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

August 10, 2007

NOTICE:

The CITR Annual Report details data received as of April 1, 2007 for all islet transplant recipients registered by December 31, 2006.

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

August 10, 2007

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: 2007 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 fourth Annual Report (2007) including data from the great majority of islet transplant programs in North America active since 1999 and one European program that joined CITR in 2006. 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

INTRODUCTION

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 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). For patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. For patients with severe hypoglycemia, an alternative experimental procedure uses insulin-producing cells (islets) extracted from a donor pancreas. These 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 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 Foundation 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 fourth report, published in 2007, summarizes information on patients who received one or more islet cell transplants between 1999 and 2006 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). About 45 medical institutions in the US and Canada have been or are currently active in islet transplantation since 1999, or are in the process of starting a program.

This year's report also includes data from one European center whose participation began in 2006. For most of the analyses, this center's 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 this European center's data. No center-specific data are presented in any CITR reports.

Most ongoing protocols are experimental in nature and have differed minimally in the entry criteria for patients and in the types of immunosuppression therapy used to prevent rejection of the infused islet cells. 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 (hypoglycemic episodes and insulin reactions) requiring the assistance of another person, wide swings of blood sugar levels (blood glucose lability), 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 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 Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, 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 CITR 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, 2007 for data on recipients that were registered in CITR as of December 31, 2006.

The 2007 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. Patients lost to follow-up are imputed to have discontinued their immunosuppression regimen and experience complete islet failure. A small number of patients have no follow-up to determine their status regarding these events, and are excluded from 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 1999-2006. All 45 North American medical institutions with an identified islet transplant program between 1999 and 2006 responded to a general questionnaire. Thirty-one of the 45 reported performing at least one islet allograft transplant. The remaining 14 programs have not had any open protocols or were in the process of starting their islet allograft transplant program. Exhibit A displays the activity of North American islet transplant centers for 1999-2006, 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 1999-2006

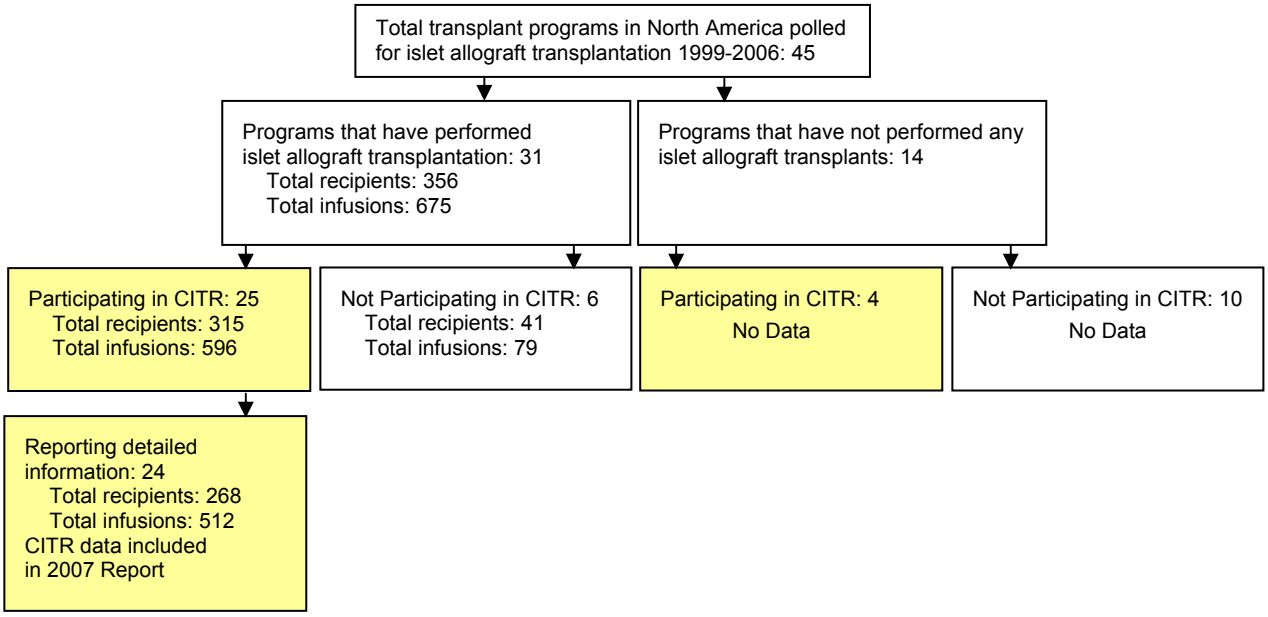
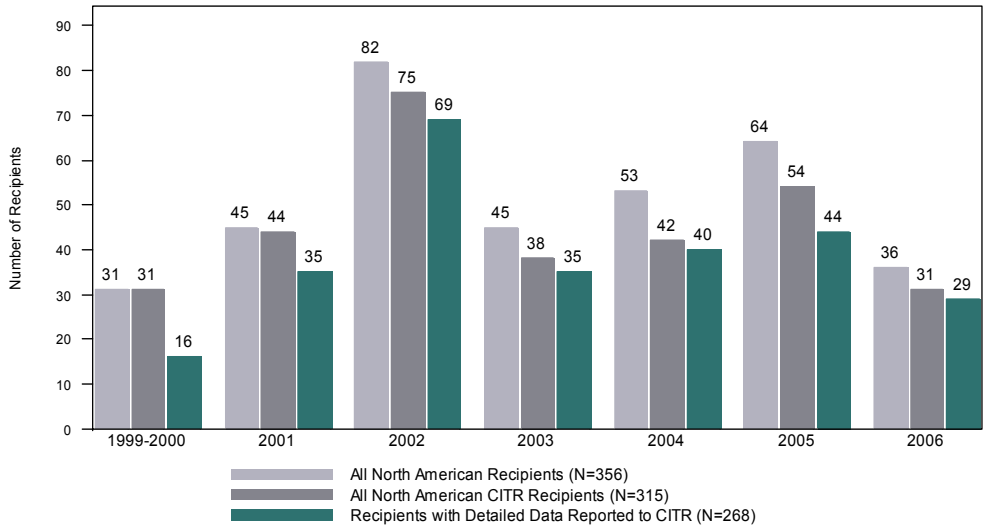


Exhibit B displays the data collected from the 31 active islet transplant programs in North America from 1999 through 2006. To the knowledge of the Registry, this table is inclusive of all human-to-human islet transplant programs in North America.

Exhibit B

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 1999-2006



One European center joined the Registry in 2006, registered all past participants and reported data for inclusion in this report. Pooling the reported data from the North American and European centers, the CITR registry comprises 292 allograft recipients with detailed data reported as of the data cutoff, and 579 infusion procedures derived from a total of 634 donors. Seventy-six of the recipients (26%) received a single islet infusion, 149 (51%) received two, 63 (22%) received three, and four (1%) received a total of four islet infusions. On average, recipients received a total of 819,160 (SD 352,575) total islet equivalents (IEQs), or 12,669 IEQs/kilogram body weight (SD 5,808).

Of the total 292 North American and European recipients included in this report, 262 (90%) were recipients without a previous kidney transplant who received one or more islet-alone infusions (IA), while 30 recipients (10%) had previously received a kidney transplant (IAK).

Recipient Characteristics. The mean age of islet allograft transplant recipients in CITR is 43.7 years (range 19-67) and the mean duration of diabetes is 29 years (range 5 to 53). The mean weight of the participant is 66 kg (range 35 to 98) and the mean body mass index (BMI) is 23.7 kg/m^2 (range 15 to 37). About 64% of the participants are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 37% of the 292 allograft islet transplant participants were on an insulin pump prior to their first infusion and 98% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, 91% of the participants had a basal C-peptide < 0.5 ng/mL and 81% had a HbA_{1C} > 6.5%. The mean daily insulin requirement of participants prior to their first infusion procedure was 36.9 units (SD 13.6) and the subset on intensive insulin therapy had received intensive therapy for a mean of 18.7 years (SD 13.1). The mean fasting blood glucose for all participants was 171.6 mg/dL (SD 91.8), 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 taking a higher baseline daily insulin dose, 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 8 to 75) and the mean body mass index was 29.1 kg/m^2 (range 13 to 69). The mean time from cross clamp to pancreas recovery was 38 minutes (SD 22) while the mean cold ischemia time was 7.3 hours (range 1 to 27). Approximately 57% of the donors were male, 13% were Hispanic and 89% were white. Fifty-seven percent of the donors had a cerebrovascular/stroke as cause of death while 29% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 19% had a history of alcohol dependency.

Thirty-three percent of the donors received a transfusion prior to organ procurement, while only 6% received a transfusion during the organ procurement surgery. Fifty-seven percent of the donors received steroids, 37% of the donors received insulin and 97% 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. 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 91% 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 (UW + PFC, UW + HTK, or SCOT + PFC), 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 (94%) followed by Thermolysin/Liberase combinations (4%). 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 30.7 hours (range 6.0 to 96.0). Of the 634 islet preparations reported to CITR, nine final preparations showed a positive aerobic culture, five showed a positive anaerobic culture, eleven showed a positive fungal culture, and one tested positive for mycoplasma.

Islet final product characteristics were related to recovery time, cold ischemic time, donor body mass index, and donor age by Spearman rank correlation (data not shown). These relationships deserve more in-depth analysis, especially in correcting correlated factors to outcomes.

Immunosuppression Therapy. The majority (60%) 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 74% of IA first infusions, and in combination with other T-cell antibodies in another 6% of first infusions. Anti-thymocyte globulin was given alone or in combination in 11% of first infusions.

Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 12% by Day 30, 37% by Day 75, 57% by Month 6, and 69% by Year 1 (Exhibit C-1). The proportion that is insulin independent without re-infusion remains fairly constant at 9-13% throughout the first year. An additional 4-14% of all IA recipients retain detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 262 IA recipients, 58% are expected at three-years post first infusion, at which time, regardless of the total number of infusions received, about 16% are insulin independent, 28% are insulin dependent with detectable C-peptide, 32% have no detectable C-peptide or lost to follow-up, and 23% 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 is insulin independent declines steadily from 46% at Month 6 to 16% at Year 3. The proportion with loss of islet function (reported graft failure or no detectable C-peptide or lost to follow-up with imputed graft failure) increases steadily from 13% at Month 6 to 42% at Year 3. A stable 18-22% retains graft function with exogenous insulin over the three years; every time point has 20-23% missing data. 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

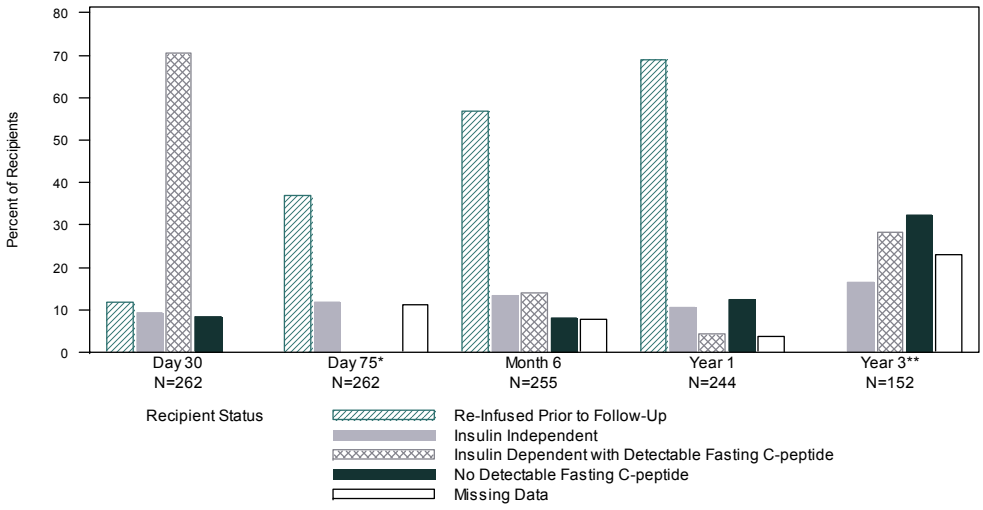
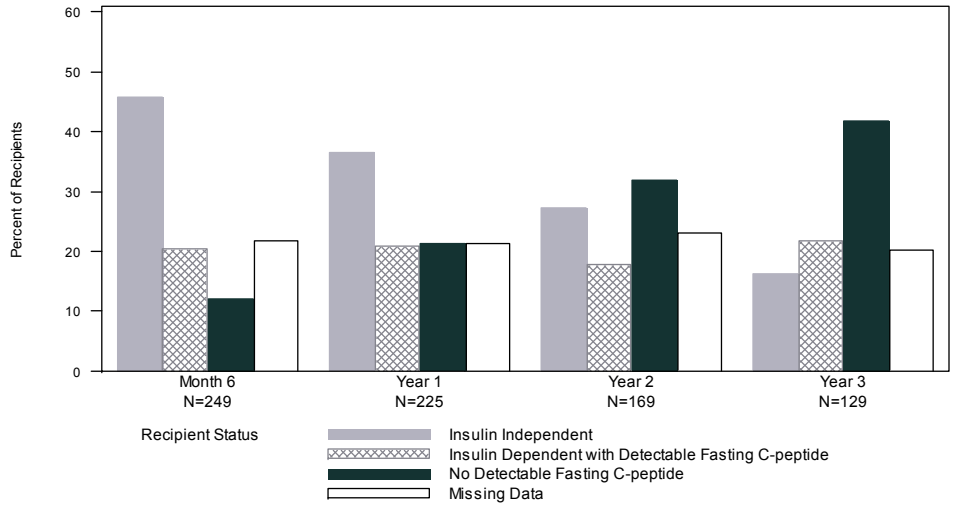


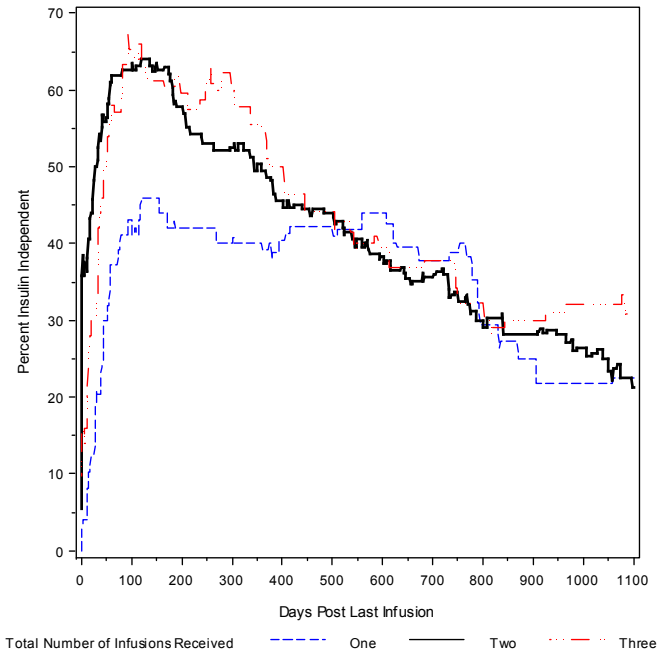
Exhibit C-2
Prevalence of Insulin Status and Detectable Fasting C-Peptide

Post Last Infusion
Islet Alone Recipients



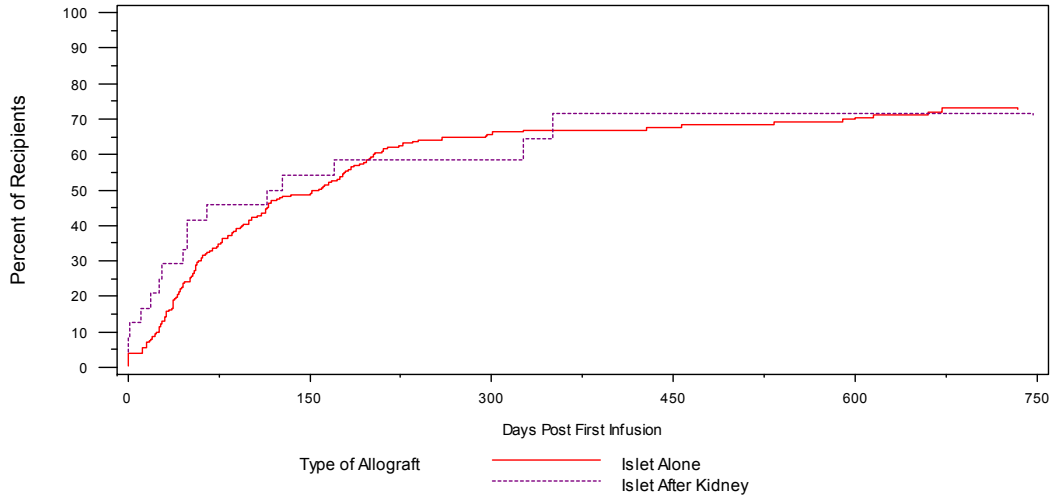
Focusing only on the insulin independence status (available daily with about 20% missing data on any day), the prevalence of insulin independence from last infusion declines from about 60% at Month 4 to about 24% at Year 3 (1100 days) post last infusion (Exhibit D). Two or three infusions boost the prevalence of insulin independence in the first year to a peak of about 64%, 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, 67% of the IA and IAK recipients combined 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 73% (Exhibit E).

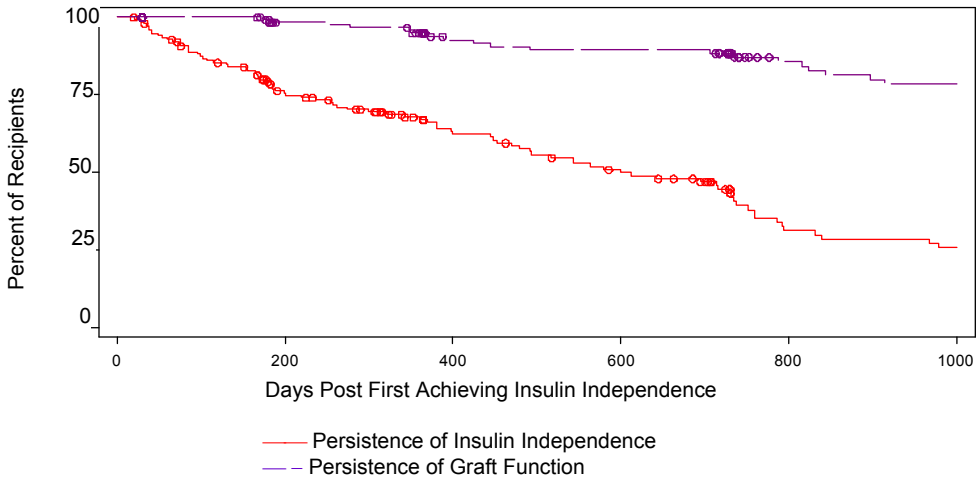
Exhibit E
Achievement of Insulin Independence After Islet Transplantation
Not Censored at Re-Infusion or Graft Loss



Stratified by the number of infusions per recipient, the greater the number of infusions, the higher the rate of achieving insulin independence (data not shown). However, the proportion of recipients attaining insulin independence quickly post each re-infusion is quite higher for second infusion and slightly higher post third infusion than for first infusion.

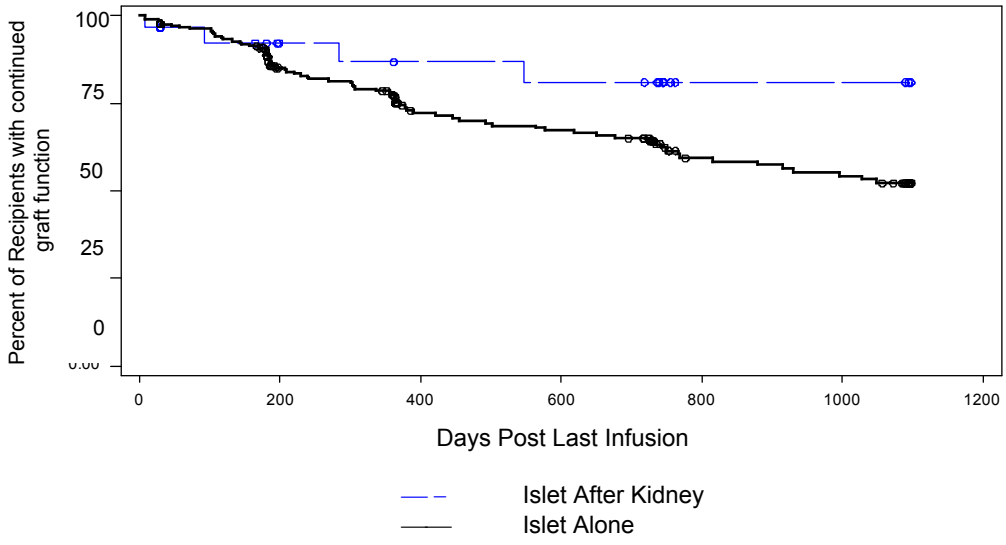
Over time there is a decrease in the sustainability of insulin independence (Exhibit F). For all participants who ever achieved insulin independence, only 67% have retained this status one year after achieving it and this decreases to 45% at two years. Three infusions increase the likelihood of retaining insulin independence.

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 estimates (Exhibit G), only 52% 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 any time during their one to several islet infusions (data not shown).

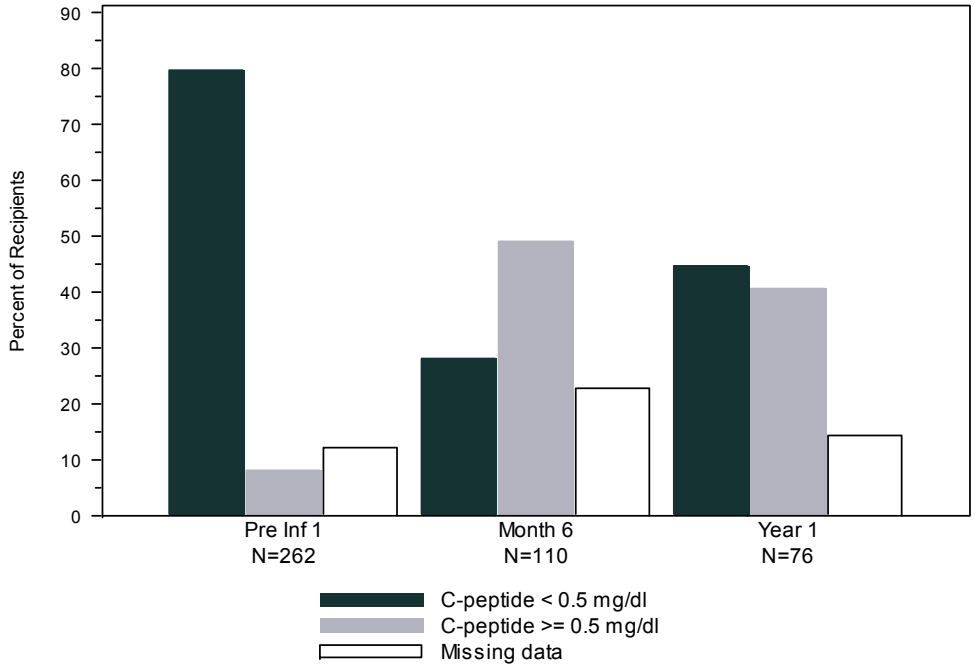
Exhibit G
Persistence of Islet Graft Function (IA, IAK)



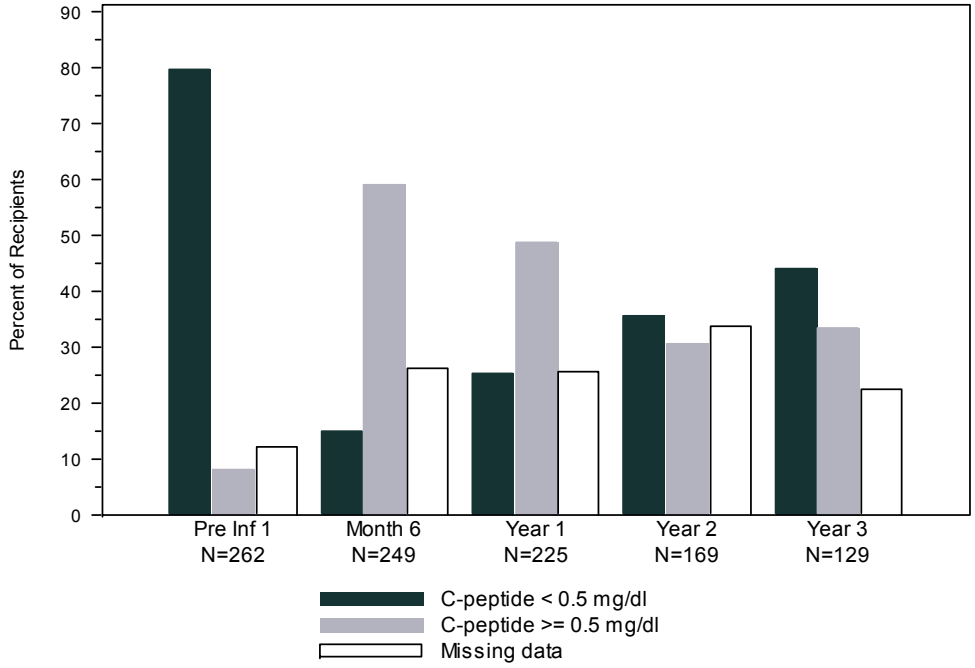
C-peptide levels are substantially increased by islet transplantation. The percent of IA recipients with C-peptide >0.5 ng/mL increases from 8% pre-infusion to 49% at Month 6 and 41% at Year 1 post first infusion (censored at re-infusion, Exhibit H, top), with 33% retaining this level of function at Year 3 post last infusion (Exhibit H, bottom).

Exhibit H
C-peptide ≥ 0.5 ng/mL

Post First Infusion



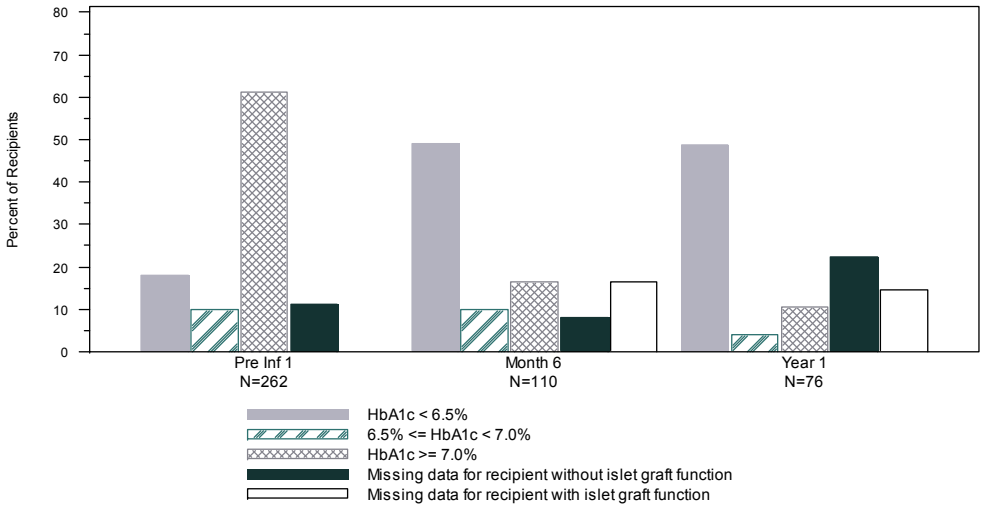
Post Last Infusion



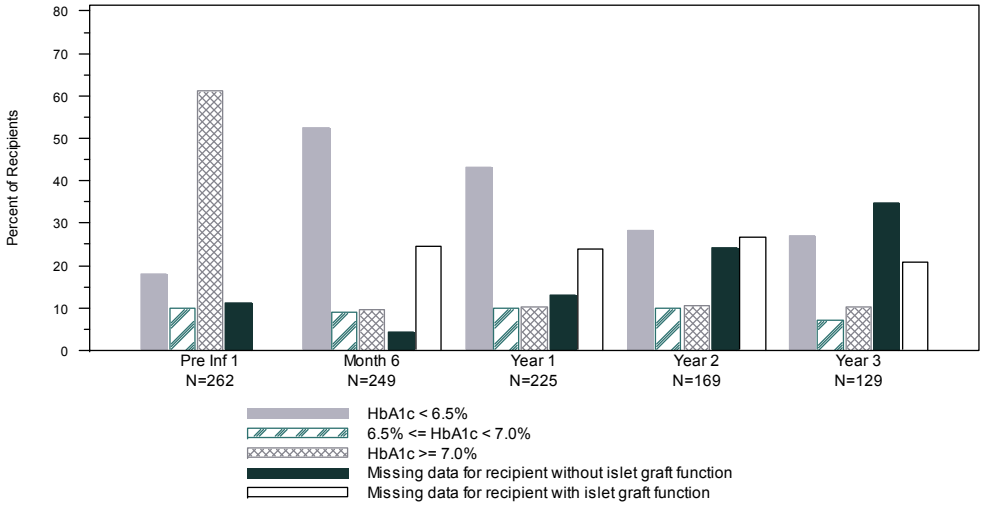
HbA_{1C}. HbA_{1C} levels are improved substantially by islet transplantation. The percent of IA recipients with HbA_{1C}< 7.0% increases from 28% pre-infusion to 59-75% at Month 6 and 53-67% at Year 1 post first infusion, censored at re-infusion (Exhibit I). In these percentile ranges, the lower estimate 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 graft function have HbA_{1C} levels < 7.0%. Post last infusion, these rates are 61-86% at Month 6 and 34-55% at Year 3. Notably, the percent with measured values ≥ 7% remains fairly constant at about 10% throughout follow-up.

Exhibit I
HbA_{1C}

Post First Infusion



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 76-87% pre-infusion to less than 5-20% throughout the first year post last infusion, and to 9-43% at three years post last infusion (Exhibit J). 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 without graft function 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 K). All participants that experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.

Exhibit J
Severe Hypoglycemia
Islet Alone Recipients

Post Last Infusion

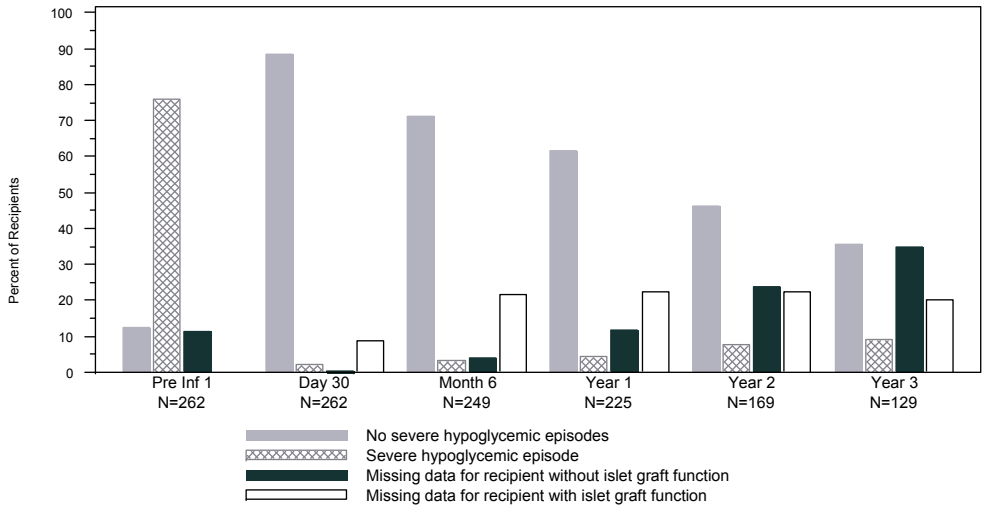
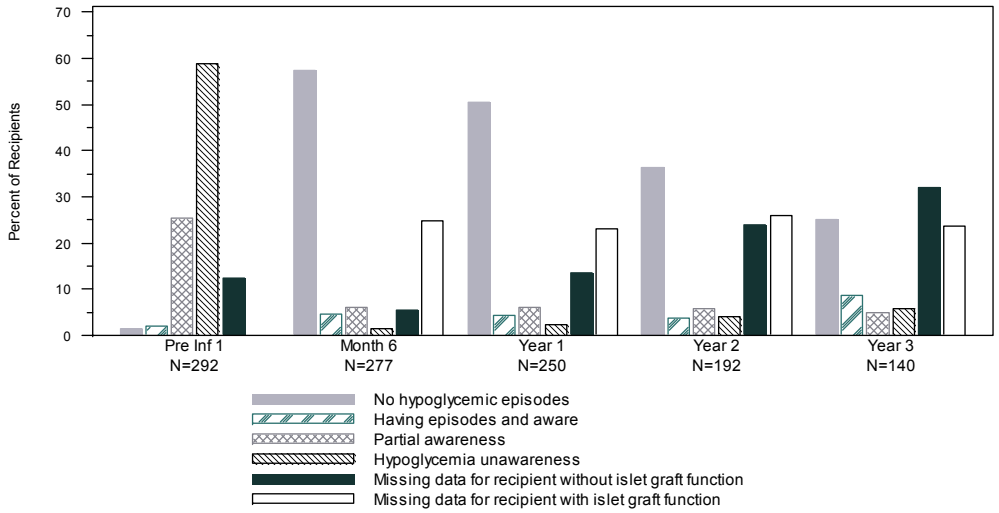


Exhibit K
Hypoglycemia Status
All Allograft Recipients

Post Last Infusion



Multivariate Cox regression models were used to investigate the effect of pre-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. Factors associated with achieving insulin independence included lower HbA1C, insulin not given on Day 0 of infusion (which is likely related to the recipient's recent or current insulin status at the time of infusion), the donor not having been given insulin in hospital, and the total islet equivalents infused (Exhibit L-1).

Exhibit L-1

Multivariate Cox regression: Insulin Independence Post Last Infusion **Censored at Complete Islet Failure or Last Follow-Up** **(103 events / 170 recipients with data on covariates)**		
	HR	p
Baseline HbA_{1C} (%)	0.784	0.002
Insulin Day 0 Last Infusion	0.540	0.003
Donor insulin in-hospital	0.693	0.07
Total IEs/kg received over all infusions	1.039	0.01

Factors protective against complete islet failure include more infusions given, higher age and/or longer diabetes duration, higher stimulation index of the graft(s), and etanercept given at induction (Exhibit L-2).

Exhibit L-2

Multivariate Cox regression: Complete Islet Failure Post Last Infusion Censored at Last Follow-Up (64 events / 204 recipients with data on covariates)		
	HR	p
Total number of infusions received	0.537	0.003
Diabetes duration (years)	0.964	0.03
Age at baseline (years)	0.952	0.01
Mean stimulation index	0.812	0.002
Etanercept at any infusion	0.195	0.006

These multivariate results are preliminary and will require validation with accruing data.

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, 40% of the recipients were on at least one anti-hypertensive medication and 31% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to 48% 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 were minimal for ALT (4%), AST (4%), alkaline phosphatase (6%) and for total bilirubin (1%). There were no reports at this level for total cholesterol and 9 reports (4.5%) for triglycerides. There were 28 reports (13%), of a participant with an increase in their serum creatinine of greater than 0.5 mg/dL above their baseline level.

Adverse Events.

Sixty-five percent of the islet alone recipients experienced at least one adverse event in Year 1; while 41% experienced one or more serious adverse events in this same period. Of the 574 adverse events reported in Year 1 post first infusion for islet alone recipients, 32.5% were related to the immunosuppression therapy and 28.4% were related to the infusion procedure. Of the 211 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 26.5% were related to the immunosuppression therapy and 45.5% were related to the islet infusion procedure. Overall, a total of 337 serious adverse events were reported to the Registry as of datafile closure, with 40.4% of them classified as life threatening and 46% requiring an inpatient hospitalization. Seventy percent (236 of 337) of serious adverse events occurred in the first year following the participants' first infusion procedure. Over 32% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 25% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator and do not necessarily represent scientific truth. Approximately 91% of the serious adverse events resolved with no residual effects. Most of the reported serious adverse events were categorized as investigations (22%), gastrointestinal disorders (19%) and blood and lymphatic system disorders (15%) as classified by the MedDRA classifications system.

Neoplasms have been diagnosed in ten allograft recipients over the reported period of follow-up (1999-2006):

- four cases of squamous cell carcinoma, three of which were treated and resolved without residual effects and without discontinuation of immunosuppression, and one with no further information;
- one case of basal cell carcinoma, treated and resolved with no residual effects, occurring after discontinuation of immunosuppression for islet graft failure;
- one case of ovarian mucinous cystadenoma, diagnosed the day after first infusion, treated and resolved with no residual effects;
- one case of breast cancer first diagnosed 22 months post first infusion, treated, with immunosuppression continued; one month later, metastatic carcinoma of lymph nodes was identified and treated; immunosuppression was discontinued.
- one case of papillary thyroid cancer at 21 months post first infusion, treated and immunosuppression continued;
- one case of pulmonary nodules, treated but persistent; further follow-up is pending;
- one case of papillary carcinoma, diagnosed two months post first infusion; treated and resolved without sequelae; previous history of thyroid adenoma.

Reported Deaths. There have been four reports of death to the Registry; a viral meningitis attributed death 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 and a death due to unknown causes (discovered in obituaries) more than four years post the person's second infusion.

Conclusions. Islet transplantation continues to show short-term benefits of insulin independence, normal or near normal HbA_{1C} levels, and sustained marked decrease in hypoglycemic episodes. Long-term primary efficacy of safety of immunosuppression as well as effects on secondary complications are less well understood and are the focus of ongoing research. The Registry is growing large enough to begin investigating factors predictive of and/or associated with primary outcomes.

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 fourth report, published in 2007, summarizes information on patients who received one or more islet cell transplants between 1999 and 2006. 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. This Annual Report (2007) summarizes information on 292 islet transplant recipients, 634 deceased donors and 579 islet infusion procedures, as of December 31, 2006. This represents a 29% increase in the number of recipients, 35% increase in the number of donors, and a 35% 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, 2006, a total of 125 autologous islet transplant recipients were registered in CITR. However, only seven of the registered autograft recipients have detailed data entered in the database. Efforts are underway to collect complete autograft information in the Registry, both prior to and going forward from December 31, 2006.

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 requested from the CITR Coordinating Center (citr@emmes.com), or 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-five 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 45 programs responded and 31 of the 45 programs had been active during 1999-2006, transplanting at least one patient. The remaining programs (N=14) 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 1999-2006. 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	675	356
1999	18	10
2000	32	21
2001	65	45
2002	142	82
2003	106	45
2004	110	53
2005	124	64
2006	78	36

In summary, this report includes data on 75% (268/356) of all islet allograft recipients in North America and 76% (512/675) 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 $\geq$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. Exceptions include absence of C-peptide data at Day 75 for insulin/C-peptide status (exhibit 5-1). Losses to follow-up are imputed as having lost graft function, and are included in the category, "No detectable fasting C-peptide." 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 and loss to follow-up were used to impute CIF: any recipient with C-peptide less than local detectable levels at their last scheduled follow-up or with a report of loss to follow-up or more than one year of missed expected visits 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.

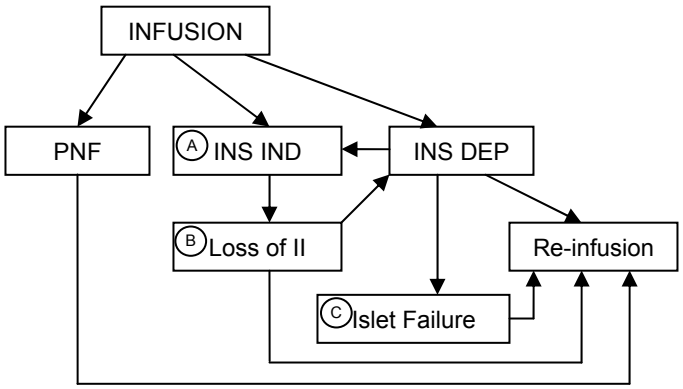


Figure 1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent)

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.

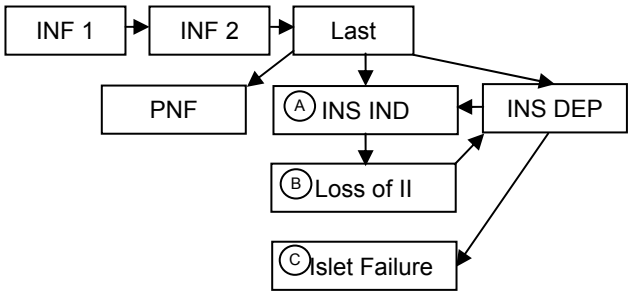


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent)

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 Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, DCTD, NCI, NIH, DHHS. 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 C-peptide 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 adjusting for size of the islet. One IEQ is equal to a single islet of 150 μm in diameter.

Islet function: C-peptide detectable by local assay.

Islet graft dysfunction:

> In *insulin independent recipients* (after completion of induction immunotherapy), islet graft dysfunction will be suspected if the recipient displays, with no evidence of infection or drug toxicity, 3 blood glucose readings more than 2 hours 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, or recipient has not provided data for the last two consecutive scheduled annual follow-up visits. Immunosuppression is most likely discontinued. Recipient is imputed as losing graft function.

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 CTCAE 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 participate in CITR (24/31; 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.

Unlike previous reports, 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 2006. 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, 2006. 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, 2007 based on the 292 recipients that had been registered for CITR at the December 31, 2006 participant registration closure date.

All participating 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

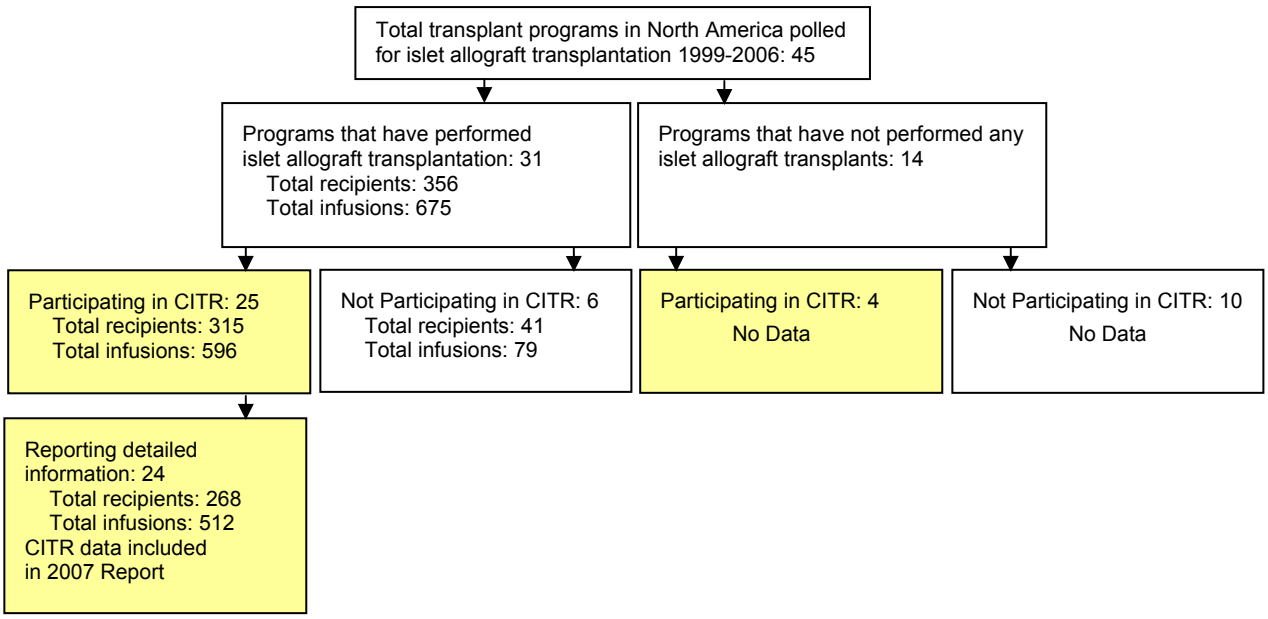
Islet Transplant Activity

As of December 31, 2006, 31 North American and European islet transplant centers were activated for participation in the Collaborative Islet Transplant Registry (CITR). Of these centers, 25 have registered 292 islet alone (IA) or islet after kidney (IAK) allograft recipients into the Registry. Exhibit 1-1 displays the locations of all 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 a 29% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 35% 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, 14 of the 16 (87.5%) active North American islet transplant programs in 2006 contributed information to the Registry.

CITR distributed a questionnaire to 45 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, 268 of 356 allograft recipients (75%) and 512 of 675 (76%) of all allograft infusions performed in North America are included in this year's Annual Report.

In 2006, five European centers were invited to participate in the Registry. One center completed registration of all their allograft recipients by December 31, 2006.

A summary of the total 579 North American and European islet allograft infusions entered in the Registry by year of infusion is included in Exhibit 1-5. These 579 infusions derived from 634 total donors; 526 were single donor preparations and 53 were multiple donor preparations. There was a large number of first islet infusions conducted by the CITR centers in 2002 (N=69) as well as a large number of recipients receiving their second infusion in 2002 (N=45). In other years, first infusions ranged from 18-51 recipients.

Seventy-six recipients (26%) have received a single islet infusion at the time of this report, 149 (51%) received a total of two infusions, 63 (22%) received three infusions, and four recipients (1%) received a total of four islet infusions (Exhibit 1-6).

Of the 292 islet allograft recipients presented in this report, 262 (90%) are islet alone recipients, and 30 (10%) are islet after kidney recipients (Exhibit 1-7). Three islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

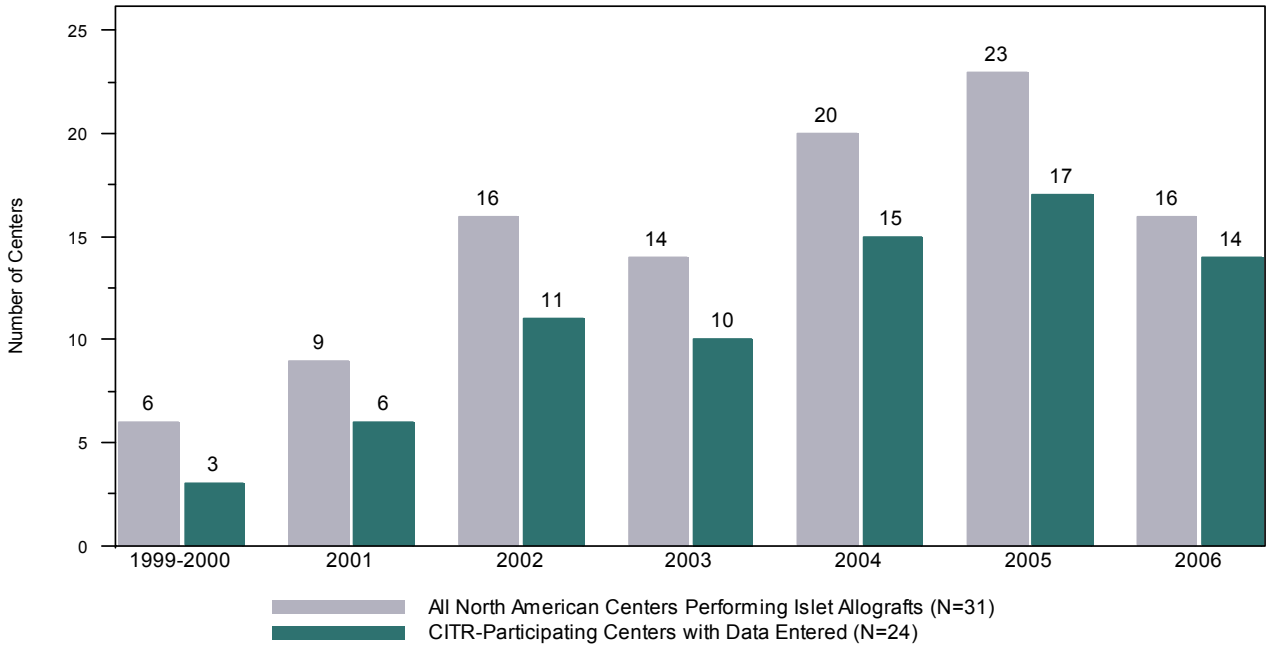
One hundred and twenty five of 282 North American autograft recipients have been reported to the Registry. Detailed data for these recipients is being collected. In the future, a supplemental Annual Report will contain analyses for autologous islet transplants.

Exhibit 1 – 1
Islet Transplant Centers Reporting Data to CITR:
Participating North American Centers 1999-2006

A - CITR Centers with at least one islet allograft infusion procedure conducted in 2006
C - CITR Centers with no islet allograft infusions in 2006
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 1999-2006

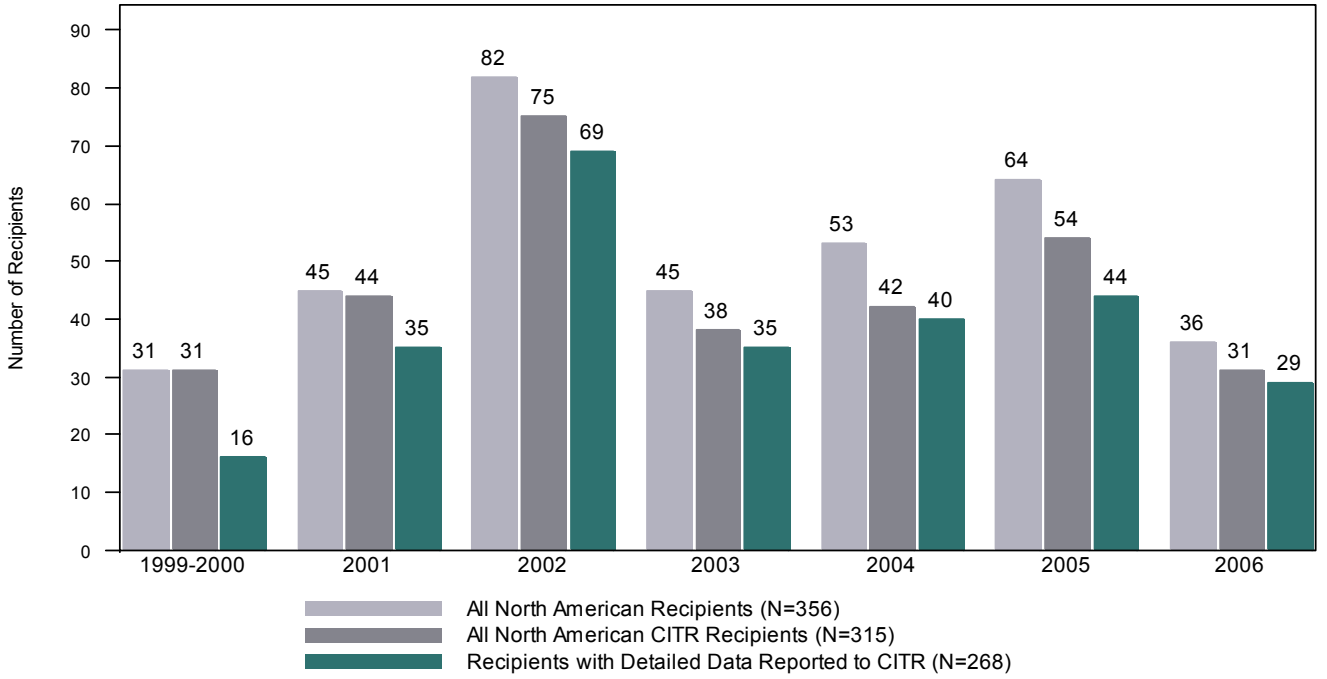


CITR distributes an Islet Transplant Summary (ITS) questionnaire to all islet transplant programs in North America regardless of their participation in the Registry. The questionnaire captures information on the number of patients who received one or more islet infusions. Of 45 North American islet transplant programs polled, all have provided information through 2006.

"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, three additional centers have joined CITR and contributed data for islet transplants performed in 2002-2005, as well as 2006.

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 1999-2006

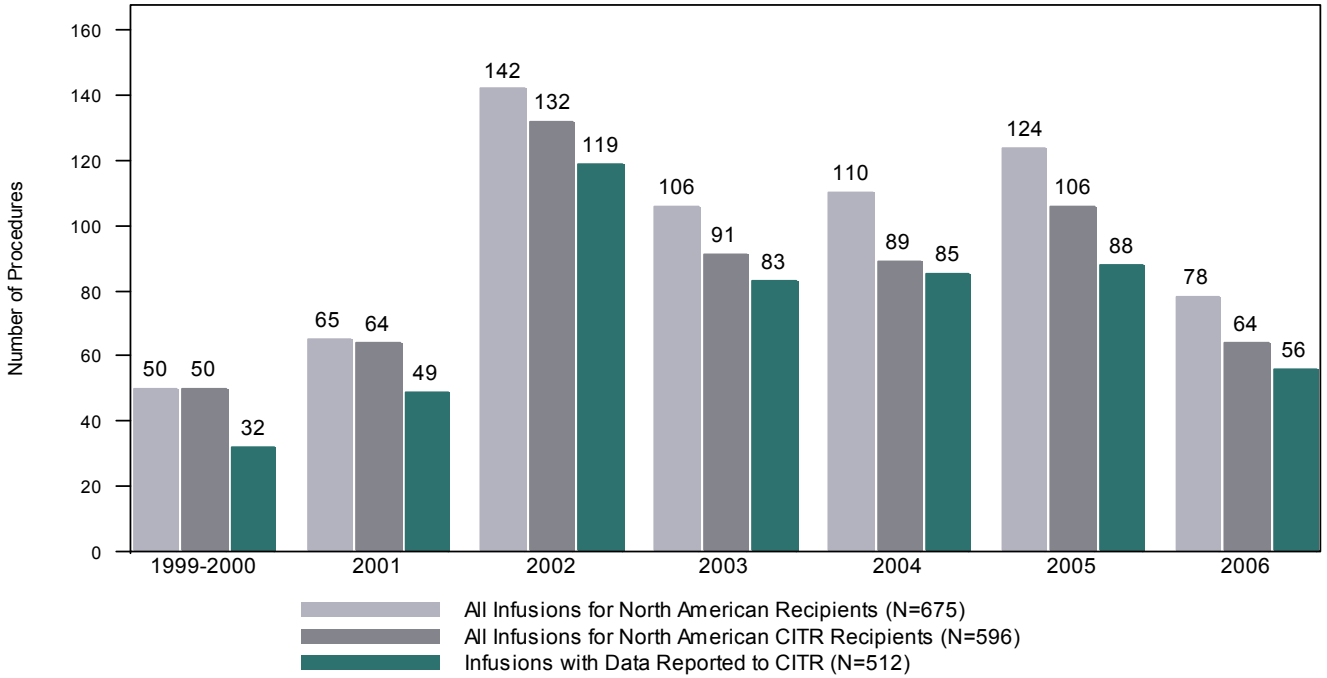


The Islet Transplant Summary (ITS) questionnaire is completed by all North American islet transplant programs regardless of their participation in the Registry. Of 45 North American islet transplant programs polled, all have provided this information through 2006.

From 1999-2006, 356 patients with Type 1 diabetes mellitus have received at least one islet allograft infusion procedure in North America. Of those 356 patients, 315 (88%) received their allograft from a CITR participating center. CITR-participating centers have reported detailed data on 268 of these recipients, representing 75% of all 356 human islet allograft recipients in North America from 1999-2006.

Since last year's report, North American centers have contributed data on 14 allograft recipients transplanted in 2002-2005 not previously reported.

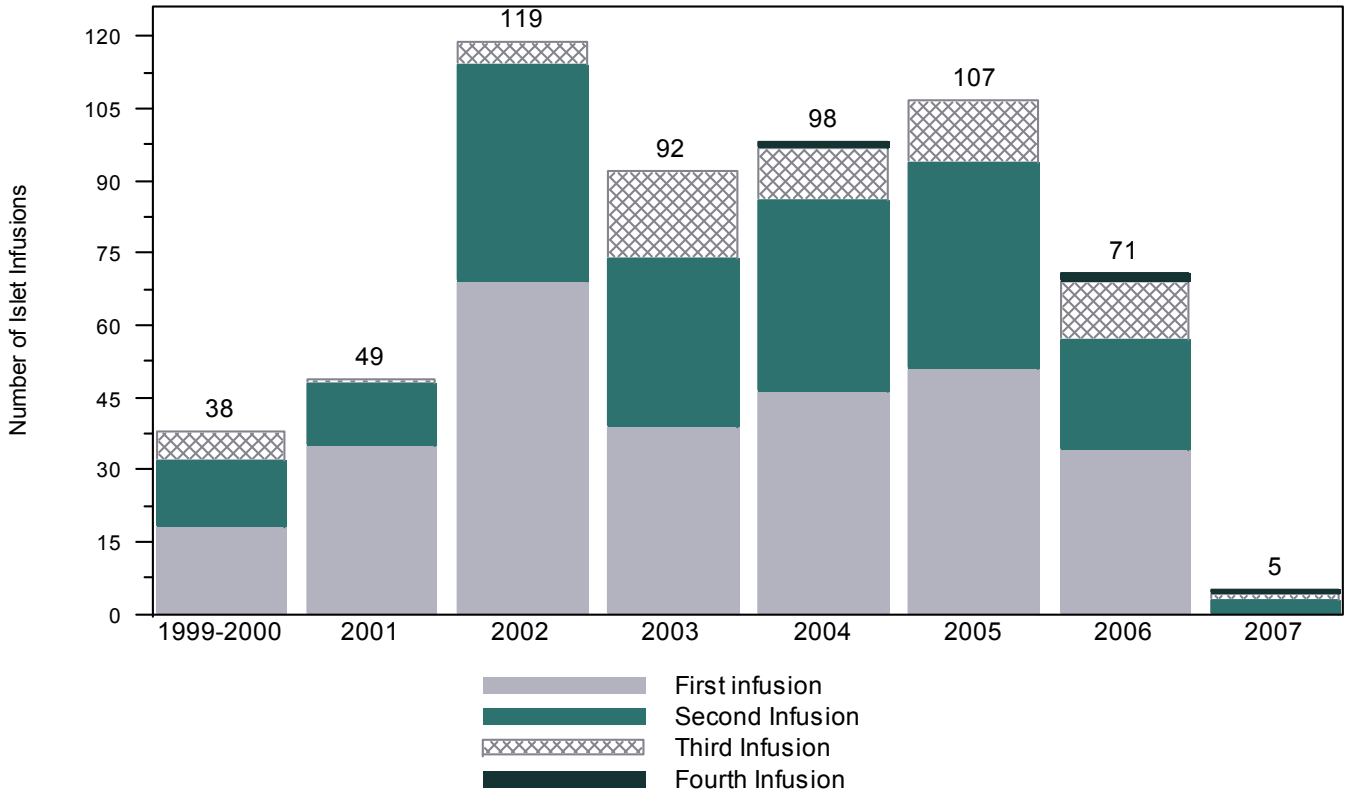
Exhibit 1 – 4
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR: CITR-Participating North American Islet Transplant Centers 1999-2006



From 1999-2006, 315 patients with Type 1 diabetes mellitus have received a total of 675 allograft infusion procedures. CITR-participating North American islet transplant centers have performed 596 of those 675 (88%) procedures. The Registry has received detailed data on 512 allograft infusion procedures performed at CITR-participating North American islet transplant centers, representing 76% of all 675 human islet allograft infusions performed in North America from 1999-2006.

Since last year's report, North American centers have reported an additional 35 allograft infusions performed in 2001-2005 not previously reported.

Exhibit 1 – 5
Total Number (N=579) of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number: CITR-Participating North American and International Centers, 1999-2006



Infusion procedure number is defined as the sequence number of 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 2006 and a subsequent infusion between January and March of 2007, data for the subsequent infusion is also included in the graph.

Exhibit 1 – 6
Total Number (N=579) of Islet Allograft Infusion Procedures Per Recipient:
CITR-Participating North American and International Centers, 1999-2006

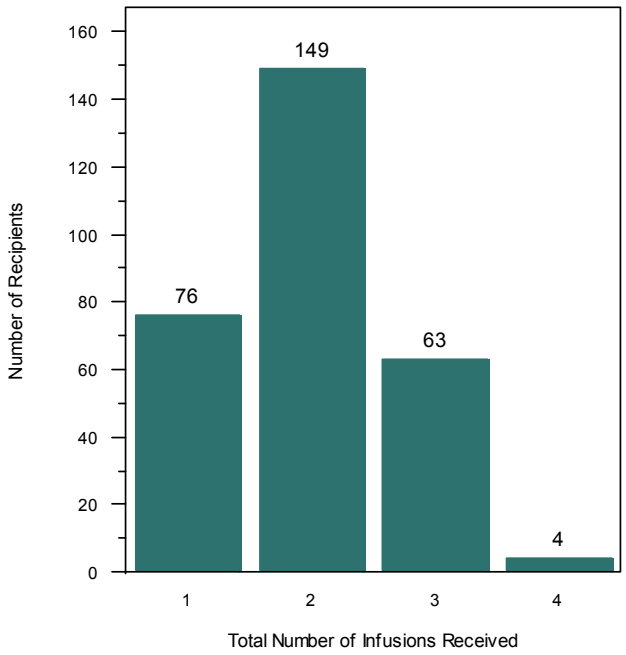
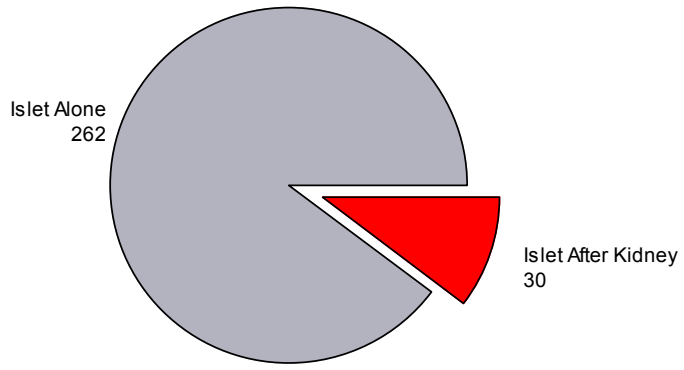


Exhibit 1 – 7
Islet Alone and Islet After Kidney Recipients:
CITR-Participating North American and International Centers, 1999-2006



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 5 to 53). 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 37). Females comprise 64% 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, 9% 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 14) and the 98% 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 7.6% (SD 1.3), and mean basal C-peptide was 0.1 ng/mL (SD 0.3).

Serology tests indicated that four participants tested positive for hepatitis B core antibodies, and four participants tested positive for hepatitis B surface antigen (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 required a higher baseline daily insulin requirement, had a higher HbA_{1C} and lower PRA percentages than those participants who had one or two infusion procedures.

Donor Information

All 634 islet preparations were derived from deceased donors. The mean age of donors was 43 years (range 8 to 75) and the mean body mass index was 29 kg/m2 (SD 7). Approximately 57% of the donors were male, 13% were Hispanic and the majority was white. Fifty-seven percent of the donors had a cerebrovascular/stroke as cause of death while 29% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 19% had a history of alcohol dependency. The mean time from cross clamp to pancreas recovery was 38 minutes (SD 22) 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 37% of the donors received insulin during their hospitalization and 97% 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.

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 70 IU/L and serum amylase 173 IU/L.

Exhibit 2 – 1
Recipient Demographics

	Islet Alone			Islet After Kidney		
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
Age (yrs)	262	43.4	0.6	30	46.5	1.2
	N	**%**		**N**	**%**	
Gender						
Female	168	64.1		20	66.7	
Male	94	35.9		10	33.3	
Ethnicity						
Non Hispanic or Latino	167	63.7		30	100.0	
Hispanic or Latino	4	1.5		-	0.0	
Unknown*	91	34.7		-	0.0	
Race						
American Indian or Alaska Native	2	0.8		-	0.0	
Asian	-	0.0		-	0.0	
Black or African American	-	0.0		1	3.3	
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	171	65.3		29	96.7	
Unknown*	90	34.4		-	0.0	
Employment status						
Working full time	130	49.6		14	46.7	
Working part time by choice	13	5.0		3	10.0	
Working part time due to disease	18	6.9		1	3.3	
Working part time, reason unknown	2	0.8		-	0.0	
Not working by choice	10	3.8		2	6.7	
Not working due to disease	31	11.8		6	20.0	
Not working, unable to find employment	2	0.8		-	0.0	
Not working, reason unknown	1	0.4		2	6.7	
Student	2	0.8		-	0.0	
Retired	14	5.3		-	0.0	
Employment status unknown	12	4.6		1	3.3	
Missing	27	10.3		1	3.3	

* 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	69	46.9	8	26.7
Non-Government Research Grant	34	23.1	19	63.3
Institutional Contribution	34	23.1	-	-
Missing	10	6.8	3	10.0
Payment for Islet Processing				
US/State Government Agency	61	41.5	8	26.7
Non-Government Research Grant	40	27.2	19	63.3
Institutional Contribution	36	24.5	-	-
Missing	10	6.8	3	10.0
Payment for transplant				
US/State Government Agency	49	33.3	8	26.7
Non-Government Research Grant	40	27.2	18	60.0
Institutional Contribution	47	32.0	-	-
Other*	1	0.7	1	3.3
Missing	10	6.8	3	10.0
Payment for Induction Medication				
US/State Government Agency	42	28.6	7	23.3
Non-Government Research Grant	46	31.3	18	60.0
Institutional Contribution	47	32.0	-	-
Other*	2	1.4	2	6.6
Missing	10	6.8	3	10.0

*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	262	100.0		30	100.0	
Diabetes Type						
Type 1 Diabetes	262	100.0		30	100.0	
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
Duration of Diabetes (yrs)	262	28.1	0.7	30	34.6	1.3
Weight (kg)	235	66.7	0.7	28	60.1	1.9
Body Mass Index (kg/m^2)	233	23.8	0.2	28	22.5	0.5
Daily insulin requirement prior to infusion (units)	233	37.3	0.9	28	33.2	2.4
Duration of intensive therapy among those on intensive therapy (yrs)	161	18.8	1.0	1	10.0	-
Avg daily insulin / kg recipient body weight	232	0.6	< 0.1	27	0.6	< 0.1
Number of days on wait list	234	296.8	20.4	28	339.8	62.2
Fasting plasma glucose (mg/dL)	231	172.6	6.0	28	163.2	18.5
Basal C-Peptide (ng/mL)	230	0.1	< 0.1	24	0.1	< 0.1
HbA_{1C} (%)	233	7.6	0.1	27	8.1	0.2
Most recent PRA (%)	214	3.3	0.8	25	0.7	0.4
Peak PRA (%)	193	4.9	1.0	21	7.5	4.7

Exhibit 2 – 4
Recipient Diabetes Characteristics at First Infusion

	Islet Alone		Islet After Kidney	
	N	**%**	**N**	**%**
Total	262	100.0	30	100.0
Use of insulin pump				
Yes	90	34.4	6	20.0
No	144	55.0	22	73.3
Missing	28	10.7	2	6.7
Number of injections per day				
N/A-on pump	90	34.4	6	20.0
1-2*	5	1.9	1	3.3
3-5	130	49.6	16	53.3
6 or more	1	0.4	2	6.7
Unknown	6	2.3	3	10.0
Missing	30	11.5	2	6.7
Use of insulin pump or 3 or more injections per day				
Yes	221	84.4	24	80.0
No	5	1.9	1	3.3
Missing	36	13.7	5	16.7
Basal C-Peptide ≥ 0.5 ng/mL				
Yes**	21	8.0	3	10.0
No	209	79.8	21	70.0
Unknown	14	5.3	5	16.7
Missing	18	6.9	1	3.3
HbA_{1C}				
<6.5%	47	17.9	2	6.7
6.5% - 7.0%	26	9.9	4	13.3
≥ 7.0%	160	61.1	21	70.0
Unknown	9	3.4	3	10.0
Missing	20	7.6	-	0.0

*Five of six participants administering two injections per day with a mean average daily insulin use of 42 units. One participant administering one injection per day with average daily insulin use of 25 units. All 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.

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

	Islet Alone		Islet After Kidney	
	N	**%**	**N**	**%**
Hypoglycemia Status				
No Occurrence	-	0.0	3	10.0
Having Episodes and Aware	5	1.9	1	3.3
Partial Awareness	67	25.6	7	23.3
Unawareness	159	60.7	14	46.7
Unknown	2	0.8	2	6.7
Missing	29	11.1	3	10.0
Pre transplant autoantibody - GAD 65				
Positive	46	17.6	2	6.7
Negative	93	35.5	8	26.7
Unknown	91	34.7	18	60.0
Missing	32	12.2	2	6.7
Pre transplant autoantibody - IA-2				
Positive	32	12.2	1	3.3
Negative	62	23.7	6	20.0
Unknown	136	51.9	20	66.7
Missing	32	12.2	3	10.0
Pre transplant autoantibody - Insulin				
Positive	87	33.2	6	20.0
Negative	16	6.1	3	10.0
Unknown	127	48.5	19	63.3
Missing	32	12.2	2	6.7
Total number of positive autoantibodies				
None	32	12.2	2	6.7
One	81	30.9	7	23.3
Two	36	13.7	1	3.3
All Three	4	1.5	-	0.0
Unknown	77	29.4	18	60.0
Missing	32	12.2	2	6.7

Exhibit 2 – 5
Recipient Infectious Disease Testing at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	262	100.0	30	100.0
HIV				
Positive	-	0.0	-	0.0
Negative	237	90.5	29	96.7
Not Done/Unknown/Missing	25	9.5	1	3.3
CMV IGG				
Positive	93	35.5	11	36.7
Negative	128	48.9	17	56.7
Not Done/Unknown/Missing	41	15.6	2	6.7
CMV IgM				
Positive	-	0.0	-	0.0
Negative	113	43.1	12	40.0
Not Done/Unknown/Missing	149	56.9	18	60.0
HepB core antibody				
Positive	4	1.5	1	3.3
Negative	171	65.3	16	53.3
Not Done/Unknown/Missing	87	33.2	13	43.3
HepB surface antigen				
Positive	4	1.5	-	0.0
Negative	217	82.8	28	93.3
Not Done/Unknown/Missing	41	15.6	2	6.7
HepC antibody				
Positive	-	0.0	-	0.0
Negative	217	82.8	29	96.7
Not Done/Unknown/Missing	45	17.2	1	3.3
EBV IgG				
Positive	190	72.5	25	83.3
Negative	25	9.5	2	6.7
Not Done/Unknown/Missing	47	17.9	3	10.0
EBV IgM				
Positive	29	11.1	6	20.0
Negative	78	29.8	11	36.7
Not Done/Unknown/Missing	155	59.2	13	43.3

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)	68	43.1	1.1	131	44.6	0.9	63	41.3	1.0	8	50.4	2.9	18	45.0	1.4	4	45.3	2.1
Duration of Diabetes (yrs)	68	29.3	1.2	131	27.9	1.0	63	27.0	1.3	8	38.1	3.7	18	33.4	1.4	4	33.0	1.9
Weight (kg)	66	64.9	1.4	122	67.1	0.9	47	68.0	1.7	7	58.1	3.1	18	59.7	2.5	3	67.4	5.1
Body Mass Index (kg/m^2)	65	23.7	0.3	122	23.7	0.2	46	24.0	0.4	7	21.6	0.6	18	22.7	0.8	3	23.1	1.5
Daily insulin requirement (units)	65	33.2	1.5	122	38.5	1.2	46	40.0	2.5	8	32.8	3.9	18	33.0	3.3	2	36.5	13.5
Average daily insulin / kg recipient body weight	65	0.5	<0.1	121	0.6	<0.1	46	0.6	<0.1	7	0.6	<0.1	18	0.6	<0.1	2	0.5	0.1
Duration of intensive insulin therapy (yrs)	44	19.3	2.3	87	19.6	1.3	30	15.8	2.1	0	-	-	1	10.0	-	0	-	-
Number of days on wait list for first infusion	66	316.6	39.6	121	324.7	30.2	47	197.5	31.9	7	205.3	75.9	18	384.8	88.5	3	383.3	137.1
Fasting plasma glucose (mg/dL)	66	169.2	10.6	117	174.3	8.6	48	173.1	13.7	7	198.6	39.0	18	166.5	22.1	3	60.7	27.7
Basal C-Peptide (ng/mL)	62	0.1	<0.1	118	0.1	<0.1	50	0.1	<0.1	7	0.1	0.1	15	0.1	<0.1	2	0.0	<0.1
HbA_{1C} (%)	63	7.4	0.1	120	7.6	0.1	50	8.0	0.2	7	8.3	0.6	18	8.1	0.3	2	7.4	1.2
Most recent PRA (%)	62	5.4	2.2	109	2.9	0.9	43	1.3	0.6	8	0.0	<0.1	16	1.1	0.6	1	0.0	-
Peak PRA (%)	58	7.1	2.6	98	4.3	1.3	37	3.2	1.2	7	2.0	1.3	13	11.0	7.5	1	0.0	-

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	20	29.4	48	36.6	26	41.3	3	37.5	4	22.2	3	75.0
Female	48	70.6	83	63.4	37	58.7	5	62.5	14	77.8	1	25.0
Pre transplant autoantibody - GAD 65												
Positive	9	13.2	31	23.7	6	9.5	1	12.5	1	5.6	-	0.0
Negative	23	33.8	53	40.5	17	27.0	3	37.5	5	27.8	-	0.0
Unknown	32	47.1	37	28.2	22	34.9	4	50.0	11	61.1	3	75.0
Missing	4	5.9	10	7.6	18	28.6	-	0.0	1	5.6	1	25.0
Pre transplant autoantibody - IA-2												
Positive	9	13.2	14	10.7	9	14.3	-	0.0	1	5.6	-	0.0
Negative	16	23.5	32	24.4	14	22.2	2	25.0	4	22.2	-	0.0
Unknown	39	57.4	75	57.3	22	34.9	5	62.5	12	66.7	3	75.0
Missing	4	5.9	10	7.6	18	28.6	1	12.5	1	5.6	1	25.0
Pre transplant autoantibody - Insulin												
Positive	19	27.9	58	44.3	10	15.9	3	37.5	3	16.7	-	0.0
Negative	4	5.9	11	8.4	1	1.6	1	12.5	2	11.1	-	0.0
Unknown	41	60.3	52	39.7	34	54.0	4	50.0	12	66.7	3	75.0
Missing	4	5.9	10	7.6	18	28.6	-	0.0	1	5.6	1	25.0
Total Number of Positive Autoantibodies												
None	6	8.8	14	10.7	12	19.0	1	12.5	1	5.6	-	0.0
One	21	30.9	50	38.2	10	15.9	2	25.0	5	27.8	-	0.0
Two	5	7.4	25	19.1	6	9.5	1	12.5	-	0.0	-	0.0
All Three	2	2.9	1	0.8	1	1.6	-	0.0	-	0.0	-	0.0
Unknown	30	44.1	31	23.7	16	25.4	4	50.0	11	61.1	3	75.0
Missing	4	5.9	10	7.6	18	28.6	-	0.0	1	5.6	1	25.0

Exhibit 2 – 8
Recipient Laboratory Values at First Infusion

	Islet Alone			Islet After Kidney		
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
HbA_{1C} (%)	233	7.6	0.1	27	8.1	0.2
ALT (U/L)	231	21.7	0.6	28	26.4	2.7
AST (U/L)	243	24.3	0.6	29	29.7	2.4
Alkaline phosphatase (U/L)	238	74.6	2.0	27	79.0	4.8
Total bilirubin (mg/dL)	239	0.6	<0.1	29	0.5	0.1
Total cholesterol (mg/dL)	237	169.2	1.8	27	187.6	5.5
HDL (mg/dL)	234	63.3	1.0	27	67.1	4.1
LDL (mg/dL)	234	92.8	1.6	27	99.5	4.5
Triglycerides (mg/dL)	237	67.5	2.3	27	97.5	8.4
Serum creatinine (mg/dL)	245	0.9	<0.1	30	1.2	0.1
Calculated creatinine clearance (mL/min/1.73m^2)	193	103.5	1.8	17	76.4	7.6
Basal C-Peptide (ng/mL)	230	0.1	<0.1	24	0.1	<0.1

Exhibit 2 – 9
Donor Demographics
All Allograft Donors

	N	Mean	SD
Age (yrs)	606*	43.2	12.6
	N	**%**	
Total	634	100.0	
Gender			
Male	341	53.8	
Female	258	40.7	
Unknown	9	1.4	
Missing	26	4.1	
Ethnicity			
Hispanic	48	7.6	
Non Hispanic	331	52.2	
Unknown**	229	36.1	
Missing	26	4.1	
Race			
American Indian or Alaska Native	-	0.0	
Asian	2	0.3	
Black or African American	43	6.8	
Indian Sub-Continent	2	0.3	
Mideast or Arabian	-	0.0	
Native Hawaiian or Other Pacific Islander	-	0.0	
White	378	59.6	
Unknown**	171	27.0	
Missing	28	4.4	

*Age was missing for 28 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)	601	86.7	21.0
Height (m)	593	1.7	0.1
Body Mass Index(kg/m^2)	593	29.1	6.8
	N	**%**	
Total	634	100.0	
Donor ABO blood group			
A	194	30.6	
A_1	32	5.0	
A_1B	1	0.2	
A_2	1	0.2	
AB	11	1.7	
B	36	5.7	
O	333	52.5	
Missing	26	4.1	
History of hypertension			
Yes	187	29.5	
No	366	57.7	
Unknown	55	8.7	
Missing	26	4.1	
Hypertension duration			
0-5 years	69	36.9	
6-10 years	15	8.0	
>10 years	29	15.5	
Unknown	74	39.6	
Hypertension control-Diet			
Yes	22	11.8	
No	38	20.3	
Unknown	127	67.9	

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

	N	%
Hypertension control-Diuretics		
Yes	21	11.2
No	62	33.2
Unknown	104	55.6
Hypertension control-Other medications		
Yes	98	52.4
No	31	16.6
Unknown	58	31.0
History of alcohol dependency		
Yes	105	16.6
No	436	68.8
Unknown	77	12.1
Missing	16	2.5
Alcohol use in past 6 months		
Yes	58	55.2
No	22	21.0
Unknown	25	23.8
History of diabetes		
Yes	-	0.0
No	602	95.0
Unknown	9	1.4
Missing	23	3.6

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)	449	53.2	81.7
Duration of cardiac arrest where cardiovascular death (mins)	58	16.0	12.9
Time from cross clamp to pancreas recovery (mins)	415	37.8	21.7
Cold ischemia time (hrs)	601	7.3	3.4
	N		**%**
Total	634		100.0
Cause of death			
Anoxia/cardiac arrest	26		4.1
CNS tumor	6		0.9
Cerebrovascular/stroke	338		53.3
Head trauma	174		27.4
Other	50		7.9
Unknown	14		2.2
Missing	26		4.1
Mechanism of death			
Asphyxiation	8		1.3
Blunt injury	76		12.0
Cardiovascular	20		3.2
Death from natural causes	3		0.5
Drowning	3		0.5
Drug intoxication	7		1.1
Gunshot wound	41		6.5
Intracranial hemorrhage/stroke	406		64.0
Seizure	2		0.3
None of the above	12		1.9
Unknown	30		4.7
Missing	26		4.1

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

	N	%
Total	634	100.0
Vasopressors used		
Epinephrine hydrochloride	43	6.8
Dobutamine hydrochloride	28	4.4
Dopamine hydrochloride	339	53.5
Norephinephrine bitartrate	254	40.1
Phenylephrine hydrochloride	159	25.1
Pitressin/DDAVP	209	33.0
Total number of vasopressors used		
None	20	3.2
One	195	30.8
Two	256	40.4
Three	117	18.5
Four	19	3.0
Five	1	0.2
Unknown	1	0.2
Missing	25	3.9

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

	N	%
Total	634	100.0
Transfusions given to donor during hospitalization		
0 units	386	60.9
0-5 units	137	21.6
6-10 units	33	5.2
>10 units	20	3.2
Unknown	38	6.0
Missing	20	3.2
Transfusions given to donor intraoperatively		
0 units	492	77.6
0-5 units	24	3.8
6-10 units	6	0.9
>10 units	1	0.2
Unknown	88	13.9
Missing	23	3.6
Steroids given to donor during hospitalization		
Yes	241	38.0
No	180	28.4
Unknown	199	31.4
Missing	14	2.2
Insulin given to donor during hospitalization		
Yes	210	33.1
No	359	56.6
Unknown	58	9.1
Missing	7	1.1

Exhibit 2 – 13
Donor Serology
All Allograft Donors

	N	%
Total	634	100.0
Anti HIV I/II		
Positive	-	0.0
Negative	606	95.6
Not Done/Unknown/Missing	28	4.4
Anti HTLV I/II		
Positive	-	0.0
Negative	587	92.6
Not Done/Unknown/Missing	47	7.4
RPR VDRL		
Positive	-	0.0
Negative	556	87.7
Not Done/Unknown/Missing	78	12.3
Anti CMV		
Positive	328	51.7
Negative	270	42.6
Not Done/Unknown/Missing	36	5.7
HBsAg		
Positive	-	0.0
Negative	599	94.5
Not Done/Unknown/Missing	35	5.5
Anti HBC		
Positive*	1	0.2
Negative	594	93.7
Not Done/Unknown/Missing	39	6.2
Anti HCV		
Positive	-	0.0
Negative	597	94.2
Not Done/Unknown/Missing	37	5.8

*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)	503	1.2	0.9
BUN (mg/dL)	409	15.0	8.6
Total bilirubin (mg/dL)	410	0.9	0.8
AST (IU/L)	428	75.4	216.1
ALT (IU/L)	431	59.3	175.6
Serum lipase (IU/L)	482	70.0	115.0
Serum amylase (IU/L)	501	172.6	349.3
Minimum pre-insulin blood glucose (mg/dL)	581	125.6	39.7
Maximum blood glucose (mg/dL)	534	239.3	92.0

Exhibit 2 – 15
Organ Crossmatch Results
All Allograft Donors

	N	%
Crossmatch for T-Cell		
Positive	2	0.3
Negative	340	54.6
Unknown	259	40.9
Missing	33	5.2
Crossmatch for B-Cell		
Positive	14	2.2
Negative	309	48.7
Unknown	276	43.5
Missing	35	5.5

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 pancreases 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 91% of the processing procedures took place at the same institution as the islet transplant center. UW and Two Layer (UW and PFC, N=217; UW and HTK, N=1; SCOT and PFC, N=1), 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, Lactated Ringer's, 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 (94%) followed by Thermolysin/Liberase combinations (4%), and Thermolysin+Collagenase P (2%). All of the pancreata processed used a density gradient for islet purification. Fifty-one percent of islets were placed in culture. Culture is defined as six or more hours in any specially prepared nutrient medium. When cultured, the median culture time was 27 hours (range 6.0 to 96.0) (Exhibit 3-2). Of the 634 preparations reported to CITR, nine final preparations showed a positive aerobic culture (1.4%), five showed a positive anaerobic culture (0.8%), eleven showed a positive fungal culture (1.7%), and one preparation tested positive for mycoplasma (0.2%).

Exhibit 3-5 shows the islet cell characteristics by pancreas preservation method. Significant correlations of islet characteristics with donor, recovery, and processing characteristics are located in Exhibit 3-6.

Islet Infusion Information

Exhibit 3-4 summarizes the core infusion procedure characteristics overall and Exhibit 3-7 by the infusion number. The mean number of islet equivalents infused was significantly 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 48 weeks after their initial one and 38 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	%
Total	634	100.0
Pancreas procurement team		
Unrelated to processing/infusion team	382	60.3
Related to processing/infusion team	214	33.8
Unknown	17	2.7
Missing	21	3.3
Islet processing/testing center		
Same location as infusion center	549	86.6
Other location than infusion center	57	9.0
Missing	28	4.4
Pancreas preservation		
UW	352	55.5
Two Layer	186	29.3
UW followed by Two Layer	33	5.2
Neither UW nor Two Layer	63	9.9
Other preservation solutions used*		
HTK	50	7.9
P Phase 2	12	1.9
Eurocollins	11	1.7
Celsior	1	0.2
Lactated Ringer's	1	0.2
SCOT	1	0.2

*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=217) as well as UW and HTK (N=1) and SCOT and PFC (N=1).

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

	N	%
Collagenase Type		
Liberase HI	584	92.1
Thermolysin/Liberase Combinations	24	3.8
Thermolysin + Collagenase P	11	1.7
Liberase HI + Collagenase P	2	0.3
Serva + NB1	1	0.2
Missing	12	1.9
Islet purification		
Density gradient	614	96.8
Unknown	2	0.3
Missing	18	2.8
Islet pretreatment		
None	301	47.5
Culture**	308	48.6
Missing	25	3.9

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

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

	N	%
Gram stain		
Positive	-	0.0
No organism seen	520	82.0
Unknown	96	15.1
Missing	16	2.5
Aerobic culture		
Positive	9	1.4
No Growth	550	86.8
Unknown	25	3.9
Not Done	29	4.6
Missing	21	3.3
Anaerobic culture		
Positive	5	0.8
No Growth	391	61.7
Unknown	132	20.8
Not Done	85	13.4
Missing	21	3.3
Fungal Culture		
Positive	11	1.7
No Growth	541	85.3
Unknown	33	5.2
Not Done	29	4.6
Missing	20	3.2
Mycoplasma		
Positive	1	0.2
Negative	420	66.2
Unknown	32	5.0
Not Done	158	24.9
Missing	23	3.6

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)	415	37.8	21.7	37.0	0.0	127.0
Duration of cold ischemia (hrs)	601	7.3	3.4	7.0	1.0	27.0
Time from brain death to pancreas recovery (hrs)	397	20.9	11.1	19.0	0.3	89.0
Culture time (hrs)	308	30.7	17.7	27.0	6.0	96.0

Time of brain death is defined as when a physician confirms the death and documents this per the medical chart. Time of cross clamp is defined as when the aorta was cross-clamped prior to organ retrieval. Duration of cold ischemia is defined as the time from when the pancreas was placed in cold preservation solution to the heating up of the organ to start the digestion process. Culture is defined as $\geq$ 6 hrs spent in a specially prepared nutrient medium. Islet preparations placed in a nutrient medium for less than six hours (N=51) 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	13	582,536	276,121	479,583	260,463	1,122,400
Post Purification (Pre culture)	362	393,946	146,720	378,180	68,467	973,133
Post Culture	234	374,847	133,375	368,306	54,452	875,583

This Exhibit represents the total Islet Equivalents (IEQs) measured from each individual pancreas at specified times of the count (eg., Post Digestion). Multiple pancreases 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)	598	3.4	2.0	3.0	0.6	15.0
Islet particle count	325	364,743.7	148,567.6	352,000.0	102,500.0	996,000.0
Embedded islets (%)	370	15.2	19.0	10.0	0.0	95.0
Islet equivalents	620	389,278.6	147,981.8	374,014.5	54,452.0	1,122,400.0
Islet equivalents/kg donor weight	592	4,638.6	2,039.2	4,354.8	713.4	27,010.6
Beta cells ($x10^6$)	231	268.5	219.0	200.0	4.0*	975.0
Beta cells ($x10^6$) / kg donor weight	221	3.4	2.8	2.6	0.0	20.3
Insulin content (µgrams)	295	3,327.0	2,136.4	2,958.0	19.0	9,914.0
DNA content (µgrams)	292	8,100.2	9,163.4	5,330.0	83.0*	55,111.0
Endotoxin units	517	18.1	38.1	5.0	0.0	540.6*
Endotoxin units/kg donor weight	493	0.2	0.5	0.1	0.0	6.6
Islet purity: Dithizone positive cells (%)	401	63.0	17.6	63.0	10.0	100.0*
Islet potency: Stimulation index	523	3.3	3.5	2.2	0.3	28.8
Islet Viability (%)						
Fluorescein Diacetate/Propidium Iodide	246	92.8	6.1	94.0	65.0	100.0*
Syto Green 13	148	86.7	7.1	88.0	63.0	99.0
Trypan Blue	108	93.1	5.0	95.0	72.0	100.0*
Fluorescein Diacetate/Ethidium Bromide	19	87.3	7.6	86.0	72.0	99.0
Syto Green/Ethidium Bromide	14	91.2	3.0	91.0	86.0	95.0

*Values verified by center as correct.

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

Exhibit 3 – 5
Islet Characteristics by Pancreas Preservation Method

	Pancreas Preservation Method						Statistically Significant at $p < 0.05$
	UW Only			Two Layer Only			
	N	Mean	SE	N	Mean	SE	
Total cell volume (mL)	309	3.5	0.1	161	3.4	0.1	
Islet particle count	170	382,522.5	10,996.7	82	345,004.5	16,965.6	
Embedded islets (%)	211	14.3	1.3	81	17.6	2.4	
Islet equivalents	330	390,532.1	7,440.2	161	366,467.6	11,418.9	
Islet equivalents/kg donor weight	310	4,751.5	122.5	158	4,230.6	119.7	*
Beta cells ($x10^6$)	135	242.8	18.5	68	302.1	27.5	
Beta cells ($x10^6$)/kg donor weight	126	3.2	0.2	67	3.7	0.4	
Insulin content (µgrams)	181	3,326.2	163.2	76	3,278.2	222.3	
DNA content (µgrams)	178	7,223.2	627.2	81	10,253.9	1,166.3	*
Endotoxin units	266	21.6	2.9	141	12.9	1.8	*
Endotoxin units/kg donor weight	249	0.3	< 0.1	139	0.1	< 0.1	*
Islet purity: Dithizone positive cells (%)	196	63.3	1.3	113	61.3	1.4	
Islet potency: Stimulation index	290	3.4	0.2	144	3.0	0.3	
Islet viability: Fluorescein Diacetate/Propidium Iodide (%)	112	91.3	0.6	74	95.3	0.6	*
Islet viability: Trypan Blue (%)	64	95.1	0.4	28	90.8	0.9	*
Islet viability: Syto Green 13 (%)	78	85.3	0.9	42	87.2	1.0	

Exhibit 3 – 6
Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations							
		Donor Age	**Donor Weight**	**Donor Body Mass Index**	**Time from Cross Clamp to Pancreas Recovery**	**Time from Brain Death to Pancreas Recovery**	**Culture Time**
Embedded islets (%)	r p N	**-0.26174** **<.0001** **355**	0.03799 0.4799 348	0.05252 0.3343 340	-0.02724 0.6838 226	0.02784 0.6820 219	0.01523 0.8374 184
Islet equivalents	r p N	-0.03996 0.3346 585	**0.34450** **<.0001** **580**	**0.29625** **<.0001** **572**	**-0.20101** **<.0001** **396**	0.08864 0.0844 380	0.09580 0.0944 306
Islet equivalents/kg donor weight	r p N	0.00212 0.9595 578	**-0.27805** **<.0001** **580**	**-0.23404** **<.0001** **572**	**-0.20025** **<.0001** **388**	0.01109 0.8311 372	0.06448 0.2688 296
Endotoxin units	r p N	0.03996 0.3804 484	0.07267 0.1115 481	0.07197 0.1168 476	**-0.21378** **<.0001** **340**	-0.03863 0.4843 330	0.22804 0.0001 276
Endotoxin units/kg donor weight	r p N	0.04599 0.3147 480	-0.02828 0.5360 481	-0.01353 0.7685 476	**-0.21361** **<.0001** **333**	0.00797 0.8865 323	**0.23616** **<.0001** **267**
Islet purity: Dithizone positive cells (%)	r p N	-0.01215 0.8159 370	0.06585 0.2051 372	0.04844 0.3515 372	**-0.21165** **0.0004** **277**	**0.21974** **0.0003** **265**	0.19727 0.0064 190
Islet viability: Fluorescein Diacetate/Propidium Iodide	r p N	-0.12149 0.0653 231	0.14360 0.0291 231	0.12016 0.0683 231	**-0.39918** **<.0001** **158**	-0.00532 0.9476 155	0.14885 0.0861 134

The rank correlation coefficient (r) measures the strength of a rank relationship between two variables.

Exhibit 3 – 7
Islet Product and Infusion Characteristics 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
Islet Equivalents infused	255	432,397	144,409	182	396,485	136,616	60	391,350	160,324	29	496,679	134,494	17	441,484	92,521	2	503,354	15,056
Islet Equivalents infused / kg recipient body weight	232	6,686	2,297	155	6,355	2,299	45	6,547	3,124	27	8,423	2,481	16	7,714	2,011	1	7,049	-
Embedded islets (%)	165	15	18	116	16	18	35	16	17	13	14	17	11	13	11	2	10	0
Cell volume (mL)	247	4.0	2.0	180	3.7	1.9	61	3.6	1.9	18	4.1	2.5	14	4.2	3.1	1	5.0	-
Time since first infusion (weeks)	0	-	-	194	23	36	63	48	48	0	-	-	22	19	27	4	56	31
Time since second infusion (weeks)	0	-	-	0	-	-	63	38	45	0	-	-	0	-	-	4	51	29

Exhibit 3 – 8
Mean Number of Islet Equivalents/Kg Recipient by Total Number of Infusions Received

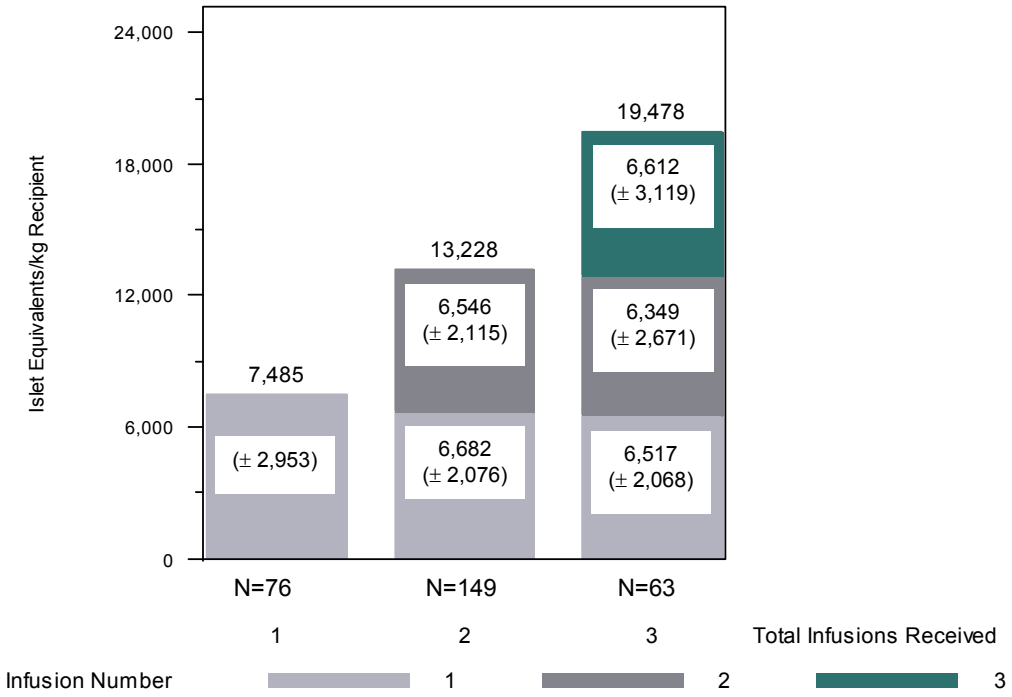


Exhibit 3 – 9
Pre Infusion Portal Pressure by Infusion Sequence

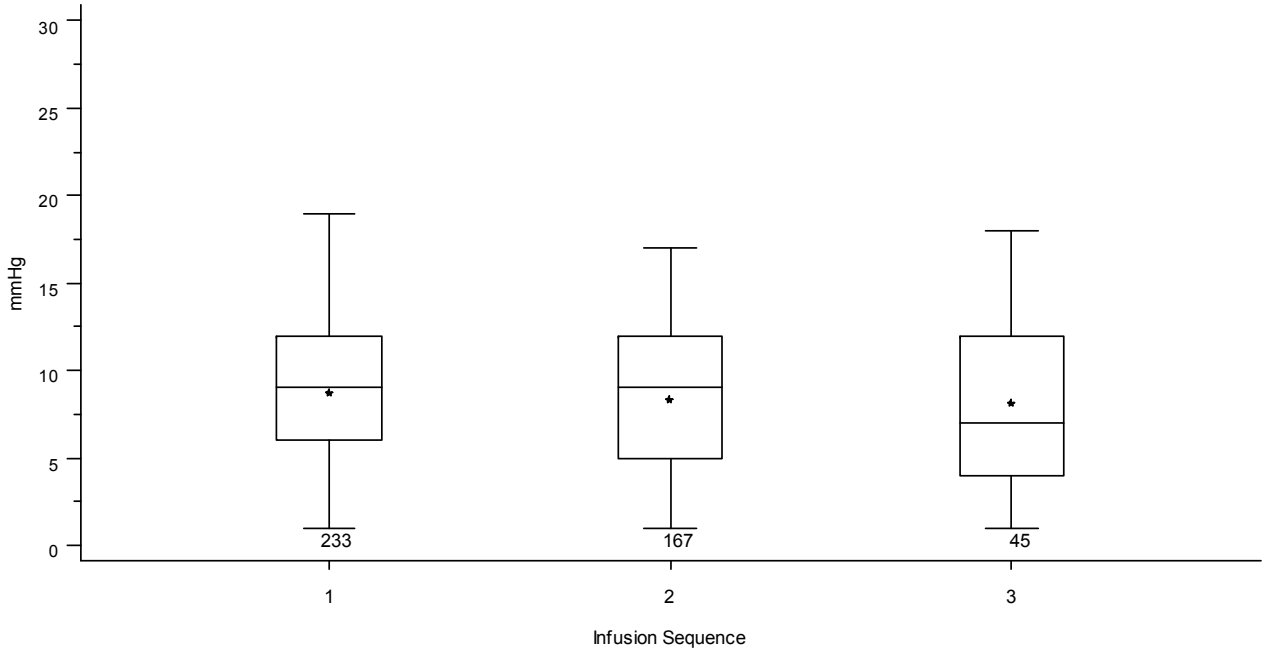


Exhibit 3 – 10
Peak Portal Pressure by Infusion Sequence

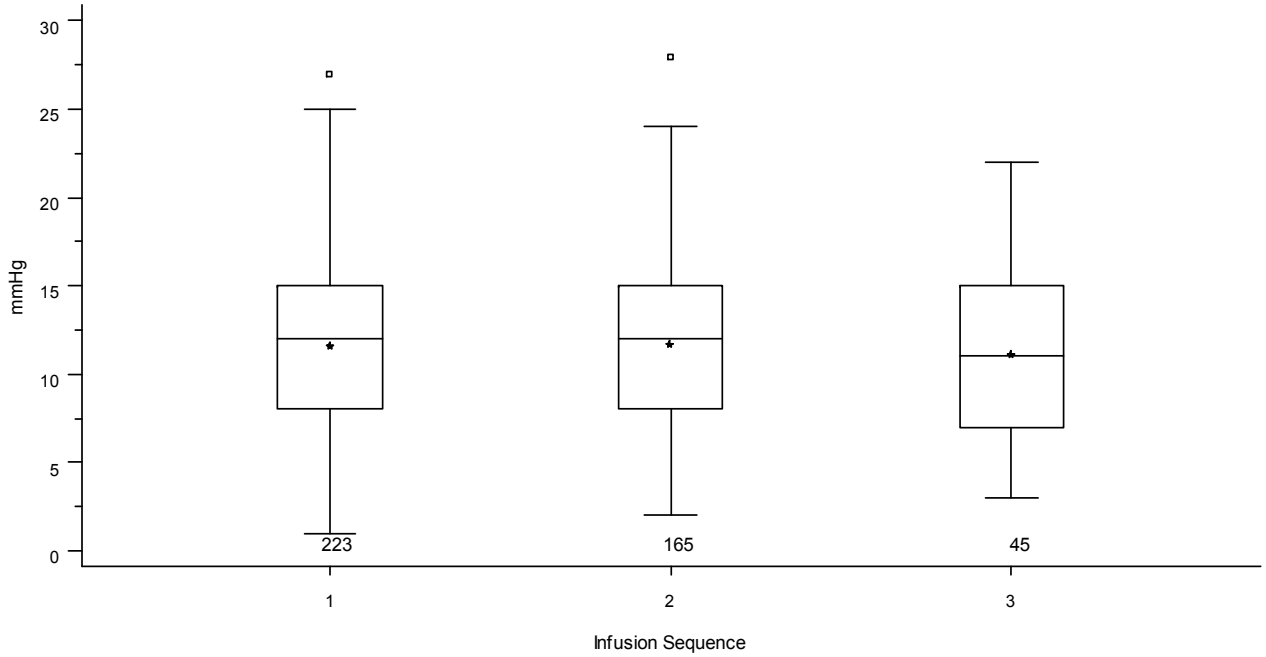


Exhibit 3 – 11
Closure Portal Pressure by Infusion Sequence

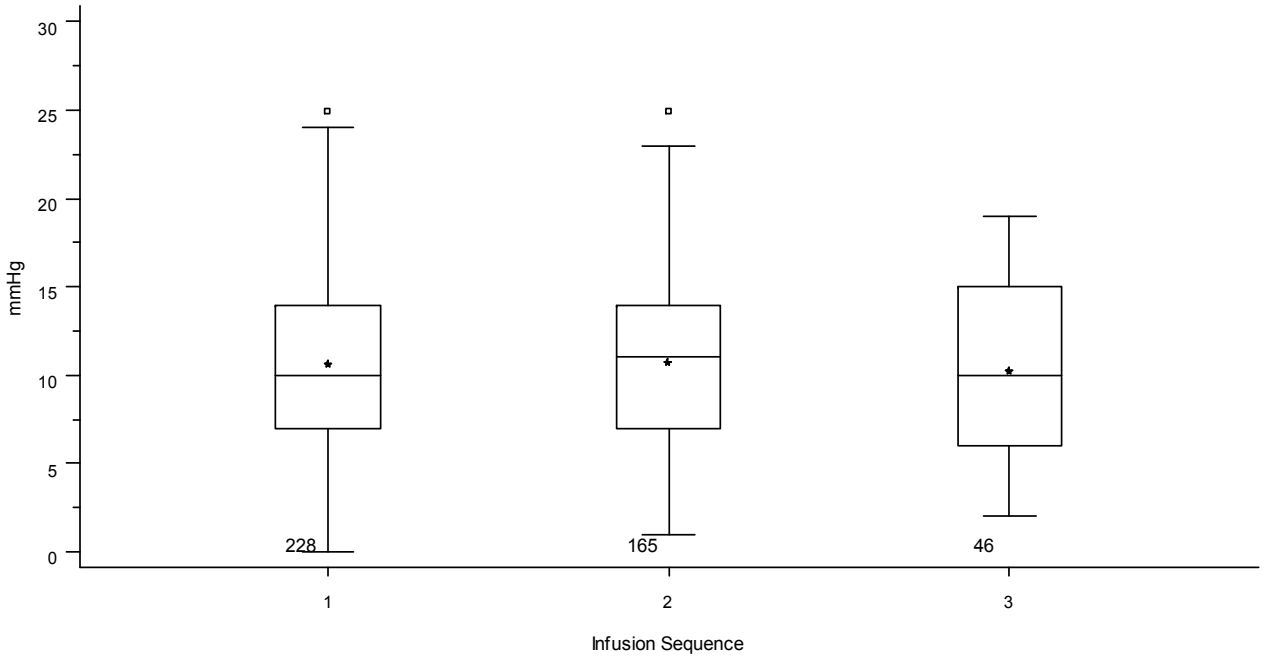


Exhibit 3 – 12
Change from Pre Infusion to Closure Portal Pressure by Infusion Sequence

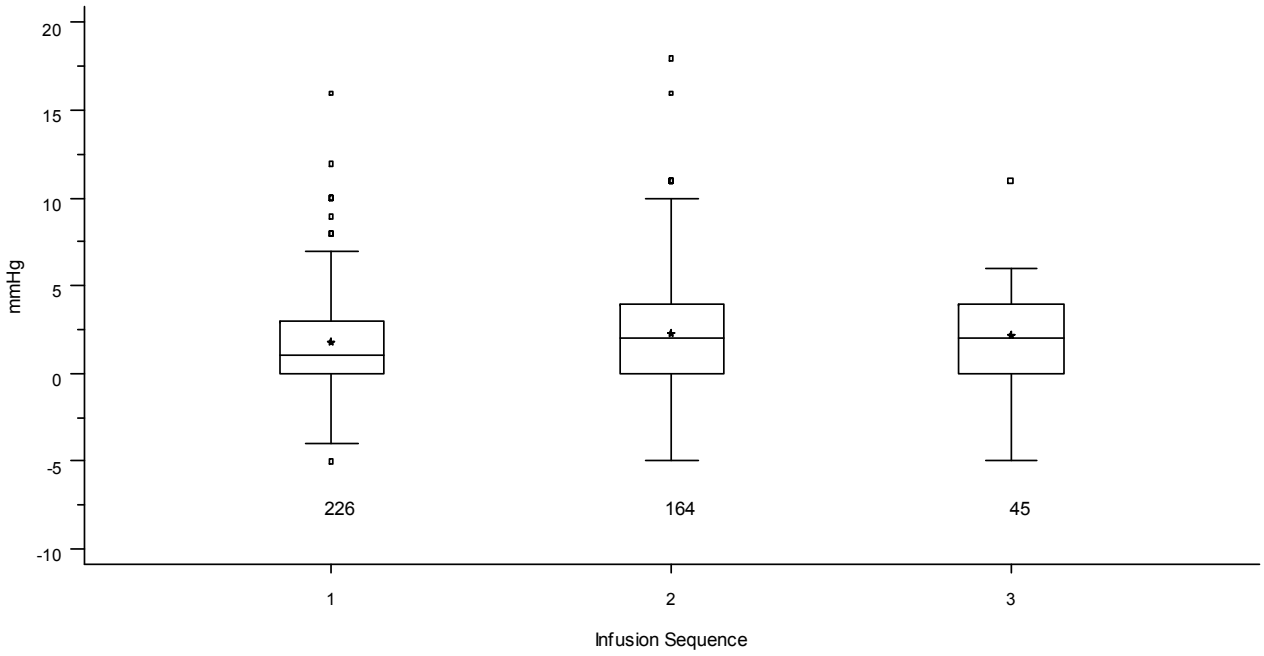


Exhibit 3 – 13
Change from Pre Infusion to Peak Portal Pressure by Infusion Sequence

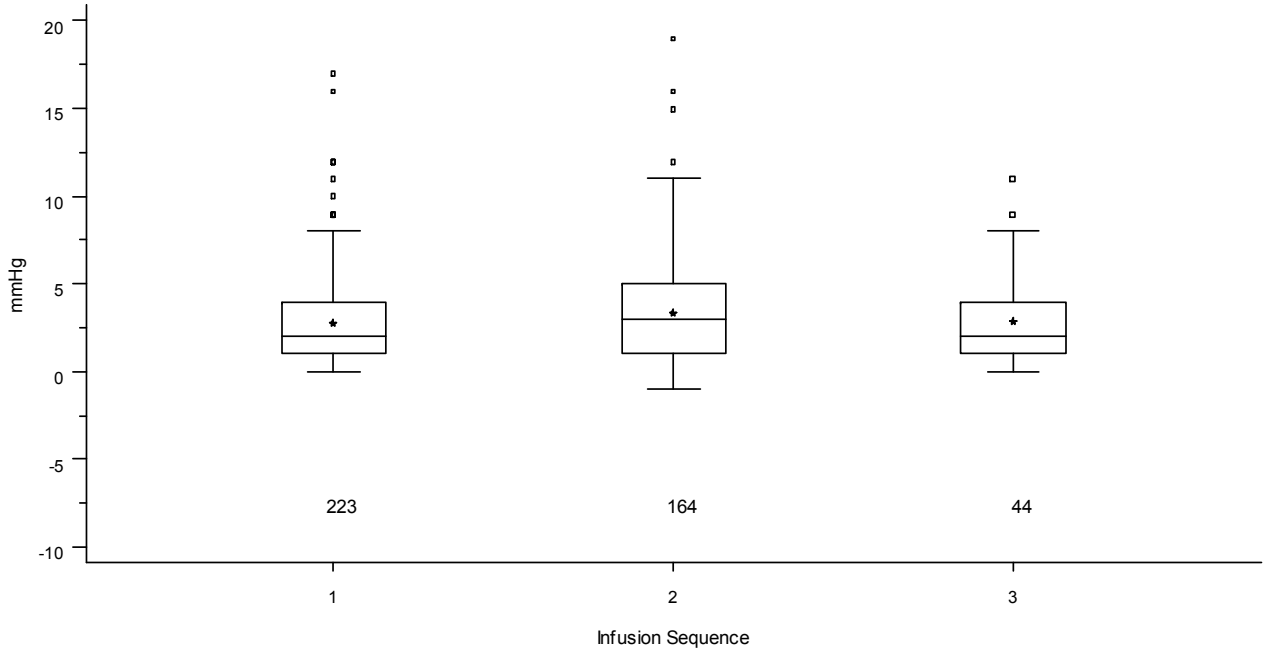
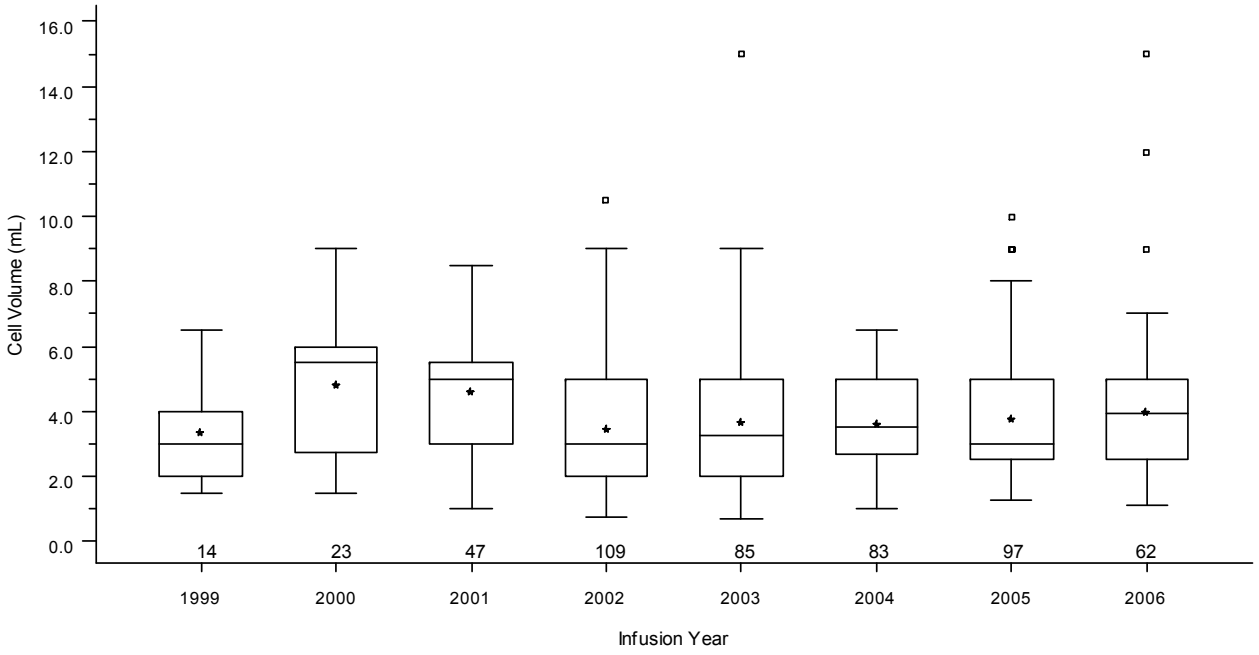


Exhibit 3 – 14
Cell Volume Infused per Infusion by Infusion Year



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 (60%). A number of other immunosuppression regimens (N=22) were used and are listed in Exhibit 4-1.

A summary of T-cell antibodies used for the participant's first infusion is displayed in Exhibit 4-2. Daclizumab was the sole T-cell antibody used in 74% 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, 40% of the recipients were on at least one anti-hypertensive medication (Exhibits 4-9 and 4-10) and 31% were on a lipid lowering medication (Exhibits 4-11 and 4-12). By Year 1 post last infusion, these rates increased to 48% 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), 98% of recipients used an antibiotic, 87% used antivirals, and 82% used vitamin supplements. The most common adjunctive therapies used during follow-up (Exhibit 4-14) included vitamin supplements (16.8% at Month 6 and 14.7% at Year 1) and Pentoxifylline (12.4% at Month 6).

Exhibit 4 – 1
Immunosuppression Regimen at Time of First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	262	100.0	30	100.0
Daclizumab + Sirolimus + Tacrolimus	158	60.3	12	40.0
Daclizumab + Sirolimus + Tacrolimus + MMF	3	1.1	1	3.3
Daclizumab + Sirolimus + Tacrolimus + Prednisone	-	0.0	2	6.7
Daclizumab + Sirolimus + Tacrolimus + MMF + Prednisone	-	0.0	1	3.3
Daclizumab + Tacrolimus + MMF + Prednisone	-	0.0	4	13.3
Daclizumab + Infliximab + Sirolimus + Tacrolimus	18	6.9	2	6.7
Daclizumab + Etanercept + Sirolimus + Tacrolimus	5	1.9	1	3.3
Daclizumab + Etanercept + Sirolimus + Tacrolimus + MMF	-	0.0	1	3.3
Daclizumab + Etanercept + Sirolimus + Tacrolimus + MMF + Methylprednisolone	-	0.0	1	3.3
Daclizumab + 15-deoxyspergualin + Sirolimus + Tacrolimus	5	1.9	-	0.0
Daclizumab + Anti-thymocyte Globulin + Sirolimus + Tacrolimus	4	1.5	-	0.0
Daclizumab + Anti-thymocyte Globulin + Sirolimus + MMF	1	0.4	-	0.0
Daclizumab + Anti-thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus	1	0.4	-	0.0
Daclizumab + Anti-thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus + MMF + Methylprednisolone	7	2.7	-	0.0
Daclizumab + Efalizumab + Tacrolimus + MMF	1	0.4	-	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 + Intravenous Immunoglobulin + Sirolimus + Tacrolimus	1	0.4	-	0.0
Anti-thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus	2	0.8	-	0.0
Anti-thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus + MMF + Methylprednisolone	-	0.0	1	3.3
Anti-thymocyte Globulin + Etanercept + Tacrolimus + MMF + Prednisone	-	0.0	1	3.3
Anti-thymocyte Globulin + Etanercept + Neoral Cyclosporine + Everolimus	1	0.4	-	0.0
Anti-thymocyte Globulin + Etanercept + Neoral Cyclosporine + Methylprednisolone + Everolimus	5	1.9	-	0.0
Alemtuzumab + Tacrolimus + MMF	4	1.5	-	0.0
Alemtuzumab + Etanercept + Sirolimus + Tacrolimus	5	1.9	-	0.0
Alemtuzumab + Infliximab + Sirolimus + Tacrolimus	1	0.4	-	0.0
Basiliximab + Sirolimus + Tacrolimus	1	0.4	-	0.0
Basiliximab + Etanercept + Sirolimus + Tacrolimus	11	4.2	-	0.0
Basiliximab + Etanercept + MMF + Mycophenolic Acid + Generic Cyclosporine	-	0.0	1	3.3
hOKT3γ-1 (Ala-Ala) + Sirolimus + Tacrolimus	4	1.5	-	0.0
hOKT3γ-1 (Ala-Ala)+ Etanercept + Sirolimus + Tacrolimus	2	0.8	-	0.0
Missing Information on Immunosuppression	18	6.9	2	6.7

Exhibit 4 – 2
T Cell Antibodies Used During First Infusion for Induction Therapy

	Allograft Type			
	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	244	100.0	28	100.0
Daclizumab Alone	181	74.2	25	89.3
Daclizumab + Anti-Thymocyte Globulin	13	5.3	-	0.0
Daclizumab + Efalizumab	1	0.4	-	0.0
Alemtuzumab Alone	18	7.4	-	0.0
Anti-Thymocyte Globulin Alone	13	5.3	2	7.1
Basiliximab Alone	12	4.9	1	3.6
hOKT3γ-1(Ala-Ala) Alone	6	2.5	-	0.0

Exhibit 4 – 3
Anti-inflammatory Therapy 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)	139	4.0	1.5	95	4.5	1.9	35	4.6	1.5	22	4.4	1.8	16	4.4	1.6	2	5.5	0.7
Etanercept (mg)	39	131.4	22.7	19	130.3	30.7	8	125.0	32.7	6	120.8	48.5	4	143.8	12.5	0	-	-
Anti-thymocyte Globulin (mg/kg)	17	5.8	0.7	0	-	-	0	-	-	2	5.3	0.8	0	-	-	0	-	-
Infliximab (mg/kg)	14	8.0	2.4	3	10.0	0.1	1	10.0	-	2	10.0	0.0	1	10.0	-	0	-	-
Basiliximab (mg)	11	38.2	6.0	6	76.7	99.9	1	20.0	-	1	20.0	-	0	-	-	0	-	-
Alemtuzumab (mg)	7	35.7	7.9	3	40.0	0.0	0	-	-	0	-	-	0	-	-	0	-	-
hOKT3γ-1 (Ala-Ala) (mg/kg)	6	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)	229	10.9	3.4	158	7.8	3.0	49	7.9	3.3	20	5.8	3.2	17	7.5	2.5	3	7.7	1.2
Tacrolimus (mg/day)	230	2.5	1.8	164	4.0	2.0	53	4.7	2.0	24	3.0	1.6	20	3.9	1.9	4	5.0	1.2
MMF (mg/day)	19	1118.4	658.1	14	1230.0	594.1	11	1340.9	726.9	9	743.3	360.2	4	937.5	427.0	1	500.0	-
Prednisone (mg/day)	0	-	-	0	-	-	0	-	-	7	4.6	0.9	5	5.0	0.0	1	5.0	-
Methylprednisolone (mg/day)	15	103.7	78.0	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	-	-	0	-	-	0	-	-	0	-	-
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	-	0	-	-

Exhibit 4 – 5
Immunosuppression Therapy Use Post Last Infusion

	Islet Alone								Islet After Kidney							
	Follow-Up								Follow-Up							
	1-6 Months		6-12 Months		1-2 Years		2-3 Years		1-6 Months		6-12 Months		1-2 Years		2-3 Years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	239	100.0	205	100.0	139	100.0	97	100.0	27	100.0	23	100.0	21	100.0	11	100.0
Daclizumab + Sirolimus + Tacrolimus	12	5.0	10	4.9	2	1.4	-	0.0	2	7.4	2	8.7	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus + MMF	-	0.0	-	0.0	-	0.0	-	0.0	1	3.7	-	0.0	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	1	3.7	1	4.3	-	0.0	-	0.0
Daclizumab + Sirolimus + MMF	1	0.4	-	0.0	1	0.7	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Tacrolimus + MMF	-	0.0	1	0.5	-	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	3.7	-	0.0	-	0.0	-	0.0
Sirolimus + Tacrolimus	108	45.2	83	40.5	50	36.0	27	27.8	8	29.6	6	26.1	6	28.6	3	27.3
Sirolimus + Tacrolimus + MMF	16	6.7	13	6.3	9	6.5	8	8.2	-	0.0	-	0.0	1	4.8	-	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	2	7.4	1	4.3	1	4.8	-	0.0
Sirolimus	-	0.0	-	0.0	1	0.7	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + MMF	8	3.3	7	3.4	3	2.2	3	3.1	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Mycophenolic Acid	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0

(continued on following page)

Exhibit 4 – 5 *(continued)*
Immunosuppression Therapy Use Post Last Infusion

	Islet Alone								Islet After Kidney							
	Follow-Up								Follow-Up							
	1-6 Months		6-12 Months		1-2 Years		2-3 Years		1-6 Months		6-12 Months		1-2 Years		2-3 Years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Sirolimus + Neoral Cyclosporine + MMF	-	0.0	-	0.0	-	0.0	1	1.0	-	0.0	-	0.0	-	0.0	-	0.0
Azathioprine + Sirolimus + Prednisone	-	0.0	1	0.5	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus	2	0.8	1	0.5	3	2.2	1	1.0	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus + MMF	18	7.5	15	7.3	10	7.2	10	10.3	1	3.7	2	8.7	2	9.5	-	0.0
Tacrolimus + Mycophenolic Acid	-	0.0	1	0.5	1	0.7	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	1	3.7	2	8.7	-	0.0	-	0.0
Tacrolimus + MMF + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	3	11.1	1	4.3	2	9.5	1	9.1
Mycophenolic Acid + Neoral Cyclosporine	1	0.4	2	1.0	-	0.0	1	1.0	-	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	2	1.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Neoral Cyclosporine + Everolimus	4	1.7	3	1.5	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Neoral Cyclosporine + MMF + Everolimus	-	0.0	1	0.5	-	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	4.3	-	0.0	1	9.1
Generic Cyclosporine + MMF	-	0.0	-	0.0	-	0.0	-	0.0	1	3.7	-	0.0	-	0.0	-	0.0
Generic Cyclosporine + MMF + Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	4.8	-	0.0
Missing Information on Immunosuppression	64	26.8	67	32.7	57	41.0	46	47.4	6	22.2	7	30.4	8	38.1	6	54.5

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

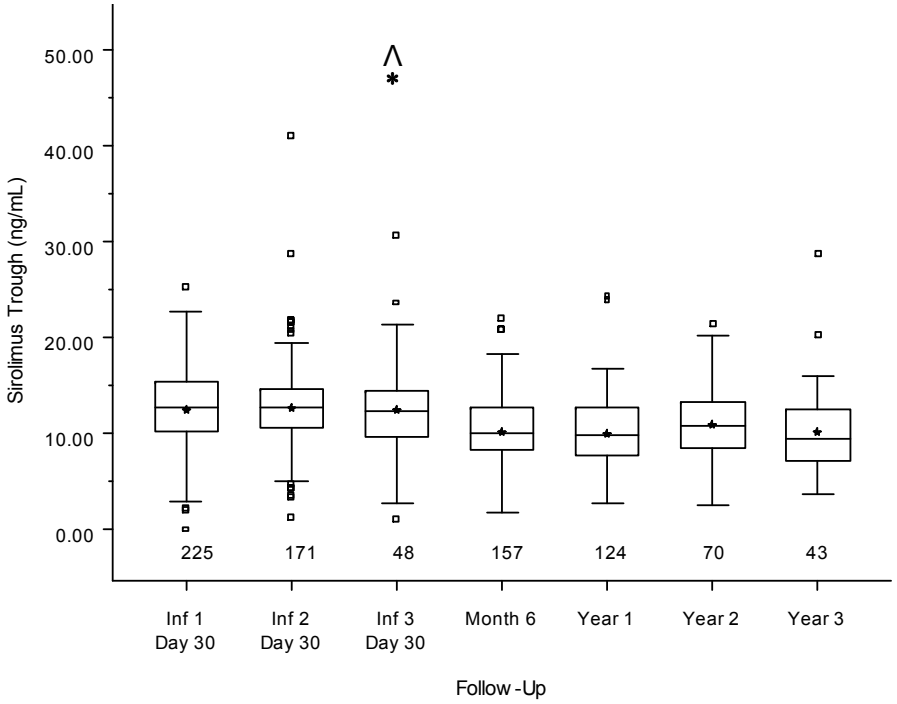
Exhibit 4 – 6
Immunosuppression Dosing Post Last Infusion

	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)	203	7.8	3.4	149	7.0	4.6	116	6.5	3.1	68	6.0	2.6	42	5.0	2.2
Tacrolimus (mg/day)	211	4.0	2.0	159	3.7	1.9	127	3.5	1.6	78	3.5	1.9	49	3.3	1.6
Neoral Cyclosporine (mg/day)	6	295.8	158.4	6	341.7	100.8	6	267.7	99.8	2	262.5	88.4	2	275.0	35.4
MMF (mg/day)	37	1195.1	746.2	44	1408.2	594.3	37	1395.6	556.3	25	1473.3	762.8	22	1617.3	755.9
Prednisone (mg/day)	0	-	-	0	-	-	1	10.0	-	0	-	-	0	-	-
Everolimus (mg/day)	6	3.3	1.5	5	3.7	1.8	4	166.0	322.7	0	-	-	0	-	-
Daclizumab (mg/kg)	0	-	-	12	1.4	1.2	9	1.0	0.0	3	1.0	0.0	0	-	-
Mycophenolic acid (mg/day)	2	1260.0	254.6	4	1350.0	453.0	3	1440.0	0.0	1	720.0	-	1	1440.0	-

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)	19	7.1	3.0	13	6.3	2.8	9	5.2	1.8	8	4.6	1.8	3	5.0	1.0
Tacrolimus (mg/day)	24	3.6	1.3	17	3.1	1.1	14	3.6	1.3	12	3.5	1.7	4	4.3	0.5
Neoral Cyclosporine (mg/day)	0	-	-	0	-	-	1	250.0	-	0	-	-	1	250.0	-
MMF (mg/day)	10	872.0	396.5	6	958.3	458.7	4	750.0	288.7	5	536.0	294.1	2	500.0	0.0
Prednisone (mg/day)	8	4.4	1.8	7	5.0	0.0	6	5.0	0.0	4	5.0	0.0	2	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

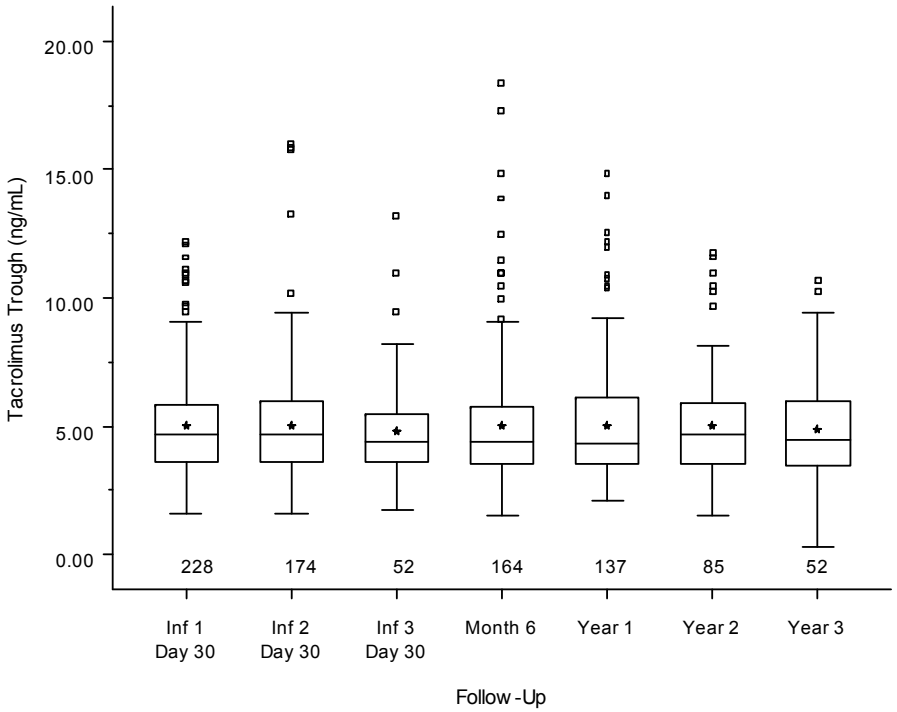


Exhibit 4 – 9
Anti-Hypertensive Medications Pre Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up Post Last Infusion									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Total	261	100.0	200	100.0	164	100.0	98	100.0	63	100.0
No Anti-Hypertensive Medications Taken	157	60.2	113	56.5	85	51.8	41	41.8	29	46.0
ACE Inhibitors	85	32.6	71	35.5	64	39.0	40	40.8	26	41.3
Alpha Adrenergic Blockers	-	0.0	2	1.0	3	1.8	-	0.0	-	0.0
Angiotensin II Receptor Blockers	15	5.7	9	4.5	11	6.7	12	12.2	4	6.3
Beta Adrenergic Blockers	15	5.7	10	5.0	8	4.9	9	9.2	7	11.1
Calcium Channel Blockers	14	5.4	12	6.0	14	8.5	8	8.2	5	7.9
Centrally Acting Agents	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0
Diuretics	10	3.8	18	9.0	21	12.8	14	14.3	9	14.3
Vasodilators	1	0.4	-	0.0	-	0.0	-	0.0	1	1.6

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

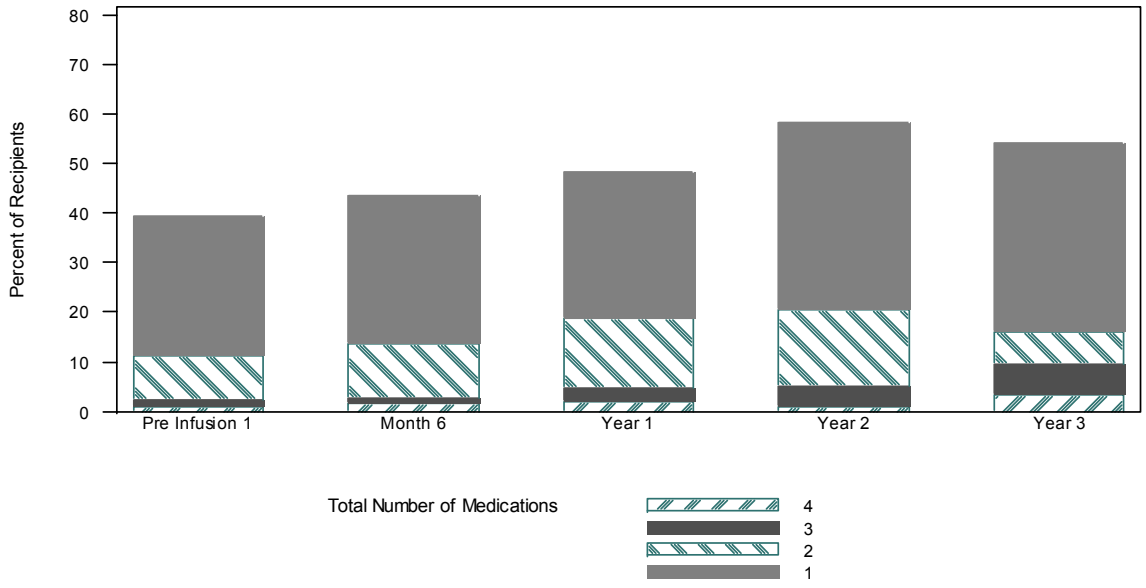


Exhibit 4 – 11
Lipid Lowering Medications Pre Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up Post Last Infusion									
	Pre First Infusion		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%
Total	262	100.0	202	100.0	163	100.0	98	100.0	63	100.0
No Lipid Lowering Medications Taken	181	69.1	92	45.5	63	38.7	33	33.7	20	31.7
Bile Acid Sequestrants	1	0.4	2	1.0	1	0.6	1	1.0	-	0.0
Cholesterol Absorption Inhibitors	5	1.9	3	1.5	2	1.2	3	3.1	2	3.2
Fibric Acid Derivatives	-	0.0	1	0.5	1	0.6	-	0.0	-	0.0
HMG CoA Reductase Inhibitors	79	30.2	103	51.0	91	55.8	57	58.2	40	63.5
Nicotinic Acid	1	0.4	8	4.0	6	3.7	4	4.1	-	0.0

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

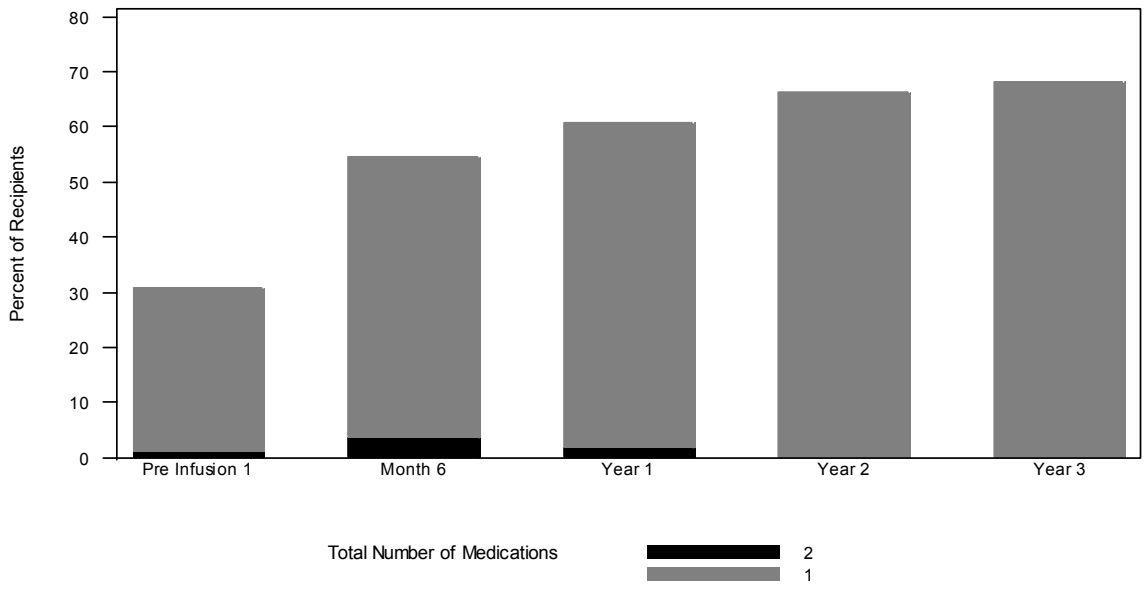


Exhibit 4 – 13
Adjunctive Therapy Used at Time of First Infusion
All Allograft Recipients

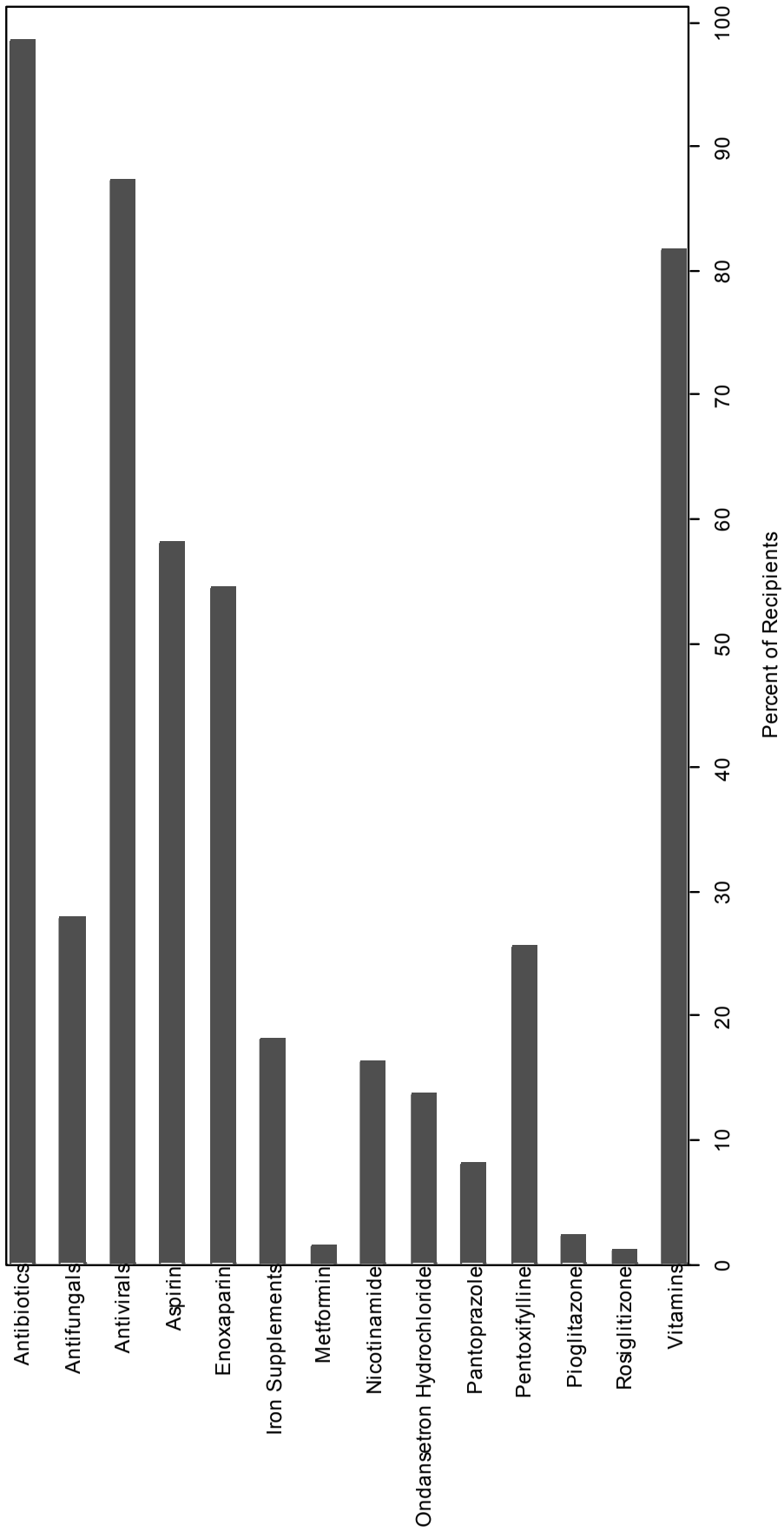


Exhibit 4 – 14
Adjunctive Therapy Post Last Infusion
All Allograft Recipients

	Follow Up Visit							
	Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%
Total	202	100.0	163	100.0	104	100.0	64	100.0
Pentoxifylline	25	12.4	-	0.0	-	0.0	-	0.0
Metformin	10	5.0	7	4.3	7	6.7	5	7.8
Rosiglitazone	3	1.5	4	2.5	4	3.8	3	4.7
Pioglitazone	2	1.0	1	0.6	1	1.0	-	0.0
Acarbose	1	0.5	1	0.6	1	1.0	-	0.0
Repaglinide	-	0.0	-	0.0	-	0.0	2	3.1
Chromium picolinate	1	0.5	1	0.6	1	1.0	-	0.0
Iron	6	3.0	8	4.9	5	4.8	-	0.0
Vitamins	34	16.8	24	14.7	7	6.7	-	0.0

Chapter 5
Graft Function

Graft Function

Chapter 5 summarizes results on graft function for the 292 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 recipients are re-infused: 12% by Day 30, 37% by Day 75, 57% by Month 6, and 69% by Year 1. The proportion that is insulin independent without re-infusion remains fairly constant at 9-13% throughout the first year. An additional 4-14% of all IA recipients retain detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 262 IA recipients, 58% are expected at three-years post first infusion, at which time, regardless of the total number of infusions received, about 16% are insulin independent, 28% are insulin dependent with detectable C-peptide, 32% have no detectable C-peptide or are lost to follow-up, and 23% have missing data (required but not yet reported).

Analyzed from last infusion (Exhibit 5-2), where re-infusion is not an issue, the percentage of all IA recipients that are insulin independent declines steadily from 46% at Month 6 to 16% at Year 3. The proportion with loss of islet function (reported graft failure or no detectable C-peptide or lost to follow-up with imputed graft failure) increases steadily from 13% at Month 6 to 42% at Year 3 (Exhibit 5-2). A stable 18-22% retains graft function with exogenous insulin over the three years; every time point has 20-23% missing data. 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 daily with about 20% missing data on any day), the prevalence of insulin independence from last infusion declines from about 60% at Month 4 to about 24% at Year 3 (1100 days) 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 64%, 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 262 IA recipients; the difference in person-time of insulin independence between the 2-3 infusion curve and the single infusion curve is not negligible.

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 other organs, but with a slower initial slope, indicative of multiple infusions. Overall, 73% of all recipients achieved insulin independence, for both IA and IAK recipients, and follow very similar cumulative event rates, with IAK recipients achieving II somewhat more quickly initially. The median time to achievement of insulin independence is slightly over 150 days after first infusion. Multiple infusions increase the likelihood of achieving insulin independence (Exhibit 5-13, Panels B-D). After achievement, 67% of IA recipients retain insulin independence by one year later, and this decreases to 45% 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: 74% still have graft function at Year 3 (Exhibit 5-14, dashed line). Three infusions tend 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 59-75% at Month 6 and 53-67% 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 graft function have HbA_{1C} levels < 7.0%. Post last infusion; these rates are 61-86% at Month 6 and 34-55% 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 49% at Month 6 and 41% at Year 1 post first infusion (censored at re-infusion, Exhibit 5-7), with 33% retaining this level of function at Year 3 post last infusion.

Severe Hypoglycemia

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 76-87% pre-infusion to less than 5-20% throughout the first year post last infusion, and to 9-43% 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 without graft function 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.

Changes in Islet Graft Function

Graft loss or dysfunction, whether measured by C-peptide levels, observed or reported by the site, or imputed from loss to follow-up with presumed cessation of immunosuppression, increases steadily over time. At Year 3 post last infusion, 42% of IA recipients lost graft function or were lost to follow-up, and another 20% had graft dysfunction (Exhibit 5-10). Viewed as Kaplan-Meier estimates (Exhibit 5-11), 48% of IA recipients lost graft function or were lost to follow-up 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 Insulin Independence (II), Maintenance of Insulin Independence (MII) and Complete Islet Failure (CIF) Post First and Post Last Infusion

Results of Cox regression analysis of time to first insulin independence (II), maintenance of insulin independence (MII) after first achievement, and complete islet failure (CIF) are presented in Exhibit 5-22 for post first infusion and in Exhibit 5-23 for post last infusion, according to the modeling paradigm presented in Methods. These events are competing risks. 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.

In this first look at the possible effects of factors on outcomes, a number of factors are univariately associated with outcomes post first infusion at p≤ 0.10 (Exhibit 5-22). The likelihood of insulin independence increases with lower pre-infusion HbA_{1C} levels, lower fasting glucose levels, lower daily insulin and/or number of injections, lower recipient weight and/or BMI, donor cardiovascular/stroke cause of death, donor O blood type, shorter cold ischemia time, higher total IEQs/kg, higher islet viability, higher total endotoxin, and when the procurement team and infusion teams are related (other factors have weaker but nominally significant effects); it decreases with donor use of vasopressors. A preliminary multivariate model eliminates all factors but fasting glucose, number of daily injections, cold ischemia time, total IEQs/kg infused, and total endotoxin infused (Exhibit 5-22 Panel D). The direction of effects is worth noting, particularly the increased likelihood of achieving II with higher levels of endotoxin. This result will need to be monitored as more data is added to the registry, and will require additional analysis. The effect of each induction therapy (see Exhibits 4-1 to 4-3) on the primary outcomes was analyzed (univariate results not shown). None of the induction therapies altered the results of the current multivariate models (Exhibit 5-22 D, E, and F).

Exhibit 5-23 presents results of univariate models of factors predictive of outcomes post last infusion at p≤ 0.10. For insulin independence, a preliminary multivariate model, Exhibit 5-23 Panel D, confirms the positive influence of lower pre-infusion HbA_{1C}, higher total IEQs/kg over all infusions, the donor not receiving insulin during the terminal hospital stay, and the recipient not given insulin on Day 0 of last infusion. The last result is detailed in Panel 5-23 G, in which the immediate response after last infusion is attributable to no insulin given on Day 0. Here, rather than giving or not giving insulin on Day 0 on a randomized basis to first-time recipients, insulin on Day 0 of last infusion is highly predicated on whether the recipient was recently or currently insulin independent by the study definition, whether they had previously been insulin independent, and how many previous infusions they had received. After the initial high response for those not given insulin on Day 0, the event rates are nearly identical (Panel 5-23 G), as they are post first infusion (data not shown). No induction drug remained significant in multivariate modeling for insulin independence post last infusion, or loss thereof. For complete islet failure, etanercept is significantly protective, without affecting the other related factors (HR=0.195 p=0.0062, Exhibit 5-23 Panel F). Etanercept was given at one or more infusions in 15% of the IA recipients. Its univariate effect -- a less impressive HR=0.4 p=0.05 -- seems to be magnified with adjustment by other factors in the model. This preliminary result will be monitored with additional data and will be investigated in greater detail in focus analyses.

Heparin given at infusion is currently withheld as a variable in these models, as the sites are revising a substantial number of responses based on a query prompted by the present analyses.

There are a number of strong correlations among some of the univariately significant factors that may make the multivariate models unstable, in addition to the influences of substantial amounts of missing data on the factors. Multivariate modeling for factors influencing outcomes will continue as the Registry matures and additional data are reported in future.

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 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 insulin independent than not (Exhibits 5-48 and 5-50).

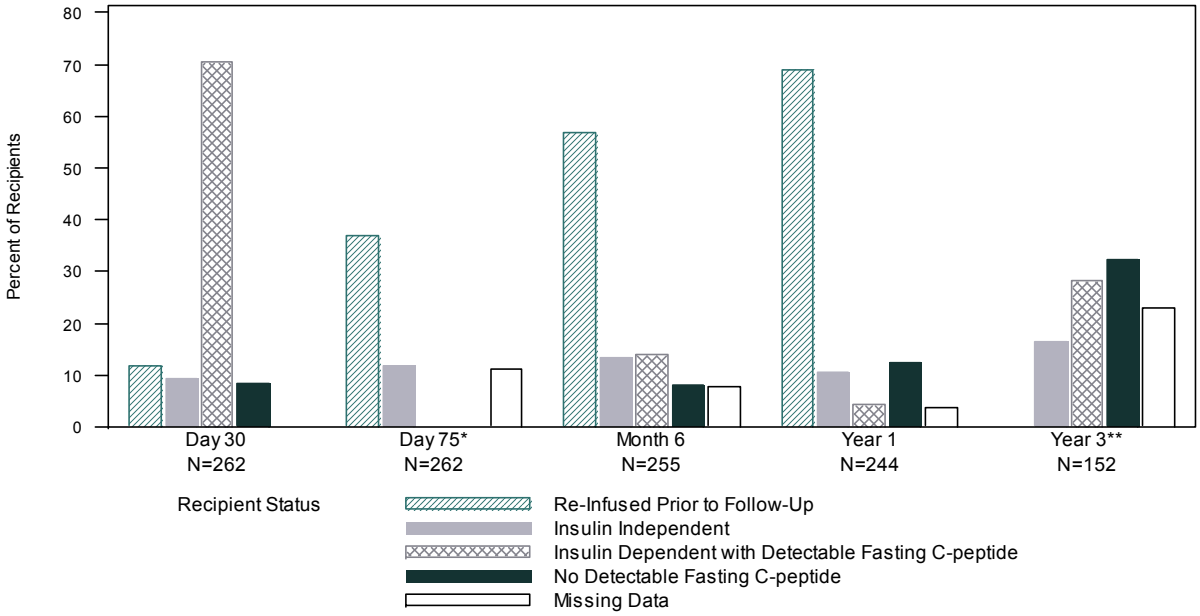
A complete set of laboratory values are summarized by infusion sequence in Exhibit 5-51. Additional metabolic test summaries are located in Exhibits 5-52 and 5-53.

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.

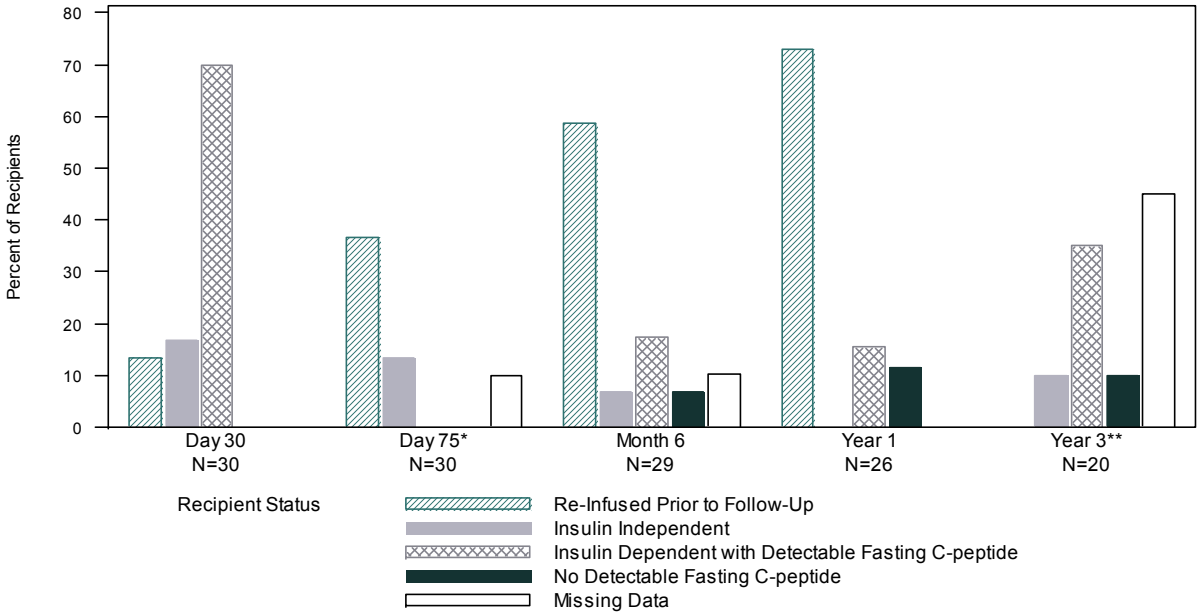
Exhibit 5 – 1
Insulin Independence, Insulin Dependence, Absence of Fasting C-peptide, or Re-Infusion Post First Infusion

A. Islet Alone Recipients



*C-peptide data not available at Day 75
**Year 3 status independent of re-infusion

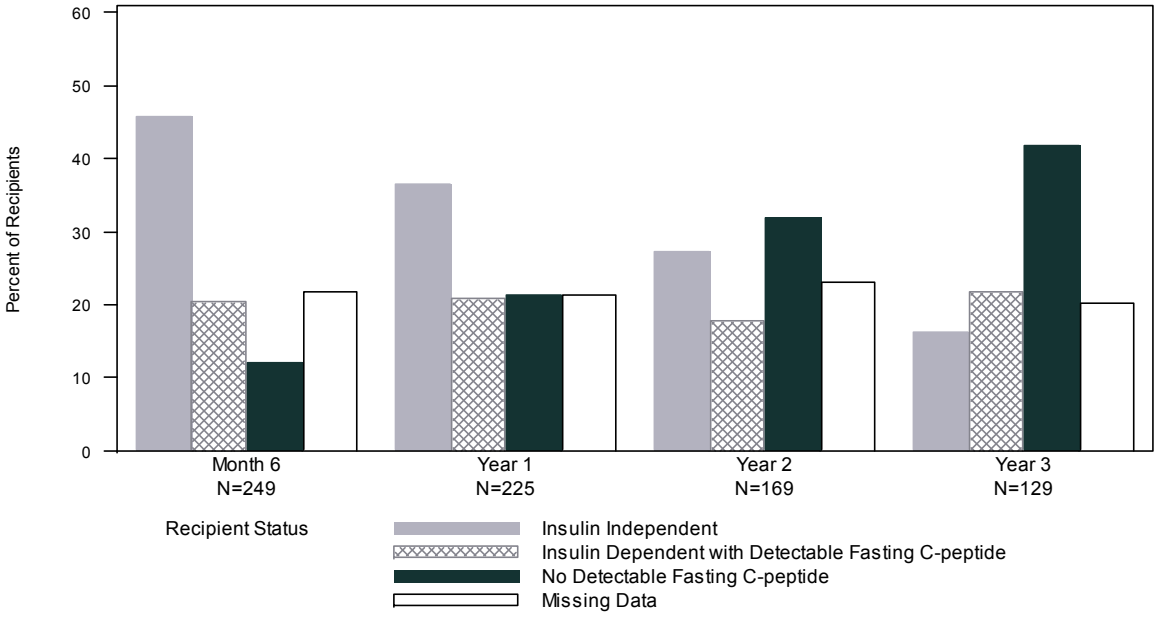
B. Islet After Kidney Recipients



*C-peptide data not available at Day 75
**Year 3 status independent 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

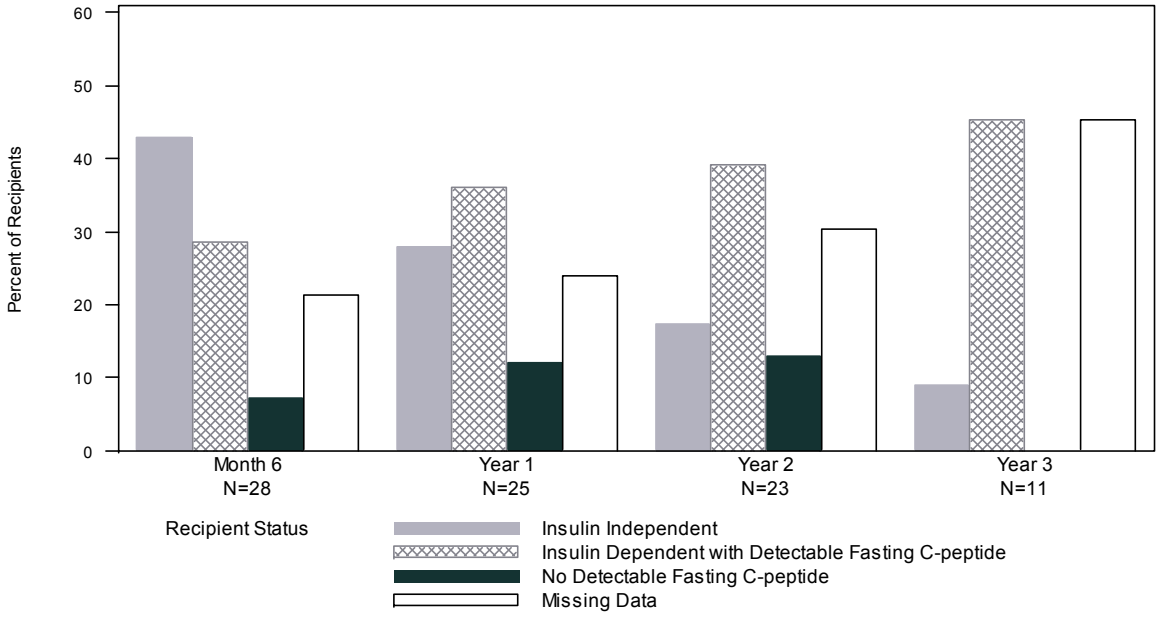
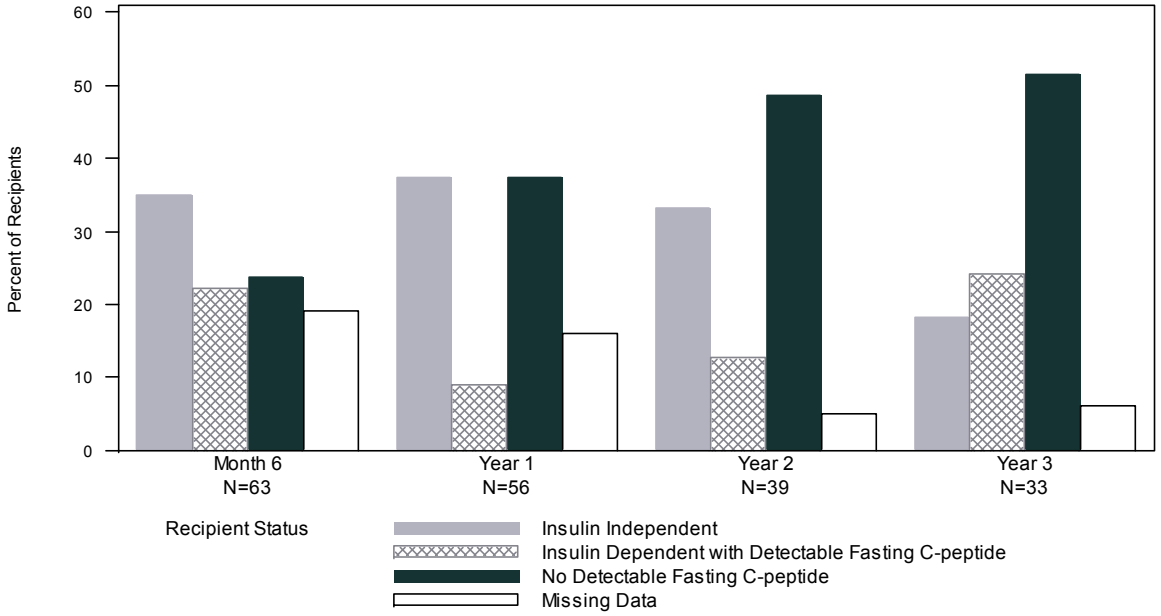


Exhibit 5 – 3
Insulin Independence, Insulin Dependence, or Absence of Fasting C-peptide Post Last Infusion by Total Number of Infusions Received
Islet Alone Recipients

A. Recipients of 1 Infusion



B. Recipients of 2 Infusions

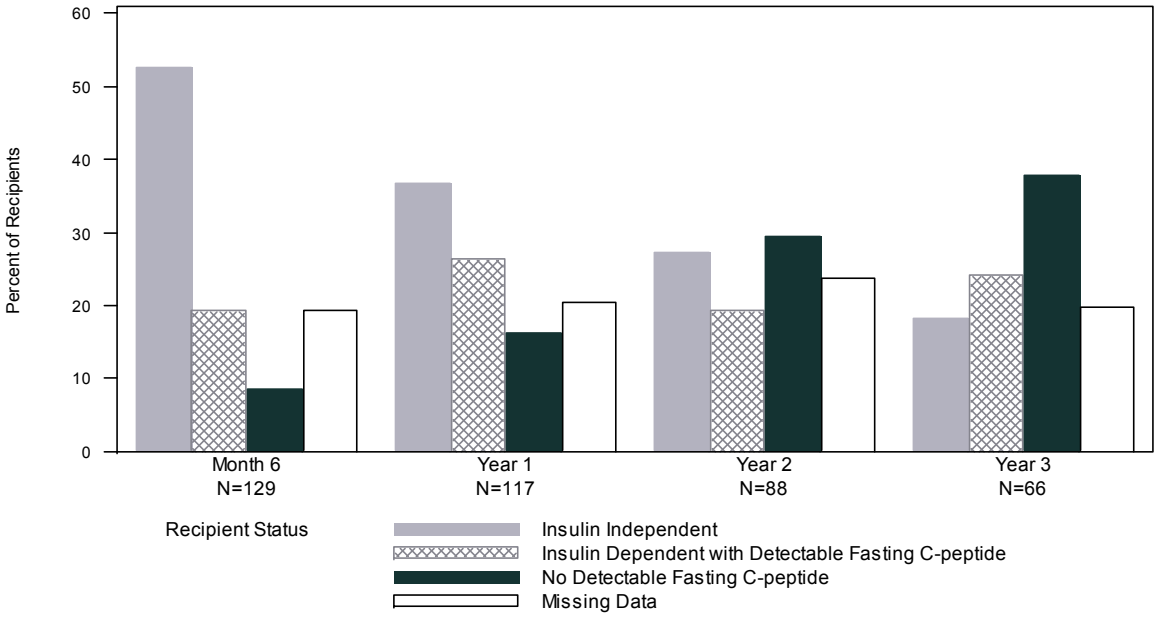


Exhibit 5 – 3 *(continued)*
Insulin Independence, Insulin Dependence, or Absence of Fasting C-peptide Post Last Infusion by Total Number of Infusions Received Islet Alone Recipients

C. Recipients of 3 Infusions

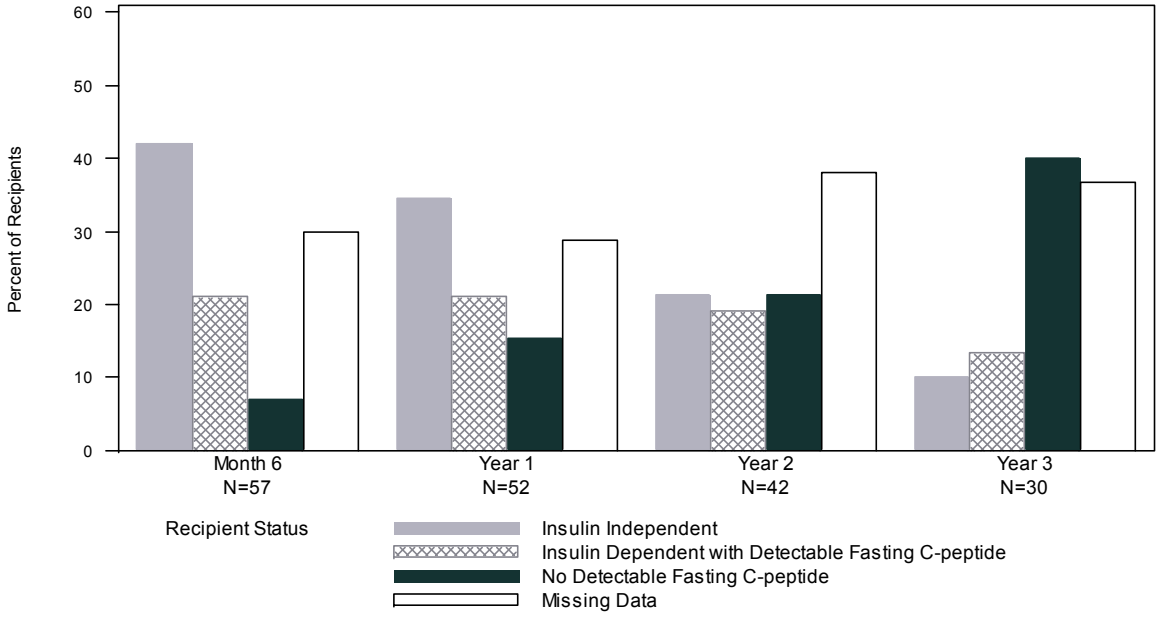
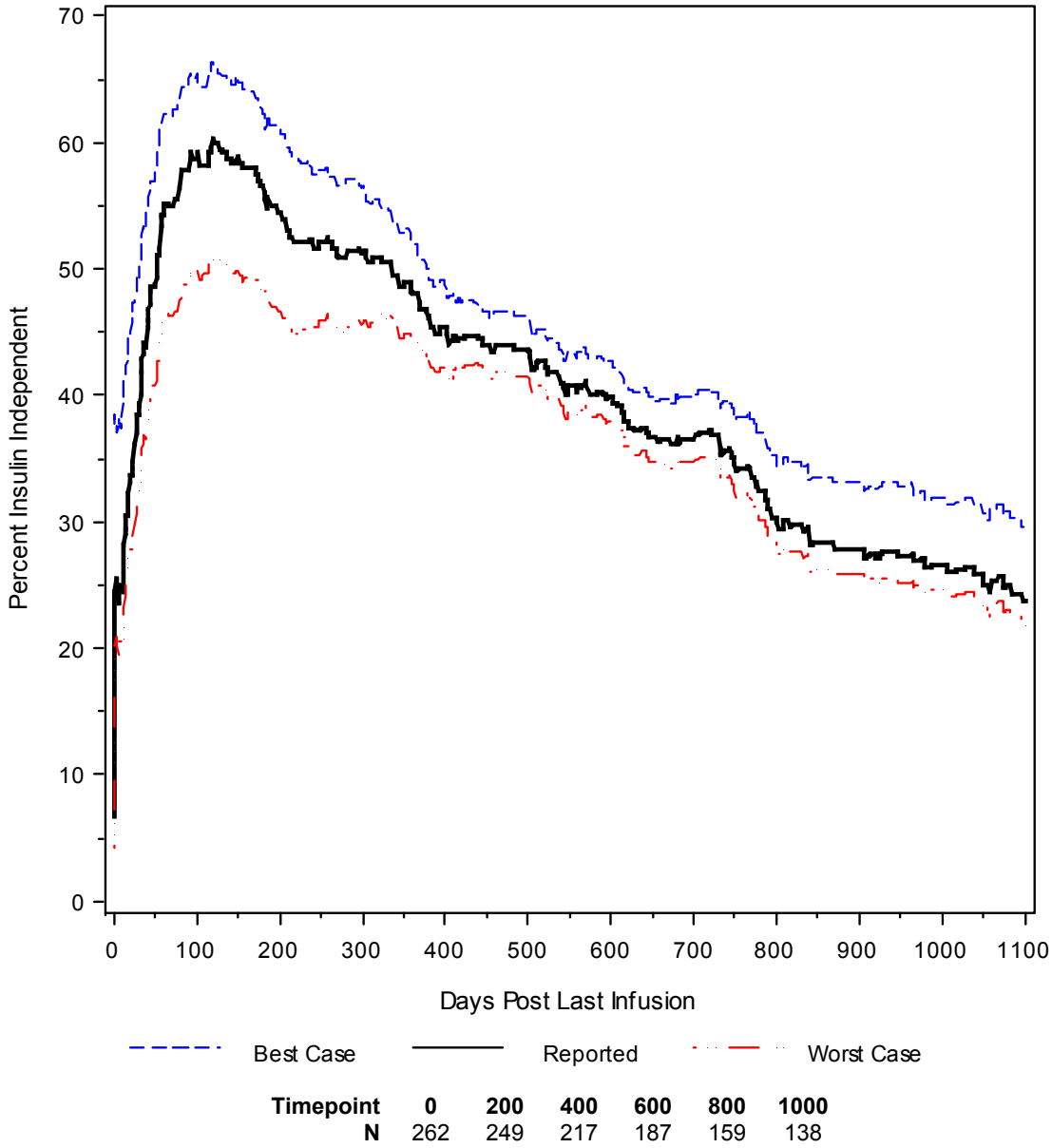


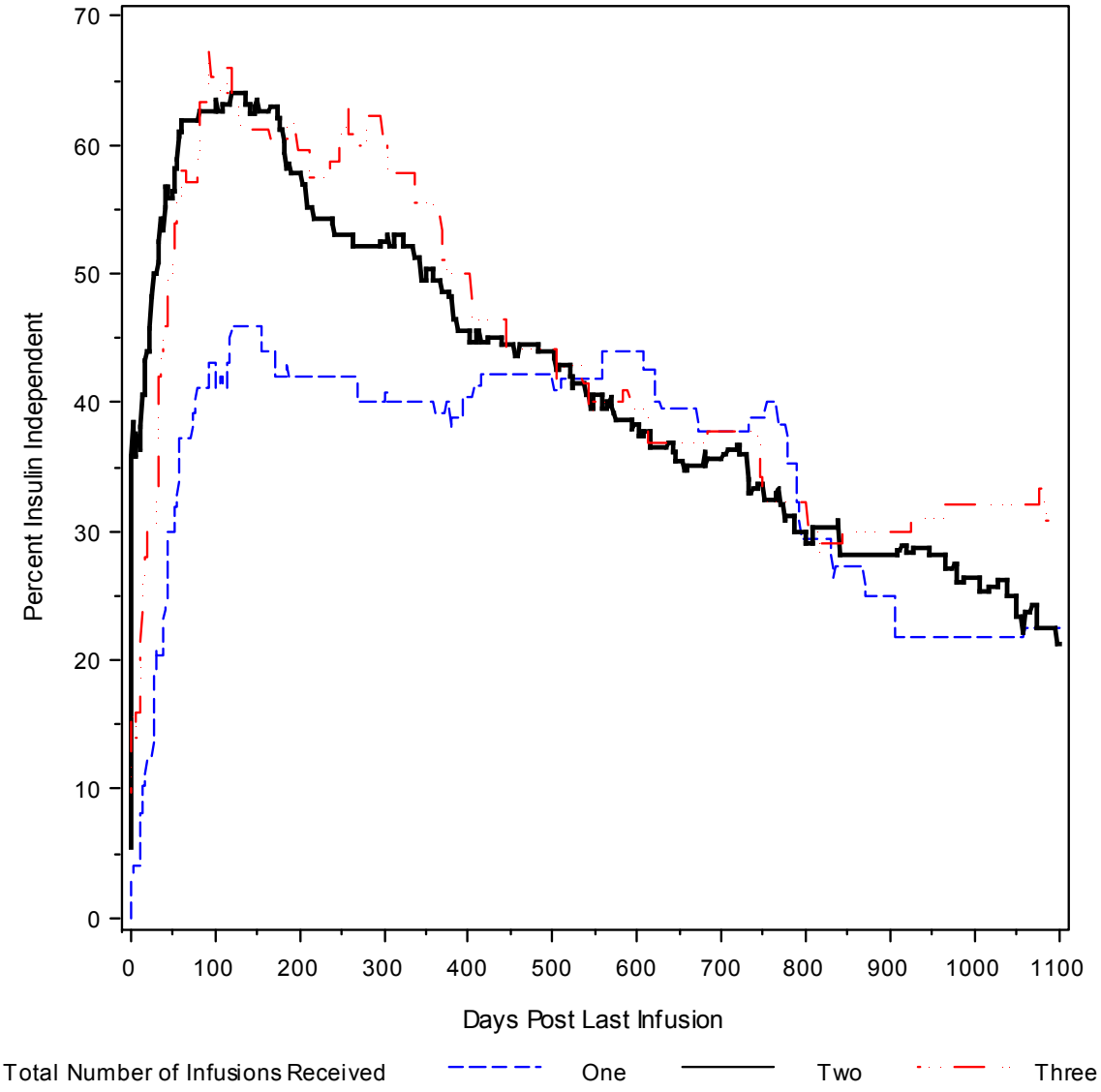
Exhibit 5 – 4
Prevalence of Insulin Independence Post Last Infusion
Islet Alone Recipients



Timepoint	0	200	400	600	800	1000
N	262	249	217	187	159	138

"Reported" 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



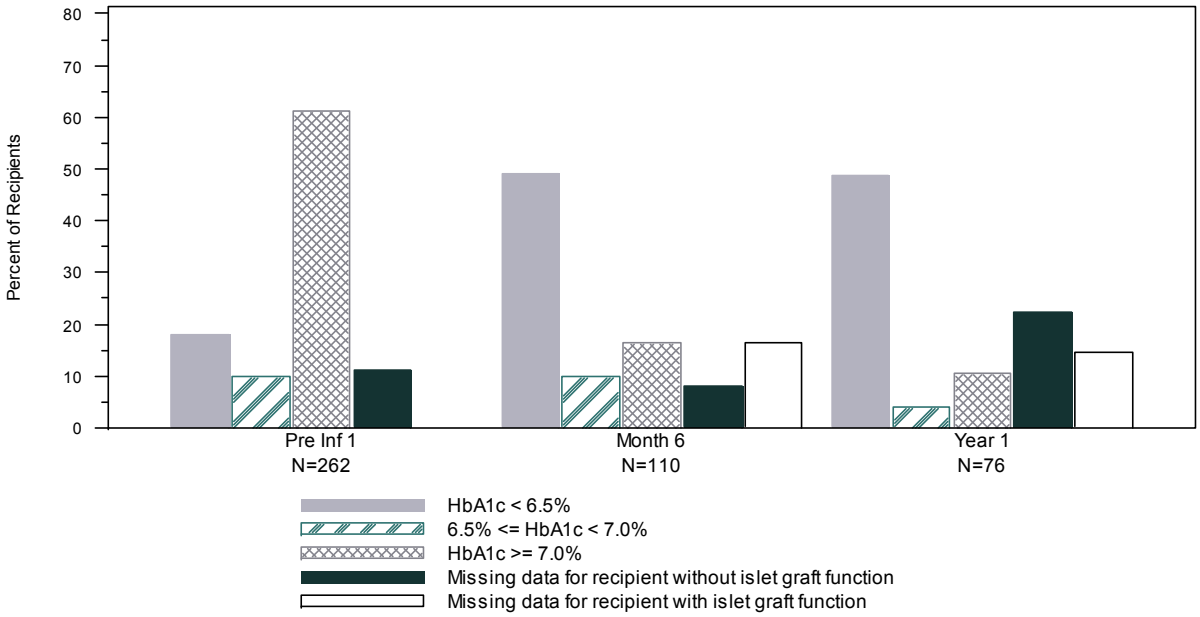
Timepoint	0	200	400	600	800	1000
N 1 Infusion	49	50	47	41	34	32
N 2 Infusions	117	116	112	99	80	68
N 3 Infusions	50	47	44	38	34	28

This Exhibit summarizes the percent of recipients that are insulin independent by time post their last infusion procedure. At Day 75, 62% of participants who received two islet infusions were insulin independent, while 57% with three infusions and 39% with one infusion were insulin independent. By Year 2, these rates drop to 36% for those with two infusions, and 38% with three infusions, and 38% 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

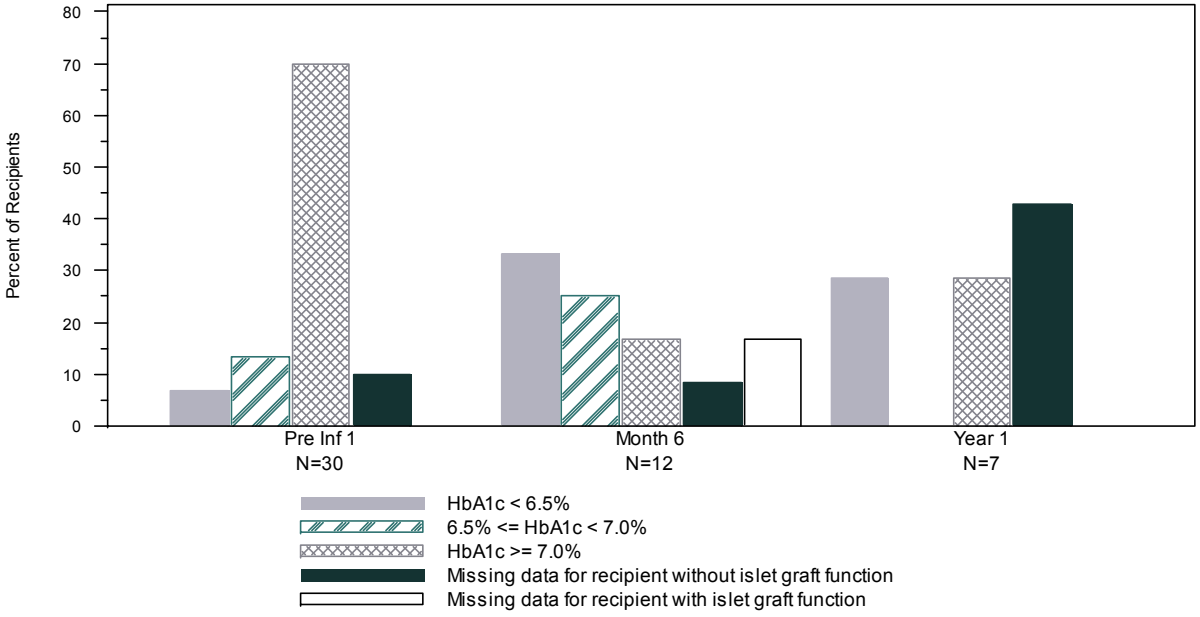
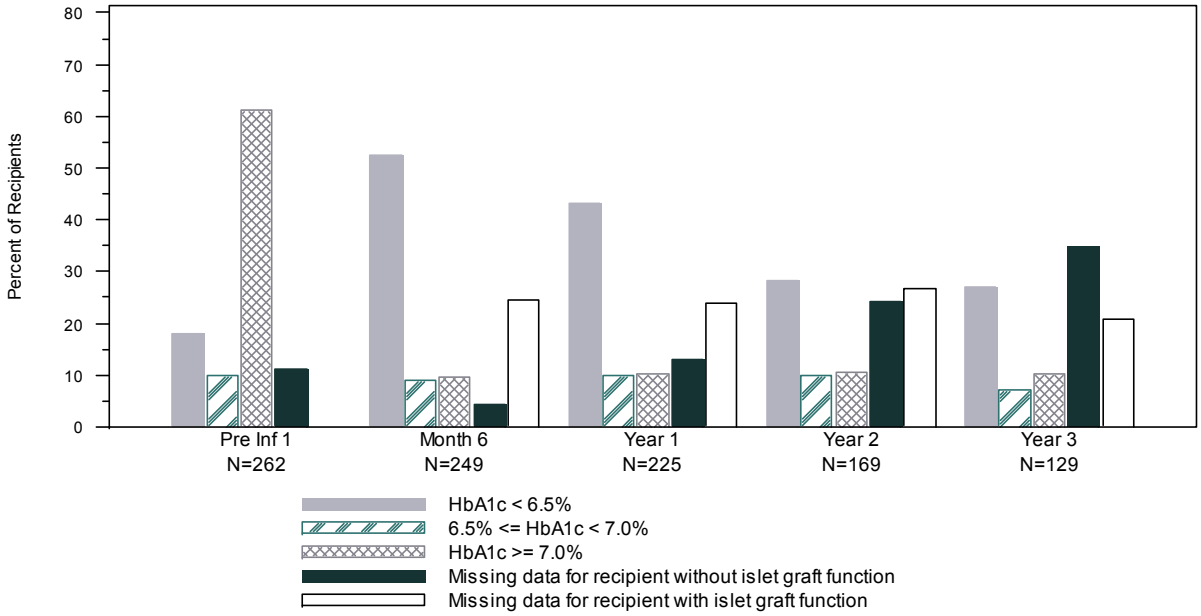


Exhibit 5 – 6 *(continued)*
HbA_{1c}

B. Post Last Infusion

Islet Alone Recipients



Islet After Kidney Recipients

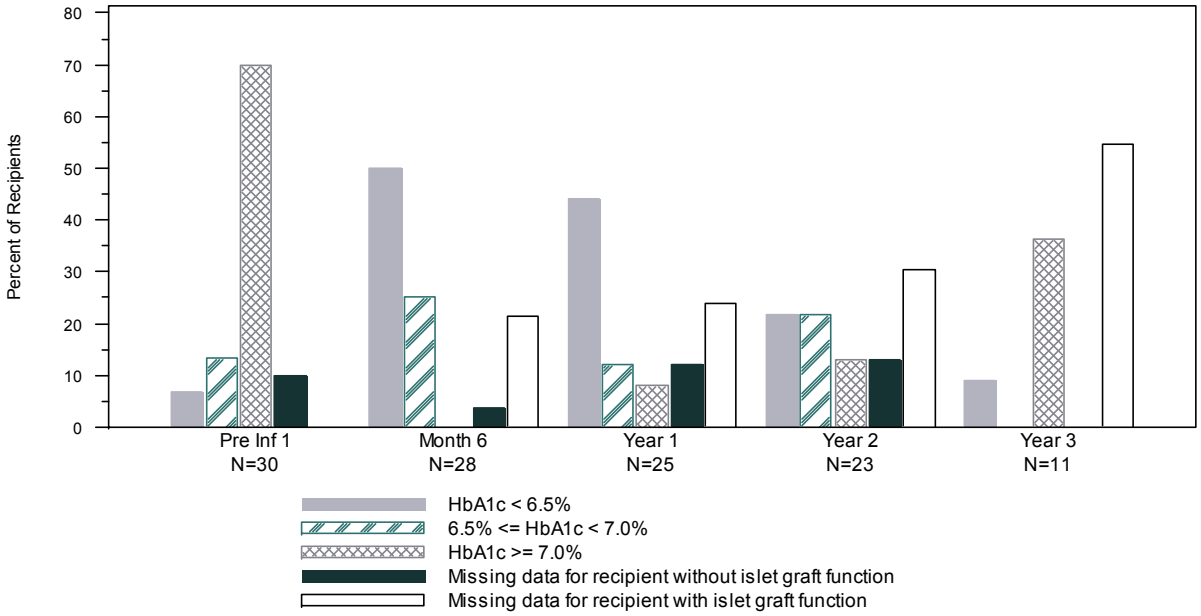
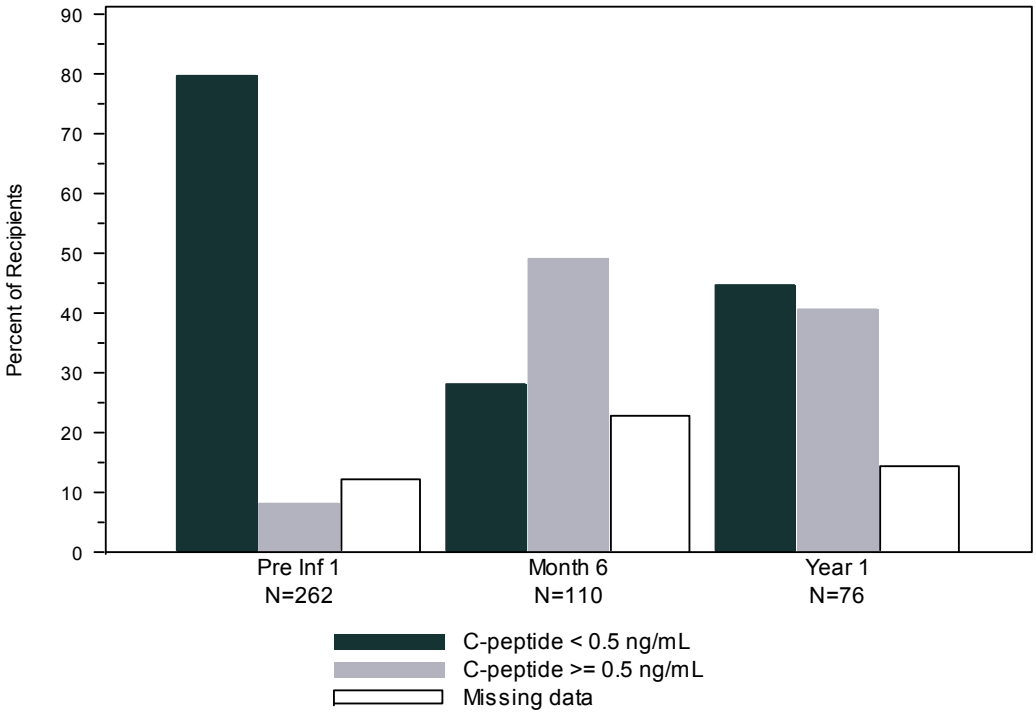


Exhibit 5 – 7
C-peptide ≥ 0.5 ng/mL

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

Islet Alone Recipients



Islet After Kidney Recipients

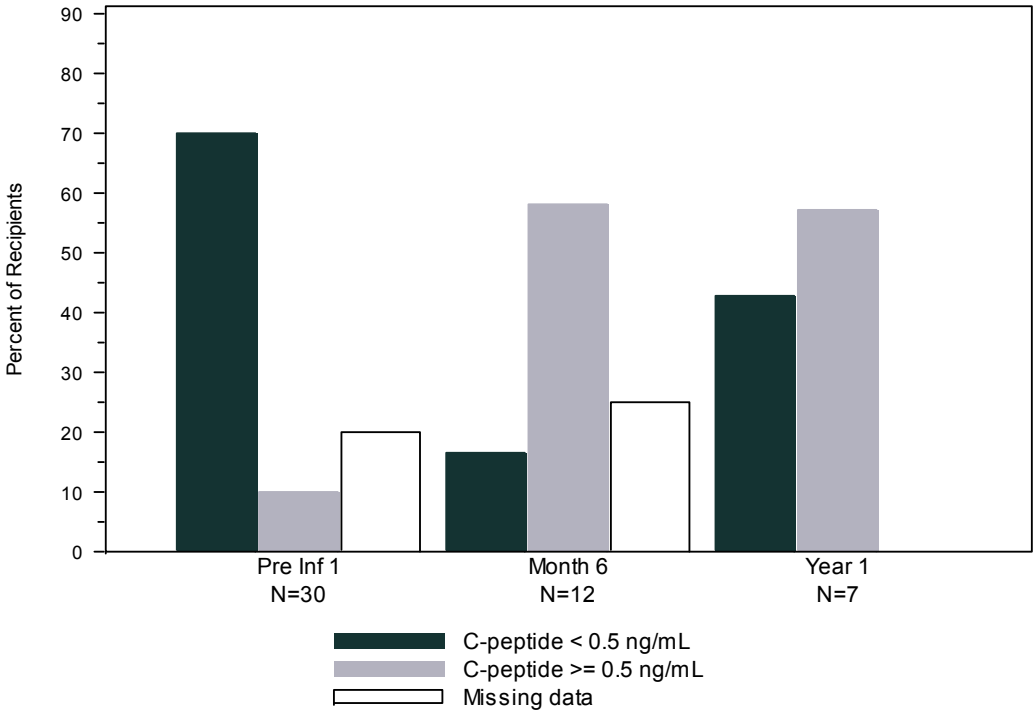
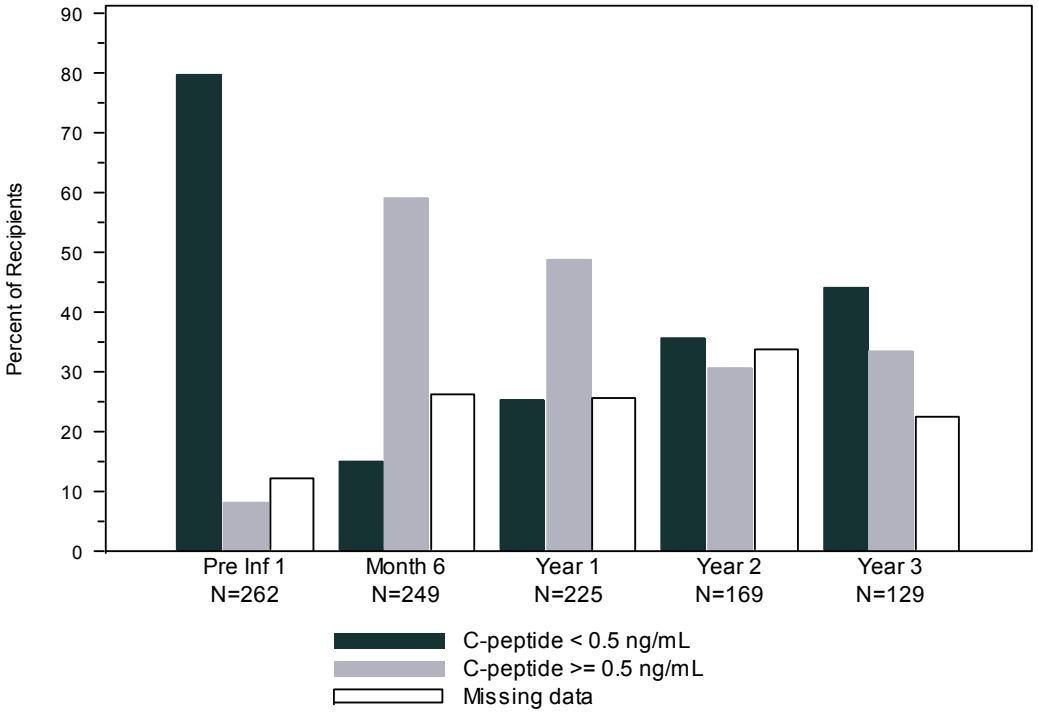


Exhibit 5 – 7 *(continued)*
C-peptide ≥ 0.5 ng/mL

B. Post Last Infusion

Islet Alone Recipients



Islet After Kidney Recipients

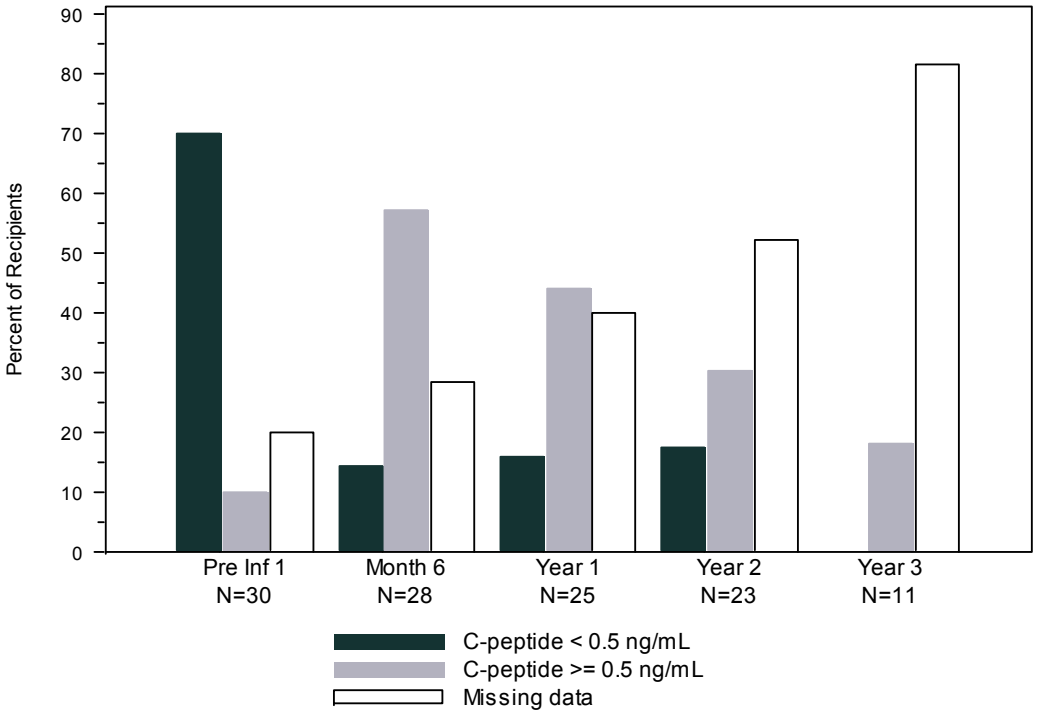
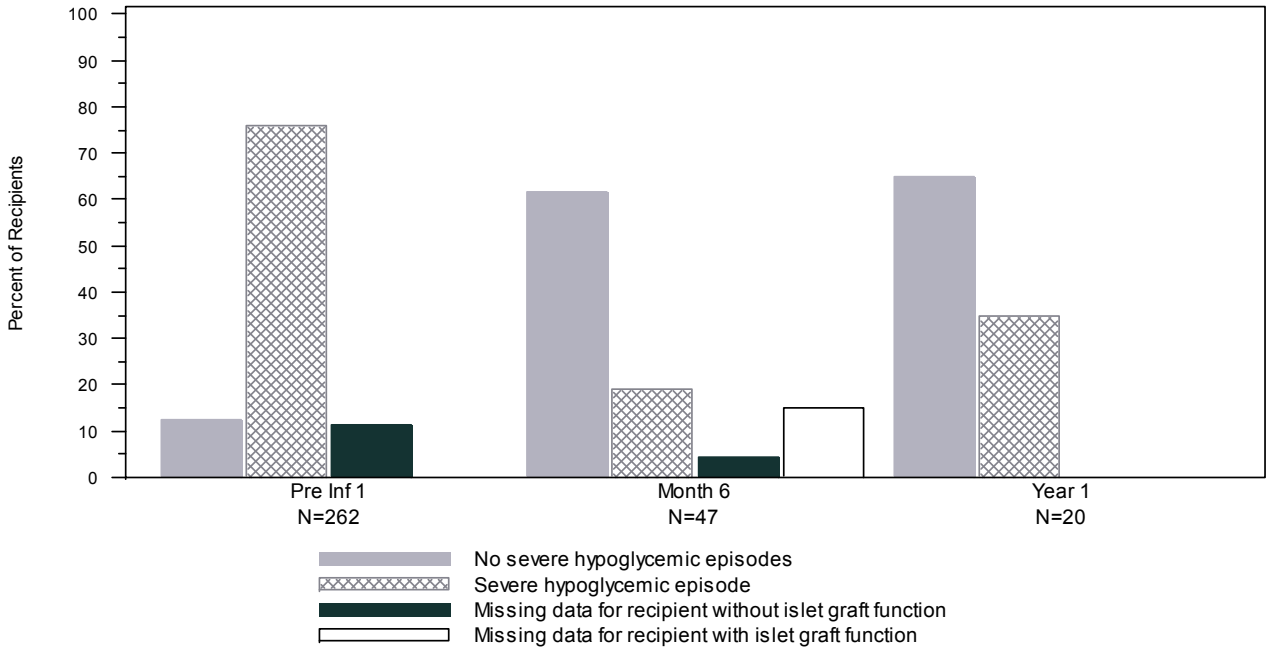


Exhibit 5 – 8
Severe Hypoglycemia

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

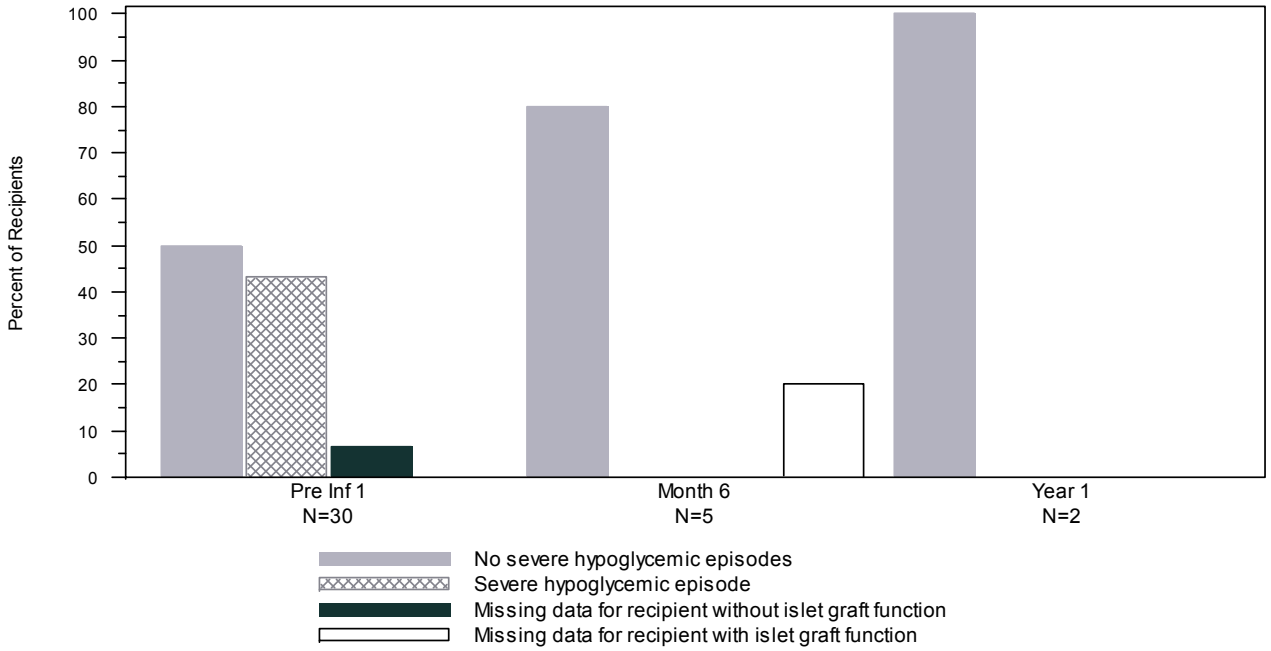
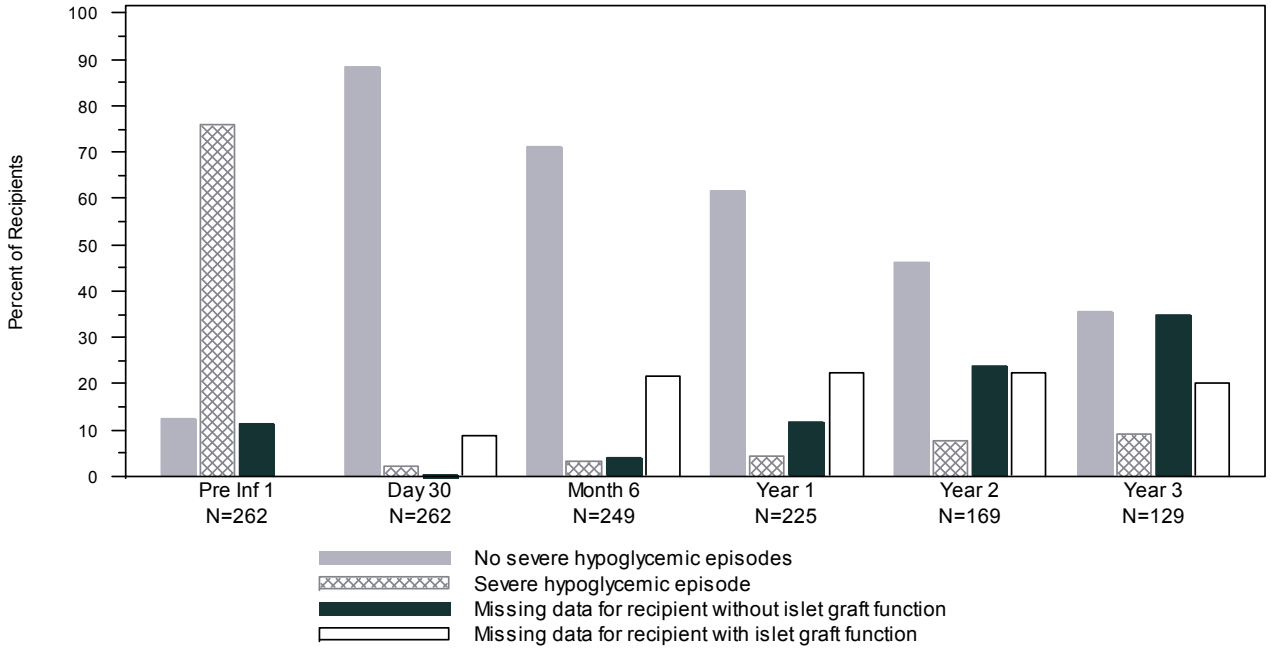


Exhibit 5 – 8 *(continued)*
Severe Hypoglycemia

C. Post Last Infusion
Islet Alone Recipients



D. Post Last Infusion
Islet After Kidney Recipients

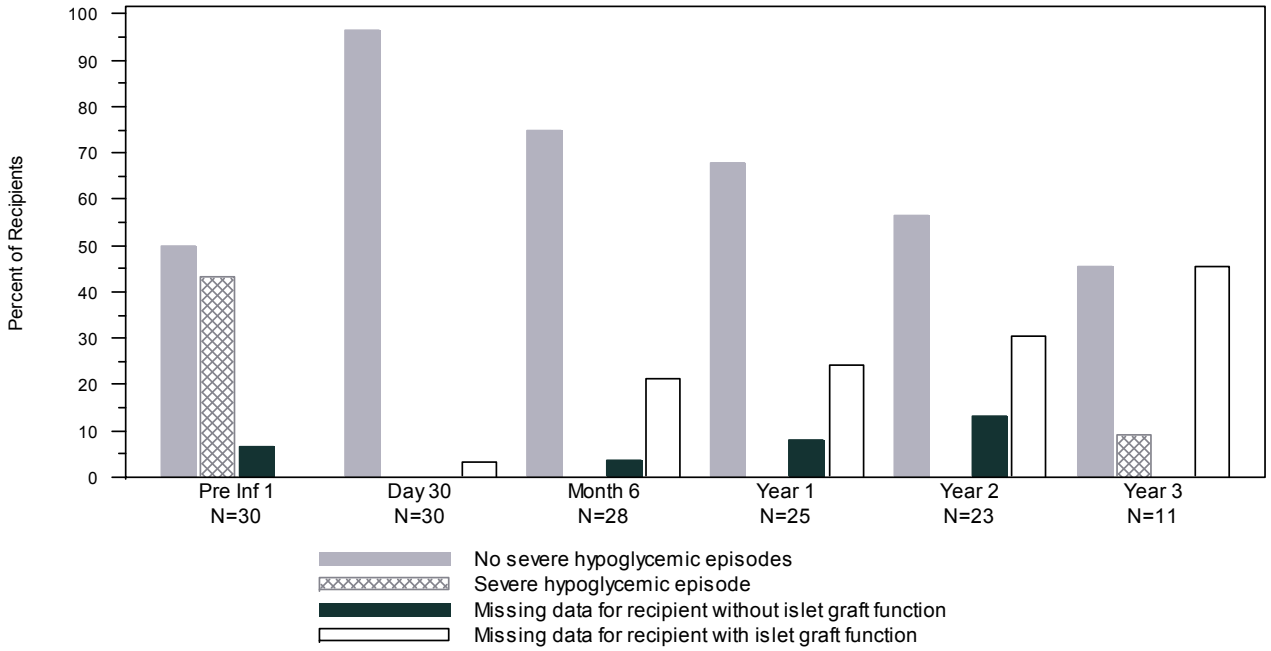
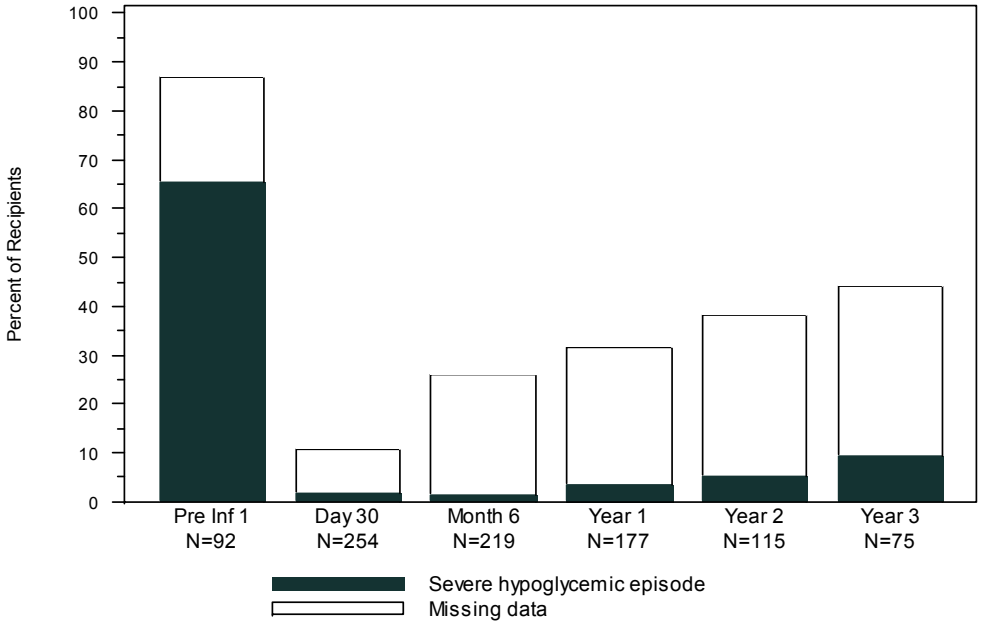


Exhibit 5 – 8 *(continued)*
Severe Hypoglycemia

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



F. Post Last Infusion
Islet Alone Recipients without Detectable Fasting C-peptide

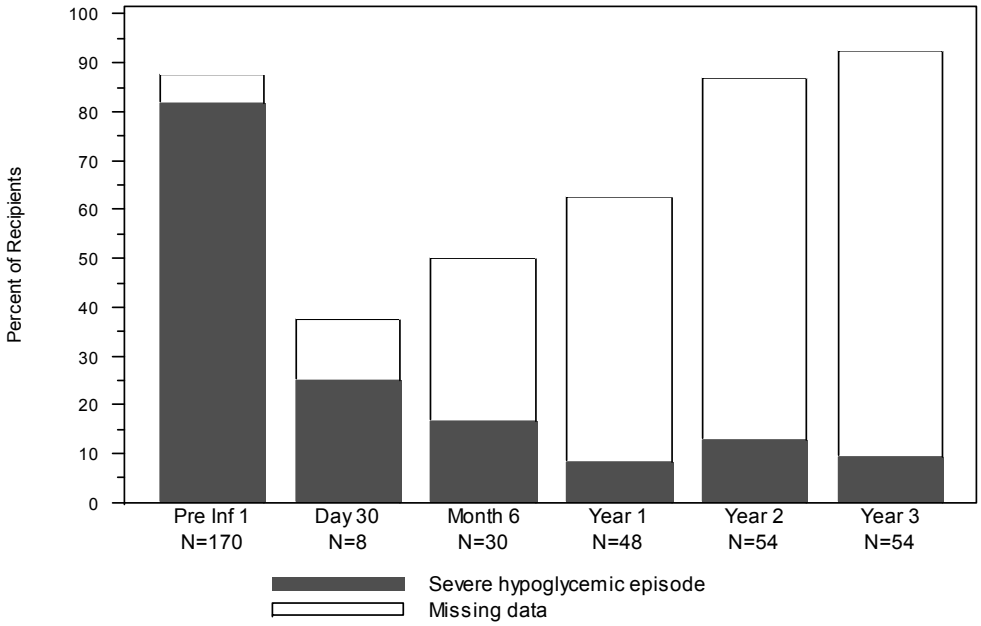


Exhibit 5 – 9
Hypoglycemia Status Pre First Infusion and Post Last Infusion
All Allograft Recipients

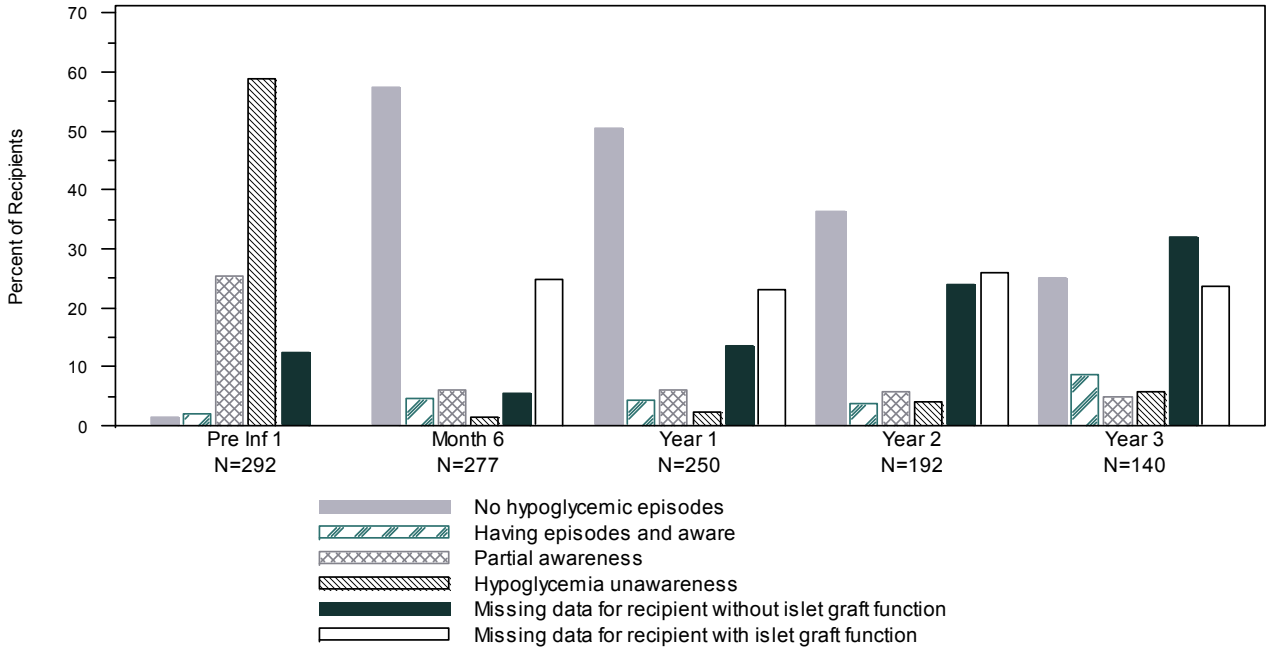
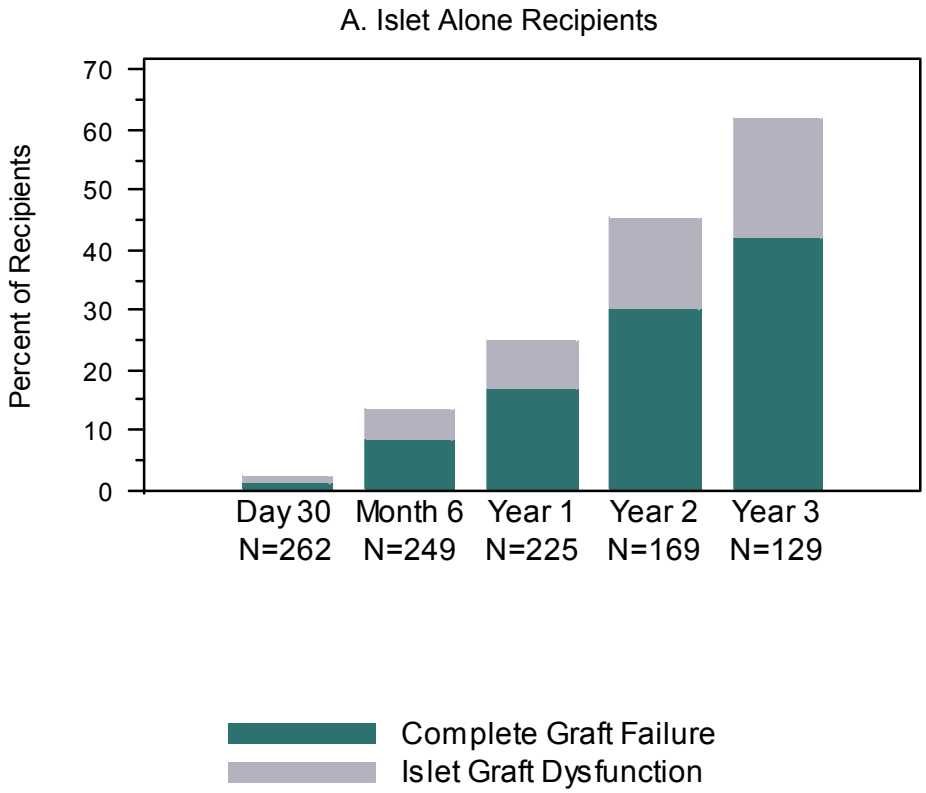


Exhibit 5 – 10
Graft Loss or Dysfunction Post Last Infusion



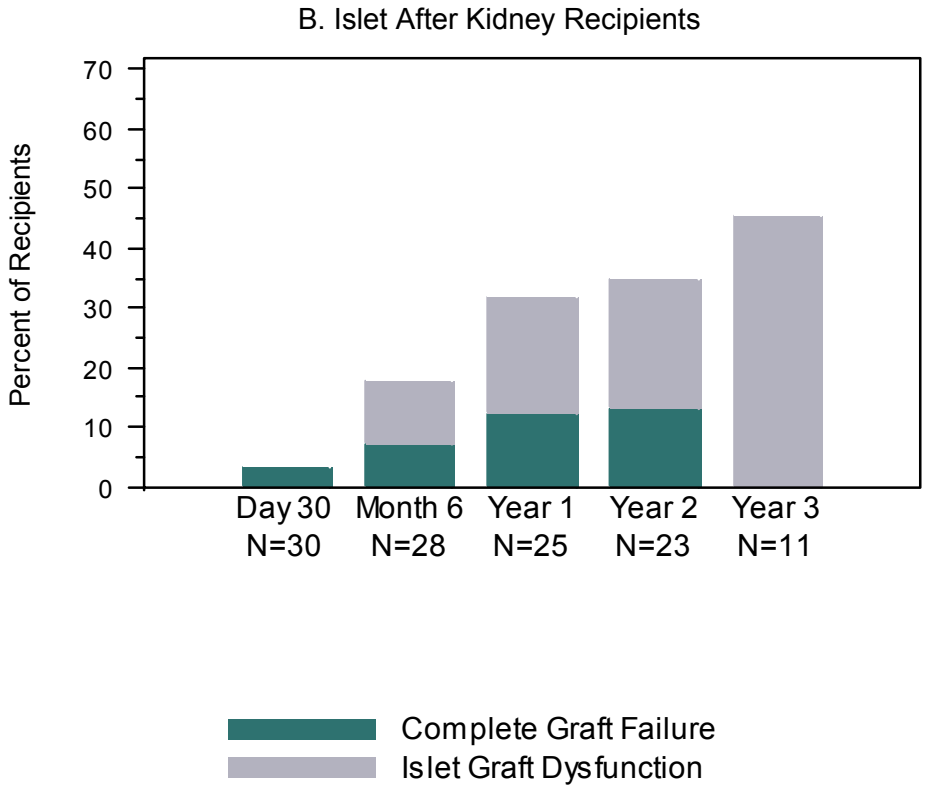
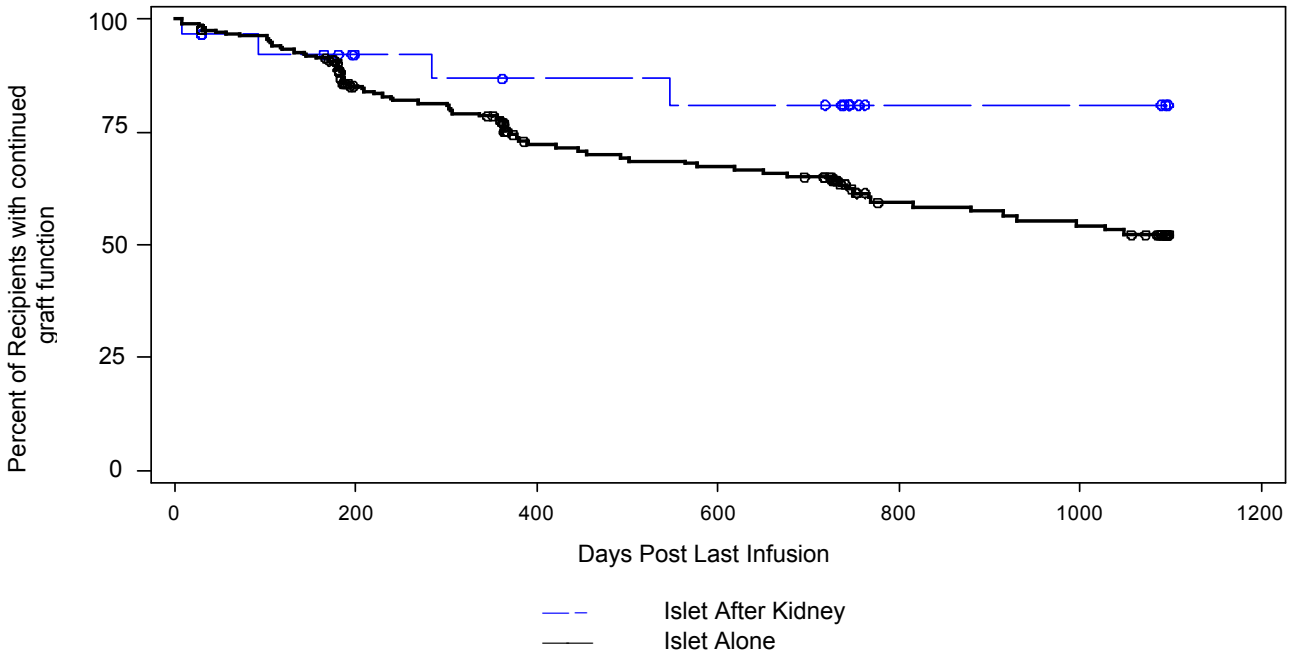


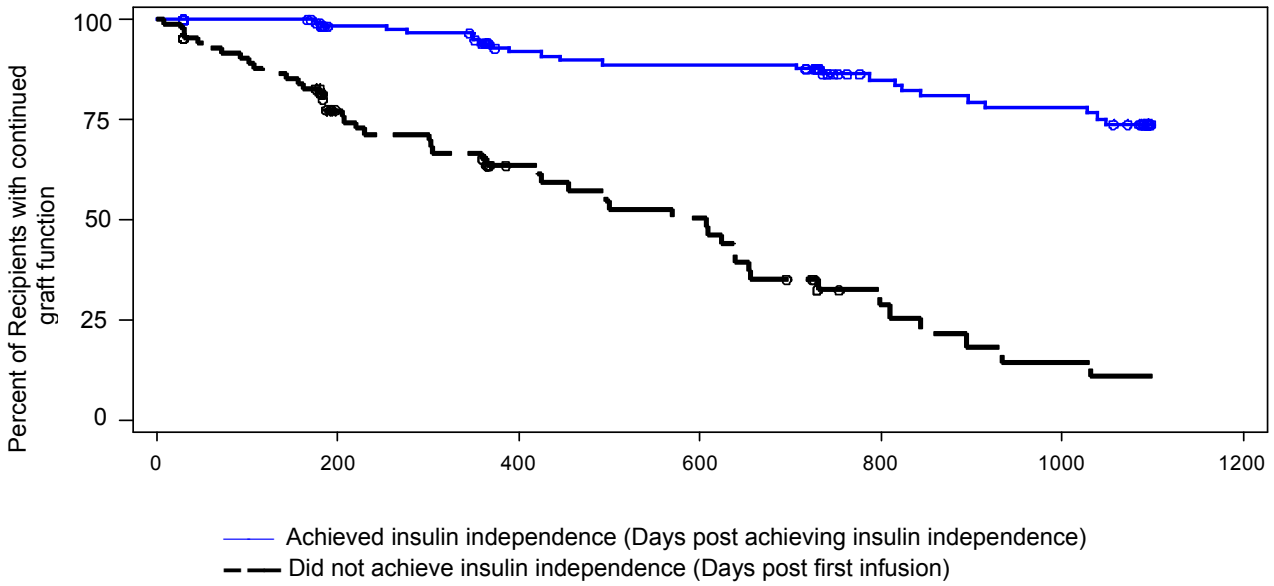
Exhibit 5 – 11
Persistence of Islet Graft Function (IA, IAK)



Timepoint	0	200	400	600	800	1000
N Islet Alone	262	155	100	93	58	53
N Islet After Kidney	30	17	15	14	6	6

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

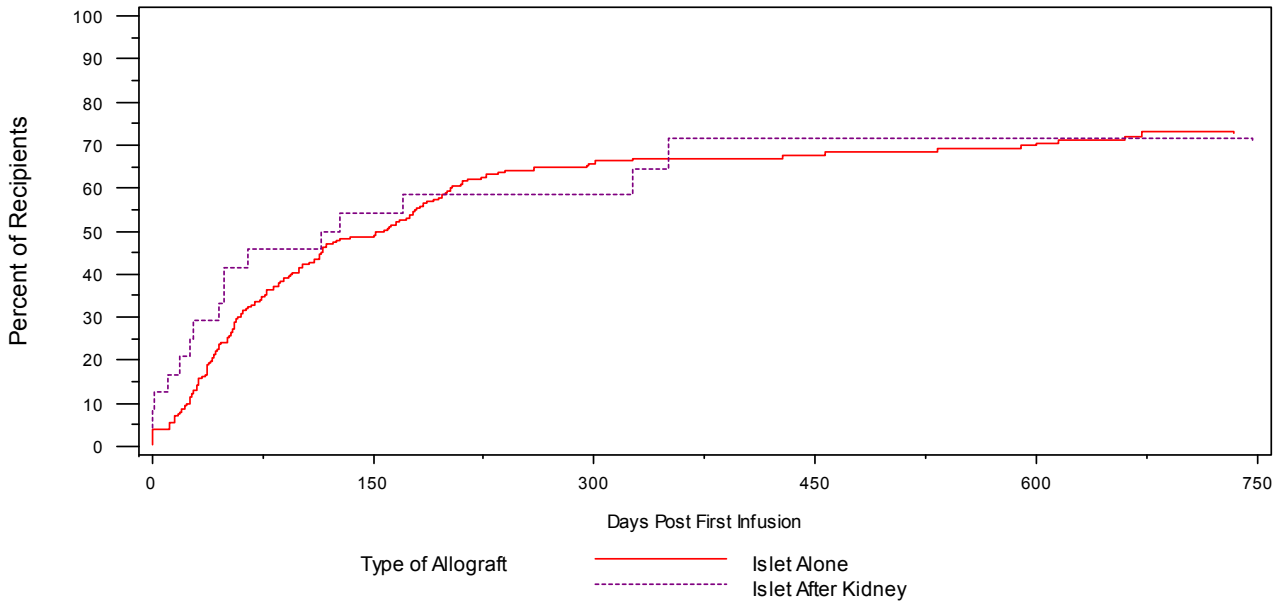
Exhibit 5 – 12
Persistence of Islet Graft Function by Ever Achieving Insulin Independence
Islet Alone Recipients
Not Censored at Re-Infusion



Timepoint	0	200	400	600	800	1000
N Achieved Insulin Independence	154	114	87	84	61	56
N Did Not Achieve Insulin Independence	108	51	29	23	8	4

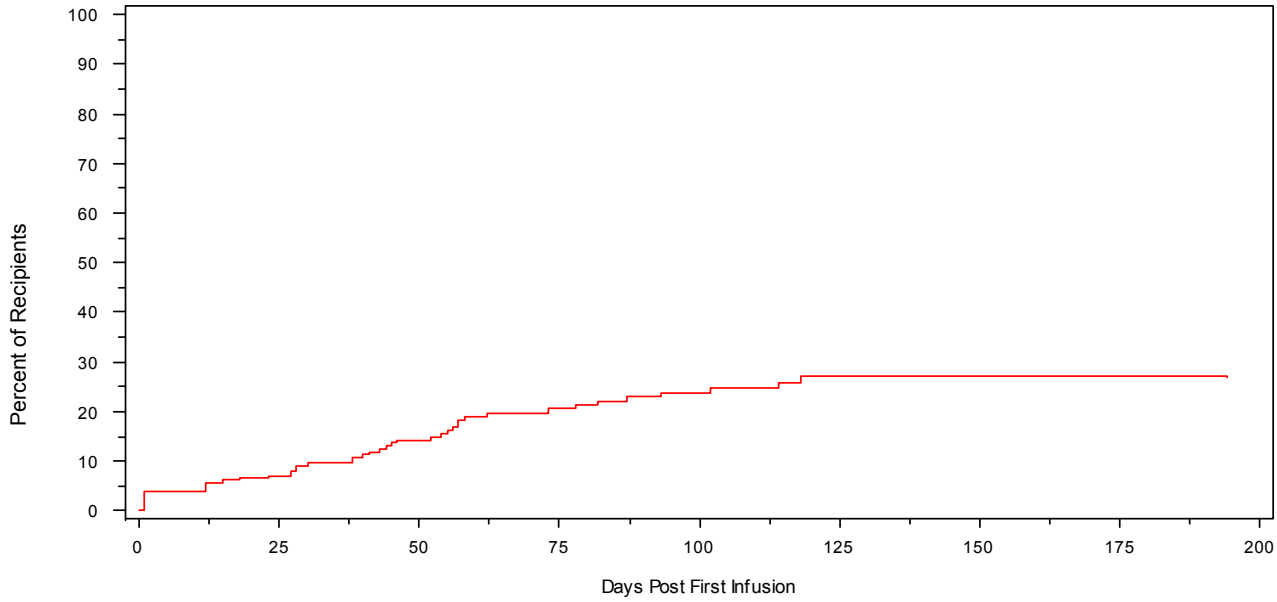
Exhibit 5 – 13
Achievement of Insulin Independence

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



Timepoint	0	150	300	450	600	750
N Islet Alone	231	110	61	48	41	28
N Islet After Kidney	24	12	8	5	5	4

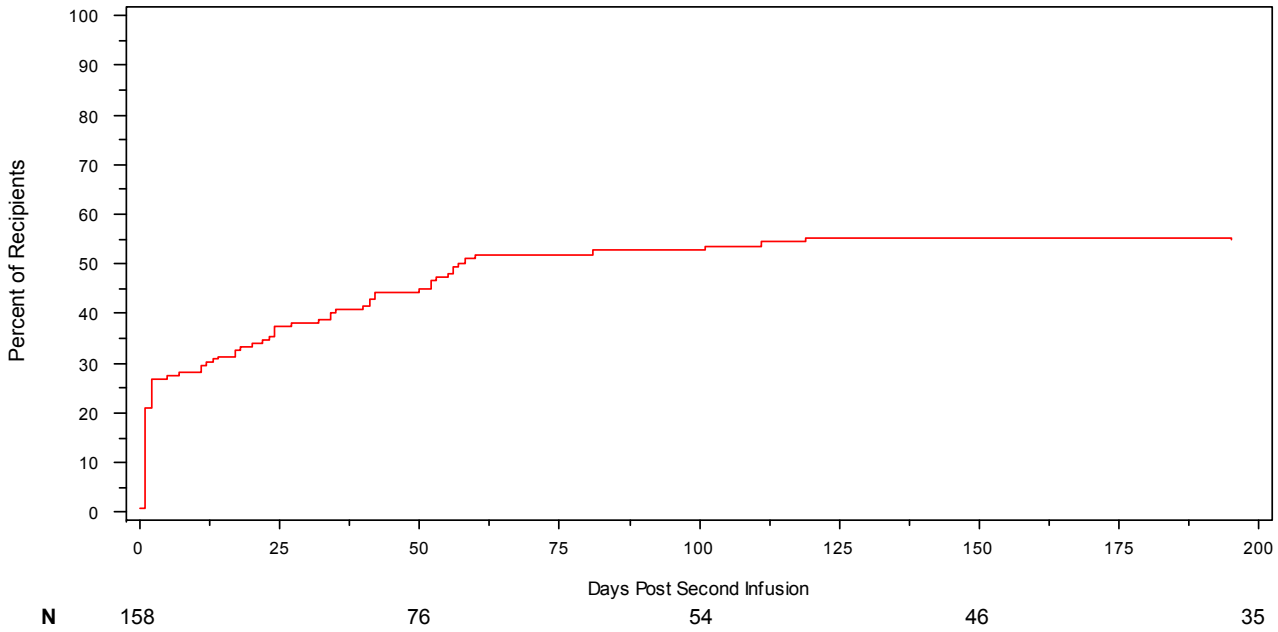
B. Islet Alone Recipients
Post First Infusion
(Censored at Re-Infusion)



N	231	134	81	58	41

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

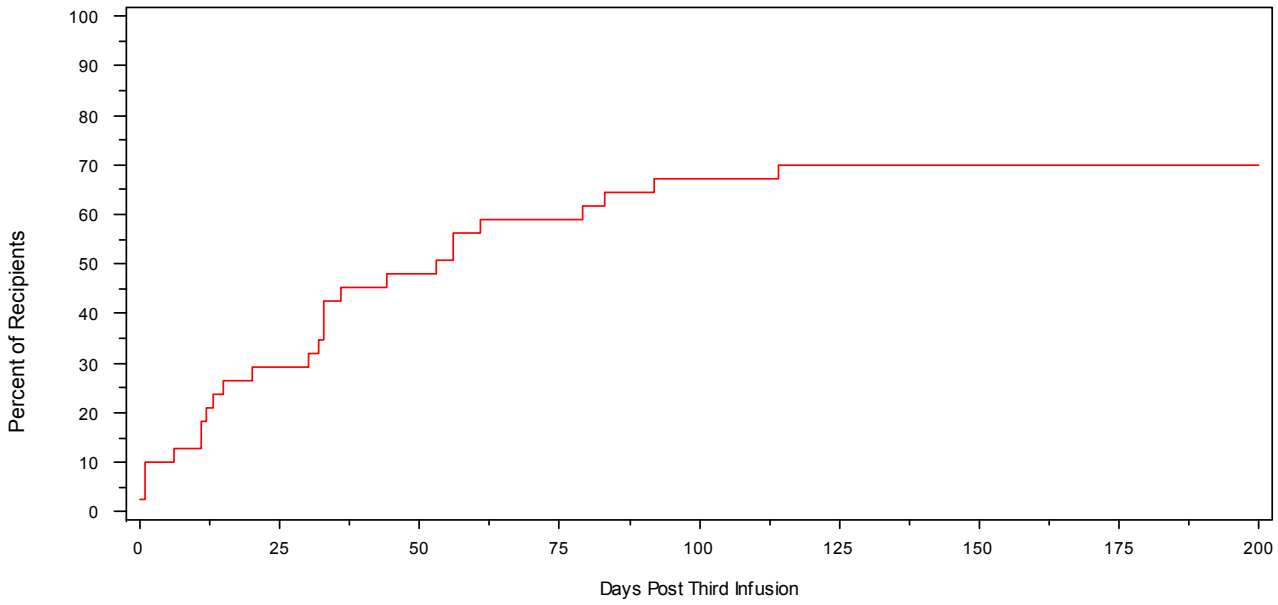
C. Islet Alone Recipients
Post Second Infusion
(Recipients Not Insulin Independent after First Infusion, Censored at Third Infusion)



N	158	76	54	46	35

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

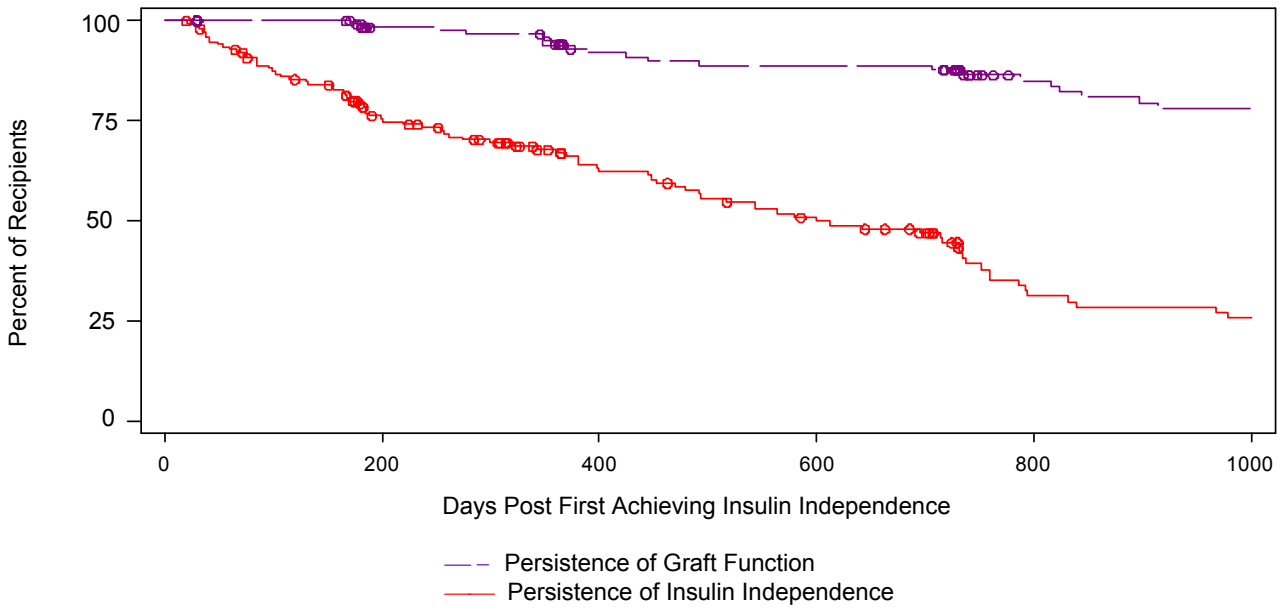
D. Islet Alone Recipients
Post Third Infusion
(Recipients Not Insulin Independent after First or Second Infusion, Censored at Fourth Infusion)



N	40	20	13	12	12

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. Some recipients were reported as insulin independent on the day of infusion (Day 0). At the time of this analysis, none of the recipients remaining on insulin were reported as insulin independent after 200 days post infusion procedure.

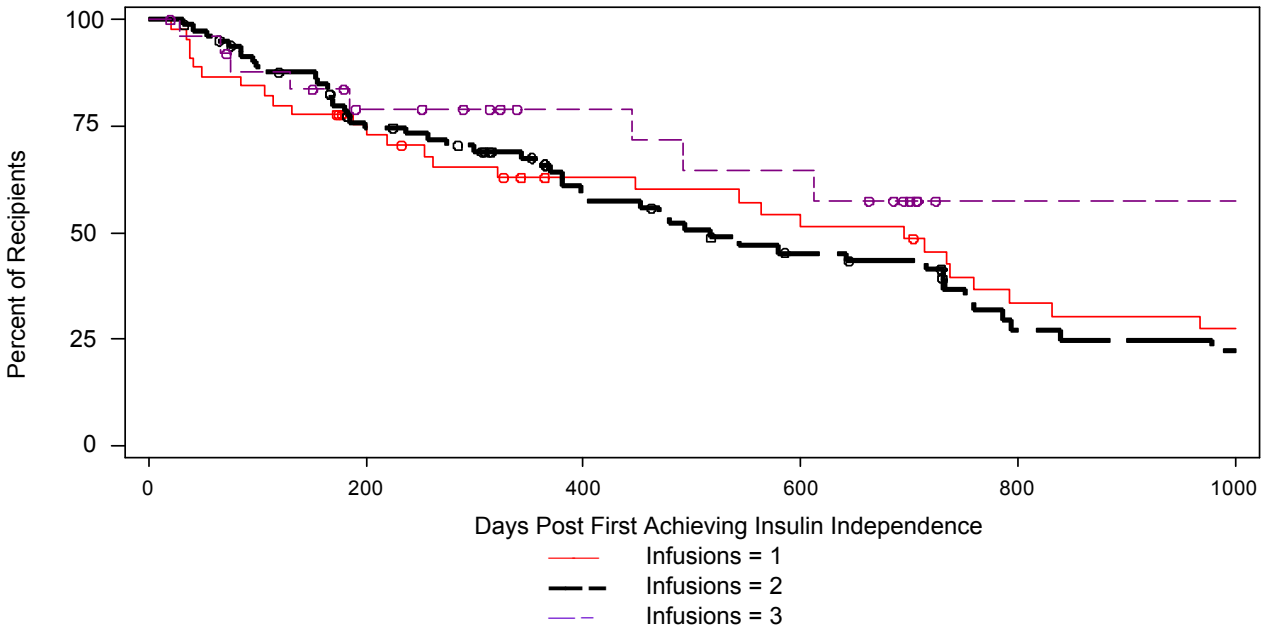
Exhibit 5 – 14
Persistence of Insulin Independence and Persistence of Graft Function
Islet Alone Recipients Achieving Insulin Independence
Not Censored at Re-Infusion



Timepoint	0	200	400	600	800	1000
N Without Graft Loss	154	114	87	84	61	56
N Insulin Independent	154	102	68	52	23	19

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). According to this analysis, by Year 2, 45% of these recipients remain insulin independent while 88% retain some 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

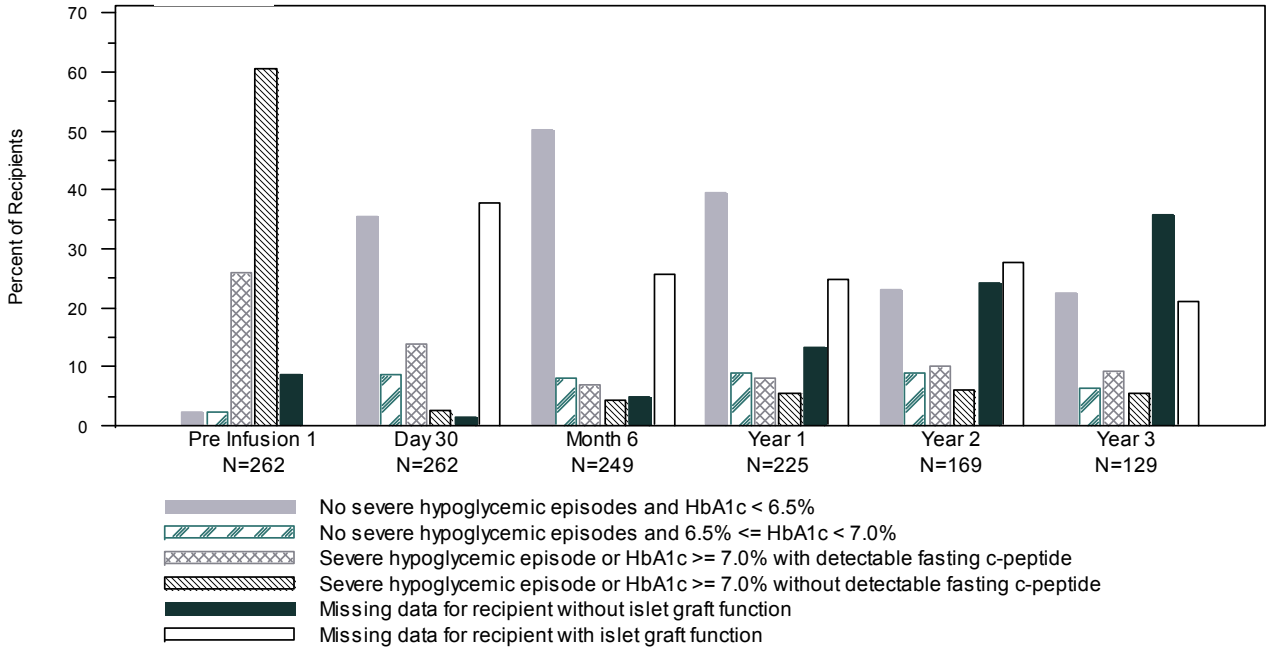


Timepoint	0	200	400	600	800	1000
N 1 Infusion	45	31	22	19	11	9
N 2 Infusions	83	55	35	24	11	9
N 3 Infusions	26	16	11	9	1	1

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 46% for those who achieved insulin independence after one infusion, 41% for those who achieved after two infusions and 57% for those who achieved after three infusions. Caution should be exercised when interpreting this Exhibit as small sample sizes may make the rates unstable.

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

A. Islet Alone Recipients



B. Islet After Kidney Recipients

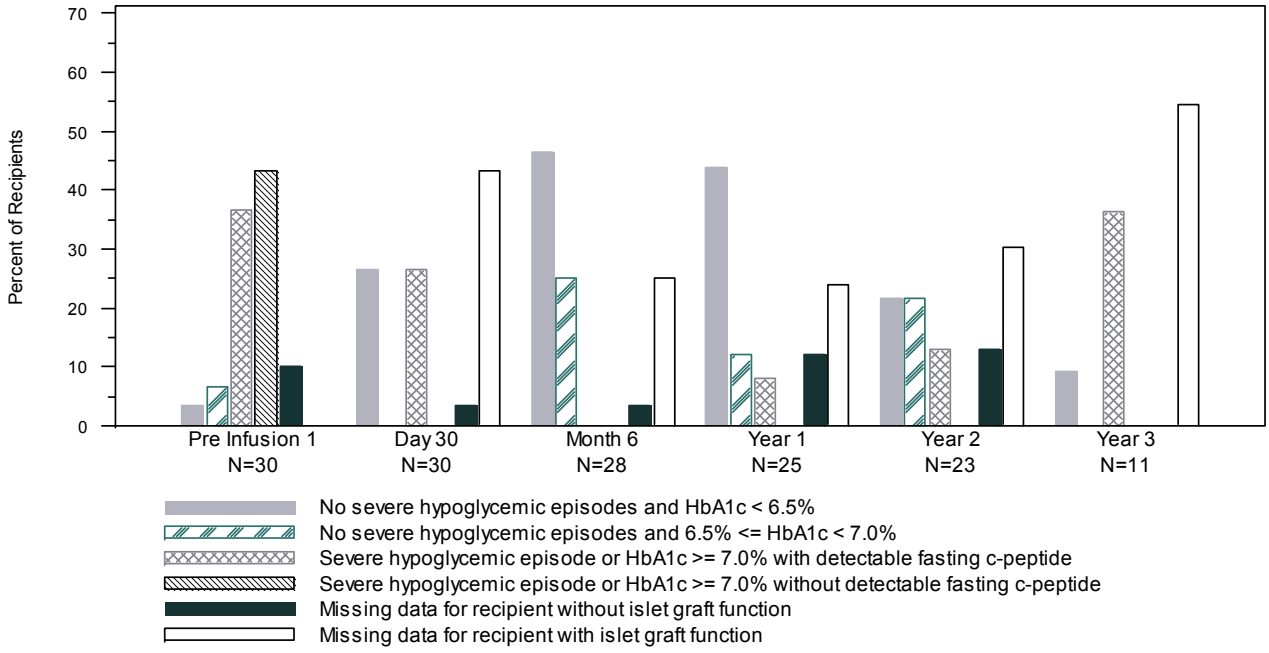


Exhibit 5 – 17
Average Daily Insulin (Units) Taken By Recipients on Insulin Baseline and Post Last Infusion

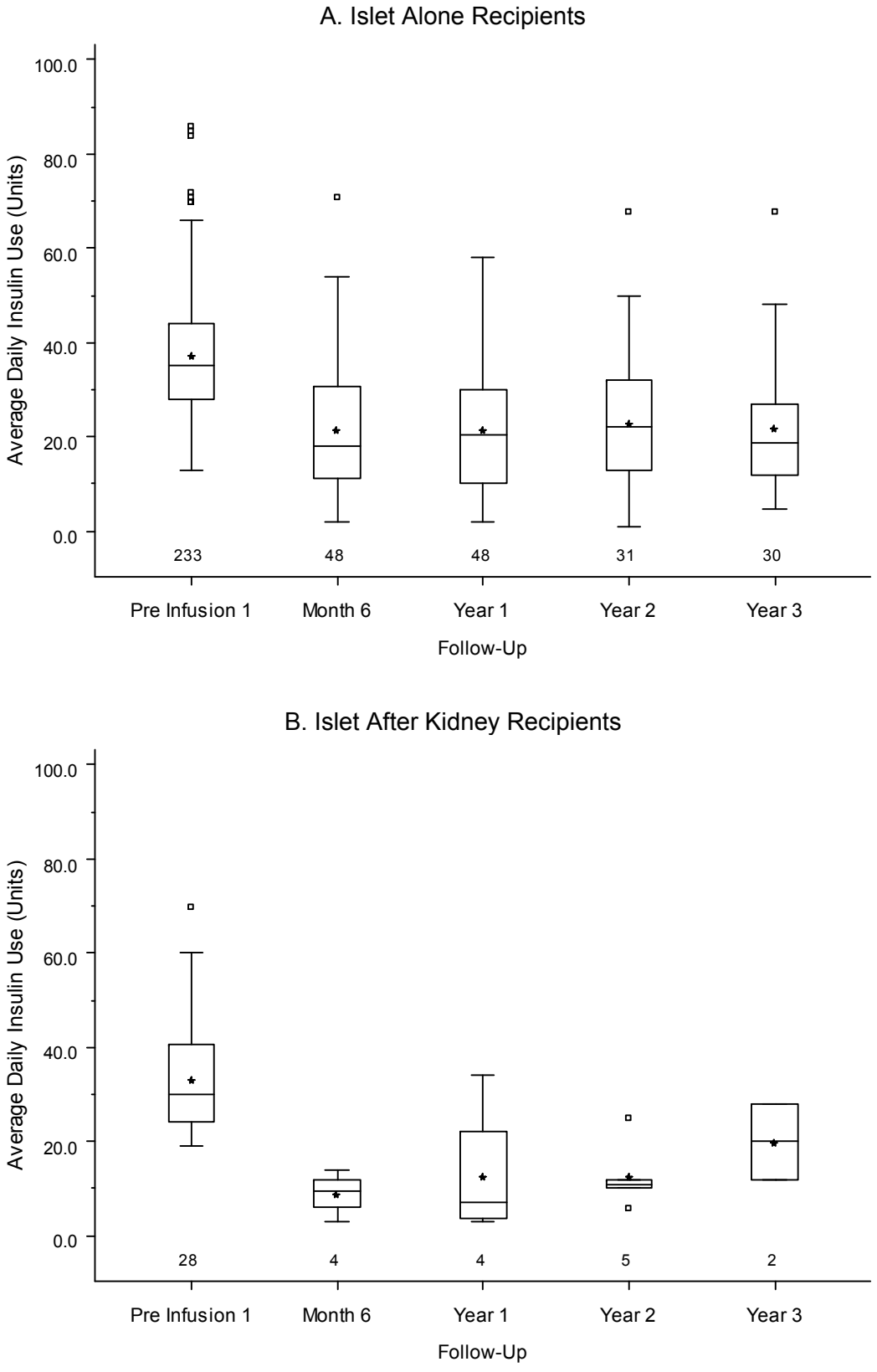


Exhibit 5 – 18
Average Daily Insulin (Units/Kg) Taken By Recipients on Insulin Baseline and Post Last Infusion

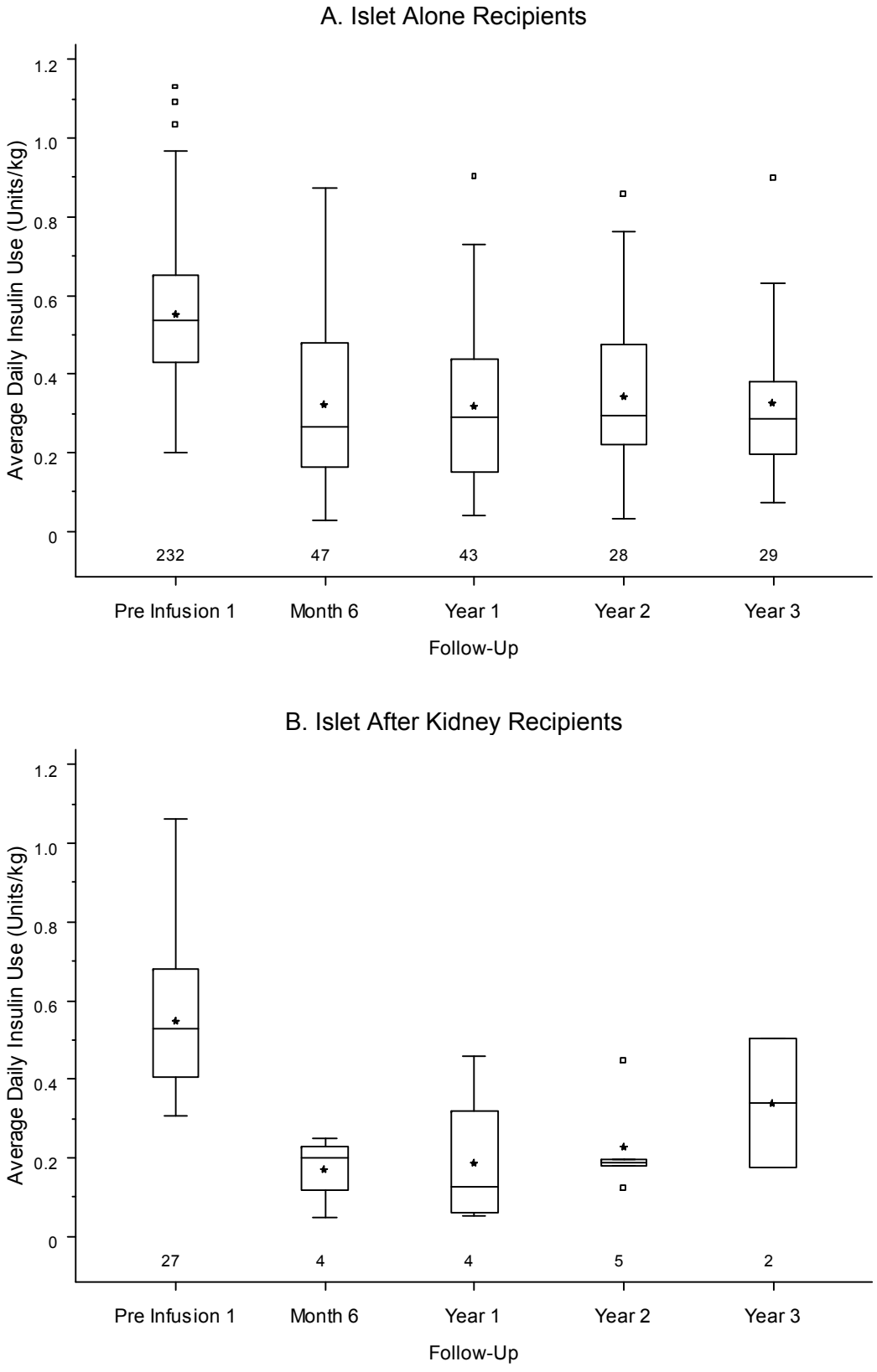
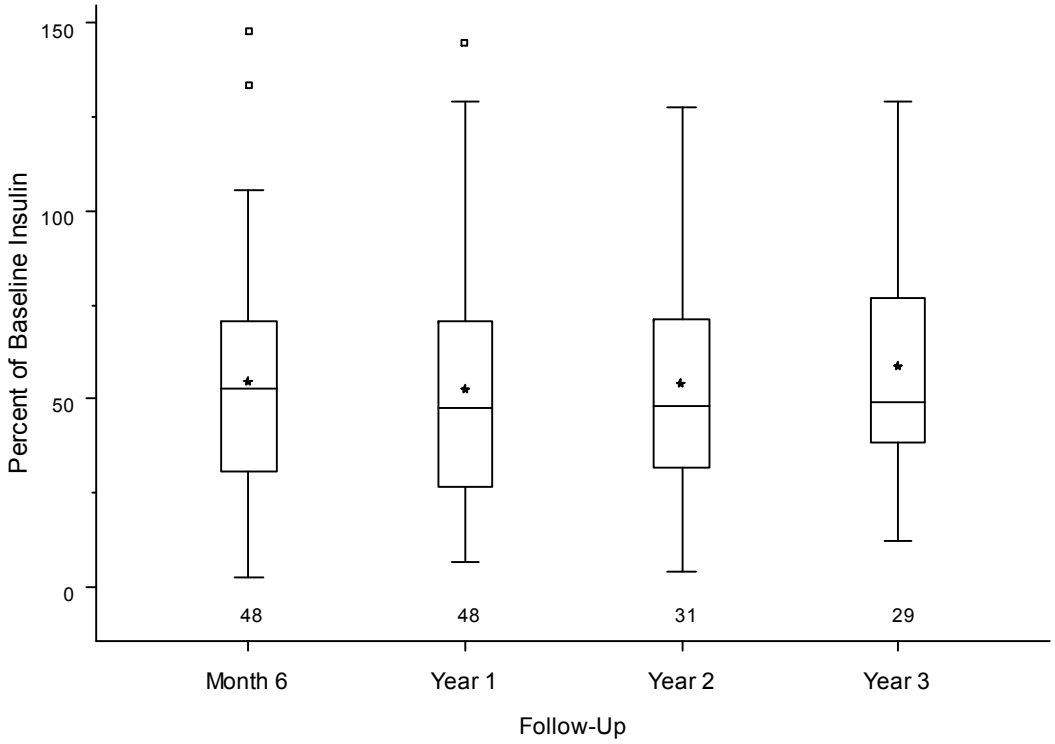


Exhibit 5 – 19
Percent of Baseline Insulin Used By Recipients on Insulin Follow-Up Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

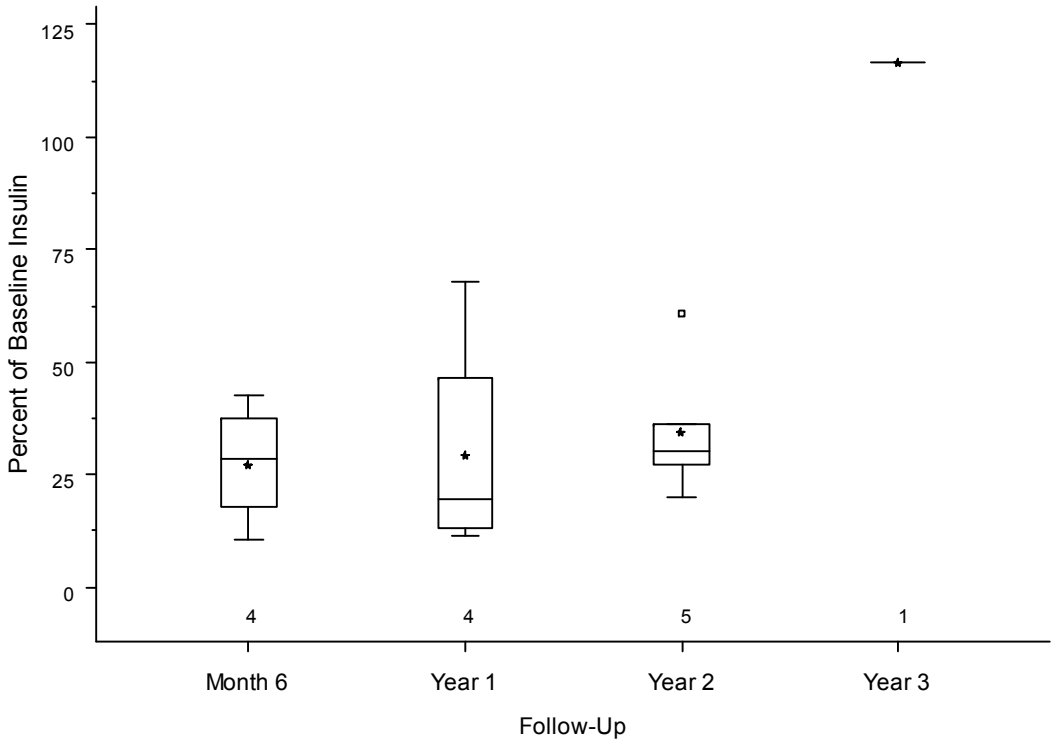


Exhibit 5 – 20
Percent of Baseline Insulin at Follow-Up Post Last Infusion
Islet Alone Recipients
who Achieved then Lost Insulin Independence

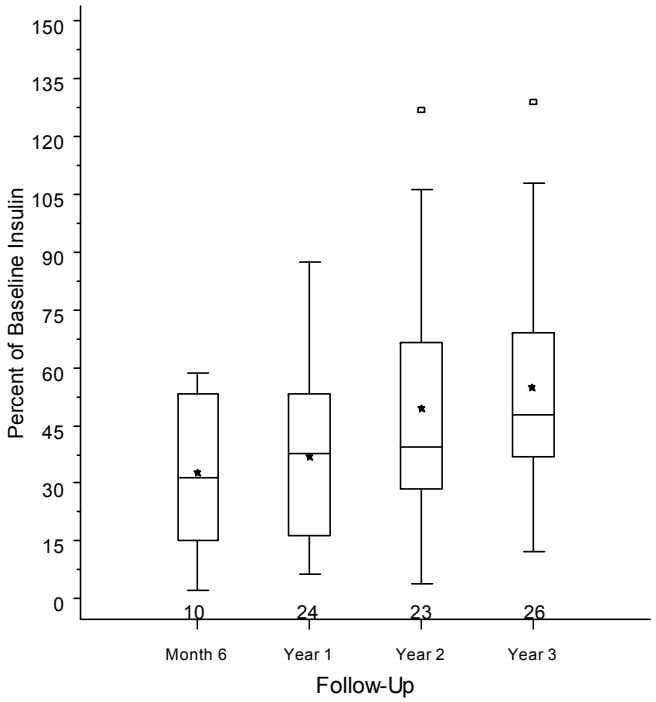


Exhibit 5 – 21
Percent of Baseline Insulin at Follow-Up Post Last Infusion
Islet Alone Recipients
Never Achieving Insulin Independence

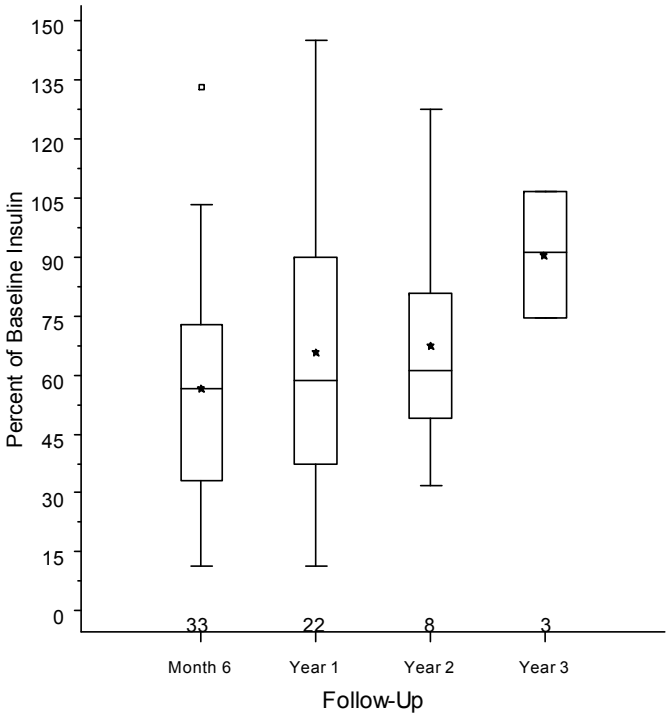


Exhibit 5 – 22
Primary Outcomes Post First Infusion
Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

Cox proportional hazard model: Hazard ratio (HR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF or Last Follow-Up			B. Loss of Insulin Independence Post First Infusion Censored at CIF or Last Follow-Up			C. Complete Islet Failure (CIF) Post First Infusion Censored at Last Follow-Up		
Events / Total >>	**44 / 240**			**26 / 44**			**30 / 240**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Recipient Factors Pre-Transplant									
Diabetes Duration (years)	.	.	.	.	.	.	240	0.964	0.05
Age at baseline (years)	.	.	.	.	.	.	240	0.943	0.006
Months listed	.	.	.	.	.	.	217	0.955	0.07
Baseline HbA_{1c} (%)	217	0.748	0.03	.	.	.	.	.	.
Baseline Fasting Glucose (mg/dL)	215	0.996	0.05	.	.	.	.	.	.
Baseline C-peptide (ng/mL)	.	.	.	.	.	.	.	.	.
Baseline insulin U/day	217	0.961	0.006	.	.	.	217	1.024	0.07
Baseline insulin U/day/kg	216	0.123	0.04	.	.	.	.	.	.
Baseline Weight (kg)	219	0.960	0.01	.	.	.	.	.	.
Baseline BMI	217	0.877	0.03	.	.	.	.	.	.
Insulin antibody + Pre-Inf	.	.	.	11	0.185	0.09	.	.	.
IA-2 Antibody + Pre-Inf	.	.	.	.	.	.	85	3.586	0.08
Years prior to first inf using ins pump or ≥ 3 injections daily	.	.	.	31	1.034	0.07	164	0.953	0.02
Baseline daily injections	150	0.694	<.001	.	.	.	.	.	.
Baseline PRA (%)	.	.	.	.	.	.	.	.	.
Baseline Peak PRA (%)	.	.	.	.	.	.	.	.	.
Donor Characteristics									
Mean Donor Age (yrs)	.	.	.	.	.	.	.	.	.
Donor-recipient age difference	.	.	.	.	.	.	.	.	.
Mean donor weight	234	1.013	0.06	.	.	.	234	1.013	0.04
Mean donor BMI	.	.	.	.	.	.	.	.	.
Donor-recipient BMI difference	210	1.038	0.07	.	.	.	.	.	.
Pre-ins donor glucose (mean of all donors)	.	.	.	44	0.988	0.10	.	.	.
Max donor glucose (mean of all donors)	.	.	.	41	0.996	0.09	.	.	.
Mean donor serum amylase	.	.	.	.	.	.	.	.	.

Exhibit 5 – 22 *(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

Cox proportional hazard model: Hazard ratio (HR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF or Last Follow-Up			B. Loss of Insulin Independence Post First Infusion Censored at CIF or Last Follow-Up			C. Complete Islet Failure (CIF) Post First Infusion Censored at Last Follow-Up		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Mean donor lipase	.	.	.	.	.	.	.	.	.
Mean donor creatinine	.	.	.	.	.	.	.	.	.
Mean donor bilirubin	.	.	.	.	.	.	.	.	.
Donor given vasopressors	239	0.373	0.06	.	.	.	.	.	.
Donor hypertension	.	.	.	.	.	.	.	.	.
Cardio-CVA death	207	1.829	0.07	.	.	.	.	.	.
Donor transfusion pre-hospital	.	.	.	.	.	.	.	.	.
Donor transfusion in-hospital	.	.	.	.	.	.	.	.	.
Donor given steroids	.	.	.	.	.	.	.	.	.
Donor insulin in-hospital	.	.	.	.	.	.	.	.	.
Donor O blood type	234	1.885	0.05	.	.	.	.	.	.
Procurement/Operative Factors									
Mean time from admission to death (hrs)	.	.	.	.	.	.	.	.	.
Mean time from death to panc recovery	.	.	.	33	1.001	0.03	156	1.001	0.008
Mean time from cross clamp to panc recovery (mins)	.	.	.	.	.	.	.	.	.
Mean Cold Ischemic Time	233	0.972	0.06	.	.	.	.	.	.
Islets cultured >6h	.	.	.	42	0.277	0.004	233	0.515	0.08
Mean Culture Time (hrs)	.	.	.	.	.	.	.	.	.
Related procure-infuse teams	223	1.779	0.07	.	.	.	.	.	.
Related process-infuse teams	.	.	.	.	.	.	232	4.494	0.003
Insulin Day0 Infusion 1	.	.	.	.	.	.	.	.	.
Islet Characteristic (First Infusion)									
IEQs Infusion 1	235	1.300	0.002	44	0.774	0.07	.	.	.
IEQs/kg Infusion 1	216	1.290	<.001	.	.	.	.	.	.
Mean embedded islets	.	.	.	.	.	.	.	.	.
Mean Islet Viability	206	1.061	0.03	42	0.934	0.04	.	.	.
Mean stimulation Index	.	.	.	44	0.871	0.08	.	.	.

Exhibit 5 – 22 *(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

Cox proportional hazard model: Hazard ratio (HR) and p-value	**A. Insulin Independence Post First Infusion Censored at CIF or Last Follow-Up**			**B. Loss of Insulin Independence Post First Infusion Censored at CIF or Last Follow-Up**			**C. Complete Islet Failure (CIF) Post First Infusion Censored at Last Follow-Up**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**p**	**HR**
Total Donor Beta Cells	.	.	.	.	.	.	.	.	.
Total Donor Beta Cells/kg donor	.	.	.	.	.	.	.	.	.
Total endotoxin infused	196	1.011	<.001	.	.	.	.	.	.
Total endotoxin infused/kg donor	188	2.669	<.001	37	1.533	0.09	.	.	.
Total insulin content of islets	.	.	.	.	.	.	.	.	.
Total islet particles infused	.	.	.	.	.	.	.	.	.

D. Multivariate Cox regression: Insulin Independence Post First Infusion
Censored at Re-Infusion, Complete Islet Failure or Last Follow-Up
Excluded: Primary Non-Function (n=15)
(44 events / 240 recipients with data on covariates)

	HR	p
Baseline Fasting Glucose (mg/dL)	0.994	0.03
Baseline daily injections	0.785	0.02
Mean Cold Ischemic Time	0.949	0.02
IEQs/kg Infusion 1	1.224	0.004
Total endotoxin infused/kg donor	2.903	<0.001

E. Multivariate Cox Regression: Loss of Insulin Independence After Achievement Post First Infusion
Censored at Re-Infusion, Complete Islet Failure or Last Follow-Up
(18 events / 44 recipients achieving insulin independence post first infusion censored at re-infusion)
Insufficient events for multivariate analysis.

F. Multivariate Cox regression: Complete Islet Failure Post First Infusion
Censored at Re-Infusion or Last Follow-Up
(21 events / 152 recipients with data on all covariates)
Insufficient events for multivariate analysis.

Exhibit 5 – 23
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 >>	**149 / 247**			**82 / 149**			**69 / 247**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Recipient Factors Pre-Infusion									
Total number of infusions received	247	1.318	0.01	147	1.341	0.08	247	0.611	0.006
Diabetes Duration (years)	.	.	.	147	0.977	0.05	247	0.954	<.001
Age at baseline (years)	.	.	.	.	.	.	247	0.943	<.001
Total number of days on waitlist	.	.	.	.	.	.	.	.	.
Baseline HbA_{1C} (%)	224	0.813	0.003	.	.	.	.	.	.
Baseline Fasting Glucose (mg/dL)	.	.	.	.	.	.	.	.	.
Baseline C-peptide (ng/mL)	222	1.978	0.03	133	1.758	0.09	.	.	.
Baseline Daily Insulin Use (Units)	.	.	.	126	1.017	0.06	.	.	.
Baseline Daily Insulin Use (Units/kg)	.	.	.	125	4.497	0.06	223	3.778	0.08
Baseline Weight (kg)	.	.	.	.	.	.	.	.	.
Baseline BMI	.	.	.	.	.	.	.	.	.
GAD antibody + Pre-Infusion									
Insulin antibody + Pre-Infusion	.	.	.	.	.	.	.	.	.
IA-2 antibody + Pre-Infusion	.	.	.	.	.	.	.	.	.
Intensive therapy pre-infusion									
Years using insulin pump or ≥ 3 injections daily	.	.	.	.	.	.	171	0.957	<.001
Baseline number of daily insulin injections	154	0.885	0.04	.	.	.	.	.	.
Baseline PRA (%)	.	.	.	.	.	.	.	.	.
Baseline Peak PRA (%)	.	.	.	.	.	.	.	.	.
Donor Characteristics (Mean of 1 to 5 donors)									
Mean Donor Age (yrs)	.	.	.	137	1.031	0.02	.	.	.
Donor-recipient age difference	.	.	.	137	1.288	0.005	234	1.349	0.002
Mean donor weight	241	0.991	0.08	.	.	.	241	1.011	0.05
Mean donor BMI	239	0.968	0.05	.	.	.	.	.	.
Donor-Recipient BMI difference	.	.	.	.	.	.	.	.	.
Mean donor creatinine	.	.	.	.	.	.	.	.	.

Exhibit 5 – 23 *(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**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Mean donor BUN	.	.	.	96	0.950	0.07	.	.	.
Mean donor bilirubin	.	.	.	.	.	.	.	.	.
Mean donor AST	.	.	.	.	.	.	.	.	.
Mean donor ALT	.	.	.	.	.	.	.	.	.
Mean donor lipase	.	.	.	.	.	.	.	.	.
Mean donor serum amylase	.	.	.	.	.	.	.	.	.
Pre-ins donor glucose (mean of all donors)	.	.	.	.	.	.	.	.	.
Max donor glucose (mean of all donors)	.	.	.	.	.	.	.	.	.
Total number of donors	246	1.262	0.008	.	.	.	246	0.697	0.02
Cardio-cerebrovascular death	.	.	.	.	.	.	.	.	.
Donor hypertension	.	.	.	.	.	.	.	.	.
Donor diabetes	.	.	.	.	.	.	.	.	.
Donor given vasopressors	.	.	.	147	0.067	<.001	.	.	.
Donor transfusion pre-hospital	.	.	.	.	.	.	.	.	.
Donor transfusion in-hospital	.	.	.	.	.	.	.	.	.
Donor given steroids	.	.	.	.	.	.	.	.	.
Donor insulin in-hospital	225	0.659	0.02	135	0.666	0.08	.	.	.
Procurement/Operative Factors (1 to 5 infusions)									
Mean time from admission to death (hrs)	.	.	.	.	.	.	.	.	.
Mean time from cross clamp to pancreas recovery (mins)	.	.	.	.	.	.	.	.	.
Mean Cold Ischemic Time	243	0.976	0.06	146	1.033	0.06	243	1.031	0.10
Islets cultured >6h	.	.	.	.	.	.	.	.	.
Mean Culture Time (hrs)	146	0.744	0.10	.	.	.	146	1.693	0.096
Mean time from Death to Panc Recovery	200	0.977	0.03	.	.	.	200	1.036	0.003
Related procurement-infusion teams	182	1.416	0.08	.	.	.	.	.	.
Related processing-infusion teams	234	0.156	0.002	142	5.557	0.005	234	3.017	0.001

Exhibit 5 – 23 *(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**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Insulin Day0 Infusion 1	.	.	.	113	0.444	0.002	.	.	.
Insulin Day0 Last Infusion	197	0.618	0.01	.	.	.	.	.	.
Islet Characteristics (1-5 infusions)									
Total IEQs infused over all infusions	234	1.000	0.08	.	.	.	.	.	.
Total IEQs/kg received over all infusions	216	1.030	0.02	.	.	.	.	.	.
Mean embedded islets	.	.	.	.	.	.	.	.	.
Mean Islet Viability	.	.	.	.	.	.	.	.	.
Mean stimulation Index	.	.	.	143	0.901	0.02	222	0.851	0.02
Total Donor Beta Cells	.	.	.	.	.	.	.	.	.
Total Donor Beta Cells/kg donor	.	.	.	.	.	.	.	.	.
Total endotoxin infused	.	.	.	.	.	.	.	.	.
Total endotoxin infused/kg donor	.	.	.	.	.	.	.	.	.
Total insulin content of islets	.	.	.	72	1.104	0.03	.	.	.
Total islet particles infused	108	1.000	0.097	82	1.001	0.01	.	.	.
Total volume infused over all infusions	227	1.057	0.006	141	1.073	0.02	227	0.941	0.10

D. Multivariate Cox regression: <u>Insulin Independence Post Last Infusion</u> Censored at Complete Islet Failure or Last Follow-Up (103 events / 170 recipients with data on covariates)		
	HR	p
Baseline HbA_{1C} (%)	0.784	0.002
Insulin Day 0 Last Infusion	0.540	0.003
Donor insulin in-hospital	0.693	0.07
Total IEQs/kg received over all infusions	1.039	0.01

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

E. Multivariate Cox regression: Loss of Insulin Independence After Achievement Post Last Infusion **Censored at Complete Islet Failure or Last Follow-Up** **(51 events / 93 recipients with data on covariates)**		
	HR	p
Donor-recipient age difference	1.437	0.002
Donor given vasopressors	0.014	<.001
Donor insulin in-hospital	0.485	0.02
Total volume infused over all infusions	1.111	0.02
Insulin Day 0 Infusion 1	0.375	0.002
Related processing-infusion teams	10.882	<.001

F. Multivariate Cox regression: Complete Islet Failure Post Last Infusion **Censored at Last Follow-Up** **(64 events / 204 recipients with data on covariates)**		
	HR	p
Total number of infusions received	0.537	0.003
Diabetes duration (years)	0.964	0.03
Age at baseline (years)	0.952	0.01
Mean stimulation index	0.812	0.002
Etanercept at any infusion	0.195	0.006

G. Insulin Independence post last infusion according to insulin given on day of infusion

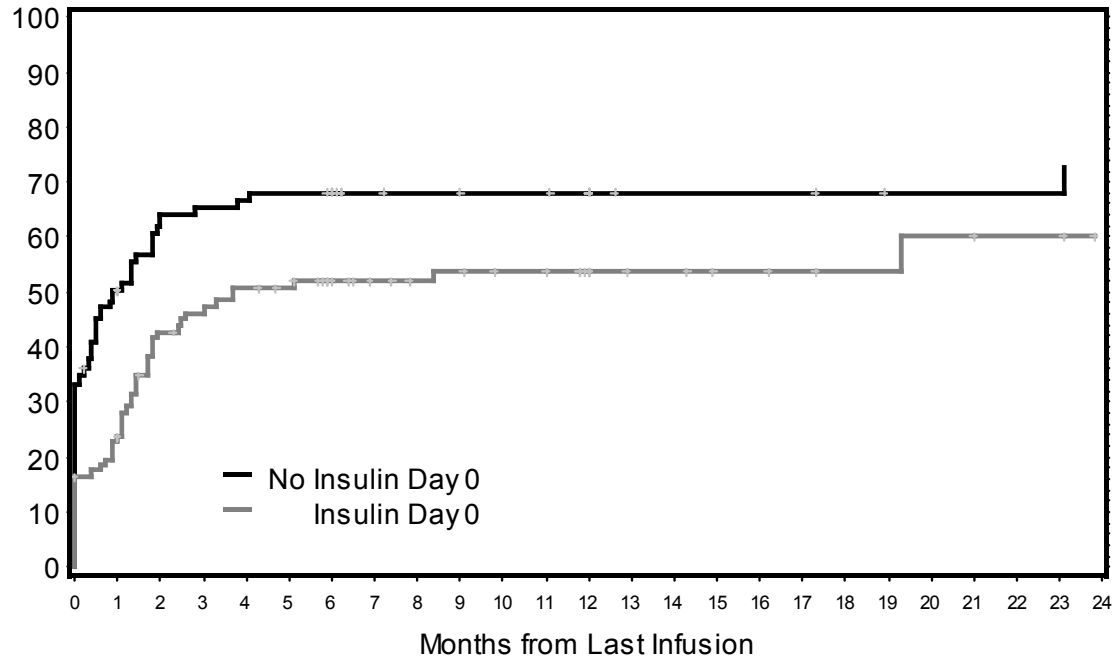
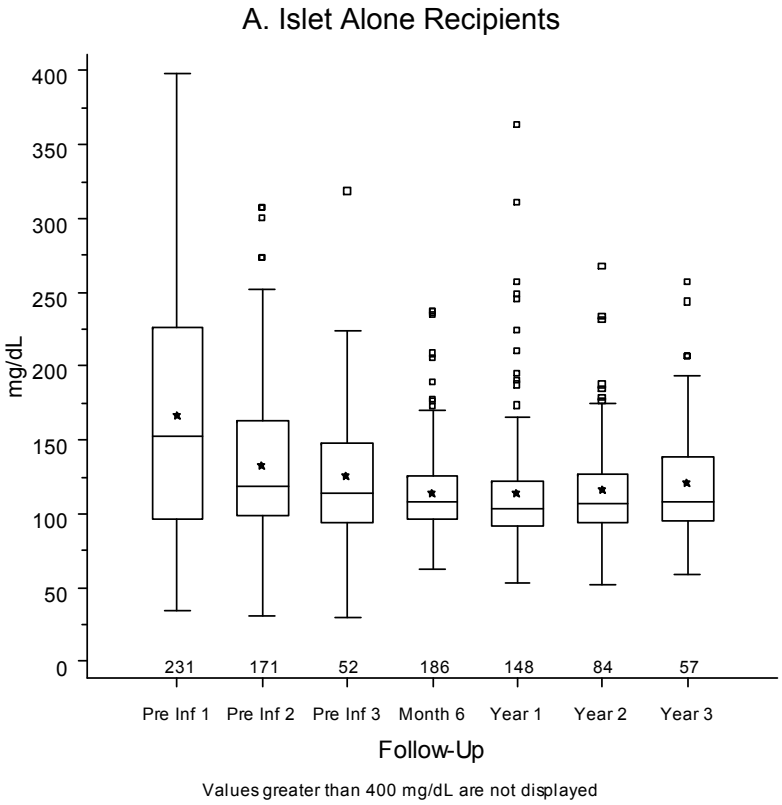


Exhibit 5 – 24
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion



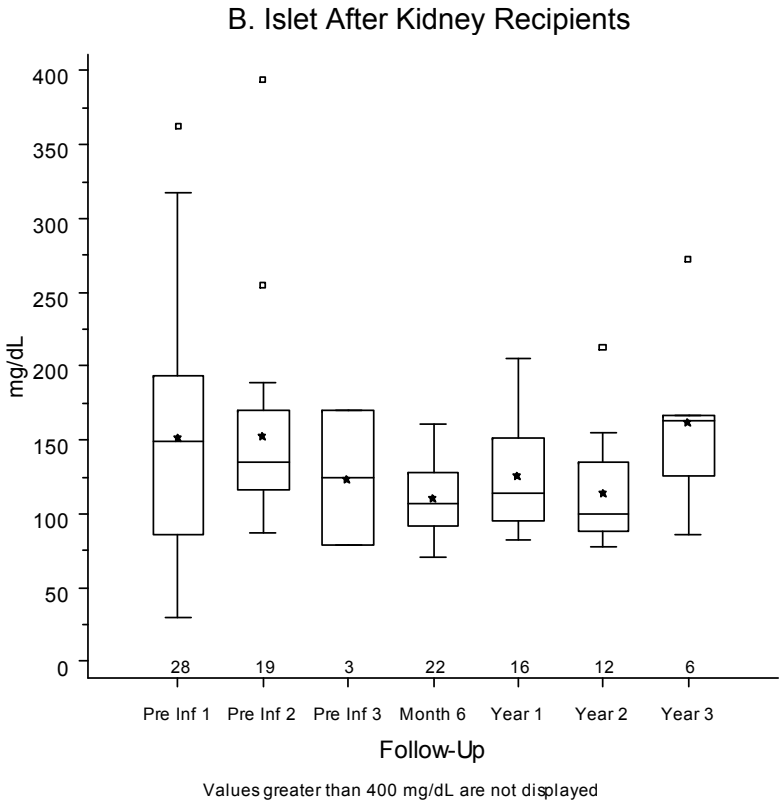


Exhibit 5 – 25
HbA_{1C} (%)
Pre Infusion and Post Last Infusion

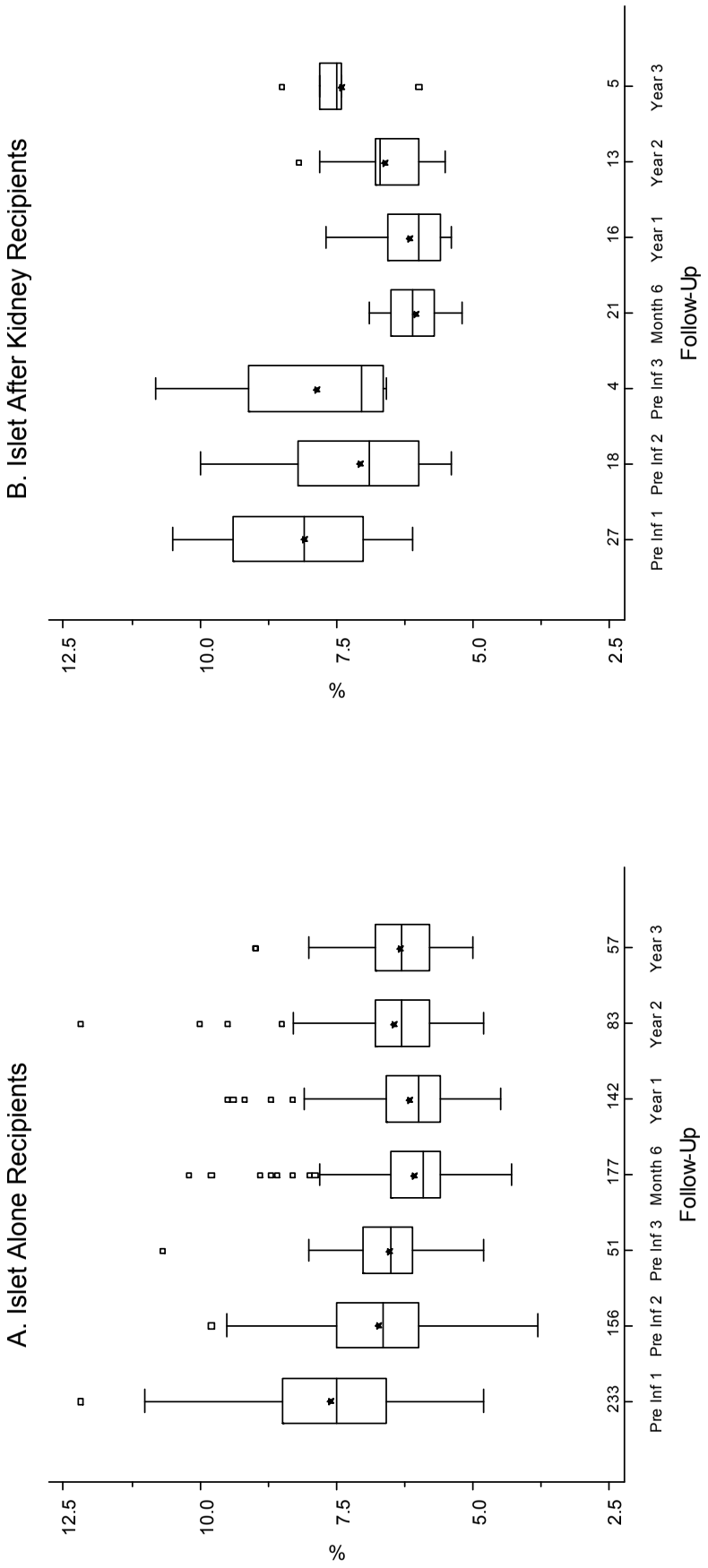


Exhibit 5 – 26
Basal Plasma C-Peptide (ng/mL)
Pre Infusion and Post Last Infusion

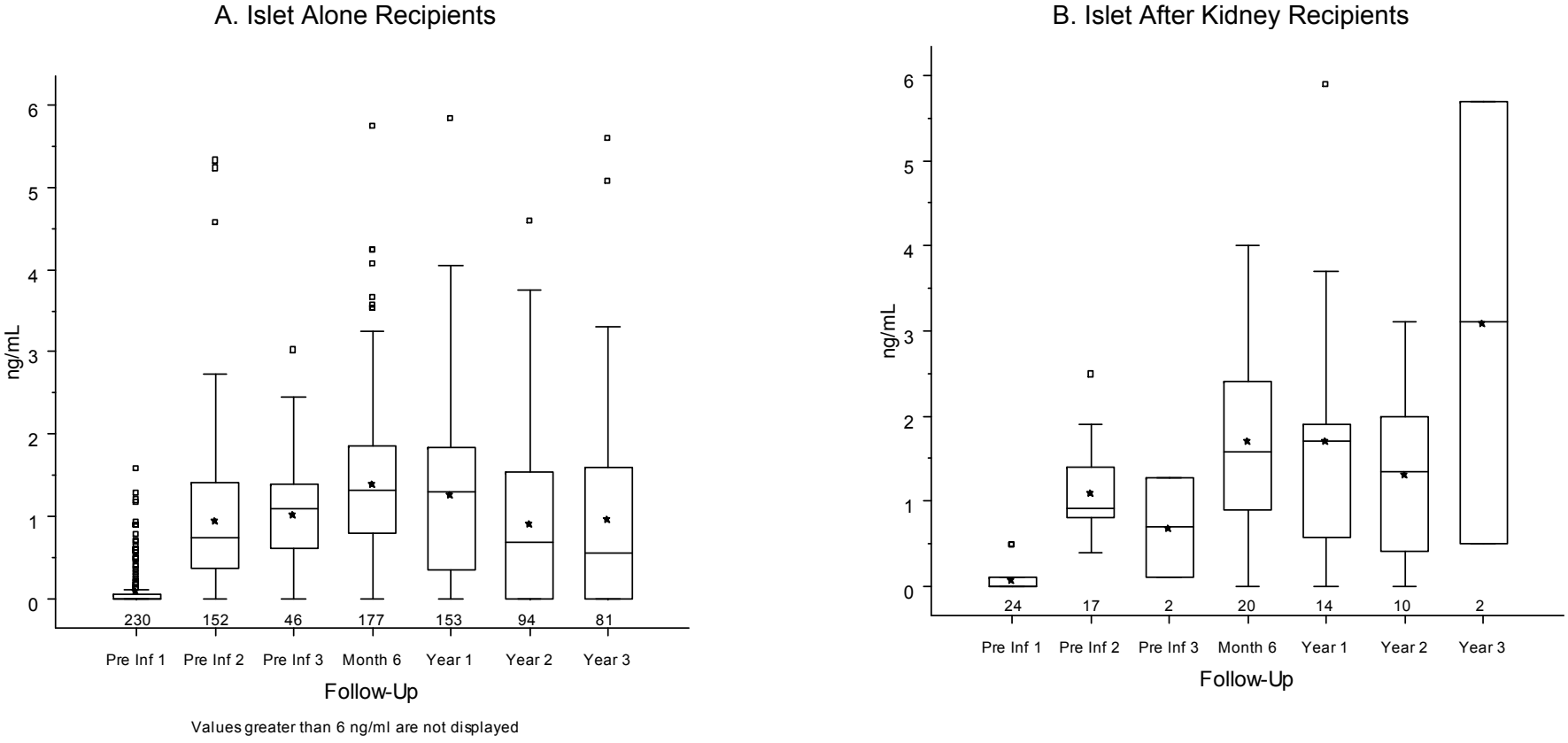


Exhibit 5 – 27
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with One Infusion

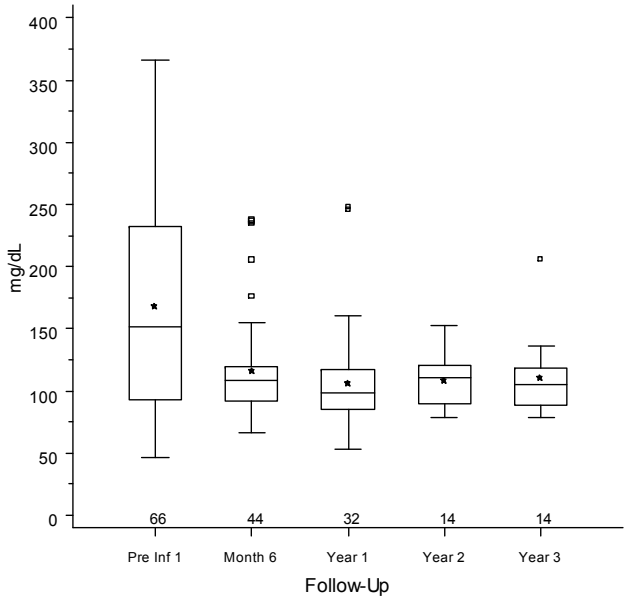


Exhibit 5 – 28
HbA_{1C} (%)
Pre-Infusion and Post Last Infusion
Islet Alone Recipients with One Infusion

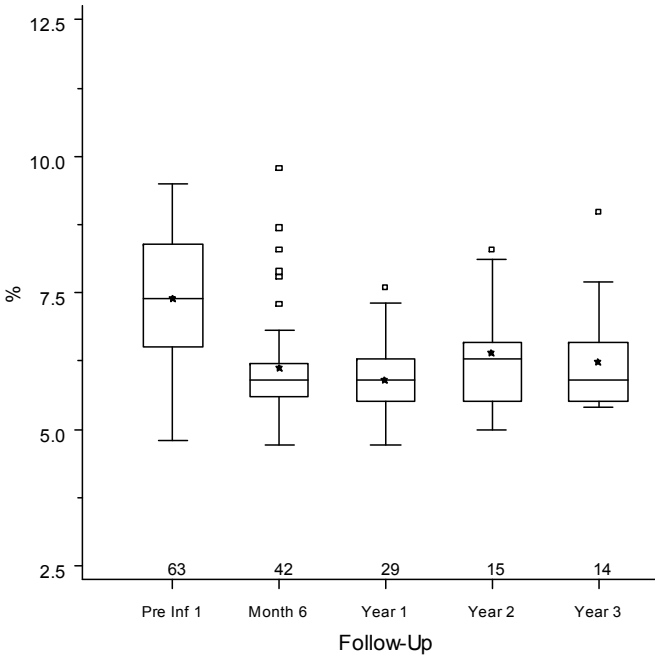


Exhibit 5 – 29
Basal Plasma C-Peptide (ng/mL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with One Infusion

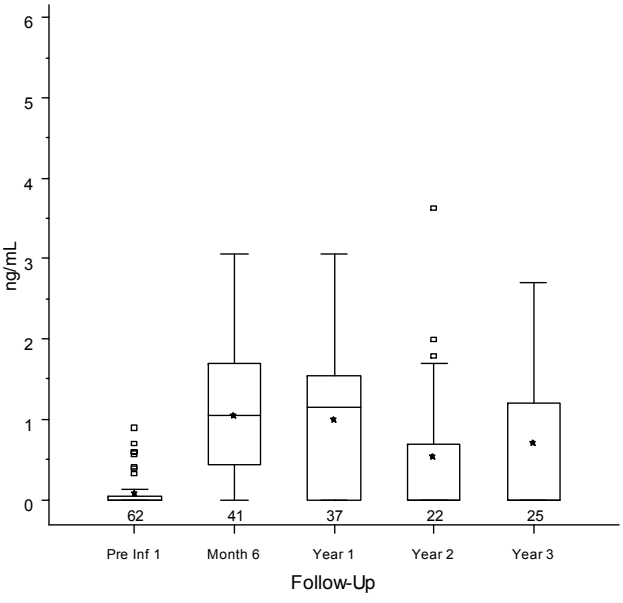


Exhibit 5 – 30
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Two Infusions

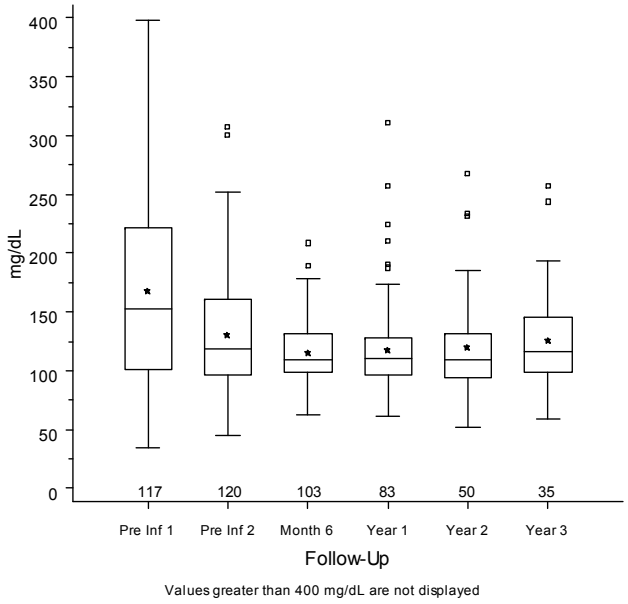


Exhibit 5 – 31
HbA_{1C} (%)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Two Infusions

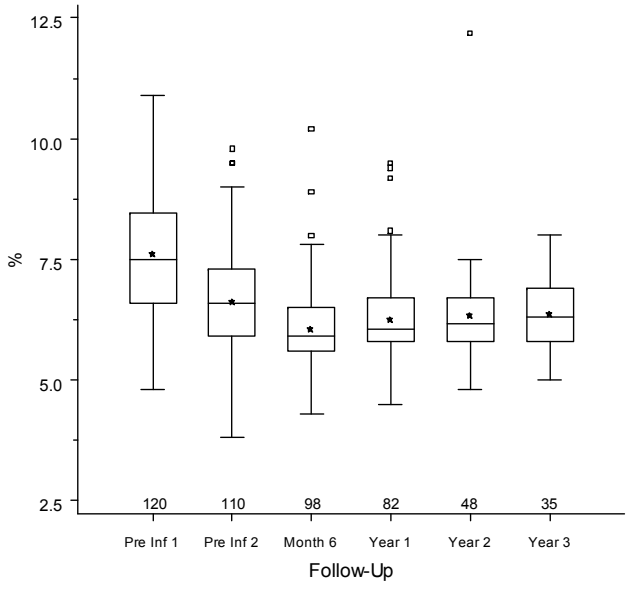


Exhibit 5 – 32
Basal Plasma C-Peptide (ng/mL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Two Infusions

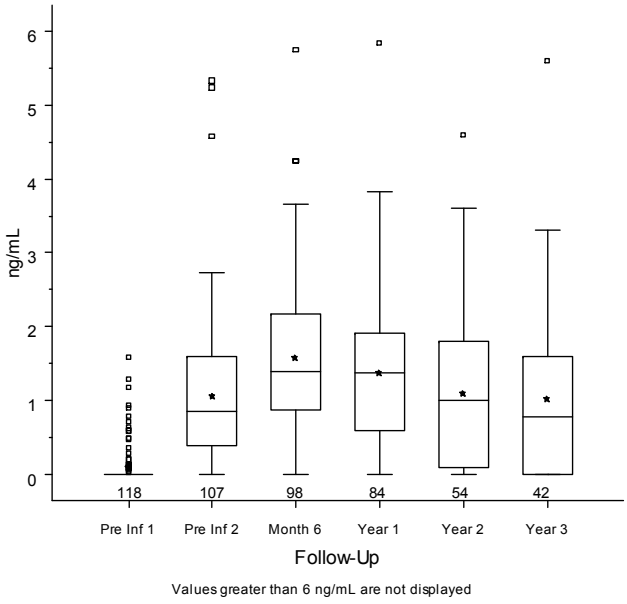


Exhibit 5 – 33
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Three Infusions

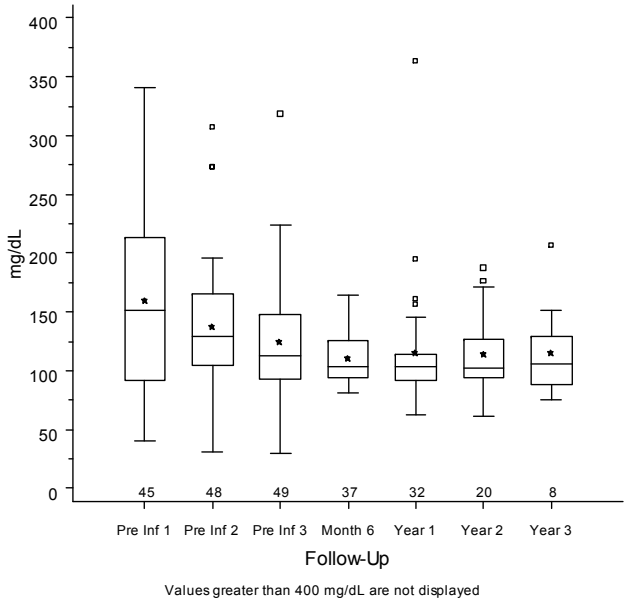


Exhibit 5 – 34
HbA_{1C} (%)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Three Infusions

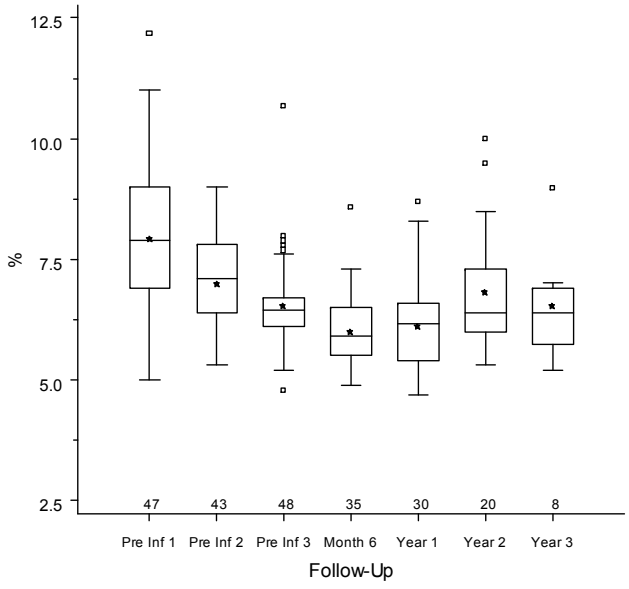


Exhibit 5 – 35
Basal Plasma C-Peptide (ng/mL)
Pre Infusion and Post Last Infusion
Islet Alone Recipients with Three Infusions

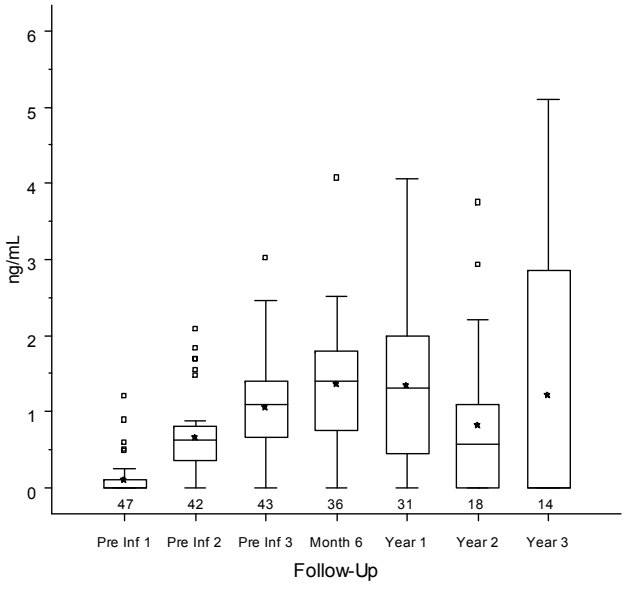
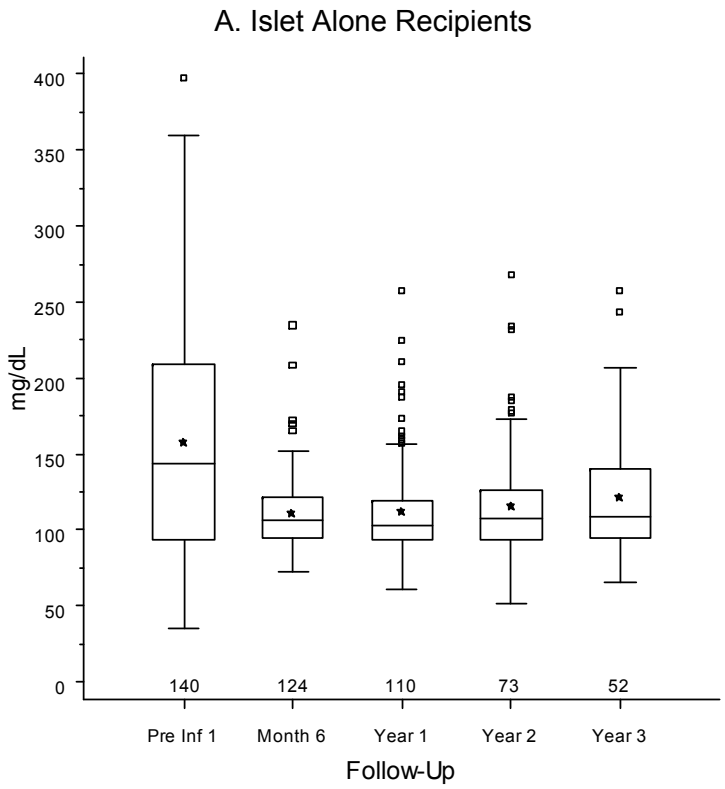
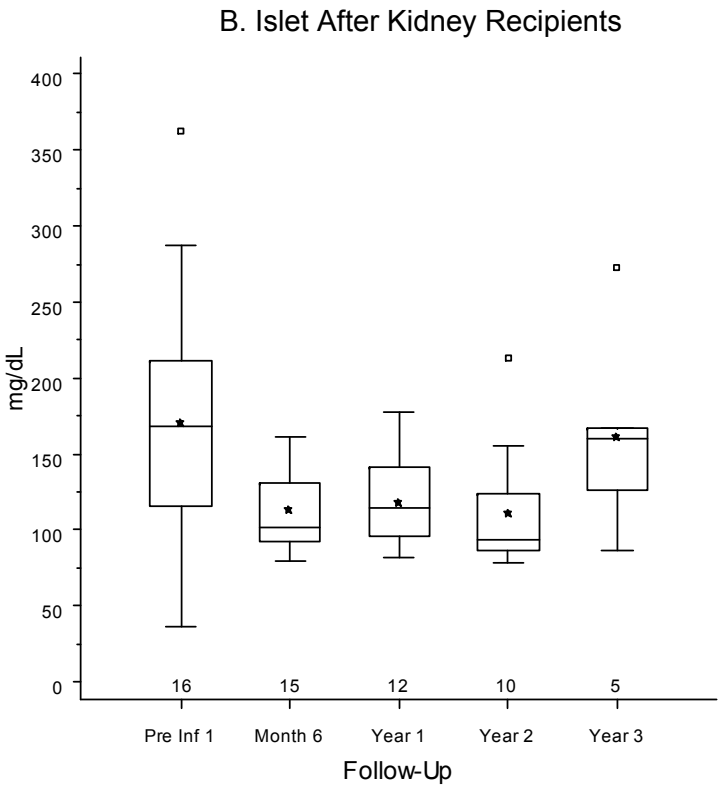


Exhibit 5 – 36
Fasting Plasma Glucose (mg/dL) Post Last Infusion
Recipients Who Ever Achieved Insulin Independence

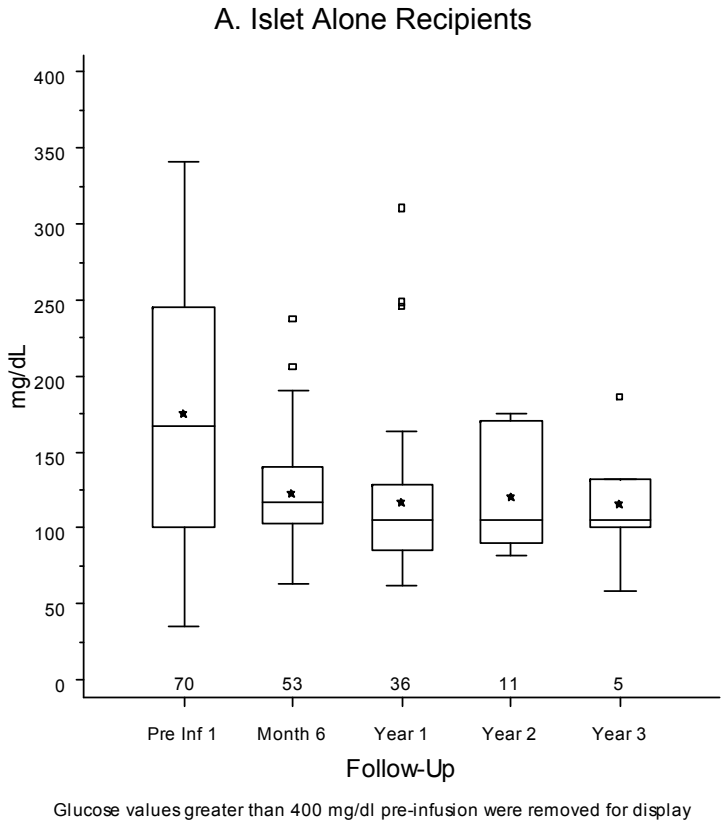


Glucose values greater than 400 mg/dl pre-infusion were removed for display

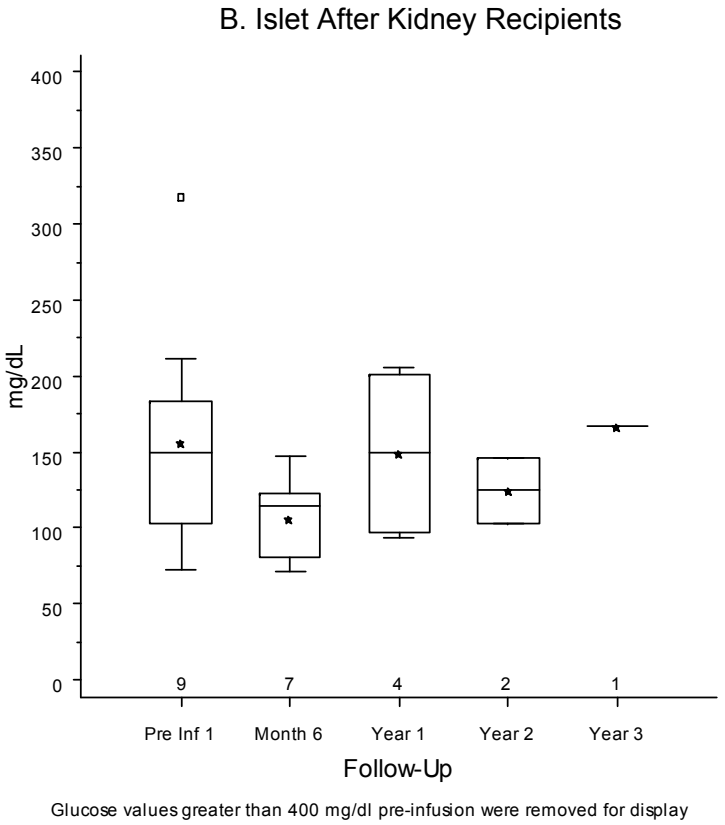


Glucose values greater than 400 mg/dl pre-infusion were removed for display

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



Glucose values greater than 400 mg/dl pre-infusion were removed for display



Glucose values greater than 400 mg/dl pre-infusion were removed for display

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

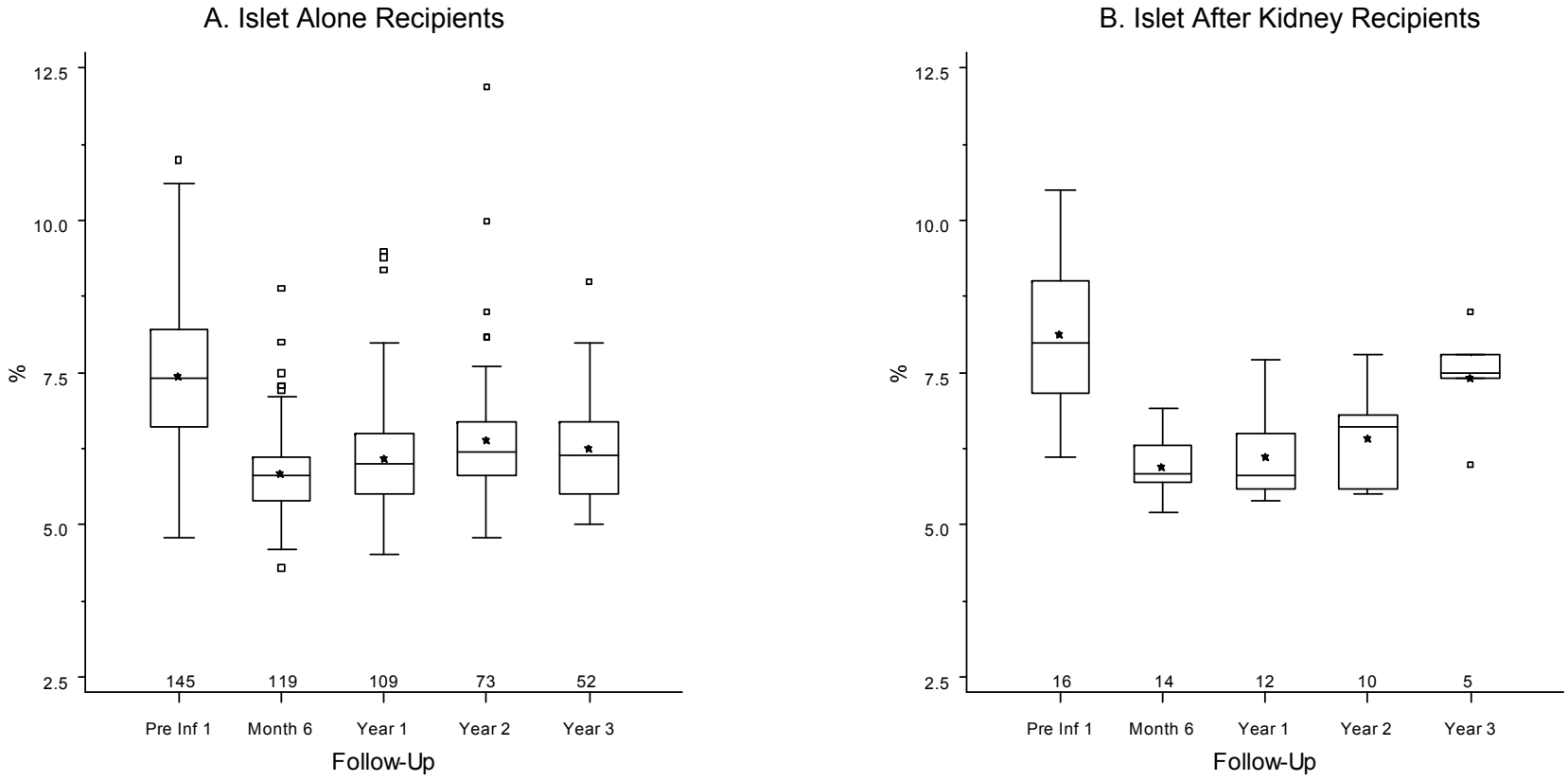


Exhibit 5 – 39
HbA_{1C} (%) Post Last Infusion
Recipients Who Never Achieved Insulin Independence

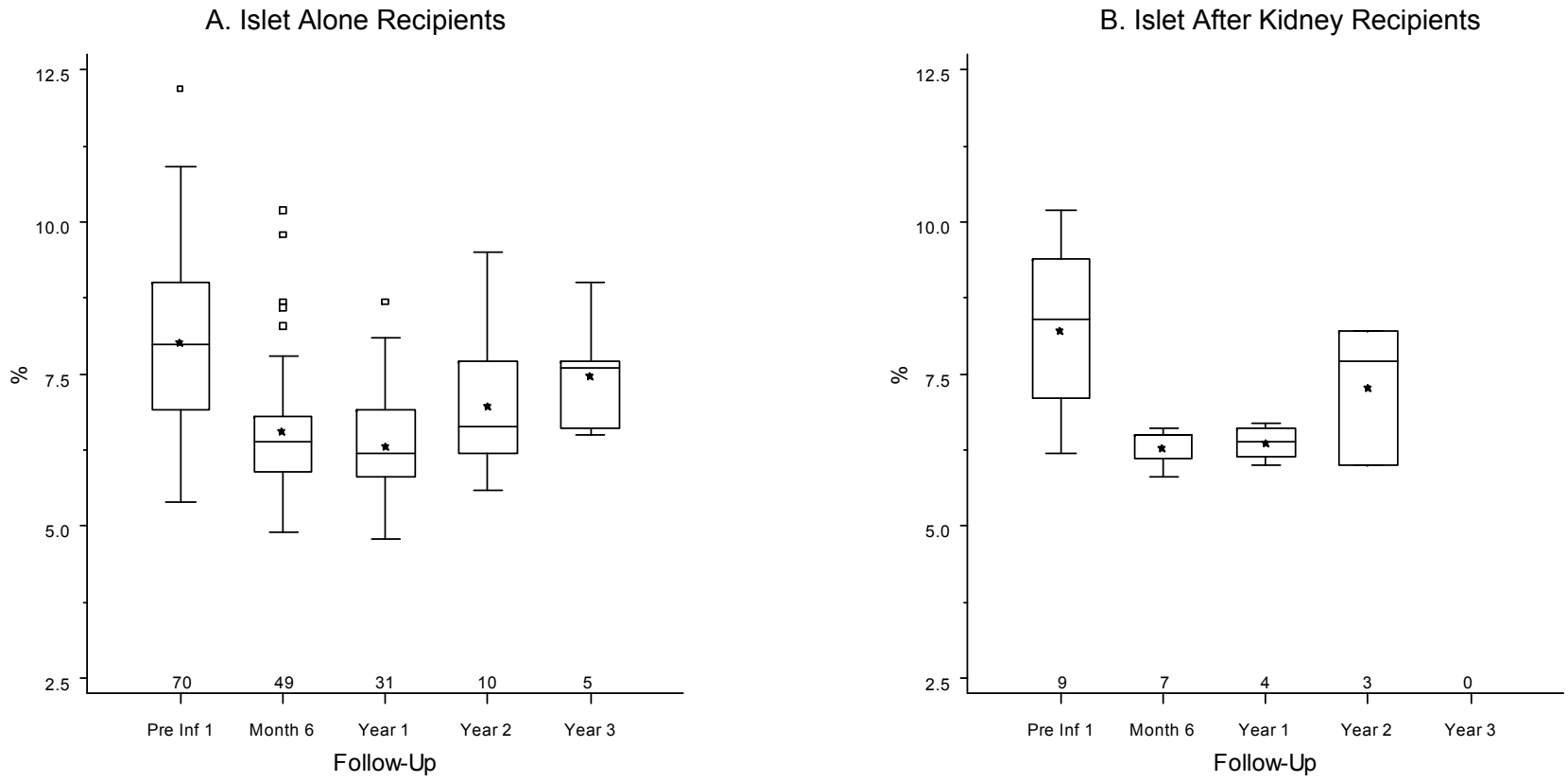
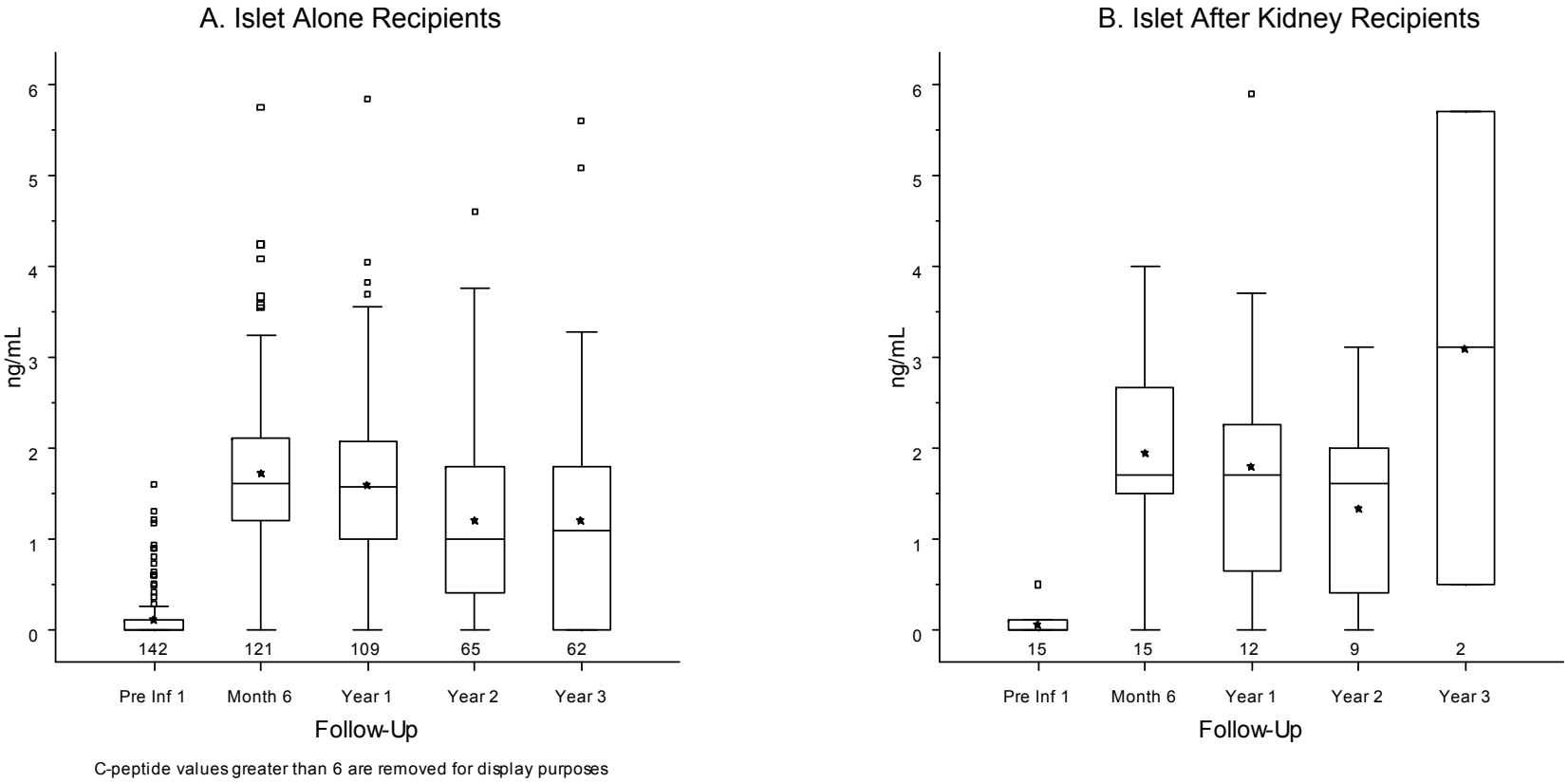
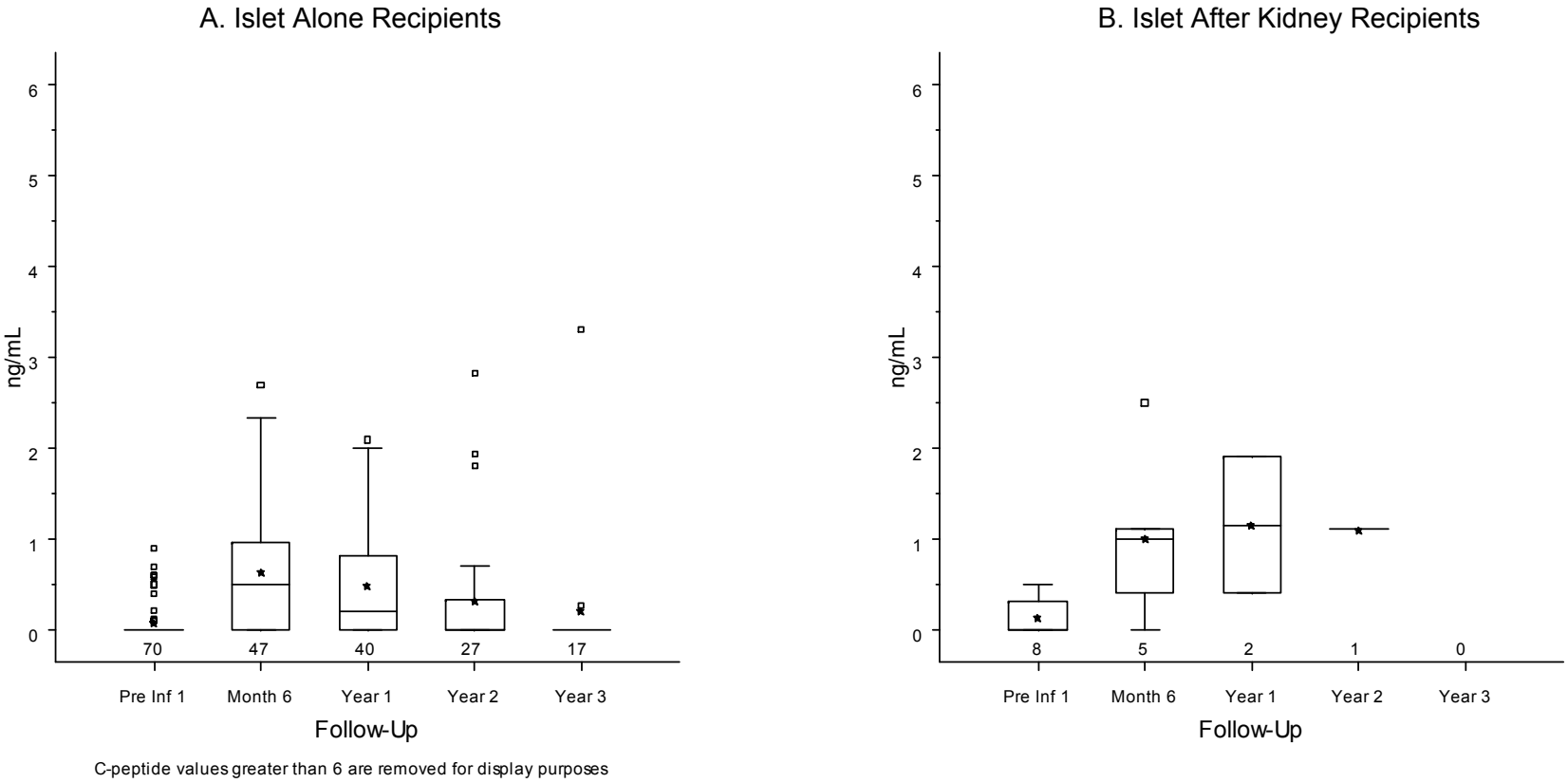


Exhibit 5 – 40
Basal Plasma C-Peptide (ng/mL) Post Last Infusion
Recipients Who Ever Achieved Insulin Independence



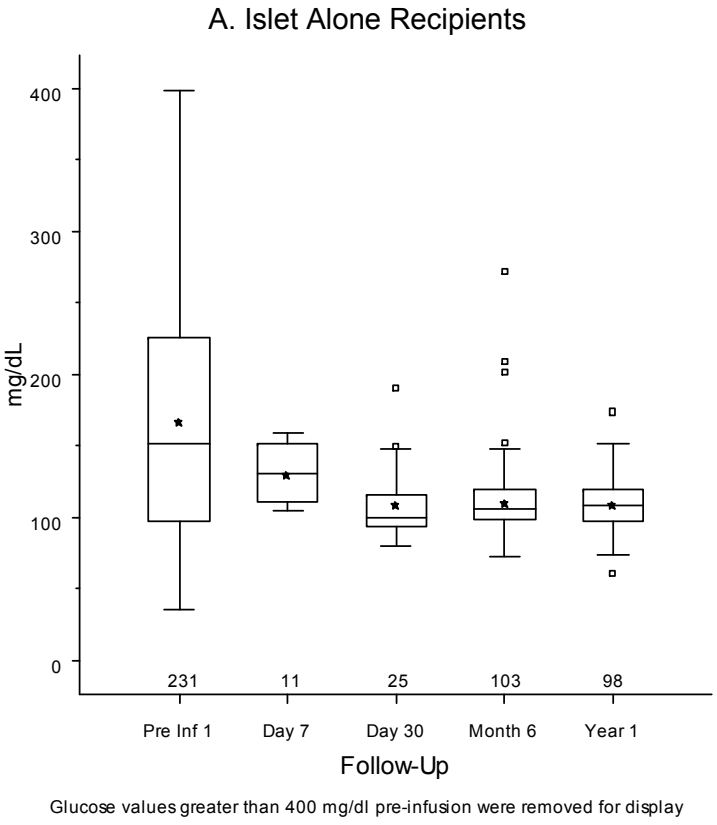
C-peptide values greater than 6 are removed for display purposes

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

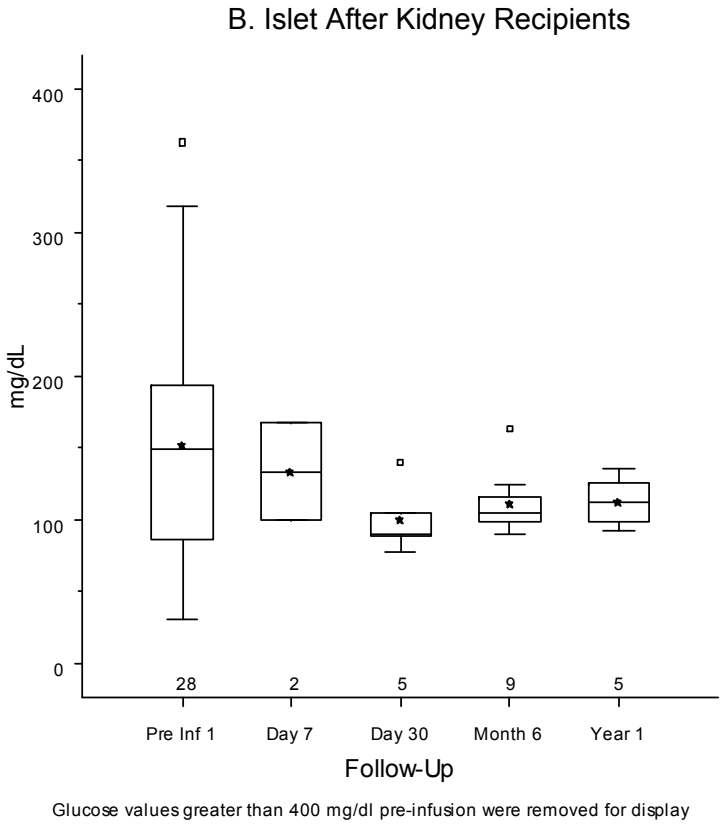


C-peptide values greater than 6 are removed for display purposes

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



Glucose values greater than 400 mg/dl pre-infusion were removed for display



Glucose values greater than 400 mg/dl pre-infusion were removed for display

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

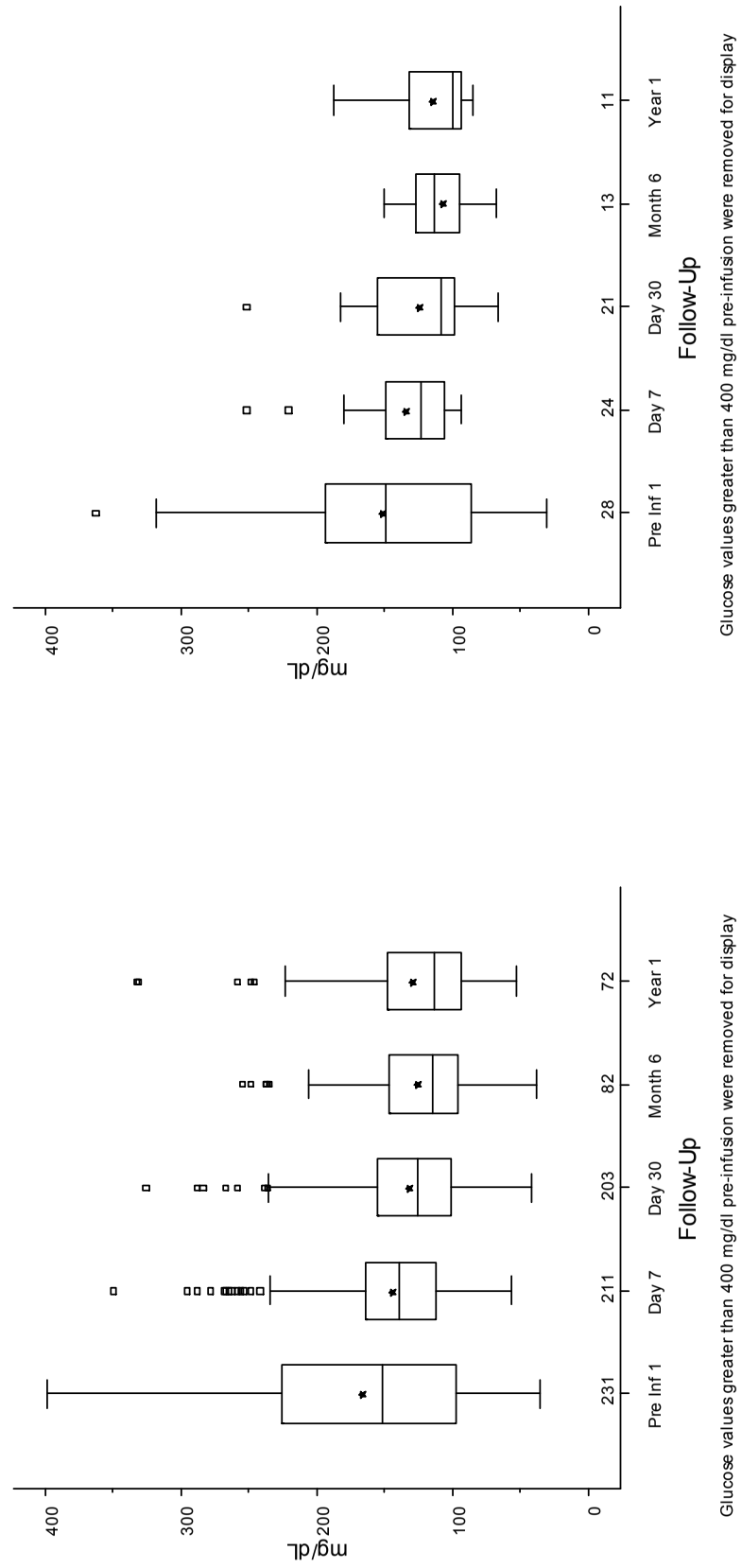


Exhibit 5 – 44
HbA_{1C} (%) Pre and Post First Infusion
Insulin Independent Recipients

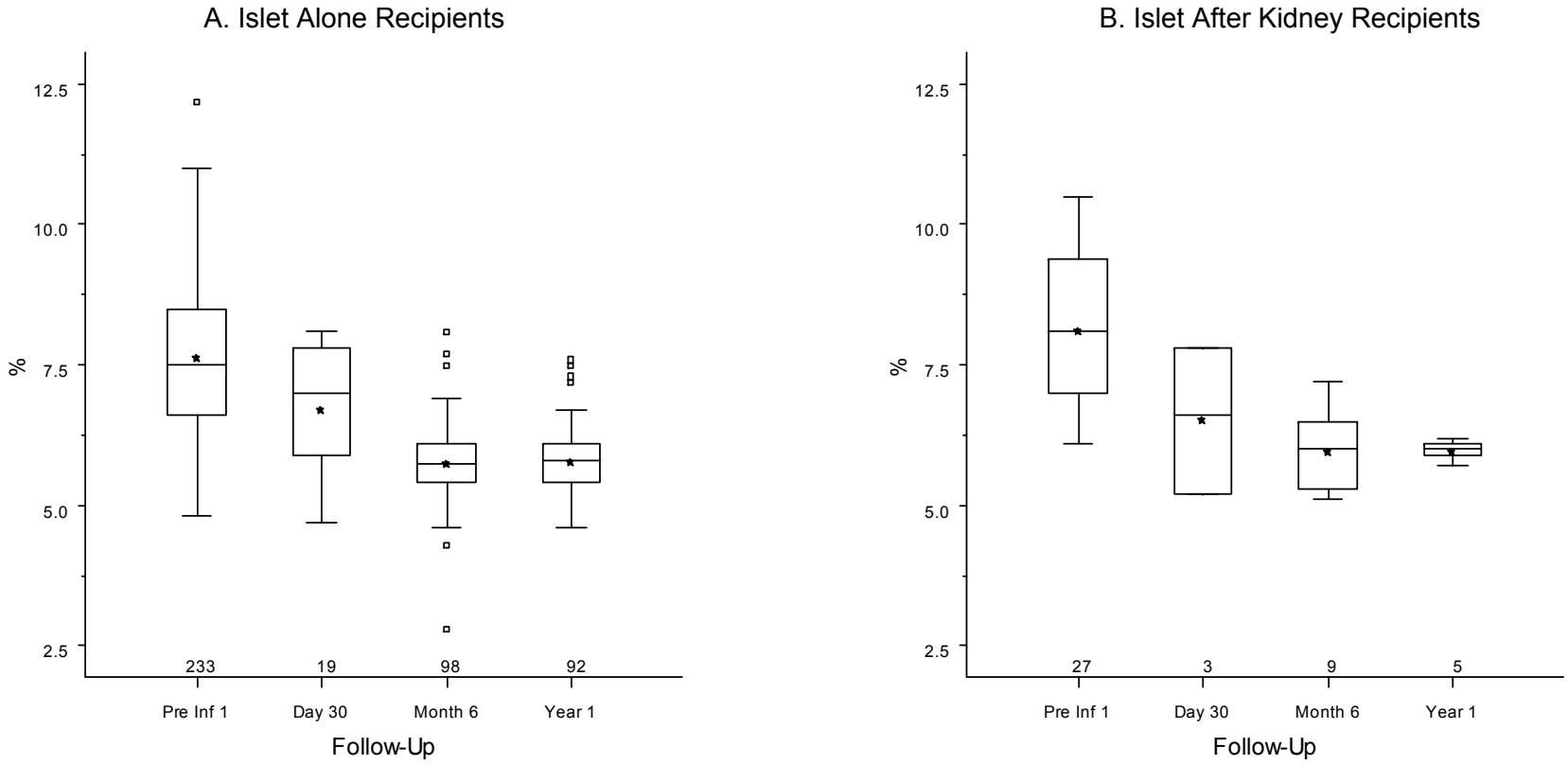


Exhibit 5 – 45
HbA_{1C} (%) Pre and Post First Infusion
Insulin Dependent Recipients

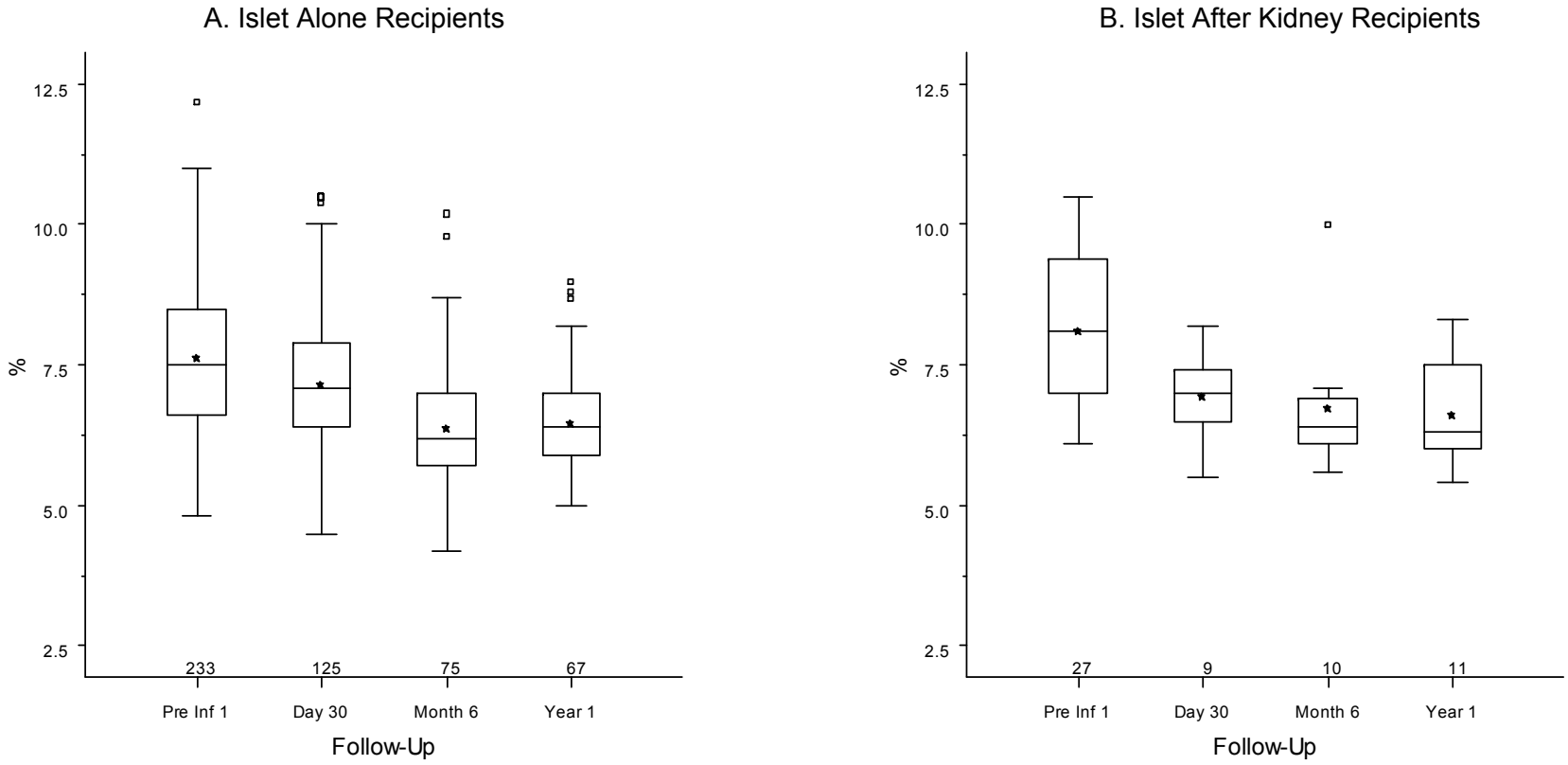
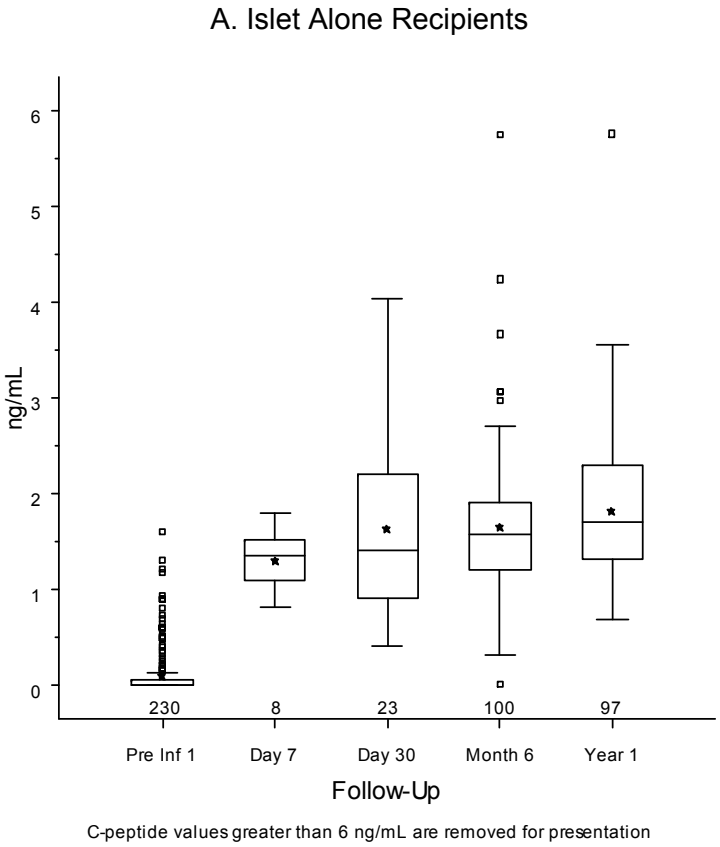


Exhibit 5 – 46
Basal Plasma C-Peptide (ng/mL) Pre and Post First Infusion
Insulin Independent Recipients



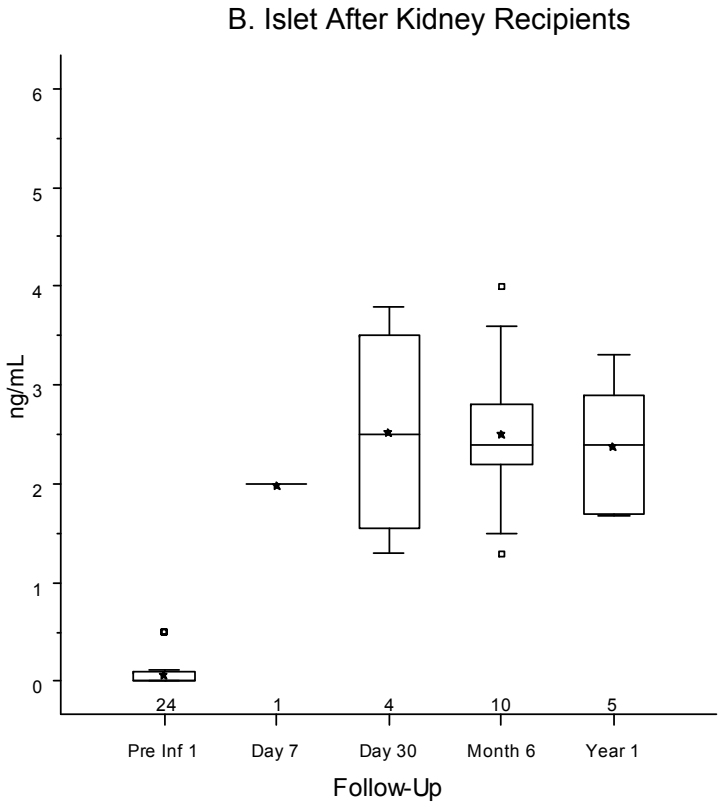


Exhibit 5 – 47
Basal Plasma C-Peptide (ng/mL) Pre and Post First Infusion
Insulin Dependent Recipients

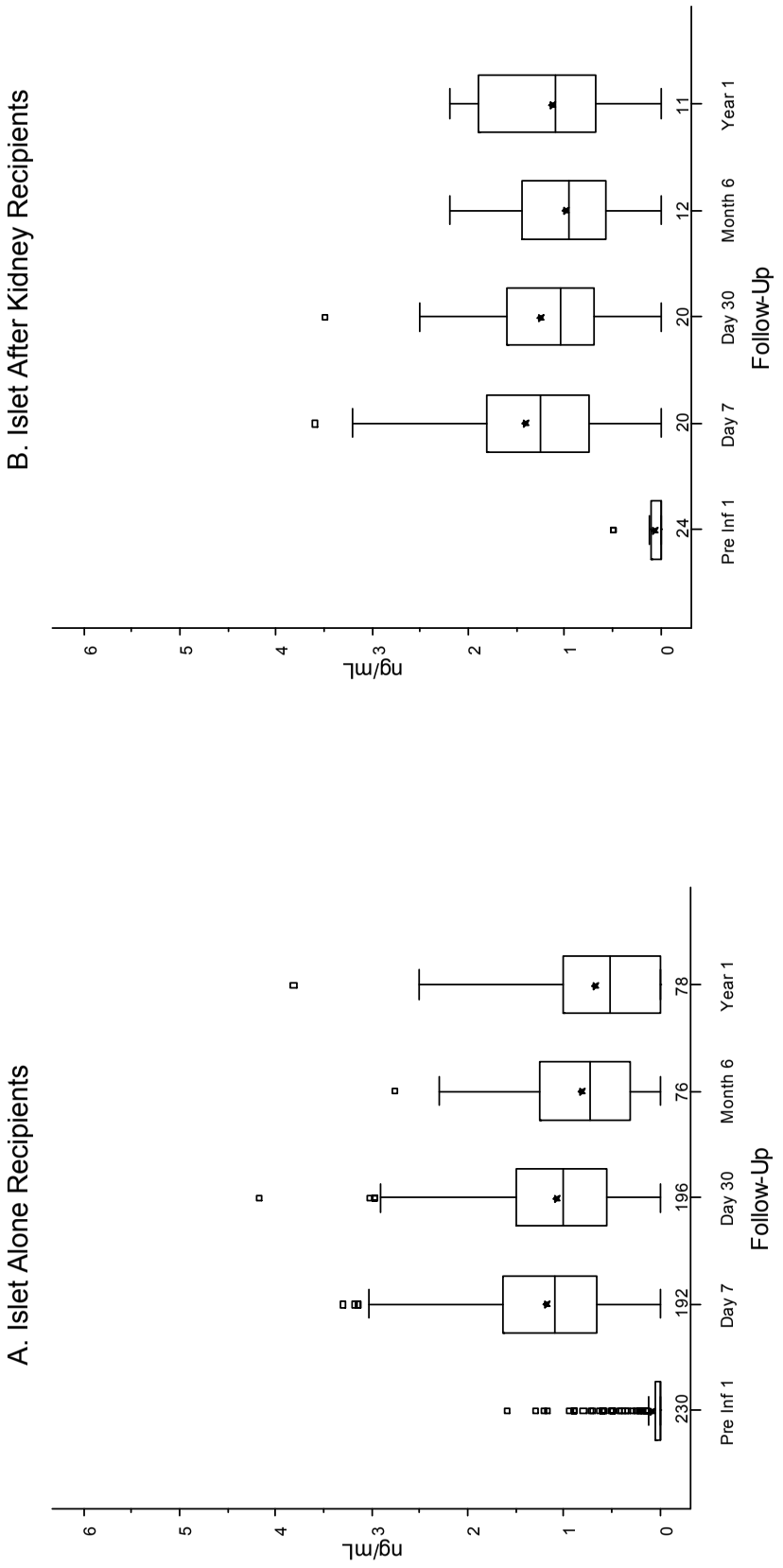
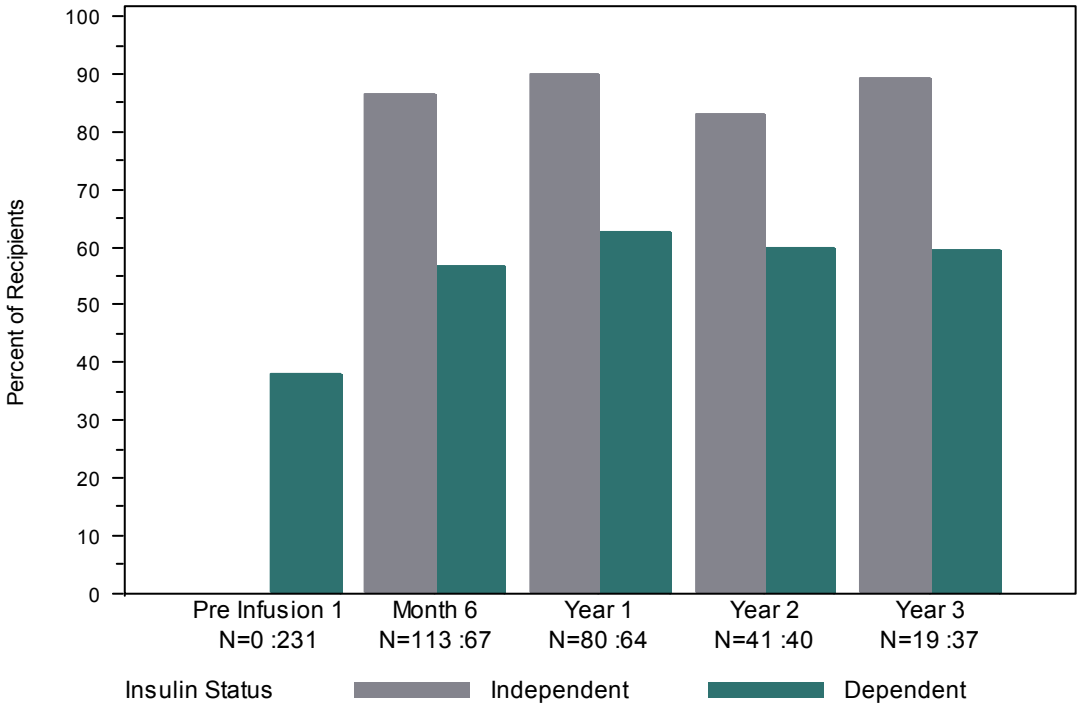


Exhibit 5 – 48
Recipients with Fasting Blood Glucose < 126 mg/dL
Post Last Infusion by Insulin Status

A. Islet Alone Recipients



B. Islet After Kidney Recipients

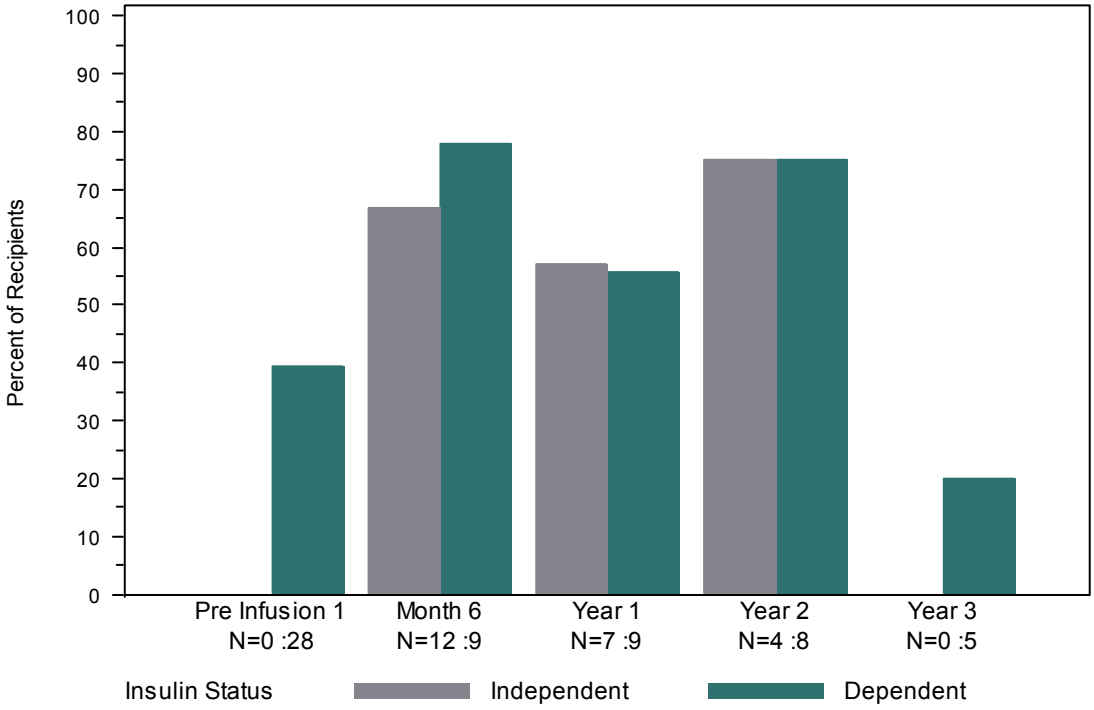
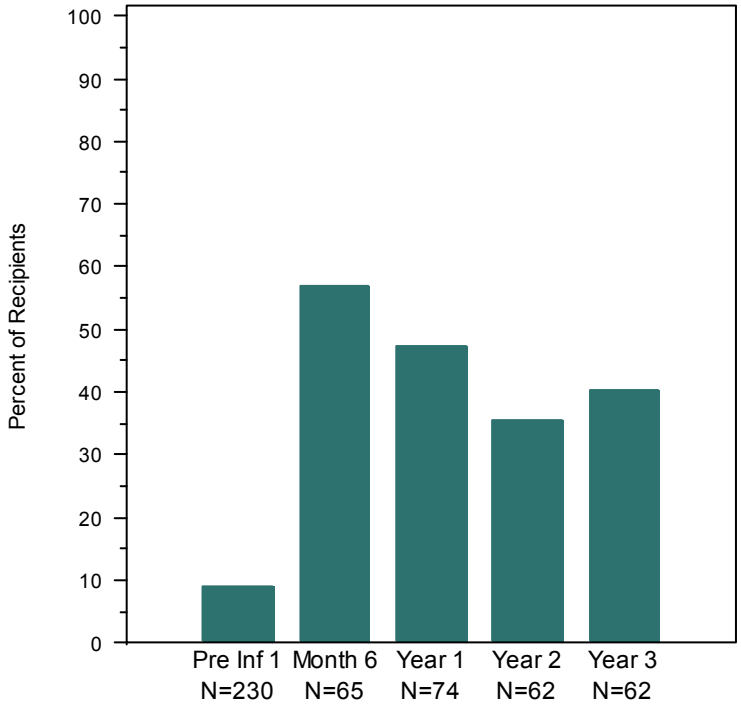


Exhibit 5 – 49
Insulin Dependent Recipients with Basal C-Peptide ≥ 0.5 ng/mL
Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

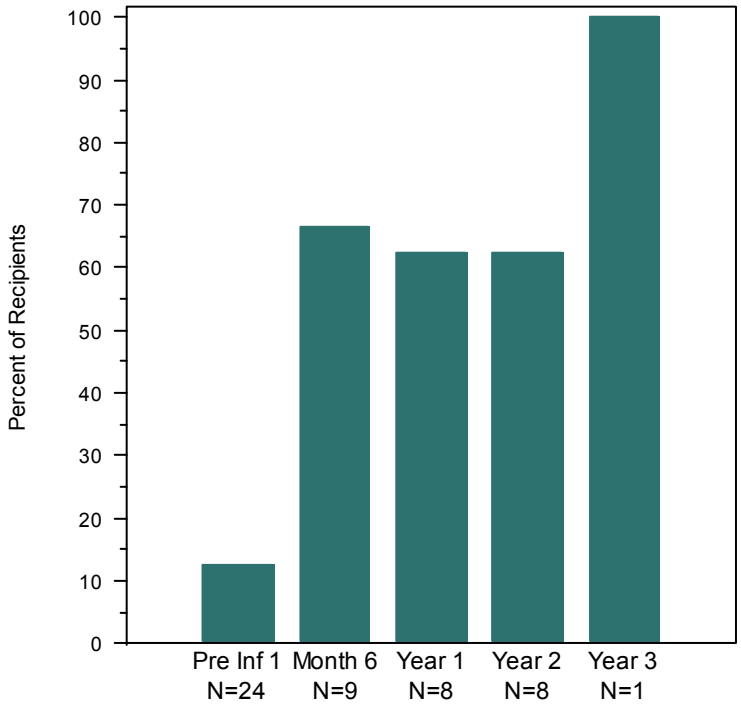
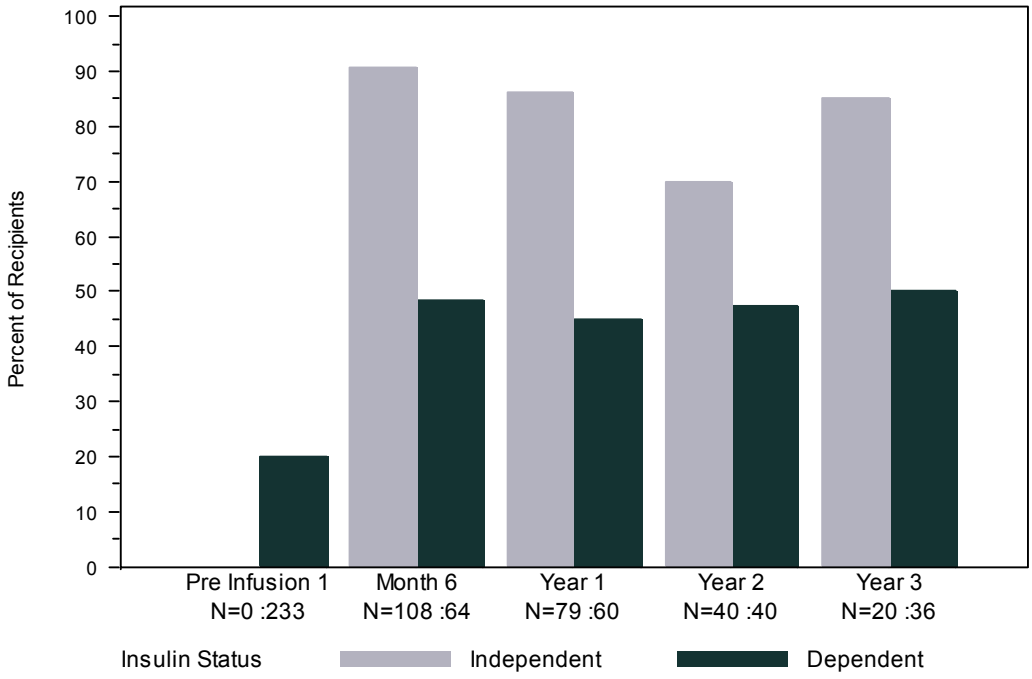


Exhibit 5 – 50
Recipients with HbA_{1C} < 6.5%
Post Last Infusion by Insulin Status

A. Islet Alone Recipients



B. Islet After Kidney Recipients

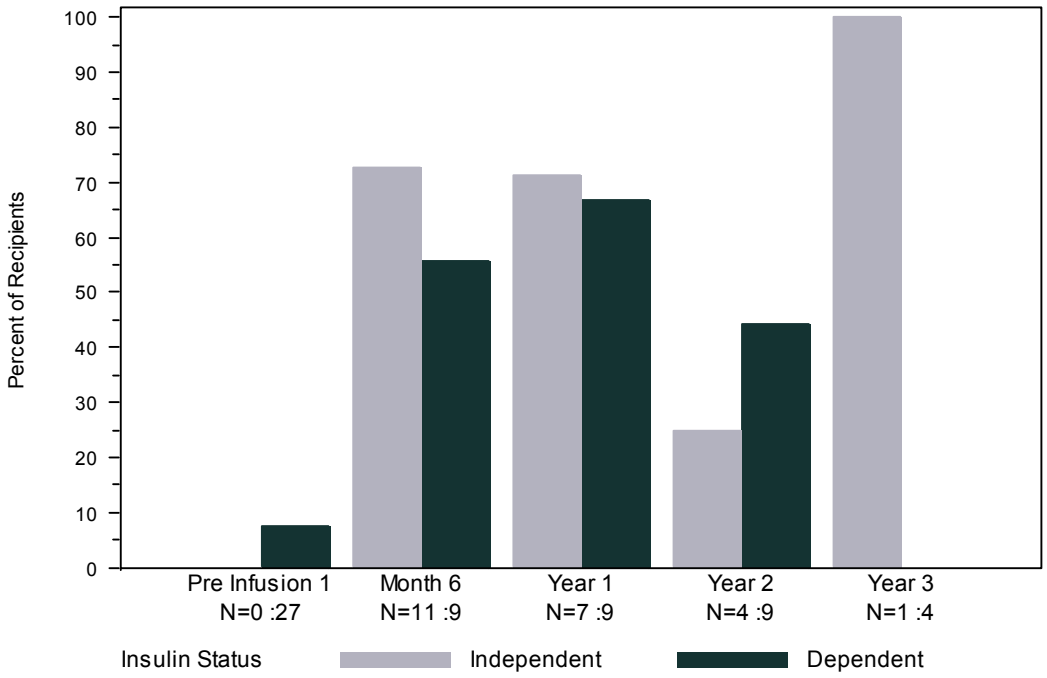


Exhibit 5 – 51
Pre-Infusion Recipient Lab Summary by Infusion Sequence
Islet Alone Recipients

	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)	231	172.6	91.2	153.0	35.0	560.0	171	133.0	50.0	119.0	31.0	308.0	52	126.0	48.9	114.5	30.0	319.0
HbA_{1c} (%)	233	7.6	1.3	7.5	4.8	12.2	156	6.7	1.1	6.7	3.8	9.8	51	6.6	0.9	6.5	4.8	10.7
ALT (IU/L)	231	21.7	9.7	19.0	3.0	72.0	154	38.8	21.5	33.0	11.0	131.0	49	38.8	20.8	33.0	11.0	121.0
AST (IU/L)	243	24.3	8.7	23.0	5.0	66.0	170	34.1	13.9	32.0	17.0	103.0	54	35.6	15.0	33.0	8.0	77.0
Alkaline Phosphatase (IU/L)	238	74.6	31.1	67.0	28.0	286.0	166	80.9	56.2	67.5	32.0	502.0	52	97.8	57.6	78.5	37.0	329.0
Total Bilirubin (mg/dL)	239	0.6	0.4	0.5	0.1	3.5	169	0.5	0.3	0.4	0.1	1.7	53	0.4	0.2	0.4	0.1	1.2
Total Cholesterol (mg/dl)	237	169.2	28.0	171.0	96.0	256.0	147	182.9	33.9	182.0	78.0	262.0	47	185.8	33.0	185.0	116.0	280.0
HDL (mg/dL)	234	63.3	15.7	63.0	31.0	123.0	137	62.1	16.0	61.0	25.0	108.0	42	60.0	16.6	59.5	24.0	103.0
LDL (mg/dL)	234	92.8	23.9	92.5	33.0	173.0	137	101.7	27.0	99.0	46.0	163.0	41	108.7	39.6	106.0	50.0	268.0
Triglycerides (mg/dL)	237	67.5	35.1	56.0	16.0	228.0	146	100.8	64.0	81.0	32.0	408.0	47	105.2	68.9	89.0	38.0	399.0
Serum Creatinine (mg/dL)	245	0.9	0.2	0.9	0.1	1.8	173	0.9	0.2	0.9	0.5	1.7	54	0.9	0.2	0.9	0.1	1.5
Calculated Creatinine Clearance (mL/min/1.73m^2)	193	103.5	24.7	99.0	50.0	196.0	90	97.8	28.2	97.0	44.0	169.0	23	101.4	40.8	94.0	40.0	227.0
Basal Plasma C-peptide (ng/mL)	230	0.1	0.3	0.0	0.0	1.6	152	1.0	0.9	0.7	0.0	5.3	46	1.0	0.7	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)	28	163.2	97.9	155.5	30.0	444.0	19	153.2	70.9	135.0	87.0	394.0	3	124.3	45.5	124.0	79.0	170.0
HbA_{1c} (%)	27	8.1	1.3	8.1	6.1	10.5	18	7.1	1.3	6.9	5.4	10.0	4	7.9	2.0	7.1	6.6	10.8
ALT (IU/L)	28	26.4	14.1	22.5	8.0	64.0	20	44.9	35.5	39.0	16.0	183.0	2	48.5	26.2	48.5	30.0	67.0
AST (IU/L)	29	29.7	12.8	25.0	16.0	80.0	20	40.9	23.3	31.0	17.0	113.0	2	40.0	12.7	40.0	31.0	49.0
Alkaline Phosphatase (IU/L)	27	79.0	25.0	75.0	40.0	134.0	20	81.7	35.4	70.5	40.0	157.0	2	104.0	58.0	104.0	63.0	145.0
Total Bilirubin (mg/dL)	29	0.5	0.3	0.4	0.1	1.2	20	0.5	0.3	0.4	0.1	1.4	2	0.8	0.1	0.8	0.7	0.8
Total Cholesterol (mg/dl)	27	187.6	28.3	181.0	100.0	240.0	12	177.9	19.4	180.5	150.0	206.0	1	189.0	-	189.0	189.0	189.0
HDL (mg/dL)	27	67.1	21.4	61.0	42.0	113.0	12	65.4	16.4	61.5	44.0	98.0	1	85.0	-	85.0	85.0	85.0
LDL (mg/dL)	27	99.5	23.4	100.0	42.0	143.0	12	93.5	13.6	89.5	75.0	114.0	1	92.0	-	92.0	92.0	92.0
Triglycerides (mg/dL)	27	97.5	43.6	86.0	34.0	217.0	12	94.4	43.0	83.5	38.0	188.0	1	60.0	-	60.0	60.0	60.0
Serum Creatinine (mg/dL)	30	1.2	0.3	1.1	0.5	2.0	19	1.3	0.3	1.3	0.7	2.0	3	1.2	0.3	1.2	1.0	1.5
Calculated Creatinine Clearance ($mL/min/1.73m^2$)	17	76.4	31.4	73.0	41.0	176.0	5	57.6	17.2	49.0	42.0	82.0	0	-	-	-	-	-
Basal Plasma C-peptide (ng/mL)	24	0.1	0.2	0.0	0.0	0.5	17	1.1	0.6	0.9	0.4	2.5	2	0.7	0.8	0.7	0.1	1.3

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	249	-	-	225	-	-	169	-	-	129	-	-
Fasting Plasma Glucose (mg/dL)	186	115.3	30.1	148	115.2	43.8	84	117.3	37.8	57	121.4	42.0
HbA_{1c} (%)	177	6.1	0.9	142	6.2	0.9	83	6.5	1.1	57	6.4	0.9
Basal Plasma C-peptide (ng/mL)	177	1.5	1.3	153	1.3	1.1	94	0.9	1.0	81	1.0	1.2
Peak Stimulated C-peptide After Meal (ng/mL)	76	3.5	1.7	64	3.1	1.8	24	2.9	1.6	14	3.2	1.5
Basal Plasma C-peptide before IV Glucagon (ng/mL)	14	1.8	0.7	9	1.4	0.7	1	1.1	-	0	-	-
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	14	3.2	1.5	9	2.4	1.6	1	1.9	-	0	-	-
Basal Plasma C-peptide Before IV Arginine (ng/mL)	77	1.6	0.9	57	1.4	0.8	17	1.3	0.8	10	1.1	0.8
Peak Stimulated C-peptide After IV Arginine (ng/mL)	75	2.6	1.3	56	2.4	1.2	17	2.2	1.1	10	1.7	1.1
Acute C-peptide Response to IV Arginine (ng/mL)	69	0.9	0.6	53	0.9	0.6	16	1.1	0.7	10	0.5	0.3
Acute Insulin Response to IV Arginine (µ/mL)	70	16.7	10.2	53	14.8	11.1	17	17.9	11.1	9	10.0	6.8
Basal Plasma C-peptide Before IV Glucose (ng/mL)	62	1.5	0.8	48	1.3	0.8	16	1.3	0.8	6	1.6	1.2
Peak Stimulated C-peptide After IV Glucose (ng/mL)	62	2.9	1.4	48	2.4	1.3	16	2.5	1.1	6	2.6	1.2
Acute C-peptide Response to IV Glucose (ng/ml)	59	0.8	0.8	48	0.8	0.7	16	1.1	1.3	6	0.3	0.2
Acute Insulin Response to IV Glucose (µ/mL)	58	16.2	12.7	51	12.2	10.8	16	14.2	12.1	6	3.6	2.1
AUC Insulin derived from 0.5 g/kg IVGTT (µ/mL x min)	19	485.5	277.1	17	590.1	368.8	4	443.8	88.5	1	374.0	-
KG-value derived from 0.5 g.kg IVGTT (KG Value)	49	0.2	1.2	39	0.3	0.9	12	-0.2	0.8	6	-0.9	0.9
2-hr 75g OGTT Plasma Glucose (mg/dL)	41	284.0	683.5	47	173.4	85.7	8	178.8	62.2	5	160.3	75.5
AUC C-peptide OGTT (ng/mL x min)	6	207.4	97.7	8	167.1	119.7	1	295.5	-	1	229.5	-
AUC C-peptide MMTT (ng/mL x min)	44	293.6	306.1	39	250.6	268.9	17	291.1	285.2	9	306.3	241.1
Mixed Meal Stimulation Index (pmol/mg)	22	0.7	0.3	18	0.7	0.3	8	0.5	0.3	5	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	28	-	-	25	-	-	23	-	-	11	-	-
Fasting Plasma Glucose (mg/dL)	22	111.5	25.9	16	126.3	39.4	12	114.3	39.5	6	163.2	62.4
HbA_{1C} (%)	21	6.1	0.5	16	6.2	0.7	13	6.6	0.9	5	7.4	0.9
Basal Plasma C-peptide (ng/mL)	20	1.7	1.2	14	1.7	1.6	10	1.3	1.0	2	3.1	3.7
Peak Stimulated C-peptide After Meal (ng/mL)	14	4.4	1.0	12	3.9	2.3	7	6.1	4.8	3	3.0	3.7
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)	8	2.4	1.0	4	1.8	0.8	3	2.7	1.0	0	-	-
Peak Stimulated C-peptide After IV Arginine (ng/mL)	8	2.9	1.2	5	2.3	1.3	4	3.4	2.2	0	-	-
Acute C-peptide Response to IV Arginine (ng/mL)	8	0.5	0.3	4	0.7	0.3	3	0.9	0.6	0	-	-
Acute Insulin Response to IV Arginine (µ/mL)	5	15.3	8.5	3	24.6	7.5	3	14.3	17.7	0	-	-
Basal Plasma C-peptide Before IV Glucose (ng/mL)	6	1.4	0.9	3	1.4	0.1	3	1.4	0.5	0	-	-
Peak Stimulated C-peptide After IV Glucose (ng/mL)	6	2.7	1.2	3	3.0	1.1	3	3.0	1.1	0	-	-
Acute C-peptide Response to IV Glucose (ng/ml)	6	0.5	0.2	3	0.6	0.2	3	0.5	0.3	0	-	-
Acute Insulin Response to IV Glucose (µ/mL)	6	12.2	9.5	3	18.7	13.8	3	7.2	4.9	0	-	-
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	3	-1.0	0.3	3	-0.7	0.2	0	-	-
2-hr 75g OGTT Plasma Glucose (mg/dL)	3	274.3	59.1	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	4	497.4	277.2	1	995.3	-	0	-	-
Mixed Meal Stimulation Index (pmol/mg)	7	0.8	0.1	4	0.7	0.2	3	0.9	0.1	0	-	-

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)	67	127.6	39.7	113	107.6	20.2	64	127.8	61.0	80	104.5	17.3
HbA_{1C} (%)	63	6.6	1.0	108	5.8	0.6	59	6.7	1.1	79	5.8	0.6
Basal Plasma C-peptide (ng/mL)	65	0.8	1.0	110	2.0	1.2	74	0.8	1.1	77	1.8	0.9
Peak Stimulated C-peptide After Meal (ng/mL)	26	2.5	1.7	50	4.0	1.5	32	2.0	1.5	32	4.3	1.3
Basal Plasma C-peptide before IV Glucagon (ng/mL)	1	0.5	-	13	1.9	0.7	2	1.2	1.2	7	1.5	0.7
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	1	0.6	-	13	3.4	1.3	2	1.5	1.3	7	2.6	1.6
Basal Plasma C-peptide Before IV Arginine (ng/mL)	21	1.1	1.0	55	1.8	0.8	14	0.9	0.7	43	1.6	0.7
Peak Stimulated C-peptide After IV Arginine (ng/mL)	19	1.5	1.3	55	3.0	1.1	13	1.3	1.1	43	2.7	1.1
Acute C-peptide Response to IV Arginine (ng/mL)	16	0.6	0.6	53	1.0	0.5	11	0.5	0.3	42	1.0	0.6
Acute Insulin Response to IV Arginine (µ/mL)	18	8.3	7.1	52	19.6	9.5	12	8.0	10.0	41	16.8	10.7
Basal Plasma C-peptide Before IV Glucose (ng/mL)	9	1.0	0.9	53	1.6	0.8	9	0.6	0.4	39	1.5	0.8
Peak Stimulated C-peptide After IV Glucose (ng/mL)	9	1.8	1.6	53	3.1	1.2	9	1.0	0.8	39	2.8	1.1
Acute C-peptide Response to IV Glucose (ng/ml)	9	0.4	0.5	50	0.9	0.8	9	0.4	0.4	39	0.8	0.7
Acute Insulin Response to IV Glucose (µ/mL)	8	9.6	12.6	50	17.3	12.5	9	5.0	8.0	42	13.7	10.8
AUC Insulin derived from 0.5 g/kg IVGTT (µ/mL x min)	1	161.0	-	18	503.6	273.4	1	133.0	-	16	618.6	361.0
KG-value derived from 0.5 g.kg IVGTT (KG Value)	7	-0.4	1.2	42	0.3	1.2	5	-0.1	0.7	34	0.3	0.9
2-hr 75g OGTT Plasma Glucose (mg/dL)	5	329.8	85.6	36	277.6	729.9	8	274.8	132.7	39	152.6	55.3
AUC C-peptide OGTT (ng/mL x min)	1	94.5	-	5	230.0	90.1	1	212.4	-	7	160.7	127.8
AUC C-peptide MMTT (ng/mL x min)	13	270.4	291.1	31	303.4	316.3	14	183.3	273.1	25	288.3	264.5
Mixed Meal Stimulation Index (pmol/mg)	6	0.5	0.5	16	0.8	0.2	4	0.4	0.4	14	0.7	0.2

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	292	100.0	279	100.0	252	100.0	194	100.0	142	100.0
Peripheral Neuropathy										
No occurrence	142	48.6	134	48.0	103	40.9	65	33.5	41	28.9
Asymptomatic	18	6.2	14	5.0	9	3.6	8	4.1	-	0.0
Symptomatic	93	31.8	39	14.0	36	14.3	16	8.2	13	9.2
Disabling	2	0.7	-	0.0	-	0.0	-	0.0	-	0.0
Unknown	5	1.7	18	6.5	19	7.5	18	9.3	13	9.2
Missing	32	11.0	74	26.5	85	33.7	87	44.8	75	52.8
Autonomic Neuropathy										
No occurrence	185	63.4	149	53.4	113	44.8	74	38.1	50	35.2
Asymptomatic	13	4.5	10	3.6	6	2.4	7	3.6	1	0.7
Symptomatic	48	16.4	28	10.0	23	9.1	6	3.1	3	2.1
Disabling	-	0.0	-	0.0	1	0.4	-	0.0	-	0.0
Unknown	14	4.8	18	6.5	24	9.5	20	10.3	13	9.2
Missing	32	11.0	74	26.5	85	33.7	87	44.8	75	52.8
Nephropathy										
No occurrence	179	61.3	141	50.5	103	40.9	60	30.9	35	24.6
Microalbuminuria	49	16.8	29	10.4	28	11.1	14	7.2	10	7.0
Macroalbuminuria	2	0.7	8	2.9	9	3.6	6	3.1	2	1.4
End stage renal disease	-	0.0	-	0.0	-	0.0	1	0.5	-	0.0
Stable allograft	20	6.8	9	3.2	12	4.8	6	3.1	4	2.8
Unknown	9	3.1	18	6.5	15	6.0	20	10.3	14	9.9
Missing	33	11.3	74	26.5	85	33.7	87	44.8	77	54.2
CAD										
Yes	22	7.5	14	5.0	9	3.6	4	2.1	5	3.5
No	238	81.5	184	65.9	148	58.7	91	46.9	56	39.4
Unknown	2	0.7	7	2.5	10	4.0	12	6.2	6	4.2
Missing	30	10.3	74	26.5	85	33.7	87	44.8	75	52.8

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	257	88.0	198	71.0	161	63.9	94	48.5	61	43.0
Unknown	3	1.0	7	2.5	6	2.4	13	6.7	6	4.2
Missing	32	11.0	74	26.5	85	33.7	87	44.8	75	52.8
PVD										
Yes	5	1.7	2	0.7	1	0.4	1	0.5	-	0.0
No	251	86.0	194	69.5	155	61.5	93	47.9	58	40.8
Unknown	4	1.4	9	3.2	11	4.4	13	6.7	9	6.3
Missing	32	11.0	74	26.5	85	33.7	87	44.8	75	52.8
Treated Hypertension										
Yes	99	33.9	78	28.0	76	30.2	53	27.3	29	20.4
No	160	54.8	121	43.4	88	34.9	46	23.7	33	23.2
Unknown	3	1.0	6	2.2	3	1.2	8	4.1	5	3.5
Missing	30	10.3	74	26.5	85	33.7	87	44.8	75	52.8
Foot Ulcers										
Yes	13	4.5	3	1.1	5	2.0	3	1.5	-	0.0
No	223	76.4	191	68.5	152	60.3	91	46.9	61	43.0
Unknown	23	7.9	11	3.9	10	4.0	13	6.7	6	4.2
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8
Lower Limb Amputation										
Yes	5	1.7	1	0.4	1	0.4	-	0.0	-	0.0
No	250	85.6	202	72.4	163	64.7	100	51.5	63	44.4
Unknown	5	1.7	2	0.7	3	1.2	7	3.6	4	2.8
Missing	32	11.0	74	26.5	85	33.7	87	44.8	75	52.8
Foot Deformity										
Yes	6	2.1	2	0.7	2	0.8	-	0.0	-	0.0
No	236	80.8	193	69.2	155	61.5	98	50.5	62	43.7
Unknown	17	5.8	10	3.6	9	3.6	9	4.6	5	3.5
Missing	33	11.3	74	26.5	86	34.1	87	44.8	75	52.8

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	%
Dysesthesia										
Yes	39	13.4	18	6.5	22	8.7	12	6.2	6	4.2
No	190	65.1	164	58.8	128	50.8	77	39.7	49	34.5
Unknown	29	9.9	23	8.2	17	6.7	18	9.3	12	8.5
Missing	34	11.6	74	26.5	85	33.7	87	44.8	75	52.8
Orthostatic Hypotension										
Yes	21	7.2	5	1.8	5	2.0	1	0.5	2	1.4
No	184	63.0	162	58.1	132	52.4	78	40.2	51	35.9
Unknown	54	18.5	38	13.6	30	11.9	28	14.4	14	9.9
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8
Gastroparesis										
Yes	30	10.3	13	4.7	11	4.4	3	1.5	2	1.4
No	204	69.9	173	62.0	141	56.0	82	42.3	54	38.0
Unknown	26	8.9	19	6.8	15	6.0	22	11.3	11	7.7
Missing	32	11.0	74	26.5	85	33.7	87	44.8	75	52.8
Constipation										
Yes	20	6.8	11	3.9	3	1.2	1	0.5	-	0.0
No	212	72.6	177	63.4	152	60.3	89	45.9	55	38.7
Unknown	27	9.2	17	6.1	12	4.8	17	8.8	12	8.5
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8
Diabetic Diarrhea										
Yes	12	4.1	10	3.6	8	3.2	6	3.1	1	0.7
No	224	76.7	163	58.4	138	54.8	82	42.3	53	37.3
Unknown	23	7.9	32	11.5	21	8.3	19	9.8	13	9.2
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8
Fecal Incontinence										
Yes	2	0.7	-	0.0	-	0.0	-	0.0	-	0.0
No	231	79.1	188	67.4	157	62.3	92	47.4	56	39.4
Unknown	26	8.9	17	6.1	10	4.0	15	7.7	11	7.7
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8

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	1.4	2	0.7	2	0.8	1	0.5	-	0.0
No	227	77.7	185	66.3	152	60.3	87	44.8	56	39.4
Unknown	28	9.6	18	6.5	13	5.2	19	9.8	11	7.7
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8
Sexual Dysfunction										
Yes	21	7.2	10	3.6	10	4.0	5	2.6	3	2.1
No	206	70.5	156	55.9	129	51.2	73	37.6	47	33.1
Unknown	32	11.0	39	14.0	28	11.1	29	14.9	17	12.0
Missing	33	11.3	74	26.5	85	33.7	87	44.8	75	52.8

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	292	100.0	279	100.0	252	0100.0	194	100.0	142	100.0
Retinopathy										
None	109	37.3	91	32.6	74	29.4	41	21.1	25	17.6
Non Proliferative	62	21.2	39	14.0	30	11.9	20	10.3	13	9.2
Proliferative	81	27.7	35	12.5	28	11.1	15	7.7	7	4.9
Unknown	10	3.4	37	13.3	32	12.7	30	15.5	20	14.1
Missing	30	10.3	77	27.6	88	34.9	88	45.4	77	54.2
Diabetic Macular Edema										
None	237	81.2	164	58.8	132	52.4	75	38.7	51	35.9
Mild	5	1.7	2	0.7	-	0.0	-	0.0	-	0.0
Moderate	3	1.0	2	0.7	1	0.4	1	0.5	-	0.0
Severe	1	0.3	-	0.0	-	0.0	1	0.5	-	0.0
Unknown	13	4.5	33	11.8	32	12.7	29	14.9	14	9.9
Missing	33	11.3	78	28.0	87	34.5	88	45.4	77	54.2
Laser photocoagulation surgery performed for proliferative retinopathy										
Yes	100	34.2	2	0.7	8	3.2	5	2.6	3	2.1
No	153	52.4	191	68.5	149	59.1	89	45.9	56	39.4
Unknown	5	1.7	8	2.9	8	3.2	13	6.7	8	5.6
Missing	34	11.6	78	28.0	87	34.5	87	44.8	75	52.8
Laser photocoagulation surgery performed for diabetic macular edema										
Yes	12	4.1	1	0.4	1	0.4	-	0.0	-	0.0
No	232	79.5	194	69.5	157	62.3	95	49.0	60	42.3
Unknown	14	4.8	6	2.2	7	2.8	12	6.2	7	4.9
Missing	34	11.6	78	28.0	87	34.5	87	44.8	75	52.8
Vitrectomy										
Yes	31	10.6	1	0.4	2	0.8	2	1.0	-	0.0
No	220	75.3	194	69.5	157	62.3	93	47.9	60	42.3
Unknown	7	2.4	6	2.2	6	2.4	12	6.2	7	4.9
Missing	34	11.6	78	28.0	87	34.5	87	44.8	75	52.8

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	25	8.6	2	0.7	5	2.0	4	2.1	1	0.7
No	217	74.3	179	64.2	147	58.3	89	45.9	57	40.1
Unknown	10	3.4	13	4.7	9	3.6	12	6.2	9	6.3
Missing	40	13.7	85	30.5	91	36.1	89	45.9	75	52.8

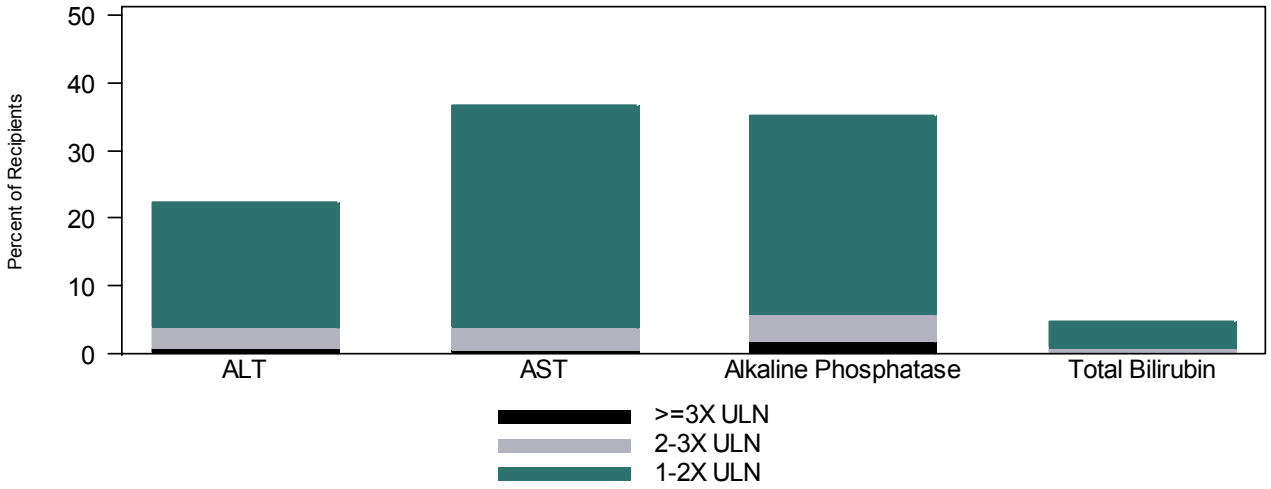
Chapter 6
Liver, Kidney, Lipid, and PRA Effects

Liver, Kidney, Lipid, and PRA Effects

This chapter provides a summary of abnormal laboratory tests. Abnormal is 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) were minimal for ALT (4%), AST (4%), alkaline phosphatase (6%) and for total bilirubin (1%) (Exhibit 6-1). There were no reports at this level for total cholesterol and 9 reports (4%) for triglycerides (Exhibit 6-6). There were reports of 24 (13%) IA recipients and 4 (18%) IAK recipients with an increase in their serum creatinine greater than 0.5 mg/dL of their baseline level (Exhibit 6-11).

Exhibit 6 – 1
Incidence of Abnormal Liver Function Tests
at Any 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 – 2
ALT (IU/L) Pre Infusion and Post Last Infusion

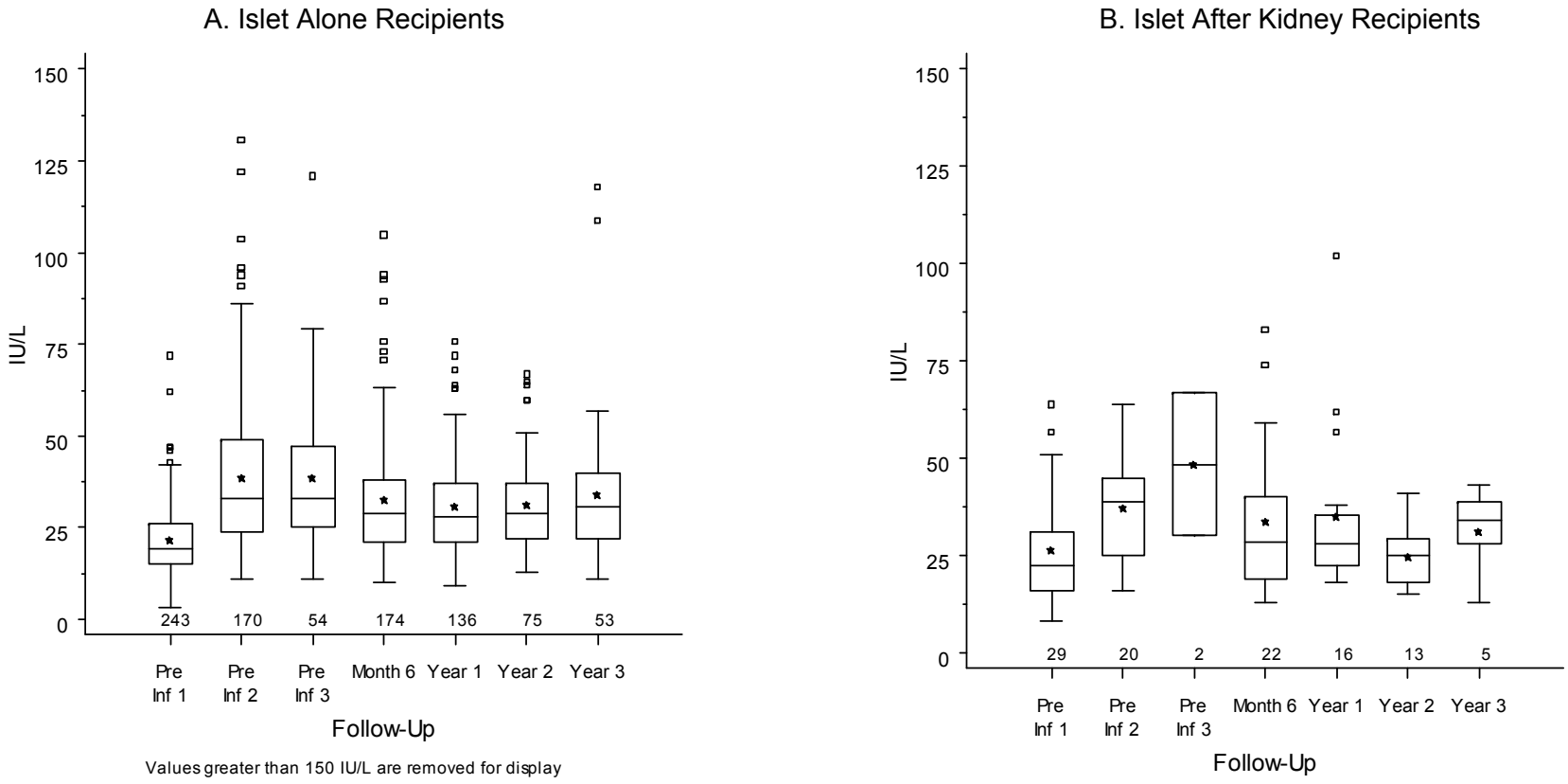


Exhibit 6 – 3
AST (IU/L) Pre Infusion and Post Last Infusion

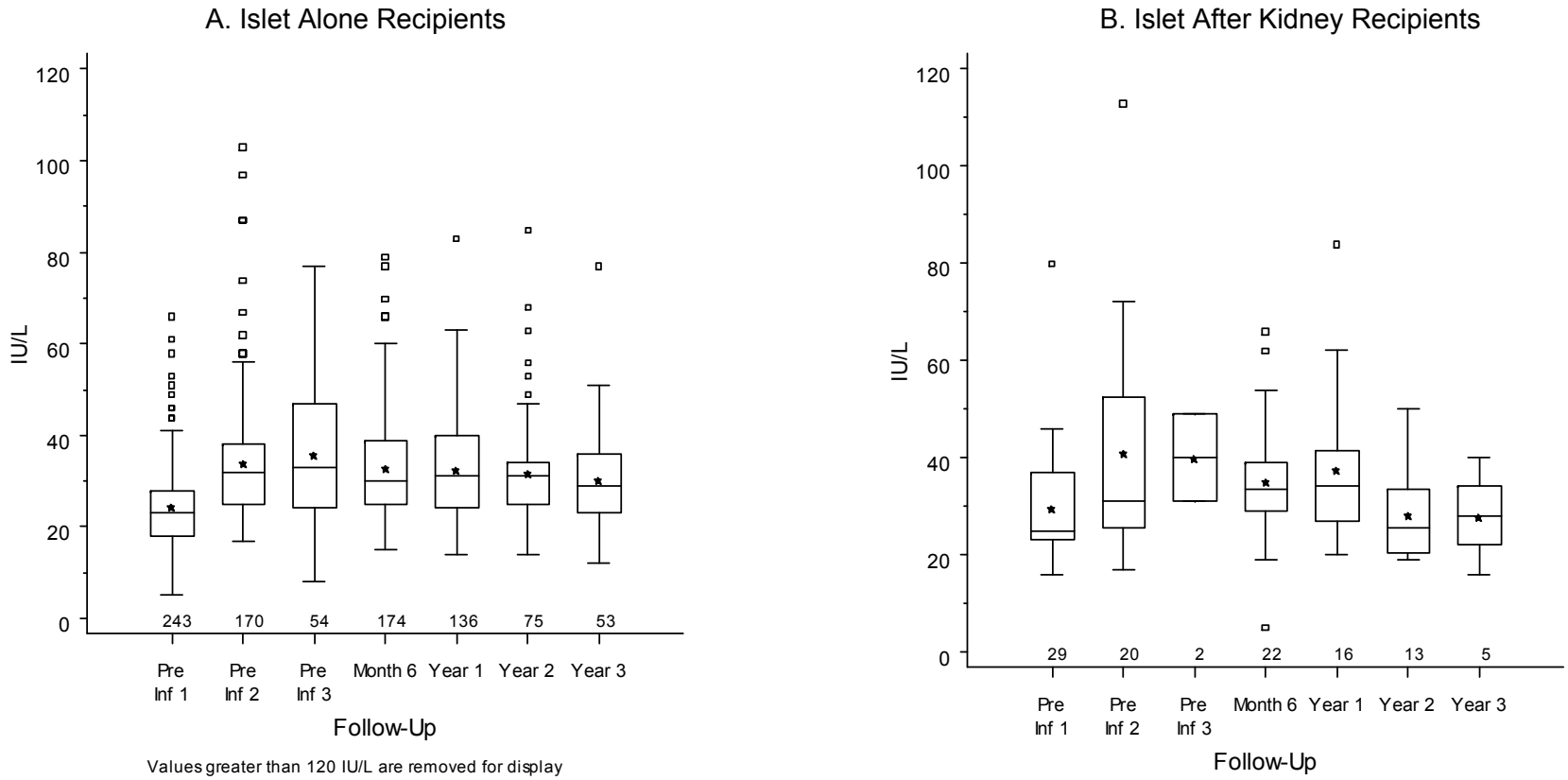


Exhibit 6 – 4
Alkaline Phosphatase (IU/L) Pre Infusion and Post Last Infusion

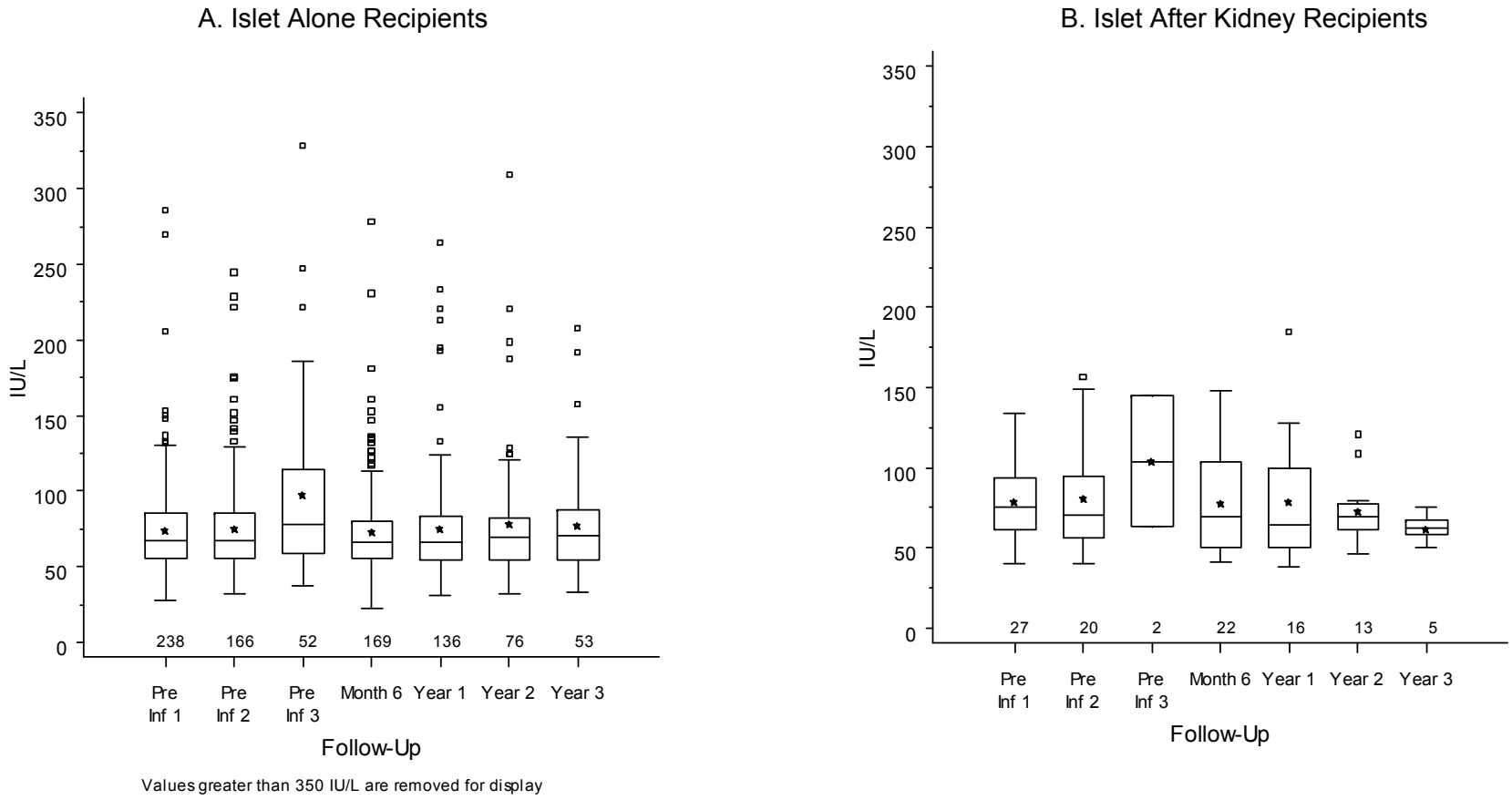


Exhibit 6 – 5
Total Bilirubin (mg/dL) Pre Infusion and Post Last Infusion

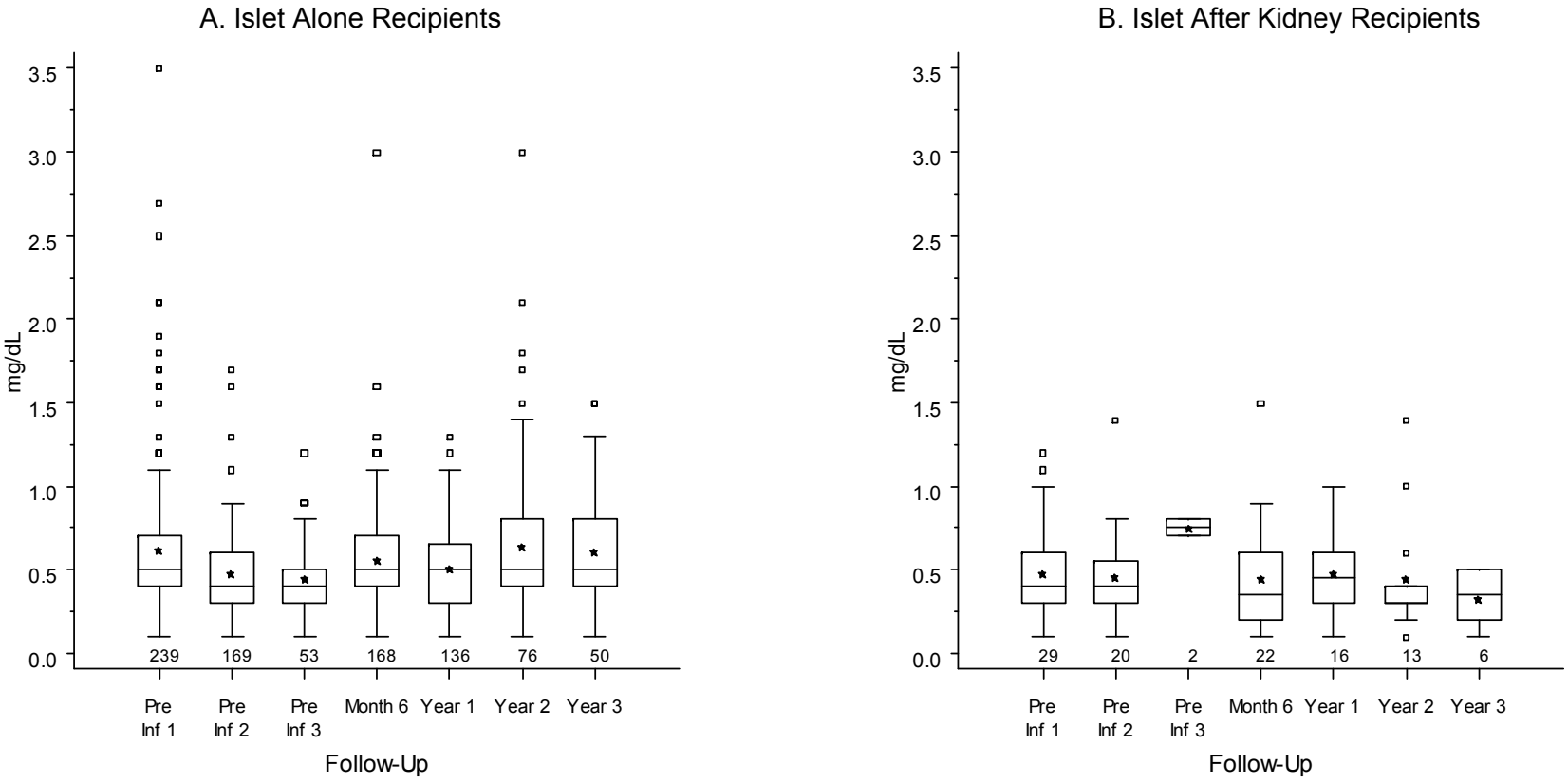
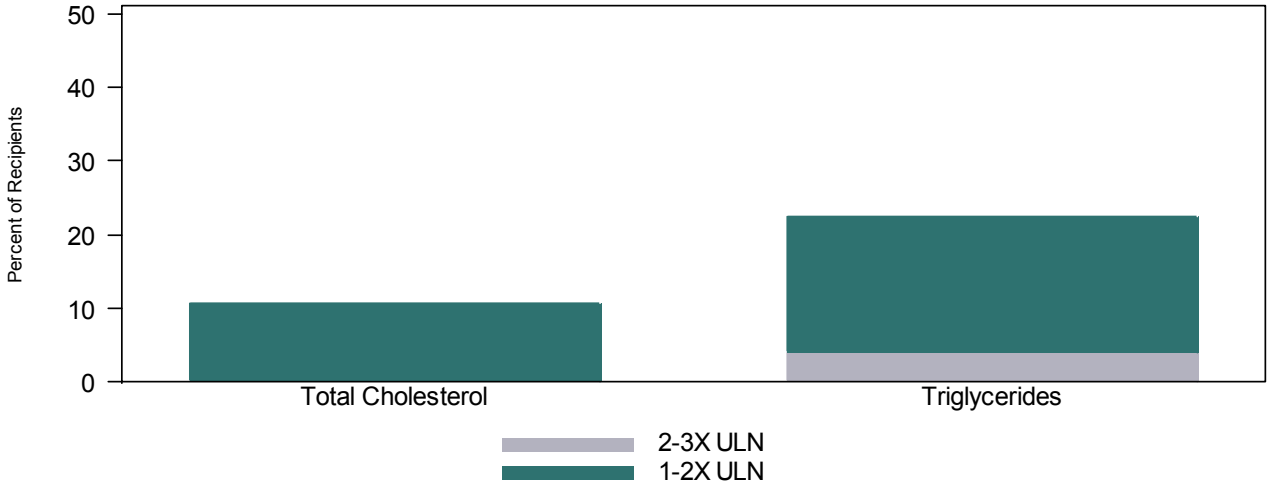


Exhibit 6 – 6
Incidence of Abnormal Lipid Tests
at Any Scheduled Time Post First Infusion
All Allograft Recipients



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

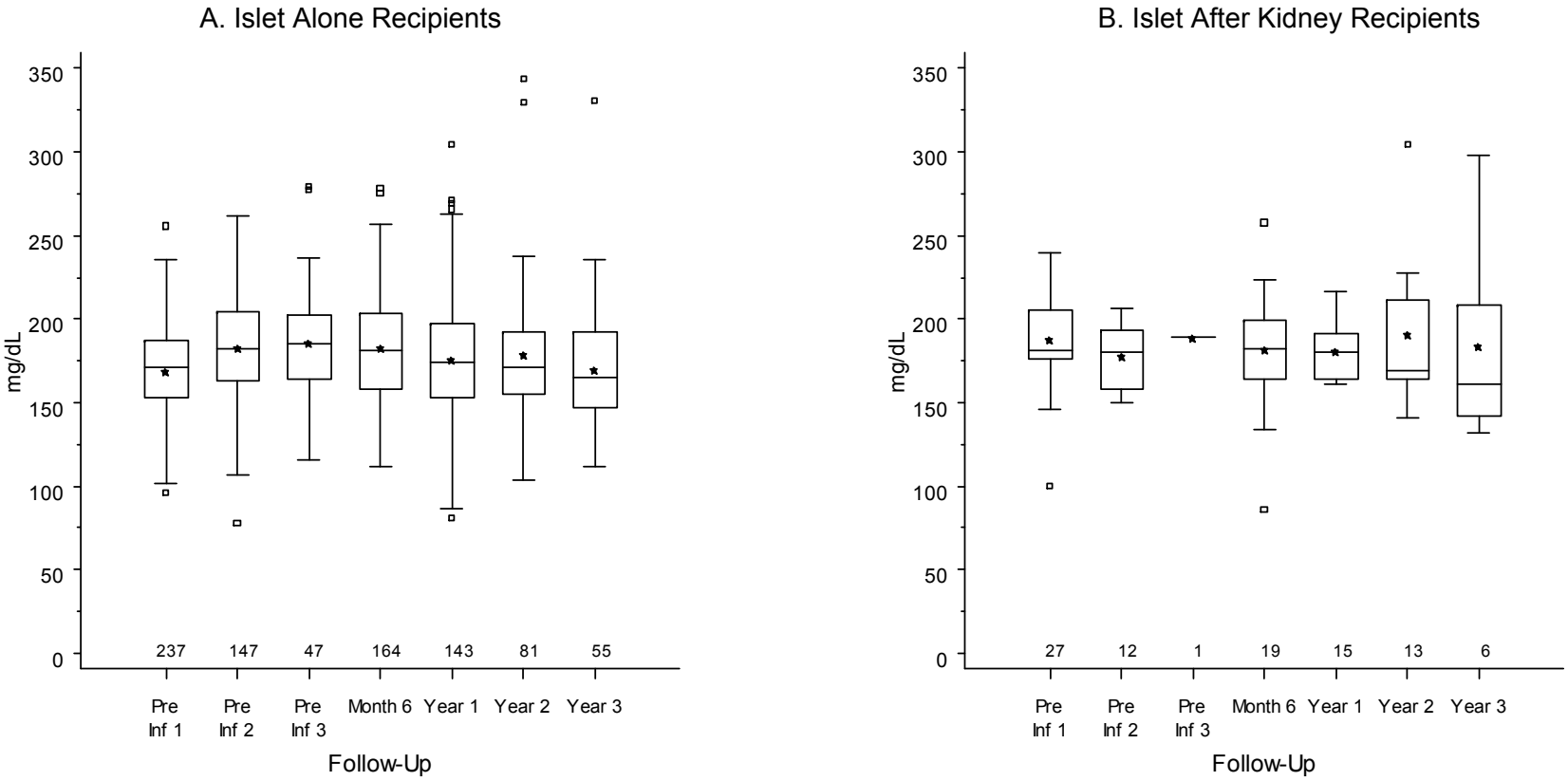


Exhibit 6 – 8
HDL (mg/dL) Pre Infusion and Post Last Infusion

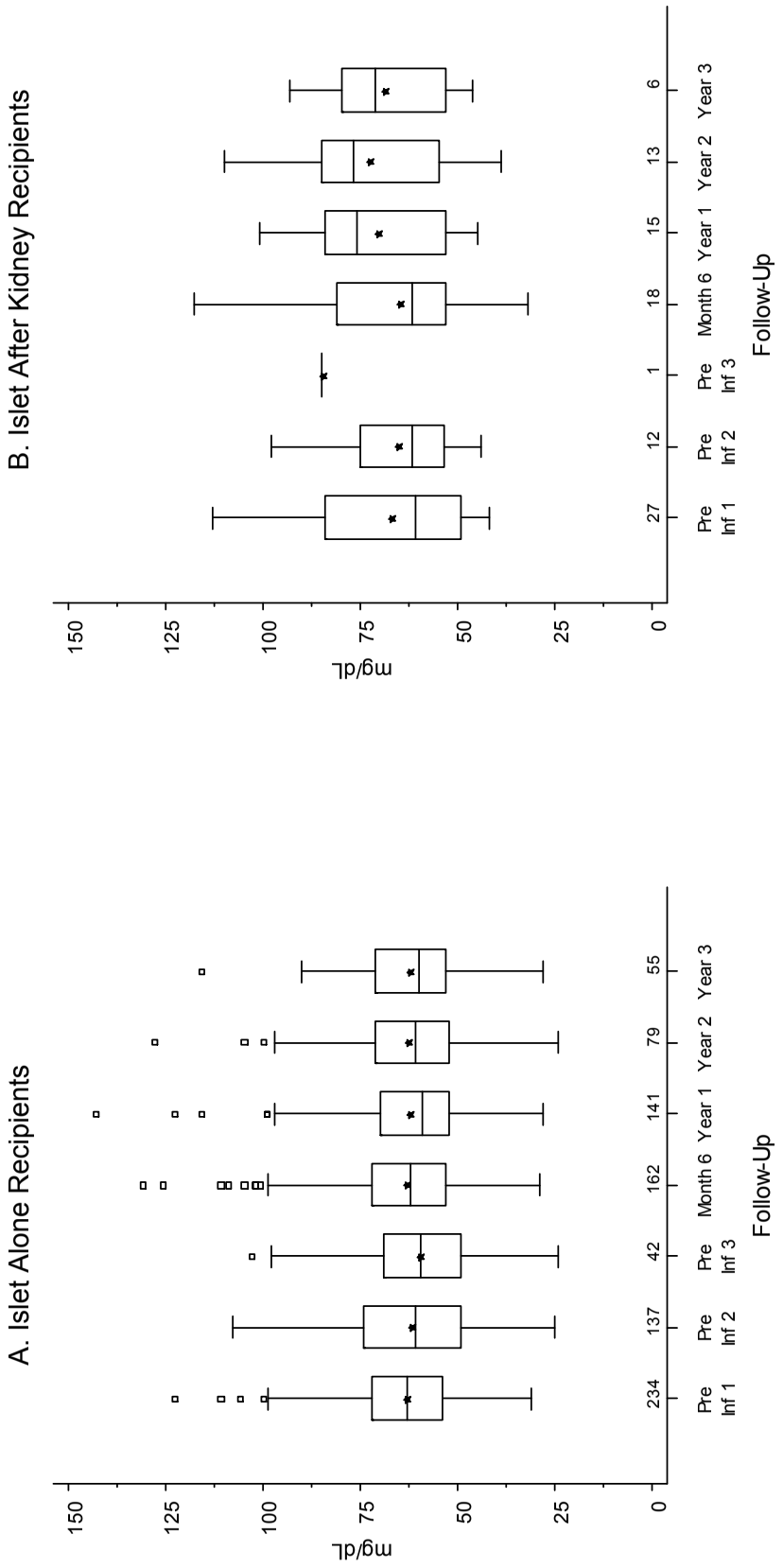


Exhibit 6 – 9
LDL (mg/dL) Pre Infusion and Post Last Infusion

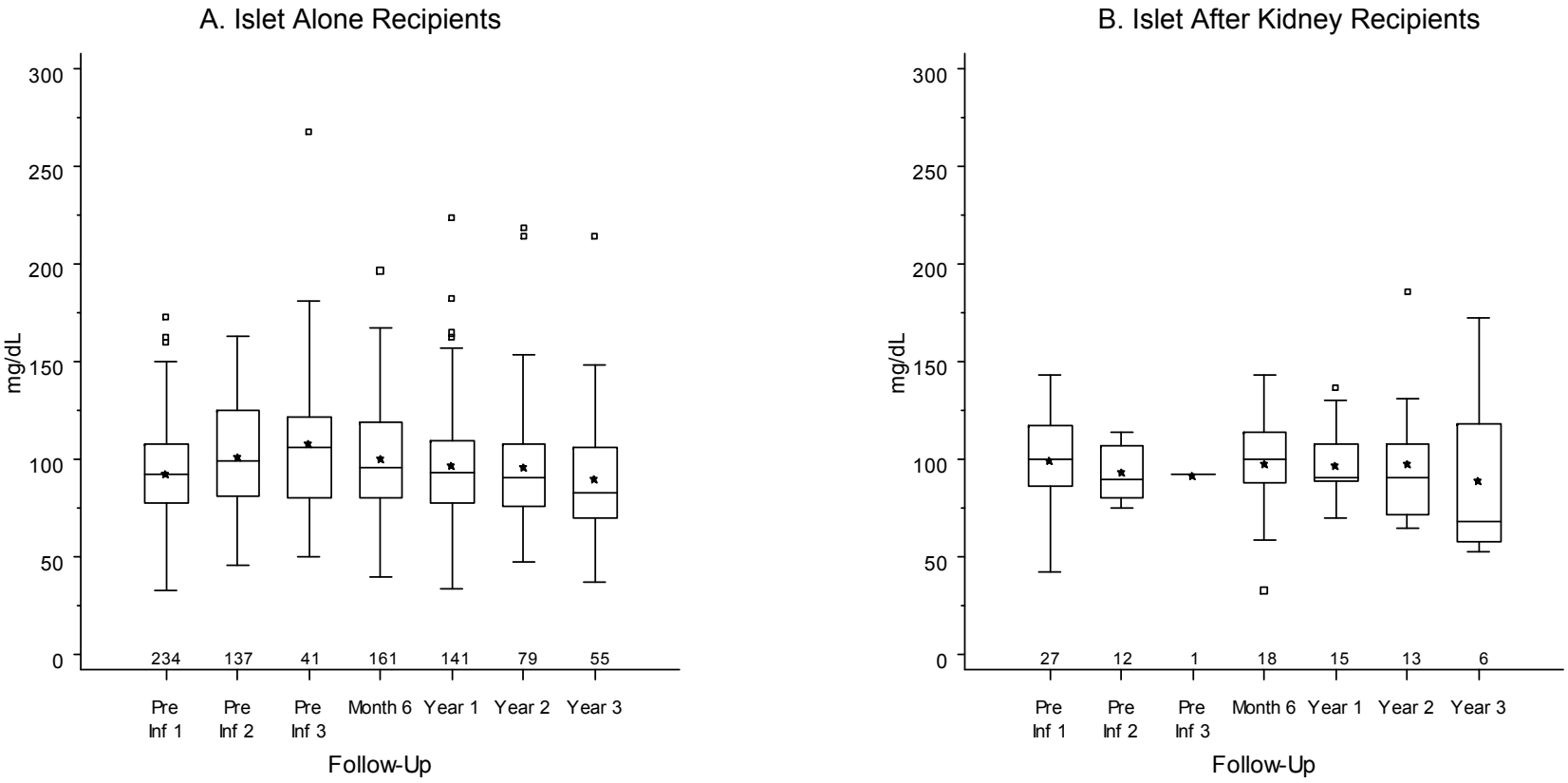


Exhibit 6 – 10
Triglycerides (mg/dL) Pre Infusion and Post Last Infusion

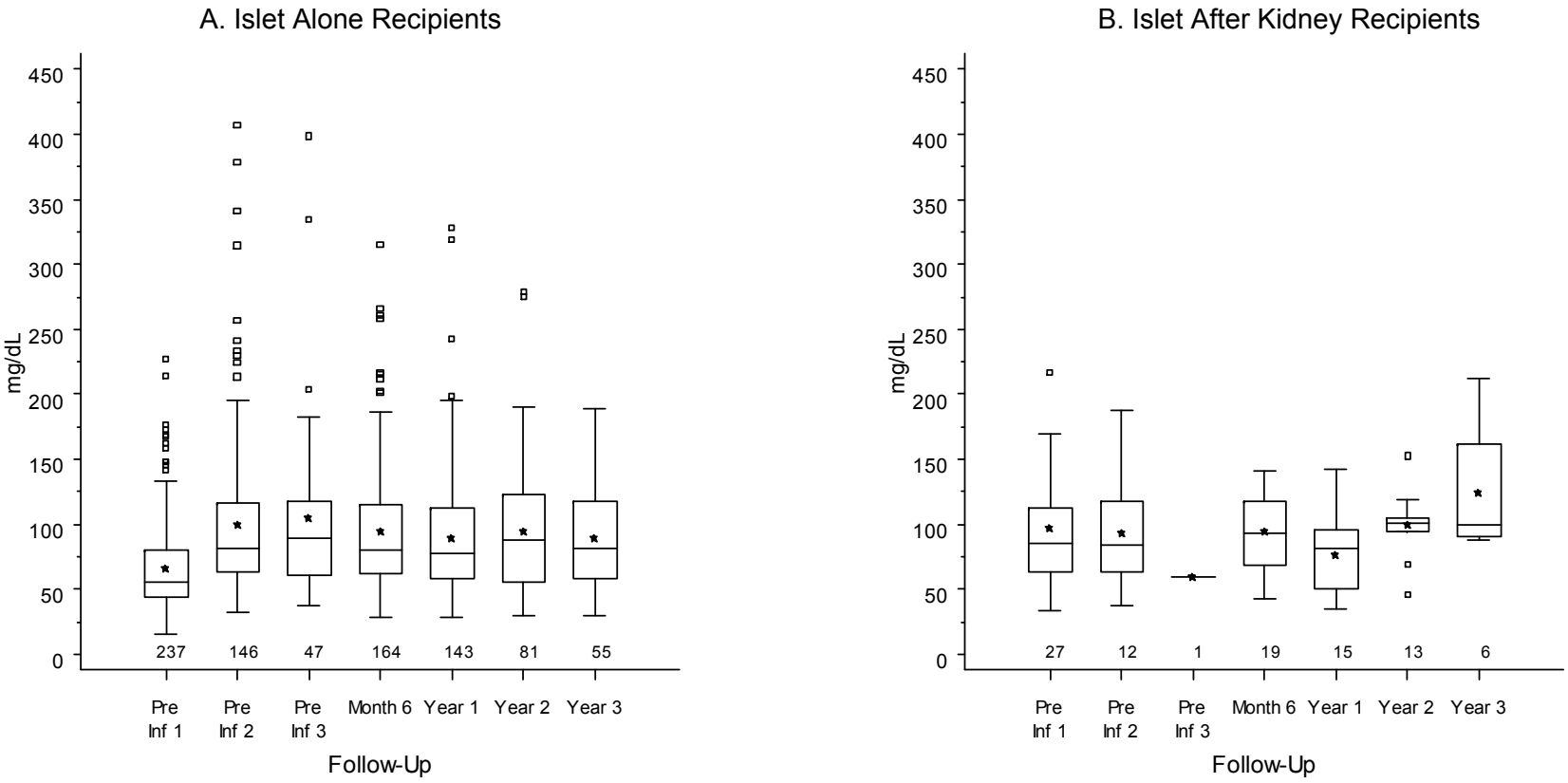
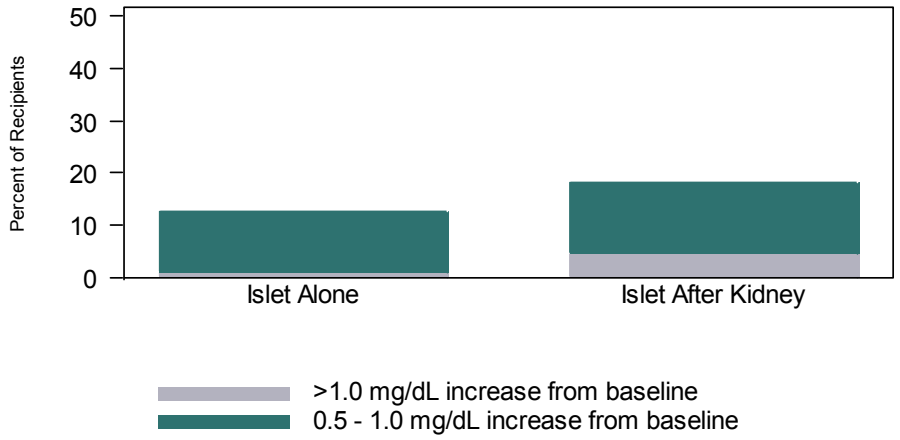


Exhibit 6 – 11
Incidence of Increase in Serum Creatinine (mg/dL) Greater than 0.5 from Baseline at Any Scheduled Time Post First Infusion
All Allograft Recipients



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

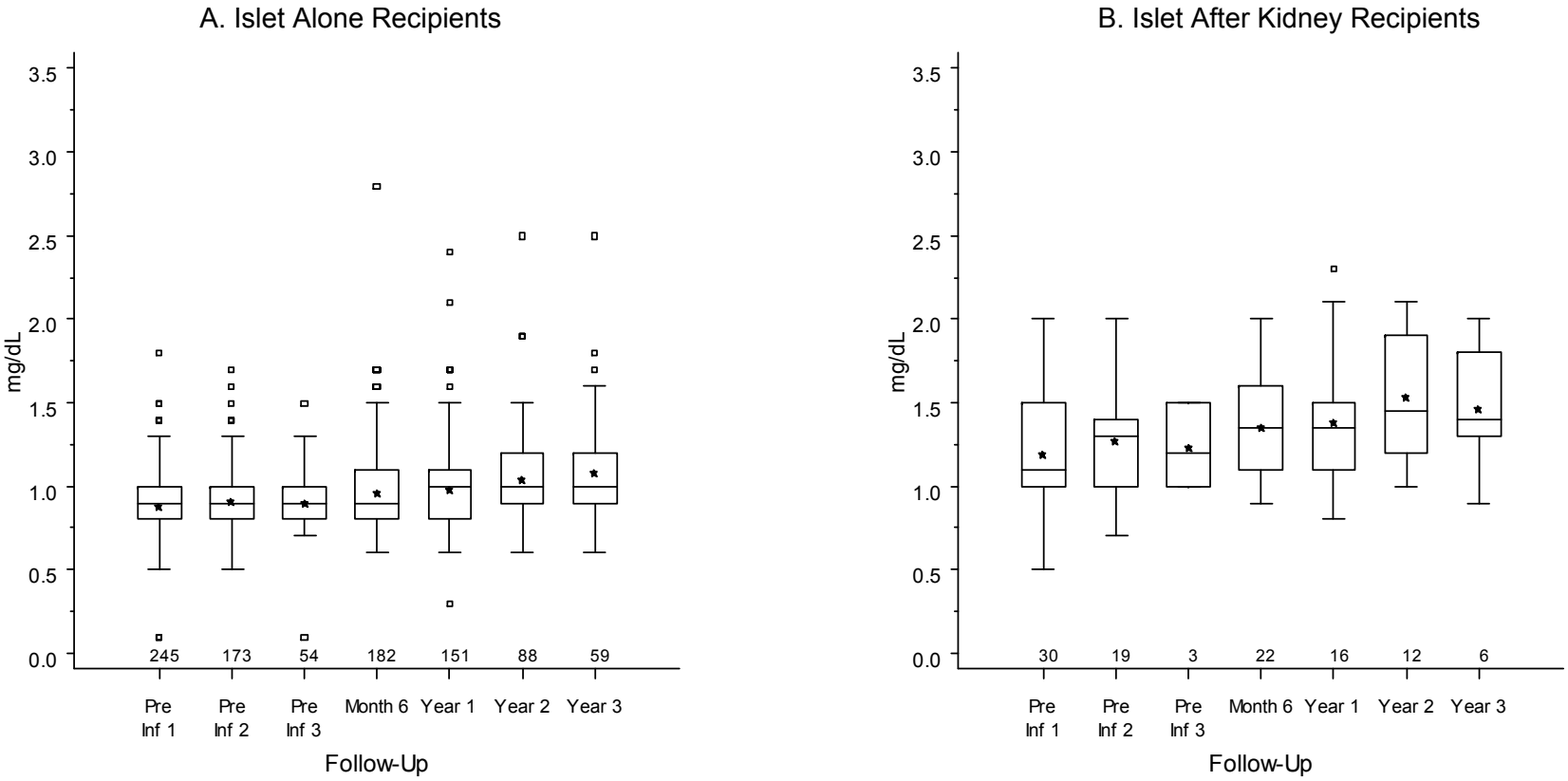


Exhibit 6 – 13
Calculated Creatinine Clearance (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

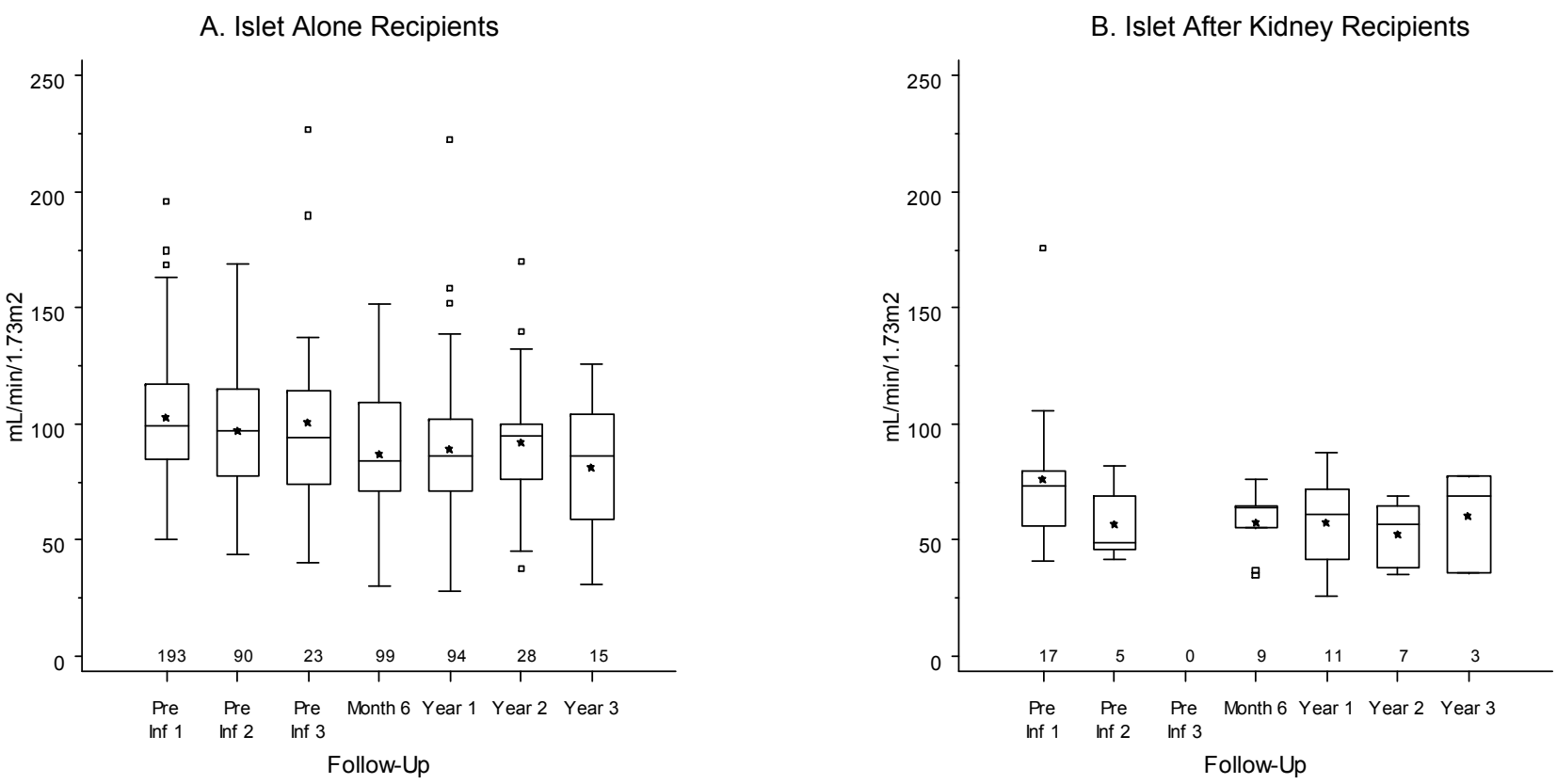


Exhibit 6 – 14
GFR (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

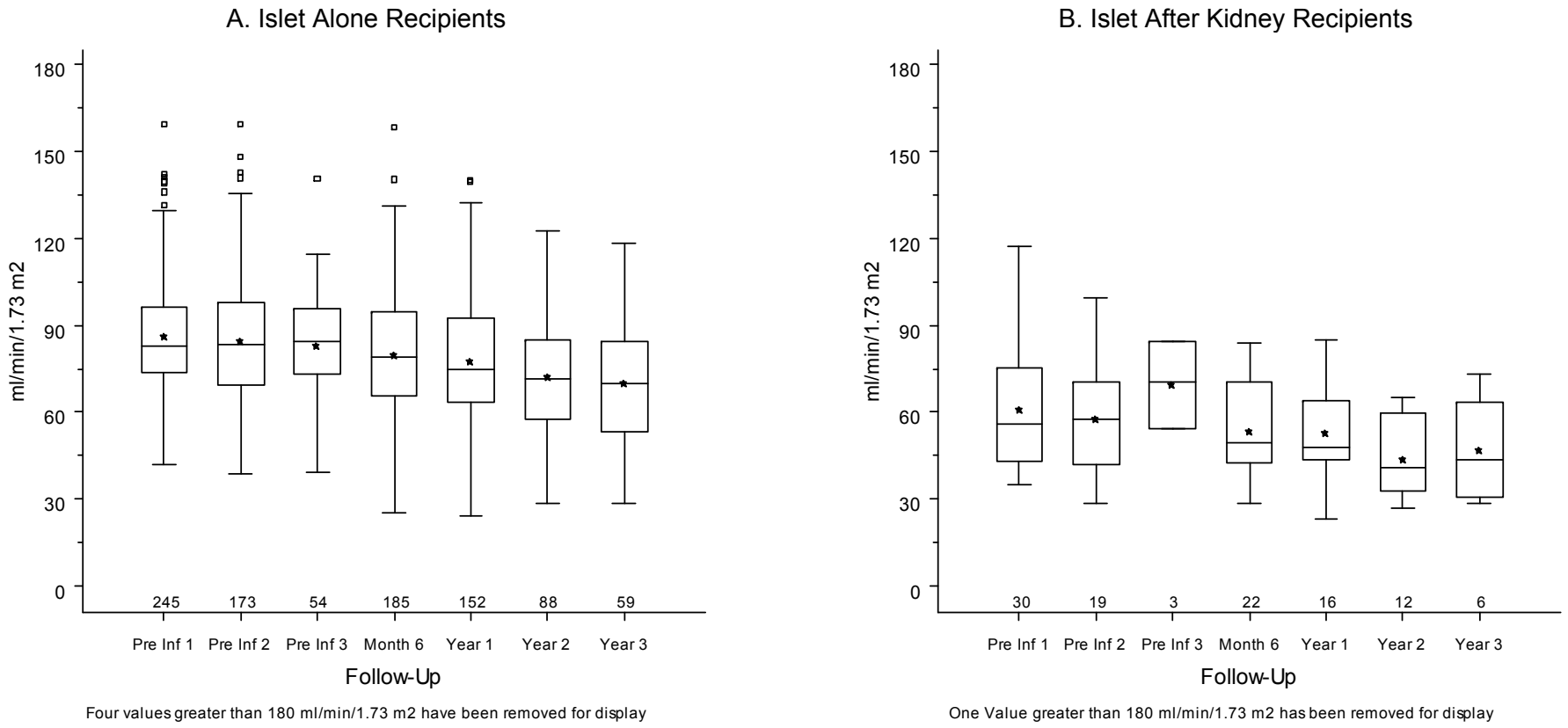


Exhibit 6 – 15
Class I PRA (%)
Pre Infusion and Post Last Infusion

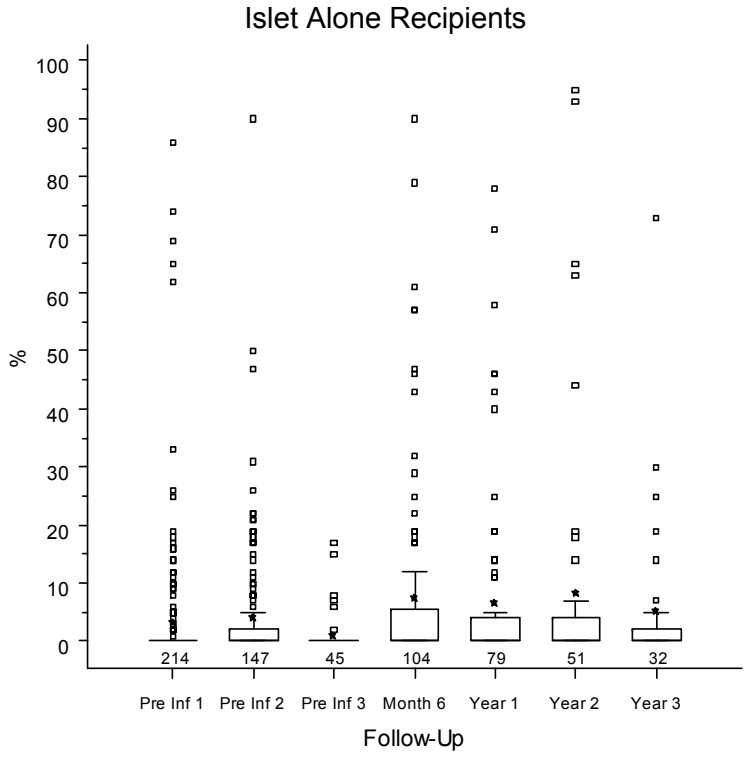


Exhibit 6 – 16
Change in Class I PRA from Pre First Infusion
Pre Subsequent Infusion and Post Last Infusion

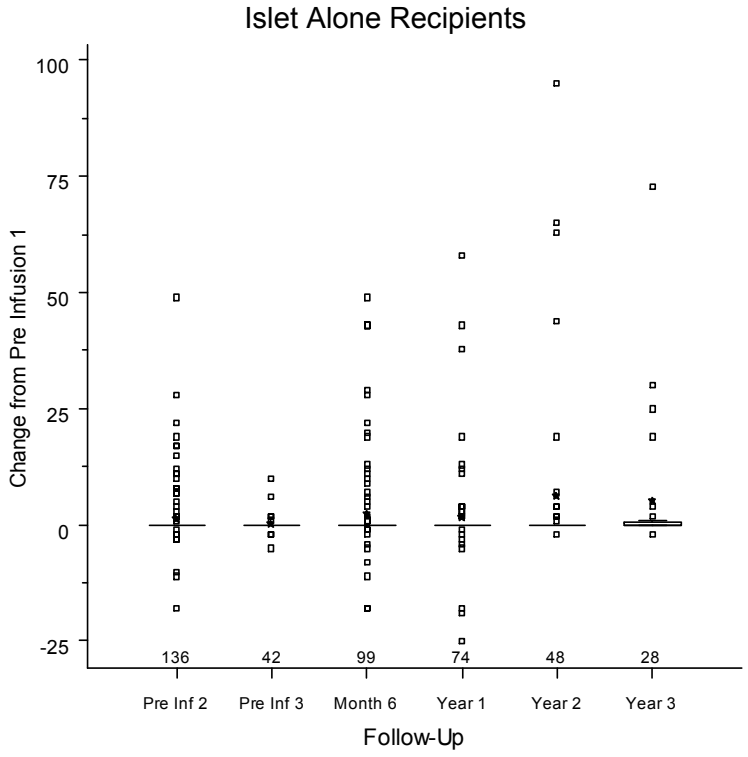


Exhibit 6 – 17
Class I PRA Post Last Infusion
Islet Alone Recipients with Complete Graft Loss

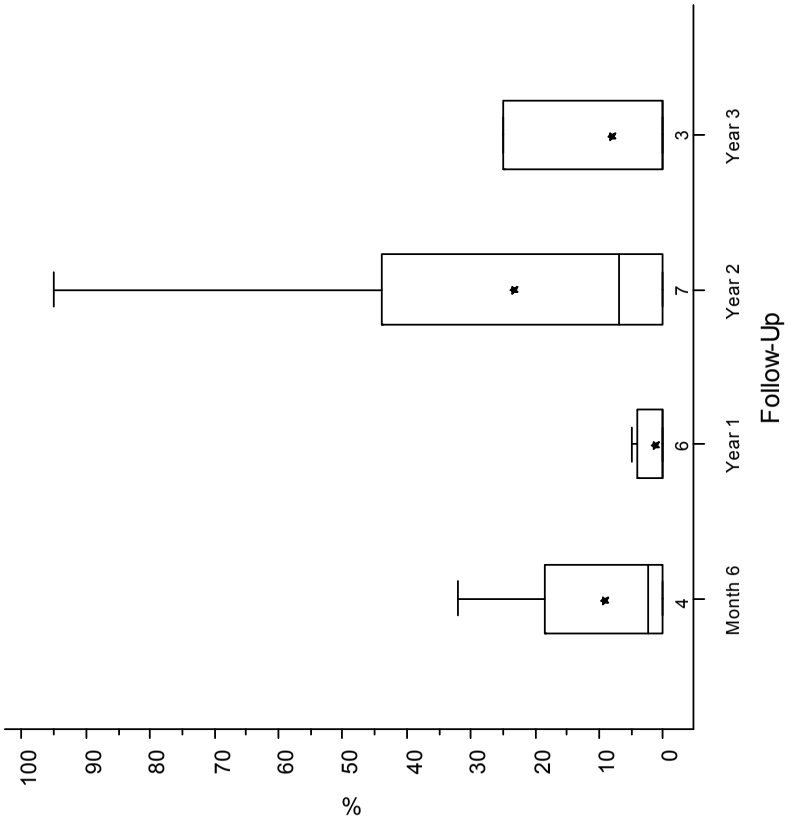
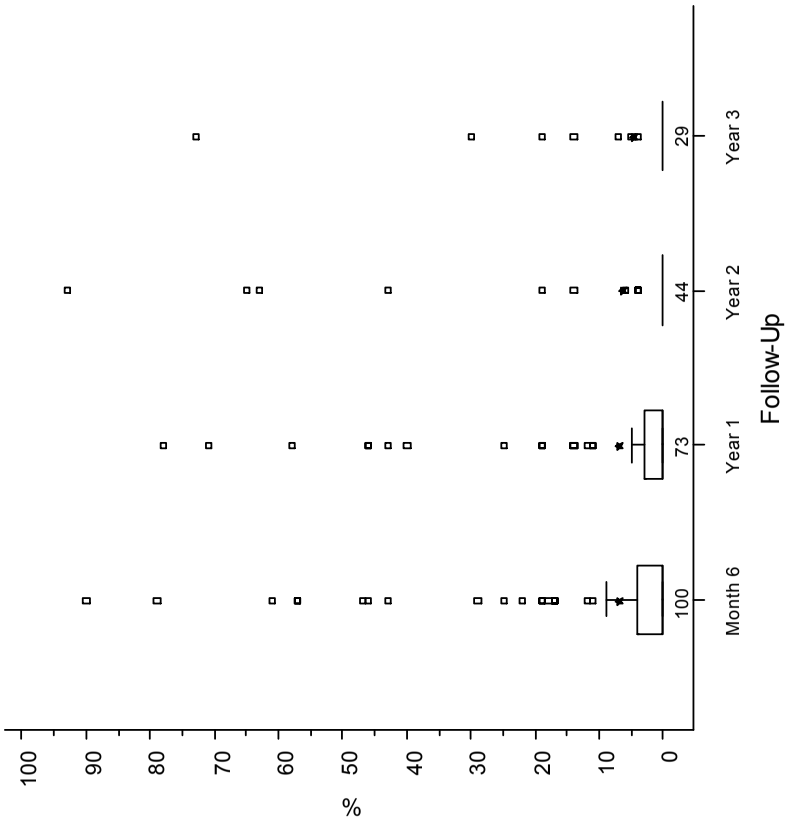


Exhibit 6 – 18
Class I PRA Post Last Infusion
Islet Alone Recipients without Complete Graft Loss



Chapter 7
Adverse Events

Adverse Events

All grade 3, 4 and 5 adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, 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-five percent of the islet alone recipients experienced at least one adverse event in Year 1, while 41% experienced one or more serious adverse events in this same period. Of the 574 adverse events reported in Year 1 post first infusion for islet alone recipients, 32.5% were related to the immunosuppression therapy and 28.4% were related to the infusion procedure. Of the 211 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 26.5% were related to the immunosuppression therapy and 45.5% 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 337 serious adverse events were reported to the Registry as of datafile closure, with 40.4% of them classified as life threatening and 46% requiring an inpatient hospitalization (Exhibit 7-4). Seventy percent (236 of 337) of serious adverse events occurred in the first year following the participants' first infusion procedure. Over 32% of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 25% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator and do not necessarily represent scientific truth. Approximately 91% of the serious adverse events resolved with no residual effects (Exhibit 7-5). Most of the reported serious adverse events were categorized as investigations (22%), gastrointestinal disorders (19%) and blood and lymphatic system disorders (15%) 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=10) 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 four reports of death to the Registry; a viral meningitis attributed death 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 and a death due to unknown causes (discovered in obituaries) more than four years post the person's second infusion.

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=262)				Islet After Kidney (N=30)			
	Recipients with an AE		Recipients with an SAE		Recipients with an AE		Recipients with an SAE	
	N	%	N	%	N	%	N	%
Any Event	170	64.9	108	41.2	19	63.3	13	43.3
Related to either the infusion procedure or immunosuppression therapy	141	53.8	84	32.1	16	53.3	10	33.3
Related to the infusion procedure	91	34.7	59	22.5	11	36.7	6	20.0
Related to immunosuppression therapy	93	35.5	38	14.5	8	26.7	5	16.7

The Exhibit above represents all adverse events reported to CITR, which occurred in the first year following the participant's first infusion procedure. It does not include adverse events reported to CITR after the first year following the participant's first infusion procedure. Subsequent Exhibits in this section are inclusive of all serious adverse events (SAEs) reported to CITR. This Exhibit summarizes the participant's transplant experience the first year following their first infusion procedure. It has been shown in previous reports and in this report that the majority of adverse events occur during 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 and do not necessarily represent scientific truth.

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	574	100.0	211	100.0	40	100.0	25	100.0
Related to the infusion procedure	137	23.9	90	42.7	13	32.5	7	28.0
Related to immunosuppression therapy	161	28.0	50	23.7	13	32.5	10	40.0
Related to both the infusion procedure and immunosuppression therapy	26	4.5	6	2.8	2	5.0	-	0.0
Related to neither the infusion procedure nor immunosuppression therapy	250	43.6	65	30.8	12	30.0	8	32.0

Exhibit 7 – 3
Percent of Recipients with a Serious Adverse Event in Year 1 Post First Infusion by Year of First Infusion
All Allograft Recipients

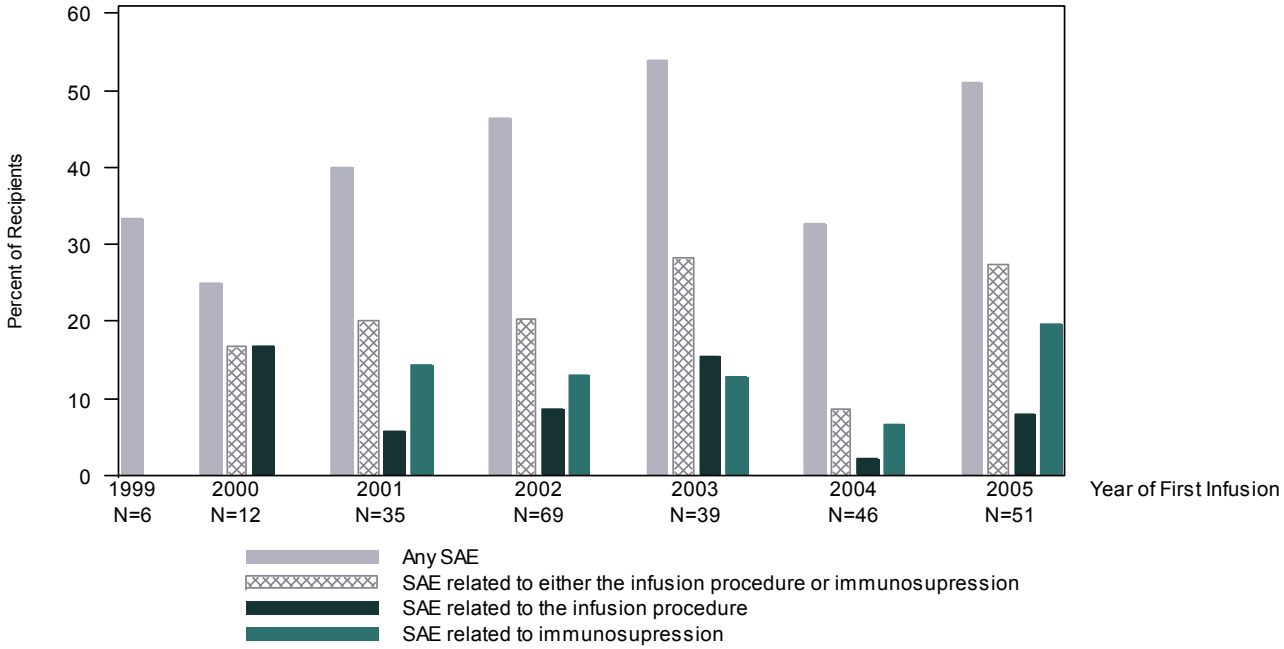


Exhibit 7 – 4
Serious Adverse Event Type by Relatedness to Islet Infusion or Immunosuppression

	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	96	100.0	64	100.0	6	100.0	129	100.0	7	100.0	14	100.0	-	0.0	21	100.0	337	100.0
Death*	-	0.0	-	0.0	-	0.0	3	2.3	-	0.0	-	0.0	-	0.0	1	4.8	4	1.2
Life Threatening	53	55.2	33	51.6	4	66.7	34	26.4	2	28.6	8	57.1	-	0.0	2	9.5	136	40.4
Inpatient Hospitalization	13	13.5	26	40.6	1	16.7	90	69.8	1	14.3	7	50.0	-	0.0	17	81.0	155	46.0
Prolongation of Existing Hospitalization	36	37.5	10	15.6	5	83.3	9	7.0	6	85.7	-	0.0	-	0.0	1	4.8	67	19.9
Persistent or Significant Disability/Incapacity**	1	1.0	4	6.3	-	0.0	3	2.3	-	0.0	-	0.0	-	0.0	-	0.0	8	2.4
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	1	1.0	3	4.7	-	0.0	5	3.9	1	14.3	-	0.0	-	0.0	1	4.8	11	3.3

Serious adverse event categories are not mutually exclusive.
*See page 185 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 337 serious adverse events, 236 (70.0%) 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 – 5
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	96	100.0	64	100.0	6	100.0	129	100.0	7	100.0	14	100.0	-	-	21	100.0	337	100.0
Outcome of Serious Adverse Event																		
Resolved with No Residual Effects	92	95.8	58	90.6	6	100.0	114	88.4	6	85.7	13	92.9	-	-	17	81.0	306	90.8
Resolved with Sequelae*	1	1.0	1	1.6	-	0.0	5	3.9	-	0.0	-	0.0	-	-	-	0.0	7	2.1
Persistent Condition, Recipient Alive**	3	3.1	5	7.8	-	0.0	7	5.4	1	14.3	1	7.1	-	-	3	14.3	20	5.9
Death caused by Adverse Event***	-	0.0	-	0.0	-	0.0	3	2.4	-	0.0	-	0.0	-	-	1	4.8	4	1.2

*Events related to the protocol include a hepatic hematoma and acute mononucleosis resulting in graft loss.
**Events related to the protocol include lymphopenia, portal vein thrombosis, neutropenia, papillary thyroid cancer, urosepsis, hemorrhage, and elevated alkaline phosphatase.
***One participant died 70 days following their third islet infusion procedure. The cause of death for this participant was reported as acute methadone and diphenhydramine toxicity unrelated to both the infusion procedure and immunosuppression therapy. A second participant died after Year 3 post last infusion. The cause of death for this participant was reported as viral meningitis possibly related to the immunosuppression therapy. A third death was discovered in the obituaries after Year 4 post last infusion and the cause of death is unknown. A fourth participant died over two years post last infusion. The cause of death was reported as hemorrhagic stroke unrelated to both the infusion procedure and immunosuppression therapy.

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

Exhibit 7 – 6
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	96	100.0	64	100.0	6	100.0	129	100.0	7	100.0	14	100.0	-	0.0	21	100.0	337	100.0
System Organ Class*																		
Blood and lymphatic system disorders	3	3.1	35	54.7	2	33.3	4	3.1	-	0.0	7	50.0	-	0.0	-	0.0	51	15.1
Cardiac disorders	-	0.0	-	0.0	-	0.0	2	1.6	-	0.0	-	0.0	-	0.0	1	4.8	3	0.9
Eye disorders	-	0.0	-	0.0	-	0.0	2	1.6	-	0.0	-	0.0	-	0.0	-	0.0	2	0.6
Gastrointestinal disorders	14	14.6	9	14.1	1	16.7	32	24.8	1	14.3	2	14.3	-	0.0	4	19.0	63	18.7
General disorders and administration site conditions	-	0.0	1	1.6	-	0.0	8	6.2	-	0.0	1	7.1	-	0.0	1	4.8	11	3.3
Hepatobiliary disorders	9	9.4	-	0.0	-	0.0	6	4.7	1	14.3	-	0.0	-	0.0	2	9.5	18	5.3
Immune system disorders	-	0.0	-	0.0	-	0.0	1	0.8	-	0.0	-	0.0	-	0.0	-	0.0	1	0.3
Infections and infestations	2	2.1	8	12.5	-	0.0	16	12.4	-	0.0	3	21.4	-	0.0	3	14.3	32	9.5
Injury, poisoning and procedural complications	14	14.6	1	1.6	-	0.0	5	3.9	1	14.3	-	0.0	-	0.0	2	9.5	23	6.8
Investigations**	53	55.2	2	3.1	3	50.0	9	7.0	1	14.3	1	7.1	-	0.0	4	19.0	73	21.7
Metabolism and nutrition disorders	-	0.0	1	1.6	-	0.0	20	15.5	-	0.0	-	0.0	-	0.0	-	0.0	21	6.2

Exhibit 7 – 6 *(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	-	0.0	-	0.0	1	0.8	-	0.0	-	0.0	-	0.0	-	0.0	1	0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	0.0	1	1.6	-	0.0	4	3.1	-	0.0	-	0.0	-	0.0	-	0.0	5	1.5
Nervous system disorders	-	0.0	1	1.6	-	0.0	3	2.3	-	0.0	-	0.0	-	0.0	1	4.8	5	1.5
Psychiatric disorders	-	0.0	1	1.6	-	0.0	2	1.6	-	0.0	-	0.0	-	0.0	-	0.0	3	0.9
Renal and urinary disorders	-	0.0	3	4.7	-	0.0	2	1.6	-	0.0	-	0.0	-	0.0	-	0.0	5	1.5
Reproductive system and breast disorders	-	0.0	1	1.6	-	0.0	3	2.3	-	0.0	-	0.0	-	0.0	-	0.0	4	1.2
Respiratory, thoracic and mediastinal disorders	-	0.0	-	0.0	-	0.0	4	3.1	1	14.3	-	0.0	-	0.0	3	14.3	8	2.4
Surgical and medical procedures	-	0.0	-	0.0	-	0.0	5	3.9	-	0.0	-	0.0	-	0.0	-	0.0	5	1.5
Vascular disorders	1	1.0	-	0.0	-	0.0	-	0.0	2	28.6	-	0.0	-	0.0	-	0.0	3	0.9

*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 – 7
Most Common Serious Adverse Events
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	96	100.0	64	100.0	6	100.0	129	100.0	295	100.0
Elevated Liver Function Tests*	52	54.2	-	0.0	3	50.0	6	4.7	61	20.7
Neutropenia	2	2.1	23	35.9	-	0.0	3	2.3	28	9.5
Hemorrhage**	15	15.6	-	0.0	1	16.7	-	0.0	16	5.4
Hypoglycaemia	-	0.0	-	0.0	-	0.0	15	11.6	15	5.1
Abdominal pain	3	3.1	1	1.6	-	0.0	10	7.8	14	4.7
Portal vein thrombosis	7	7.3	-	0.0	-	0.0	-	0.0	7	2.4
Anaemia	1	1.0	2	3.1	1	16.7	2	1.6	6	2.0
Diarrhoea	-	0.0	2	3.1	-	0.0	4	3.1	6	2.0
Vomiting	-	0.0	2	3.1	-	0.0	4	3.1	6	2.0
Lymphopenia	-	0.0	5	7.8	-	0.0	-	0.0	5	1.7
Leukopenia	-	0.0	3	4.7	1	16.7	-	0.0	4	1.4
Pneumonia	-	0.0	1	1.6	-	0.0	3	2.3	4	1.4
Pyrexia	-	0.0	1	1.6	-	0.0	3	2.3	4	1.4

*Elevated Liver Function Tests include elevations in aspartate aminotransferase, alanine aminotransferase, and blood alkaline phosphatase.
**Hemorrhage includes peritoneal, intra-abdominal, 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 – 8
Most Common Serious Adverse Events
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	7	100.0	14	100.0	-	0.0	21	100.0	42	100.0
Neutropenia	-	0.0	7	50.0	-	0.0	-	0.0	7	16.7
Blood creatinine increased	-	0.0	1	7.1	-	0.0	3	14.3	4	9.5
Pneumonia	-	0.0	2	14.3	-	0.0	1	4.8	3	7.1
Colitis	-	0.0	-	0.0	-	0.0	2	9.5	2	4.8
Haemoglobin decreased	1	14.3	-	0.0	-	0.0	1	4.8	2	4.8

Exhibit 7 – 9
Most Common Serious Adverse Events Reported
Within One Year of Any Infusion
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	102	100.0	65	100.0	6	100.0	98	100.0	271	100.0
Elevated Liver Function Tests*	51	50.0	0	0.0	3	50.0	6	6.1	60	22.1
Neutropenia	2	2.0	24	36.9	0	0.0	3	3.1	29	10.7
Hemorrhage**	16	15.7	0	0.0	1	16.7	0	0.0	17	6.3
Abdominal pain	3	2.9	1	1.5	0	0.0	9	9.2	13	4.8
Portal vein thrombosis	8	7.8	0	0.0	0	0.0	0	0.0	8	3.0
Pneumonia	0	0.0	3	4.6	0	0.0	4	4.1	7	2.6
Anaemia	1	1.0	2	3.1	1	16.7	2	2.0	6	2.2
Diarrhoea	0	0.0	3	4.6	0	0.0	3	3.1	6	2.2
Hypoglycaemia	0	0.0	0	0.0	0	0.0	6	6.1	6	2.2
Lymphopenia	0	0.0	5	7.7	0	0.0	0	0.0	5	1.8
Cholecystitis	0	0.0	0	0.0	0	0.0	4	4.1	4	1.5
Leukopenia	0	0.0	3	4.6	1	16.7	0	0.0	4	1.5
Vomiting	0	0.0	1	1.5	0	0.0	3	3.1	4	1.5

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

Exhibit 7 – 10
Most Common Serious Adverse Events Reported
More than One Year after Any Infusion
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	13	100.0	0	-	52	100.0	66	100.0
Hypoglycaemia	0	0.0	0	0.0	0	-	9	17.3	9	13.6
Neutropenia	0	0.0	6	46.2	0	-	0	0.0	6	9.1
Blood creatinine increased	0	0.0	1	7.7	0	-	3	5.8	4	6.1
Vomiting	0	0.0	1	7.7	0	-	2	3.8	3	4.5
Abdominal pain	0	0.0	0	0.0	0	-	2	3.8	2	3.0
Chest pain	0	0.0	0	0.0	0	-	2	3.8	2	3.0
Infection	0	0.0	0	0.0	0	-	2	3.8	2	3.0
Pyrexia	0	0.0	0	0.0	0	-	2	3.8	2	3.0
Elevated Liver Function Tests*	1	100.0	0	0.0	0	-	0	0.0	1	1.5
Herpes simplex	0	0.0	1	7.7	0	-	0	0.0	1	1.5
Insomnia	0	0.0	1	7.7	0	-	0	0.0	1	1.5
Papillary thyroid cancer	0	0.0	1	7.7	0	-	0	0.0	1	1.5
Postoperative infection	0	0.0	1	7.7	0	-	0	0.0	1	1.5
Urosepsis	0	0.0	1	7.7	0	-	0	0.0	1	1.5

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

Exhibit 7 – 11
Summary of Reported Neoplasms

Reported Neoplasm	Timing	Relation to Islet Infusion Procedure	Relation to Immuno-suppression Therapy	Outcome of Event / Narrative
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 was continued.
Basal Cell Carcinoma	395 days post 2nd infusion	Unrelated	Possible	Event resolved, no residual effects. / Event occurred after islet graft failure and discontinuation of immunosuppression.
Matastatic Breast Cancer	469 days post 3rd Infusion	Possible	Possible	Resolved, with sequelae. / Invasive focal lobular carcinoma in situ diagnosed on routine screening 22 months post first infusion. Bilateral section performed, patient continued immunosuppression. One month later, metastatic carcinoma of lymph nodes identified followed by section and chemotherapy. Tacrolimus was tapered.
Squamous cell carcinoma of skin	576 days post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. / Immunosuppression was continued for another 8 months. No further follow-up available.
Squamous cell carcinoma of skin	591 days post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. / Immunosuppression was continued. Follow-up is up to date.
Squamous cell carcinoma of skin	640 days post 1st Infusion	Unrelated	Probable	Resolved, no residual effects. / Immunosuppression continued until patient lost to follow-up for over a year.
Papillary thyroid cancer	656 days post 2nd Infusion	Unrelated	Probable	Persistent condition. Last follow-up was 15 months post event, with immunosuppression continued. Patient since lost to follow-up for over two years.
Squamous cell carcinoma of skin	Timing missing	Missing	Missing	Missing
Pulmonary nodules*	738 days post 2nd infusion	Unrelated	Possible	Persistent condition. / Details pending.
Papillary carcinoma*	55 days 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.

* Event reported and/or recipient enrolled after Report cut-off date. However, since these events occurred within the period covered by the report, they are included in this listing.

Exhibit 7 – 12
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosupression 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 – 12 *(continued)*
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosupression 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
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
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

Exhibit 7 – 12 *(continued)*
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosupression Therapy	Treatment Required	Outcome of Event
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
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

Exhibit 7 – 13
Number of Days Hospitalized at Infusion (from Admission to Discharge)
by Infusion Sequence
Islet Alone Recipients

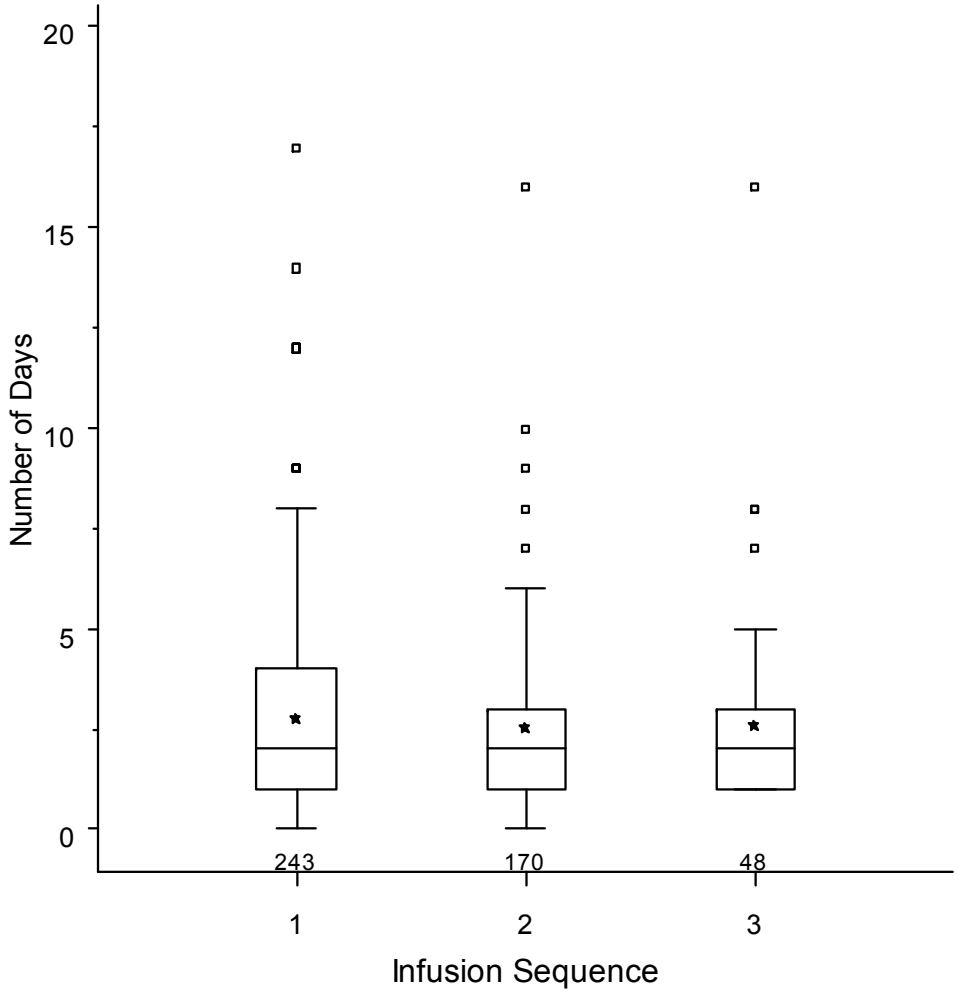


Exhibit 7 – 14
Number of Days Hospitalized at Infusion (from Admission to Discharge)
by Infusion Sequence
Islet After Kidney Recipients

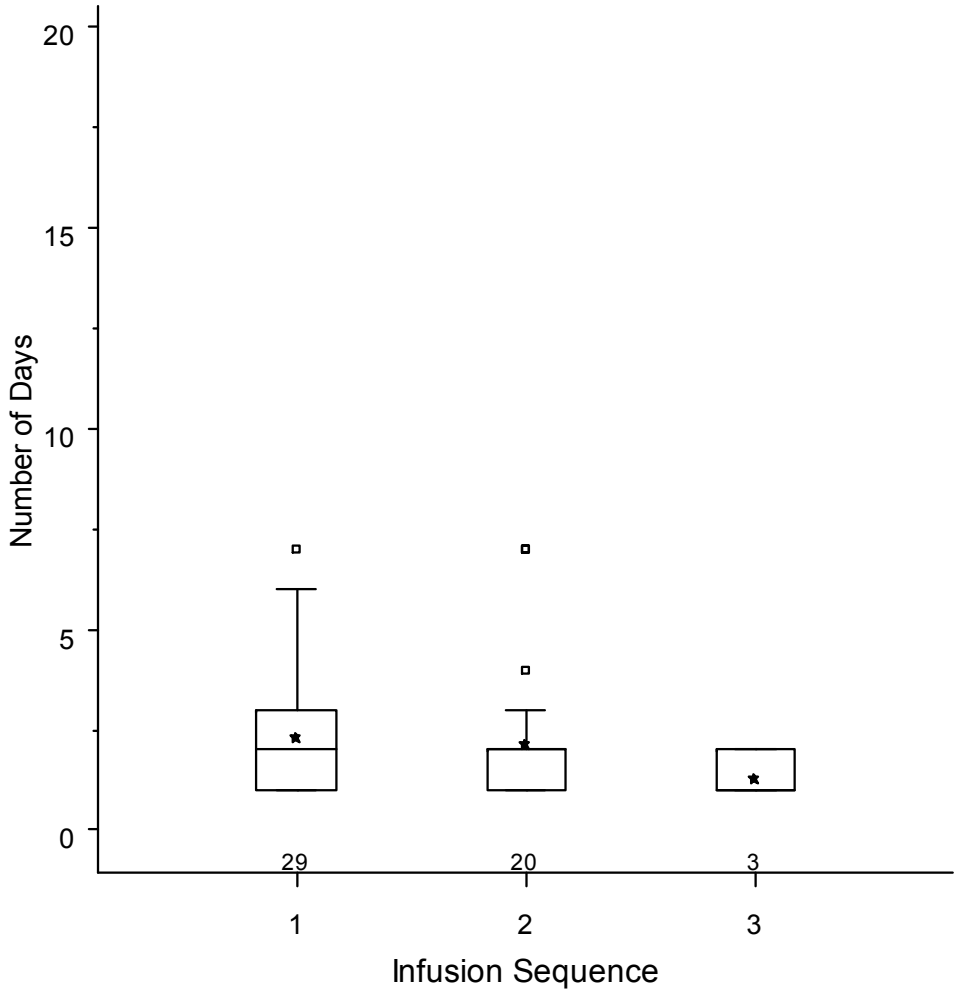


Exhibit 7 – 15
Hospitalization Experienced Post Last Infusion by Total Number of Infusions Received
Islet Alone Recipients

	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	39	100.0	30	100.0	14	100.0	13	100.0	102	100.0	82	100.0	45	100.0	33	100.0	35	100.0	32	100.0	18	100.0	7	100.0
Participants Requiring at Least One Hospitalization	7	17.9	1	3.3	2	14.3	-	0.0	21	20.6	14	17.1	5	11.1	3	9.1	3	8.6	5	15.6	1	5.6	2	28.6
Number of Hospitalizations																								
1	6	15.4	1	3.3	1	7.1	-	0.0	16	15.7	12	14.6	4	8.9	3	9.1	3	8.6	5	15.6	1	5.6	2	28.6
2	1	2.6	-	0.0	1	7.1	-	0.0	4	3.9	1	1.2	1	2.2	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
3	-	0.0	-	0.0	-	0.0	-	0.0	1	1.0	1	1.2	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0

Exhibit 7 – 16
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	4	100.0	3	100.0	2	100.0	-	0.0	15	100.0	12	100.0	10	100.0	5	100.0	2	100.0	2	100.0	-	0.0	1	100.0
Participants Requiring at Least One Hospitalization	2	50.0	-	0.0	-	0.0	-	0.0	4	26.7	4	33.3	2	20.0	1	20.0	1	50.0	-	0.0	-	0.0	-	0.0
Number of Hospitalizations																								
1	1	25.0	-	0.0	-	0.0	-	0.0	2	13.3	2	16.7	2	20.0	-	0.0	1	50.0	-	0.0	-	0.0	-	0.0
2	1	25.0	-	0.0	-	0.0	-	0.0	2	13.3	1	8.3	-	0.0	1	20.0	-	0.0	-	0.0	-	0.0	-	0.0
3	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	8.3	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0

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 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 292 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, 2006. 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 80% at Month 6 to 71% at Year 1. Post the participant's last infusion procedure rates are similar for Month 6 (77%) and Year 1 (70%). However, the submitted forms for Year 2 drops to 57%, to 49% in Year 3, 38% in Year 4, and 37% in Year 5 (Exhibit 8-2). The low submission rates for Years 2-5 are currently being reviewed by the CITR Scientific Advisory Committee and Compliance Committees.

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
All Allograft Recipients

	Infusion Sequence									Overall		
	1			2			3					
	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent
Deceased Donor Forms	328	327	100%	228	227	100%	73	72	99%	629	626	100%
Islet Processing Forms	328	326	99%	228	227	100%	73	72	99%	629	625	99%
Pre Infusion Forms	292	267	91%	216	184	85%	67	51	76%	575	502	87%
Pre Infusion Lab Forms	292	276	95%	216	195	90%	67	58	87%	575	529	92%
Infusion Forms	292	292	100%	216	216	100%	67	67	100%	575	575	100%
Induction Therapy Forms	292	282	97%	216	201	93%	67	63	94%	575	546	95%

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	291	232	80%	5	1	53	18%
	Year 1	279	198	71%	10	0	71	25%
Post Last Infusion	Month 6	277	214	77%	5	2	56	20%
	Year 1	250	174	70%	13	5	58	23%
	Year 2	192	109	57%	28	16	39	20%
	Year 3	140	69	49%	33	5	33	24%
	Year 4	94	36	38%	26	6	26	28%
	Year 5	46	17	37%	12	6	11	24%

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	292	18.7	18.0	12.0	1.0	73.0
Extent of Insulin Log Completion	292	17.9	17.6	12.0	0.0	75.1
Participants Lost to Follow Up	50	18.8	12.6	15.6	1.5	54.6

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