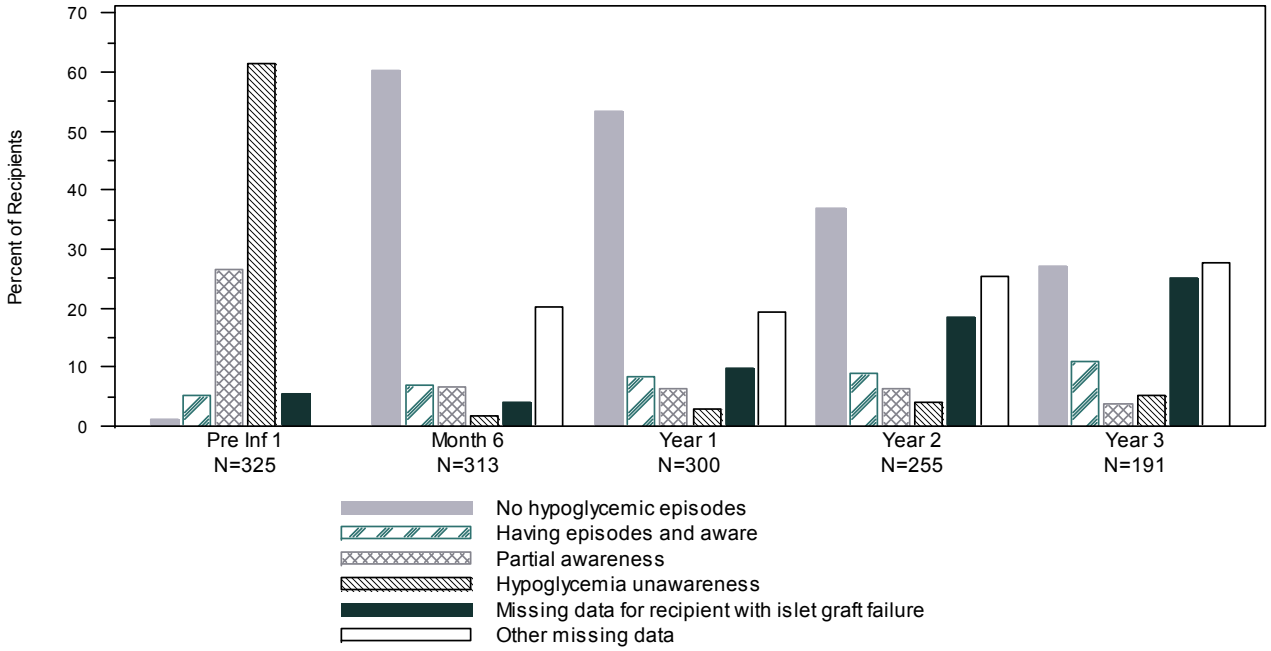
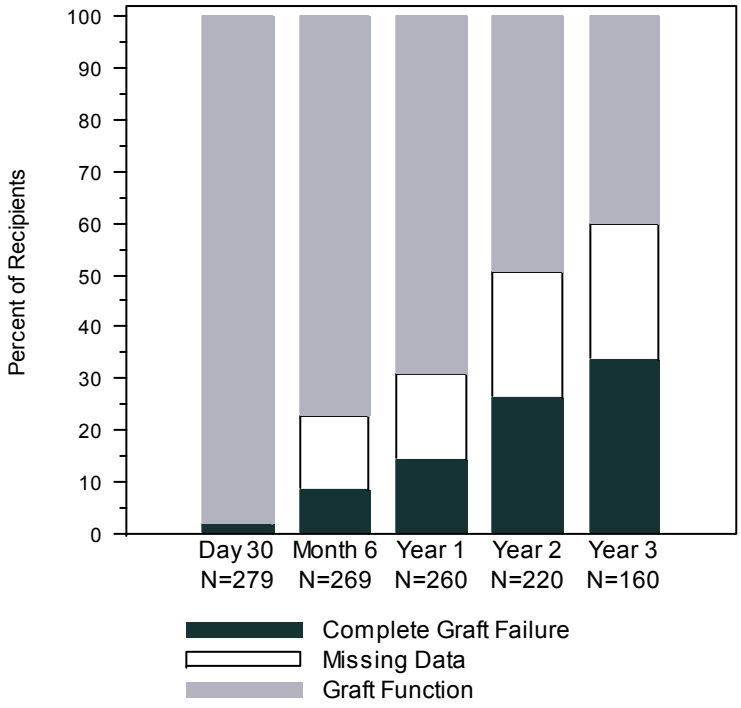


Exhibit 5 – 10
Graft Loss Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

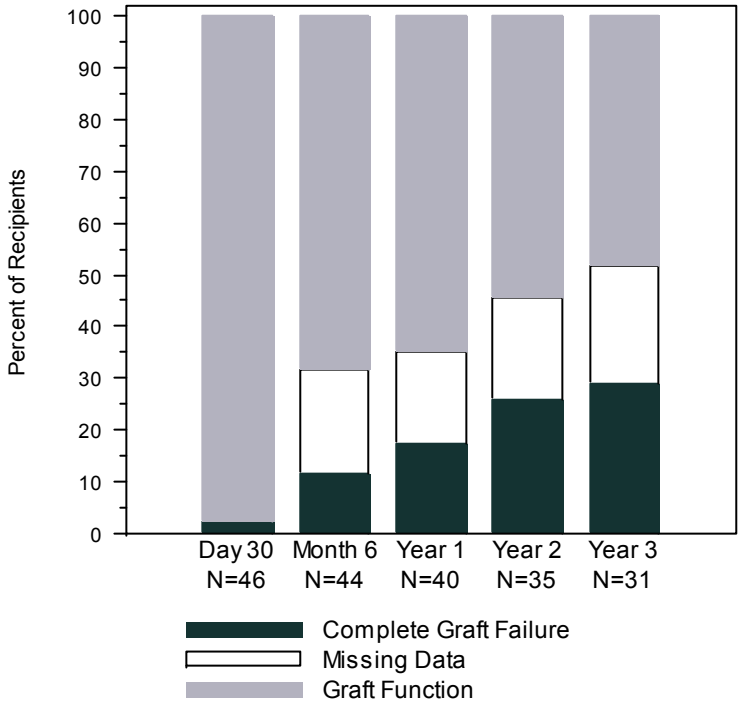
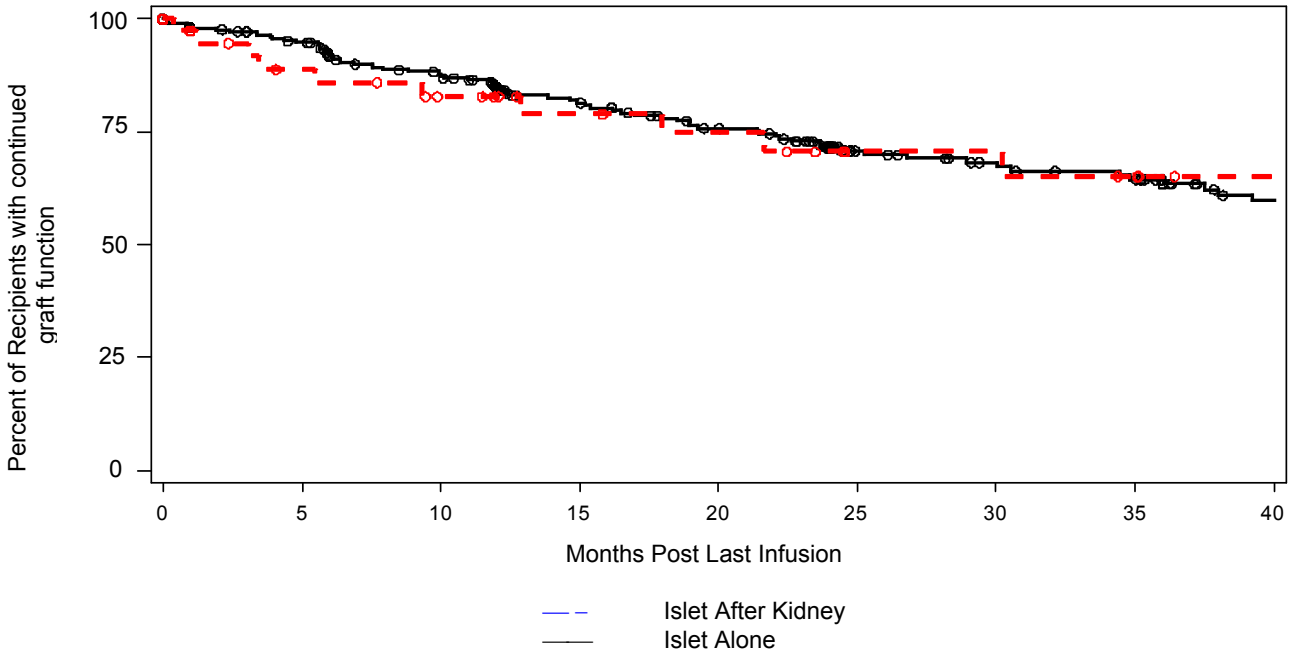


Exhibit 5 – 11
Persistence of Islet Graft Function (IA, IAK)

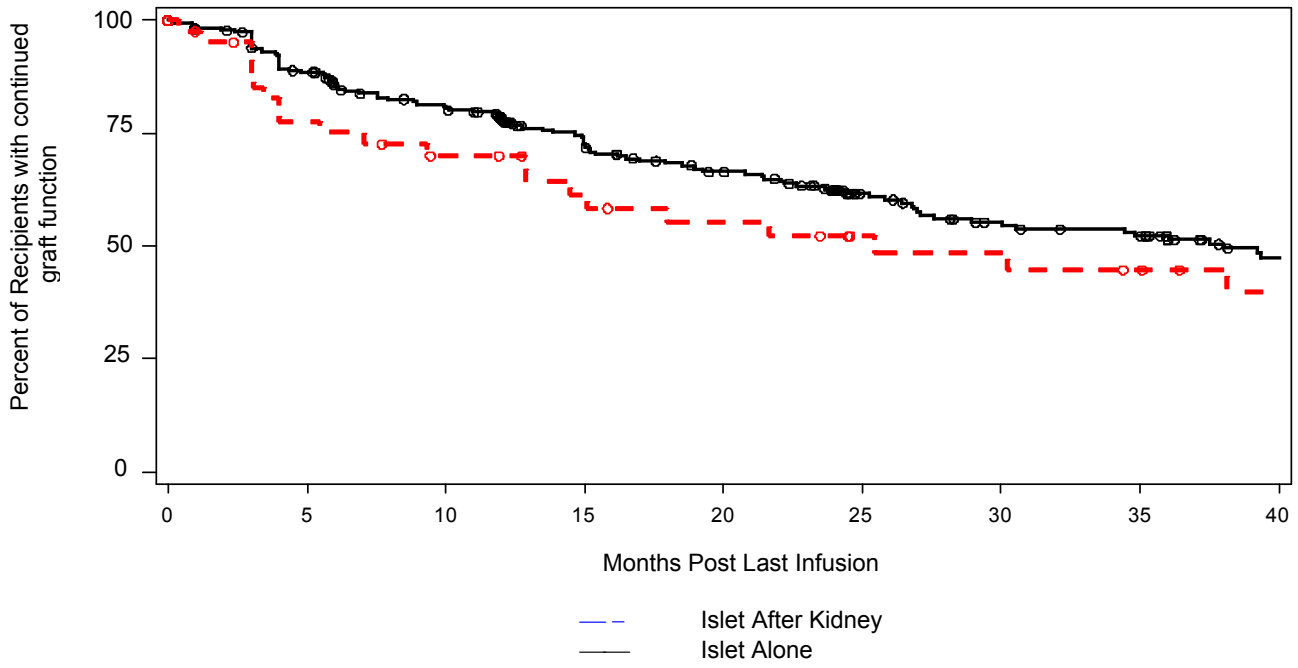
A. Reported Data



Timepoint	0	6	12	18	24	30	36
N Islet Alone	279	211	169	137	102	74	61
N Islet After Kidney	46	29	23	18	15	13	9

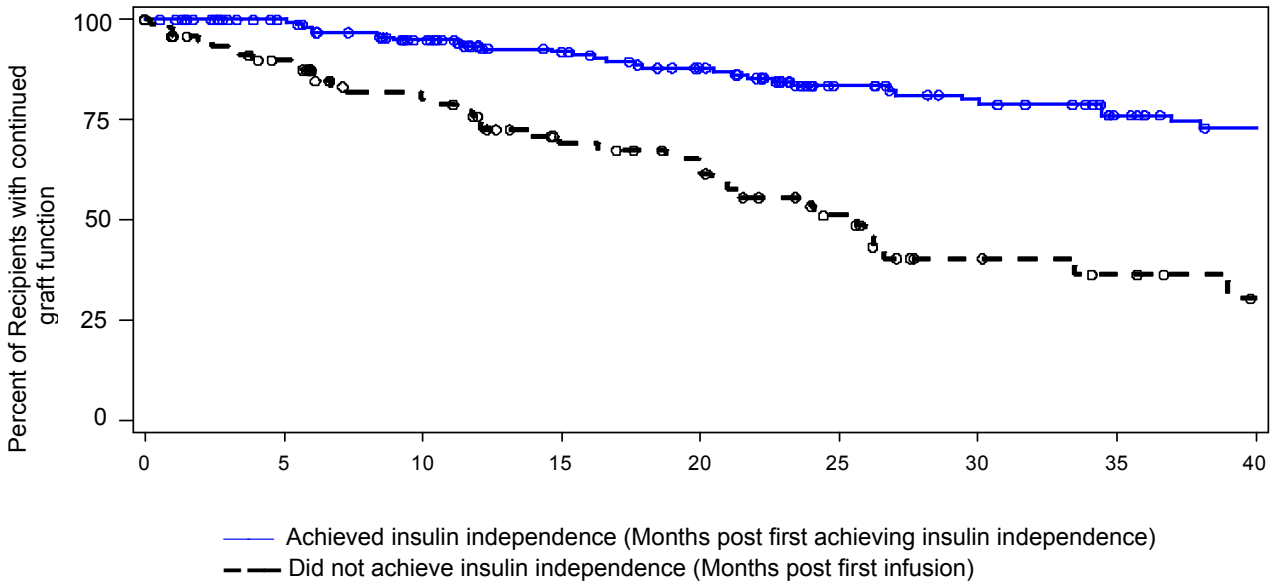
The difference in graft function persistence between islet alone and islet after kidney recipients is not significant at $p<0.05$.

Exhibit 5 – 11 *(continued)*
Persistence of Islet Graft Function (IA, IAK)
B. Participants with More than Two Years of Missing Follow-Up
Imputed as Graft Failure at Three Months after Last Follow-Up



Timepoint	0	6	12	18	24	30	36
N Islet Alone	279	214	174	138	106	74	61
N Islet After Kidney	46	30	25	18	16	13	10

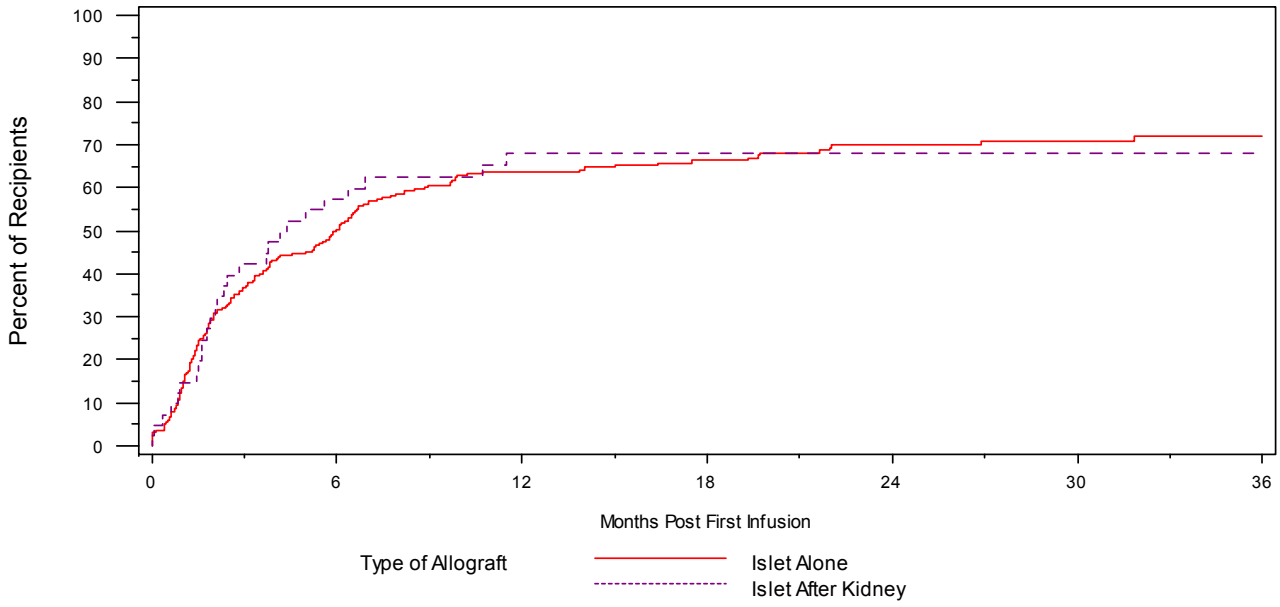
Exhibit 5 – 12
Persistence of Islet Graft Function by Ever Achieving Insulin Independence
Islet Alone Recipients
Not Censored at Re-Infusion



Timepoint	0	6	12	18	24	30	36
N Achieved Insulin Independence	177	154	125	109	79	66	52
N Did Not Achieve Insulin Independence	102	63	48	36	23	11	7

Exhibit 5 – 13
Achievement of Insulin Independence

A. All Allograft Recipients
Post First Infusion
(Not Censored at Re-Infusion)

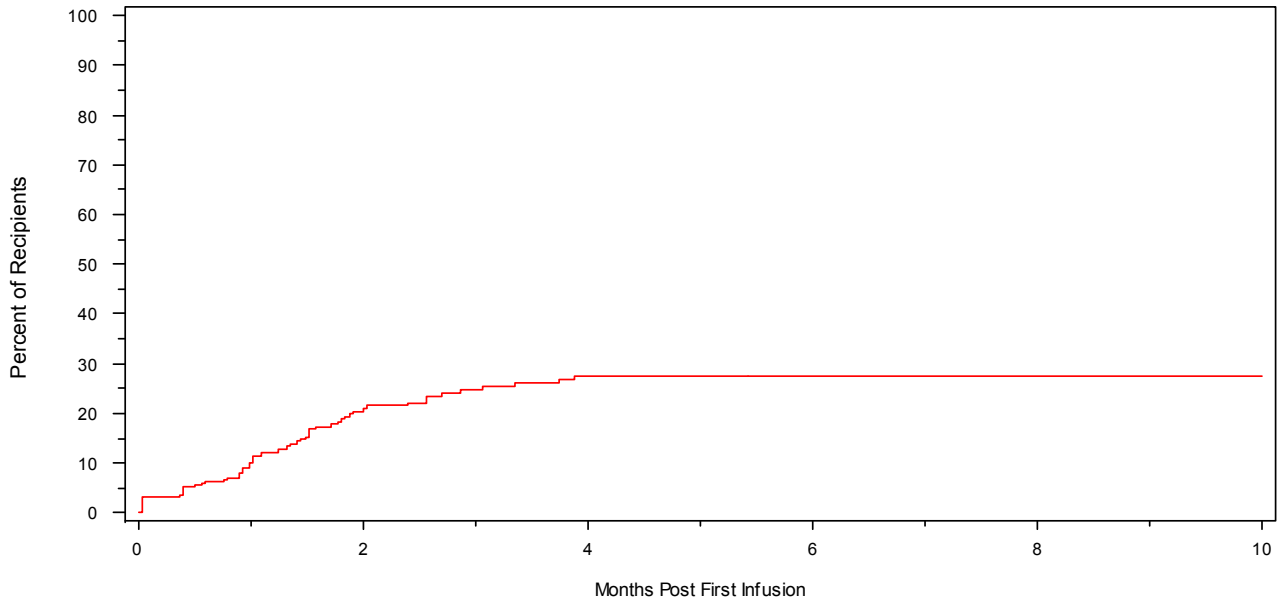


Timepoint	0	6	12	18	24	30	36
N Islet Alone	279	113	73	58	46	29	23
N Islet After Kidney	46	15	9	9	9	5	4

Exhibit 5-13 (A-D) displays the cumulative percent of recipients who have ever achieved insulin independence. They do not represent the percentage of recipients who remain insulin independent. A recipient is counted as achieving insulin independence on the first day they achieve insulin independence and remain insulin free for 14 or more consecutive days. The day in which they became insulin independent is the first day of that insulin free span and that day is included in the analysis for these Exhibits.

Exhibit 5 – 13 *(continued)*
Achievement of Insulin Independence

B. Islet Alone Recipients
Post First Infusion
(Censored at Re-Infusion)



N	279	144	91	65	50	37

C. Islet Alone Recipients
Post Second Infusion
(Recipients Not Insulin Independent after First Infusion, Censored at Third Infusion)

N	201	75	57	49	44	39

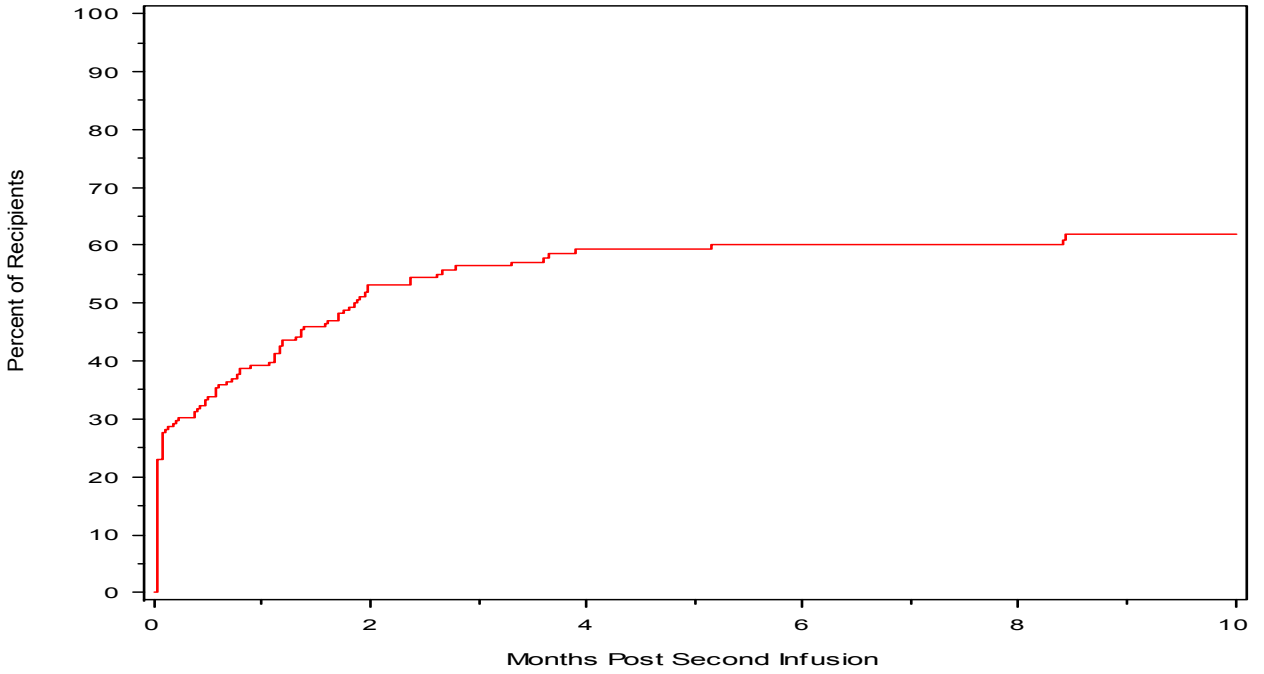
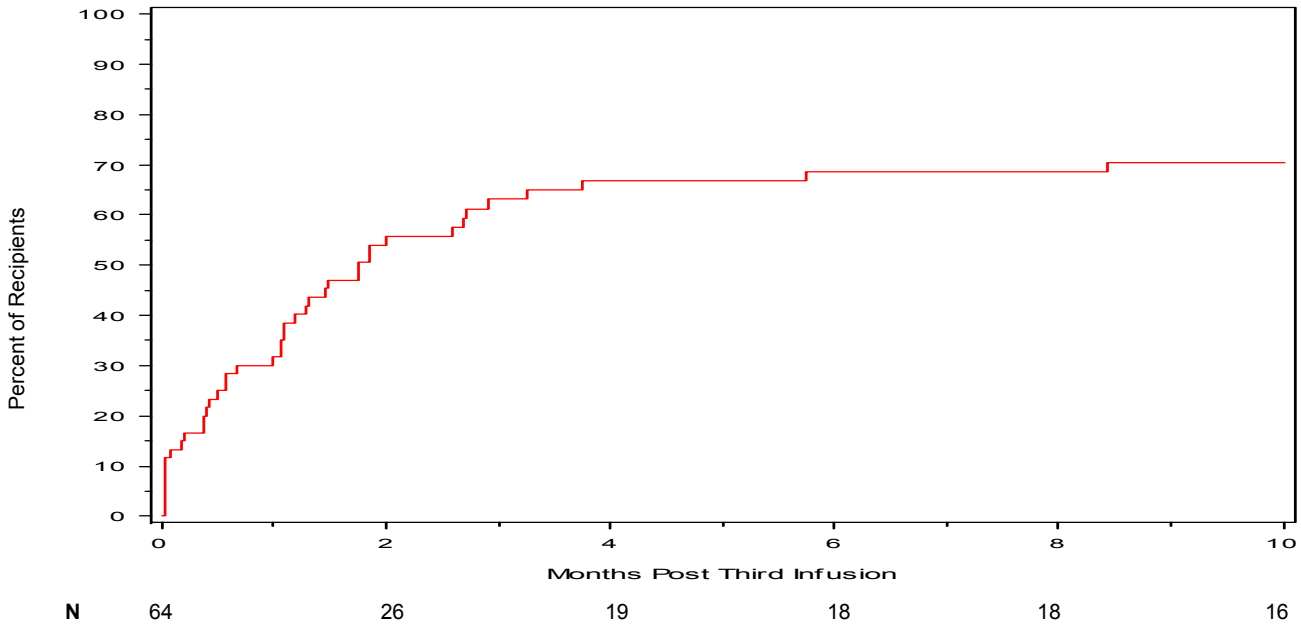


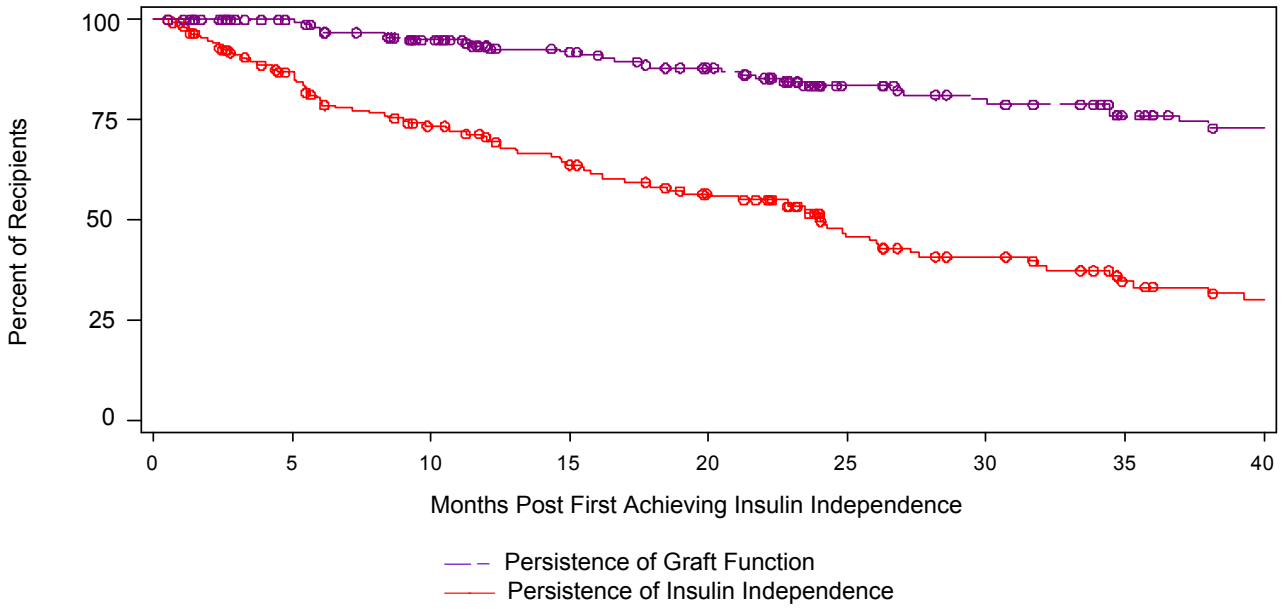
Exhibit 5 – 13 *(continued)*
Achievement of Insulin Independence

D. Islet Alone Recipients
Post Third Infusion
(Recipients Not Insulin Independent after Second Infusion, Censored at Fourth Infusion)



All instances of achieving insulin independence, post any infusion, occurred within nine months of an infusion procedure, the vast majority occurring within four months.

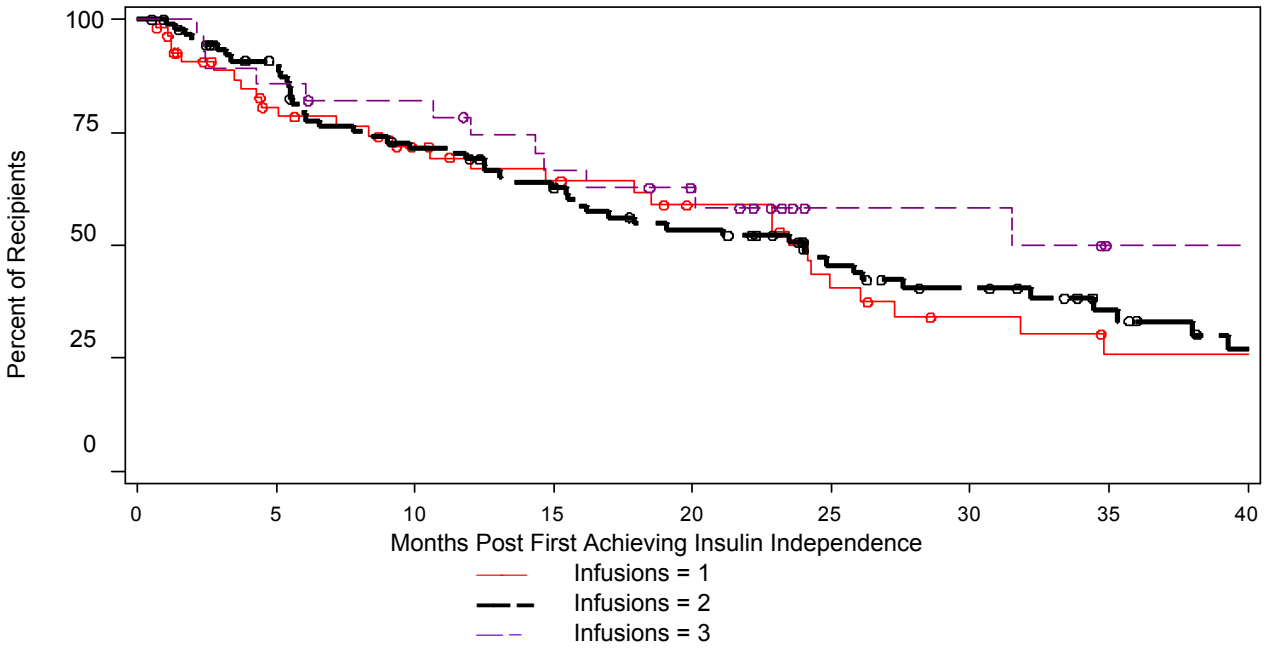
Exhibit 5 – 14
Persistence of Insulin Independence and Persistence of Graft Function
Islet Alone Recipients Achieving Insulin Independence
Not Censored at Re-Infusion



Timepoint	0	6	12	18	24	30	36
N Without Graft Loss	177	154	125	109	79	66	52
N Insulin Independent	177	126	102	80	55	37	22

This Exhibit examines all insulin independent participants starting on the first day they achieve insulin independence for 14 or more consecutive days, and follows them over time noting if and when they return to insulin use (for 14 or more consecutive days), as well as if and when they lose all islet graft function (absence of detectable C-peptide). Of the 70% of all IA recipients who achieved insulin independence, 52% remain insulin independent for two years while 84% retain graft function.

Exhibit 5 – 15
Persistence of Insulin Independence
By Total Number of Infusions Given Prior to Achievement of Insulin Independence
Islet Alone Recipients Achieving Insulin Independence

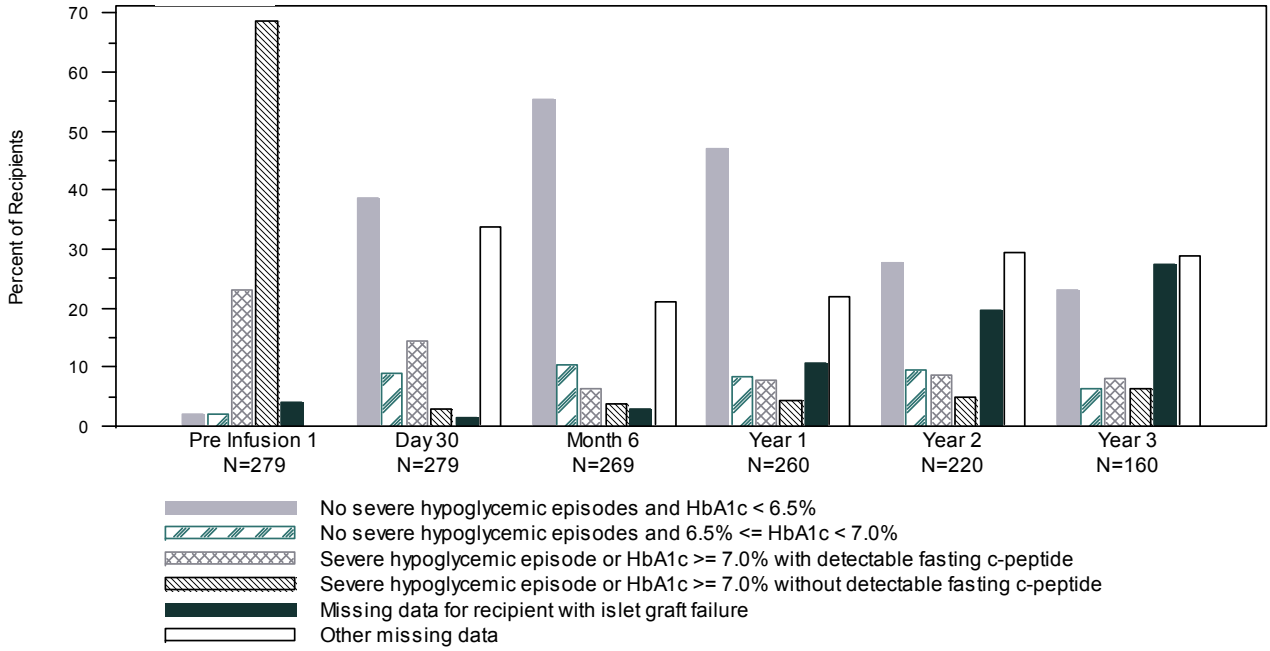


Timepoint	0	6	12	18	24	30	36
N 1 Infusion	56	36	27	23	16	9	6
N 2 Infusions	92	66	55	41	31	21	12
N 3 Infusions	28	24	20	16	8	7	4

In this Exhibit, sustainability of insulin independence is examined by the total number of infusion procedures required per participant to gain insulin independence. By Year 2, sustainability of insulin independence drops to 50% for those who achieved insulin independence after one infusion, 51% for those who achieved after two infusions and 58% for those who achieved after three infusions. Event rates at later time points are unstable due to small sample sizes.

Exhibit 5 – 16
Composite Outcome (Hypoglycemia and HbA_{1c}) Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

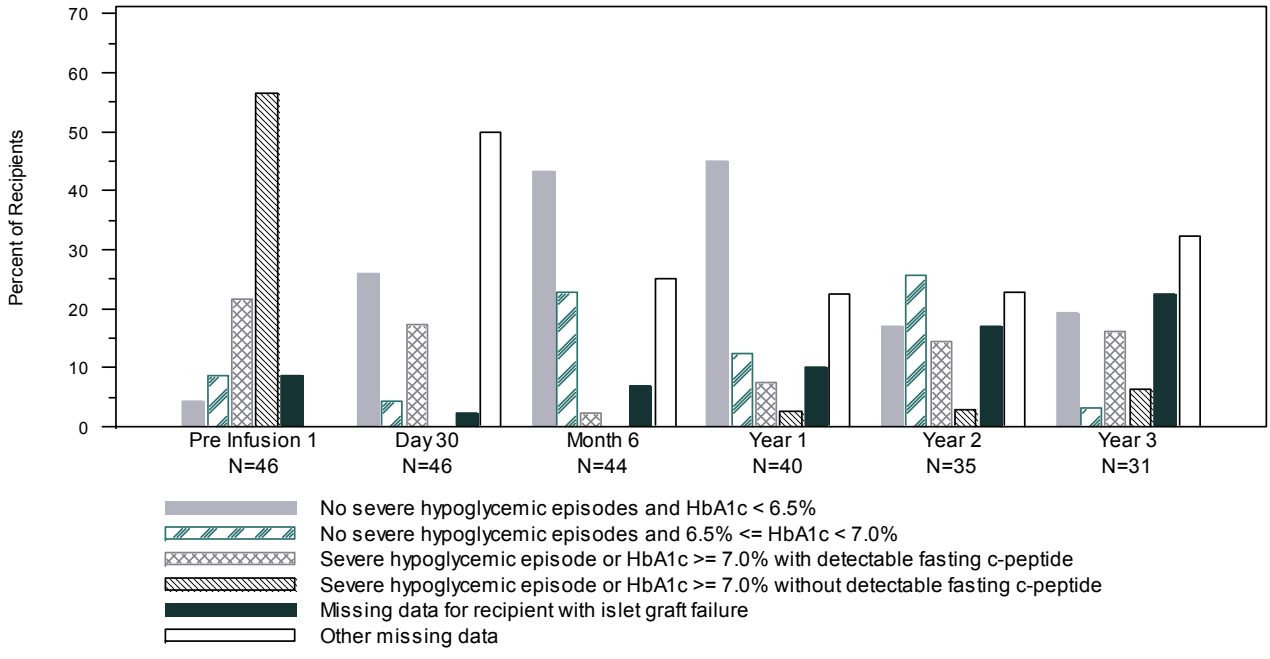
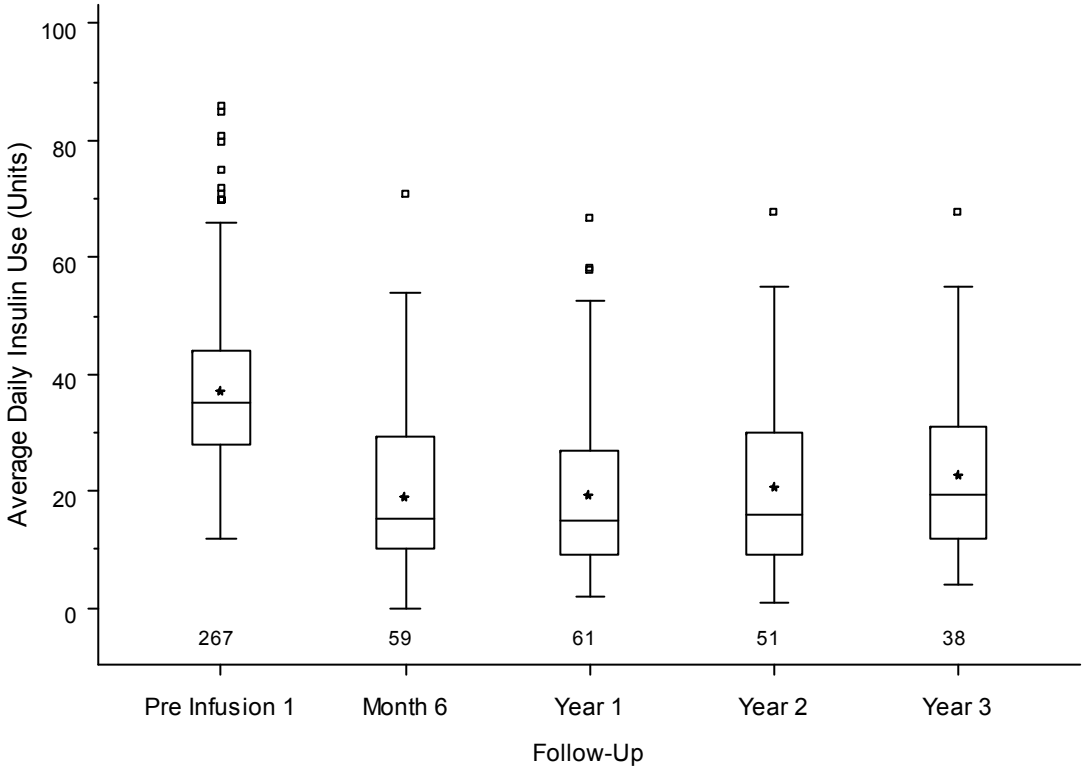
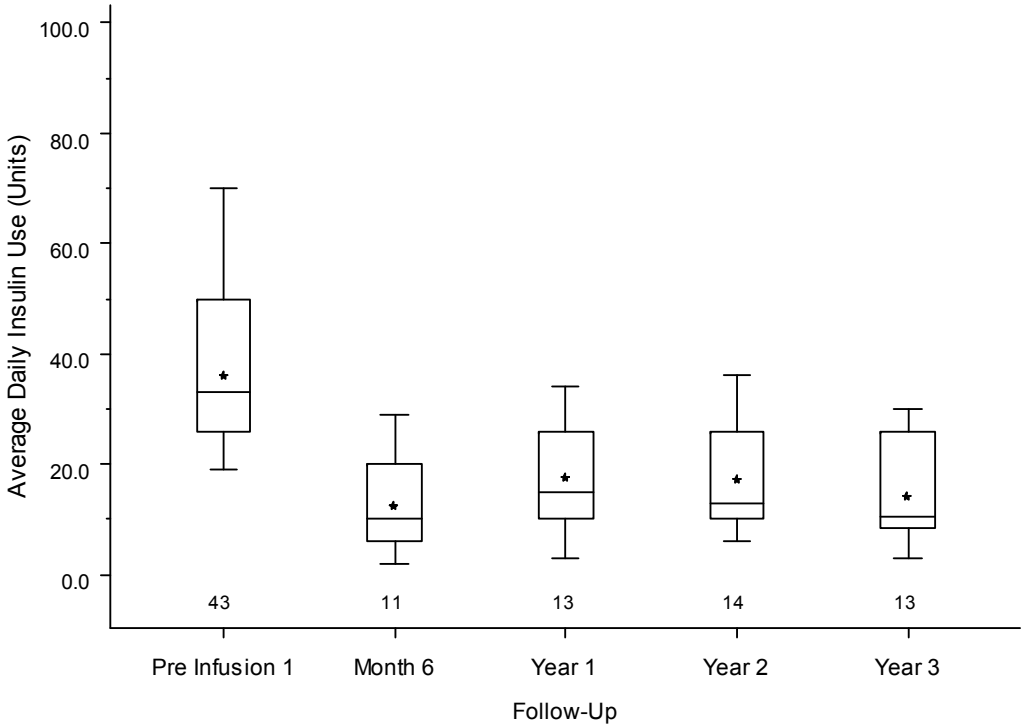


Exhibit 5 – 17
Average Daily Insulin (Units) Taken By Recipients on Insulin Baseline and Post Last Infusion

A. Islet Alone Recipients

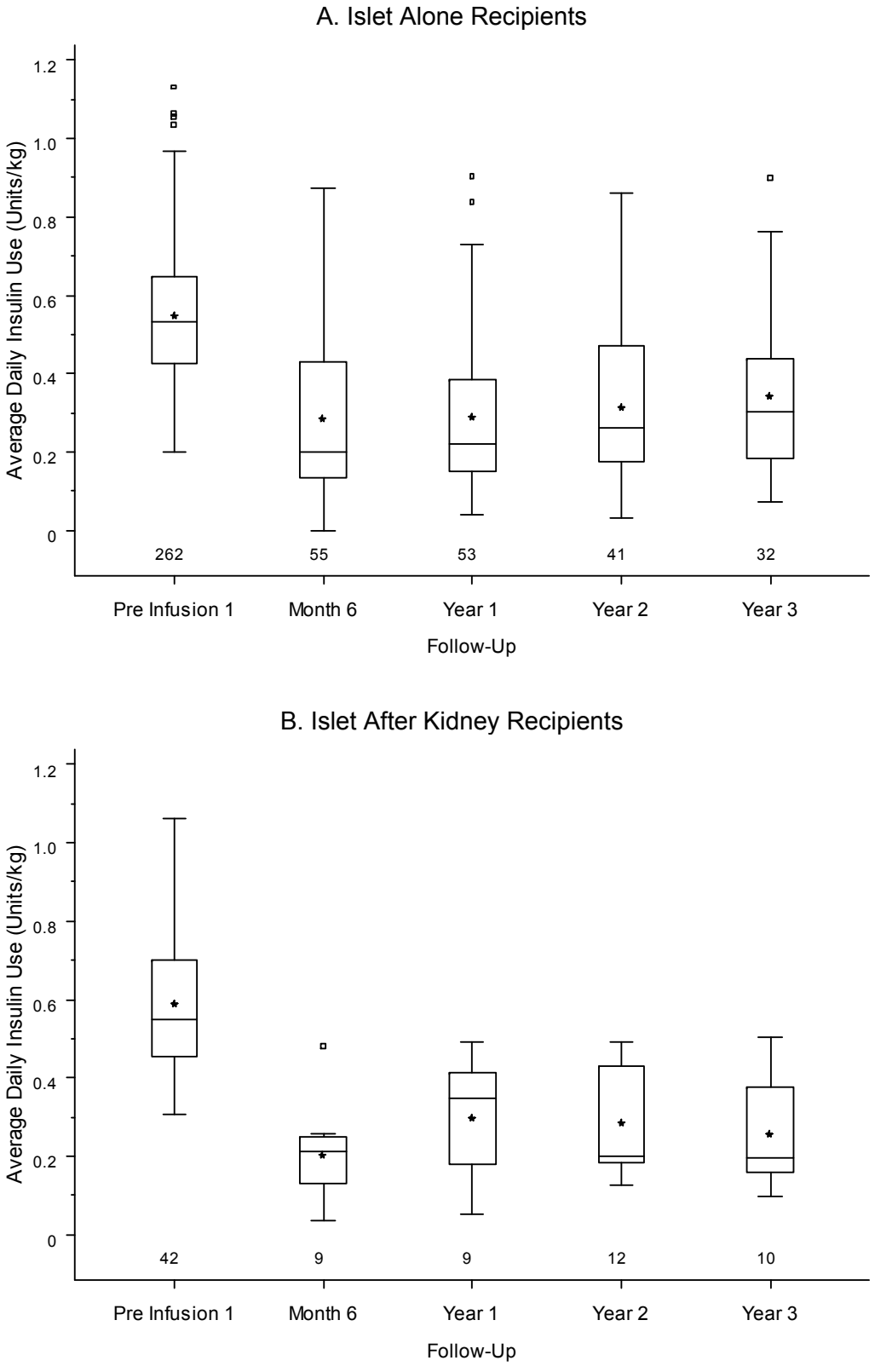


B. Islet After Kidney Recipients



For both IA and IAK, insulin use at each follow up is significantly less than pre-infusion ($p<0.01$).

Exhibit 5 – 18
Average Daily Insulin (Units/Kg) Taken By Recipients on Insulin Baseline and Post Last Infusion



For both IA and IAK, insulin use at each follow up is significantly less than pre-infusion ($p<0.01$).

Exhibit 5 – 19
Percent of Baseline Insulin Used By Recipients on Insulin
Follow-Up Post Last Infusion

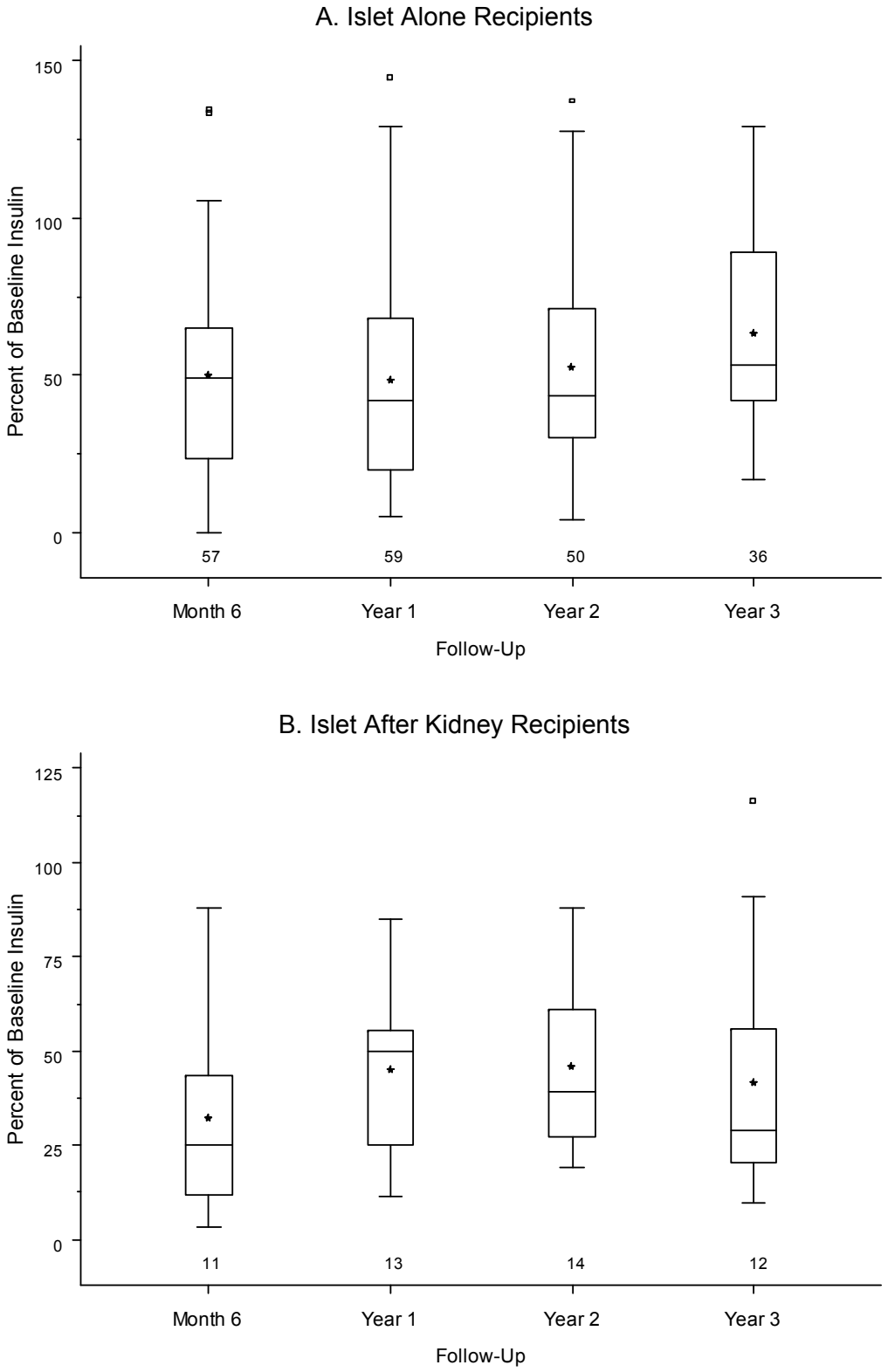


Exhibit 5 – 20
Percent of Baseline Insulin at Follow-Up Post Last Infusion
Islet Alone Recipients
who Achieved then Lost Insulin Independence

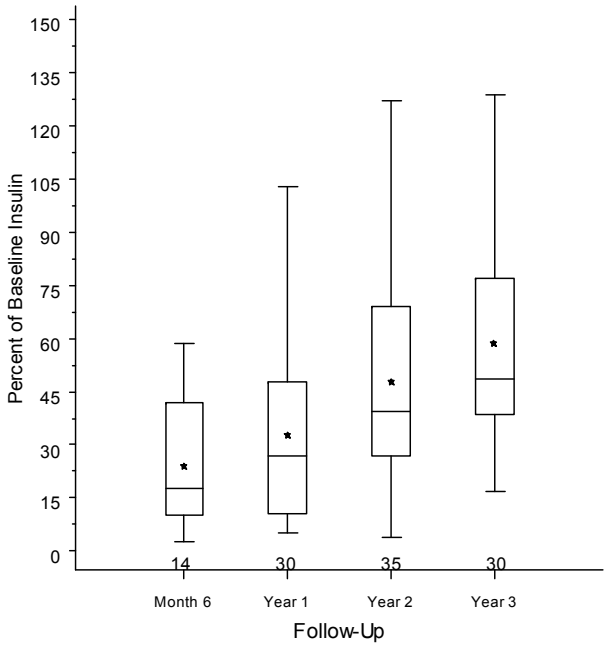
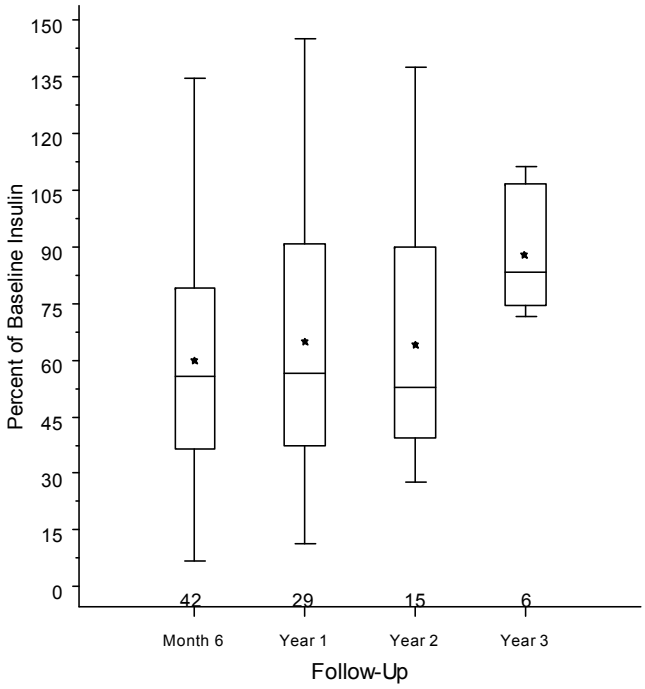


Exhibit 5 – 21
Percent of Baseline Insulin at Follow-Up Post Last Infusion
Islet Alone Recipients
Never Achieving Insulin Independence



All IA recipients who never achieve insulin independence (II) after islet transplantation require increasing amounts of daily insulin. Those who gain then lose insulin independence require somewhat less than those who never achieve II.

Exhibit 5–22A
Cox Modeling of Primary Outcomes Post First Infusion (Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up) According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics (Factors) Islet Alone Recipients with Data Available on Key Predictors

All variables describing recipient, donor, islet and immunosuppressant characteristics were included in univariate Cox models to identify factors that influence primary outcomes (achievement of insulin independence, loss after achievement, complete graft failure and re-infusion). Factors that were significant at $p<0.10$ univariately (shown in Tables 5-22A post first infusion and 5-23A post last infusion) were added or withdrawn in multivariate models one at a time, to assess joint effects on the outcomes. However, due to *de facto* imbalances, spurious or expected correlations among the variables, and unbalanced numbers with data available, several potentially important variables could not be included in the multivariate modeling. Hence these variables cannot be definitively excluded or retained as important factors. These are readily identified in Exhibits 5-22A and 5-23A as those with substantially lower sample sizes (N) than the other variables.

Cox regression was used to analyze time to first insulin independence of two or more weeks' duration, loss of insulin independence after achievement but before re-infusion or last follow-up (censoring), and time to complete islet failure before re-infusion or last follow-up (censoring). Logistic regression was used to analyze re-infusion, in part because time to re-infusion relates to non-biological factors such as organ supply and medical management decisions. Nonetheless, identifying factors associated with likelihood of re-infusion may be useful.

Definitive ascertainment of complete islet failure has improved substantially since last year's report, but remains challenging. Cases with unknown group status are censored as of their last observed follow-up with graft function, to minimize estimation bias.

Univariate results are displayed tabularly (Exhibit 5-22-A for outcomes of first infusion and 5-23-A for outcomes of last infusion), and graphically as forest plots (Exhibits 5-22-B-E and Exhibits 5-23-B-D, respectively).

Exhibit 5 – 22A *(continued)*
Primary Outcomes Post First Infusion
Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1]			D. ReInfusion Post First Infusion[2]		
Events / Total >>	**60 / 264**			**37 / 60**			**52 / 264**			**191 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Cohort 1999-2003/04-06/07-08	.	.		.	.		264	0.613	0.09	264	0.4742	0.001
Recipient gender (0=M 1=F)	264	1.721	0.08	.	.		.	.		264	0.4247	0.005
Recipient age (years)	.	.		.	.		264	0.709	0.03	.	.	
Employment impacted by dx	.	.		.	.		.	.		.	.	
Diabetes Duration (years)	.	.		.	.		264	0.708	0.01	.	.	
Months on waitlist	.	.		.	.		.	.		.	.	
Baseline daily insulin use (Units)	258	0.634	<0.001	.	.		.	.		258	1.4789	<0.001
Baseline weight (10-kg)	257	0.671	0.003	.	.		.	.		257	1.2910	0.05
Baseline PRA (%)	.	.		.	.		.	.		.	.	
Baseline BMI	255	0.878	0.01	.	.		.	.		.	.	
Baseline use of insulin pump (0=N 1=Y)	.	.		.	.		.	.		.	.	
Baseline number of daily insulin injections	175	0.765	0.002	.	.		.	.		.	.	
Baseline use of insulin pump or >=3 insulin inject	.	.		.	.		.	.		.	.	
Years prior to first inf using ins pump or >= 3 in	.	.		.	.		.	.		.	.	
Intensive therapy <10/10-25/>=25 yrs	.	.		.	.		.	.		.	.	
Baseline HbA_{1c} (%)	250	0.747	0.01	59	0.746	0.07	250	1.267	0.04	250	1.2226	0.08
Baseline fasting glucose (mg/dL)	.	.		.	.		.	.		.	.	
Baseline C-peptide (ng/mL)	.	.		.	.		.	.		.	.	
Baseline GAD 65 autoantibodies (0,1)	.	.		.	.		.	.		.	.	
Baseline IA-2 autoantibodies (0,1)	.	.		.	.		112	2.595	0.03	.	.	
Baseline insulin autoantibodies (0,1)	.	.		.	.		.	.		.	.	
Baseline total positive autoantobodies (0,1,2,3)	.	.		.	.		174	1.897	0.02	.	.	
Donor gender (1=M 1.5=Mix 2=F)	.	.		.	.		.	.		255	1.6852	0.09
Donor age (x10 yrs)	.	.		.	.		.	.		.	.	
Donor(s) Hispanic (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor race (0=W 1=Non-white)	.	.		.	.		258	0.453	0.09	.	.	
Donor(s) blood type (1=A,B,AB 2=O)	.	.		.	.		250	0.425	0.004	.	.	

Exhibit 5 – 22A *(continued)*
Primary Outcomes Post First Infusion
Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1]			D. ReInfusion Post First Infusion[2]		
Events / Total >>	**60 / 264**			**37 / 60**			**52 / 264**			**191 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
CVS death(s) (0=N 1=Y)	222	0.619	0.09	.	.		.	.		.	.	
Donor(s) hx hypertension (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) ETOH (0=N 1=Y)	.	.		52	3.061	0.007	.	.		218	2.0206	0.10
Donor(s) diabetes (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) given vasopressors (0=N 1=Y)	264	0.380	0.06	.	.		.	.		.	.	
Donor transfused prior to hospitalization (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) transfused in hospital (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) given steroids (0=N 1=Y)	157	0.542	0.06	.	.		.	.		.	.	
Donor(s) insulin (0=N 1=Y)	.	.		53	0.459	0.04	.	.		228	0.3483	<0.001
Donor(s) weight (10-kg)	254	1.104	0.004	.	.		.	.		254	0.8441	<0.001
Donor(s) height (cm)	252	1.005	0.09	.	.		.	.		252	0.9932	0.10
Donor(s) BSA	252	1.620	0.01	.	.		.	.		252	0.4335	0.003
Donor(s) BMI	252	1.016	0.006	.	.		.	.		252	0.9728	0.004
Donor(s) creatinine	202	1.333	0.06	.	.		.	.		.	.	
Donor(s) BUN	.	.		42	0.942	0.04	.	.		161	0.9607	0.06
Donor(s) bilirubin	.	.		.	.		.	.		.	.	
Donor(s) AST	.	.		45	0.991	0.09	.	.		.	.	
Donor(s) ALT	.	.		.	.		.	.		.	.	
Donor(s) serum lipase	.	.		.	.		.	.		.	.	
Donor(s) serum amylase	.	.		.	.		.	.		.	.	
Donor(s) pre-insulin glucose	.	.		.	.		.	.		.	.	
Max donor(s) glucose (mg/dL)	214	1.003	0.02	.	.		.	.		214	0.9951	0.002
Any positive crossmatch (0=N 1=Y)	.	.		.	.		.	.		.	.	
Procurement/infusion teams (0-Unrelated 1-Related)	243	2.107	0.006	.	.		.	.		.	.	
Processing/infusion center (0-Unrelated 1-Related)	.	.		59	0.274	0.04	247	0.278	0.001	.	.	
Collagenase (1=Liberase alone 2=Other)	.	.		.	.		.	.		255	0.3461	0.006
Cultured >6 hrs (0=N 1=Y)	.	.		56	0.305	<0.001	255	0.579	0.05	255	0.5121	0.02

Exhibit 5 – 22A *(*continued*)*
Primary Outcomes Post First Infusion
Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1]			D. ReInfusion Post First Infusion[2]		
Events / Total >>	**60 / 264**			**37 / 60**			**52 / 264**			**191 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Culture time (hrs)	.	.		59	0.966	<0.001	247	0.982	0.02	247	0.9799	0.004
Donor(s)-recipient age difference (x10-yrs)	.	.		.	.		.	.		.	.	
Donor(s)-recipient BMI difference (x10)	246	1.634	<0.001	.	.		.	.		246	0.5345	<0.001
Genders match (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) CMV+ / Recipient CMV- (0=N 1=Y)	242	0.378	0.007	.	.		.	.		242	2.1224	0.02
Pancreas preservation (1-UW 2-2L 3-Both)	.	.		.	.		.	.		.	.	
Recipient insulin day 0 (0=N 1=Y)	.	.		.	.		.	.		212	0.4583	0.02
Time from cross clamp to panc recovery (hrs)	.	.		.	.		.	.		.	.	
Time from admission to death (hrs)	.	.		51	0.993	0.06	.	.		.	.	
Death to pancreas recovery (hrs)	165	5.861	0.005	.	.		.	.		165	0.0551	<0.001
Recovery to transplant (hrs)	.	.		41	0.980	0.04	171	0.984	0.05	.	.	
Death to cross-clamp (hrs)	.	.		.	.		.	.		247	0.1127	0.03
Death to transplant (hrs)	.	.		57	0.987	0.04	249	0.990	0.06	249	0.9853	0.001
Cold ischemia time (hrs)	253	0.926	0.06	.	.		.	.		.	.	
Embedded islets (%)	.	.		.	.		.	.		.	.	
Stimulation index	.	.		56	0.880	0.04	.	.		238	0.8637	0.003
Stimulation index <2/2-3.5/>=3.5	.	.		.	.		.	.		238	0.6032	0.008
Islet Viability (%)	234	1.011	0.04	.	.		234	0.975	0.07	234	0.9815	0.02
Viability > 87% (0=N 1=Y)	.	.		.	.		.	.		.	.	
Total beta cells (1000s)	.	.		.	.		.	.		95	0.2001	0.02
Total beta cells/kg donor	.	.		.	.		.	.		92	0.0000	0.06
Total insulin content of islets	.	.		.	.		.	.		.	.	
Insulin content <3/3-5/>=5	.	.		20	1.880	0.03	.	.		.	.	
Total endotoxin infused	.	.		.	.		.	.		.	.	
Total endotoxin infused/kg donor	.	.		.	.		.	.		.	.	
Endotoxin/kg <0.6/.06-3.0/>=3.0	.	.		.	.		.	.		205	1.4576	0.09

Exhibit 5 – 22A *(continued)*
Primary Outcomes Post First Infusion
Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1]			D. ReInfusion Post First Infusion[2]		
Events / Total >>	**60 / 264**			**37 / 60**			**52 / 264**			**191 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Total IEQs at time of islet count (1000s)	258	5.301	0.003	.	.		.	.		258	0.1478	0.01
Total islet particles infused (1000s)	.	.		.	.		.	.		.	.	
Total volume infused over all infusions (ml)	241	0.923	0.03	60	1.169	<0.001	.	.		241	1.5765	<0.001
Cumulative IEQs infused (1000s)	259	6.824	0.001	60	0.158	0.08	.	.		259	0.0713	<0.001
Cumulative IEQs infused (1:<400K 2:>=400K)	.	.		.	.		.	.		.	.	
Cumulative IEQs infused/kg recipient (100s)	254	1.162	<0.001	.	.		.	.		254	0.8208	<0.001
IEQ/islet particle ratio	.	.		.	.		.	.		.	.	
Islet size (0-small 1-large)	.	.		.	.		.	.		.	.	
Sirolimus	.	.		.	.		.	.		.	.	
Tacrolimus	.	.		.	.		.	.		260	6.4576	<0.001
DSG	.	.		.	.		.	.		.	.	
Everolimus	.	.		.	.		.	.		.	.	
Thymoglobulin	.	.		55	0.324	0.04	.	.		252	0.2686	0.001
Daclizumab	.	.		58	4.165	0.02	.	.		257	2.7957	0.001
h-OOKT3g-1	.	.		55	0.181	0.10	.	.		250	0.1124	0.004
Lymphocyte IG	.	.		.	.		.	.		.	.	
ALG	.	.		.	.		.	.		.	.	
Basiliximab	.	.		.	.		.	.		.	.	
Alemtuzumab	.	.		.	.		.	.		.	.	
Infliximab	.	.		.	.		.	.		248	7.1332	0.01
Etanercept	248	1.831	0.04	56	0.511	0.10	.	.		248	0.4363	0.02
Cyclosporin	.	.		.	.		.	.		.	.	
Poly T-cell depleting	256	1.779	0.07	59	0.409	0.07	.	.		256	0.2069	<0.001
Mono T-cell depleting	.	.		.	.		.	.		.	.	
Anti-Il2	.	.		59	4.348	0.02	.	.		256	4.5122	<0.001
Anti-CD3	.	.		59	0.177	0.09	.	.		256	0.1184	0.005
TNF blocker	.	.		.	.		.	.		.	.	

Exhibit 5 – 22A *(continued)*
Primary Outcomes Post First Infusion
Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1]			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1]			D. ReInfusion Post First Infusion[2]		
Events / Total >>	**60 / 264**			**37 / 60**			**52 / 264**			**191 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Deoxyspergualin	.	.		.	.		.	.		.	.	
Calcineurin inhibitor	256	0.386	0.07	.	.		256	0.313	0.05	256	26.6853	<0.001
Sirolimus or Everolimus	.	.		.	.		.	.		256	4.1769	0.03
MMF or mycophenolic acid	.	.		.	.		.	.		256	0.1352	<0.001
Prednisone, Methylprednisolone, or other steroid	257	3.219	<0.001	60	0.437	0.09	.	.		257	0.0774	<0.001
Poly or mono T-cell AB + calc inh + (mtor OR inosine)	.	.		.	.		.	.		264	0.2808	0.005
Poly or mono T-cell AB + TNF-alpha ant + calc inh + (mtor OR inos	.	.		.	.		.	.		.	.	
Monoclonal anti-IL2R + calc inh + (mtor OR inosine)	.	.		60	3.250	0.002	.	.		264	2.5926	<0.001
Monoclonal anti-IL2R + TNF-alpha ant + calc inh + (mtor OR inosin	.	.		.	.		.	.		.	.	
Number of A locus mismatches	.	.		.	.		.	.		.	.	
Number of B locus mismatches	.	.		.	.		.	.		.	.	
Number of DR locus mismatches	.	.		.	.		.	.		.	.	
Number of DQ locus mismatches	.	.		.	.		.	.		.	.	
Number of Class I locus mismatches	.	.		.	.		.	.		.	.	
Number of Class II locus mismatches	.	.		.	.		.	.		.	.	
Number of A/B/DR locus mismatches	.	.		.	.		.	.		.	.	
Number of A/B/DR/DQ locus mismatches	.	.		.	.		.	.		.	.	

The final multivariate model for insulin independence post first infusion is:

Variable	HR	p
Baseline daily insulin use (Units)	0.724	0.02
Baseline HbA_{1c} (%)	0.768	0.04
Donor CMV+ / Recipient CMV -	0.413	0.02
Procurement infusions teams (0-Unrelated 1-Related)	1.998	0.02
IEQs infused per kg recipient BW (x100)	1.119	0.002

Many relationships exist among the independent variables (see 2008 Annual Report Supplemental Materials at www.CITRegistry.org): baseline daily insulin is substantially correlated with baseline weight, baseline BMI, baseline HbA_{1c}, fasting glucose, and number of daily injections. Any of these measures of initial control suffices to explain its influence on achieving insulin independence: the

better the control, the more likely to achieve insulin independence. Greater number of IEQs infused per body weight improves the chances of achieving insulin independence as well as reducing the need for re-infusion. Islets from donors positive for CMV given to recipients negative for CMV reduce the chances of achieving insulin independence post first infusion. When the procurement team is related to the transplant center, insulin independence is more likely. Whether the donor was given steroids cannot be excluded as significantly associated with this outcome. Additionally, there is substantial imbalance between immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of those immunosuppressant therapies in a multivariate model. Their univariate effects cannot be dismissed. Particularly, the apparently disadvantageous univariate effect of calcineurin is in fact eclipsed by the most likely outcome in those recipients of calcineurin is that they were re-infused much more frequently and quickly, which most likely led to this spurious relationship.

Loss of insulin independence lacks sufficient events to permit multivariate modeling of factors.

The final multivariate model for complete islet failure post first infusion is:

Variable	**HR**	**p**
Diabetes duration (years)	0.702	0.01
Donor blood type (1=A,B,AB 2=O)	0.362	0.001
Processing/infusion centers (0=unrelated 1= related)	0.325	0.06
Cultured >6 hrs (0=N 1=Y)	0.536	0.04

Longer diabetes duration and older recipient age predict lower risk of losing the graft, while worse diabetic control as measured by higher HbA_{1c} predicts increased risk of losing the first graft. Related processing and infusion centers substantially reduce the chances of losing the first graft, as do donor O blood type and culturing the islets > 6 hours. Higher baseline autoantibodies cannot be ruled out as a risk factor of losing the first graft.

Exhibit 5–22B
Achievement of Insulin Independence Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
Of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated.

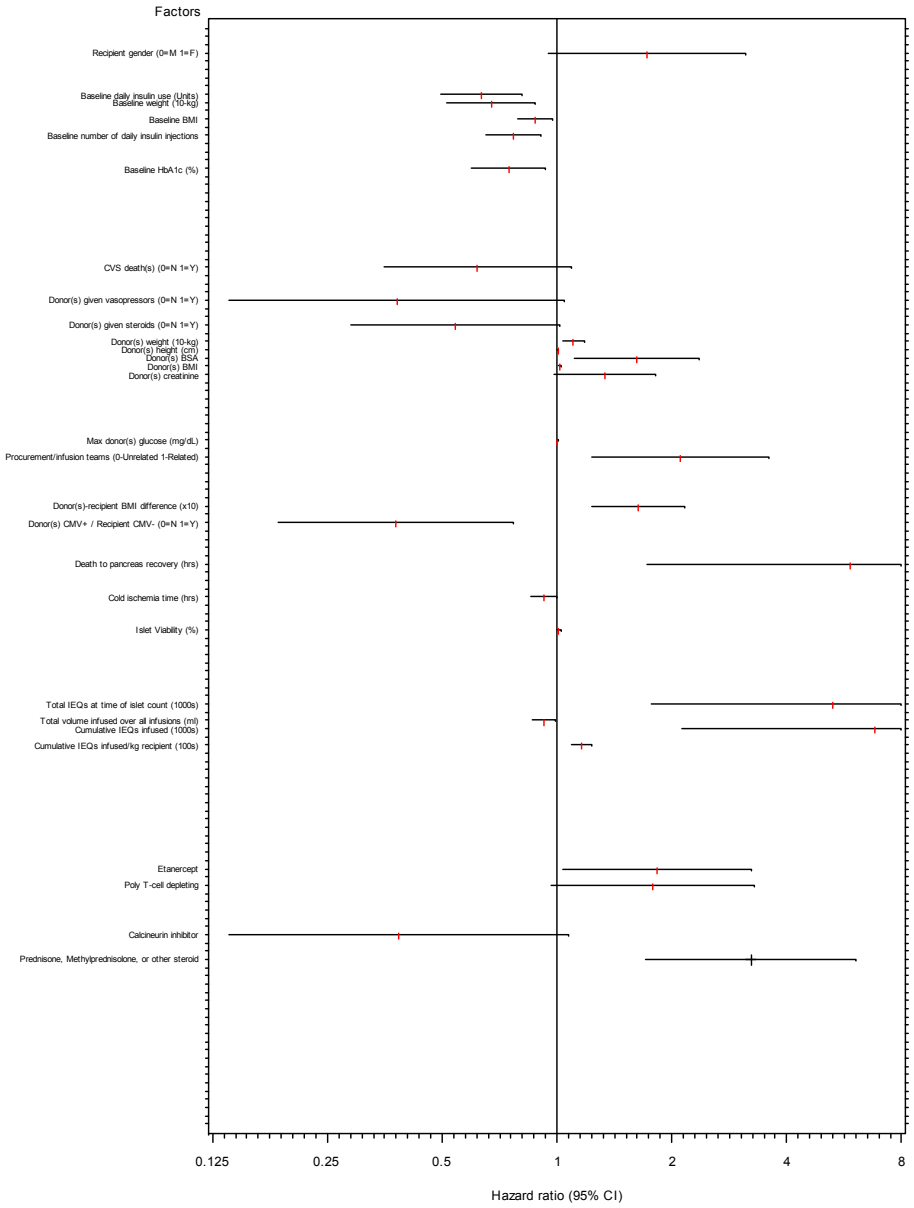


Exhibit 5–22C
Loss of Insulin Independence Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
Of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated.

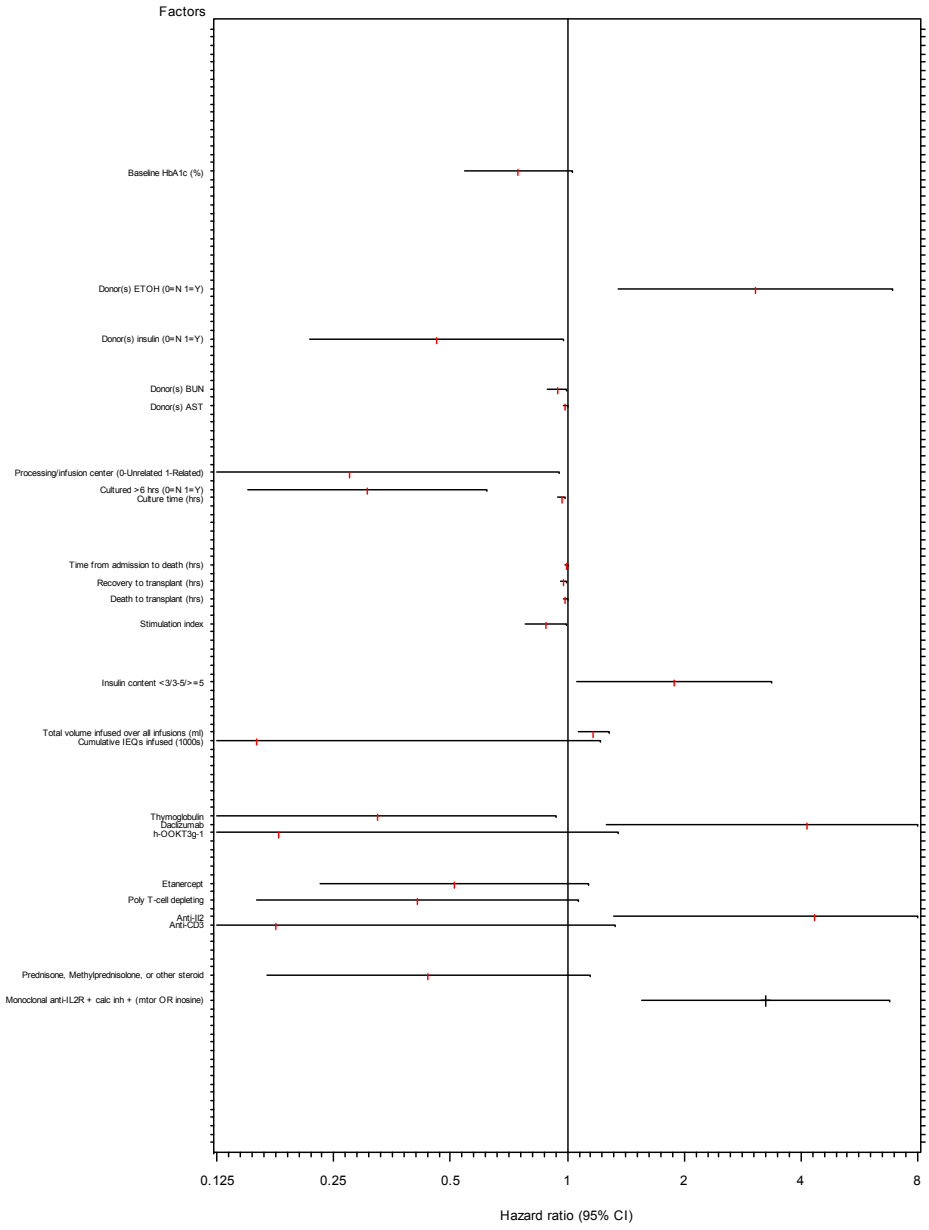


Exhibit 5–22D
Complete Islet Failure Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
Of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated.

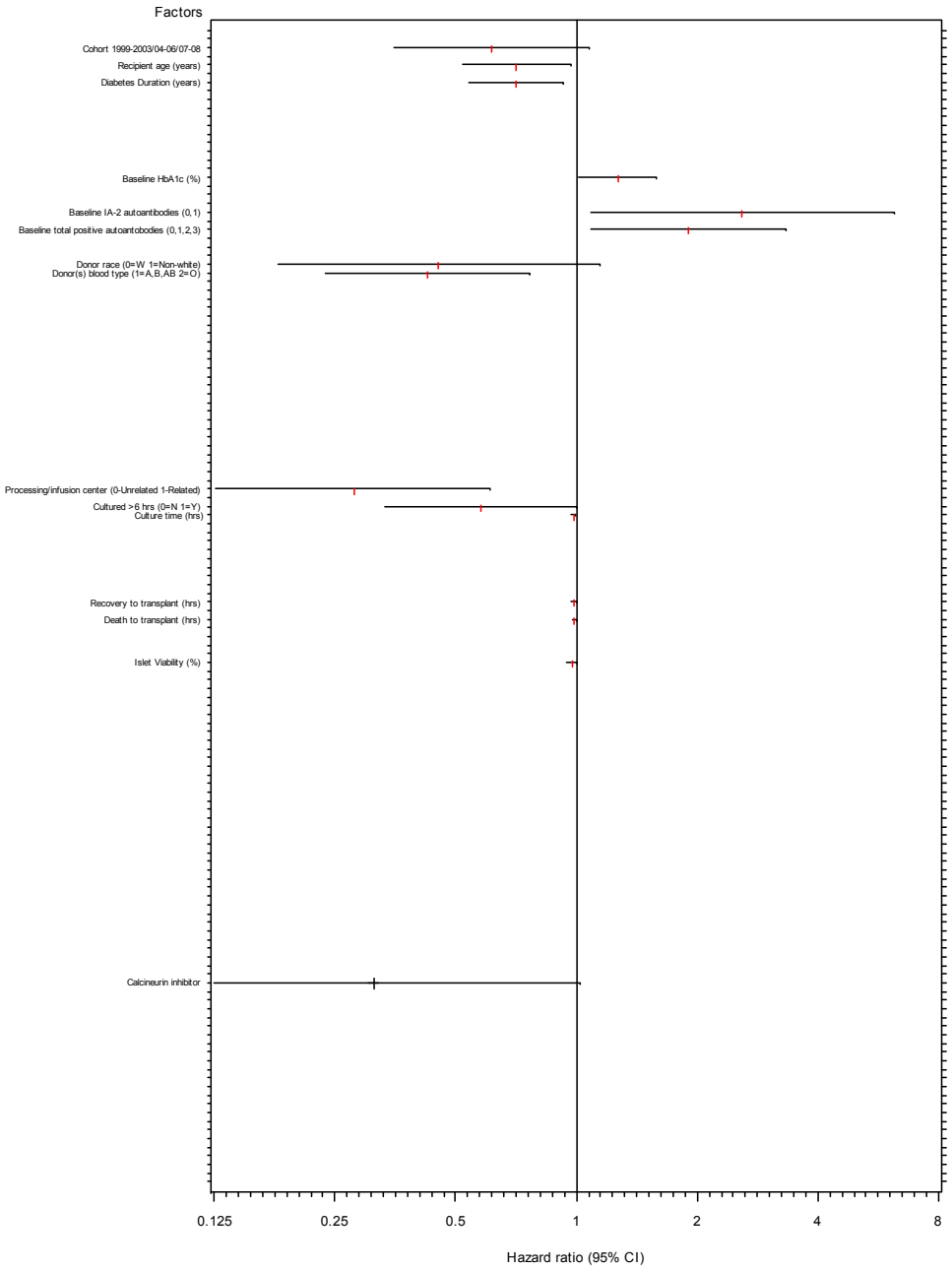


Exhibit 5–22E
Reinfusion Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated.

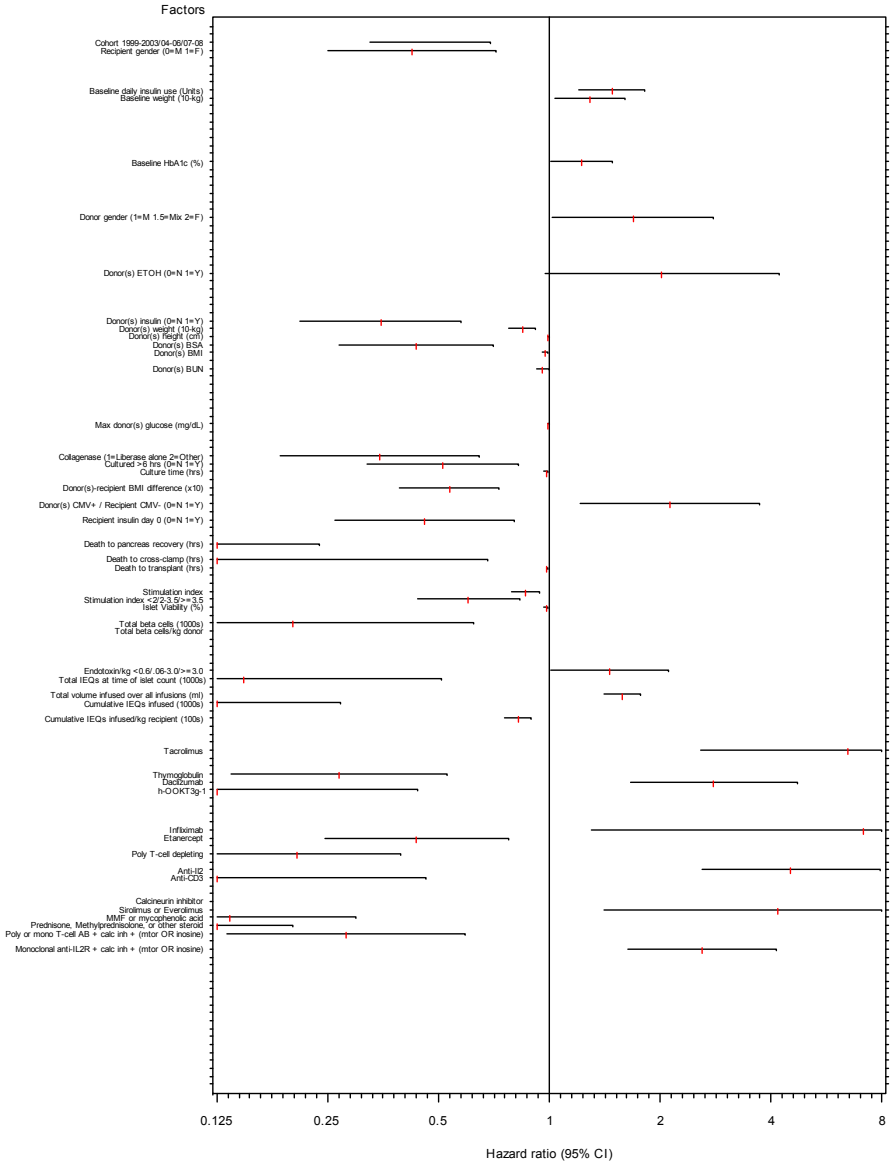


Exhibit 5–23A
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Methods of univariate and multivariate analysis are summarized in the text leading Exhibit 5-22A.

Cox proportional hazard model: Hazard ratio (HR) and p-value	**A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up**		
Events / Total >>	**174 / 264**			**86 / 174**			**78 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Cohort 1999-2003/04-06/07-08	.	.		.	.		.	.	
Recipient gender (0=M 1=F)	.	.		.	.		.	.	
Recipient age (years)	.	.		.	.		264	0.598	<0.001
Employment impacted by dx	.	.		160	0.630	0.10	.	.	
Diabetes Duration (years)	.	.		173	0.733	0.004	264	0.671	<0.001
Months on waitlist	.	.		.	.		.	.	
Baseline daily insulin use (Units)	.	.		169	1.242	0.01	.	.	
Baseline weight (10-kg)	.	.		.	.		.	.	
Baseline PRA (%)	.	.		.	.		.	.	
Baseline BMI	.	.		.	.		.	.	
Baseline use of insulin pump (0=N 1=Y)	.	.		.	.		.	.	
Baseline number of daily insulin injections	.	.		.	.		.	.	
Baseline use of insulin pump or >=3 insulin inject	.	.		.	.		.	.	
Years prior to first inf using ins pump or >= 3 in	.	.		.	.		186	0.982	0.09
Intensive therapy <10/10-25/>=25 yrs	.	.		.	.		.	.	
Baseline HbA_{1c} (%)	251	0.823	0.002	.	.		251	1.167	0.10
Baseline fasting glucose (mg/dL)	.	.		.	.		.	.	
Baseline C-peptide (ng/mL)	.	.		166	2.318	0.007	.	.	
Baseline GAD 65 autoantibodies (0,1)	.	.		107	2.097	0.009	.	.	
Baseline IA-2 autoantibodies (0,1)	.	.		.	.		113	1.857	0.07
Baseline insulin autoantibodies (0,1)	.	.		.	.		.	.	
Baseline total positive autoantobodies (0,1,2,3)	.	.		.	.		.	.	
Donor gender (1=M 1.5=Mix 2=F)	257	1.523	0.04	.	.		.	.	
Donor age (x10 yrs)	.	.		.	.		.	.	

Exhibit 5 – 23A *(continued)*
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Cox proportional hazard model: Hazard ratio (HR) and p-value	**A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up**		
Events / Total >>	**174 / 264**			**86 / 174**			**78 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Donor(s) Hispanic (0=N 1=Y)	264	0.570	0.02	.	.		.	.	
Donor race (0=W 1=Non-white)	.	.		.	.		258	0.456	0.05
Donor(s) blood type (1=A,B,AB 2=O)	.	.		.	.		.	.	
CVS death(s) (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) hx hypertension (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) ETOH (0=N 1=Y)	222	1.336	0.09	.	.		.	.	
Donor(s) diabetes (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) given vasopressors (0=N 1=Y)	.	.		.	.		.	.	
Donor transfused prior to hospitalization (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) transfused in hospital (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) given steroids (0=N 1=Y)	163	0.664	0.05	.	.		.	.	
Donor(s) insulin (0=N 1=Y)	238	0.730	0.05	157	0.584	0.02	.	.	
Donor(s) weight (10-kg)	.	.		.	.		.	.	
Donor(s) height (cm)	.	.		.	.		.	.	
Donor(s) BSA	.	.		.	.		.	.	
Donor(s) BMI	.	.		.	.		.	.	
Donor(s) creatinine	231	1.179	0.003	.	.		.	.	
Donor(s) BUN	.	.		.	.		.	.	
Donor(s) bilirubin	.	.		.	.		.	.	
Donor(s) AST	186	1.000	0.08	.	.		.	.	
Donor(s) ALT	.	.		.	.		.	.	
Donor(s) serum lipase	.	.		.	.		.	.	
Donor(s) serum amylase	.	.		.	.		.	.	
Donor(s) pre-insulin glucose	.	.		.	.		.	.	
Max donor(s) glucose (mg/dL)	.	.		.	.		.	.	

Exhibit 5 – 23A *(continued)*
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Cox proportional hazard model: Hazard ratio (HR) and p-value	**A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up**		
Events / Total >>	**174 / 264**			**86 / 174**			**78 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Any positive crossmatch (0=N 1=Y)	.	.		.	.		.	.	
Procurement/infusion teams (0-Unrelated 1-Related)	251	1.624	0.002	.	.		251	0.595	0.03
Processing/infusion center (0-Unrelated 1-Related)	250	3.182	<0.001	166	0.435	0.05	250	0.379	0.004
Collagenase (1=Liberase alone 2=Other)	.	.		.	.		.	.	
Cultured >6 hrs (0=N 1=Y)	.	.		.	.		.	.	
Culture time (hrs)	.	.		.	.		.	.	
Donor(s)-recipient age difference (x10-yrs)	.	.		165	1.121	0.006	251	1.125	0.006
Donor(s)-recipient BMI difference (x10)	.	.		.	.		.	.	
Genders match (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) CMV+ / Recipient CMV- (0=N 1=Y)	.	.		.	.		.	.	
Pancreas preservation (1-UW 2-2L 3-Both)	.	.		.	.		.	.	
Recipient insulin day 0 (0=N 1=Y)	.	.		.	.		.	.	
Time from cross clamp to panc recovery (hrs)	203	1.160	0.09	.	.		.	.	
Time from admission to death (hrs)	.	.		143	0.998	0.09	.	.	
Death to pancreas recovery (hrs)	.	.		135	0.425	0.07	.	.	
Recovery to transplant (hrs)	204	0.996	0.06	.	.		.	.	
Death to cross-clamp (hrs)	.	.		.	.		.	.	
Death to transplant (hrs)	.	.		.	.		.	.	
Cold ischemia time (hrs)	.	.		.	.		.	.	
Embedded islets (%)	.	.		.	.		.	.	
Stimulation index	.	.		.	.		244	0.955	0.07
Stimulation index <2/2-3.5/>=3.5	.	.		.	.		.	.	
Islet Viability (%)	.	.		.	.		.	.	
Viability > 87% (0=N 1=Y)	.	.		.	.		243	0.321	0.005

Exhibit 5 – 23A *(continued)*
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Cox proportional hazard model: Hazard ratio (HR) and p-value	A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up			B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up			C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up		
Events / Total >>	**174 / 264**			**86 / 174**			**78 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Total beta cells (1000s)	112	0.590	0.07	.	.		.	.	
Total beta cells/kg donor	109	0.011	0.05	.	.		.	.	
Total insulin content of islets	.	.		.	.		.	.	
Insulin content <3/3-5/>=5	.	.		.	.		.	.	
Total endotoxin infused	.	.		.	.		.	.	
Total endotoxin infused/kg donor	.	.		.	.		.	.	
Endotoxin/kg <0.6/.06-3.0/>=3.0	220	0.791	0.07	.	.		.	.	
Total IEQs at time of islet count (1000s)	.	.		.	.		.	.	
Total islet particles infused (1000s)	.	.		.	.		.	.	
Total volume infused over all infusions (ml)	.	.		.	.		.	.	
Cumulative IEQs infused (1000s)	.	.		.	.		.	.	
Cumulative IEQs infused (1:<400K 2:>=400K)	.	.		.	.		.	.	
Cumulative IEQs infused/kg recipient (100s)	.	.		.	.		.	.	
IEQ/islet particle ratio	.	.		.	.		.	.	
Islet size (0-small 1-large)	212	1.659	0.004	.	.		212	0.648	0.08
Sirolimus	.	.		.	.		.	.	
Tacrolimus	.	.		.	.		.	.	
DSG	.	.		.	.		.	.	
Everolimus	.	.		.	.		.	.	
Thymoglobulin	.	.		164	0.412	0.06	.	.	
Daclizumab	258	1.502	0.09	170	2.525	0.05	.	.	
h-OOKT3g-1	.	.		.	.		.	.	
Lymphocyte IG	.	.		.	.		.	.	
ALG	.	.		.	.		.	.	
Basiliximab	.	.		.	.		.	.	

Exhibit 5 – 23A *(continued)*
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Cox proportional hazard model: Hazard ratio (HR) and p-value	**A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up**		
Events / Total >>	**174 / 264**			**86 / 174**			**78 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Alemtuzumab	.	.		.	.		.	.	
Infliximab	.	.		163	1.862	0.04	.	.	
Etanercept	.	.		.	.		248	0.397	0.03
Cyclosporin	.	.		.	.		.	.	
Poly T-cell depleting	.	.		.	.		.	.	
Mono T-cell depleting	.	.		.	.		.	.	
Anti-Il2	.	.		161	2.318	0.08	.	.	
Anti-CD3	.	.		161	0.142	0.07	.	.	
TNF blocker	.	.		.	.		.	.	
Calcineurin inhibitor	.	.		161	0.249	0.06	242	0.136	<0.001
Sirolimus or Everolimus	.	.		.	.		.	.	
MMF or mycophenolic acid	.	.		161	0.434	0.04	.	.	
Prednisone, Methylprednisolone, or other steroid	.	.		.	.		.	.	
Poly or mono T-cell AB + calc inh + (mtor OR inosine)	264	0.419	0.06	173	0.158	0.07	.	.	
Poly or mono T-cell AB + TNF-alpha ant + calc inh + (mtor OR inos	.	.		.	.		.	.	
Monoclonal anti-IL2R + calc inh + (mtor OR inosine)	264	1.317	0.08	.	.		.	.	
Monoclonal anti-IL2R + TNF-alpha ant + calc inh + (mtor OR inosin	.	.		.	.		.	.	
Deoxyspergualin	.	.		.	.		.	.	
Number of A locus mismatches	.	.		.	.		.	.	
Number of B locus mismatches	186	1.100	0.07	.	.		.	.	
Number of DR locus mismatches	.	.		.	.		.	.	
Number of DQ locus mismatches	.	.		.	.		.	.	
Number of Class I locus mismatches	181	1.061	0.05	.	.		.	.	

Exhibit 5 – 23A *(continued)*
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Cox proportional hazard model: Hazard ratio (HR) and p-value	**A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up**			**C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up**		
Events / Total >>	**174 / 264**			**86 / 164**			**78 / 264**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Number of Class II locus mismatches	.	.		.	.		.	.	
Number of A/B/DR locus mismatches	.	.		.	.		.	.	
Number of A/B/DR/DQ locus mismatches	68	1.044	0.09	.	.		.	.	
Reexposed to A locus mismatch	255	1.361	0.06	.	.		.	.	
Reexposed to B locus mismatch	.	.		.	.		.	.	
Reexposed to DR locus mismatch	.	.		.	.		.	.	
Reexposed to DQ locus mismatch	.	.		.	.		.	.	
Reexposed to Class I	.	.		.	.		.	.	
Reexposed to Class II locus mismatch	.	.		.	.		.	.	
Reexposed to A/B/DR locus mismatch	.	.		.	.		.	.	
Reexposed to A/B/DR/DQ locus mismatch	.	.		.	.		.	.	

The final multivariate model for insulin independence post last infusion is:

Variable	**HR**	**p**
Baseline HbA_{1c} (%)	0.878	0.0541
Donor(s) Hispanic (0=N 1=Y)	0.543	0.0444
Processing/infusion center (0-Unrelated 1-Related	4.074	0.0058
Islet size (0-small 1-large)	1.719	0.0031
Daclizumab (0-N 1-Y)	1.951	0.0183

Baseline HbA_{1c} is substantially correlated with baseline weight, baseline BMI, baseline daily insulin, fasting glucose, and number of daily injections. Any of these measures of initial control suffices to explain its influence on achieving insulin independence: the better the control, the more likely to achieve insulin independence. Larger islet size (estimated by IEQs/ total particles at time of islet counting, here cumulated over all infusions) favors achieving insulin independence. Hispanicity is correlated with receiving insulin, steroids and various HLA markers: these predict less success. Processing centers related to the transplant center favor the endpoint. Daclizumab is favorable. Variables that cannot be excluded as significantly associated with this outcome are donor's given steroids, HLA factors and islet beta cell counts (see Exhibit 5-23A). Again here, there is substantial imbalance between most immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of those immunosuppressant therapies in a multivariate model. Their univariate effects cannot be dismissed. Daclizumab is stable in this model and seems to be favorable for insulin independence.

Exhibit 5 – 23A *(continued)*
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

Loss of insulin independence lacks sufficient events to permit multivariate modeling of factors.

The final model for complete islet failure post last infusion is:

Variable	**HR**	**P**
Recipient age (years)	0.523	<0.001
Processing/infusion center (0-Unrelated 1-Related)	0.329	0.003
Viability > 87% (0=N 1=Y)	0.317	0.012
Etanercept	0.352	0.016
Calcineurin inhibitor	0.120	<0.001

Older recipient age predicts lower risk of losing the graft. Related processing and infusion centers substantially reduce the chances of losing the last graft. Higher islet viability reduces risk of islet loss. Etanercept and calcineurin inhibitors seem favorable for persistent function.

There are significant correlations among the factors investigated for association with the primary outcomes that influence how the multivariate models operate.

Exhibit 5-23B
Achievement of Insulin Independence Post Last Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated.

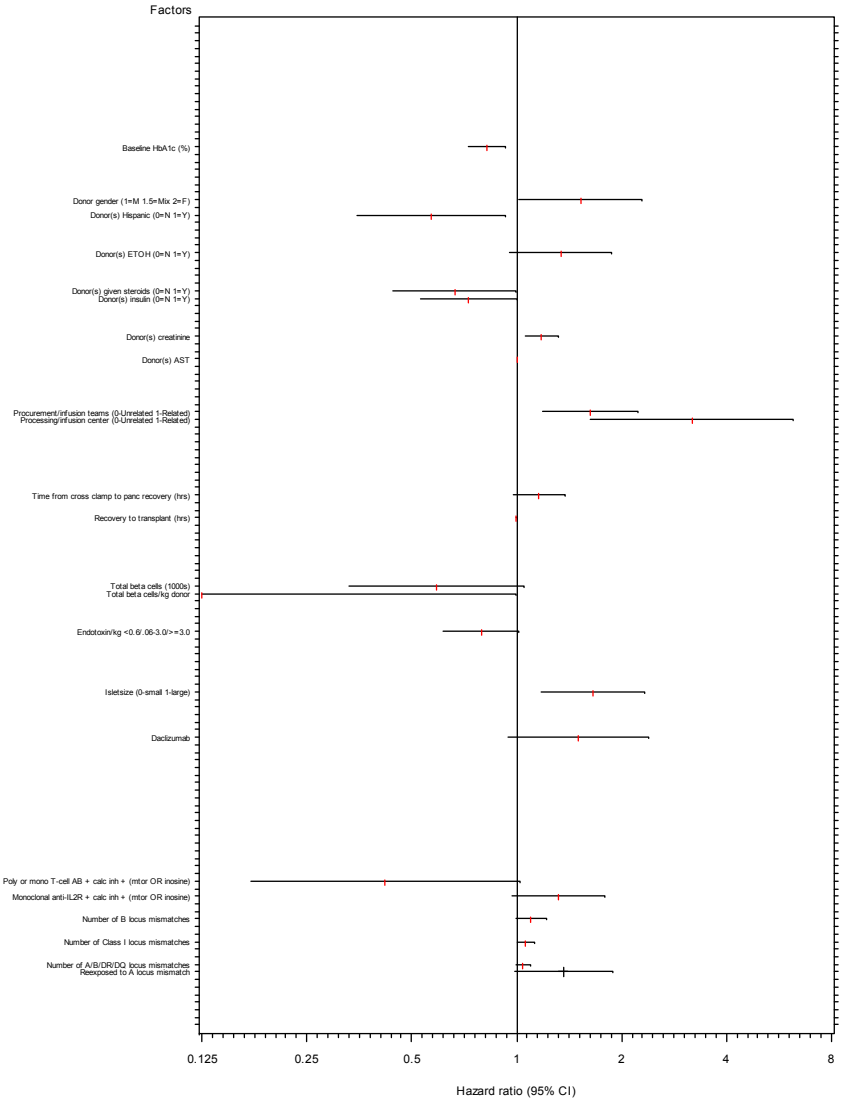


Exhibit 5-23C
Loss of Insulin Independence Post Last Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated.

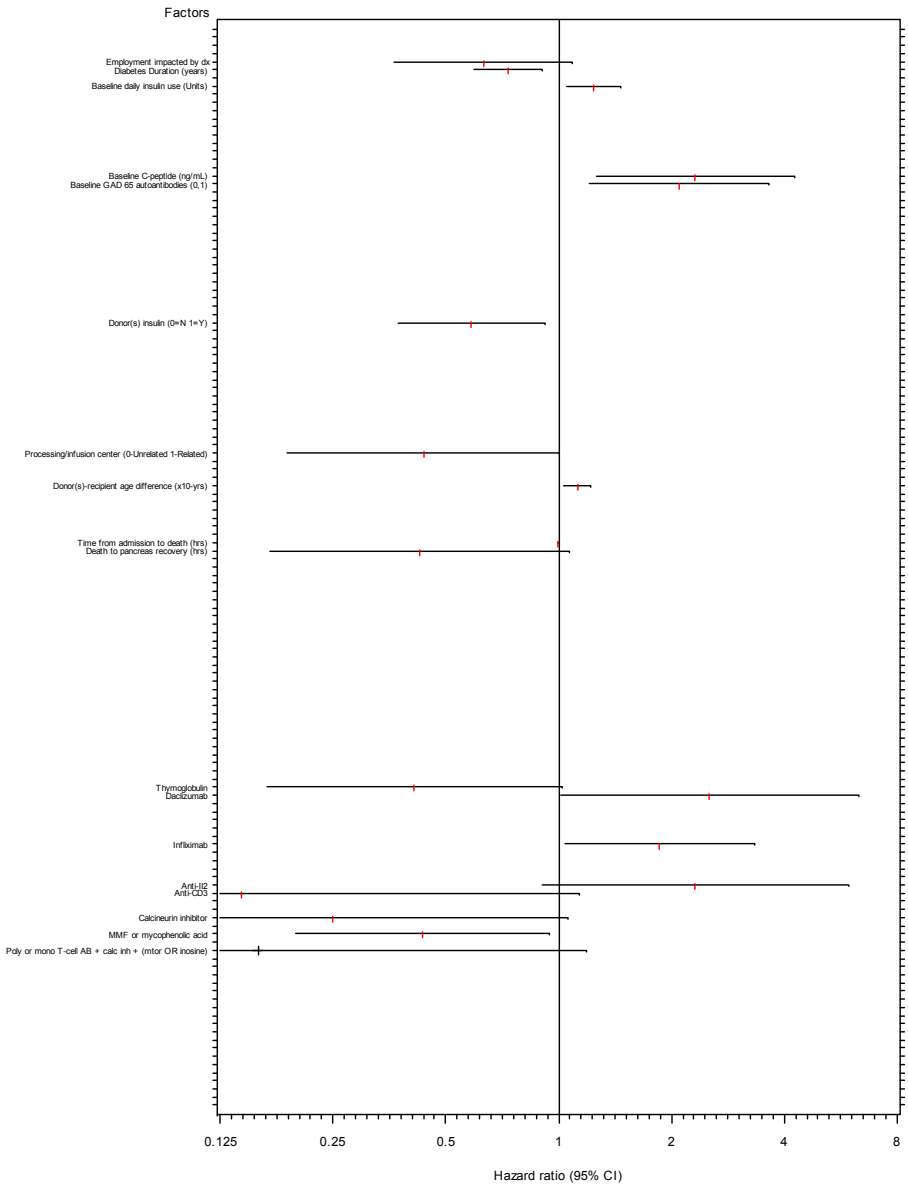


Exhibit 5-23D
Complete Islet Failure Post Last Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

Only variables significant at the p<0.10 are shown on the Forest plots. Forest plots show the hazard ratio (HR; small central vertical bar) ± 95% confidence interval (horizontal line) of Cox regression, or the odds ratio (OR) ± 95% confidence interval for logistic regression. If the 95%-CI extends beyond the limits of the graph, the CI is truncated

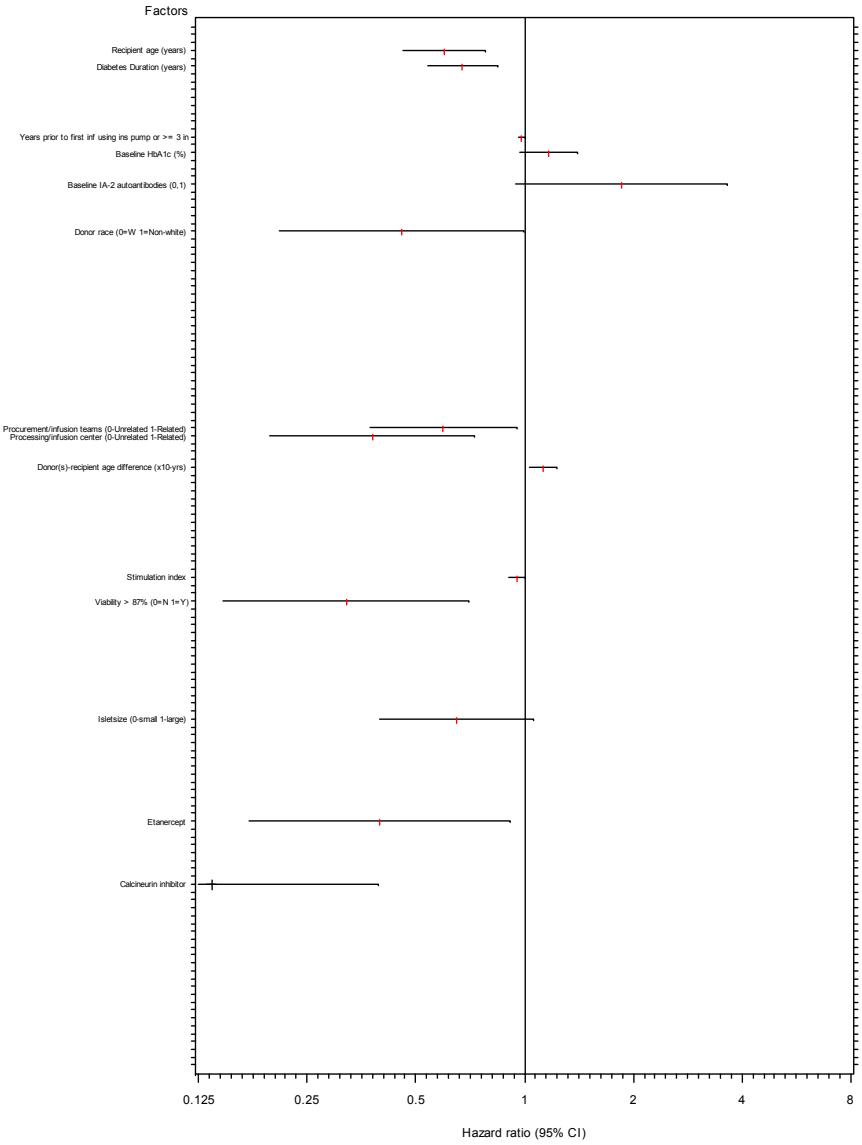
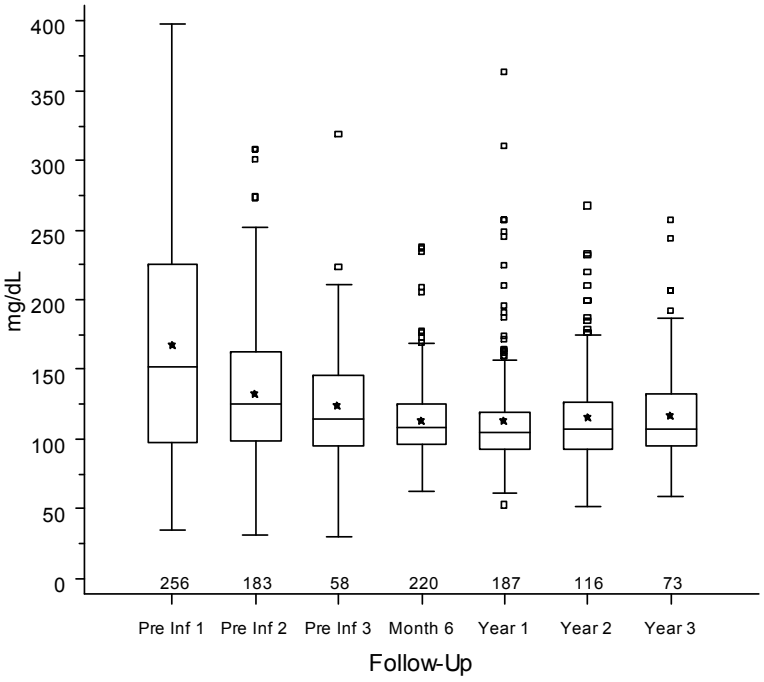


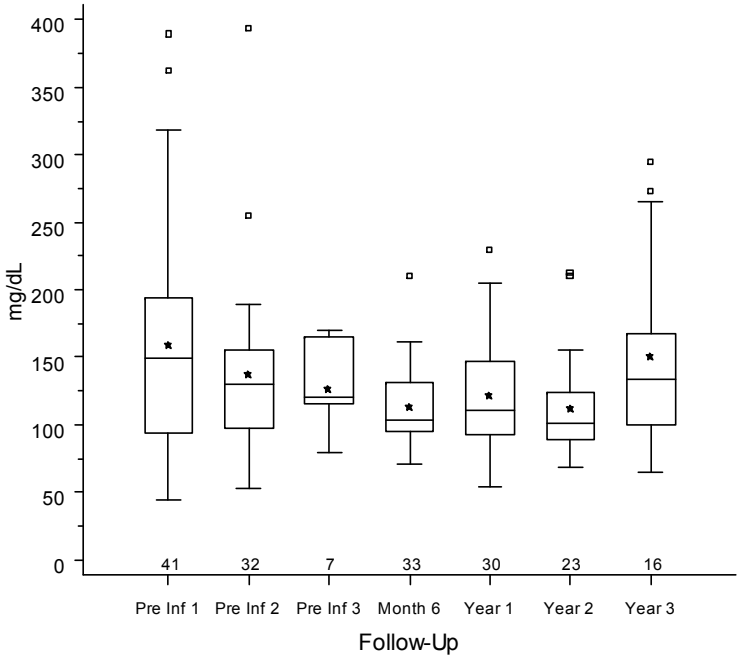
Exhibit 5 – 24
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 400 mg/dL are not displayed
(Five at pre-inf 1)

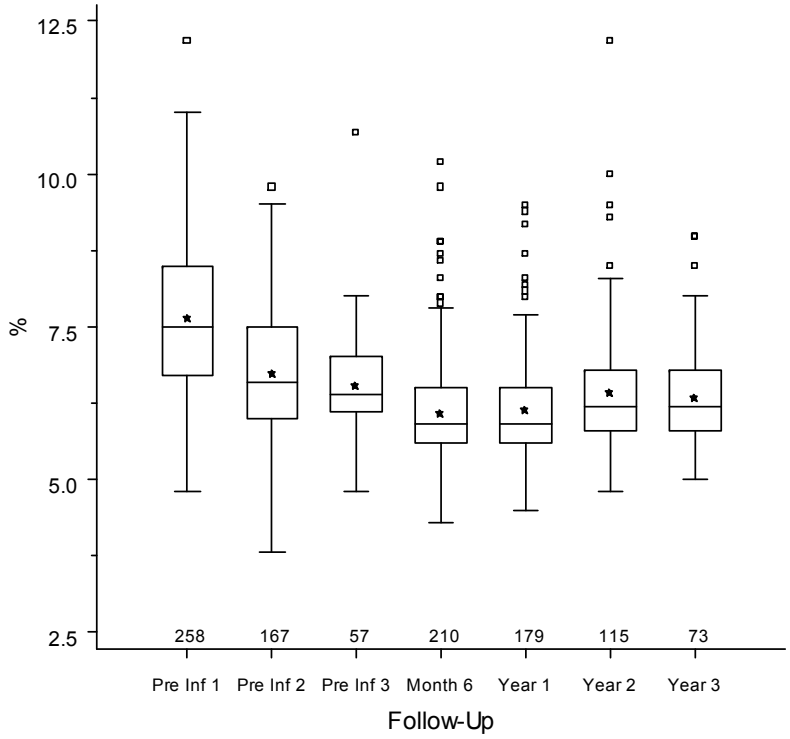
B. Islet After Kidney Recipients



Values greater than 400 mg/dL are not displayed
(Two at pre-inf 1)

Exhibit 5 – 25
HbA_{1c} (%)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

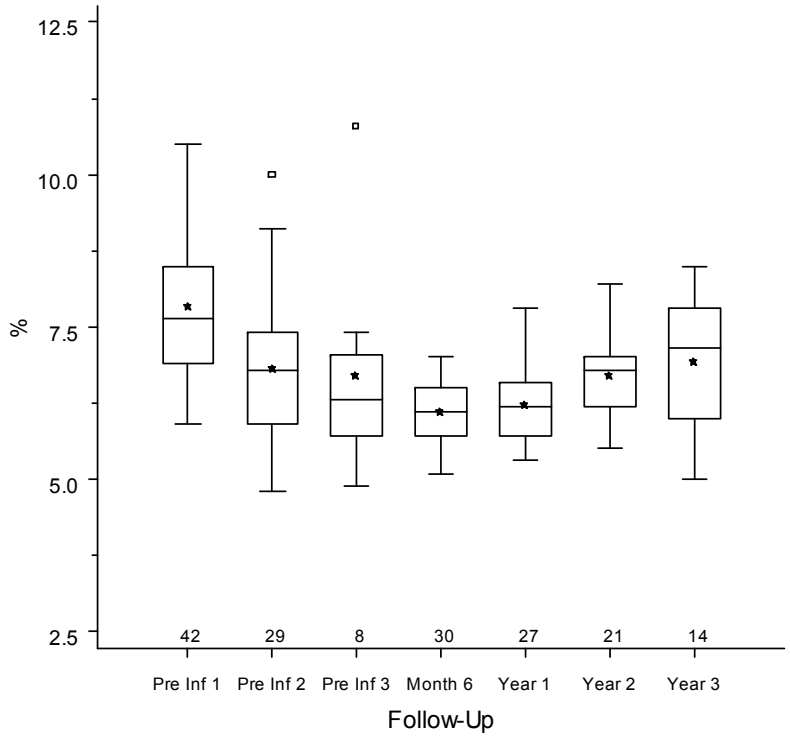
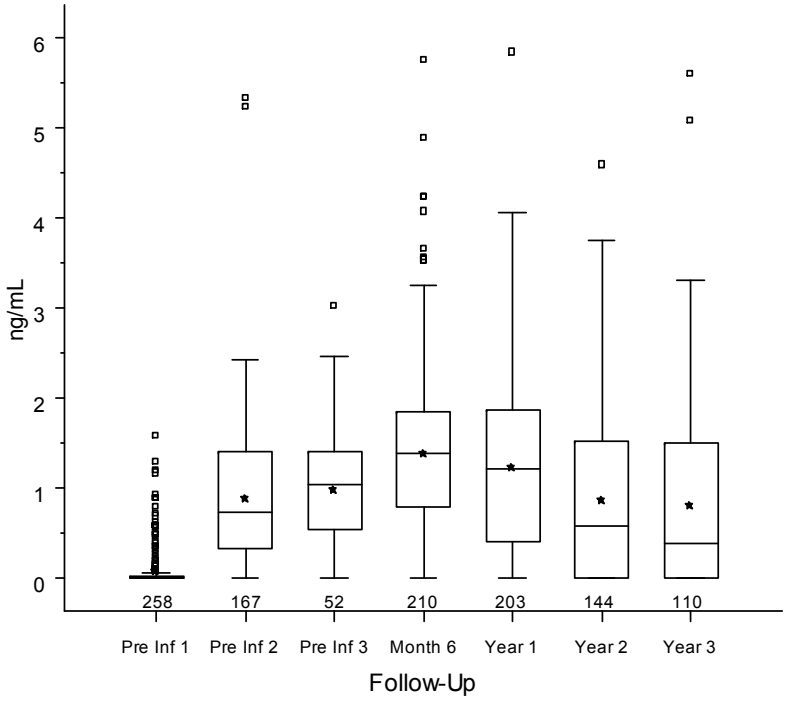


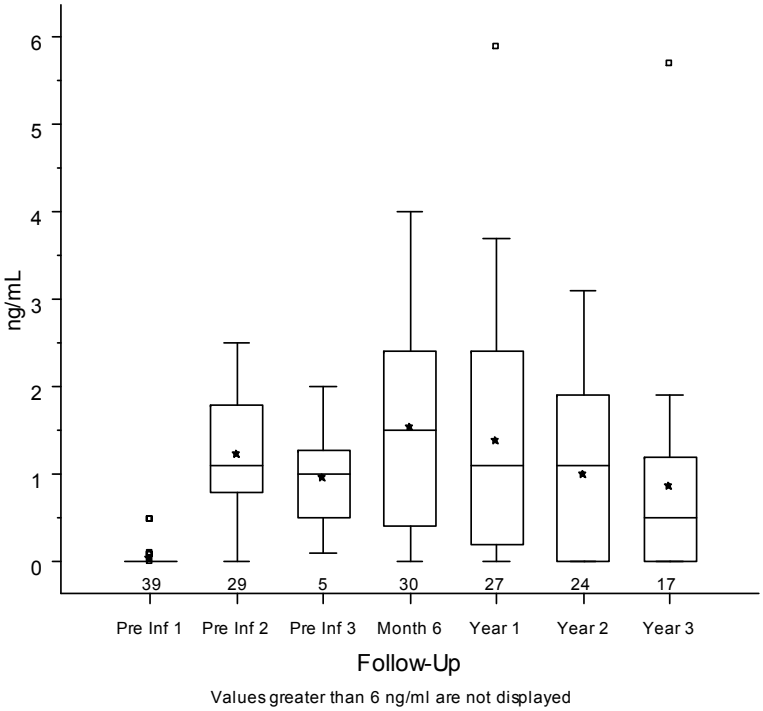
Exhibit 5 – 26
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 6 ng/ml are not displayed
(One at pre-inf 2, three at month 6 and one at year 1)

B. Islet After Kidney Recipients



Values greater than 6 ng/ml are not displayed
(One at year 2)

Exhibit 5 – 27
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with One Infusion

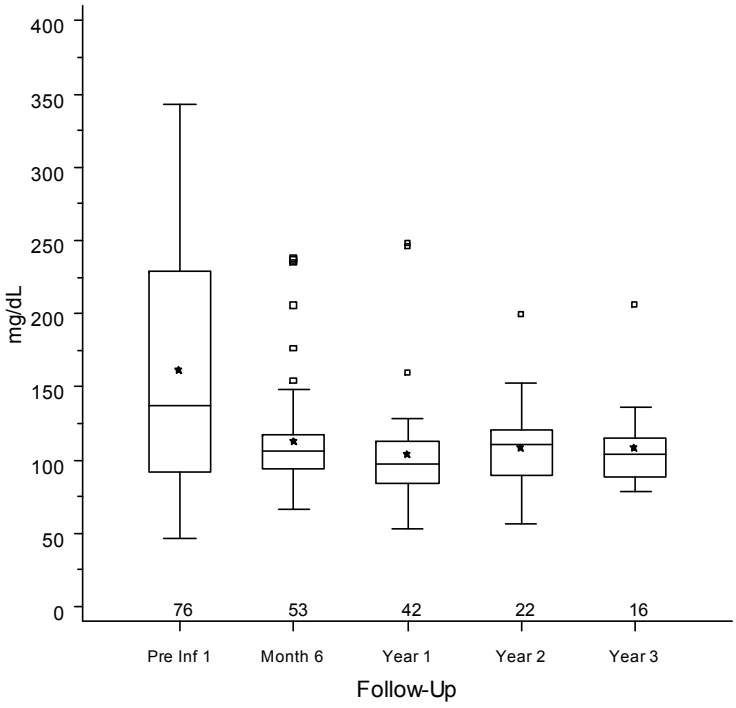


Exhibit 5 – 28
HbA_{1c} (%)
Pre-Infusion and Post Last Infusion
Islet Alone Recipients with One Infusion

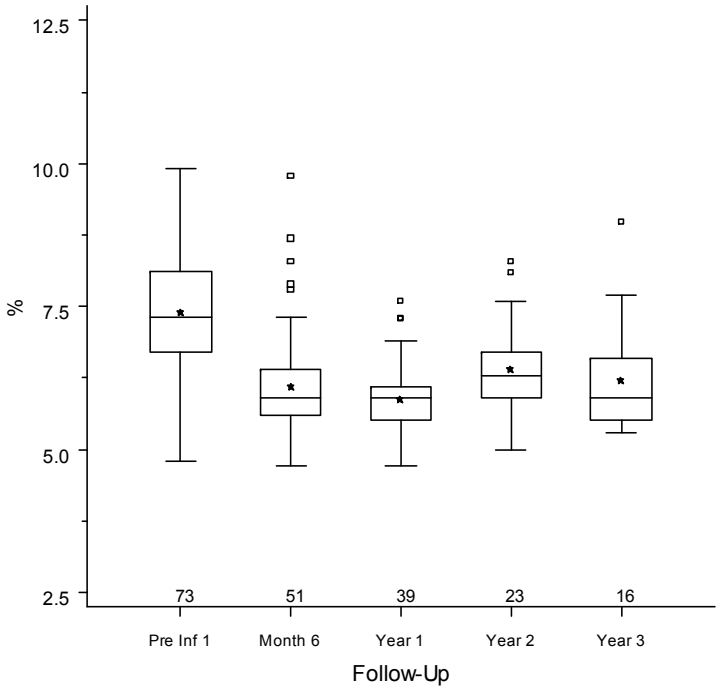


Exhibit 5 – 29
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with One Infusion

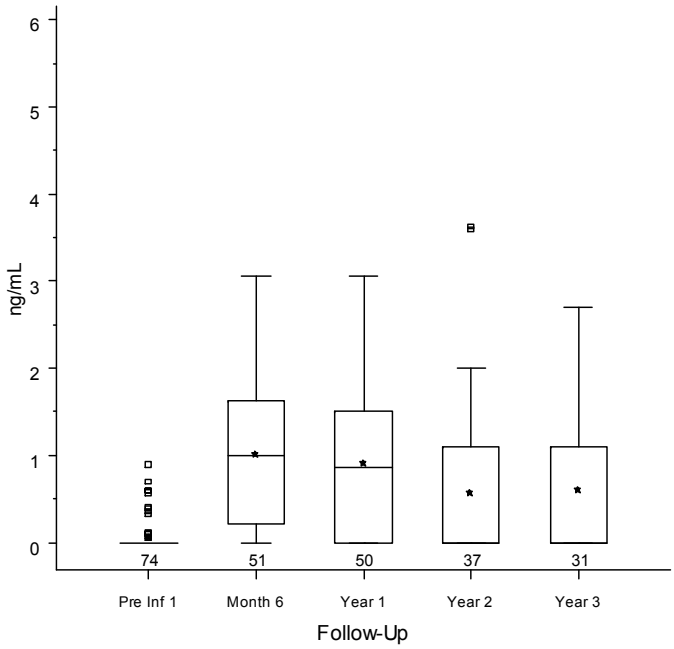


Exhibit 5 – 30
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Two Infusions

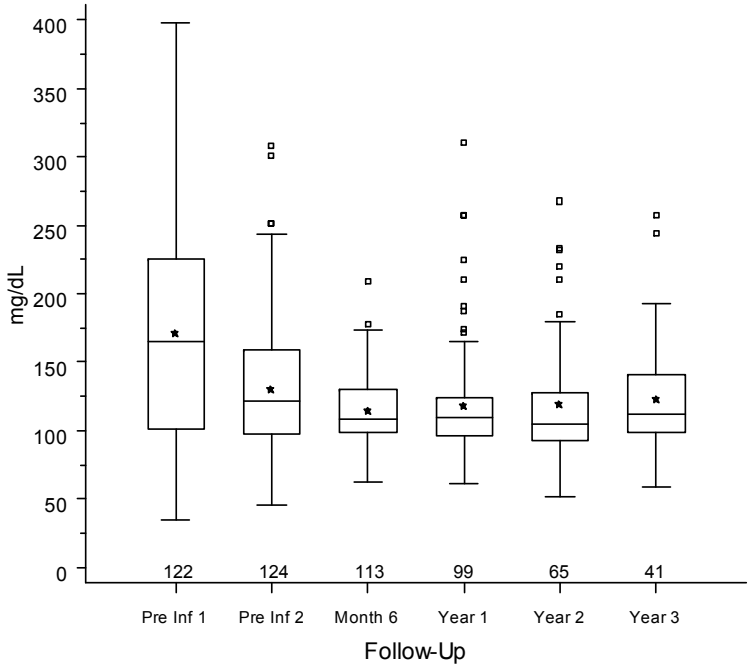


Exhibit 5 – 31
HbA_{1c} (%)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Two Infusions

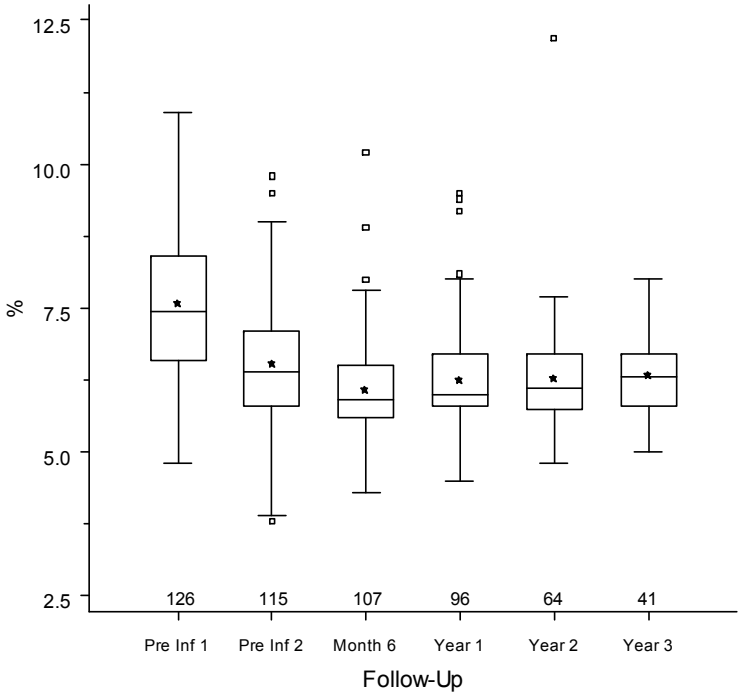


Exhibit 5 – 32
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Two Infusions

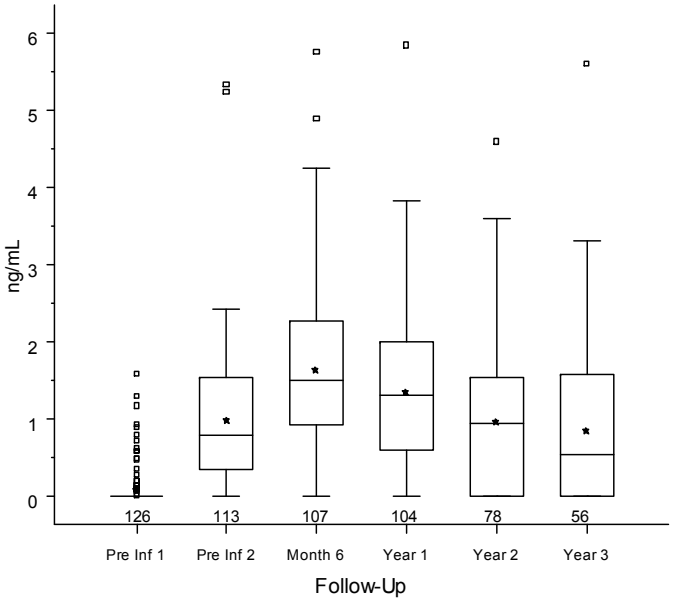


Exhibit 5 – 33
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Three Infusions

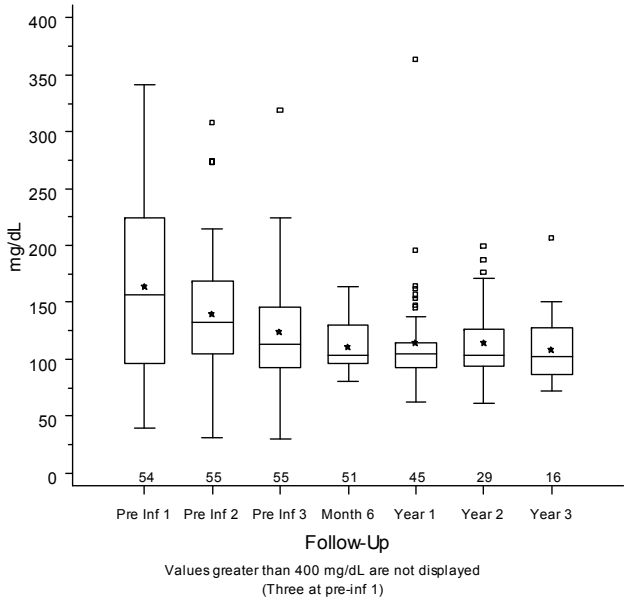


Exhibit 5 – 34
HbA_{1c} (%)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Three Infusions

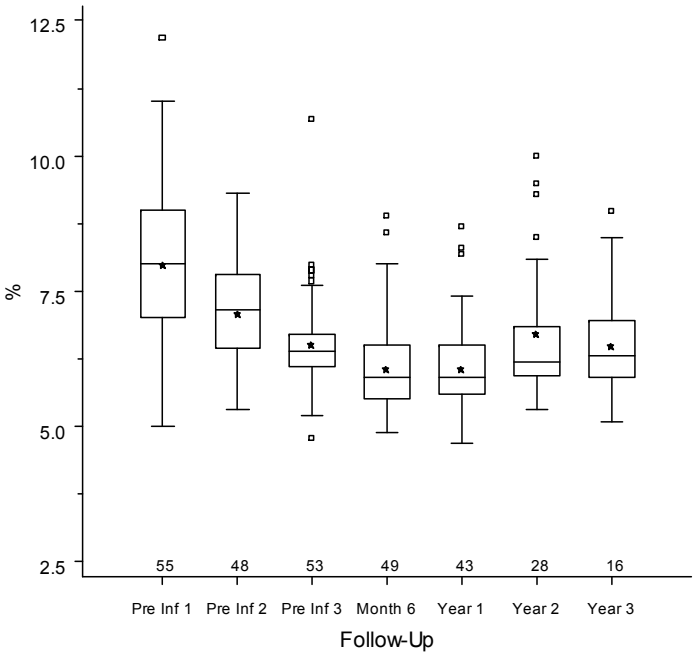


Exhibit 5 – 35
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Three Infusions

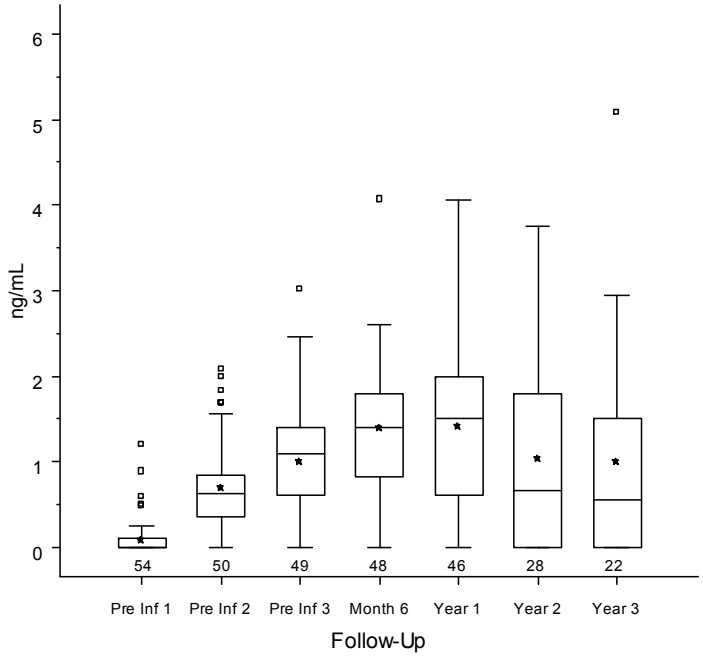
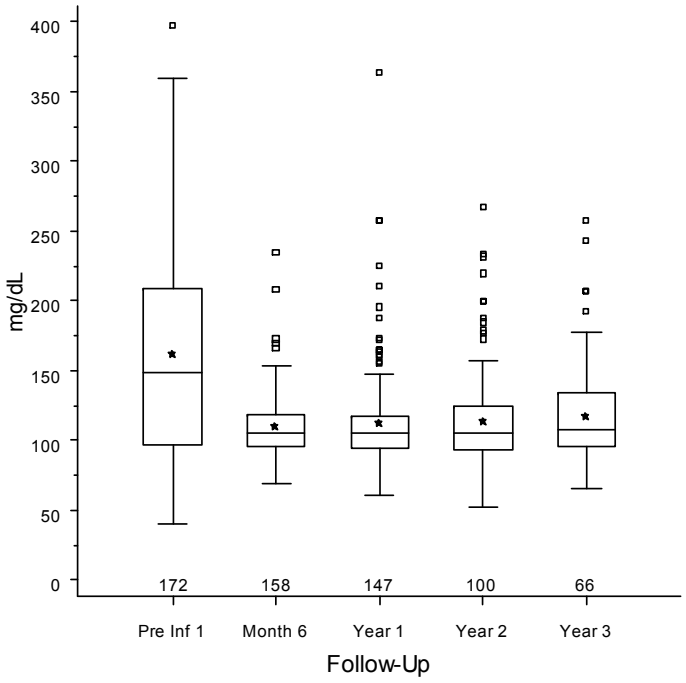


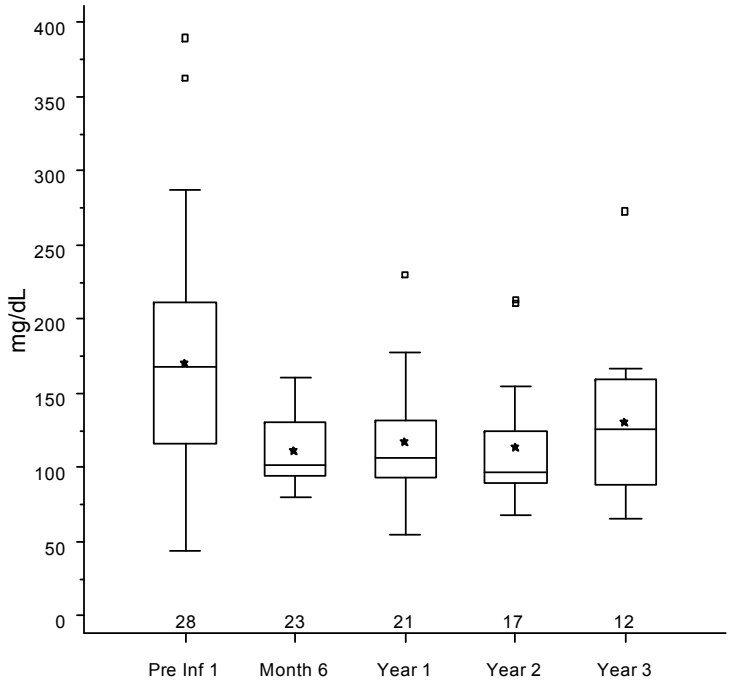
Exhibit 5 – 36
Fasting Plasma Glucose (mg/dL) Post Last Infusion
Recipients Who Ever Achieved Insulin Independence

A. Islet Alone Recipients



Values greater than 400 mg/dl are not displayed
(Four at pre-inf 1)

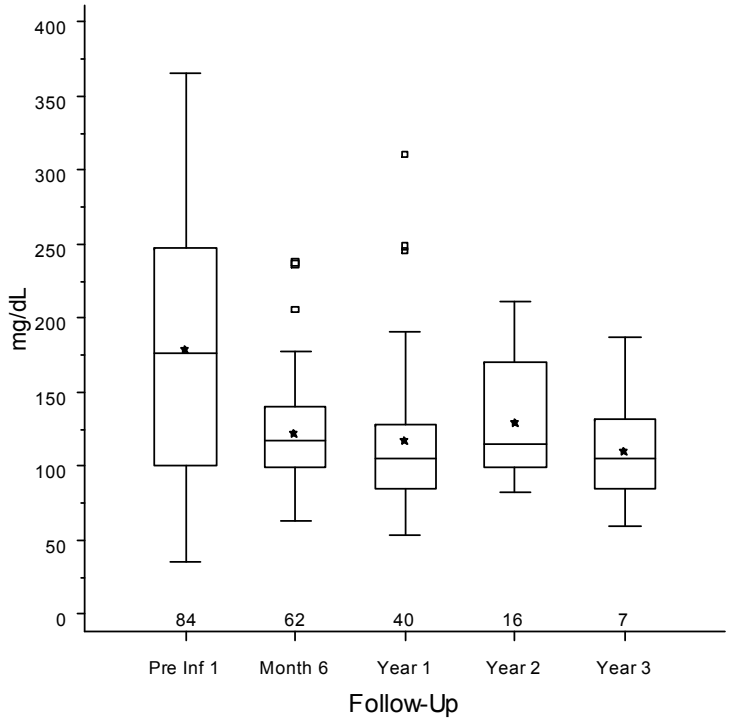
B. Islet After Kidney Recipients



Values greater than 400 mg/dl are not displayed
(One at pre-inf 1)

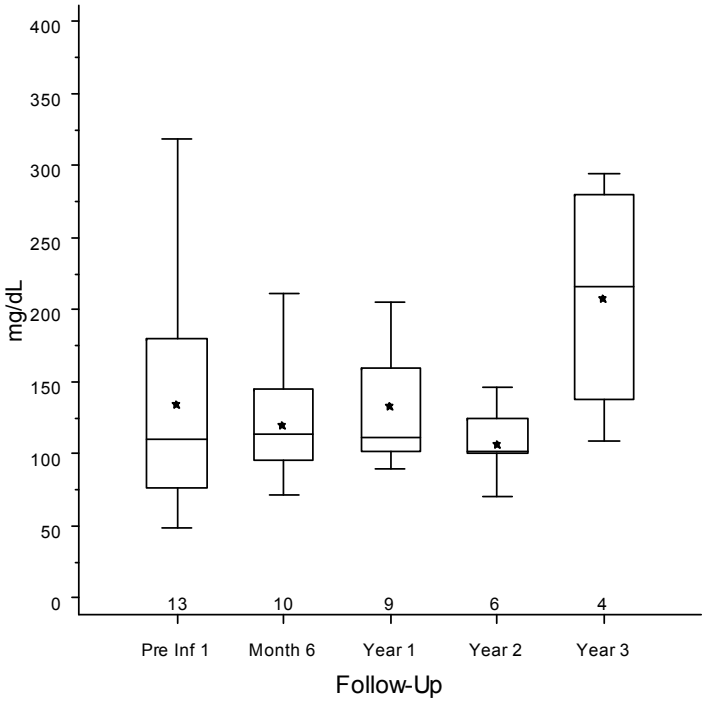
Exhibit 5 – 37
Fasting Plasma Glucose (mg/dL) Post Last Infusion
Recipients Who Never Achieved Insulin Independence

A. Islet Alone Recipients



Values greater than 400 mg/dl are not displayed
(One at pre-inf 1)

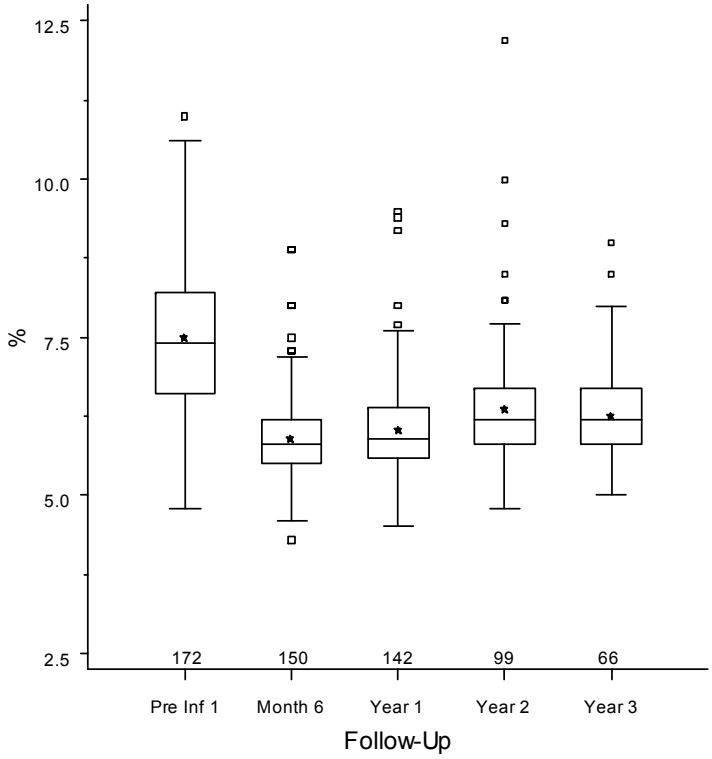
B. Islet After Kidney Recipients



Values greater than 400 mg/dl are not displayed
(One at pre-inf 1)

Exhibit 5 – 38
HbA_{1c} (%) Post Last Infusion
Recipients Who Ever Achieved Insulin Independence

A. Islet Alone Recipients



B. Islet After Kidney Recipients

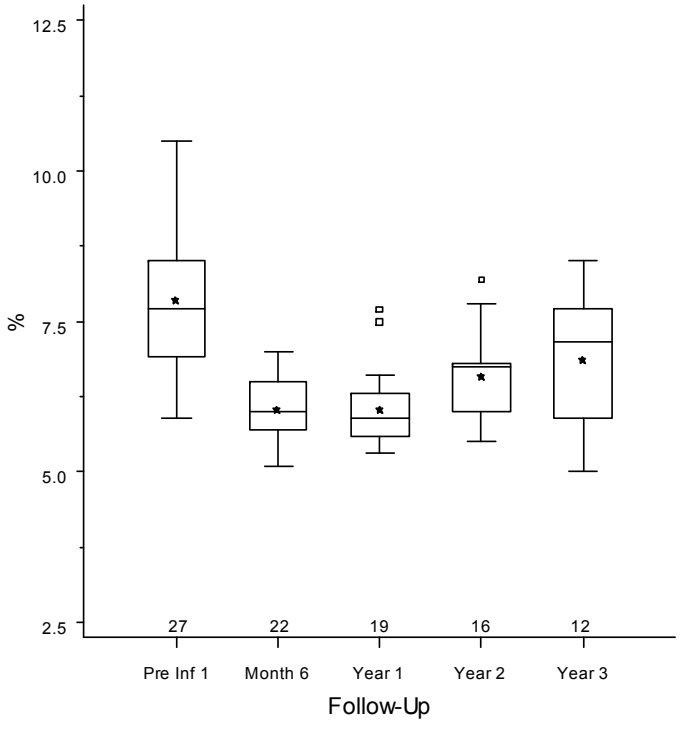
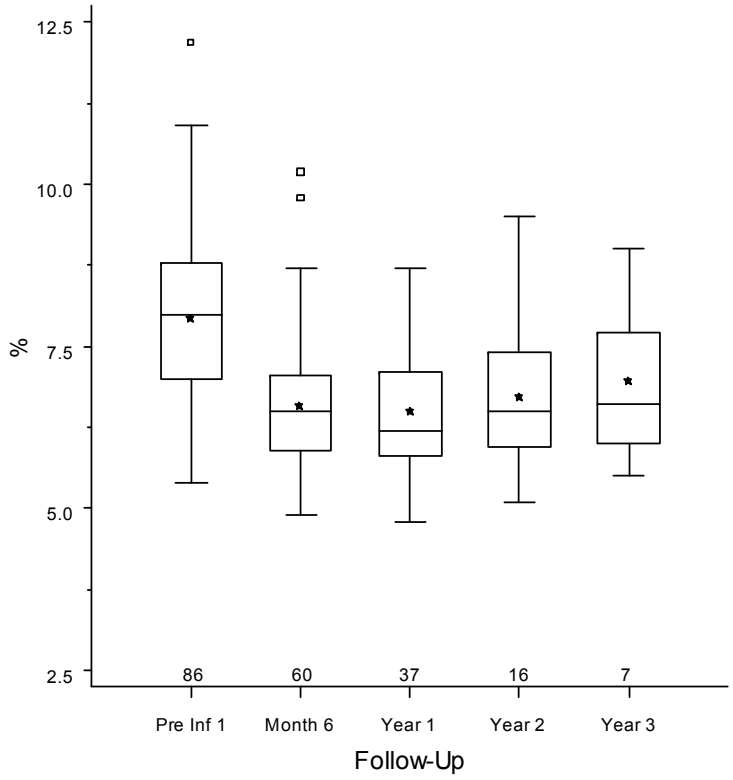


Exhibit 5 – 39
HbA_{1c} (%) Post Last Infusion
Recipients Who Never Achieved Insulin Independence

A. Islet Alone Recipients



B. Islet After Kidney Recipients

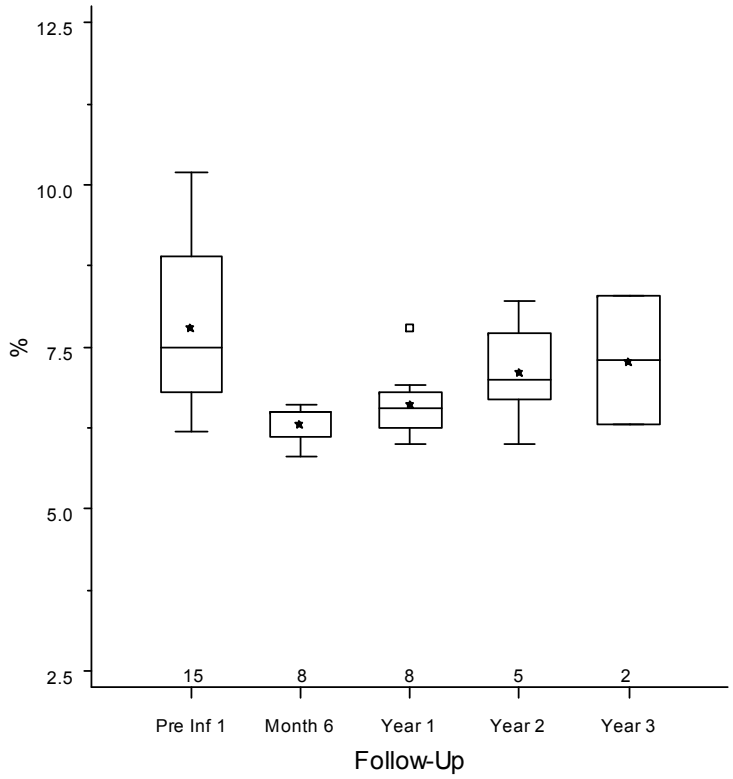
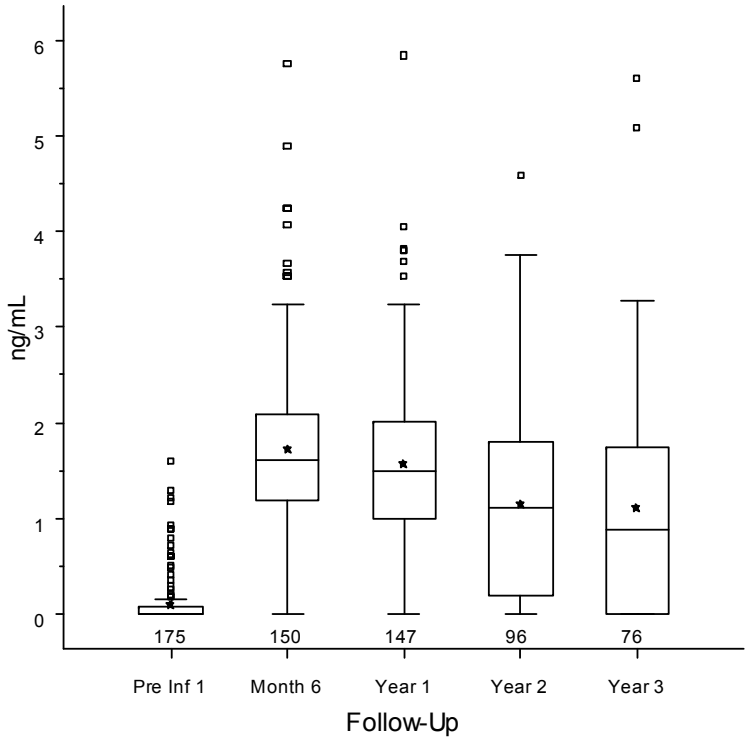


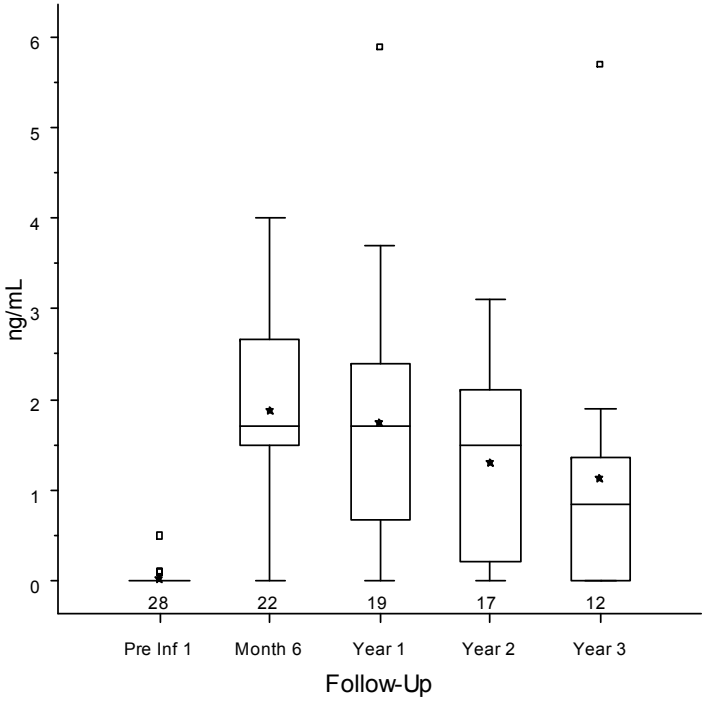
Exhibit 5 – 40
Basal Plasma C-peptide (ng/mL) Post Last Infusion
Recipients Who Ever Achieved Insulin Independence

A. Islet Alone Recipients



Values greater than 6 ng/mL are not displayed
(Two at month 6)

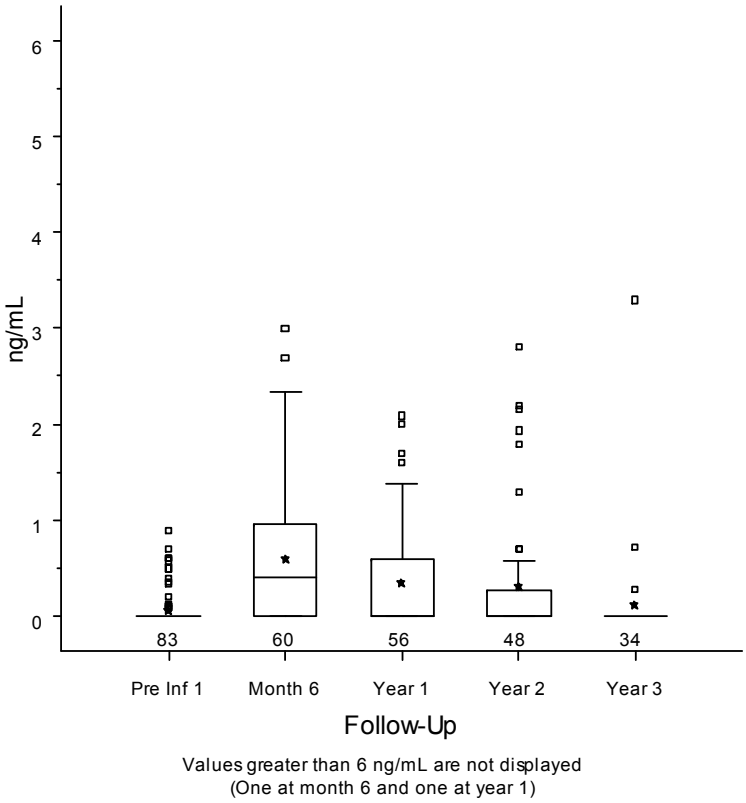
B. Islet After Kidney Recipients



Values greater than 6 ng/mL are not displayed
(One at year 2)

Exhibit 5 – 41
Basal Plasma C-peptide (ng/mL) Post Last Infusion
Recipients Who Never Achieved Insulin Independence

A. Islet Alone Recipients



Values greater than 6 ng/mL are not displayed
(One at month 6 and one at year 1)

B. Islet After Kidney Recipients

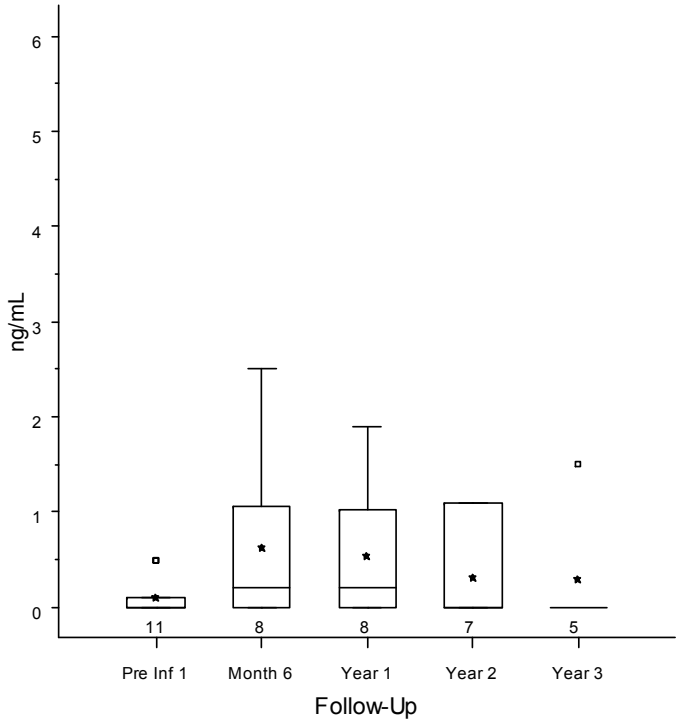
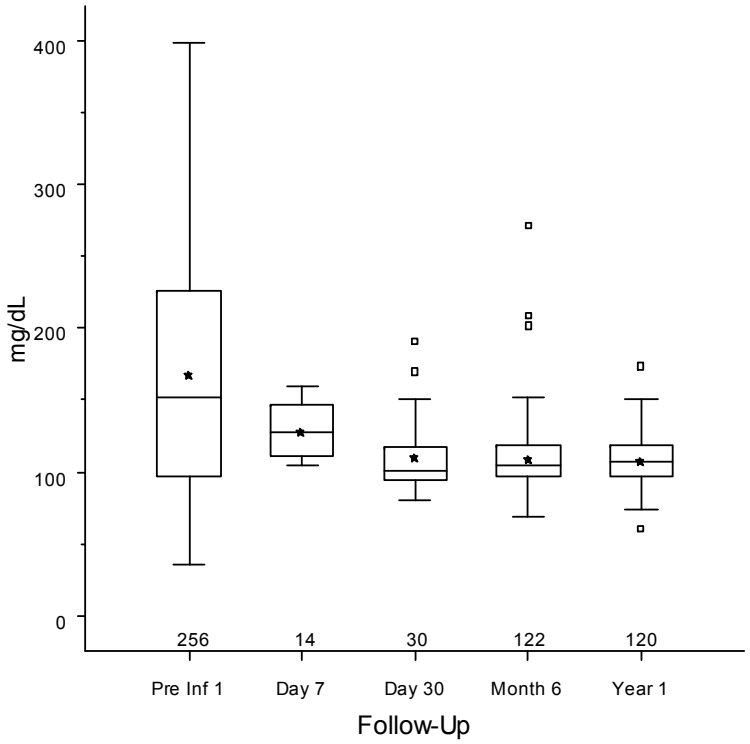


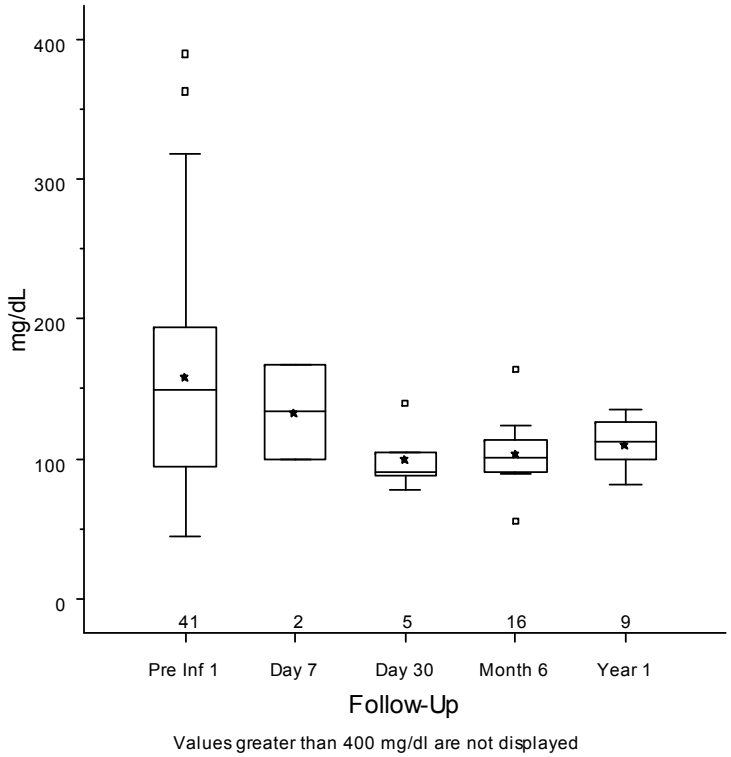
Exhibit 5 – 42
Fasting Plasma Glucose (mg/dL) Pre and Post First Infusion
Insulin Independent Recipients

A. Islet Alone Recipients



Values greater than 400 mg/dl are not displayed
(Five at pre-inf 1)

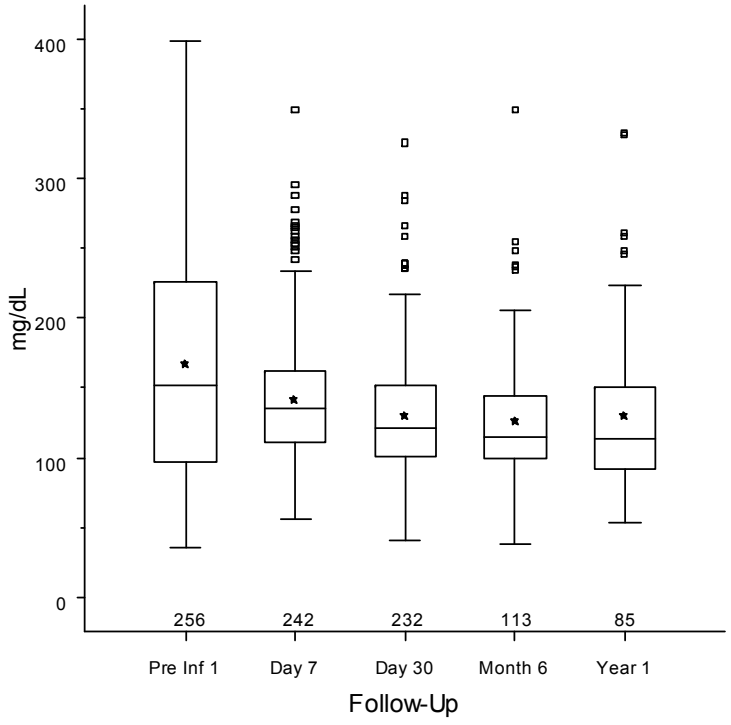
B. Islet After Kidney Recipients



Values greater than 400 mg/dl are not displayed
(Two at pre-inf 1)

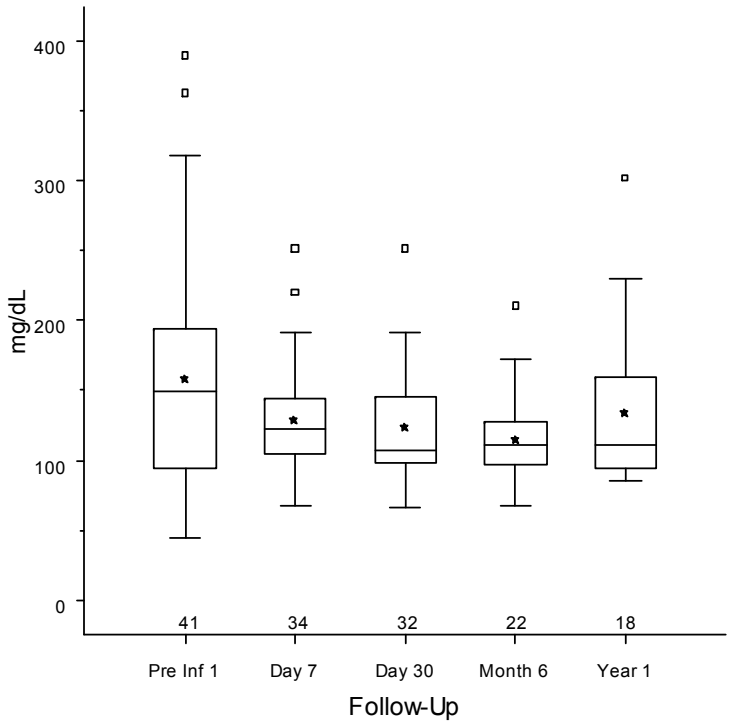
Exhibit 5 – 43
Fasting Plasma Glucose (mg/dL) Pre and Post First Infusion
Insulin Dependent Recipients

A. Islet Alone Recipients



Values greater than 400 mg/dl are not displayed
(Five at pre-inf 1)

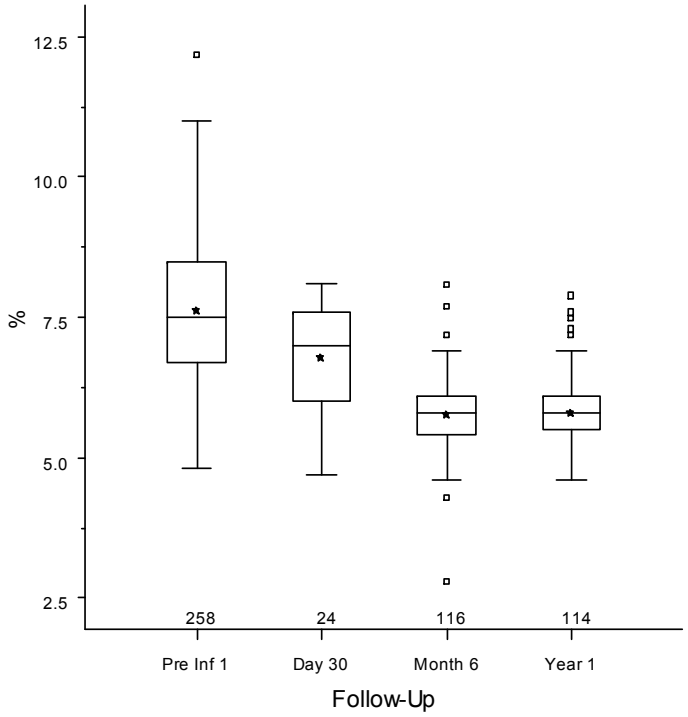
B. Islet After Kidney Recipients



Values greater than 400 mg/dl are not displayed
(Two at pre-inf 1)

Exhibit 5 – 44
HbA_{1c} (%) Pre and Post First Infusion
Insulin Independent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

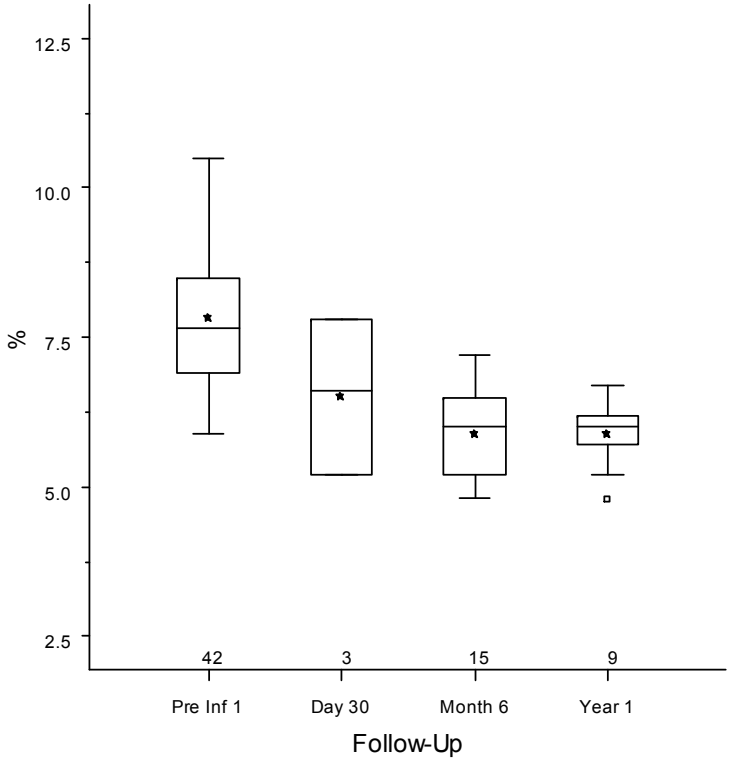
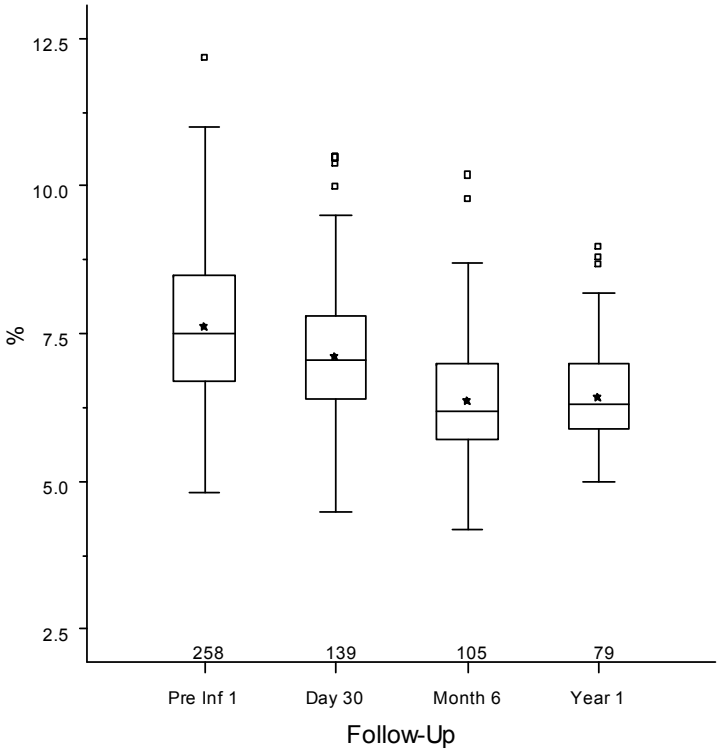


Exhibit 5 – 45
HbA_{1c} (%) Pre and Post First Infusion
Insulin Dependent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

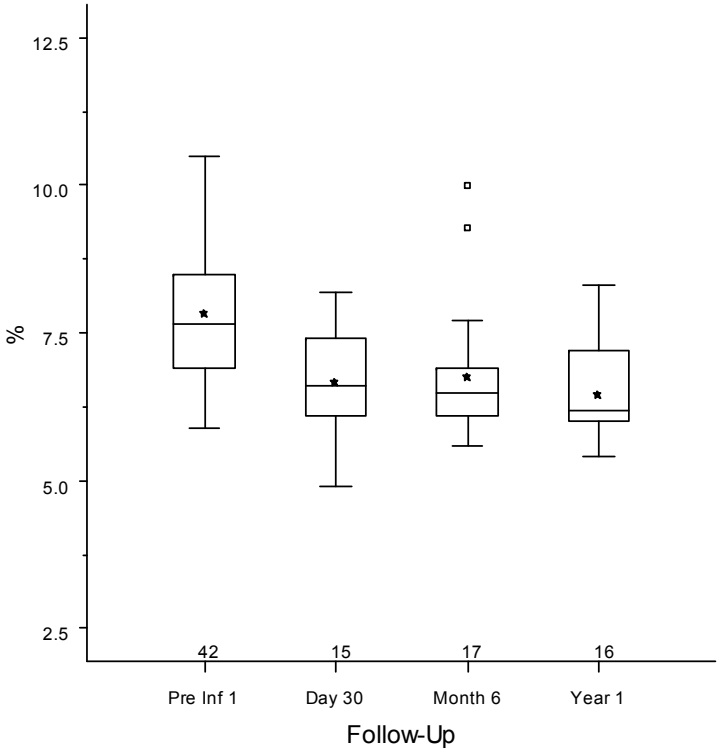
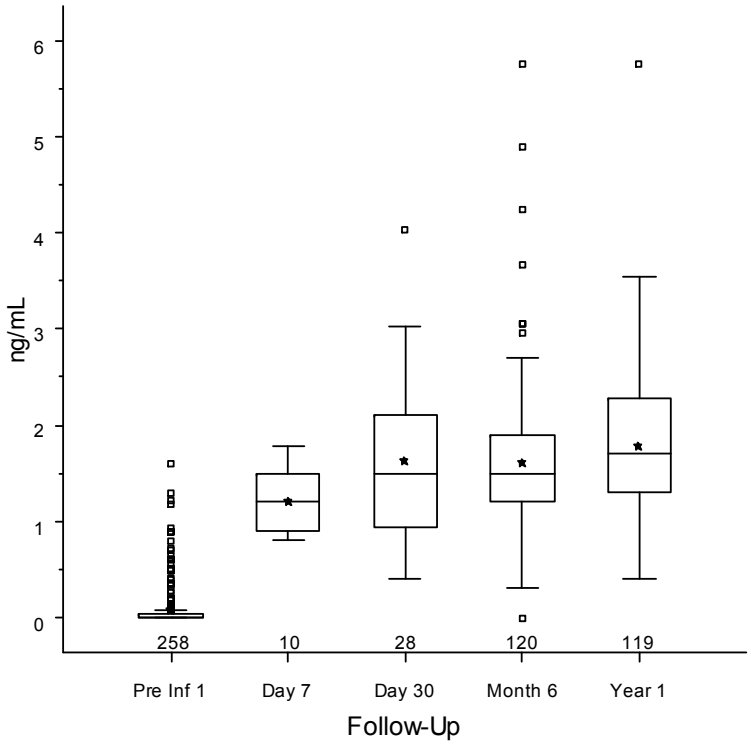


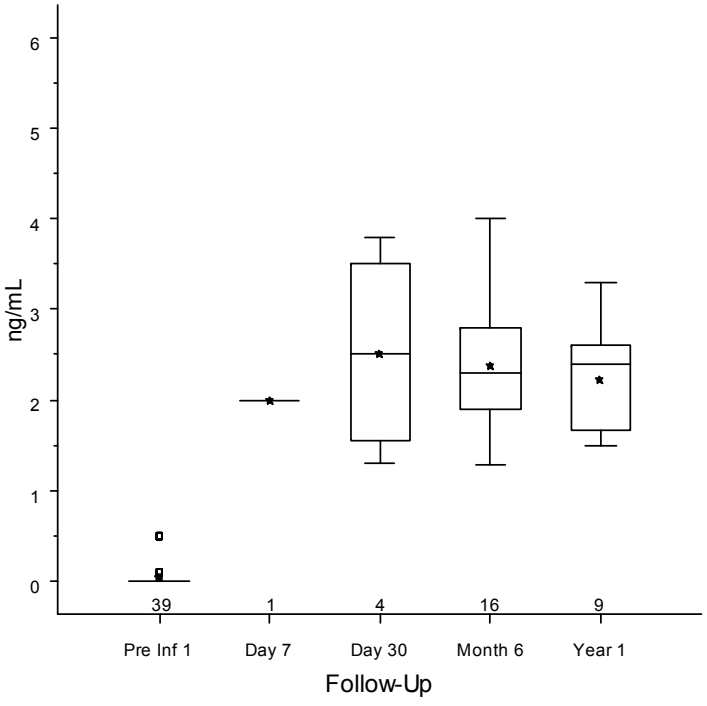
Exhibit 5 – 46
Basal Plasma C-peptide (ng/mL) Pre and Post First Infusion
Insulin Independent Recipients

A. Islet Alone Recipients



Values greater than 6 ng/mL are not displayed
(Two at month 6)

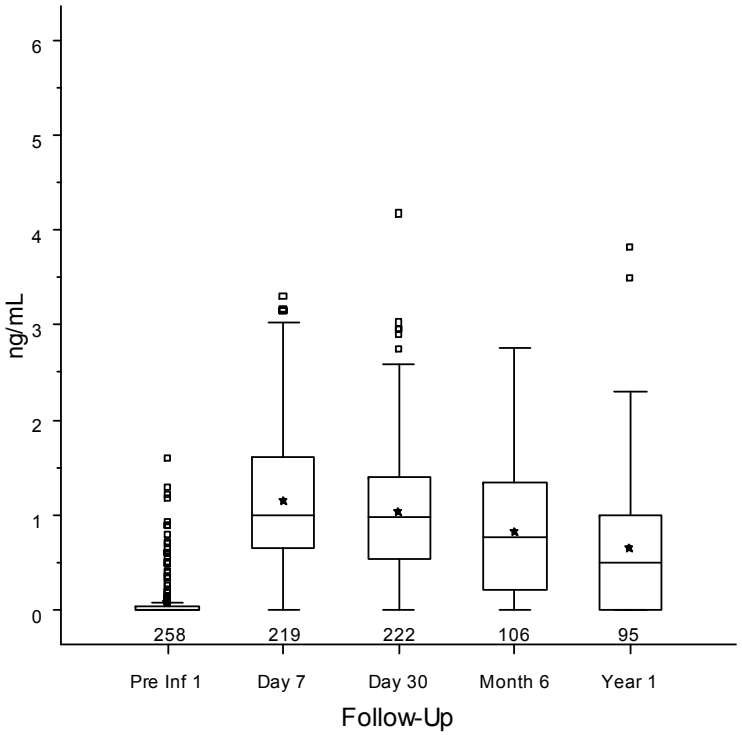
B. Islet After Kidney Recipients



Values greater than 6 ng/mL are not displayed
(One at year 2)

Exhibit 5 – 47
Basal Plasma C-peptide (ng/mL) Pre and Post First Infusion
Insulin Dependent Recipients

A. Islet Alone Recipients



Values greater than 6 ng/mL are not displayed
(One at month 6 and one at year 1)

B. Islet After Kidney Recipients

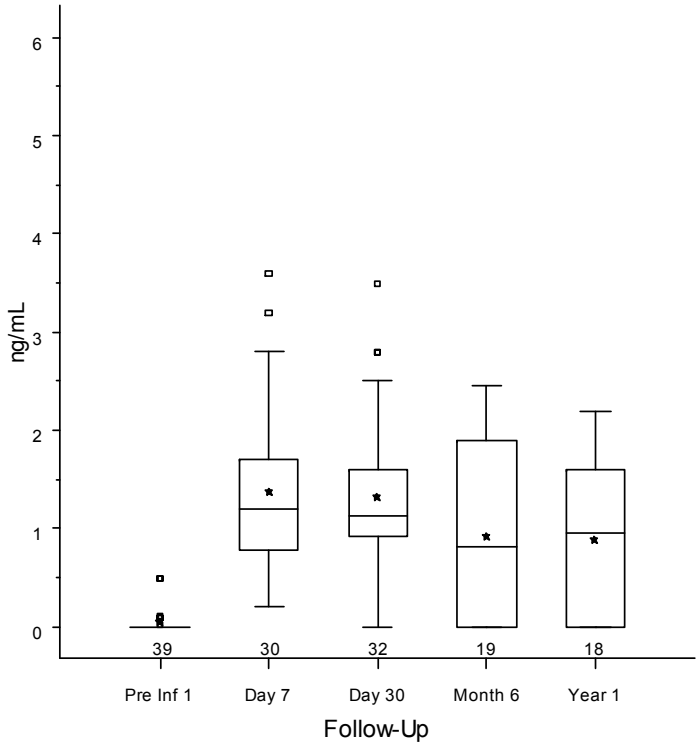
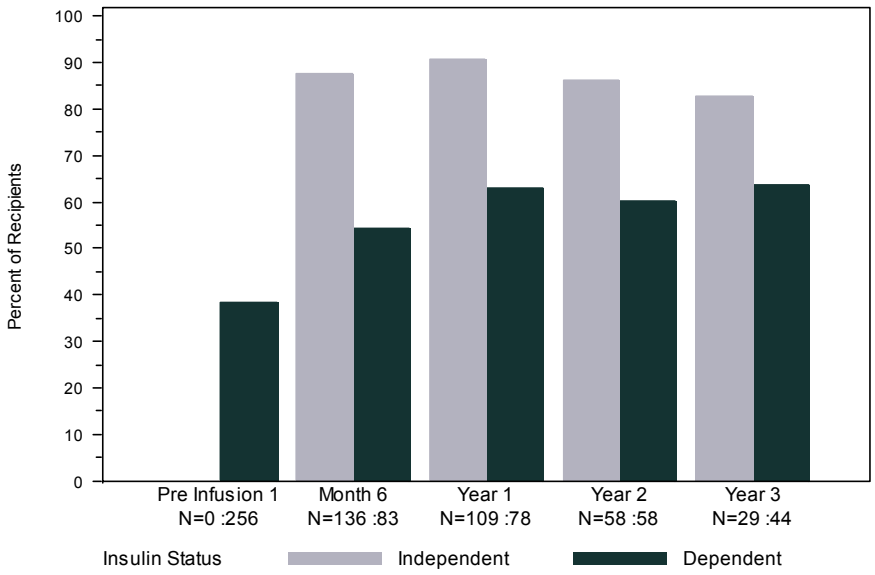


Exhibit 5 – 48
Recipients with Fasting Blood Glucose < 126 mg/dL
Post Last Infusion by Insulin Status

A. Islet Alone Recipients



B. Islet After Kidney Recipients

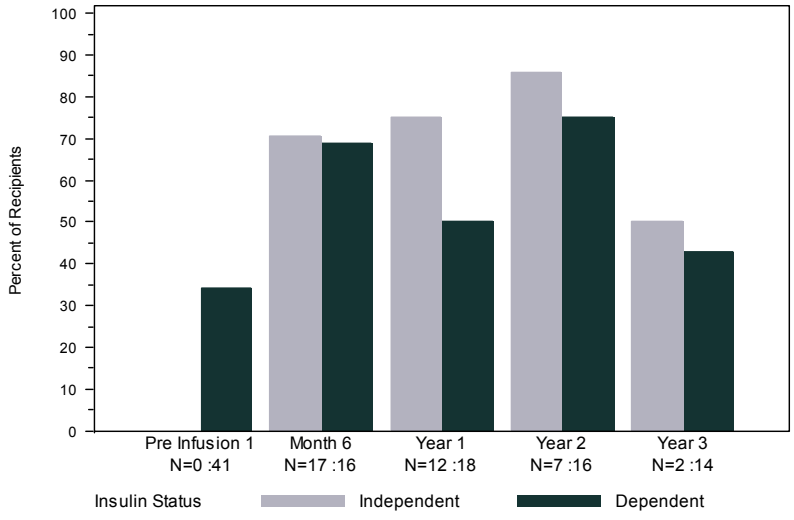
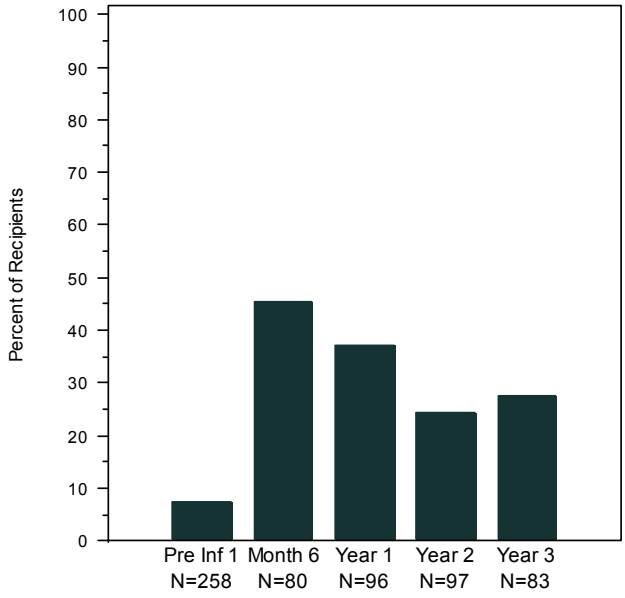


Exhibit 5 – 49
Insulin Dependent Recipients with Basal C-peptide ≥ 0.5 ng/mL
Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

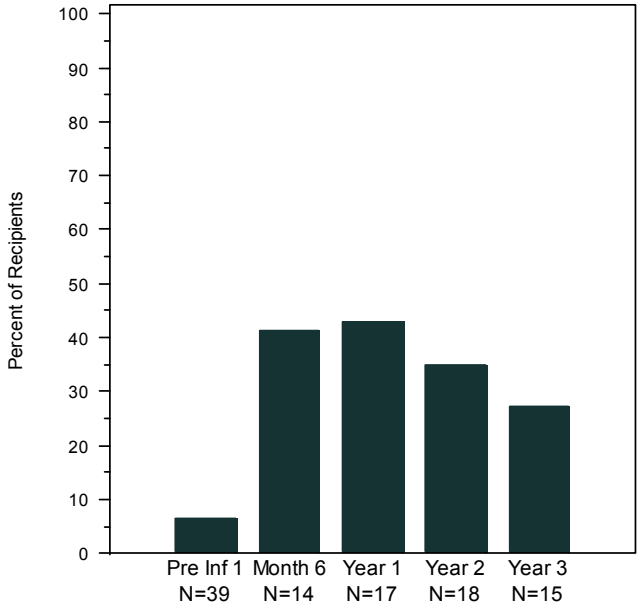
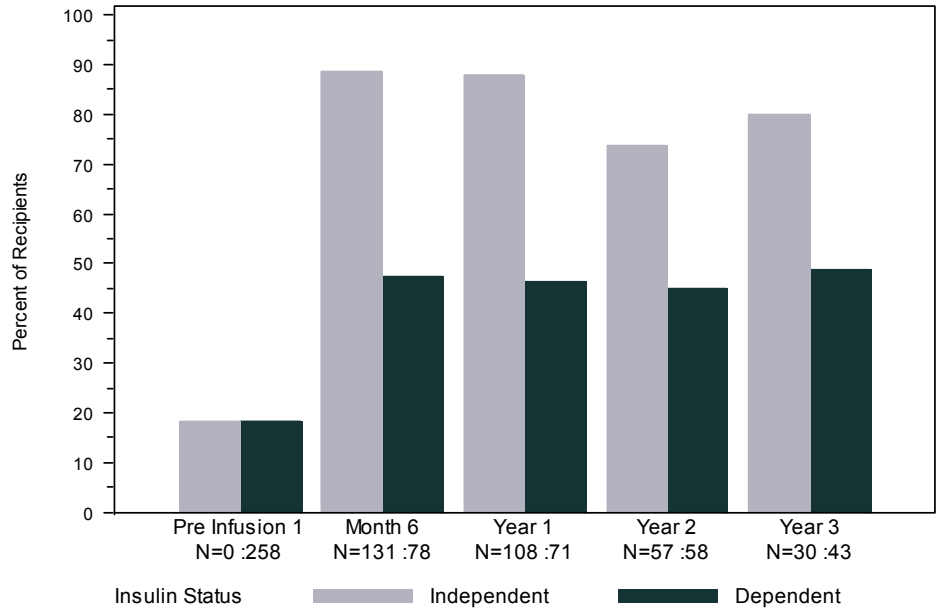


Exhibit 5 – 50
Recipients with HbA_{1c} < 6.5%
Post Last Infusion by Insulin Status

A. Islet Alone Recipients



B. Islet After Kidney Recipients

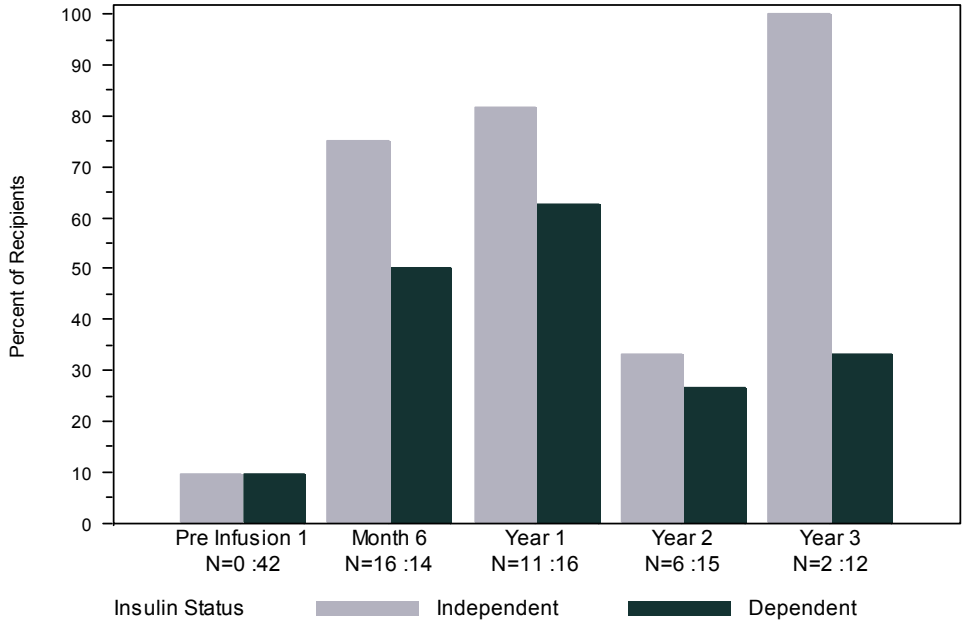


Exhibit 5 – 51
Pre-Infusion Recipient Lab Summary by Infusion Sequence
Islet Alone Recipients

	Infusion Sequence																	
	1						2						3					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	256	173.2	90.5	153.0	35.0	560.0	183	133.2	49.4	125.0	31.0	308.0	58	125.3	46.8	114.5	30.0	319.0
HbA_{1c} (%)	258	7.7	1.3	7.5	4.8	12.2	167	6.7	1.1	6.6	3.8	9.8	57	6.5	0.9	6.4	4.8	10.7
ALT (IU/L)	256	22.1	11.4	20.0	3.0	123.0	167	40.7	29.3	33.0	11.0	298.0	55	39.3	20.3	33.0	11.0	121.0
AST (IU/L)	269	24.5	8.8	23.0	5.0	66.0	183	36.1	25.9	32.0	17.0	329.0	61	36.9	15.6	33.0	8.0	77.0
Alkaline Phosphatase (IU/L)	264	74.4	32.1	67.0	24.0	286.0	179	81.6	55.7	69.0	32.0	502.0	59	102.4	62.9	80.0	37.0	329.0
Total Bilirubin (mg/dL)	265	0.6	0.4	0.5	0.1	2.7	182	0.5	0.2	0.4	0.1	1.7	59	0.5	0.2	0.4	0.1	1.2
Total Cholesterol (mg/dl)	263	169.8	28.5	171.0	96.0	256.0	158	183.0	32.9	182.5	78.0	262.0	55	186.1	32.4	189.0	116.0	280.0
HDL (mg/dL)	260	64.0	16.4	63.0	31.0	124.0	146	62.4	16.1	62.0	25.0	108.0	46	59.3	16.5	59.0	24.0	103.0
LDL (mg/dL)	260	92.9	24.4	92.0	33.0	173.0	146	101.8	26.5	99.0	46.0	163.0	45	107.6	38.6	106.0	50.0	268.0
Triglycerides (mg/dL)	263	67.9	38.2	55.0	16.0	317.0	157	99.4	62.3	81.0	32.0	408.0	55	104.7	65.9	89.0	38.0	399.0
Serum Creatinine (mg/dL)	271	0.9	0.2	0.9	0.1	1.8	186	0.9	0.2	0.9	0.5	1.7	61	0.9	0.2	0.9	0.1	1.5
Calculated Creatinine Clearance ($mL/min/1.73m^2$)	222	103.1	28.0	97.5	37.0	224.0	96	97.0	27.9	96.5	44.0	169.0	26	98.1	39.5	92.5	40.0	227.0
Basal Plasma C-peptide (ng/mL)	258	0.1	0.2	0.0	0.0	1.6	164	0.9	0.9	0.7	0.0	6.3	51	1.0	0.6	1.1	0.0	3.0

Exhibit 5 – 51 *(continued)*
Pre-Infusion Recipient Lab Summary by Infusion Sequence
Islet After Kidney Recipients

	Infusion Sequence																	
	1						2						3					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	41	176.4	110.5	162.0	44.0	568.0	32	137.8	61.7	130.5	53.0	394.0	7	127.4	31.3	120.0	79.0	170.0
HbA_{1c} (%)	42	7.9	1.2	7.7	5.9	10.5	29	6.8	1.2	6.8	4.8	10.0	8	6.7	1.8	6.3	4.9	10.8
ALT (IU/L)	42	28.6	13.9	25.0	8.0	64.0	33	43.5	29.9	39.0	16.0	183.0	7	58.4	45.9	33.0	21.0	146.0
AST (IU/L)	43	32.1	17.3	25.0	12.0	82.0	33	41.5	21.2	34.0	17.0	113.0	6	35.3	9.8	35.5	22.0	49.0
Alkaline Phosphatase (IU/L)	41	127.3	100.5	91.0	40.0	445.0	33	145.3	138.7	95.0	40.0	597.0	6	149.7	58.1	155.0	63.0	215.0
Total Bilirubin (mg/dL)	42	0.5	0.2	0.5	0.1	1.2	33	0.4	0.2	0.4	0.1	1.4	7	1.0	1.0	0.7	0.3	3.3
Total Cholesterol (mg/dl)	41	185.3	37.9	181.0	89.0	258.0	25	177.3	36.2	180.0	100.0	251.0	5	192.4	29.4	186.0	170.0	243.0
HDL (mg/dL)	36	67.5	21.3	61.5	42.0	113.0	15	63.0	17.1	59.0	39.0	98.0	2	77.0	11.3	77.0	69.0	85.0
LDL (mg/dL)	36	98.3	26.6	99.5	34.0	149.0	15	90.8	27.1	89.0	42.0	152.0	2	91.5	0.7	91.5	91.0	92.0
Triglycerides (mg/dL)	41	95.5	39.2	86.0	34.0	217.0	25	95.1	34.1	91.0	38.0	188.0	5	90.0	27.8	80.0	60.0	120.0
Serum Creatinine (mg/dL)	44	1.3	0.4	1.2	0.5	2.7	32	1.3	0.4	1.3	0.7	2.9	8	1.5	0.6	1.3	0.8	2.6
Calculated Creatinine Clearance (mL/min/1.73m^2)	28	79.8	32.3	76.5	26.0	176.0	8	52.5	19.6	47.5	20.0	82.0	1	17.0	-	17.0	17.0	17.0
Basal Plasma C-peptide (ng/mL)	39	0.0	0.1	0.0	0.0	0.5	29	1.2	0.7	1.1	0.0	2.5	5	1.0	0.7	1.0	0.1	2.0

Exhibit 5 – 52
Metabolic Summary by Follow-Up Post Last Infusion
Islet Alone Recipients

	Month 6			Year 1			Year 2			Year 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Total Expected												
Fasting Plasma Glucose (mg/dL)	220	114.1	28.6	187	114.2	41.7	116	116.8	38.8	73	117.5	38.5
HbA_{1c} (%)	210	6.1	0.9	179	6.1	0.9	115	6.4	1.1	73	6.3	0.9
Basal Plasma C-peptide (ng/mL)	209	1.5	1.3	202	1.3	1.1	144	0.9	1.0	110	0.8	1.1
Peak Stimulated C-peptide After Meal (ng/mL)	93	3.6	1.8	88	3.2	1.7	40	3.1	1.7	23	2.7	1.4
Basal Plasma C-peptide before IV Glucagon (ng/mL)	16	1.7	0.7	16	1.6	0.6	4	1.8	0.7	0	-	-
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	16	2.8	1.0	16	2.6	1.3	4	2.7	0.7	0	-	-
Basal Plasma C-peptide Before IV Arginine (ng/mL)	89	1.7	1.0	69	1.6	0.9	22	1.4	0.7	11	1.1	0.8
Peak Stimulated C-peptide After IV Arginine (ng/mL)	87	2.7	1.3	68	2.6	1.3	22	2.2	1.1	12	1.7	1.1
Acute C-peptide Response to IV Arginine (ng/mL)	80	1.0	0.8	65	0.9	0.6	20	1.1	0.7	12	0.5	0.3
Acute Insulin Response to IV Arginine (µ/mL)	81	16.7	10.1	65	15.1	10.6	20	16.0	11.3	11	10.3	6.9
Basal Plasma C-peptide Before IV Glucose (ng/mL)	66	1.5	0.8	57	1.3	0.7	22	1.3	0.7	8	1.4	1.1
Peak Stimulated C-peptide After IV Glucose (ng/mL)	66	2.9	1.3	57	2.6	1.3	22	2.6	1.0	8	2.4	1.2
Acute C-peptide Response to IV Glucose (ng/ml)	62	0.8	0.8	56	0.8	0.7	21	1.1	1.2	8	0.4	0.3
Acute Insulin Response to IV Glucose (µ/mL)	62	17.5	14.0	63	13.7	12.4	23	16.3	13.1	8	6.1	7.1
AUC Insulin derived from 0.5 g/kg IVGTT (µ/mL x min)	21	507.4	330.0	21	570.5	394.8	4	523.8	145.3	1	374.0	-
KG-value derived from 0.5 g.kg IVGTT (KG Value)	54	0.1	1.2	49	0.1	1.0	17	-0.7	1.0	8	-1.1	0.9
2-hr 75g OGTT Plasma Glucose (mg/dL)	46	273.9	645.5	54	259.8	666.3	14	186.5	71.4	5	160.3	75.5
AUC C-peptide OGTT (ng/mL x min)	5	230.0	90.1	8	167.1	119.7	1	295.5	-	1	229.5	-
AUC C-peptide MMTT (ng/mL x min)	48	366.3	357.9	46	350.0	338.1	23	435.0	360.8	13	332.3	251.4
Mixed Meal Stimulation Index (pmol/mg)	30	0.8	0.3	30	0.7	0.3	15	0.6	0.3	9	0.5	0.2

Exhibit 5 – 52 *(continued)*
Metabolic Summary by Follow-Up Post Last Infusion
Islet After Kidney Recipients

	Month 6			Year 1			Year 2			Year 3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Total expected												
Fasting Plasma Glucose (mg/dL)	33	114.2	29.1	30	122.6	40.5	23	112.7	38.8	16	150.9	71.1
HbA_{1c} (%)	30	6.1	0.5	27	6.2	0.7	21	6.7	0.8	14	6.9	1.1
Basal Plasma C-peptide (ng/mL)	30	1.5	1.2	27	1.4	1.4	24	1.2	1.5	17	0.9	1.4
Peak Stimulated C-peptide After Meal (ng/mL)	19	4.5	2.0	20	3.8	2.4	14	4.9	4.3	8	3.1	2.4
Basal Plasma C-peptide before IV Glucagon (ng/mL)	0	-	-	0	-	-	0	-	-	0	-	-
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	0	-	-	0	-	-	0	-	-	0	-	-
Basal Plasma C-peptide Before IV Arginine (ng/mL)	10	2.5	1.5	5	2.0	0.8	6	2.3	0.8	4	0.9	0.3
Peak Stimulated C-peptide After IV Arginine (ng/mL)	10	2.6	1.4	6	2.5	1.2	7	3.2	1.7	4	1.4	0.7
Acute C-peptide Response to IV Arginine (ng/mL)	10	0.4	0.3	5	0.6	0.3	6	0.9	0.4	3	0.2	0.0
Acute Insulin Response to IV Arginine (µ/mL)	5	15.3	8.5	4	20.9	9.7	5	17.4	13.2	1	3.9	-
Basal Plasma C-peptide Before IV Glucose (ng/mL)	6	1.4	0.9	4	1.2	0.3	4	1.2	0.5	2	0.5	0.2
Peak Stimulated C-peptide After IV Glucose (ng/mL)	6	2.7	1.2	4	2.8	1.0	4	2.8	1.0	2	1.3	0.7
Acute C-peptide Response to IV Glucose (ng/ml)	6	0.5	0.2	4	0.5	0.2	4	0.4	0.3	2	0.3	0.0
Acute Insulin Response to IV Glucose (µ/mL)	6	12.2	9.5	4	14.7	13.9	4	5.5	5.2	2	2.3	1.3
AUC Insulin derived from 0.5 g/kg IVGTT (µ/mL x min)	0	-	-	0	-	-	0	-	-	0	-	-
KG-value derived from 0.5 g.kg IVGTT (KG Value)	6	-0.9	0.4	4	-0.9	0.3	4	-0.8	0.2	2	-0.8	0.1
2-hr 75g OGTT Plasma Glucose (mg/dL)	5	255.6	102.6	5	265.0	79.9	0	-	-	0	-	-
AUC C-peptide OGTT (ng/mL x min)	0	-	-	0	-	-	0	-	-	0	-	-
AUC C-peptide MMTT (ng/mL x min)	7	737.0	373.3	5	614.9	356.1	3	515.0	491.3	2	765.8	36.1
Mixed Meal Stimulation Index (pmol/mg)	7	0.8	0.1	5	0.7	0.2	5	0.6	0.4	2	0.6	0.2

Exhibit 5 – 53
Metabolic Summary Post Last Infusion by Insulin Status
Islet Alone Recipients

	Month 6						Year 1					
	Insulin Independent			Insulin Dependent			Insulin Independent			Insulin Dependent		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Fasting Plasma Glucose (mg/dL)	83	126.6	36.0	136	106.4	19.5	78	127.0	56.8	109	105.1	22.4
HbA_{1c} (%)	78	6.6	1.1	131	5.8	0.6	71	6.6	1.0	108	5.8	0.6
Basal Plasma C-peptide (ng/mL)	80	0.9	1.0	129	1.9	1.2	96	0.7	1.1	106	1.8	0.8
Peak Stimulated C-peptide After Meal (ng/mL)	31	2.6	1.7	61	4.1	1.6	41	2.2	1.5	47	4.1	1.3
Basal Plasma C-peptide before IV Glucagon (ng/mL)	1	1.0	-	15	1.7	0.7	2	1.2	1.2	14	1.6	0.5
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	1	1.7	-	15	2.9	1.0	2	1.5	1.3	14	2.7	1.2
Basal Plasma C-peptide Before IV Arginine (ng/mL)	26	1.2	1.0	63	1.9	0.9	16	1.3	1.1	53	1.7	0.8
Peak Stimulated C-peptide After IV Arginine (ng/mL)	24	1.7	1.3	63	3.0	1.2	15	1.9	1.5	53	2.8	1.2
Acute C-peptide Response to IV Arginine (ng/mL)	20	0.6	0.5	60	1.1	0.9	13	0.5	0.3	52	1.0	0.6
Acute Insulin Response to IV Arginine (µ/mL)	20	8.4	6.8	61	19.4	9.6	14	9.4	9.4	51	16.7	10.4
Basal Plasma C-peptide Before IV Glucose (ng/mL)	11	1.1	0.8	55	1.6	0.8	11	0.8	0.4	46	1.5	0.7
Peak Stimulated C-peptide After IV Glucose (ng/mL)	11	2.1	1.5	55	3.1	1.3	11	1.3	0.9	46	2.9	1.2
Acute C-peptide Response to IV Glucose (ng/ml)	9	0.5	0.5	53	0.9	0.8	11	0.3	0.3	45	1.0	0.8
Acute Insulin Response to IV Glucose (µ/mL)	8	10.4	12.2	54	18.6	14.0	12	4.2	7.0	51	16.0	12.3
AUC Insulin derived from 0.5 g/kg IVGTT (µ/mL x min)	1	161.0	-	20	524.7	328.7	2	200.2	95.0	19	609.5	394.8
KG-value derived from 0.5 g.kg IVGTT (KG Value)	8	-0.3	1.1	46	0.2	1.2	9	-0.3	0.6	40	0.1	1.1
2-hr 75g OGTT Plasma Glucose (mg/dL)	4	347.0	88.3	42	266.9	675.4	9	808.4	1587.3	45	150.1	53.2
AUC C-peptide OGTT (ng/mL x min)	0	-	-	5	230.0	90.1	1	212.4	-	7	160.7	127.8
AUC C-peptide MMTT (ng/mL x min)	15	355.0	350.6	33	371.4	366.4	18	307.7	351.8	28	377.2	332.6
Mixed Meal Stimulation Index (pmol/mg)	8	0.6	0.5	22	0.8	0.2	9	0.5	0.3	21	0.7	0.2

Exhibit 5 – 53 (*continued*)
Metabolic Summary Post Last Infusion by Insulin Status
Islet Alone Recipients

	Year 2						Year 3					
	Insulin Independent			Insulin Dependent			Insulin Independent			Insulin Dependent		
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD
Fasting Plasma Glucose (mg/dL)	58	128.6	49.6	58	105.0	17.0	44	123.1	47.2	29	109.1	16.7
HbA_{1c} (%)	58	6.8	1.3	57	6.1	0.6	43	6.6	1.0	30	6.0	0.5
Basal Plasma C-peptide (ng/mL)	97	0.4	0.7	47	1.8	0.9	83	0.5	0.8	27	1.9	1.2
Peak Stimulated C-peptide After Meal (ng/mL)	20	2.2	1.4	20	4.0	1.4	12	2.2	1.3	11	3.3	1.4
Basal Plasma C-peptide before IV Glucagon (ng/mL)	1	1.1	-	3	2.1	0.6	0	-	-	0	-	-
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	1	1.9	-	3	2.9	0.6	0	-	-	0	-	-
Basal Plasma C-peptide Before IV Arginine (ng/mL)	9	1.3	1.0	13	1.4	0.4	8	0.9	0.9	3	1.5	0.4
Peak Stimulated C-peptide After IV Arginine (ng/mL)	9	1.8	1.3	13	2.6	0.7	8	1.3	1.1	4	2.6	0.4
Acute C-peptide Response to IV Arginine (ng/mL)	7	0.6	0.4	13	1.3	0.6	8	0.4	0.2	4	0.9	0.1
Acute Insulin Response to IV Arginine (microU/mL)	8	7.6	7.5	12	21.7	10.0	7	6.1	3.9	4	17.8	3.1
Basal Plasma C-peptide Before IV Glucose (ng/mL)	6	1.2	0.8	16	1.3	0.7	3	1.2	0.9	5	1.6	1.2
Peak Stimulated C-peptide After IV Glucose (ng/mL)	6	2.2	1.2	16	2.8	0.9	3	1.9	1.3	5	2.7	1.2
Acute C-peptide Response to IV Glucose (ng/ml)	6	0.4	0.2	15	1.4	1.3	3	0.4	0.1	5	0.4	0.4
Acute Insulin Response to IV Glucose (microU/mL)	6	6.7	5.8	17	19.7	13.3	3	2.6	1.4	5	8.2	8.5
AUC Insulin derived from 0.5 g/kg IVGTT (microU/mL x min)	1	497.0	-	3	532.7	176.6	0	-	-	1	374.0	-
KG-value derived from 0.5 g.kg IVGTT (KG Value)	6	-0.5	0.8	11	-0.8	1.0	3	-1.2	0.3	5	-1.0	1.1
2-hr 75g OGTT Plasma Glucose (mg/dL)	1	183.0	-	13	186.7	74.4	0	-	-	5	160.3	75.5
AUC C-peptide OGTT (ng/mL x min)	0	-	-	1	295.5	-	0	-	-	1	229.5	-
AUC C-peptide MMTT (ng/mL x min)	8	404.2	398.8	15	451.4	352.4	6	378.0	272.7	7	293.1	246.1
Mixed Meal Stimulation Index (pmol/mg)	6	0.5	0.4	9	0.7	0.2	5	0.4	0.3	4	0.6	0.1

Exhibit 5 – 54
Secondary Complications of Diabetes
Pre First Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Total	325	100.0	313	100.0	300	100.0	257	100.0	193	100.0
Peripheral Neuropathy										
No occurrence	162	49.8	155	49.5	136	45.3	86	33.5	52	26.9
Asymptomatic	32	9.8	24	7.7	17	5.7	26	10.1	8	4.1
Symptomatic	109	33.5	47	15.0	45	15.0	24	9.3	20	10.4
Disabling	2	0.6	-	0.0	-	0.0	-	0.0	-	0.0
Unknown	7	2.2	21	6.7	21	7.0	20	7.8	15	7.8
Missing	13	4.0	66	21.1	81	27.0	101	39.3	98	50.8
Autonomic Neuropathy										
No occurrence	209	64.3	174	55.6	151	50.3	105	40.9	68	35.2
Asymptomatic	24	7.4	18	5.8	10	3.3	13	5.1	5	2.6
Symptomatic	62	19.1	35	11.2	33	11.0	15	5.8	6	3.1
Disabling	-	0.0	-	0.0	1	0.3	1	0.4	-	0.0
Unknown	17	5.2	19	6.1	24	8.0	22	8.6	15	7.8
Missing	13	4.0	67	21.4	81	27.0	101	39.3	99	51.3
Nephropathy										
No occurrence	212	65.2	169	54.0	136	45.3	84	32.7	44	22.8
Microalbuminuria	51	15.7	33	10.5	39	13.0	25	9.7	18	9.3
Macroalbuminuria	2	0.6	8	2.6	9	3.0	9	3.5	3	1.6
End stage renal disease	1	0.3	1	0.3	-	0.0	1	0.4	1	0.5
Stable allograft	34	10.5	18	5.8	20	6.7	13	5.1	11	5.7
Unknown	11	3.4	19	6.1	15	5.0	23	8.9	16	8.3
Missing	14	4.3	65	20.8	81	27.0	102	39.7	100	51.8
CAD										
Yes	29	8.9	19	6.1	15	5.0	11	4.3	11	5.7
No	281	86.5	220	70.3	194	64.7	130	50.6	78	40.4
Unknown	3	0.9	9	2.9	10	3.3	15	5.8	6	3.1
Missing	12	3.7	65	20.8	81	27.0	101	39.3	98	50.8

Exhibit 5 – 54 *(continued)*
Secondary Complications of Diabetes
Pre First Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
CVA										
No	309	95.1	239	76.4	213	71.0	140	54.5	89	46.1
Unknown	3	0.9	9	2.9	6	2.0	16	6.2	6	3.1
Missing	13	4.0	65	20.8	81	27.0	101	39.3	98	50.8
PVD										
Yes	9	2.8	4	1.3	3	1.0	3	1.2	4	2.1
No	297	91.4	232	74.1	205	68.3	137	53.3	82	42.5
Unknown	6	1.8	12	3.8	11	3.7	16	6.2	9	4.7
Missing	13	4.0	65	20.8	81	27.0	101	39.3	98	50.8
Treated Hypertension										
Yes	121	37.2	99	31.6	109	36.3	77	30.0	42	21.8
No	189	58.2	143	45.7	109	36.3	69	26.8	47	24.4
Unknown	4	1.2	7	2.2	2	0.7	9	3.5	6	3.1
Missing	11	3.4	64	20.4	80	26.7	102	39.7	98	50.8
Foot Ulcers										
Yes	19	5.8	9	2.9	9	3.0	5	1.9	2	1.0
No	268	82.5	230	73.5	202	67.3	136	52.9	88	45.6
Unknown	24	7.4	10	3.2	9	3.0	15	5.8	6	3.1
Missing	14	4.3	64	20.4	80	26.7	101	39.3	97	50.3
Lower Limb Amputation										
Yes	7	2.2	1	0.3	1	0.3	-	0.0	-	0.0
No	298	91.7	246	78.6	217	72.3	147	57.2	92	47.7
Unknown	6	1.8	2	0.6	2	0.7	9	3.5	4	2.1
Missing	14	4.3	64	20.4	80	26.7	101	39.3	97	50.3
Foot Deformity										
Yes	9	2.8	2	0.6	2	0.7	1	0.4	3	1.6
No	285	87.7	238	76.0	209	69.7	144	56.0	88	45.6
Unknown	17	5.2	9	2.9	8	2.7	11	4.3	5	2.6
Missing	14	4.3	64	20.4	81	27.0	101	39.3	97	50.3

Exhibit 5 – 54 *(continued)*
Secondary Complications of Diabetes
Pre First Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Dysesthesia										
Yes	47	14.5	20	6.4	25	8.3	15	5.8	7	3.6
No	234	72.0	208	66.5	178	59.3	121	47.1	77	39.9
Unknown	29	8.9	21	6.7	17	5.7	20	7.8	12	6.2
Missing	15	4.6	64	20.4	80	26.7	101	39.3	97	50.3
Orthostatic Hypotension										
Yes	30	9.2	7	2.2	7	2.3	3	1.2	7	3.6
No	224	68.9	203	64.9	185	61.7	121	47.1	73	37.8
Unknown	57	17.5	38	12.1	28	9.3	32	12.5	15	7.8
Missing	14	4.3	65	20.8	80	26.7	101	39.3	98	50.8
Gastroparesis										
Yes	38	11.7	18	5.8	16	5.3	7	2.7	6	3.1
No	243	74.8	211	67.4	189	63.0	122	47.5	77	39.9
Unknown	31	9.5	20	6.4	15	5.0	27	10.5	12	6.2
Missing	13	4.0	64	20.4	80	26.7	101	39.3	98	50.8
Constipation										
Yes	26	8.0	15	4.8	9	3.0	7	2.7	2	1.0
No	253	77.8	216	69.0	201	67.0	129	50.2	81	42.0
Unknown	32	9.8	18	5.8	10	3.3	20	7.8	12	6.2
Missing	14	4.3	64	20.4	80	26.7	101	39.3	98	50.8
Diabetic Diarrhea										
Yes	16	4.9	17	5.4	19	6.3	16	6.2	6	3.1
No	268	82.5	200	63.9	181	60.3	118	45.9	77	39.9
Unknown	27	8.3	32	10.2	20	6.7	22	8.6	13	6.7
Missing	14	4.3	64	20.4	80	26.7	101	39.3	97	50.3
Fecal Incontinence										
Yes	2	0.6	1	0.3	1	0.3	-	0.0	-	0.0
No	280	86.2	228	72.8	208	69.3	138	53.7	84	43.5
Unknown	29	8.9	20	6.4	10	3.3	18	7.0	11	5.7
Missing	14	4.3	64	20.4	81	27.0	101	39.3	98	50.8

Exhibit 5 – 54 *(continued)*
Secondary Complications of Diabetes
Pre First Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Diabetic Bladder Dysfunction										
Yes	4	1.2	2	0.6	2	0.7	1	0.4	-	0.0
No	276	84.9	227	72.5	205	68.3	132	51.4	82	42.5
Unknown	31	9.5	20	6.4	13	4.3	23	8.9	12	6.2
Missing	14	4.3	64	20.4	80	26.7	101	39.3	99	51.3
Sexual Dysfunction										
Yes	29	8.9	14	4.5	12	4.0	9	3.5	6	3.1
No	244	75.1	191	61.0	176	58.7	115	44.7	70	36.3
Unknown	38	11.7	44	14.1	32	10.7	32	12.5	19	9.8
Missing	14	4.3	64	20.4	80	26.7	101	39.3	98	50.8

Exhibit 5 – 55
Ocular Complications
Pre First Infusion and Post last Infusion
All Allograft Recipients

	Follow-Up									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Total	325	100.0	313	100.0	300	100.0	257	100.0	193	100.0
Retinopathy										
None	128	39.4	110	35.1	95	31.7	55	21.4	33	17.1
Non Proliferative	84	25.8	52	16.6	44	14.7	35	13.6	24	12.4
Proliferative	89	27.4	40	12.8	33	11.0	21	8.2	10	5.2
Unknown	13	4.0	42	13.4	41	13.7	43	16.7	25	13.0
Missing	11	3.4	69	22.0	87	29.0	103	40.1	101	52.3
Diabetic Macular Edema										
None	282	86.8	201	64.2	167	55.7	107	41.6	70	36.3
Mild	7	2.2	4	1.3	3	1.0	2	0.8	1	0.5
Moderate	5	1.5	2	0.6	2	0.7	2	0.8	1	0.5
Severe	1	0.3	-	0.0	-	0.0	1	0.4	-	0.0
Unknown	16	4.9	37	11.8	43	14.3	42	16.3	20	10.4
Missing	14	4.3	69	22.0	85	28.3	103	40.1	101	52.3
Laser photocoagulation surgery performed for proliferative retinopathy										
Yes	122	37.5	5	1.6	12	4.0	5	1.9	3	1.6
No	181	55.7	219	70.0	184	61.3	120	46.7	71	36.8
Unknown	7	2.2	8	2.6	8	2.7	12	4.7	8	4.1
Missing	15	4.6	81	25.9	96	32.0	120	46.7	111	57.5
Laser photocoagulation surgery performed for diabetic macular edema										
Yes	16	4.9	-	0.0	3	1.0	-	0.0	-	0.0
No	278	85.5	226	72.2	194	64.7	125	48.6	75	38.9
Unknown	16	4.9	6	1.9	7	2.3	12	4.7	7	3.6
Missing	15	4.6	81	25.9	96	32.0	120	46.7	111	57.5
Vitrectomy										
Yes	33	10.2	1	0.3	2	0.7	2	0.8	-	0.0
No	268	82.5	225	71.9	196	65.3	123	47.9	75	38.9
Unknown	9	2.8	6	1.9	6	2.0	12	4.7	7	3.6
Missing	15	4.6	81	25.9	96	32.0	120	46.7	111	57.5

Exhibit 5 – 55 *(continued)*
Ocular Complications
Pre First Infusion and Post last Infusion
All Allograft Recipients

	Follow-Up									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Other Surgery										
Yes	33	10.2	1	0.3	5	1.7	6	2.3	2	1.0
No	259	79.7	212	67.7	186	62.0	118	45.9	71	36.8
Unknown	12	3.7	13	4.2	9	3.0	12	4.7	9	4.7
Missing	21	6.5	87	27.8	100	33.3	121	47.1	111	57.5

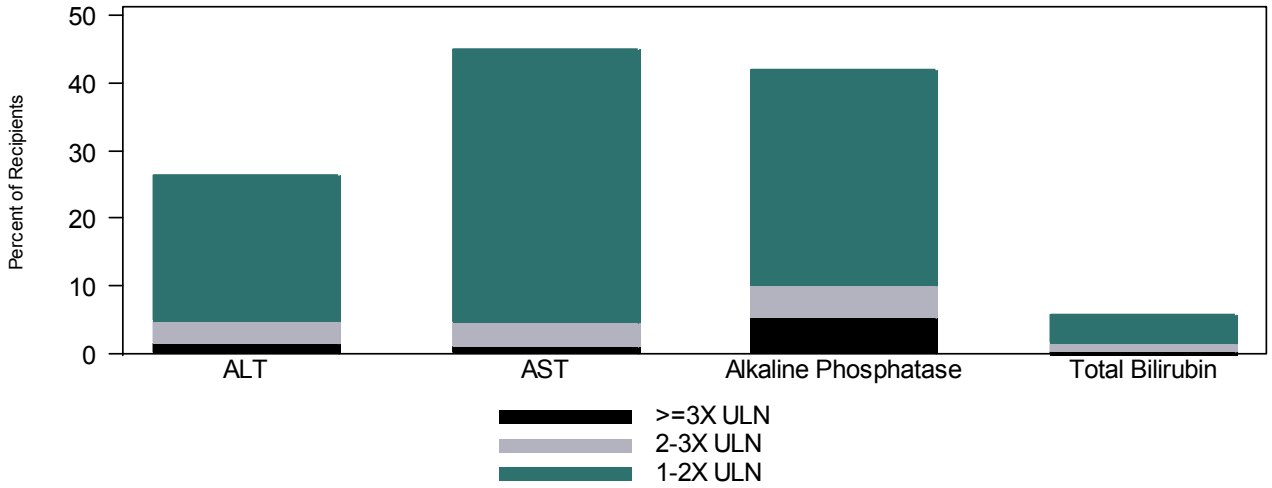
Chapter 6
Liver, Kidney, Lipid, and PRA Effects

Liver, Kidney, Lipid, and PRA Effects

This chapter provides a summary of abnormal laboratory tests, defined as above the upper limit of normal (ULN) for the test.

Occurrence of two times or greater than the ULN at any of the specified follow-up time points (pre-subsequent infusion, 6 months, 1 year, 2 year, and 3 year post infusion) were minimal for ALT (5%), AST (4%), alkaline phosphatase (10%) and for total bilirubin (1%) (Exhibit 6-1). There were no reports at this level for total cholesterol and 10 reports (4%) for triglycerides (Exhibit 6-6). There were reports of 37 (15%) IA recipients and 9 (22%) IAK recipients with an increase in serum creatinine greater than 0.5 mg/dL of the baseline level (Exhibit 6-11). These estimates of incidence of elevated laboratory studies might be higher if CITR reported time points were more frequent.

Exhibit 6 – 1
Incidence of Abnormal Liver Function Tests
at Any CITR Scheduled Time Post First Infusion
All Allograft Recipients

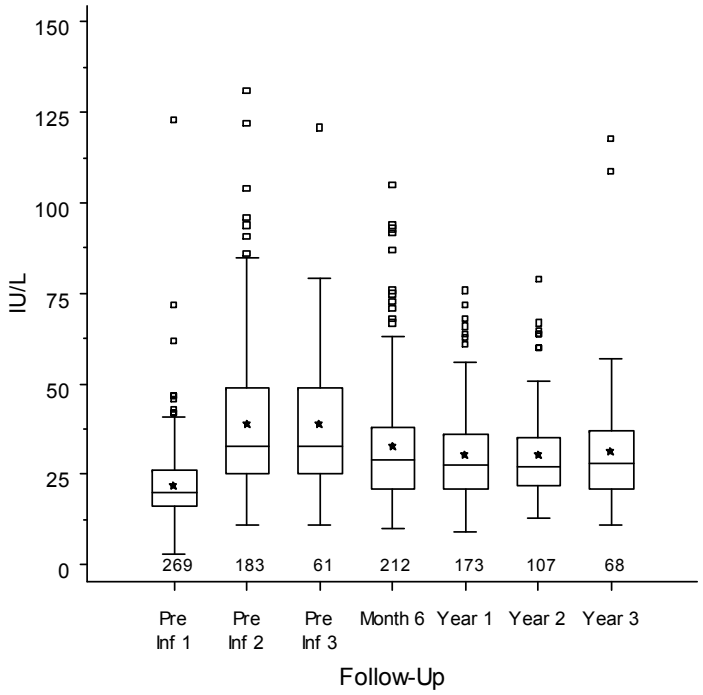


Lab values analyzed in this Exhibit are taken prior to each subsequent infusion
and at Month 6, Year 1, Year 2, and Year 3 after the last infusion procedure occurs.

There have been no reports of total bilirubin elevation >2x ULN concurrent with ALT or AST elevation >3x ULN at the scheduled CITR time points.

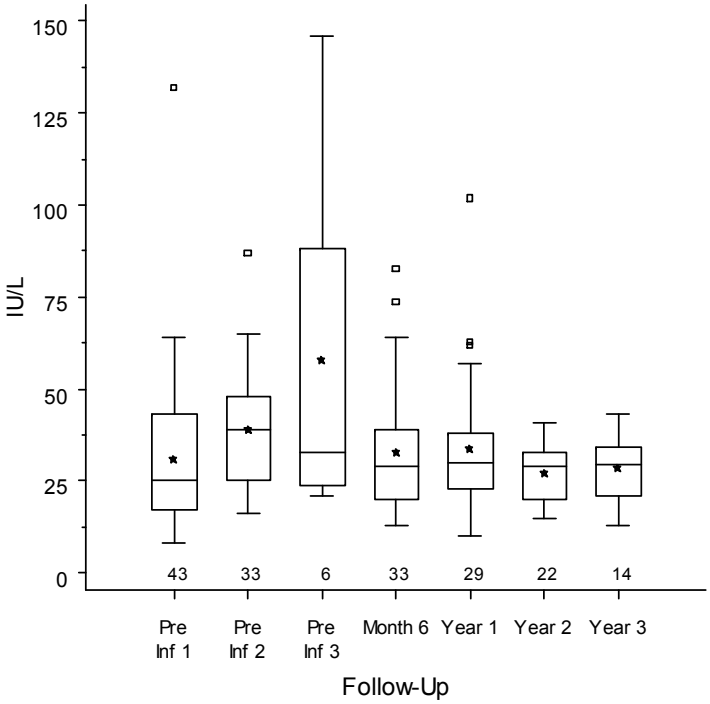
Exhibit 6 – 2
ALT (IU/L) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 150 IU/L are not displayed
(One at pre-inf 2)

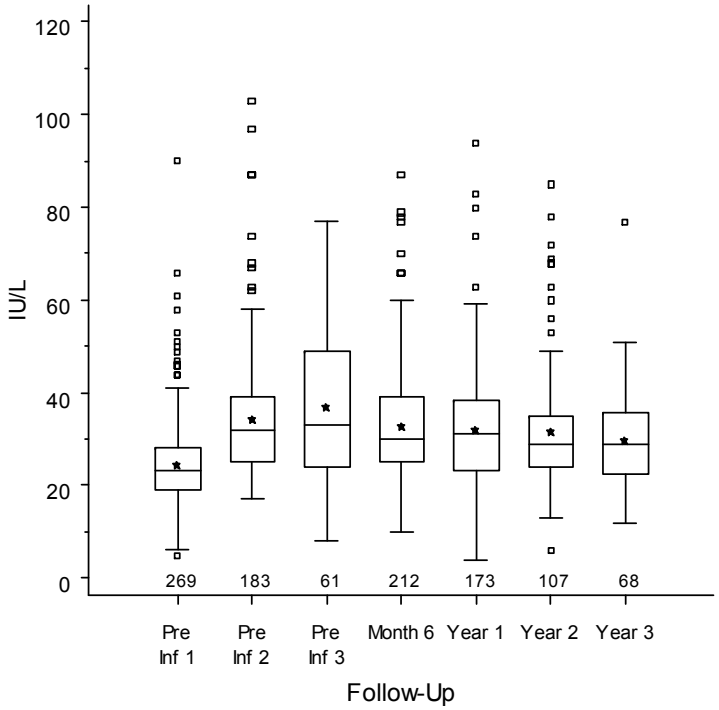
B. Islet After Kidney Recipients



Values greater than 150 IU/L are not displayed
(One at pre-inf 2)

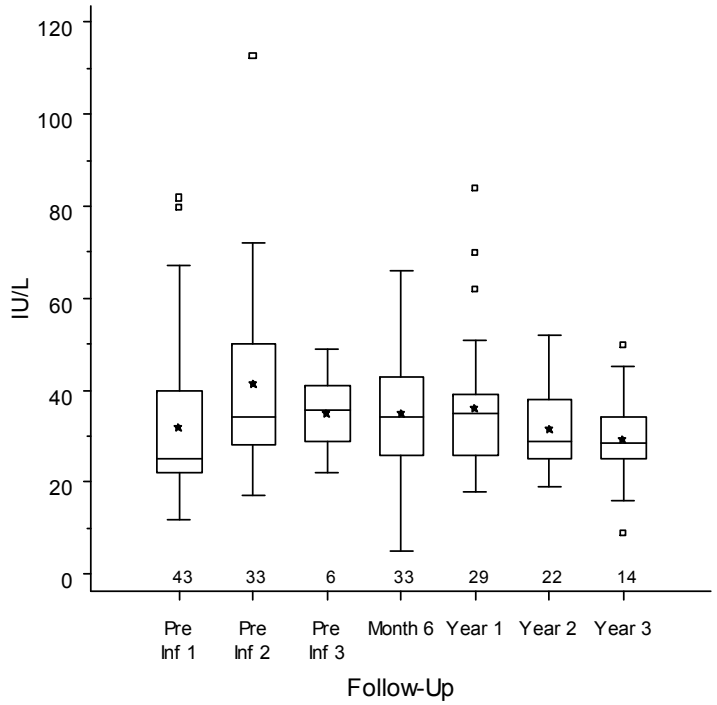
Exhibit 6 – 3
AST (IU/L) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 120 IU/L are removed for display
(One at pre-inf 2)

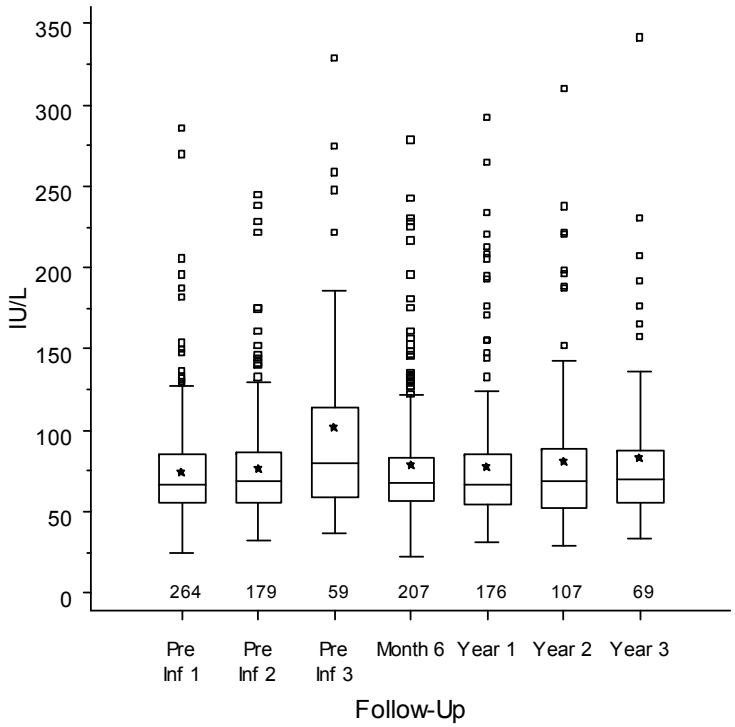
B. Islet After Kidney Recipients



Values greater than 150 IU/L are not displayed
(One at pre-inf 2)

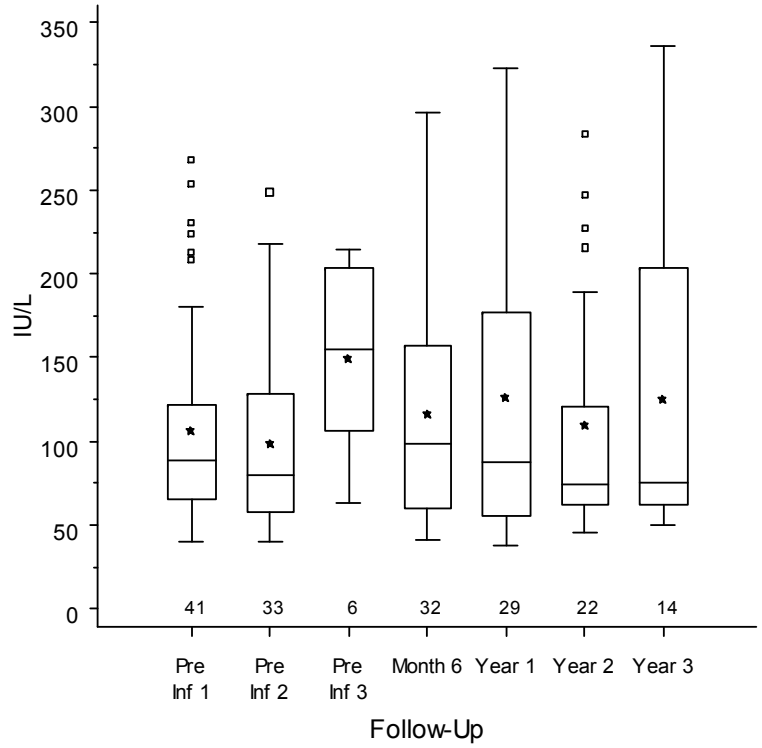
Exhibit 6 – 4
Alkaline Phosphatase (IU/L) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 350 IU/L are removed for display
(Two at pre-inf 2, one at month 6, and one at year 1)

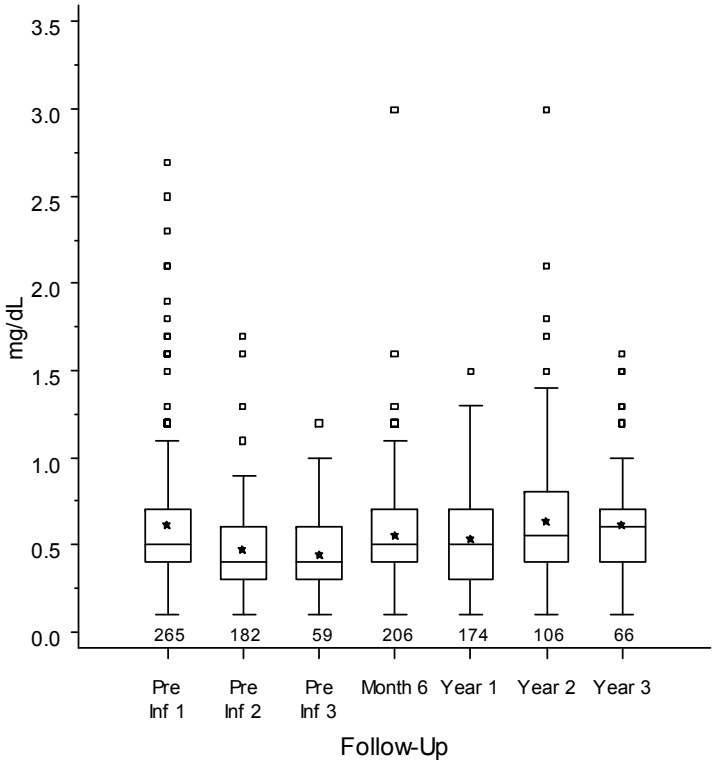
B. Islet After Kidney Recipients



Values greater than 350 IU/L are removed for display
(Three at pre-inf 1, four at pre-inf 2, two at year 1, and one at year 2)

Exhibit 6 – 5
Total Bilirubin (mg/dL) Pre Infusion and Post Last Infusion

. Islet Alone Recipients



B. Islet After Kidney Recipients

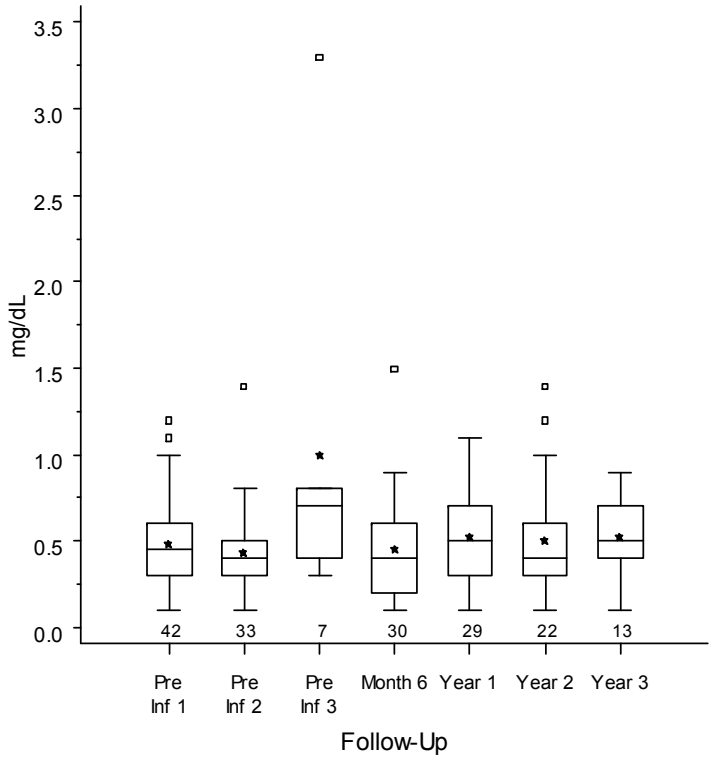
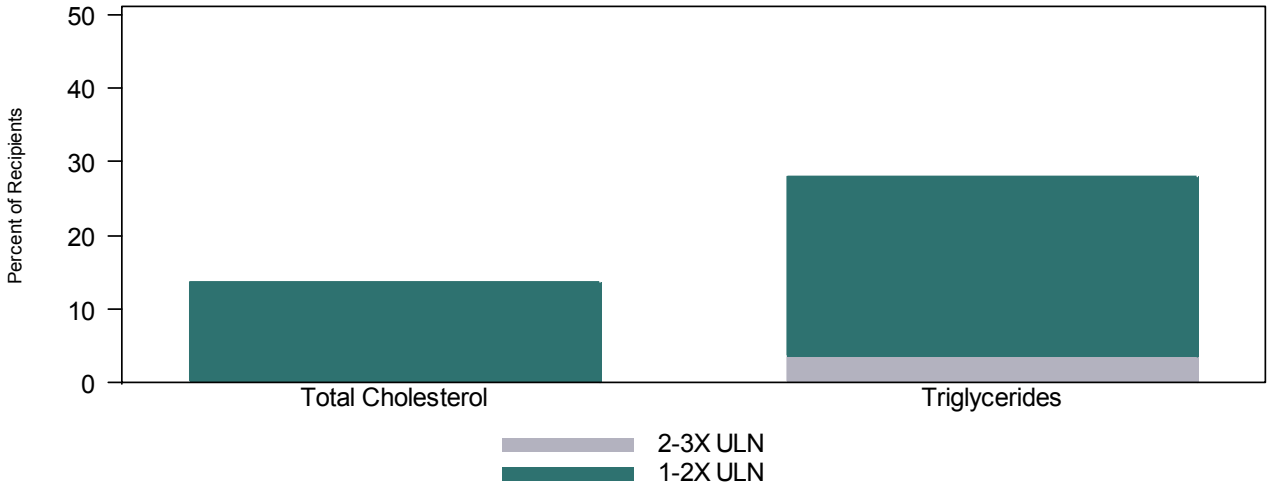


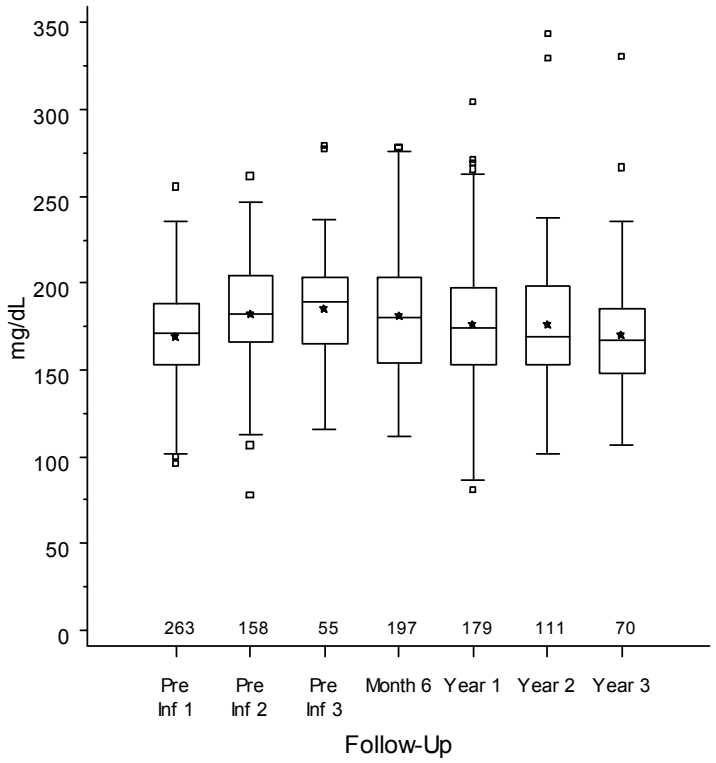
Exhibit 6 – 6
Incidence of Abnormal Lipid Tests
at Any CITR Scheduled Time Post First Infusion
All Allograft Recipients



Lab values analyzed in this Exhibit are taken prior to each subsequent infusion and at Month 6, Year 1, Year 2, and Year 3 after the last infusion procedure occurs.

Exhibit 6 – 7
Total Cholesterol (mg/dL) Pre Infusion and Post Last Infusion

. Islet Alone Recipients



B. Islet After Kidney Recipients

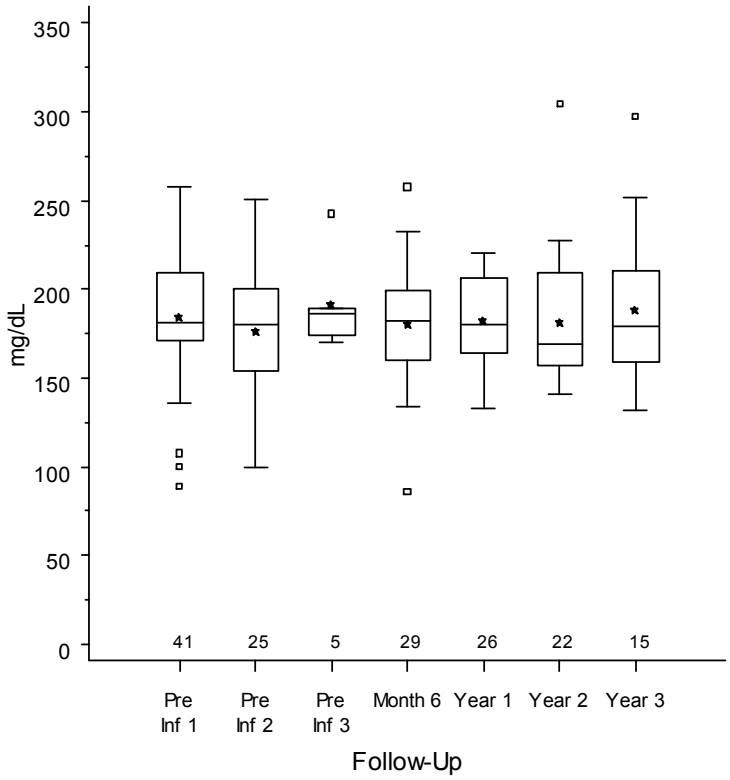
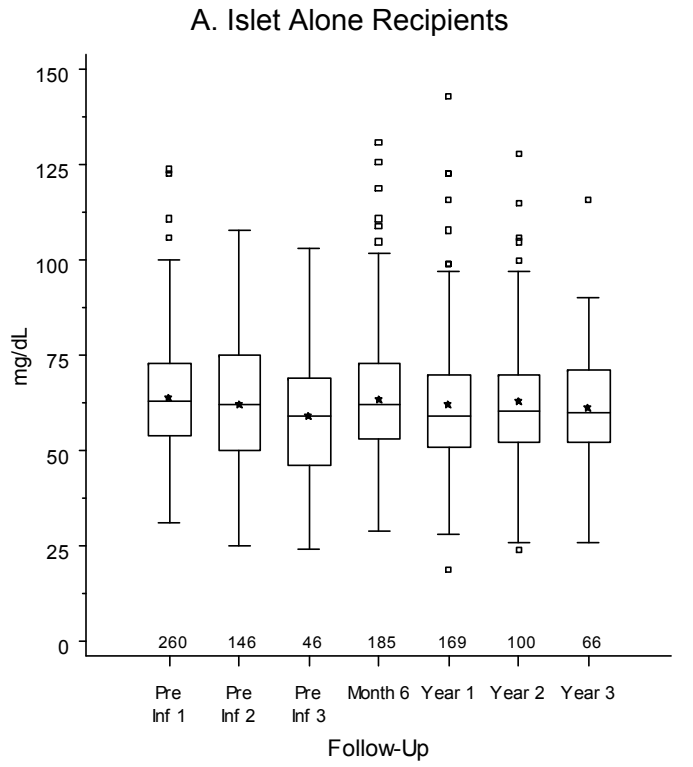


Exhibit 6 – 8
HDL (mg/dL) Pre Infusion and Post Last Infusion



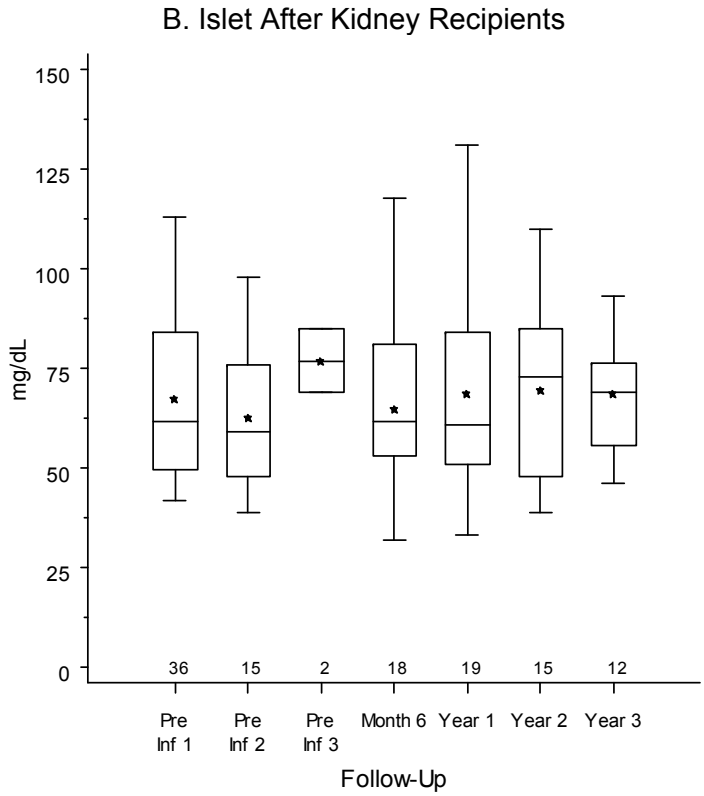
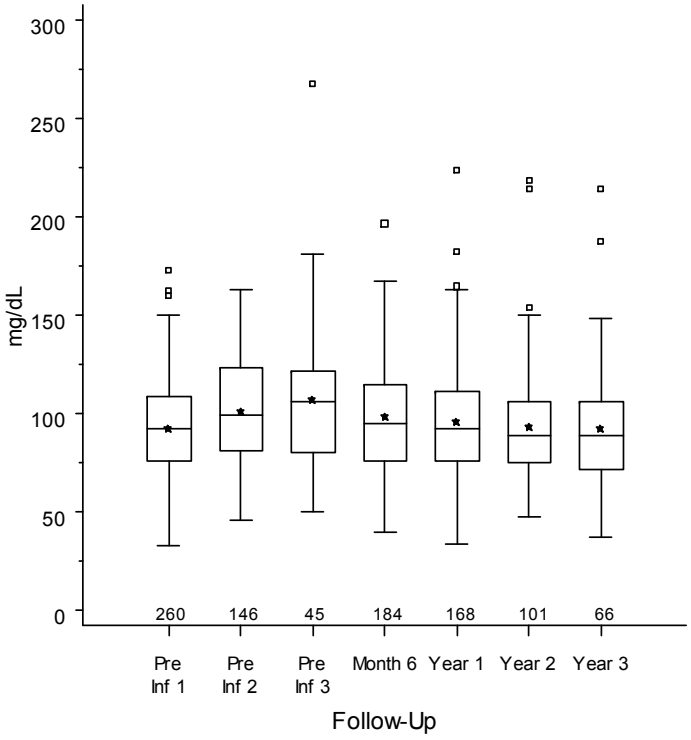


Exhibit 6 – 9
LDL (mg/dL) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

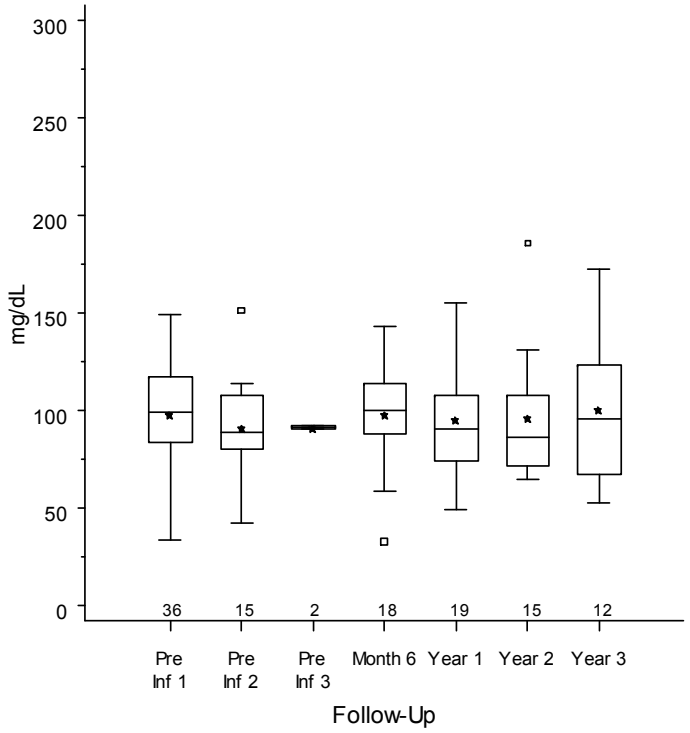
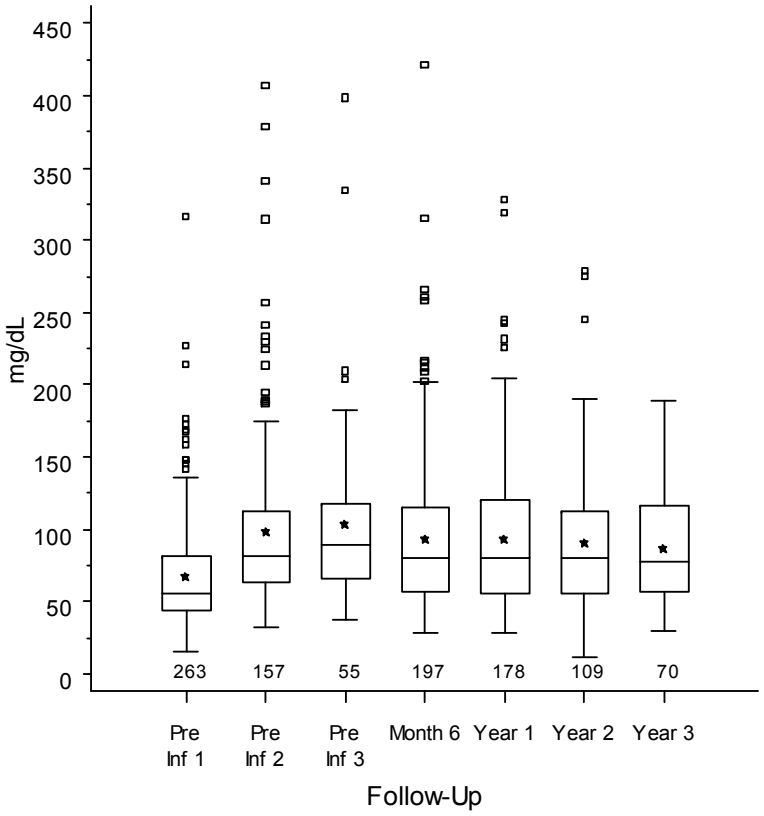


Exhibit 6 – 10
Triglycerides (mg/dL) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

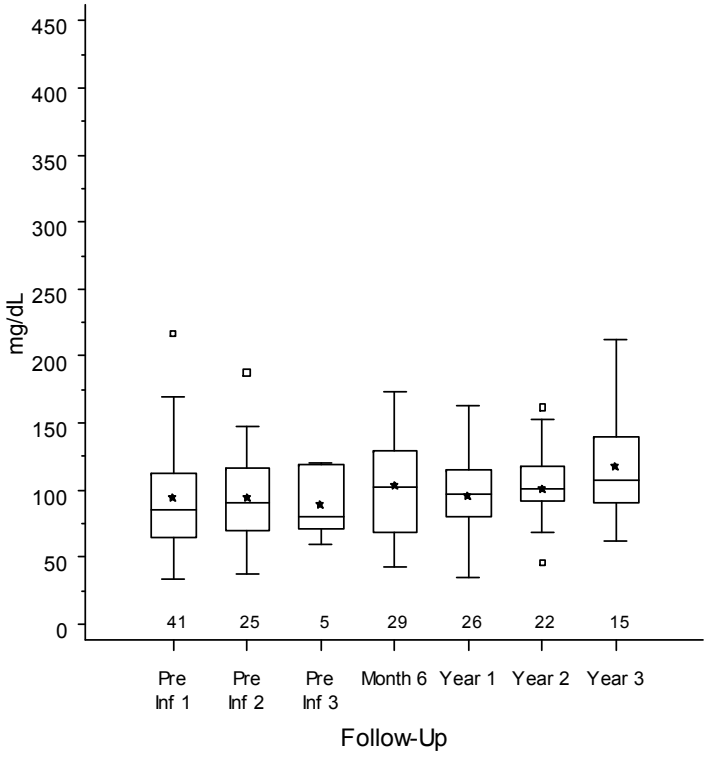
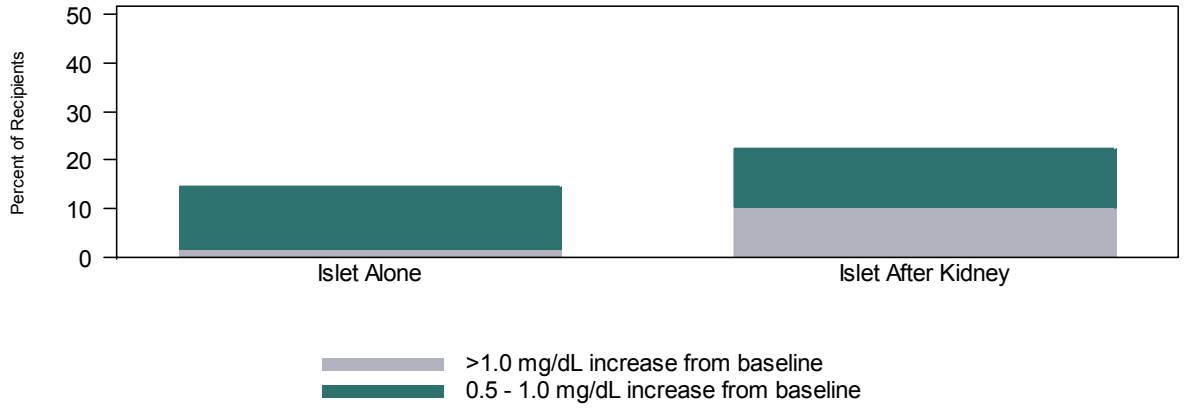


Exhibit 6 – 11
Incidence of Increase in Serum Creatinine (mg/dL) Greater than 0.5 from Baseline at Any CITR Scheduled Time Post First Infusion

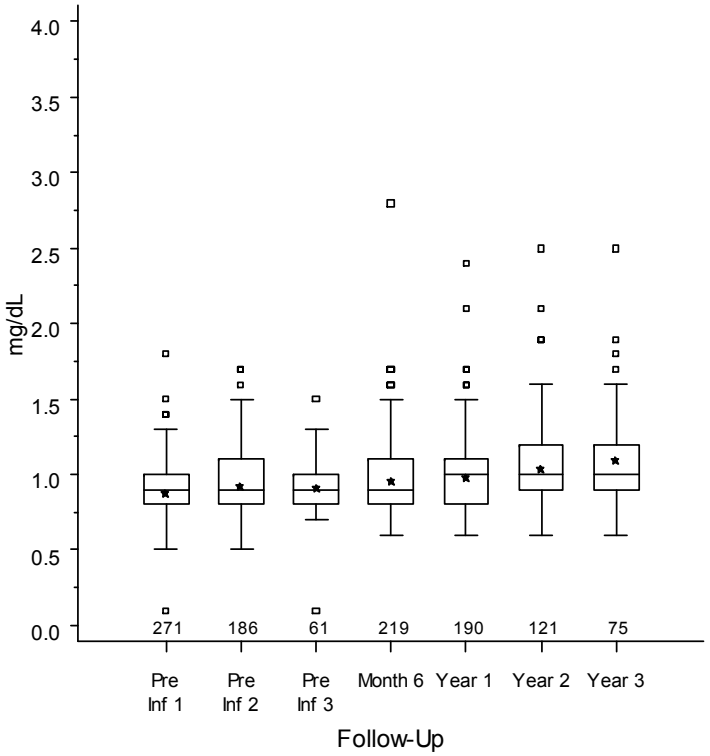
All Allograft Recipients



Lab values analyzed in this Exhibit are taken prior to each subsequent infusion and at Month 6, Year 1, Year 2, and Year 3 after the last infusion procedure occurs.

Exhibit 6 – 12
Serum Creatinine (mg/dL) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

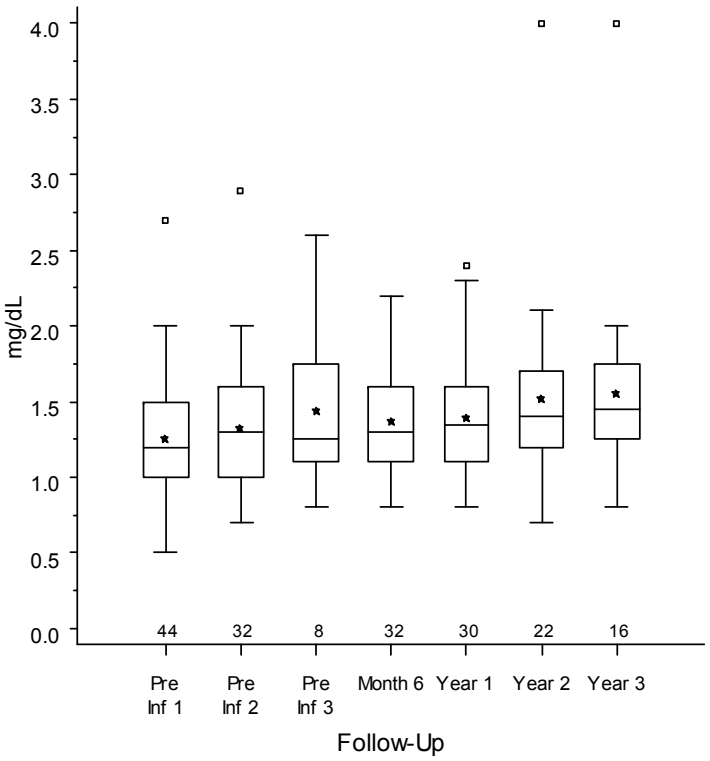
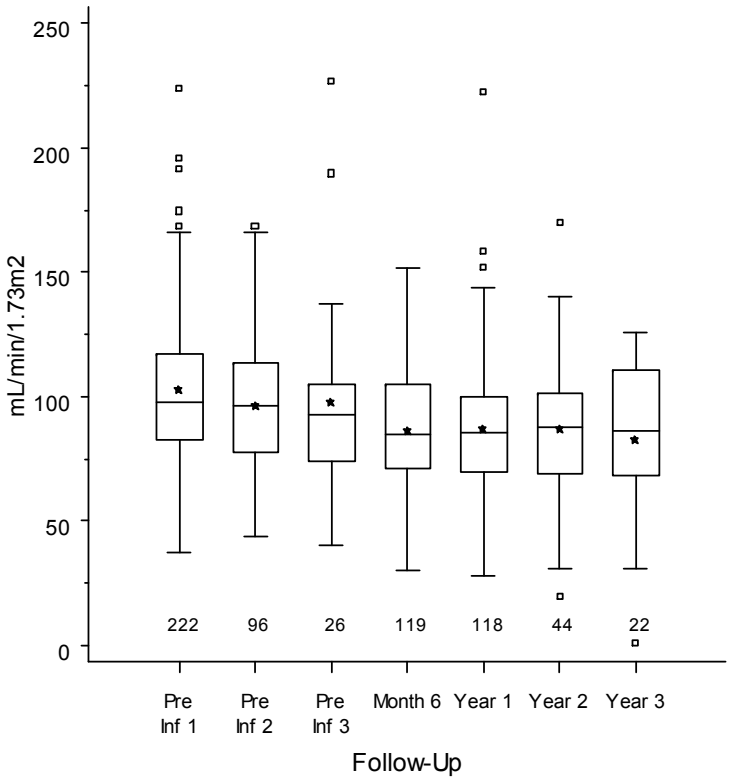


Exhibit 6 – 13
Calculated Creatinine Clearance (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

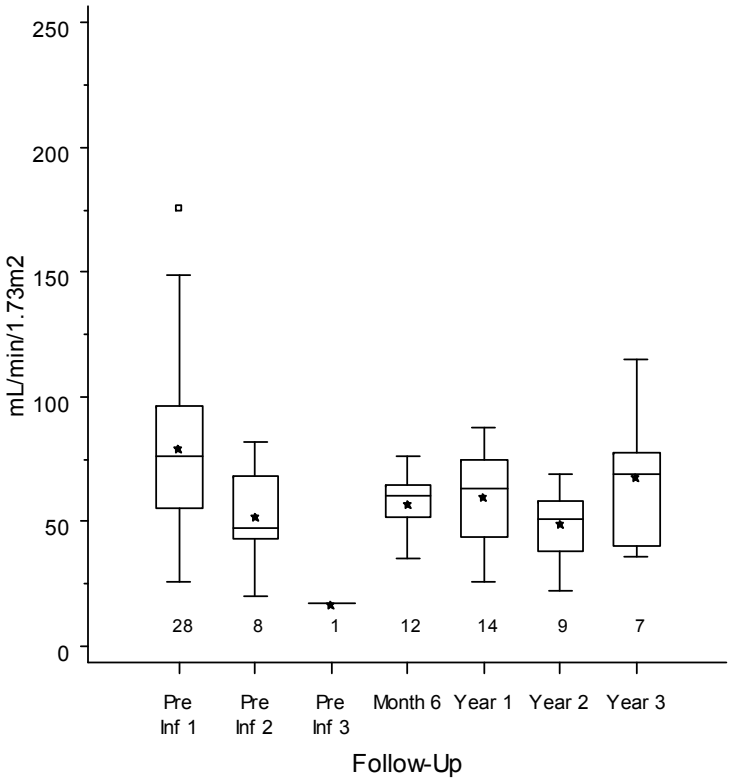
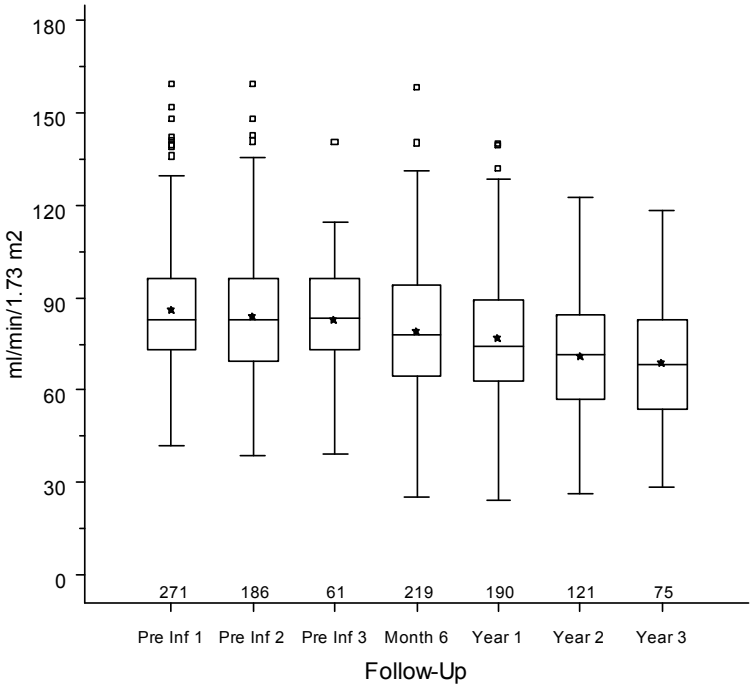


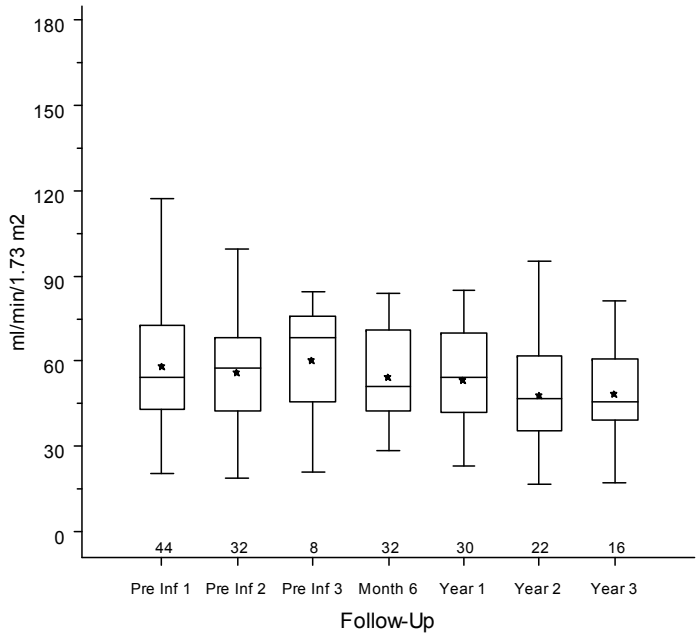
Exhibit 6 – 14
Estimated GFR (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 180 ml/min/1.73 m2 have been removed for display

B. Islet After Kidney Recipients



Values greater than 180 ml/min/1.73 m2 have been removed for display

Exhibit 6 – 15
Class I PRA (%)
Pre Infusion and Post Last Infusion

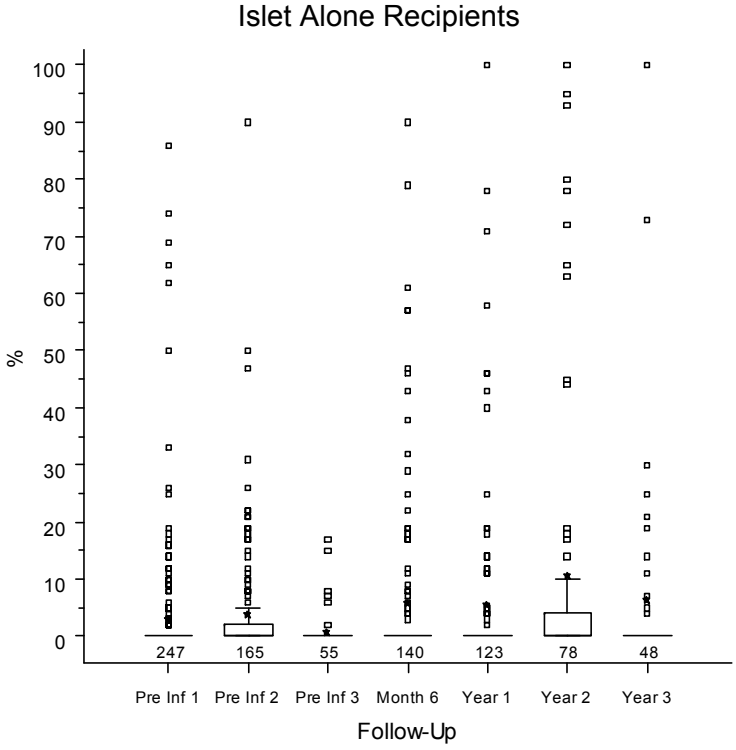


Exhibit 6 – 16
Change in Class I PRA from Pre First Infusion
Pre Subsequent Infusion and Post Last Infusion

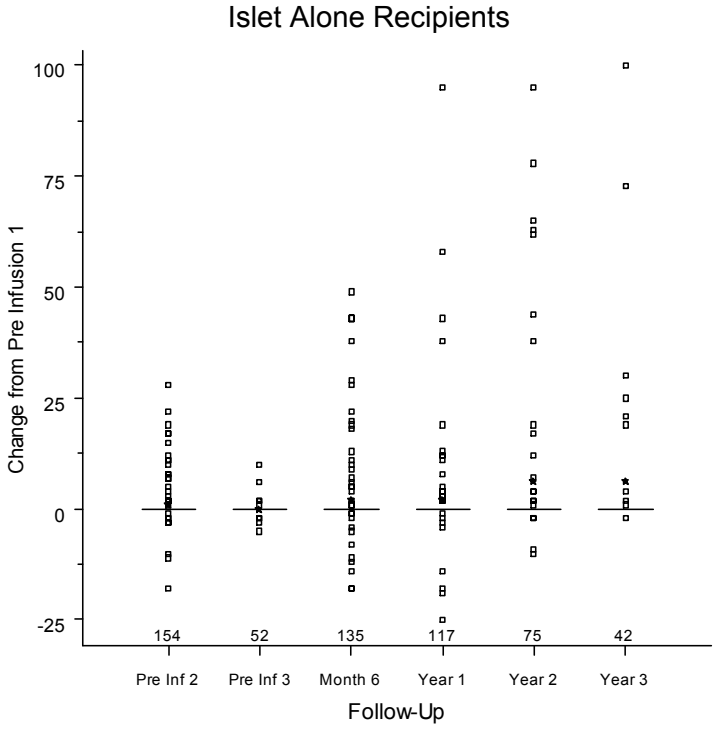


Exhibit 6 – 17
Class I PRA Post Last Infusion
Islet Alone Recipients with Complete Graft Loss

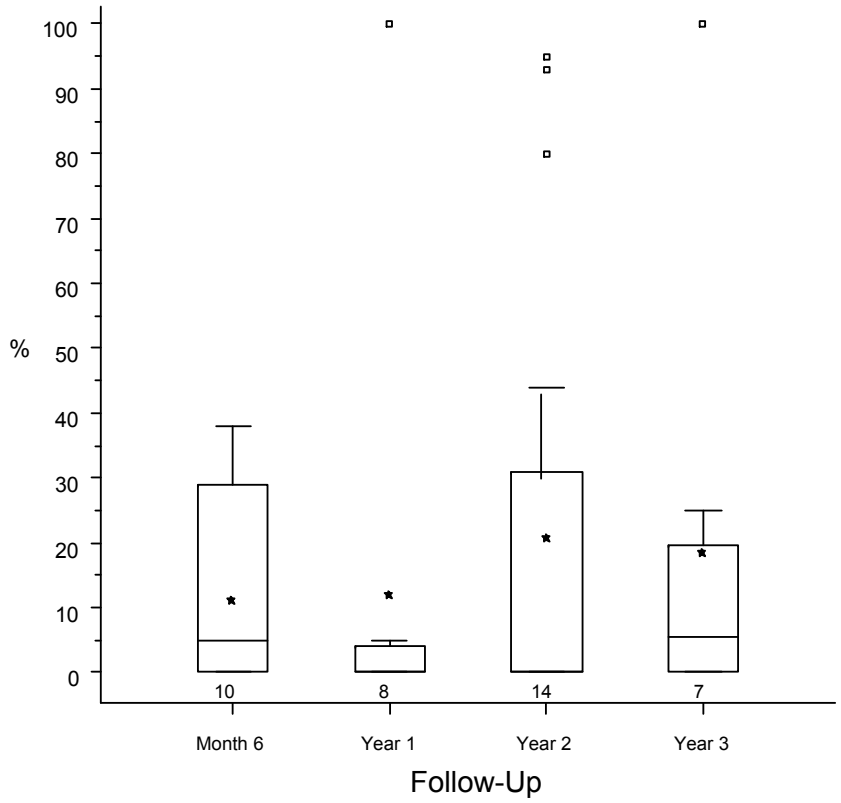


Exhibit 6 – 18
Class I PRA Post Last Infusion
Islet Alone Recipients without Complete Graft Loss

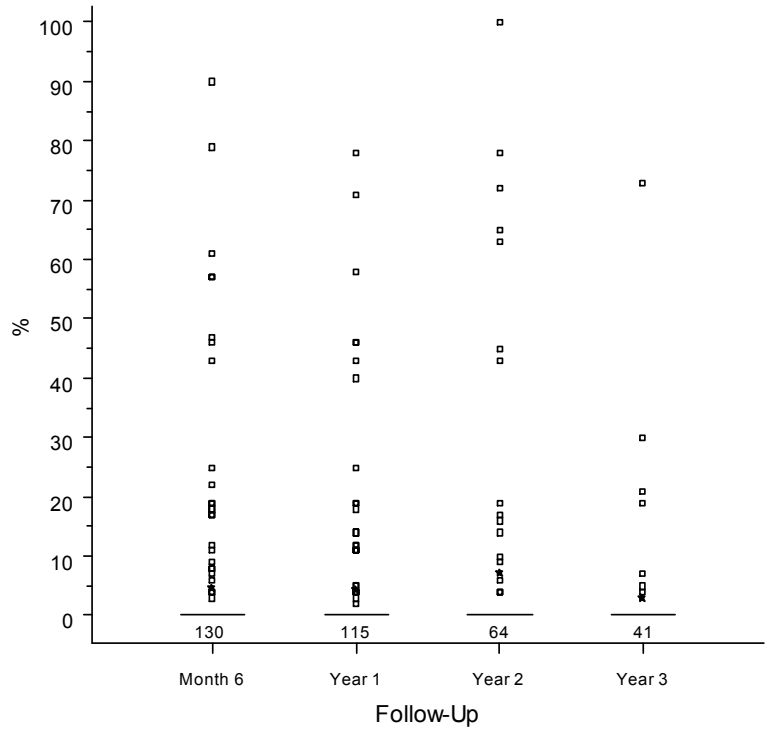


Exhibit 6 – 19
Class I PRA Post Last Infusion
Non-Immunosuppressed Islet Alone Recipients

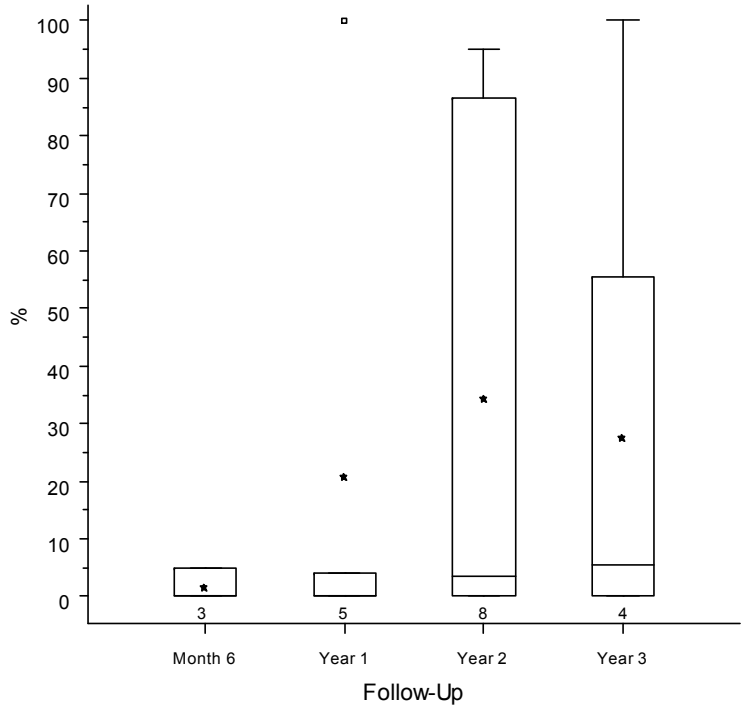
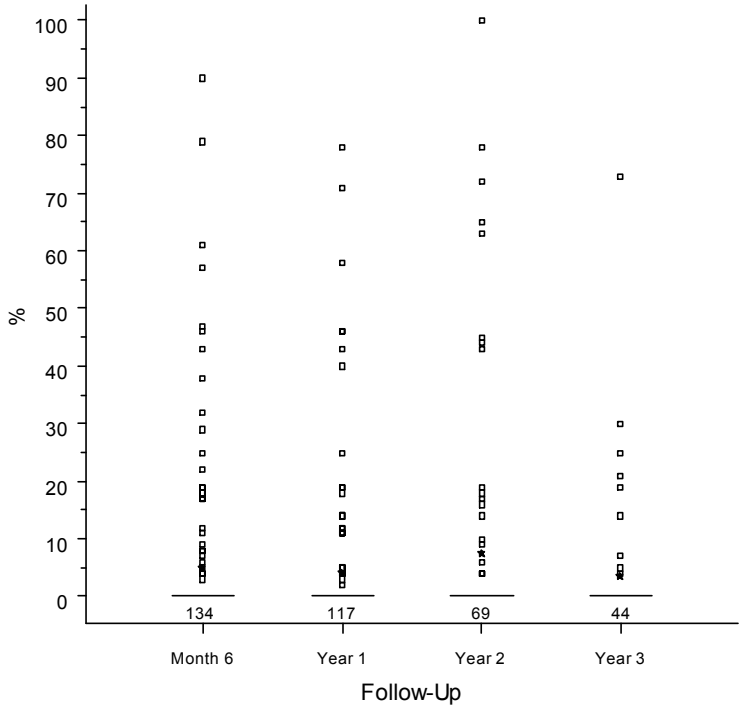


Exhibit 6 – 20
Class I PRA Post Last Infusion
Immunosuppressed Islet Alone Recipients



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Chapter 7
Adverse Events

Adverse Events

All grade 3, 4 and 5 adverse events, according to the Terminology Criteria for Adverse Events (TCAE) of the Clinical Islet Transplantation Consortium (CIT), and all serious adverse events (regardless of grade) are reported to CITR. Respective CITR Principal Investigators currently determine the relationship of the adverse event to the immunosuppression therapy and to the islet infusion procedure at the time adverse event forms are completed.

Exhibit 7-1 presents the adverse event and serious adverse event rate for islet alone and islet after kidney transplant recipients in Year 1 post their first islet infusion. Sixty-four percent of the islet alone recipients experienced at least one adverse event in Year 1, while 46% experienced one or more serious adverse events in this same period. Of the 509 adverse events reported in Year 1 post first infusion for islet alone recipients, 35% were related to the immunosuppression therapy and 33% were related to the infusion procedure. Of the 252 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 28% were related to the immunosuppression therapy and 41% were related to the islet infusion procedure. Exhibits 7-1 and 7-2 display the number of serious adverse events reported and percent of participants with at least one reported serious adverse event in Year 1 post first infusion.

Overall, a total of 440 serious adverse events were reported to the Registry as of datafile closure, with 37% of them classified as life threatening and 51% requiring an inpatient hospitalization (Exhibit 7-4). Sixty five percent (286 of 440) of serious adverse events occurred in the first year following the participants' first infusion procedure. Over 27% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 26% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator. Approximately 87% of the serious adverse events resolved with no residual effects (Exhibit 7-5). Most of the reported serious adverse events were categorized as investigations (18%), gastrointestinal disorders (18%) and blood and lymphatic system disorders (14%) as classified by the MedDRA classifications system (Exhibit 7-6). The most common SAEs reported are summarized in Exhibits 7-7 through 7-10.

A listing of reported neoplasms (N=14) is included in Exhibit 7-11. A listing of reported hemorrhages and portal vein thromboses is included in Exhibit 7-12. Duration of hospitalization for the infusion procedure is presented in Exhibits 7-13 and 7-14 and in Exhibits 7-15 and 7-16 hospitalizations experienced post the recipient's last infusion procedure are tabulated.

Reported Deaths

There have been seven reports of death to the Registry for islet allograft recipients; a viral meningitis attributed death possibly related to the immunosuppressant therapy occurring more than three years following the person's second islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post the person's third infusion, a stroke more than two years post the person's second infusion, another stroke more than three years post the person's only infusion and three deaths due to unknown causes.

Exhibit 7 – 1
Percent of Recipients with an Adverse Event (AE) or Serious Adverse Event (SAE)
in Year 1 Post First Infusion

	Islet Alone (N=279)				Islet After Kidney (N=46)			
	Recipients with an AE		Recipients with an SAE		Recipients with an AE		Recipients with an SAE	
	N	%	N	%	N	%	N	%
Any Event	179	64%	127	46%	24	52%	20	43%
Related to either the infusion procedure or immunosuppression therapy	147	53%	95	34%	19	41%	15	33%
Related to the infusion procedure	93	33%	66	24%	12	26%	9	20%
Related to immunosuppression therapy	97	35%	47	17%	9	20%	8	17%

Exhibit 7-1 represents all adverse events reported to CITR which occurred in the first year following the participant's first infusion procedure. Relationships of the adverse event to the immunosuppression therapy and to the infusion procedure are based on classification of "Probable" or "Definite" by the local CITR Investigator.

Exhibit 7 – 2
Total Number of Adverse Events and Serious Adverse Events
in Year 1 Post First Infusion

	Islet Alone				Islet After Kidney			
	Adverse Events		Serious Adverse Events		Adverse Events		Serious Adverse Events	
	N	%	N	%	N	%	N	%
Total	509	100.0	252	100.0	44	100.0	34	100.0
Related to the infusion procedure	146	28.7	95	37.7	16	36.4	10	29.4
Related to immunosuppression therapy	155	30.5	63	25.0	16	36.4	14	41.2
Related to both the infusion procedure and immunosuppression therapy	23	4.5	8	3.2	-	0.0	-	0.0
Related to neither the infusion procedure nor immunosuppression therapy	185	36.3	86	34.1	12	27.3	10	29.4

Exhibit 7– 3
IA: Incidence of Post-Transplant Adverse Events Related to Infusion Procedure

A. By Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.9	1	0.34	0.01 - 1.91	1	0.34	0.01 - 1.91
2000	10.0	2	0.20	0.02 - 0.72	2	0.20	0.02 - 0.72
2001	27.9	16	0.57	0.33 - 0.93	5	0.18	0.06 - 0.42
2002	72.3	46	0.64	0.47 - 0.85	26	0.36	0.23 - 0.53
2003	115.0	45	0.39	0.29 - 0.52	22	0.19	0.12 - 0.29
2004	120.3	19	0.16	0.10 - 0.25	9	0.07	0.03 - 0.14
2005	144.9	36	0.25	0.17 - 0.34	24	0.17	0.11 - 0.25
2006	148.1	20	0.14	0.08 - 0.21	17	0.11	0.07 - 0.18
2007	81.2	12	0.15	0.08 - 0.26	5	0.06	0.02 - 0.14
01Jan2008-01Apr2008	2.6	0	0.00	0.00 - 1.44	0	0.00	0.00 - 1.44

B. By Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	252.5	178	0.71	0.61 - 0.82	103	0.41	0.33 - 0.49
2	184.5	7	0.04	0.02 - 0.08	3	0.02	0.00 - 0.05
3	124.0	7	0.06	0.02 - 0.12	2	0.02	0.00 - 0.06
4	84.1	3	0.04	0.01 - 0.10	2	0.02	0.00 - 0.09
5	48.0	1	0.02	0.00 - 0.12	0	0.00	0.00 - 0.08
6	18.9	1	0.05	0.00 - 0.29	1	0.05	0.00 - 0.29
7	4.5	0	0.00	0.00 - 0.81	0	0.00	0.00 - 0.81
8	0.3	0	0.00	0.00 - 14.15	0	0.00	0.00 - 14.15

Exhibit 7– 4
IAK: Incidence of Post-Transplant Adverse Events Related to Infusion Procedure

A. By Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	0.6	0	0.00	0.00 - 6.51	0	0.00	0.00 - 6.51
2000	1.6	0	0.00	0.00 - 2.31	0	0.00	0.00 - 2.31
2001	2.1	1	0.48	0.01 - 2.66	1	0.48	0.01 - 2.66
2002	4.6	3	0.66	0.14 - 1.92	0	0.00	0.00 - 0.81
2003	14.2	8	0.57	0.24 - 1.11	5	0.35	0.11 - 0.82
2004	25.2	4	0.16	0.04 - 0.41	1	0.04	0.00 - 0.22
2005	28.9	2	0.07	0.01 - 0.25	2	0.07	0.01 - 0.25
2006	29.2	1	0.03	0.00 - 0.19	0	0.00	0.00 - 0.13
2007	19.0	1	0.05	0.00 - 0.29	1	0.05	0.00 - 0.29
01Jan2008-01Apr2008	1.1	0	0.00	0.00 - 3.34	0	0.00	0.00 - 3.34

B. By Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	38.7	19	0.49	0.30 - 0.77	10	0.26	0.12 - 0.47
2	31.4	0	0.00	0.00 - 0.12	0	0.00	0.00 - 0.12
3	26.9	1	0.04	0.00 - 0.21	0	0.00	0.00 - 0.14
4	18.5	0	0.00	0.00 - 0.20	0	0.00	0.00 - 0.20
5	6.5	0	0.00	0.00 - 0.57	0	0.00	0.00 - 0.57
6	1.2	0	0.00	0.00 - 3.14	0	0.00	0.00 - 3.14
7	1.0	0	0.00	0.00 - 3.69	0	0.00	0.00 - 3.69
8	0.0	0	0.00	0.00 - 185.84	0	0.00	0.00 - 185.84

Exhibit 7– 5
IA: Incidence of Post-Transplant Adverse Events Related to Immunosuppression Therapy
Follow-up based on completed scheduled visits

A. By Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.9	1	0.34	0.01 - 1.91	1	0.34	0.01 - 1.91
2000	10.0	1	0.10	0.00 - 0.55	0	0.00	0.00 - 0.37
2001	27.9	15	0.54	0.30 - 0.89	2	0.07	0.01 - 0.26
2002	72.3	69	0.95	0.74 - 1.21	21	0.29	0.18 - 0.44
2003	115.0	39	0.34	0.24 - 0.46	10	0.09	0.04 - 0.16
2004	120.3	44	0.37	0.27 - 0.49	11	0.09	0.05 - 0.16
2005	144.9	65	0.45	0.35 - 0.57	29	0.20	0.13 - 0.29
2006	148.1	36	0.24	0.17 - 0.34	17	0.11	0.07 - 0.18
2007	81.2	6	0.07	0.03 - 0.16	3	0.04	0.01 - 0.11
01Jan2008-01Apr2008	2.6	0	0.00	0.00 - 1.44	0	0.00	0.00 - 1.44

B. By Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	252.5	219	0.87	0.76 - 0.99	70	0.28	0.22 - 0.35
2	184.5	38	0.21	0.15 - 0.28	12	0.07	0.03 - 0.11
3	124.0	9	0.07	0.03 - 0.14	6	0.05	0.02 - 0.11
4	84.1	5	0.06	0.02 - 0.14	3	0.04	0.01 - 0.10
5	48.0	2	0.04	0.01 - 0.15	1	0.02	0.00 - 0.12
6	18.9	0	0.00	0.00 - 0.19	0	0.00	0.00 - 0.19
7	4.5	0	0.00	0.00 - 0.81	0	0.00	0.00 - 0.81
8	0.3	0	0.00	0.00 - 14.15	0	0.00	0.00 - 14.15

Exhibit 7– 6
Incidence of Post-Transplant at Adverse Events Related to Immunosuppression Therapy
Follow-up based on completed scheduled visits

A. By Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	0.6	0	0.00	0.00 - 6.51	0	0.00	0.00 - 6.51
2000	1.6	0	0.00	0.00 - 2.31	0	0.00	0.00 - 2.31
2001	2.1	0	0.00	0.00 - 1.76	0	0.00	0.00 - 1.76
2002	4.6	3	0.66	0.14 - 1.92	0	0.00	0.00 - 0.81
2003	14.2	4	0.28	0.08 - 0.72	4	0.28	0.08 - 0.72
2004	25.2	12	0.48	0.25 - 0.83	9	0.36	0.16 - 0.68
2005	28.9	4	0.14	0.04 - 0.35	4	0.14	0.04 - 0.35
2006	29.2	2	0.07	0.01 - 0.25	2	0.07	0.01 - 0.25
2007	19.0	0	0.00	0.00 - 0.19	0	0.00	0.00 - 0.19
01Jan2008-01Apr2008	1.1	0	0.00	0.00 - 3.34	0	0.00	0.00 - 3.34

B. By Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	38.7	19	0.49	0.30 - 0.77	14	0.36	0.20 - 0.61
2	31.4	5	0.16	0.05 - 0.37	4	0.13	0.03 - 0.33
3	26.9	1	0.04	0.00 - 0.21	1	0.04	0.00 - 0.21
4	18.5	0	0.00	0.00 - 0.20	0	0.00	0.00 - 0.20
5	6.5	0	0.00	0.00 - 0.57	0	0.00	0.00 - 0.57
6	1.2	0	0.00	0.00 - 3.14	0	0.00	0.00 - 3.14
7	1.0	0	0.00	0.00 - 3.69	0	0.00	0.00 - 3.69
8	0.0	0	0.00	0.00 - 185.8	0	0.00	0.00 - 185.8

Exhibit 7 – 7
Percent of Recipients with a Serious Adverse Event
in Year 1 Post First Infusion by Year of First Infusion
All Allograft Recipients

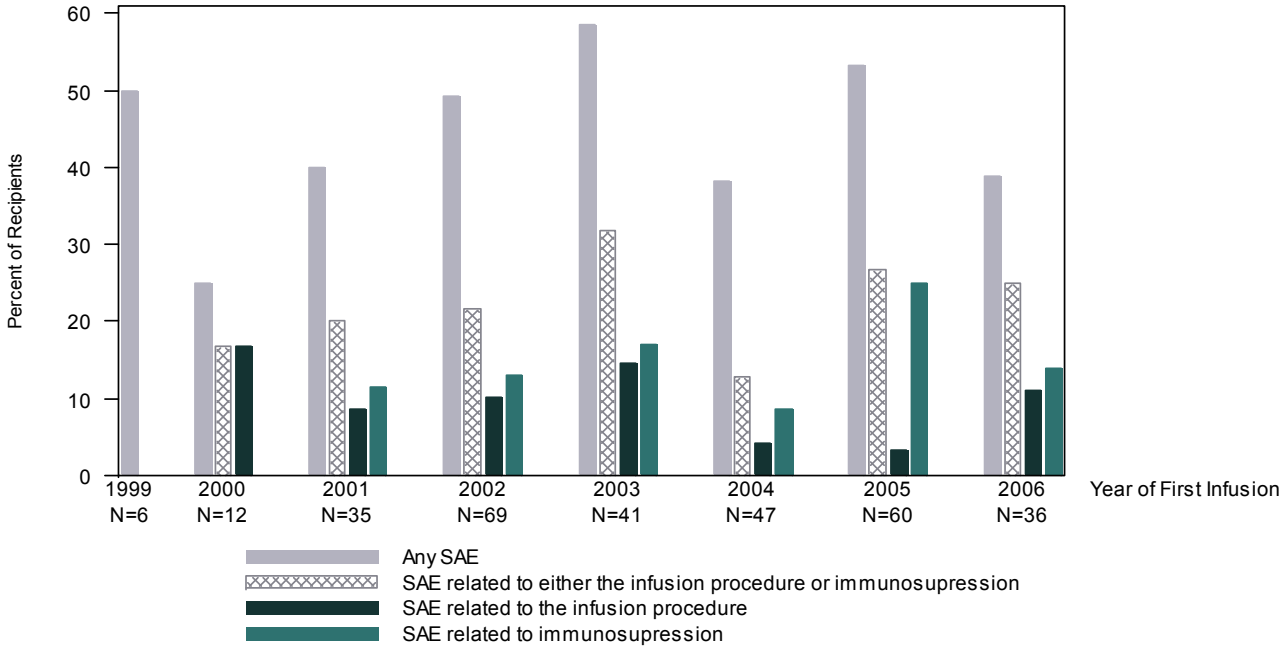

Exhibit 7 – 8
Serious Adverse Event Type by Relatedness to Islet Infusion or Immunosuppression

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	103	100.0	86	100.0	8	100.0	172	100.0	10	100.0	19	100.0	-	0.0	42	100.0	440	100.0
Death*	-	0.0	-	0.0	-	0.0	5	2.8	-	0.0	-	0.0	-	0.0	2	4.8	7	1.6
Life Threatening	53	51.5	39	45.3	5	62.5	42	24.4	5	50.0	8	42.1	-	0.0	9	21.4	161	36.6
Inpatient Hospitalization	21	20.4	41	47.7	2	25.0	115	66.9	1	10.0	12	63.2	-	0.0	31	73.8	223	50.7
Prolongation of Existing Hospitalization	38	36.9	12	14.0	6	75.0	13	7.6	9	90.0	-	0.0	-	0.0	2	4.8	80	18.2
Persistent or Significant Disability/Incapacity**	1	1.0	4	4.7	-	0.0	6	3.5	-	0.0	-	0.0	-	0.0	-	0.0	11	2.5
Congenital Anomaly/Birth Defect	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Required intervention to prevent permanent damage	4	3.9	10	11.6	1	12.5	14	8.1	1	10.0	-	0.0	-	0.0	9	21.4	39	8.9

Serious adverse event categories are not mutually exclusive.
*See page 197 for summary of reported deaths.
**The event related to the infusion procedure was a portal vein thrombosis requiring continued anticoagulation. The four events related to immunosuppression therapy were a tongue ulceration, memory deficit, tacrolimus induced neurotoxicity, and diarrhea. All four events have since resolved with no residual side effects.

Of the 440 serious adverse events, 286 (65%) occurred in the first year following their first infusion procedure. Relationships to immunosuppression therapy and to the infusion procedure are based on classification of “Probable” or “Definite” by the local CITR Investigator.

Exhibit 7 – 9
Outcome of Serious Adverse Events by Relatedness to Islet Infusion or Immunosuppression

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	103	100.0	86	100.0	8	100.0	172	100.0	10	100.0	19	100.0	-	-	42	100.0	440	100.0
Outcome of Serious Adverse Event																		
Resolved with No Residual Effects	102	99.0	74	86.0	7	87.5	148	86.0	9	90.0	16	84.2	-	-	27	64.3	383	87.0
Resolved with Sequelae*	-	0.0	6	7.0	1	12.5	9	5.2	-	0.0	2	10.5	-	-	5	11.9	23	5.2
Persistent Condition, Recipient Alive**	1	1.0	6	7.0	-	0.0	10	5.8	1	10.0	1	5.3	-	-	8	19.0	27	6.1
Death caused by Adverse Event***	-	0.0	-	0.0	-	0.0	5	2.9	-	0.0	-	0.0	-	-	2	4.8	7	1.6

*Events related to the protocol include: two hospitalizations for kidney rejection in one participant, four hospitalizations due to complications associated with ovarian cyst removal and heavy menstrual bleeding in one patient resulting in a total abdominal hysterectomy, two myonecrosis episodes in one patient, and acute mononucleosis resulting in graft loss.
**Events related to the protocol include: neutropenia, diarrhea, lymphopenia, hematoma and portal vein thrombosis.
***See page 197 for summary of reported deaths.

Relationships to immunosuppression therapy and to the infusion procedure are based on classification of “Probable” or “Definite” by the local CITR Investigator.

Exhibit 7 – 10
Serious Adverse Events MedDRA System/Organ Class
by Relatedness to Islet Infusion or Immunosuppression

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	103	100.0	86	100.0	8	100.0	172	100.0	10	100.0	19	100.0	-	-	42	100.0	440	100.0
System Organ Class*																		
Blood and lymphatic system disorders	3	2.9	41	47.7	3	37.5	8	4.7	-	0.0	8	42.1	-	-	1	2.4	64	14.5
Cardiac disorders	-	0.0	-	0.0	-	0.0	2	1.2	-	0.0	-	0.0	-	-	1	2.4	3	0.7
Eye disorders	-	0.0	-	0.0	-	0.0	3	1.7	-	0.0	-	0.0	-	-	2	4.8	5	1.1
Gastrointestinal disorders	18	17.5	12	14.0	1	12.5	38	22.1	1	10.0	3	15.8	-	-	5	11.9	78	17.7
General disorders and administration site conditions	1	1.0	1	1.2	-	0.0	14	8.1	-	0.0	1	5.3	-	-	2	4.8	19	4.3
Hepatobiliary disorders	11	10.7	-	0.0	-	0.0	7	4.1	2	20.0	-	0.0	-	-	1	2.4	21	4.8
Immune system disorders	-	0.0	-	0.0	-	0.0	1	0.6	-	0.0	2	10.5	-	-	-	0.0	3	0.7
Infections and infestations	2	1.9	12	14.0	1	12.5	22	12.8	-	0.0	4	21.1	-	-	8	19.0	49	11.1
Injury, poisoning and procedural complications	14	13.6	1	1.2	-	0.0	5	2.9	2	20.0	-	0.0	-	-	2	4.8	24	5.5
Investigations**	50	48.5	5	5.8	3	37.5	11	6.4	1	10.0	1	5.3	-	-	6	14.3	77	17.5
Metabolism and nutrition disorders	1	1.0	1	1.2	-	0.0	24	14.0	-	0.0	-	0.0	-	-	1	2.4	27	6.1

Exhibit 7 – 10 *(continued)*
Serious Adverse Events MedDRA System/Organ Class
by Relatedness to Islet Infusion or Immunosuppression

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Musculoskeletal and connective tissue disorders	-	0.0	1	1.2	-	0.0	4	2.3	-	0.0	-	0.0	-	-	5	11.9	10	2.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	0.0	1	1.2	-	0.0	6	3.5	-	0.0	-	0.0	-	-	1	2.4	8	1.8
Nervous system disorders	-	0.0	1	1.2	-	0.0	5	2.9	-	0.0	-	0.0	-	-	1	2.4	7	1.6
Psychiatric disorders	-	0.0	1	1.2	-	0.0	4	2.3	-	0.0	-	0.0	-	-	-	0.0	5	1.1
Renal and urinary disorders	-	0.0	3	3.5	-	0.0	3	1.7	-	0.0	-	0.0	-	-	1	2.4	7	1.6
Reproductive system and breast disorders	-	0.0	4	4.7	-	0.0	3	1.7	-	0.0	-	0.0	-	-	-	0.0	7	1.6
Respiratory, thoracic and mediastinal disorders	-	0.0	-	0.0	-	0.0	5	2.9	1	10.0	-	0.0	-	-	4	9.5	10	2.3
Surgical and medical procedures	-	0.0	2	2.3	-	0.0	5	2.9	-	0.0	-	0.0	-	-	1	2.4	8	1.8
Vascular disorders	3	2.9	-	0.0	-	0.0	2	1.2	3	30.0	-	0.0	-	-	-	0.0	8	1.8

*MedDRA Classification (http://www.meddramsso.com/newweb2003/index.htm).
**MedDRA system organ class designation for lab procedures and test results. For example, elevated liver function tests are included in this category.

Relationships to immunosuppression therapy and to the infusion procedure are based on classification of “Probable” or “Definite” by the local CITR Investigator.

Exhibit 7 – 11
Most Common Serious Adverse Events
MedDRA Preferred Term
Islet Alone Recipients

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	103	100.0	86	100.0	8	100.0	171	100.0	368	100.0
Elevated Liver Function Tests*	49	47.6	0	0.0	3	37.5	8	4.7	60	16.3
Neutropenia	2	1.9	27	31.4	0	0.0	5	2.9	34	9.2
Hypoglycaemia	1	1.0	0	0.0	0	0.0	18	10.5	19	5.2
Hemorrhage**	16	15.5	0	0.0	1	12.5	0	0.0	17	4.6
Abdominal pain	4	3.9	1	1.2	0	0.0	11	6.4	16	4.3
Anaemia	1	1.0	3	3.5	2	25.0	4	2.3	10	2.7
Diarrhoea	0	0.0	5	5.8	0	0.0	5	2.9	10	2.7
Vomiting	0	0.0	2	2.3	0	0.0	6	3.5	8	2.2
Pneumonia	0	0.0	3	3.5	0	0.0	4	2.3	7	1.9
Portal vein thrombosis	7	6.8	0	0.0	0	0.0	0	0.0	7	1.9
Infection	0	0.0	1	1.2	0	0.0	5	2.9	6	1.6
Lymphopenia	0	0.0	5	5.8	0	0.0	0	0.0	5	1.4
Ovarian cyst	0	0.0	3	3.5	0	0.0	2	1.2	5	1.4
Pyrexia	0	0.0	1	1.2	0	0.0	4	2.3	5	1.4
Cholecystitis	0	0.0	0	0.0	0	0.0	4	2.3	4	1.1
Leukopenia	0	0.0	3	3.5	1	12.5	0	0.0	4	1.1
Ascites	2	1.9	1	1.2	0	0.0	0	0.0	3	0.8

*Elevated Liver Function Tests include elevations in aspartate aminotransferase, alanine aminotransferase, and blood alkaline phosphatase.
**Hemorrhage includes peritoneal, intra-abdominal, hepatic, operative, and post procedural hemorrhage.

Relationships to immunosuppression therapy and to the infusion procedure are based on classification of “Probable” or “Definite” by the local CITR Investigator.

Exhibit 7 – 12
Most Common Serious Adverse Events
MedDRA Preferred Term
Islet After Kidney Recipients

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	10	100.0	19	100.0	0	-	41	100.0	70	100.0
Neutropenia	0	0.0	8	42.1	0	-	0	0.0	8	11.4
Trigger finger	0	0.0	0	0.0	0	-	5	12.2	5	7.1
Blood creatinine increased	0	0.0	1	5.3	0	-	3	7.3	4	5.7
Pneumonia	0	0.0	2	10.5	0	-	1	2.4	3	4.3
Bronchopneumonia	0	0.0	0	0.0	0	-	2	4.9	2	2.9
Colitis	0	0.0	0	0.0	0	-	2	4.9	2	2.9
Diarrhoea	0	0.0	1	5.3	0	-	1	2.4	2	2.9
Haemoglobin decreased	1	10.0	0	0.0	0	-	1	2.4	2	2.9
Haemorrhage	2	20.0	0	0.0	0	-	0	0.0	2	2.9
Kidney transplant rejection	0	0.0	2	10.5	0	-	0	0.0	2	2.9

Exhibit 7 – 13
Most Common Serious Adverse Events Reported
Within One Year of Any Infusion
MedDRA Preferred Term
All Allograft Recipients

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	112	100.0	86	100.0	8	100.0	132	100.0	338	100.0
Elevated Liver Function Tests*	48	42.9	0	0.0	3	37.5	8	6.1	59	17.5
Neutropenia	2	1.8	28	32.6	0	0.0	5	3.8	35	10.4
Hemorrhage**	21	18.8	0	0.0	1	12.5	0	0.0	22	6.5
Abdominal pain	4	3.6	1	1.2	0	0.0	10	7.6	15	4.4
Anaemia	1	0.9	3	3.5	2	25.0	3	2.3	9	2.7
Hypoglycaemia	1	0.9	0	0.0	0	0.0	8	6.1	9	2.7
Pneumonia	0	0.0	5	5.8	0	0.0	4	3.0	9	2.7
Diarrhoea	0	0.0	4	4.7	0	0.0	4	3.0	8	2.4
Portal vein thrombosis	8	7.1	0	0.0	0	0.0	0	0.0	8	2.4
Vomiting	0	0.0	1	1.2	0	0.0	5	3.8	6	1.8
Cholecystitis	0	0.0	0	0.0	0	0.0	5	3.8	5	1.5
Lymphopenia	0	0.0	5	5.8	0	0.0	0	0.0	5	1.5
Trigger finger	0	0.0	0	0.0	0	0.0	5	3.8	5	1.5
Leukopenia	0	0.0	3	3.5	1	12.5	0	0.0	4	1.2
Mucositis/Stomatitis***	0	0.0	3	3.5	0	0.0	1	0.8	4	1.2
Ovarian cyst	0	0.0	3	3.5	0	0.0	1	0.8	4	1.2

*Elevated Liver Function Tests include elevations in aspartate aminotransferase, alanine aminotransferase, and blood alkaline phosphatase.
**Hemorrhage includes peritoneal, intra-abdominal, hepatic, operative, and post procedural hemorrhage.
***Mucositis/Stomatitis includes mouth ulceration, tongue ulceration and Stomatitis.

Exhibit 7 – 14
Most Common Serious Adverse Events Reported
More than One Year after Any Infusion
MedDRA Preferred Term
All Allograft Recipients

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	1	100.0	19	100.0	0	-	80	100.0	100	100.0
Hypoglycaemia	0	0.0	0	0.0	0	-	10	12.5	10	10.0
Neutropenia	0	0.0	7	36.8	0	-	0	0.0	7	7.0
Blood creatinine increased	0	0.0	1	5.3	0	-	3	3.8	4	4.0
Diarrhoea	0	0.0	2	10.5	0	-	2	2.5	4	4.0
Infection	0	0.0	1	5.3	0	-	3	3.8	4	4.0
Vomiting	0	0.0	1	5.3	0	-	2	2.5	3	3.0
Abdominal pain	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Anaemia	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Bronchopneumonia	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Chest pain	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Colitis	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Death	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Dehydration	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Hyperglycaemia	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Osteoarthritis	0	0.0	0	0.0	0	-	2	2.5	2	2.0
Pyrexia	0	0.0	0	0.0	0	-	2	2.5	2	2.0

Exhibit 7 – 15
Summary of Reported Neoplasms

Reported Neoplasm	Timing	Relation to Islet Infusion Procedure	Relation to Immuno-suppression Therapy	Outcome of Event / Narrative
Ovarian Cysts	2 months post 3rd infusion	Unlikely	Probable	Participant with a personal and family history of ovarian cysts diagnosed with ovarian hyperstimulation syndrome. Several surgeries performed to remove bilateral cysts and an endometrial polyp. Persistent heavy menses resulted in a total abdominal hysterectomy. Participant continued on immunosuppression through 16 months post hysterectomy with no additional events.
Right Ovarian Mucinous Cystadenoma	1 day post 1st infusion	Unrelated	Unrelated	Resolved, no residual effects. Mass was diagnosed at time of first infusion. Removal of adnexal mass and bilateral oopherectomy performed. Immunosuppression continued through five years post event with no residual effects.
Basal Cell Carcinoma	13 months post 2nd infusion	Unrelated	Possible	Resolved, no residual effects. Skin lesion removed from lower leg. Immunosuppression continued for over two years with no residual effects at which time graft failure occurred and immunosuppression was discontinued.
Basal Cell Carcinoma	37 months post 2nd infusion	Unrelated	Probable	Resolved, no residual effects. Skin lesion removed from nose. Immunosuppression continued over one year post event with no additional events.
Metastatic Breast Cancer	16 months post 3rd Infusion	Possible	Possible	Resolved, with sequelae. Invasive focal lobular carcinoma in situ diagnosed on routine screening 16 months post third infusion. Bilateral section performed participant continued immunosuppression. One month later, metastatic carcinoma of lymph nodes identified followed by section and chemotherapy. Participant decided to leave study due to chemotherapy. Immunosuppression was tapered.
Squamous cell carcinoma of skin	17 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Skin lesion removed from back. Immunosuppression was continued for another 8 months. No further follow-up available.
Squamous cell carcinoma of skin	20 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Immunosuppression was continued for one month until participant withdrew from the trial. Subsequent two years of follow-up indicate no residual effects.

Exhibit 7 – 15 *(continued)*
Summary of Reported Neoplasms

Squamous cell carcinoma of skin	21 months days post 1st Infusion	Unrelated	Probable	Resolved, no residual effects. Immunosuppression continued. Eighteen months later, participant diagnosed with skin basal cell carcinoma. Immunosuppression continued through an additional 18 months with no residual effects.
Squamous cell carcinoma of skin	43 months post 2nd infusion	Unrelated	Possible	Resolved, no residual effects. Skin lesion removed from cheek. Immunosuppression continued at a modified dose through 3 months post event with no additional events.
Squamous cell carcinoma of skin	6 months post 2nd infusion	Missing	Missing	Missing
Squamous cell carcinoma of skin	60 months post 2nd infusion	Unlikely	Possible	Skin cancer removed from chest. Immunosuppression continued.
Pulmonary nodules	25 months post 2nd infusion	Unrelated	Possible	Bronchoscopy cultures indicated a myobacterial infection. Increased lesions two months later required thorasoscopic surgery. Persistent condition four months post surgery. IAK recipient remains on steroid immunosuppression.
Papillary thyroid cancer	22 months post 2nd Infusion	Unrelated	Probable	Malignancy removed with total thyroidectomy. No follow-up data has been reported following the surgery.
Papillary carcinoma	2 months post 1st infusion	Possible	Possible	Resolved with sequelae. Nodule diagnosed 2 months post infusion. Thyroidectomy performed, immunosuppression continued. Partial thyroidectomy performed about 17 years earlier for adenoma. No residual effects 4 months post thyroidectomy.

Exhibit 7 – 16
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosuppression Therapy	Treatment Required	Outcome of Event
Portal vein thrombosis	2000	1 day post 2nd infusion	Inpatient hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2001	0 days post 1st Infusion	Life threatening + Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2001	0 days post 2nd Infusion	Life threatening + Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Portal vein thrombosis	2001	0 days post 3rd Infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Intra-abdominal haemorrhage	2002	0 days post 1st Infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Intra-abdominal haemorrhage	2002	0 days post 2nd Infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2002	0 days post 1st Infusion	Missing	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2002	2 days post 2nd Infusion	Prolongation of existing hospitalization	Definite	Probable	No treatment or modification of treatment required for AE	Resolved, no residual effects
Portal vein thrombosis	2002	1 day post 1st infusion	Prolongation of existing hospitalization	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 7 – 16 *(continued)*
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosuppression Therapy	Treatment Required	Outcome of Event
Post procedural haemorrhage	2002	0 days post 2nd Infusion	Life threatening + Prolongation of existing hospitalization	Definite	Possible	Required additional treatment for AE	Resolved, no residual effects
Haemorrhage	2003	1 day post 2nd infusion	Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Operative haemorrhage	2003	0 days post 1st Infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Operative haemorrhage	2003	0 days post 2nd Infusion	Prolongation of existing hospitalization	Definite	Unrelated	Current treatment modified based on AE	Resolved, no residual effects
Peritoneal haemorrhage	2003	0 days post 2nd Infusion	Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2003	1 day post 2nd infusion	Prolongation of existing hospitalization	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Peritoneal haemorrhage	2003	1 day post 2nd infusion	Prolongation of existing hospitalization	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Peritoneal haemorrhage	2003	1 day post 3rd infusion	Prolongation of existing hospitalization	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 7 – 16 *(continued)*
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosuppression Therapy	Treatment Required	Outcome of Event
Portal vein thrombosis	2003	5 days post 1st Infusion	Persistent or significant disability/incapacity	Definite	Unrelated	Required additional treatment for AE	Persistent Condition, Recipient Alive
Portal vein thrombosis	2003	6 days post 3rd Infusion	Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Portal vein thrombosis	2003	7 days post 2nd Infusion	Life threatening	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Post procedural haemorrhage	2003	0 days post 2nd Infusion	Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Post procedural haemorrhage	2003	1 day post 1st infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Portal vein thrombosis	2004	35 days post 1st Infusion	Inpatient hospitalization	Definite	Unrelated	Required additional treatment for AE	Persistent Condition, Recipient Alive
Post procedural haemorrhage	2004	1 day post 2nd infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects

Exhibit 7 – 16 *(continued)*
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Haemorrhage	2005	0 days post 1st Infusion	Inpatient hospitalization	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Hepatic haemorrhage	2005	1 day post 1st infusion	Life threatening + Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Portal vein thrombosis	2005	1 day post 1st infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Post procedural haemorrhage	2005	0 days post 1st Infusion	Life threatening + Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Post procedural haemorrhage	2006	1 day post 1st infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Persistent Condition, Recipient Alive
Haemorrhage	2007	2 days post 2nd Infusion	Life threatening + Prolongation of existing hospitalization + Required intervention to prevent permanent damage	Definite	Unlikely	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Peritoneal haemorrhage	2007	0 days post 1st Infusion	Prolongation of existing hospitalization	Definite	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 7 – 17
Number of Days Hospitalized at Infusion (from Admission to Discharge)
by Infusion Sequence
Islet Alone Recipients

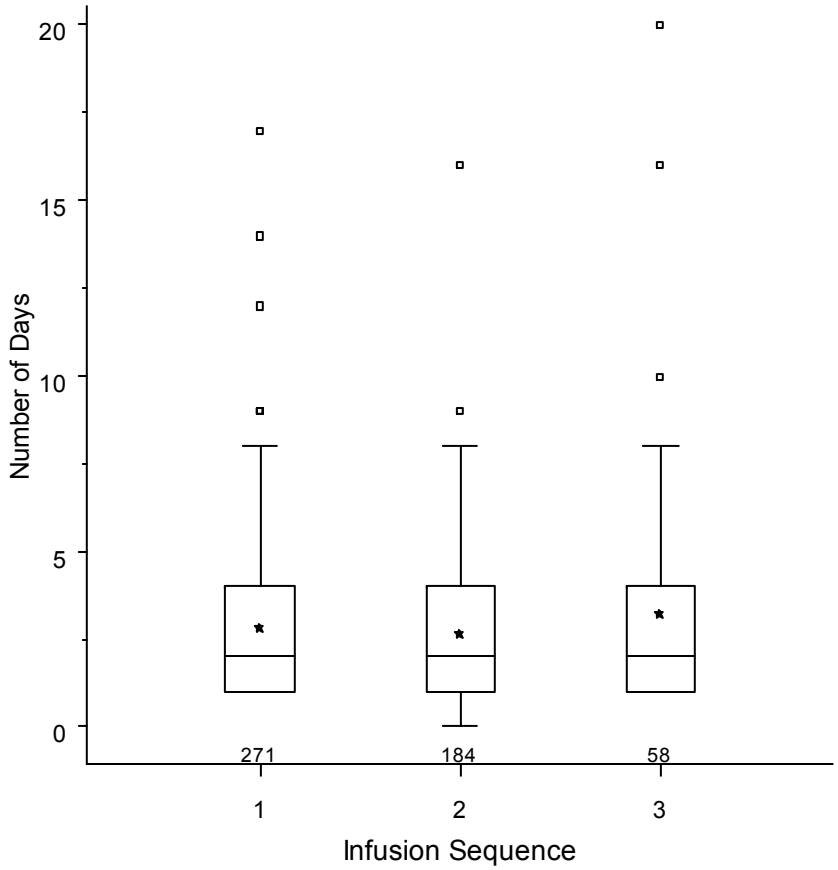

Exhibit 7 – 18
Number of Days Hospitalized at Infusion (from Admission to Discharge)
by Infusion Sequence
Islet After Kidney Recipients

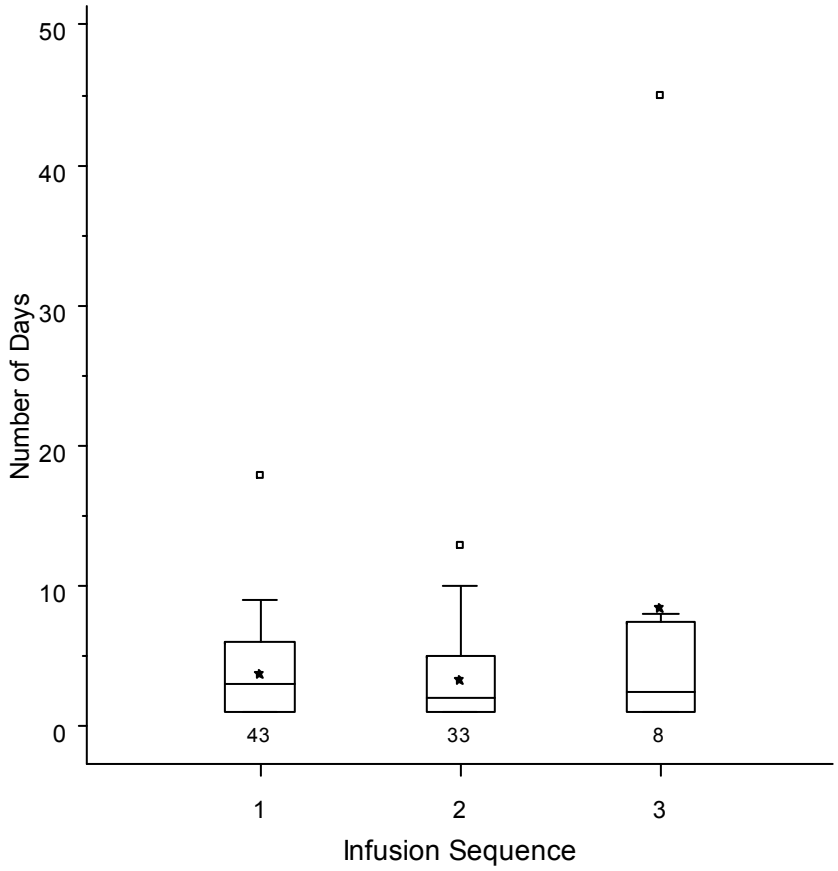

Exhibit 7 – 19
Hospitalization Experienced Post Last Infusion by Total Number of Infusions Received
Islet Alone Recipients

	Total Infusions Received																							
	1								2								3							
	Follow-Up								Follow-Up								Follow-Up							
	Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	46	100.0	41	100.0	22	100.0	15	100.0	111	100.0	98	100.0	60	100.0	37	100.0	48	100.0	45	100.0	29	100.0	15	100.0
Participants Requiring at Least One Hospitalization	8	17.4	2	4.9	6	27.3	1	6.7	23	20.7	17	17.3	5	8.3	4	10.8	5	10.4	9	20.0	3	10.3	4	26.7
Number of Hospitalizations																								
1	5	10.9	1	2.4	4	18.2	1	6.7	17	15.3	15	15.3	4	6.7	4	10.8	5	10.4	8	17.8	2	6.9	4	26.7
2	2	4.3	0	0	2	9.1	0	0	5	4.5	1	1.0	1	1.7	0	0	0	0	1	2.2	0	0	0	0
3	1	2.2	1	2.4	0	0	0	0	1	0.9	1	1.0	0	0	0	0	0	0	0	0	0	0	0	0
4	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	3.4	0	0

Exhibit 7 – 20
Hospitalization Experienced Post Last Infusion by Total Number of Infusions Received
Islet After Kidney Recipients

	Total Infusions Received																							
	1								2								3							
	Follow-Up								Follow-Up								Follow-Up							
	Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	6	100.0	4	100.0	2	100.0	1	100.0	21	100.0	20	100.0	18	100.0	13	100.0	6	100.0	6	100.0	3	100.0	3	100.0
Participants Requiring at Least One Hospitalization	2	33.3	0	0	0	0	1	100.0	7	33.3	4	20.0	5	27.8	2	15.4	2	33.3	1	16.7	0	0	0	0
Number of Hospitalizations																								
1	1	16.7	0	0	0	0	1	100.0	4	19.0	2	10.0	5	27.8	1	7.7	2	33.3	1	16.7	0	0	0	0
2	1	16.7	0	0	0	0	0	0	2	9.5	1	5.0	0	0	1	7.7	0	0	0	0	0	0	0	0
3	0	0	0	0	0	0	0	0	1	4.8	1	5.0	0	0	0	0	0	0	0	0	0	0	0	0

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Chapter 8
Registry Data Quality Review

Registry Data Quality Review

Data quality and assurance is an integral component of the Registry. Each islet transplant program that joins CITR and wishes to contribute data completes an application process that assures their compliance with current Good Clinical Practices (cGCP) and data integrity. In addition, each islet transplant center enters into an agreement with the CITR Coordinating Center indicating that they will submit data in a timely manner and respond to all queries and discrepancy reports. All centers are visited and trained periodically by CITR Coordinating Center staff. This training includes an initial detailed review of data collection forms, definitions, and CITR standards as well as timely and periodic training updates. Initial and continued training in data entry and navigation of the Internet based data collection system is conducted and monitored frequently.

Real time quality control and assurance programs and reports are implemented during data entry and monthly reports are generated and reviewed by the participating islet transplant centers. Each North American center is audited on-site with respect to their source documentation after three islet transplant recipients are entered in the CITR database. Subsequent data audits occur after an additional 10 recipients are registered or at the discretion of the Coordinating Center if less than 10 new recipients are registered.

Included in Chapter 8 are summaries of the data collected and reported on for this Annual Report. Exhibit 8-1 is a summarization for all 325 participants and the number of CITR required forms that were submitted to the CITR Coordinating Center by the time of the final data lock on April 1, 2008. This summarization is separated by infusion sequence (1, 2 or 3) and an overall summary is provided. The form submission rate of 100% for Infusion Forms is due to the fact that this was one of the criteria for closing the Annual Report analysis database (the participant had to have at least one Infusion Form submitted to be included in the analysis database).

Form submission for follow-up post the participant's first infusion procedure ranged from 88% at Month 6 to 77% at Year 1. Post the participant's last infusion procedure rates are similar for Month 6 (83%) and Year 1 (76%). However, the submitted forms for Year 2 drops to 62%, to 51% in Year 3, 47% in Year 4, and 34% in Year 5 (Exhibit 8-2). The low submission rates for Years 2-5 are due in large part to difficulties obtaining information from participants who have completed their protocol and are no longer returning to their transplant center.

A complete review of all local islet transplant protocols and patients were conducted to verify that all patients were approached to join the Registry and that there was not selective registration of participants for CITR. Source documents were reviewed and compared with data entered in the CITR database. Queries generated from the reviews included potential conflicts between source documentation and the CITR database, as well as errors that were identified on-site with data entry. In addition, the Registry sponsor reviews all audit reports.

Exhibit 8 – 1
Expected and Submitted Forms by Infusion Sequence

A) Islet Alone Recipients

	Infusion Sequence									Overall		
	1			2			3					
	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent
Deceased Donor Forms	311	307	99%	213	212	100%	73	72	99%	597	591	99%
Islet Processing Forms	311	305	98%	213	212	100%	73	72	99%	597	589	99%
Pre Infusion Forms	279	277	99%	202	191	95%	65	62	95%	546	530	97%
Pre Infusion Lab Forms	279	275	99%	202	191	95%	65	62	95%	546	528	97%
Infusion Forms	279	279	100%	202	202	100%	65	65	100%	546	546	100%
Induction Therapy Forms	279	272	97%	202	188	93%	65	61	94%	546	521	95%

Exhibit 8 – 1
Expected and Submitted Forms by Infusion Sequence
B) Islet After Kidney Recipients

	Infusion Sequence									Overall		
	1			2			3					
	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent
Deceased Donor Forms	55	55	100%	41	41	100%	12	12	100%	108	108	100%
Islet Processing Forms	55	54	98%	41	40	98%	12	12	100%	108	106	98%
Pre Infusion Forms	46	45	98%	39	35	90%	12	11	92%	97	91	94%
Pre Infusion Lab Forms	46	46	100%	39	36	92%	12	12	100%	97	94	97%
Infusion Forms	46	46	100%	39	39	100%	12	12	100%	97	97	100%
Induction Therapy Forms	46	46	100%	39	36	92%	12	12	100%	97	94	97%

Exhibit 8 – 2
Expected and Submitted Follow-Up Forms Post Last infusion
All Allograft Recipients

		Expected	Submitted	Percent Submitted	Lost to Follow up	Data not available	Missing Forms	Percent Missing
Post First Infusion	**Month 6**	324	284	88%	6	1	33	10%
	Year 1	313	242	77%	12	0	59	19%
Post Last Infusion	**Month 6**	313	259	83%	7	2	45	14%
	Year 1	300	229	76%	18	5	48	16%
	Year 2	255	157	62%	34	16	48	19%
	Year 3	191	98	51%	44	10	39	20%
	Year 4	137	64	47%	38	6	29	21%
	Year 5	91	31	34%	31	5	24	26%

Exhibit 8 – 3
Extent of Follow-Up Post Last Infusion
All Allograft Recipients

	Months Post Last Infusion					
	N	**Mean**	**Std**	**Median**	**Min**	**Max**
Extent of Participant Follow Up	325	23.7	19.9	23.4	1.0	84.0
Extent of Insulin Log Completion	325	26.7	22.2	24.0	0.0	106.3
Participants Lost to Follow Up	62	20.0	13.9	17.3	1.5	64.3

Appendix A: Islet Transplant Center Contributors

(Centers and Staff are listed in alphabetical order)

Baylor College of Medicine/ The Methodist Hospital
Houston, Texas, USA
PI: John A. Goss
Cheryl Durkop
Tiffany Zgabay

Baylor Regional Transplant Institute
Dallas, Texas, USA
PI: Marlon Levy
Darrell Grimes
Bashoo Naziruddin
Lori Otken
Kerri Purcell

Benaroya Research Institute
Seattle, Washington, USA
PI: Carla Greenbaum
Marli McCulloch-Olson
Marilyn Reeve

Carolinas Medical Center
Charlotte, North Carolina, USA
PI: Paul Gores
Melissa McGraw

Center for Islet Transplantation at Harvard Medical School
Boston, Massachusetts, USA
PI: Enrico Cagliero

Columbia University
New York, New York, USA
PI: Mark A. Hardy
Joan Kelly
Zhuoru Liu
Piotr Witkowski

Emory Transplant Center
Atlanta, Georgia, USA
PI: Mark Rigby
Jenny Joseph
Elizabeth Holbrook
Marti Sears

GenevaGRAGIL Network
Geneva, Switzerland
PI: Thierry Berney
Elsa Boely
Sandrine Demuylder-Mischler

Mayo Clinic
Rochester, Minnesota, USA
PI: Yogish Kudva
Jarrett Anderson
LeAnn Batterson
Deborah Dicke-Henslin
Jane Fasbender
Michelle Kreps

NIH Clinical Transplant Center
Bethesda, Maryland, USA
PI: David Harlan
Eric Liu
Pat Swanson

Lille University Hospital
Lille Cedex, France
PI: Francois Pattou
Rimed Ezzouaoui
Valery Gmyr
Julie Kerr-Conte
Violeta Raverdy
Marie Christine Vantyghem

Northwestern University
Chicago, Illinois, USA
PI: Dixon Kaufman
Patrice Al-Saden
Angela Hecyk
Elyse Stuart

Scripps Health
La Jolla, California, USA
PI: Christopher Marsh
Denadra Holland
Jonathan Fisher
Amy Knight
Lynn Dee Knight
Jaime Rullman
Daniel Salomon

Southern California Islet Consortium (SCIC)
Duarte, California, USA
PI: Fouad Kandeel
Jeannette Hacker
Lisa Johnson
Jeffrey Longmate
Aria Miller
Keiko Omori
KD Shiang

Swedish Medical Center
Seattle, Washington, USA
PI: William Marks
Terri Baker

Toronto General Hospital
Toronto, Ontario, CANADA
PI: Mark Cattral
Dianne Donat
Mark Heslegrave
Gary Levy
Meerna Nsouli
Jill Sheedy
Elizabeth Wright

The University of Tennessee, Memphis
Memphis, Tennessee, USA
PI: A. Osama Gaber
Barbara Culbreath

UMass Memorial Hospital
Worcester, Massachusetts, USA
PI: Aldo Rossini
Celia Hartigan

University of Alabama
Birmingham, Alabama, USA
PI: Juan Luis Contreras
Deborah Seale
Patricia Wilson

University of Alberta
Edmonton, Alberta, CANADA
PI: A. M. James Shapiro
Co-PI: Peter Senior
Parastoo Dinyari
Tatsuya Kin
Janet Wright

University of California, San Francisco
San Francisco, California, USA
PI: Peter Stock
Co-PI: Andrew Posselt
Jeffrey Bluestone
Charlotte Garwood
Kristina Johnson
Joan McElroy
Debbie Ramos
Tara Rojas
Greg Szot
Mehdi Tavakol
Michael Worden

University of Chicago
Chicago, Illinois, USA
PI: Marc Garfinkel
Matthew Connors
Mark Lockwood
Melissa Roberts
Monalee Shah
Kathleen Singraber

University of Colorado Health Sciences Center
Auora, Colorado, USA
PI: Alexander Wiseman
Meyer Belzer
Betsy Britz
Susan George
Ron Gill
Heather Sours
Antony Valentine

Appendix A: Islet Transplant Center Contributors *(continued)*

(Centers and Staff are listed in alphabetical order)

University of Illinois, Chicago

Chicago, Illinois, USA

PI: Jose Oberholzer
Co-PI: Enrico Benedetti
Co-PI: James Bui
Co-PI: Charles Owens
Barbara Barbaro
Leelamma George
Martha Gracia-Knuttinen
Michael Hansen
Bruce Kaplan
Joan Martellotto
Pablo Pallan
Merigeng Qi
Travis Romagnoli
Elaine Shestokas
Shusen Wang

University of Miami

Miami, Florida, USA

PI: Rodolfo Alejandro
Co-PI: Camillo Ricordi
David Baidal
Pablo Cure
Tatiana Froud
Maricruz Silva-Ramos

University of Minnesota

Minneapolis, Minnesota, USA

PI: Bernhard J. Hering
Barbara Bland
Dan Fraga
Robin Jevne
Anne Nettles
Jamen Parkey
David Radosevich
Sandra White

University of Nebraska

Omaha, Nebraska, USA

PI: R. Brian Stevens
Kristi DeHaai
Suzanne Miller

University of Pennsylvania

Philadelphia, Pennsylvania, USA

PI: Ali Naji
Chenyang Lu
Eileen M. Markmann
Diane McLaughlin
Maral Palanjian

University of Virginia

Charlottesville, Virginia, USA

Kenneth Brayman, PI
John Angle
Donna Broshek
Jason Freeman
Courtney Garbee
Klaus Hagspiel
Boris Kovatchev
Anthony McCall
Claire McKinley
Timothy Pruett
Robert Sawyer
Timothy Schmitt

University of Wisconsin

Madison, Wisconsin, USA

PI: Matthew Hanson
Luis Fernandez
Janice Kalvin
Jon Odorico
Nancy Radke
Kristi Schneider
Larry Westby

Virginia Commonwealth University

Richmond, Virginia, USA

PI: Adrian Cotterell
Martha Behnke
Melissa Thompson
Donna Winborne

Washington University, St. Louis

St. Louis, Missouri, USA

PI: Niraj Desai
Mona Awan
Heather Robertson

CITR Coordinating Center

PI: Franca Benedicty Barton

Donald Stablein
Steve Wease
Yamini Damodharan
Christina Mandzuk
Andrew Heitman
RuthDanoff
Jodi DeStefano
Krista Huang

CITR Committees *(Members are listed in alphabetical order)*

Scientific Advisory Committee (SAC)

Chair: Bernhard J. Hering
Michael Appel
Franca Benedicty Barton
Michael Cecka
Philip E. Cryer
Olle Korsgren
Maureen McBride
Jerry P. Palmer
Camillo Ricordi
Gordon Weir

Publications/Presentations Committee
(2008)

Chair: Rodolfo Alejandro
Michael Appel
Nancy Bridges
Shari Messinger Cayetano
Brian Flanagan
Elizabeth Holbrook
Robert Ketchum
Bashoo Naziruddin
Craig Smith

Compliance Committee
(2008)

Chair: Fouad Kandeel
Michael Appel
Parastoo Dinyari
Albert Hwa
Carol Kramer
Joan Martellotto
Violetta Raverdi
Marti Sears
Elyse Stuart

Data Elements Committee
(2008)

Chair: Marti Sears
David Baidal
Enrico Cagliero
Marc Garfinkel
Fouad Kandeel
Dixon Kaufman
Robert Ketchum
Francois Pattou
David Sutherland

Transplant Coordinators'/Data Managers' Committee
(2008)
Chair: Parastoo Dinyari
Jarrett Anderson
David Baidal
LeAnn Batterson
Meyer Belzer
Elsa Boely
Jane Fasbender
Courtney Garbee
Susan George
Debbie Grice
Darrell Grimes
Jeannette Hacker
Celia Hartigan
Elizabeth Holbrook
Robin Jevne
Jenny Joseph
Debra Kemp
Mark Lockwood
Eileen Markmann
Joan Martellotto
Marli McCulloch-Olson
Joan McElroy
Melissa McGraw
Suzanne Miller
Bashoo Naziruddin
Lori Otken
Maral Palanjian
Jamen Parkey
Nancy Radke
Violeta Raverdy
Marilyn Reeve
Kristi Schneider
Marti Sears
Jill Sheedy
KD Shiang
Elyse Stuart
Pat Swanson
Heather Turgeon
Patricia Wilson
Dona Winborne
Piotr Witkowski


citr
Collaborative Islet Transplant Registry