Sixth Annual Report

Prepared by:
CITR Coordinating Center
The EMMES Corporation
Rockville, MD

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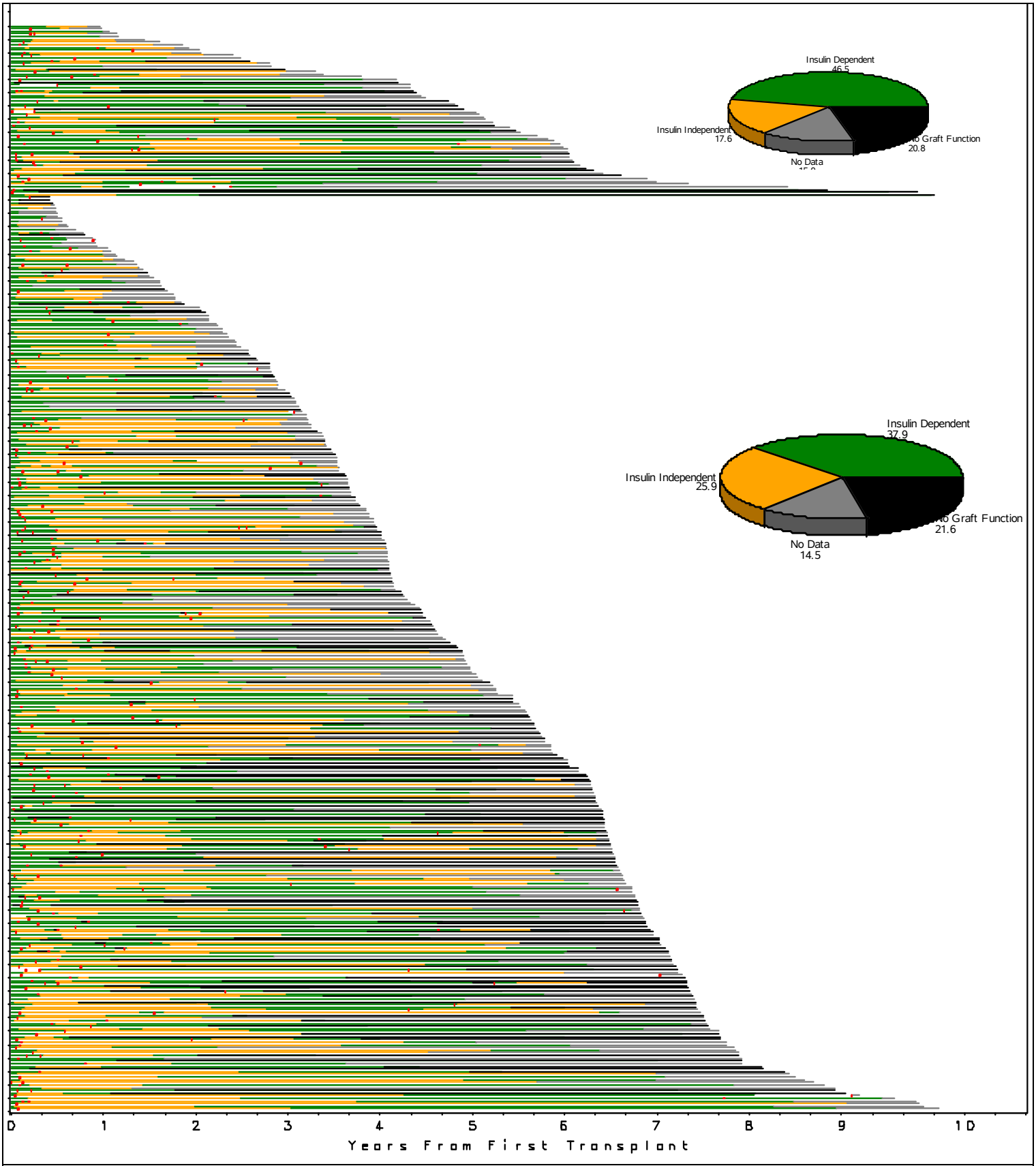

Collaborative Islet Transplant Registry 2009.

Follow-up time after initial infusion for each recipient. Top: islet after kidney (N=65), bottom: islet alone (N=347). Yellow: insulin independence; green: insulin-using with graft function (70% average reduction in daily insulin use from baseline); black: no islet function; gray: missing data. Red marks indicate reinfusions. Pie charts show percent of all follow-up time with insulin independence.

November 1, 2009

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 &
CITR Scientific Advisory Committee Chair

SUBJECT: 2009 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 human-to-human islet/beta cell transplants performed in North America, and Juvenile Diabetes Research Institute-sponsored European and Australian sites.

We are pleased to present this sixth Annual Report (2009) including data from the great majority of the islet transplant programs active in 1999-2008. We also are privileged to have the collaboration of the United Network for Organ Sharing and the Islet Cell Resource Center Consortium (coordinated by the Administrative and Bioinformatics Coordinating Center, City of Hope, CA), 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 transplant programs and especially 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 islet transplantation.

NOTICE:

The CITR Annual Report details data received as of April 1, 2009 for all islet transplant recipients registered by December 31, 2008.

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BACKGROUND AND PURPOSE

Islets of Langerhans are located in the pancreas and contain insulin producing cells (beta cells). In patients with Type 1 diabetes mellitus (T1DM), beta cells are destroyed by an autoimmune attack and patients need to inject insulin every day to stay alive. The total prevalence of diagnosed insulin dependent diabetes mellitus (IDDM) in the United States (US) is approximately 1.5 million people (National Institute of Diabetes and Digestive and Kidney Diseases. National Diabetes Statistics, 2007 fact sheet). In patients with T1DM and poor kidney function, a whole pancreas transplant is sometimes performed. T1DM patients with severe hypoglycemia may be eligible for an alternative procedure using islets extracted from a deceased donor pancreas.

The National Institute of Diabetes & Digestive & Kidney Diseases funded the Collaborative Islet Transplant Registry (CITR) for data collection from North American programs to accumulate and compile the data from all completed and ongoing studies between 1999 and the present. The Juvenile Diabetes Research Foundation (JDRF) has granted additional funding to include the participation of selected European and Australian centers. 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). Individual transplant units initiate their own independent research protocols to advance the field of islet transplantation. It is the goal of these studies to help determine if improvement in glycemic control can be achieved and to assess the risks of the infusion procedure and associated immunosuppressive medication. 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. In addition, CITR developed a map of North American clinical trials that can be accessed at www.citregistry.org.

PATIENTS AND METHODS

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

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators for scientific evaluations and for reports to the multiple agencies and entities required by US Food and Drug Administration (FDA) regulated trials or according to the requirements of the respective nation.

Detailed follow-up data are abstracted pre-infusion and at Month 6, Month 12, and annually post infusion. At each new infusion, a new follow-up schedule is established. All grade 3, 4 and 5 adverse events, according to the Terminology Criteria for Adverse Events (TCAE) of the Clinical Islet Transplantation Consortium (CIT), and all serious adverse events (regardless of grade) are reported to CITR. 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. Data are also obtained through data sharing agreements with the United Network for Organ Sharing (UNOS), the Administrative and Bioinformatics Coordinating Center (ABCC) of the Islet Cell Resource Centers (ICR), and the Data Coordinating Center (DCC) of the Clinical Islet Transplant Consortium (CIT).

The Registry data exists because of the voluntary participation of the transplanting centers, with written informed consent for participation in the Registry by the islet recipients. While the Registry 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 database was closed for analysis on April 1, 2009 for data on recipients that were registered in CITR as of December 31, 2008.

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. 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.

RESULTS

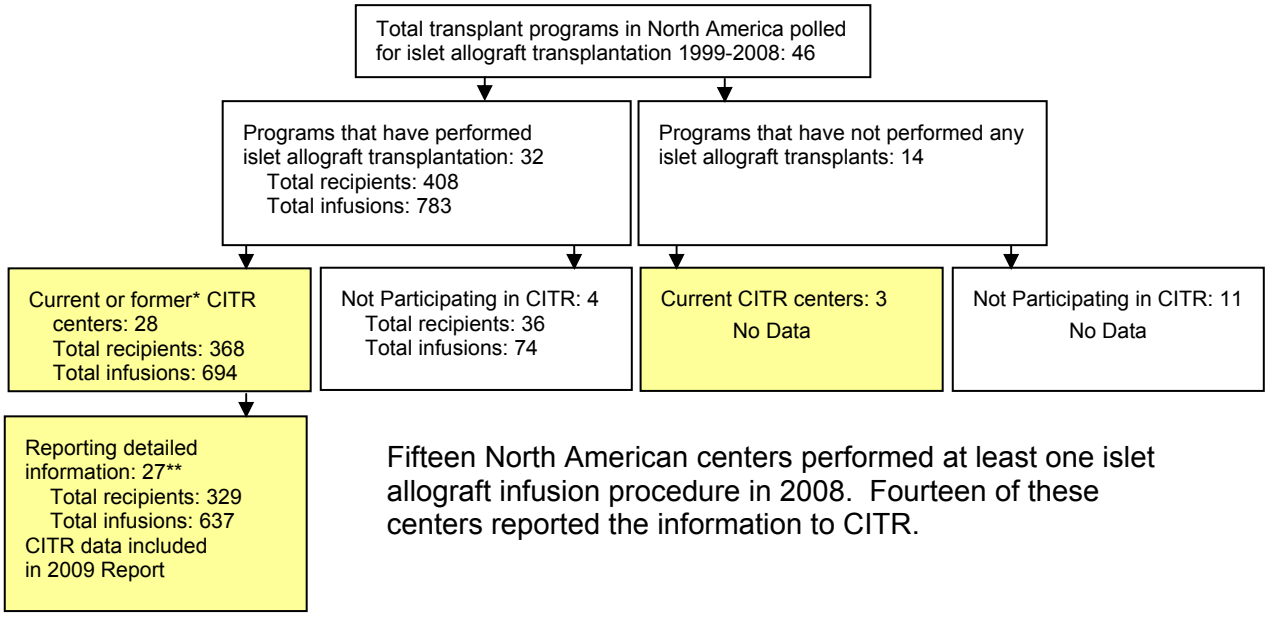
Islet Allograft Transplantation Activity 1999-2008. Forty-six North American medical institutions with an identified islet transplant program or interest in starting an islet program between 1999 and 2008 responded to a general questionnaire. Thirty-two of the 46 reported performing at least one islet allograft transplant. Exhibit A displays the activity of North American islet transplant centers for 1999-2008, including the total number of recipients and infusions, and according to the centers' participation in CITR. To the knowledge of the Registry, this table is inclusive of all human-to-human islet transplant programs in North America.

Exhibits B1 and B2 display the data collected from the 32 active islet transplant programs in North America and the JDRF-funded European and Australian sites from 1999 through 2008.

Three European and two Australian JDRF-funded centers joined the Registry in 2006-2008 and contributed data for this report. Pooling the reported data from the North American and JDRF centers, the Registry comprises 412 allograft recipients with detailed data reported as of the data cut-off, and 828 infusion procedures derived from a total of 905 donors. One hundred seven of the recipients (26%) received a single islet infusion, 202 (49%) received two, 95 (23%) received three, and eight (2%) received a total of four islet infusions. On average, recipients received a total of 842 $x10^3$ (SD 376 $x10^3$) total islet equivalents (IEQs), or 13 $x10^3$ (SD 6.0 $x10^3$) IEQs/kilogram body weight.

Of the total 412 recipients included in this report, 347 (84%) were recipients without a previous kidney transplant who received one or more islet-alone infusions (IA), while 65 recipients (16%) had previously received a kidney transplant (IAK).

Exhibit A
North American Islet Allograft Transplant Centers, Recipients and Infusions
Total Performed and Total Reported to CITR 1999-2008



Fifteen North American centers performed at least one islet allograft infusion procedure in 2008. Fourteen of these centers reported the information to CITR.

* Former CITR centers (N=3) are those that reported data to CITR then subsequently stopped performing islet cell transplants and discontinued CITR participation.
** One center with three allograft participants who did not provide CITR consent.

Exhibit B – 1

Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
All North American Islet Transplant Centers 1999-2008

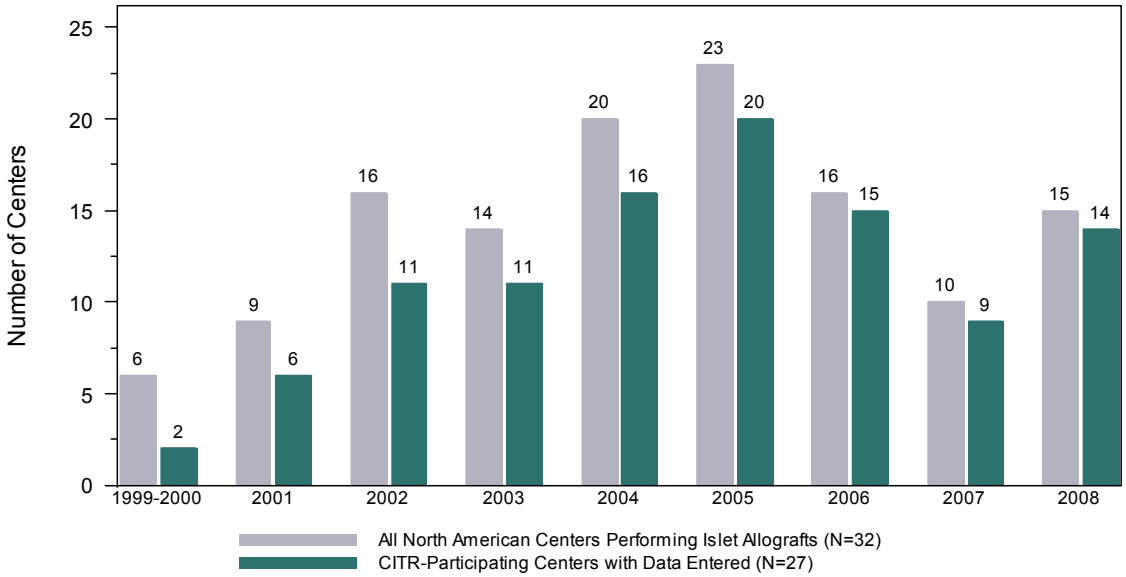
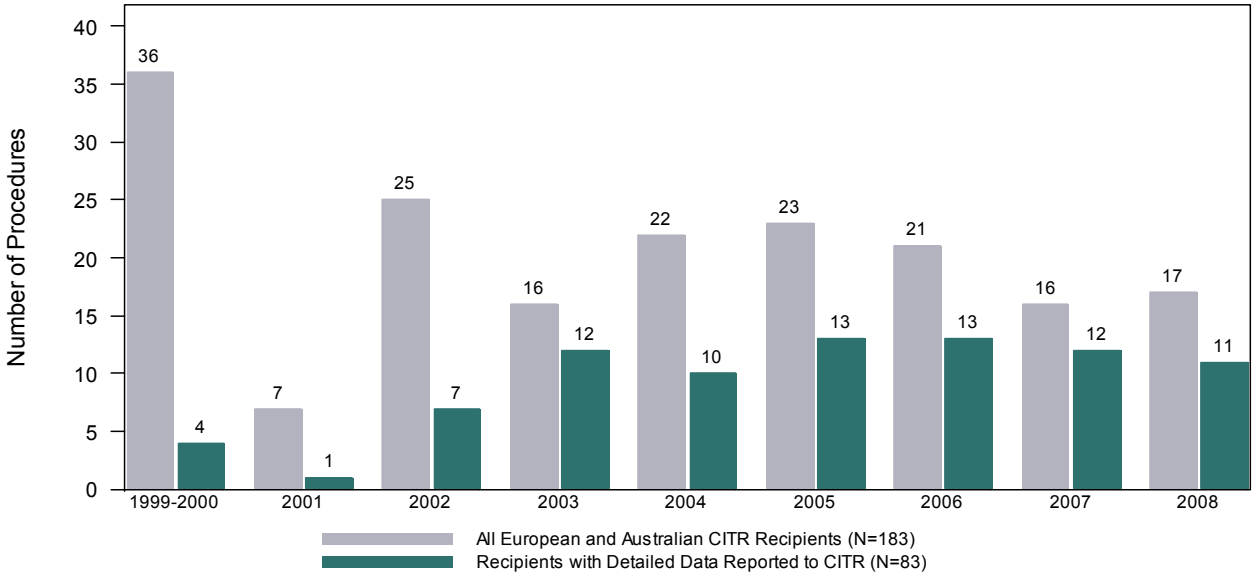


Exhibit B – 2

Total Number of Islet Allograft Recipients and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion
CITR Participating European and Australian JDRF Centers 1999-2008



Recipient Characteristics. The mean age of islet allograft transplant recipients in CITR is 44 Years (range 19 to 67) and the mean duration of diabetes is 28 years (range 2 to 54). The mean weight of the participant is 66 kg (range 35 to 98) and the mean body mass index (BMI) is 24 kg/m^2 (range 16 to 32). About 63% of the recipients are female. There is limited racial and ethnic diversity among the participants with this data reported.

Approximately 35% of the 412 allograft islet transplant participants were on an insulin pump prior to their first infusion and 97% of the participants were on the pump or were taking three or more insulin injections per day. At baseline, 92% of the participants had a basal C-peptide <0.5 ng/mL and 85% had an HbA_{1C} >6.5%. The mean daily insulin requirement of participants prior to their first infusion procedure was 37 units (SD 13.5) and the subset on intensive insulin therapy had received intensive therapy for a mean of 19 years (SD 13.5). The mean fasting blood glucose for all participants was 173 mg/dL (SD 88), mean HbA_{1C} was 7.7% (SD 1.3), and the mean basal C-peptide was 0.1 ng/mL (SD 0.26).

Thirty three percent of islet recipients do not have reported data on autoantibody (GAD-65, IA-2, and Insulin) levels. Of known data, 73% have at least one positive autoantibody measurement. Measurement of autoantibody levels is strongly encouraged for all potential islet transplant recipients.

Donor Information. There were no living donors. The mean age of donors was 44 years (range 1 to 75) and the mean body mass index was 29 kg/m^2 (SD 6.5). Approximately 59% of the donors were male, 10% were Hispanic and 90% were white. Fifty-six percent of the donors had a cerebrovascular/stroke as cause of death while 31% experienced a head trauma. Approximately 34% of the donors had a history of hypertension and 19% had a history of alcohol dependency.

Thirty-two percent of the donors received a transfusion during hospitalization, while only 6% received a transfusion intraoperatively. Fifty nine percent of the donors received steroids, 40% of the donors received insulin and 95% received at least one vasopressor during the donor's terminal hospitalization. There was a report of one donor testing positive for anti-HBC, and one testing positive for RPR-VDRL. The mean serum creatinine of the donors was 1.1 mg/dL.

Pancreas Procurement. In 63% of the 905 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 mean time from cross clamp to pancreas recovery was 44 minutes (SD 22) while the mean cold ischemia time was 7.3 hours (range 1 to 27). UW and Two Layer were the most common (85%) methods used for pancreas preservation.

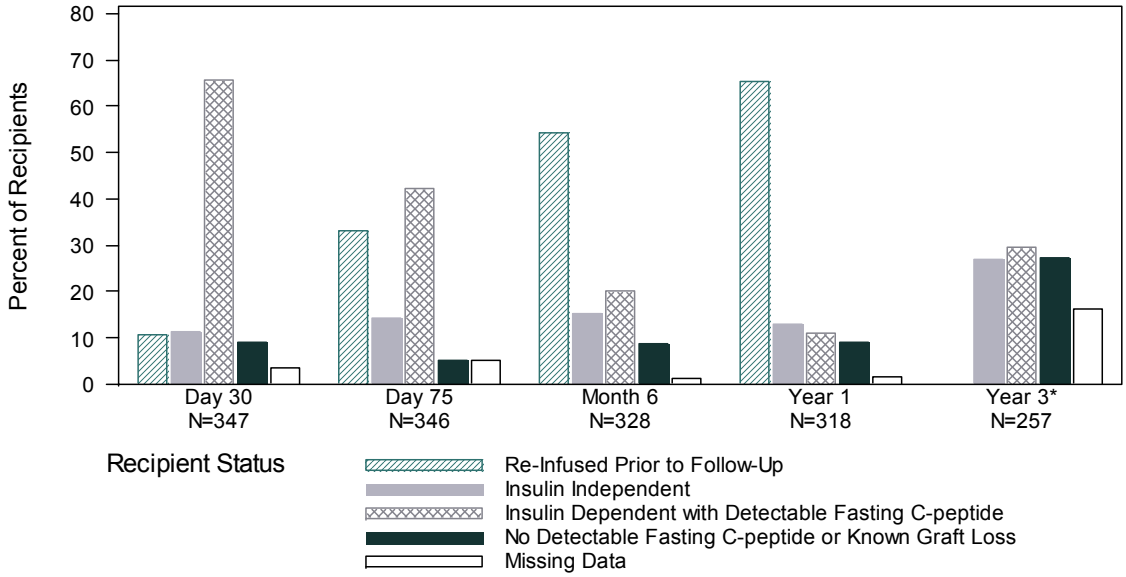
Liberase HI was the collagenase type used during most islet processing (77%) followed by NB1 (18%). All of the pancreata processed used a density gradient for islet purification. Fifty four percent of islets were placed in culture, defined as six or more hours in a specially prepared nutrient medium. When cultured, the median culture time was 27 hours (range 6 to 96). Of the 905 islet preparations reported to CITR, thirteen final preparations showed a positive aerobic culture (1.7%), five showed a positive anaerobic culture (0.8%), four showed a positive fungal culture (0.5%), and one tested positive for mycoplasma (0.2%).

Immunosuppression Therapy. The majority (52%) of the islet transplant alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus only immunosuppression regimen. Daclizumab was the sole antibody used in 59% of first infusions. Anti-thymocyte globulin was given

alone or in combination in 14% of first infusions. Substantial shifts away from anti-IL2 induction and away from Sirolimus / Tacrolimus maintenance have occurred over the last five years.

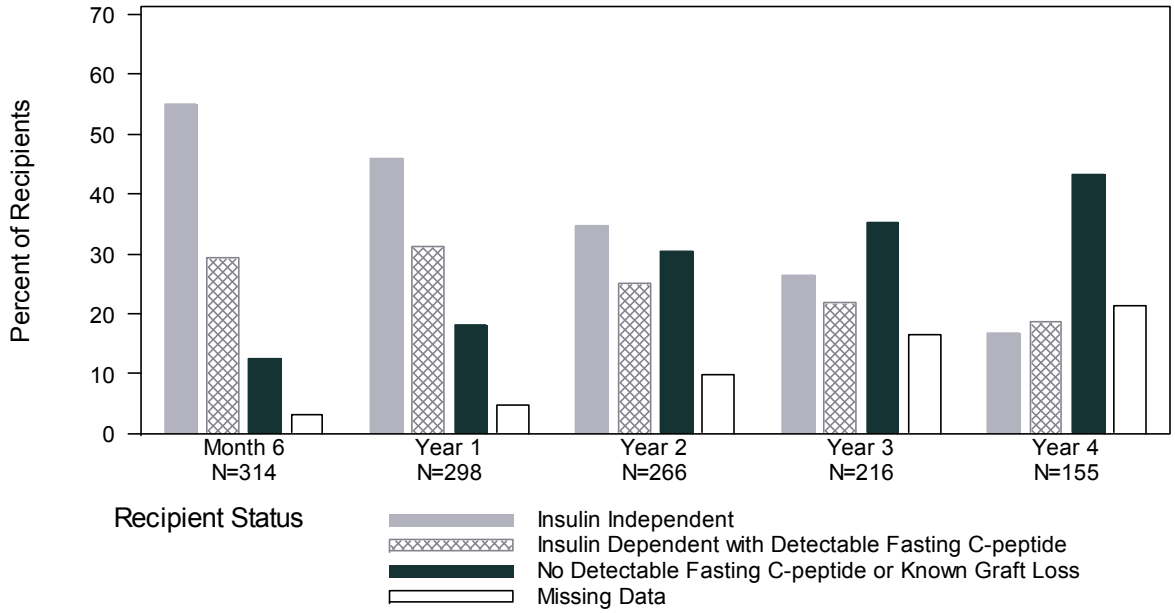
Graft Function. After the first infusion, increasing proportions of islet-alone recipients are re-infused: 11% by Day 30, 33% by Day 75, 54% by Month 6, and 65% by Year 1 (Exhibit C-1). The proportion that is insulin independent without re-infusion remains fairly constant at 11-15% throughout the first year. An additional 8-12% of all IA recipients retain detectable C-peptide over the first year with insulin dependence but without re-infusion. Of all 347 IA recipients, 74% have at least three years follow up post first infusion, at which time, regardless of the total number of infusions received, about 27% are insulin independent, 30% are insulin dependent with detectable C-peptide, 27% have no detectable C-peptide, and 16% have missing data (required but not yet reported).

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



*Year 3 status regardless of re-infusion

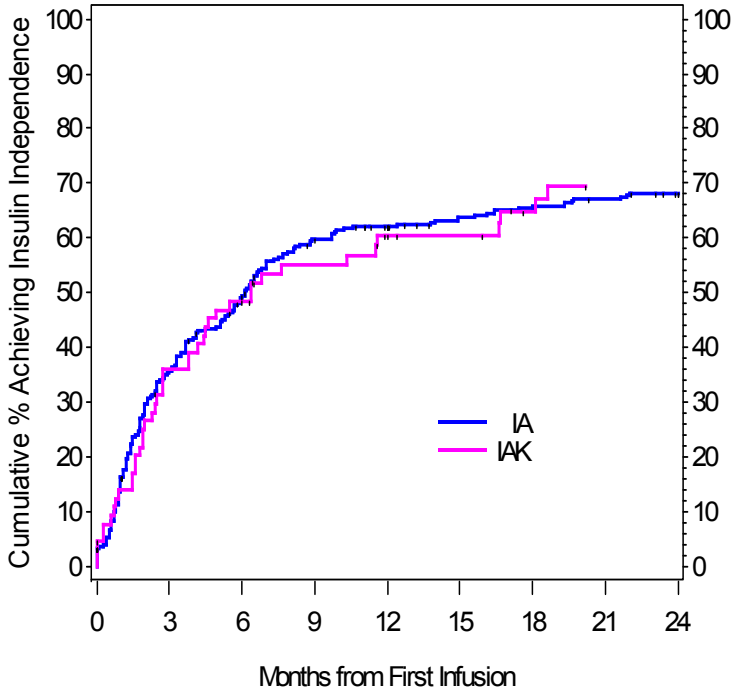
Exhibit C – 2
Insulin Independence, Insulin Dependence
or Absence of Fasting C-peptide
Post Last Infusion
Islet Alone Recipients



Analyzed from last infusion (Exhibit C-2), the percentage of all IA recipients that are insulin independent declines steadily from 55% at Month 6 to 16% at Year 4. The proportion with loss of islet function (reported graft failure or no detectable C-peptide) increases steadily from 12% at Month 6 to 42% at Year 4. A stable 19-31% retains graft function with exogenous insulin over the four years; the percentage of missing data increases over time.

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 follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Achievement of insulin independence is indistinguishable between islet alone and islet after kidney patients. As incidence or cumulative rates of ever achieving insulin independence after islet transplantation, 62% of the IA and IAK recipients combined to achieve insulin independence in the first year post first infusion (not censored at re-infusion or graft loss), and by Year 2 this increases to 68% (Exhibit D).

Exhibit D
Achievement of Insulin Independence After Islet Transplantation
Not Censored at Re-Infusion or Graft Loss
Post First Infusion
Islet Alone vs. Islet After Kidney



Over time there is a decrease in the sustainability of insulin independence (Exhibit E1). For islet alone participants who ever achieved insulin independence, 70% have retained this status one year after achieving it and this decreases to 45% at three years. Recipients transplanted since 2005 retained insulin independence significantly longer than those transplanted in 1999-2004 (Exhibit E2).

Exhibit E – 1
Persistence of Insulin Independence
Allograft Recipients Achieving Insulin Independence
Post Last Infusion
Islet Alone vs. Islet After Kidney

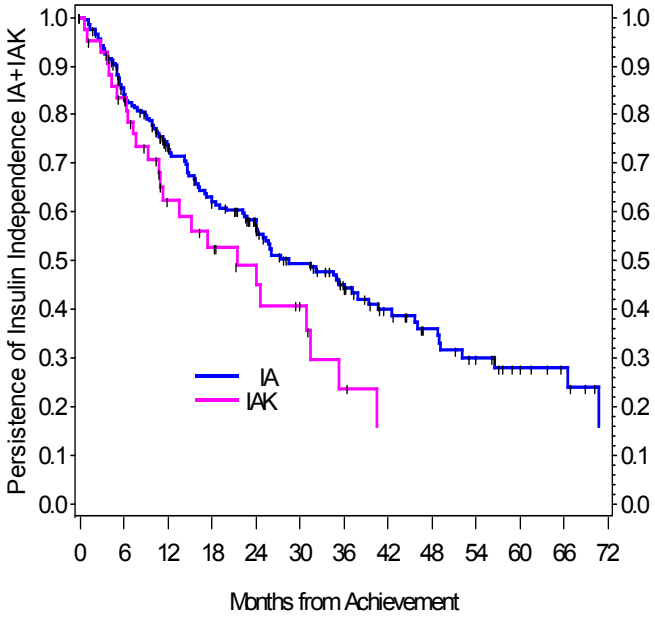


Exhibit E – 2
Persistence of Insulin Independence
Allograft Recipients Achieving Insulin Independence
Post Last Infusion
by Era of First Infusion

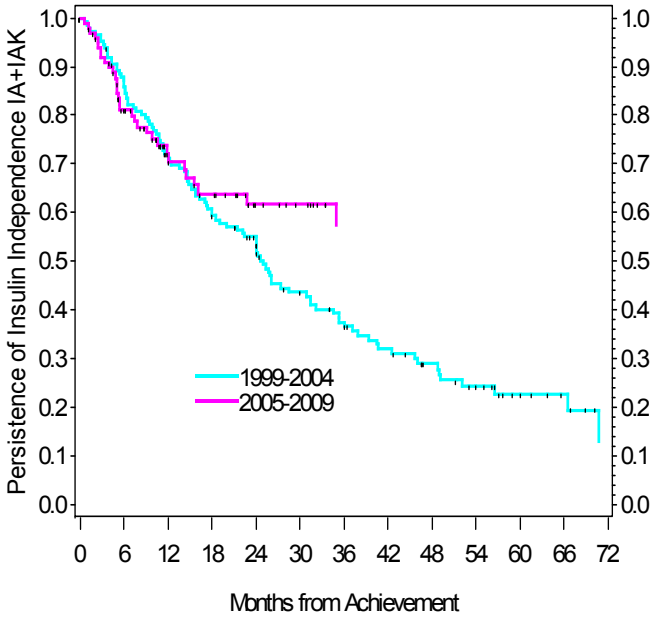
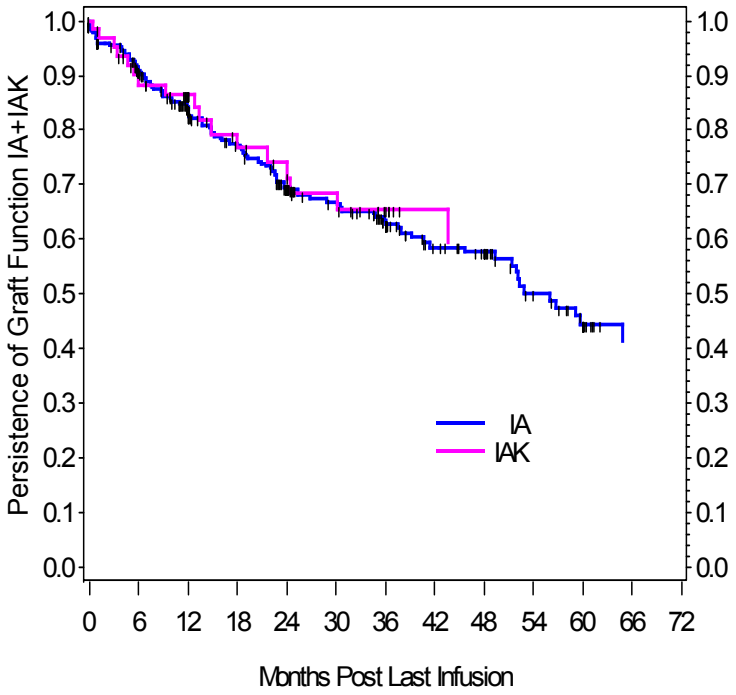


Exhibit F
Persistence of Islet Graft Function (IA, IAK)



Similarly, graft function is lost over time. Viewed as Kaplan-Meier survival estimates (Exhibit F) 65% of IA recipients retain function by Year 3 post last infusion.

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 C-peptide values substantially increase. The percent of IA recipients with C-peptide >0.5 ng/mL increases from 7% pre-infusion to 77% at Month 6 post last infusion with 45% retaining this level of function at Year 3 post last infusion. These trends are seen both overall and by total number of infusions. Results are affected by the recipients' transient insulin status and whether or not they ever achieved insulin independence.

Severe Hypoglycemia and HbA_{1C}. The prevalence of severe hypoglycemic events decreases dramatically following islet transplantation. Islet transplants also substantially improve HbA_{1C} levels. Taken as a composite outcome, the percent of IA recipients with HbA_{1c} <6.5% and absence of severe hypoglycemic episodes increases from 2% pre-infusion to 51-60% at Year 1 post last infusion with a subsequent decline to 20-45% by Year 4 post last infusion (Exhibit G-1). In these ranges, the lower estimate represents the case where all missing data are counted as not achieving the outcome whereas the upper estimate assumes all missing data for recipients with confirmed or unknown graft function do achieve the outcome. Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit G-2).

Exhibit G – 1

Composite Outcome (Hypoglycemia and HbA_{1c}) Post Last Infusion

Islet Alone Recipients

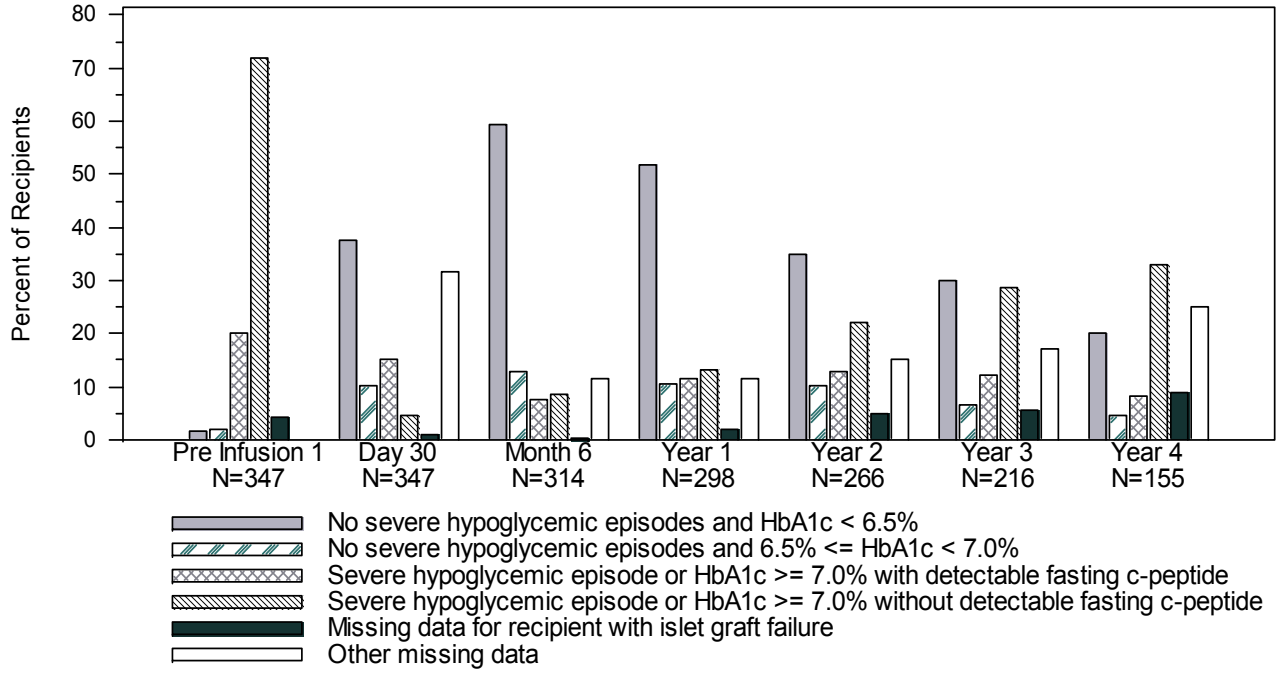
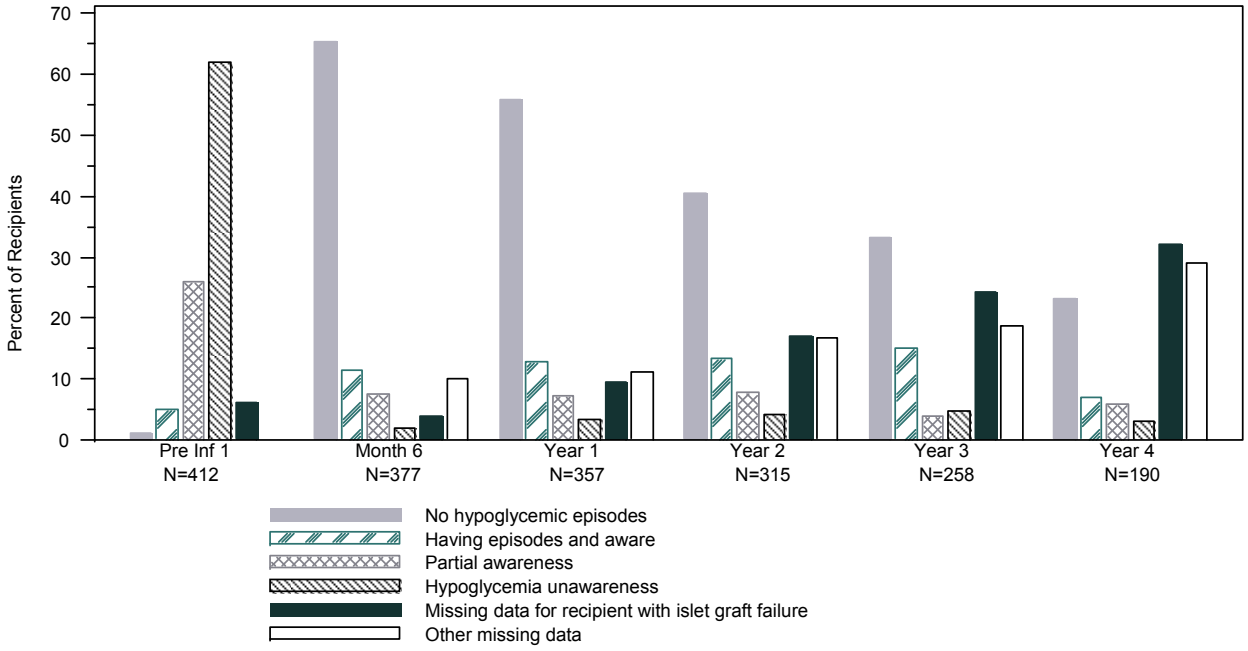


Exhibit G – 2

Hypoglycemia Status Pre First Infusion and Post Last Infusion

All Allograft Recipients



Factors of Primary Outcomes. Multivariate Cox regression models were used to investigate the effect of pre-infusion and cumulative infusion factors on primary outcomes of islet transplantation post last infusion. Hazard ratios (HR) less than one indicate a lower risk of the event with higher levels of the factor. Binary factors are coded 0=absent and 1=present.

The final multivariate model for achieving insulin independence post last infusion (209 events / 341 recipients) is:

Variable	HR		p
Baseline HbA_{1c}	0.89	Lower HbA1c favorable	0.03
Procurement/infusion center (0=unrelated 1=related)	1.32	Related is favorable	0.08
Processing/infusion center (0-unrelated 1=related)	2.88	Related is favorable	0.002
Daclizumab (0=N 1=Y)	1.79	Daclizumab is favorable	0.005

Baseline HbA1c, baseline weight, baseline BMI, baseline daily insulin, fasting glucose, and number of daily injections are substantially mutually correlated: any of these measures of initial control suffices to explain its influence on achieving insulin independence: the better the control, the more likely to achieve insulin independence. The processing center being related to the transplant center is favorable. Daclizumab is favorable. Variables that cannot be excluded as significantly associated with this outcome are donor's given steroids, HLA factors and islet beta cell counts. There is substantial imbalance between most immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of those immunosuppressant therapies in a multivariate model. Their univariate effects cannot be dismissed. Daclizumab is stable in this model and seems to be favorable for insulin independence.

The final model for complete islet failure post last infusion (111 events / 341 recipients) is:

Variable	HR		p
Age	0.68	Higher age is favorable	<0.001
Processing/infusion center (0-unrelated 1=related)	0.42	Related is favorable	0.003
Etanercept (0=N 1=Y)	0.47	Etanercept is favorable	0.02
Calcineurin Inhibitor (0=N 1=Y)	0.26	Calcineurin inhibitor is favorable	0.003

Older recipient age predicts lower risk of losing the graft. Related processing and infusion centers substantially reduce the chances of losing the last graft. Etanercept and calcineurin inhibitors are confirmed as favorable for persistent function.

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

Concomitant Medications. Prior to the first infusion, 43% of the recipients were on at least one anti-hypertensive medication and 34% were on a lipid lowering medication. By Year 1 post last infusion, these rates increased to 53% and 61%, respectively.

Adverse Events. CITR is the leading resource for adverse event information in islet transplant recipients. Sixty-two percent of the islet alone recipients experienced at least one adverse event in Year 1, while 44% experienced one or more serious adverse events in this same period. Of the 594 adverse events reported in Year 1 post first infusion for islet alone recipients, 32% were related to the immunosuppression therapy and 27% were related to the infusion procedure. Of the 312 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 29% were related to the immunosuppression therapy and 33% were related to the islet infusion procedure.

Overall, a total of 592 serious adverse events were reported to the Registry as of datafile closure, with 29% of them classified as life threatening and 52% requiring an inpatient hospitalization. Sixty-two percent (365 of 592) of serious adverse events occurred in the first year following the participants' first infusion procedure. Twenty-five percent of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 29% related to the immunosuppression therapy. Approximately 82% of the serious adverse events resolved with no residual effects. Most of the reported serious adverse events were categorized as gastrointestinal disorders (17%), investigations (14%) and blood and lymphatic system disorders (13%) as classified by the MedDRA classifications system.

Neoplasms have been diagnosed in 21 of the 412 islet recipients. None were related to the islet infusion procedure while nine may have been related to the immunosuppression therapy (basal cell carcinoma (x2), squamous cell carcinoma (x3), breast cancer, ovarian cysts, and papillary thyroid cancer (x2)). The most frequent type of neoplasm was squamous cell carcinoma (nine recipients). Seventeen recipients continued their islet transplant immunosuppression regimen; two withdrew voluntarily; and two have missing follow-up.

Reported Deaths. There have been nine reports of death to the Registry for islet allograft recipients; a viral meningitis attributed death possibly related to the immunosuppressant therapy occurring three years following the person's last islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post the person's last infusion, a stroke two years post the person's last infusion, another stroke three years post the person's last infusion, a death due to acute respiratory distress syndrome five years post last islet infusion, pneumonia eight years after the person's last infusion, diabetic ketoacidosis six years after the person's last infusion, atherosclerotic coronary artery disease 16 months after the person's last infusion and one death due to unknown causes.

CONCLUSIONS

In the years since 2005, fewer North American centers performed an islet transplant and there were half as many islet transplant recipients in 2008. However, more centers transplanted and more people received an islet transplant in 2008 compared to 2007. With the continuation of Clinical Islet Transplantation (CIT) Consortium protocols that began in 2008, the number of new islet cell recipients is expected to rise. Islet transplantation continues to show short-term benefits of insulin independence, normal or near normal HbA_{1C} levels, sustained marked decrease in severe hypoglycemic episodes and a return of hypoglycemia awareness. Long-term primary efficacy and safety of immunosuppression as well as effects on secondary complications are less well understood. The accumulated experience in islet transplantation indicates that the best candidates for islet transplantation are older recipients in better glycemic control; close relationships between procurement, processing, and transplant teams as well as use of Daclizumab, Etanercept, and Calcineurin inhibitors are associated with favorable outcomes. Not all other factors can be discounted as favorable.

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, and JDRF-sponsored European and Australian centers since 1999. The main vehicle of communicating accumulated results is the CITR Annual Report. This sixth report, published in 2009, summarizes information on patients who received one or more islet cell transplants between 1999 and 2008. All CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Status and History

This report focuses on 412 islet allograft recipients (347 islet alone and 65 islet after kidney). Islet autografts are also conducted (over 400 procedures so far in North America) for other indications (principally pancreatitis) and centers may voluntarily report these data also to the Registry. As of December 31, 2008, a total of 206 autologous islet transplant recipients were registered in CITR. Efforts are underway to collect complete autograft information in the Registry, both prior to and going forward from December 31, 2008.

CITR opened participation to North American centers early in the fall of 2002. The following table summarizes the cumulative numbers of allograft recipients, infusions and donors of the CITR Annual Reports to date.

CITR Annual Report	Allograft Recipients	Allograft Infusions	Allograft Donors
First (2004)	86	158	173
Second (2005)	138	256	266
Third (2006)	227	429	469
Fourth (2007)	292	579	634
Fifth (2008)	325	649	712
Sixth (2009)	412	828	905

The current report represents a 27% increase in the number of recipients, donors, and infusion procedures compared to last year's report.

Data Sources

CITR implements web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry and obtain donor, organ procurement, and islet processing data through data sharing agreements with respective organizations (the United Network for Organ Sharing and the Islet Cell Resource Centers). These data characterize and follow trends in safety and efficacy for recipients of islet transplantation, including donor information, islet processing, transplant techniques, and

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

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

CITR also collects basic survey information from all islet allograft transplant centers in North America, regardless of their participation with CITR. Forty-six islet transplant programs were sent a questionnaire requesting the number of islet transplant infusions performed at their islet transplant center as well as the number of recipients. All 46 programs responded and 32 had been active during 1999-2008, 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 32 active islet allograft transplant programs in North America for 1999-2008. 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	783	408
1999	18	10
2000	32	20
2001	64	45
2002	142	82
2003	106	45
2004	110	53
2005	125	65
2006	78	36
2007	42	20
2008	66	32

In summary, this report includes data on 81% (329/408) of all human islet allograft recipients and 81% (637/783) of all human islet allograft procedures conducted in North America from 1999-2008, as well as 83 recipients of 182 human islet allograft infusions reported from three European and two Australian centers.

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. 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 5-6. 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. Changes in insulin status including transition to and from insulin independence are recorded. A change from insulin dependence to independence by definition requires at least 14 consecutive days of no insulin use. A change from insulin independence to insulin dependence by definition requires a minimum of 14 consecutive days of insulin use. Average daily insulin use is recorded for periods of insulin use before and after any re-infusion procedures, changes in islet graft function, and all CITR follow-up visits.

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

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

Statistical significance of analyses, not adjusted for repeated testing, is shown for a number of the Exhibits. These are provided to the reader for their own interpretation. Conclusions should recognize

that the significance levels control for random variance, but not systematic biases in the data nor multiple testing. It may be that statistical significance of the analyses in subsequent reports based on a greater sample size will vary from this year's report. However, these analyses do provide insight and direction for future questions and analyses.

Statistical Modeling

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

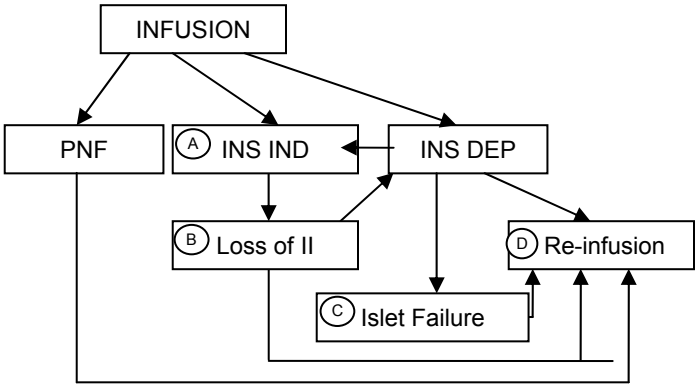


Figure1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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 the final multivariate results in the text) 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 D). This continues to be analyzed in each Annual Report 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. Analysis of this outcome state is done by logistic regression, as time to event is meaningless.

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.

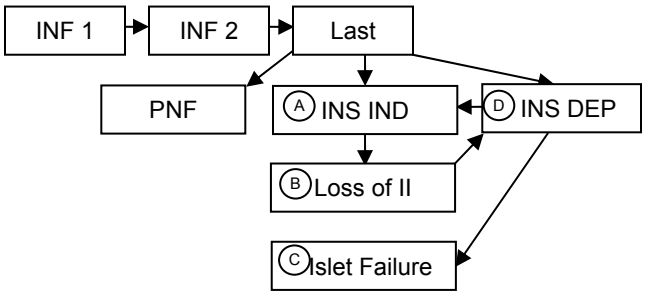


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

We call these analyses "post last infusion," defined as all infusions performed in a recipient 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 following Exhibit 5-23.

Definitions

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

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

ALT (alanine aminotransferase):	*56 IU/L*
AST (asparate aminotransferase):	*40 IU/L*
Alkaline phosphatase:	*90 IU/L*
Total bilirubin:	*1.3 mg/dL*
Total cholesterol:	*240 mg/dL*
Triglycerides:	*150 mg/dL*

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

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

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

Complete graft loss (CGL): Synonymous with "complete islet graft failure."

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, relative hazard 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 prior or simultaneous kidney transplantation.

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

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

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

Islet graft dysfunction:

In *insulin independent recipients* (after completion of induction immunotherapy), islet graft dysfunction is defined as when the recipient displays, with no evidence of infection or drug toxicity, 3 blood glucose readings 2 hours or longer post prandial over 180 mg/dL in any 1-week period OR 3 pre-prandial blood glucose readings over 140 mg/dL in any 1-week period.

In *insulin dependent recipients* (after completion of induction immunotherapy), islet graft dysfunction will be suspected if the recipient displays, with no evidence of infection or drug toxicity, a 50% increase in insulin requirements (with a minimum increase of 5 units per day) OR an increase of 10 units per day over a 1-2 week period.

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

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

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

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

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

Partial recovery: Recovery achieved but not to the functional level (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

Full recovery: Recipient was able to obtain the same level of functioning (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

PRA: Panel Reactive Antibody is a blood test that measures anti-human antibodies. The PRA score represents the percentage of the population that react with the anti-human antibodies in the blood

Serious Adverse Event: Any adverse event involving death, life threatening event, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity, congenital anomaly/birth defect, or required intervention to prevent permanent damage, regardless of the TCAE grading. Serious adverse event relationships to the infusion procedure and to the immunosuppression regimen are determined by the local CITR Investigator.

Severe hypoglycemia: Having hypoglycemic events requiring the assistance of another person to diagnose symptoms or administer treatment. Prior to the first infusion, this is defined as the number of episodes in one year prior to infusion. At follow-up, it is defined as the number of

episodes during the follow-up period (0 to 30 days post infusion, 30 days to 6 months post infusion, 6 to 12 months post infusion, or at yearly intervals thereafter).

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

Data contained in this report must be interpreted cautiously. Even with the combined efforts of the participating centers, the total number of reports is still small. As with any registry, a number of potential biases may exist. First, not all active islet transplant centers in North America have submitted data to CITR (27/32; 84%). Second, not all of the islet transplant recipients or all of the infusion procedures have been reported. Third, some information may be reported selectively based on the center's protocol or other local decisions.

This report presents islet alone (IA) and islet-after-kidney (IAK) allogenic islet transplant results side-by-side in most exhibits. Chapter 1 summarizes the reported human islet transplant activity from 1999 through 2008. 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, 2008. 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, 2009 based on the 412 recipients that had been registered for CITR at the December 31, 2008 participant registration closure date.

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

Chapter 1
Islet Transplant Activity

Islet Transplant Activity

As of December 31, 2008, 37 North American, and JDRF European and Australian islet transplant centers were enrolled in the Collaborative Islet Transplant Registry (CITR). Of these centers, 32 have registered 347 islet alone (IA) and 65 islet after kidney (IAK) allograft recipients to the Registry for a total of 412 human-to-human islet transplant recipients.

The following table summarizes the total allograft recipients, donors and infusions in this report.

CITR 04/2009	Islet Alone			Islet After Kidney		
	Total	North America	Europe/ Australia	Total	North America	Europe/ Australia
Recipients	347	293	54	65	36	29
Infusions	692	573	119	136	70	66
Donors	753	623	130	152	77	75

Exhibit 1-1A displays the locations of all current and former CITR-participating North American centers. A listing of CITR-participating centers and their staff is found in Appendix A.

Overall, there was a steady increase in the number of islet transplant programs joining CITR up to 2005, followed by a decline in centers performing islet transplantation in 2006-2007, then a resurgence in 2008 (Exhibit 1-2). There has been a 27% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 28% increase in the total number of islet allograft infusion procedures reported.

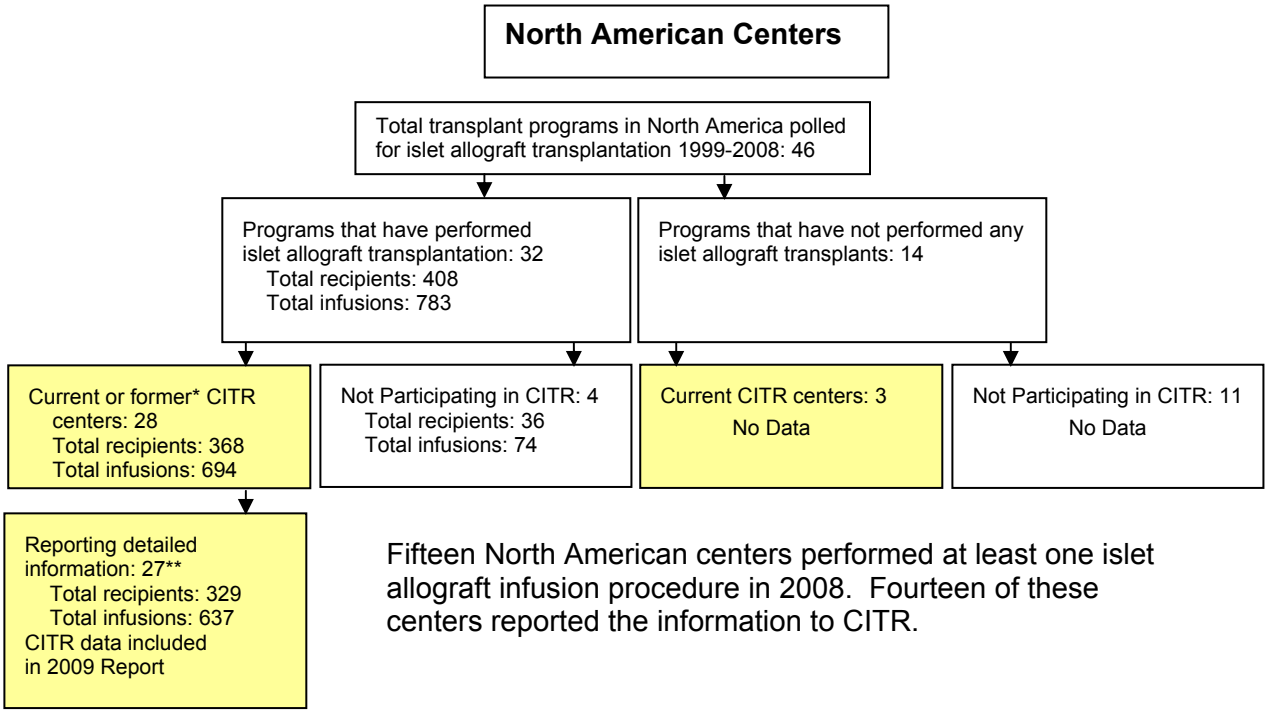
North American Centers

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 15 (93%) active North American islet transplant programs in 2008 contributed information to the Registry.

Exhibits 1-3A and 1-4A 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, 329 of 408 allograft recipients (81%) and 637 of 783 (81%) allograft infusions performed in North America are included in this year's Annual Report.

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

North American Islet Allograft Transplant Centers, Recipients and Infusions
Total Performed and Total Reported to CITR 1999-2008



* A former CITR center (N=3) is a center that reported data to CITR then subsequently stopped performing islet cell transplants and discontinued CITR participation.
** One center with three allograft participants who did not provide CITR consent.

JDRF Centers

Three European (Exhibit 1-1B) and two Australian (Exhibit 1-1C) JDRF centers have contributed detailed data to the Registry. Overall, 83 of 183 (45%) allograft recipients and 182 of 326 (56%) allograft infusions performed between 1999 and 2008 at these five centers are included in this year's Annual Report.

All Centers

A summary of the total 828 North American and JDRF islet allograft infusions entered in the Registry by year of infusion is included in Exhibit 1-5. These 828 infusions derived from 905 total donors; 754 were single donor preparations and 74 were multiple donor preparations. There was a large number of first islet infusions reported by the CITR centers in 2002 (N=78) as well as a large number of second islet infusions in 2002 (N=52). In other years, first infusion reports range from 7-68 recipients.

One hundred seven recipients (26%) have received a single islet infusion at the time of this report, 202 (49%) received a total of two infusions, 95 (23%) received three infusions, and eight recipients (2%) received a total of four islet infusions (Exhibit 1-6).

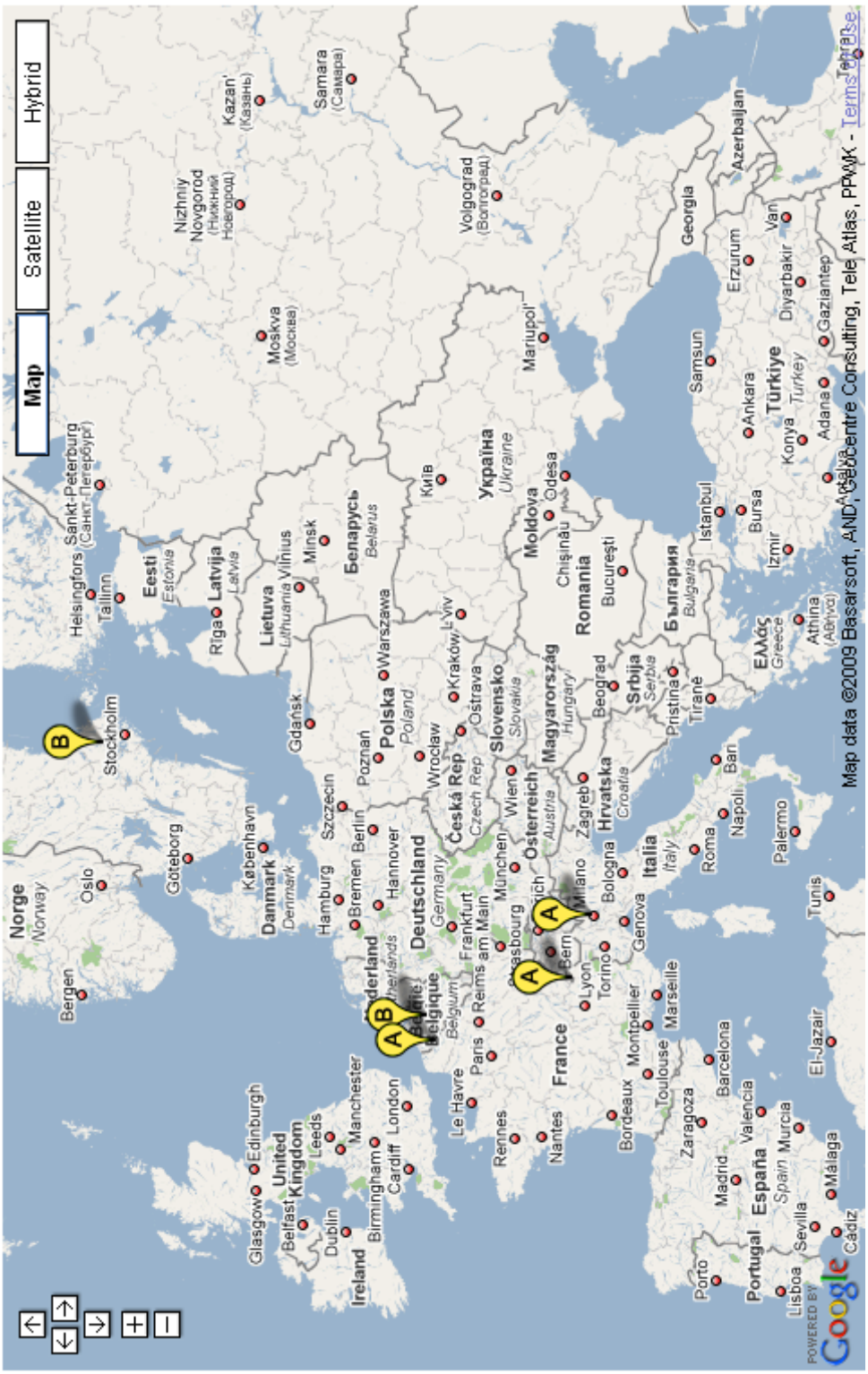
Of the 412 islet allograft recipients presented in this report, 347 (84%) are islet alone recipients, and 65 (16%) are islet after kidney recipients (Exhibit 1-8). Three islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

One hundred ninety one of 431 North American autograft recipients have been registered in the Registry. Detailed data for these recipients is being collected. When complete data are available, a supplemental Annual Report will present analyses for autologous islet transplants.

Exhibit 1 – 1A
Islet Transplant Centers Reporting Data to CITR
Participating North American Centers 1999-2008

A - CITR Centers with at least one islet allograft infusion procedure in 2008 (N=14)
C - CITR Centers with no islet allograft infusions in 2008 (N=17; three have never performed an islet transplant)
D - CITR Coordinating Center
For more information on North American islet transplant programs, please visit the CITR Website at www.CITRegistry.org.

Exhibit 1 – 1B
Islet Transplant Centers Reporting Data to CITR
Participating European Centers 1999-2008

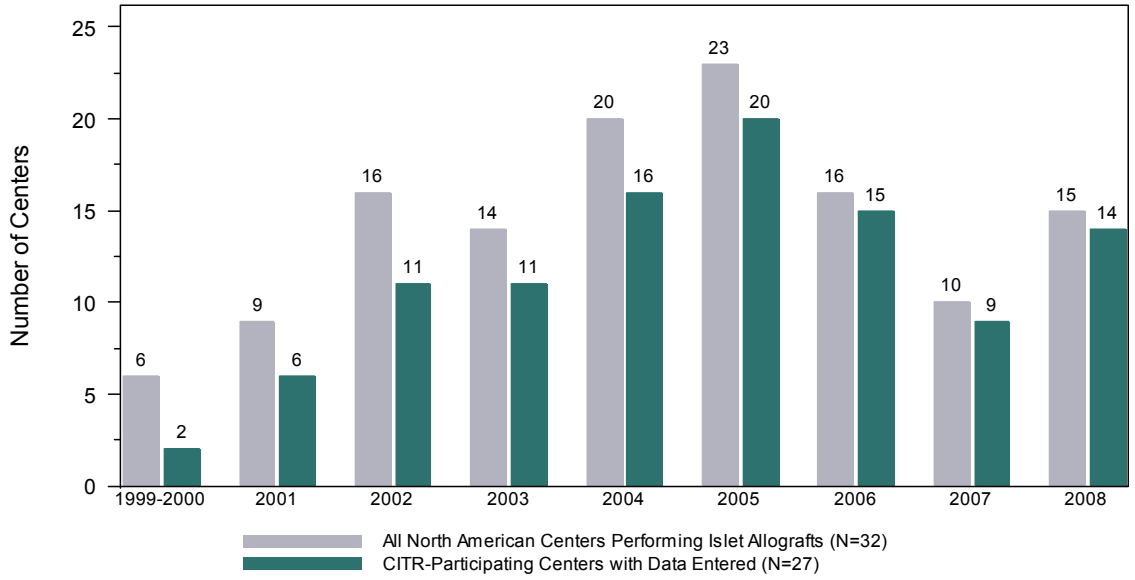


A - CITR Centers with at least one islet allograft infusion procedure conducted in 2008
B – CITR Centers with data reports pending

Exhibit 1 – 1C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2008

A - CITR Centers with at least one islet allograft infusion procedure conducted in 2008
C - CITR Centers with no islet allograft infusions in 2008

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 1999-2008

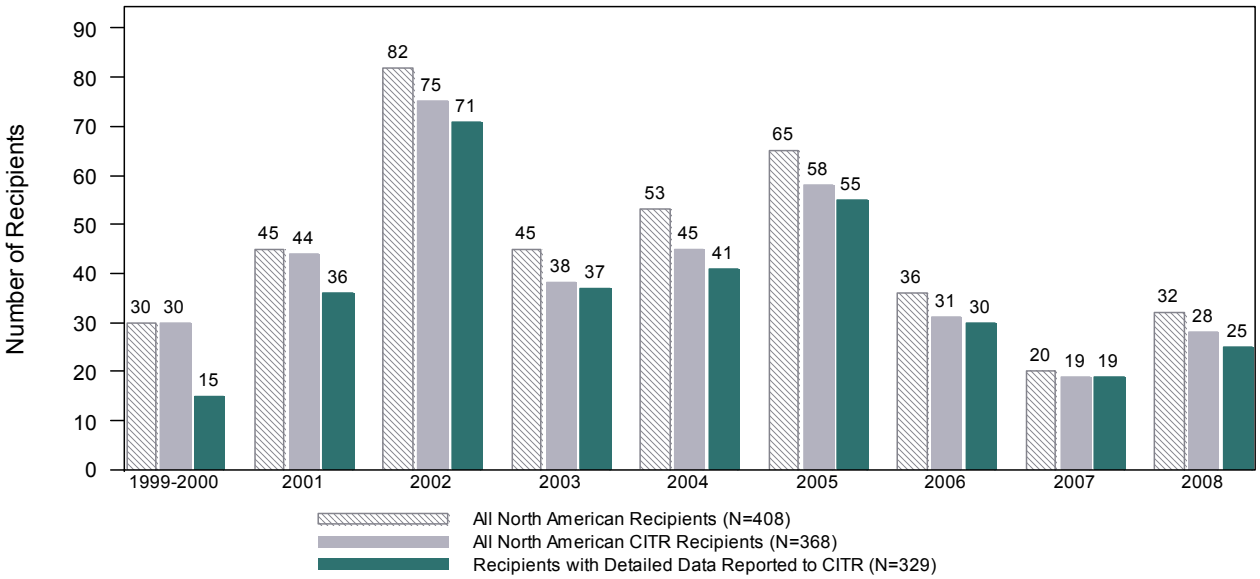


CITR distributes an Islet Transplant Summary (ITS) questionnaire to all known islet transplant programs in North America regardless of their participation in the Registry. The questionnaire captures information on the number of patients who received one or more islet infusions. Of 46 North American islet transplant programs polled, all have provided information through 2008.

"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. Three 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, two additional North American centers have contributed data for islet transplants performed.

Exhibit 1 – 3A
Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion
<u>All North American</u> Islet Transplant Centers 1999-2008



The Islet Transplant Summary (ITS) questionnaire is completed by all North American islet transplant programs regardless of their participation in the Registry. Of 46 North American islet transplant programs polled, all have provided this information through 2008.

From 1999-2008, 408 patients with Type 1 diabetes mellitus have received at least one islet allograft infusion procedure in North America. Of those 408 patients, 368 (90%) received their allograft from a CITR participating center. CITR-participating centers have reported detailed data on 329 of these recipients, representing 81% of all 408 human-to-human islet allograft recipients in North America from 1999-2008.

Since last year's report, North American centers have contributed data on 8 allograft recipients transplanted in 2002-2007 not previously reported.

Exhibit 1 – 3B
Total Number of Islet Allograft Recipients and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion
CITR-Participating European and Australian JDRF Centers 1999-2008

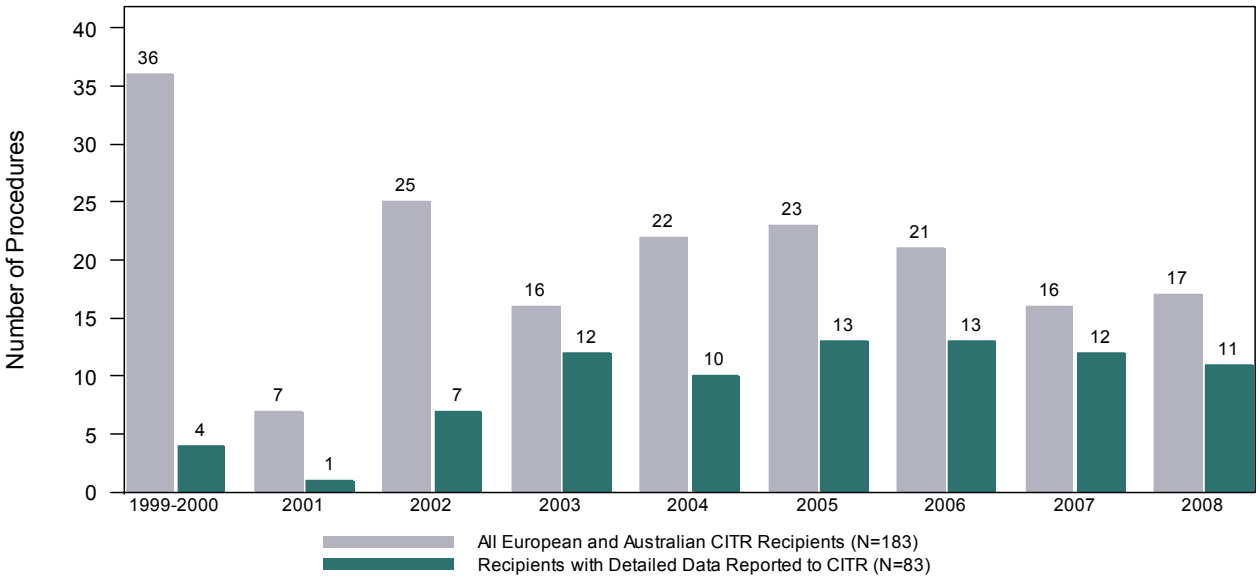
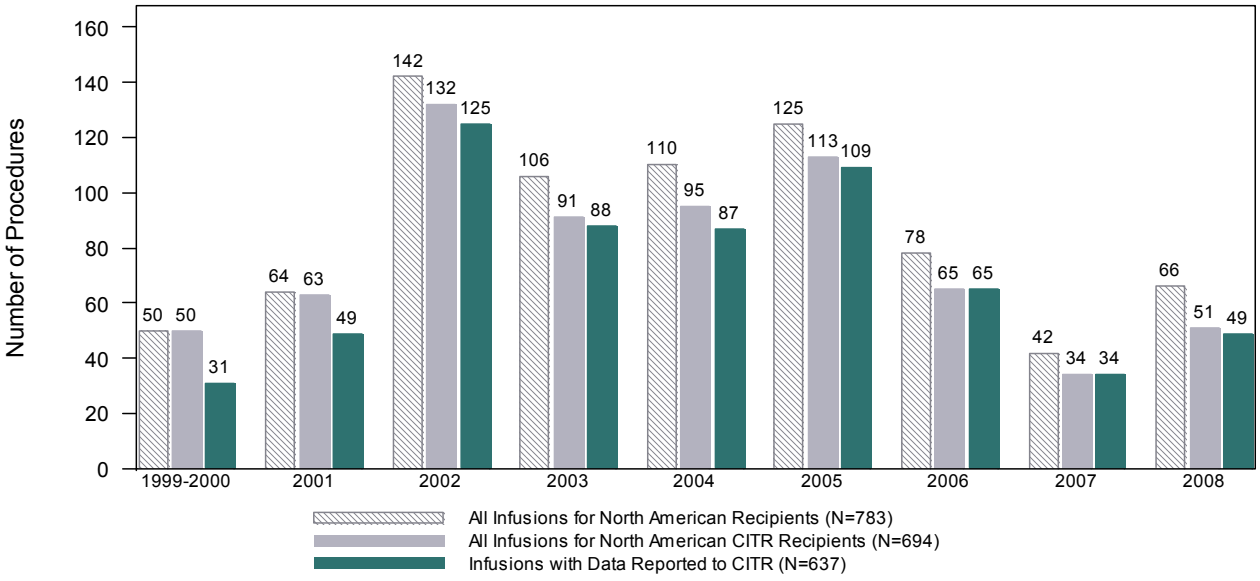


Exhibit 1 – 4A
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR
CITR-Participating North American Islet Transplant Centers 1999-2008



From 1999-2008, 408 patients with Type 1 diabetes mellitus have received a total of 783 allograft infusion procedures. CITR-participating North American islet transplant centers have performed 694 of those 783 (89%) procedures. The Registry has received detailed data on 637 allograft infusion procedures performed at CITR-participating North American islet transplant centers, representing 81% of all 783 human-to-human islet allograft infusions performed in North America from 1999-2008.

Since last year's report, North American centers have reported an additional 19 allograft infusions not previously reported.

Exhibit 1 – 4B
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR
CITR-Participating European and Australian JDRF Centers 1999-2008

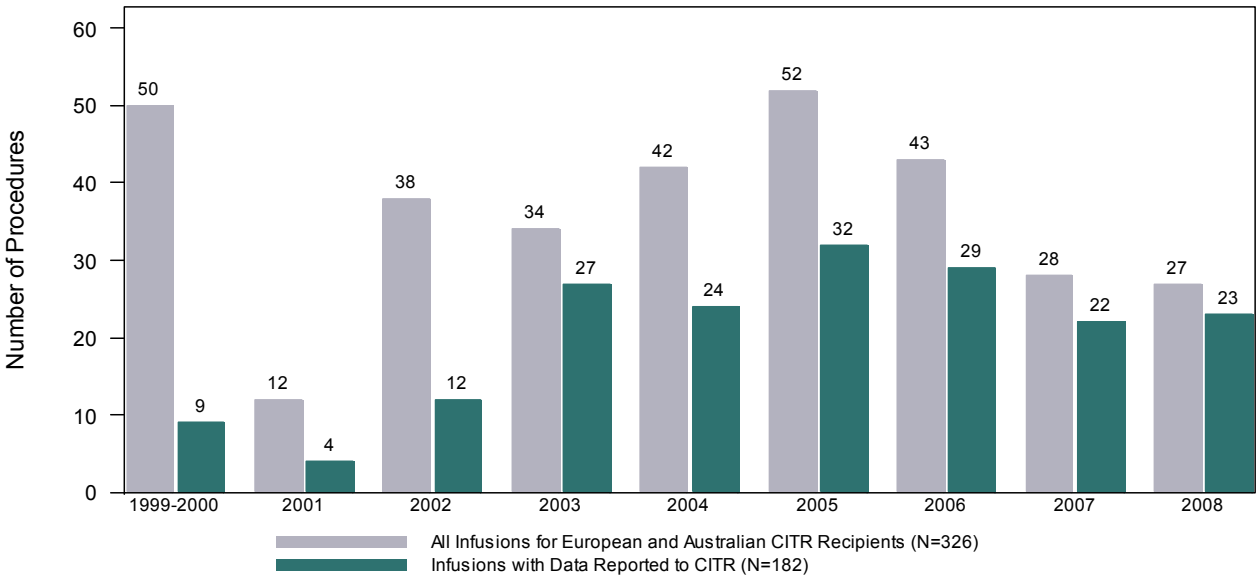
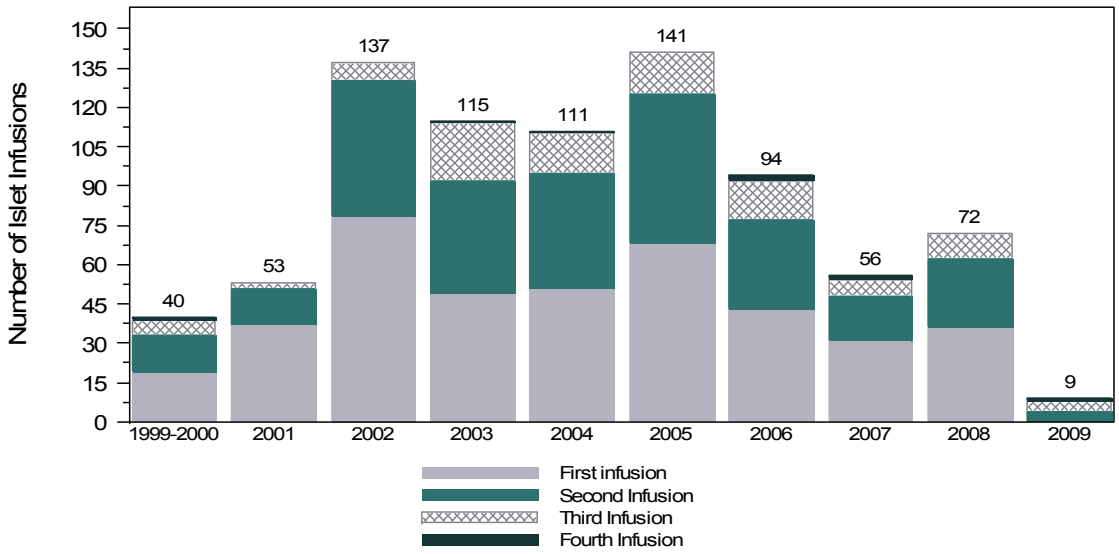


Exhibit 1 – 5
Total Number (N=828) of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number
CITR-Participating North American and JDRF Centers, 1999-2008



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

For example, in 2001, 37 participants received their first infusion, 14 received their second, while 2 received their third infusion. If a participant received their first islet infusion between 1999 and 2008 and a subsequent infusion between January and March of 2009, data for the subsequent infusion is also included in the graph.

Exhibit 1 – 6
Total Number (N=828) of Islet Allograft Infusion Procedures Per Recipient:
CITR-Participating North American and JDRF Centers, 1999-2008

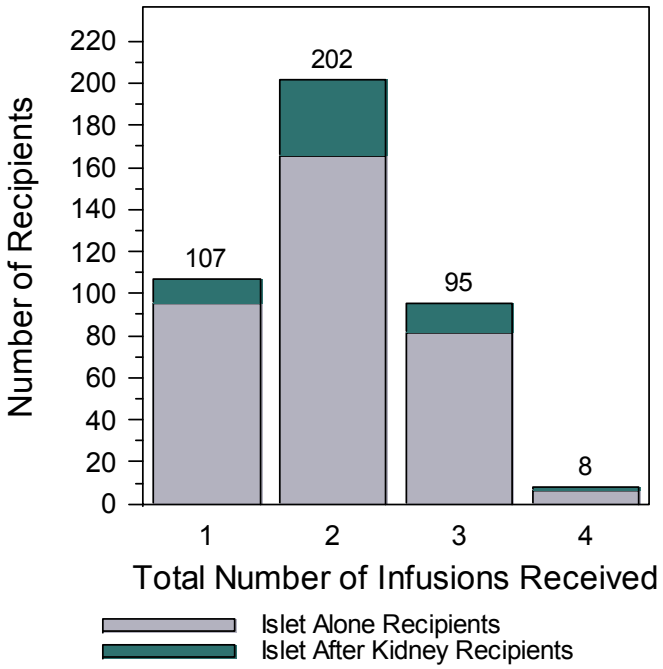


Exhibit 1 – 7
Total Number (N=905) of Deceased Donors per Islet Allograft Infusion Procedure
CITR-Participating North American and JDRF Centers, 1999-2008

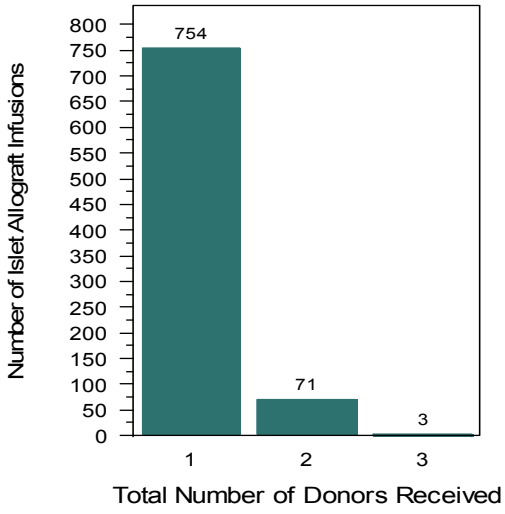
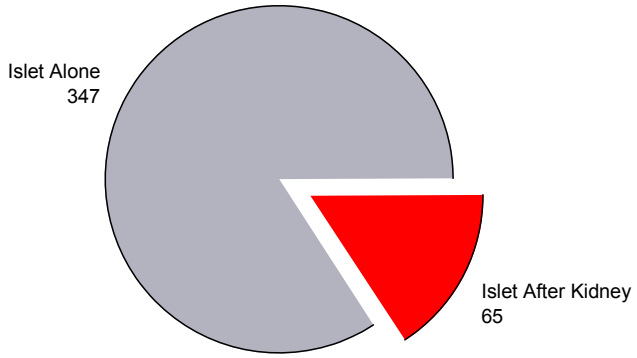


Exhibit 1 – 8
Islet Alone and Islet After Kidney Allograft Recipients
CITR-Participating North American and JDRF Centers, 1999-2008



Chapter 2
Recipient and Donor Characteristics

Recipient and Donor Characteristics

Islet Alone Recipient Information

The mean age of the islet alone transplant recipient is 44 years (range 19 to 67) and the mean duration of diabetes is 28 years (range 2 to 54). The mean weight of the recipient is 66 kg (range 35 to 98) and the mean body mass index (BMI) is 24 kg/m^2 (range 16 to 32). Females comprise 63% 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, 6% of the participants had a basal C-peptide $\geq$ 0.5 ng/mL and 68% had an $HbA_{1c} \geq 7.0\%$ (Exhibit 2-4). The mean daily insulin requirement prior to their first infusion procedure was 37 units (SD 13.5) and the 97% on intensive insulin therapy had received intensive therapy for a mean of 19 years (SD 13.5) (Exhibit 2-3). At pre-transplant mean fasting plasma glucose for all recipients was 173 mg/dL (SD 87.9), mean HbA_{1c} was 7.7% (SD 1.3), and mean basal C-peptide was 0.1 ng/mL (SD 0.26).

Recipient autoantibody data are missing 40-50% across the board, rendering meaningful inference difficult at best. All centers are strongly encouraged to ascertain and report these data from past cases and going forward.

Serology tests indicated that six participants (4 IA, 2 IAK) tested positive for hepatitis B core antibodies, three participants tested positive for hepatitis B surface antigen, six participants tested positive for CMV IgM, one tested positive for HIV and two tested positive for hepatitis C (Exhibit 2-6).

Exhibits 2-7 and 2-8 describe participant baseline characteristics prior to first infusion by the total number of infusions received. In comparison, participants who received a total of three infusions were younger, on the waitlist for less time, had diabetes for less time and required more insulin than those participants who had one or two infusion procedures.

Donor Information

All 905 islet preparations were derived from deceased donors. The mean age of donors was 44 years (range 1 to 75) and the mean body mass index was 29 kg/m^2 (SD 6.5). Approximately 59% of the donors were male, 10% were Hispanic and the majority was white. Fifty-six percent of the donors had cerebrovascular/stroke as cause of death while 31% 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 42 minutes (SD 23.4) while the mean cold ischemia time was 7.3 hours (SD 3.4) (Exhibit 2-12).

About 32% of the donors received a transfusion during hospitalization; 6% received a transfusion intraoperatively. About 40% of the donors received insulin during their hospitalization and 95% of the donors received at least one vasopressor during the donor's terminal hospitalization (Exhibit 2-13).

Donor serology is presented in Exhibit 2-14. There was a report of one donor testing positive for Anti HBC. Another donor tested positive for RPR-VDRL.

Donor laboratory data are presented in Exhibit 2-15. The mean serum creatinine of the donors is 1.1 mg/dL, total bilirubin 0.9 mg/dL, AST 73 IU/L, ALT 58 IU/L, serum lipase 74 IU/L and serum amylase 169 IU/L.

Exhibit 2 – 1
Recipient Demographics

	Islet Alone			Islet After Kidney		
	N	**Mean**	**SE**	**N**	**Mean**	**SE**
Age (yrs)	347	44.3	0.5	65	46.2	0.9
	N	**%**		**N**	**%**	
Gender						
Female	220	63.4		39	60.0	
Male	127	36.6		26	40.0	
Ethnicity						
Non Hispanic or Latino	222	64.0		60	92.3	
Hispanic or Latino	6	1.7		1	1.5	
Unknown*	119	34.3		4	6.2	
Race						
American Indian or Alaska Native	2	0.6		-	0.0	
Asian	-	0.0		-	0.0	
Black or African American	1	0.3		1	1.5	
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	227	65.4		60	92.3	
Unknown*	118	34.0		4	6.2	
Employment status						
Working full time	179	51.6		18	27.7	
Working part time by choice	19	5.5		3	4.6	
Working part time due to disease	20	5.8		3	4.6	
Working part time, reason unknown	2	0.6		-	0.0	
Not working by choice	16	4.6		2	3.1	
Not working due to disease	46	13.3		23	35.4	
Not working, unable to find employment	1	0.3		-	0.0	
Not working, reason unknown	3	0.9		4	6.2	
Student	2	0.6		1	1.5	
Retired	16	4.6		1	1.5	
Employment status unknown	28	8.1		8	12.3	

Race and ethnicity are not collected or reported in some countries.

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	72	38.5	9	25.0
Non-Government Research Grant	52	27.8	21	58.3
Institutional Contribution	46	24.6	1	2.8
Other*	2	1.0	1	2.8
Missing	15	8.0	4	11.1
Payment for Islet Processing				
US/State Government Agency	65	34.8	9	25.0
Non-Government Research Grant	58	31.0	21	58.3
Institutional Contribution	47	25.1	1	2.8
Other*	2	1.0	1	2.8
Missing	15	8.0	4	11.1
Payment for transplant				
US/State Government Agency	50	26.7	8	22.2
Non-Government Research Grant	48	25.7	18	50.0
Institutional Contribution	70	37.4	3	8.3
Other*	4	2.1	3	8.3
Missing	15	8.0	4	11.1
Payment for Induction Medication				
US/State Government Agency	43	23.0	7	19.4
Non-Government Research Grant	60	32.1	19	52.8
Institutional Contribution	64	34.2	2	5.6
Medicare	-	-	1	2.8
Other*	5	2.6	4	11.1
Missing	15	8.0	4	11.1

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

Exhibit 2 – 3
Recipient Characteristics at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	347	100.0	65	100.0
Diabetes Type				
Type 1 Diabetes	345	99.4	65	100.0
Pancreatectomy Induced	1	0.3	-	-
Cystic Fibrosis Related	1	0.3	-	-

	Islet Alone			Islet After Kidney		
	N	Mean	SE	N	Mean	SE
Duration of Diabetes (yrs)	347	28.3	0.6	65	33.0	1.1
Weight (kg)	336	66.4	0.6	61	61.4	1.2
Body Mass Index (kg/m^2)	329	23.7	0.2	61	22.6	0.3
Daily insulin requirement prior to infusion (units)	330	37.0	0.7	62	34.6	1.5
Duration of intensive therapy (yrs)	196	18.6	1.0	3	32.7	11.6
Avg daily insulin / kg recipient body weight	326	0.5	0.0	60	0.6	0.0
Number of days on wait list	312	305.2	19.1	58	297.4	43.9
Fasting plasma glucose (mg/dL)	320	172.5	4.9	56	181.2	14.1
Basal C-Peptide (ng/mL)	325	0.1	0.0	57	0.1	0.0
HbA_{1C} (%)	329	7.7	0.1	59	7.9	0.2
Most recent PRA (%)	303	3.4	0.7	45	1.3	1.0
Peak PRA (%)	282	4.9	0.8	35	6.7	3.2

Exhibit 2 – 4
Recipient Diabetes Characteristics at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	347	100.0	65	100.0
Use of insulin pump				
Yes	126	36.3	12	18.5
No	204	58.8	49	75.4
Missing	17	4.9	4	6.1
Number of injections per day				
N/A-on pump	126	36.3	12	18.5
1-2*	8	2.3	2	3.1
3-5	178	51.3	31	47.7
6 or more	5	1.4	3	4.6
Unknown	12	3.5	14	21.5
Missing	18	5.2	3	4.6
Use of insulin pump or 3 or more injections per day				
Yes	309	89.0	46	70.8
No*	8	2.3	2	3.1
Missing	30	8.6	17	26.1
Basal C-Peptide ≥ 0.5 ng/mL				
Yes**	18	5.2	4	6.2
No	307	88.5	53	81.5
Unknown	12	3.5	5	7.7
Missing	10	2.9	3	4.6
HbA1C				
<6.5%	52	15.0	5	7.7
6.5% - 7.0%	42	12.1	9	13.8
≥ 7.0%	235	67.7	45	69.2
Unknown	8	2.3	5	7.7
Missing	10	2.9	1	1.5
Hypoglycemia Status				
No Occurrence	0	0.0	3	4.6
Having Episodes and Aware	7	2.0	14	21.5
Partial Awareness	93	26.8	14	21.5
Unawareness	228	65.7	27	41.5
Unknown	3	0.9	3	4.6
Missing	16	4.6	4	6.2

*Participants with a mean daily insulin use of 36 units (SD=8.9) and mean HbA_{1c} of 7.9 (SD=1.5). Nine of ten participants had experienced severe hypoglycemic episodes in the year prior to transplant.
**Recipients with positive fasting C-peptide verified correct by center.

Exhibit 2 – 5
Recipient Autoantibodies at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Pre transplant autoantibody - GAD 65				
Positive	67	19.3	11	16.9
Negative	150	43.2	24	36.9
Unknown	109	31.4	24	36.9
Missing	21	6.1	6	9.2
Pre transplant autoantibody - IA-2				
Positive	48	13.8	1	1.5
Negative	111	32.0	29	44.6
Unknown	167	48.1	28	43.1
Missing	21	6.1	7	10.8
Pre transplant autoantibody - Insulin				
Positive	124	35.7	12	18.5
Negative	43	12.4	17	26.2
Unknown	159	45.8	30	46.2
Missing	21	6.1	6	9.2
Total number of positive autoantibodies				
None	64	18.4	17	26.2
One	111	32.0	14	21.5
Two	49	14.1	5	7.7
All Three	10	2.9	-	0.0
Unknown	92	26.5	23	35.4
Missing	21	6.1	6	9.2

Recipient autoantibody levels are highly regarded data; CITR encourages its collection for all islet transplant recipients.

Exhibit 2 – 6
Recipient Infectious Disease Testing at First Infusion

	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	347	100.0	65	100.0
HIV screening				
Positive	-	0.0	1	1.5
Negative	313	90.2	52	80.0
Not Done/Unknown/Missing	34	9.8	12	18.5
CMV IGG				
Positive	139	40.1	31	47.7
Negative	176	50.7	29	44.6
Not Done/Unknown/Missing	32	9.2	5	7.7
CMV IgM				
Positive	0	0.0	6	9.2
Negative	169	48.7	28	43.1
Not Done/Unknown/Missing	178	51.3	31	47.7
HepB core antibody				
Positive	4	1.2	2	3.1
Negative	259	74.6	42	64.6
Not Done/Unknown/Missing	84	24.2	21	32.3
HepB surface antigen				
Positive	2	0.6	1	1.5
Negative	319	91.9	58	89.2
Not Done/Unknown/Missing	26	7.5	6	9.2
HepC antibody				
Positive	-	0.0	2	3.1
Negative	315	90.8	58	89.2
Not Done/Unknown/Missing	32	9.2	5	7.7
EBV IgG				
Positive	285	82.1	56	86.2
Negative	27	7.8	3	4.6
Not Done/Unknown/Missing	35	10.1	6	9.2
EBV IgM				
Positive	30	8.6	7	10.8
Negative	138	39.8	36	55.4
Not Done/Unknown/Missing	179	51.6	22	33.8

Exhibit 2 – 7
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)	95	44.9	1.0	165	45.9	0.8	87	40.7	0.9	12	47.2	2.2	37	46.0	1.2	16	46.1	1.7
Duration of Diabetes (yrs)	95	29.1	1.2	165	28.8	0.9	87	26.5	1.1	12	33.6	4.1	37	33.2	1.4	16	32.3	1.4
Weight (kg)	95	63.8	1.1	162	67.3	0.8	79	67.6	1.1	11	59.7	2.9	36	60.4	1.6	14	65.2	1.8
Body Mass Index (kg/m2)	91	23.3	0.3	160	23.9	0.2	78	23.6	0.3	11	21.9	0.6	36	22.6	0.5	14	23.1	0.6
Daily insulin requirement	89	32.8	1.4	160	37.0	1.0	81	41.6	1.7	12	35.3	2.9	36	34.8	2.1	14	33.4	3.5
Average daily insulin / kg recipient body weight	89	0.5	<0.1	159	0.5	<0.1	78	0.6	<0.1	11	0.6	<0.1	36	0.6	<0.1	13	0.5	<0.1
Duration of intensive insulin therapy (yrs)	47	16.4	2.3	107	20.2	1.2	42	17.0	1.9	0	-	-	3	32.7	11.6	0	-	-
Number of days on wait list for first infusion	84	338.0	43.2	149	340.3	28.0	79	204.0	25.7	10	374.3	149.9	35	335.1	54.2	13	136.6	50.7
Fasting plasma glucose (mg/dL)	92	161.4	8.9	147	177.7	7.4	81	175.4	9.7	9	208.2	37.9	34	162.9	14.2	13	210.4	40.1
Basal C-Peptide (ng/mL)	86	0.1	<0.1	157	0.1	<0.1	82	0.1	<0.1	10	0.0	<0.1	34	0.1	<0.1	13	0.0	<0.1
HbA_{1C} (%)	89	7.5	0.1	157	7.7	0.1	83	7.9	0.1	10	7.9	0.4	35	8.0	0.2	14	7.6	0.3
Most recent PRA (%)	81	4.2	1.6	144	3.5	1.0	78	2.3	1.1	7	0.0	<0.1	30	2.0	1.5	8	0.0	<0.1
Peak PRA (%)	78	6.3	2.0	134	4.8	1.1	70	3.3	1.3	5	0.4	0.4	25	9.3	4.4	5	0.0	<0.1

Exhibit 2 – 8
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	23	24.2	66	40.0	38	43.7	5	41.7	10	27.0	9	56.3
Female	72	75.8	99	60.0	49	56.3	7	58.3	27	73.0	7	43.8
Pre transplant autoantibody - GAD 65												
Positive	15	15.8	34	20.6	18	20.7	1	8.3	7	18.9	3	18.8
Negative	39	41.1	76	46.1	35	40.2	5	41.7	13	35.1	6	37.5
Unknown	33	34.7	49	29.7	27	31.0	4	33.3	15	40.5	5	31.3
Missing	8	8.4	6	3.6	7	8.0	2	16.7	2	5.4	2	12.5
Pre transplant autoantibody - IA-2												
Positive	14	14.7	16	9.7	18	20.7	-	-	1	2.7	-	-
Negative	29	30.5	54	32.7	28	32.2	4	33.3	16	43.2	9	56.3
Unknown	44	46.3	89	53.9	34	39.1	5	41.7	18	48.6	5	31.3
Missing	8	8.4	6	3.6	7	8.0	3	25.0	2	5.4	2	12.5
Pre transplant autoantibody - Insulin												
Positive	27	28.4	65	39.4	32	36.8	4	33.3	6	16.2	2	12.5
Negative	13	13.7	22	13.3	8	9.2	-	-	12	32.4	5	31.3
Unknown	47	49.5	72	43.6	40	46.0	6	50.0	17	45.9	7	43.8
Missing	8	8.4	6	3.6	7	8.0	2	16.7	2	5.4	2	12.5
Total Number of Positive Autoantibodies												
None	16	16.8	32	19.4	16	18.4	2	16.7	9	24.3	6	37.5
One	29	30.5	56	33.9	26	29.9	3	25.0	8	21.6	3	18.8
Two	9	9.5	25	15.2	15	17.2	1	8.3	3	8.1	1	6.3
All Three	3	3.2	3	1.8	4	4.6	-	-	-	-	-	-
Unknown	30	31.6	43	26.1	19	21.8	4	33.3	15	40.5	4	25.0
Missing	8	8.4	6	3.6	7	8.0	2	16.7	2	5.4	2	12.5

Exhibit 2 – 9
Recipient Laboratory Values at First Infusion

	Islet Alone			Islet After Kidney		
	N	Mean	SE	N	Mean	SE
HbA_{1C} (%)	329	7.7	0.1	59	7.9	0.2
ALT (U/L)	307	22.5	0.6	57	28.4	1.9
AST (U/L)	320	25.4	1.0	58	30.6	2.2
Alkaline phosphatase (U/L)	317	77.5	2.1	56	123.9	12.9
Total bilirubin (mg/dL)	319	0.7	0.0	57	0.5	0.0
Total cholesterol (mg/dL)	327	172.3	1.7	56	187.7	5.2
HDL (mg/dL)	319	64.7	1.0	49	67.6	3.0
LDL (mg/dL)	313	94.0	1.5	47	98.6	3.9
Triglycerides (mg/dL)	327	68.9	2.0	55	95.3	5.4
Serum creatinine (mg/dL)	338	0.9	0.0	62	1.5	0.1
Calculated creatinine clearance (mL/min/1.73m2)	271	101.1	1.7	42	72.2	5.0
Basal C-Peptide (ng/mL)	325	0.1	0.0	57	0.1	0.0

Exhibit 2 – 10
Donor Demographics
All Allograft Donors

	Overall		
	N	**Mean**	**SD**
Age (yrs)	847*	43.7	12.6
	Overall		
	N		**%**
Total	905		100.0
Gender			
Male	493		54.5
Female	349		38.6
Unknown	10		1.1
Missing	53		5.9
Ethnicity			
Hispanic	53		5.9
Non Hispanic	474		52.4
Unknown**	324		35.8
Missing			
Race			
American Indian or Alaska Native	1		0.1
Asian	3		0.3
Black or African American	52		5.7
Indian Sub-Continent	2		0.2
Mideast or Arabian	-		0.0
Native Hawaiian or Other Pacific Islander	1		0.1
White	503		55.6
Unknown**	289		31.9
Missing	54		6.0

*Age was missing for 58 donors.
**Race and ethnicity are not collected or reported in some countries.

Exhibit 2 – 11
Donor Characteristics
All Allograft Donors

	Overall		
	N	**Mean**	**SD**
Weight (kg)	842	87.0	20.9
Height (m)	833	1.7	0.1
Body Mass Index(kg/m2)	833	29.1	6.5

	Overall	
	N	**%**
Total	905	100.0
Donor ABO blood group		
A	279	30.8
A1	46	5.1
A_1B	1	0.1
A_2	3	0.3
AB	13	1.4
B	47	5.2
O	465	51.4
Missing	51	5.6
History of hypertension		
Yes	259	28.6
No	496	54.8
Unknown	97	10.7
Missing	53	5.9
Hypertension duration		
0-5 years	97	37.5
6-10 years	23	8.9
>10 years	35	13.5
Unknown	101	39.0
Hypertension control-Diet		
Yes	27	10.4
No	55	21.2
Unknown	177	68.3

Exhibit 2 – 11 (continued)
Donor Characteristics
All Allograft Donors

	Overall	
	N	**%**
Hypertension control-Diuretics		
Yes	27	10.4
No	85	32.8
Unknown	147	56.8
Hypertension control-Other medications		
Yes	125	48.3
No	46	17.8
Unknown	88	34.0
History of alcohol dependency		
Yes	138	15.2
No	602	66.5
Unknown	110	12.2
Missing	55	6.1
Alcohol use in past 6 months		
Yes	73	52.9
No	27	19.6
Unknown	38	27.5
History of diabetes		
Yes	1	0.1
No	817	90.3
Unknown	32	3.5
Missing	55	6.1

Exhibit 2 – 12
Characteristics of Organ Procurement and Donor Cause of Death
All Allograft Donors

	Overall		
	N	Mean	SD
Time from admission to brain death (hrs)	573	50.5	65.1
Duration of cardiac arrest where cardiovascular death (mins)	79	15.9	12.2
Time from cross clamp to pancreas recovery (mins)	569	42.2	23.4
Cold ischemia time (hrs)	799	7.3	3.4
	Overall		
	N		%
Total	905		100.0
Cause of death			
Anoxia/cardiac arrest	41		4.5
CNS tumor	7		0.8
Cerebrovascular/stroke	466		51.5
Head trauma	254		28.1
Other	64		7.1
Missing	53		5.9
Unknown	20		2.2
Mechanism of death			
Asphyxiation	12		1.3
Blunt injury	115		12.7
Cardiovascular	30		3.3
Death from natural causes	6		0.7
Drowning	4		0.4
Drug intoxication	10		1.1
Gunshot wound	51		5.6
Intracranial hemorrhage/stroke	546		60.3
Seizure	3		0.3
None of the above	20		2.2
Unknown	55		6.1
Missing	53		5.9

Exhibit 2 – 13
Treatments Given to Donor During Hospitalization
All Allograft Donors

	Overall	
	N	%
Total	905	100.0
Vasopressors used*		
Epinephrine hydrochloride	51	5.6
Dobutamine hydrochloride	38	4.2
Dopamine hydrochloride	422	46.6
Norephinephrine bitartrate	367	40.5
Phenylephrine hydrochloride	192	21.2
Pitressin/DDAVP	287	31.7
Total number of vasopressors used		
None	45	5.0
One	276	30.5
Two	329	36.4
Three	146	16.1
Four	25	2.8
Five	2	0.2
Unknown	14	1.5
Missing	68	7.5

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

Exhibit 2 – 13 (continued)
Treatments Given to Donor During Hospitalization
All Allograft Donors

	Overall	
	N	**%**
Total	905	100.0
Transfusions given to donor during hospitalization		
0 units	511	56.5
0.5 units	172	19.0
6-10 units	39	4.3
>10 units	27	3.0
Unknown	89	9.8
Missing	67	7.4
Transfusions given to donor intraoperatively		
0 units	616	68.1
0.5 units	32	3.5
6-10 units	5	0.6
>10 units	2	0.2
Unknown	183	20.2
Missing	67	7.4
Steroids given to donor during hospitalization		
Yes	313	34.6
No	217	24.0
Unknown	309	34.1
Missing	66	7.3
Insulin given to donor during hospitalization		
Yes	295	32.6
No	438	48.4
Unknown	114	12.6
Missing	58	6.4

Exhibit 2 – 14
Donor Serology
All Allograft Donors

	N	%
Total	905	100.0
Anti HIV I/II		
Positive	-	0.0
Negative	833	92.0
Not Done/Unknown/Missing	72	8.0
Anti HTLV I/II		
Positive	-	0.0
Negative	775	85.6
Not Done/Unknown/Missing	130	14.4
RPR VDRL		
Positive	1	0.1
Negative	748	82.7
Not Done/Unknown/Missing	156	17.2
Anti CMV		
Positive	444	49.1
Negative	365	40.3
Not Done/Unknown/Missing	96	10.6
HBsAg		
Positive	-	0.0
Negative	824	91.0
Not Done/Unknown/Missing	81	9.0
Anti HBC		
Positive*	1	0.1
Negative	811	89.6
Not Done/Unknown/Missing	93	10.3
Anti HCV		
Positive	-	0.0
Negative	821	90.7
Not Done/Unknown/Missing	84	9.3

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

Exhibit 2 – 15
Donor Laboratory Data
All Allograft Donors

	N	Mean	SD
Serum creatinine (mg/dL)	716	1.1	0.7
BUN (mg/dL)	562	15.2	8.7
Total bilirubin (mg/dL)	599	0.9	0.8
AST (IU/L)	615	73.0	198.4
ALT (IU/L)	616	58.2	160.1
Serum lipase (IU/L)	651	73.7	127.3
Serum amylase (IU/L)	701	169.4	388.7
Minimum pre-insulin blood glucose (mg/dL)	724	127.1	38.9
Maximum blood glucose (mg/dL)	713	234.5	87.9
HbA_{1C} (%)	158	5.5	0.5

Exhibit 2 – 16
Organ Crossmatch Results
All Allograft Donors

	Overall	
	N	%
Crossmatch for T-Cell		
Positive	3	0.3
Negative	518	57.2
Unknown	303	33.5
Missing	81	9.0
Crossmatch for B-Cell		
Positive	18	2.0
Negative	427	47.2
Unknown	379	41.9
Missing	81	9.0

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 procedure data reported on islet alone and IAK participants. Only pancreata used for clinical islet transplantation are included in this report. Exhibits in this section include data for all pancreata processed for islet cell allografts or all islet allograft infusions where applicable.

In about 63% of the 905 procedures reported, 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 were the most common (85%) methods used for pancreas preservation (Exhibit 3-1). Other preservation solutions used in conjunction or in absence of UW and/or PFC included HTK, Eurocollins, Celsoir, IGL-1, SCOT and ET-Kyoto 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 (77%) followed by NB1 (18%, Exhibit 3-1). All of the pancreata processed used a density gradient for islet purification. Fifty-four percent of islets were placed in culture, defined as six or more hours in any specially prepared nutrient medium. When cultured, the median culture time was 27 hours (range 6 to 96) (Exhibit 3-2). Of the 905 preparations reported to CITR, thirteen final preparations showed a positive aerobic culture (1.7%), five showed a positive anaerobic culture (0.8%), four showed a positive fungal culture (0.5%), and one preparation tested positive for mycoplasma (0.2%).

Exhibit 3-5 shows the islet cell characteristics by pancreas preservation method.

Significant univariate correlations of islet product characteristics with donor, recovery, and processing characteristics are located in Exhibits 3-6 (boxplots of continuous variables by discrete ones) and 3-7 (correlations between continuous variables). These results are described more thoroughly in a focus analysis currently in development. The results require further characterization with multivariate methods.

Islet Infusion Information

Exhibit 3-4A summarizes the core infusion procedure characteristics overall and Exhibit 3-4B by the infusion number. The mean number of islet equivalents infused was lower for the second infusion compared to the first infusion. On average, second infusions occurred 28 weeks following the first infusion, while those receiving a third infusion received this infusion 81 weeks after their initial one and 69 weeks after their second infusion.

Portal pressures did not differ by infusion sequence (Exhibits 3-8A-D). Change from pre-infusion to closure averaged 2-3 mmHg for all infusions.

Exhibit 3 – 1
Pancreas Procurement and Islet Processing

	N	%	% of Known
Total	905	100.0	100.0
Pancreas procurement team			
Unrelated to processing/infusion team	507	56.0	63.2
Related to processing/infusion team	295	32.6	36.8
Unknown	26	2.9	
Missing	75	8.38.5	
Islet processing/testing center			
Same location as infusion center	756	83.5	91.1
Other location than infusion center	74	8.2	8.9
Missing	75	8.3	
Pancreas Preservation			
UW	458	50.6	55.5
Two Layer	241	26.6	29.2
UW followed by Two Layer	28	3.1	3.4
Neither UW nor Two Layer	98	10.8	11.9
Missing	80	8.8	
Other preservation solutions used*			
HTK	88	9.7	10.7
Eurocollins	12	1.3	1.5
Celsior	13	1.4	1.6
IGL-1	8	0.9	1.0
SCOT	1	0.1	0.1
ET-Kyoto	1	0.1	0.1
Collagenase Type			
Liberase HI	645	71.3	76.8
NB1	152	16.8	18.1
Blandzyme	63	7.0	7.5
Collagenase P	8	0.9	1.0
Missing	67	7.4	
Islet purification			
Density gradient	829	91.6	100.0
Missing	76	8.4	

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

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

	N	%	% of Known
Islet pretreatment			
None	380	42.0	45.9
Culture**	448	49.5	54.1
Missing	77	8.5	
Gram stain			
Positive	0	0.0	0.0
No organism seen	712	78.7	100.0
Unknown	126	13.9	
Missing	67	7.4	
Aerobic culture			
Positive	13	1.4	1.7
No Growth	758	83.8	98.3
Unknown	55	6.1	
Not Done	5	0.6	
Missing	74	8.2	
Anaerobic culture			
Positive	5	0.6	0.8
No Growth	605	66.9	99.2
Unknown	142	15.7	
Not Done	78	8.6	
Missing	75	8.3	
Fungal Culture			
Positive	4	0.4	0.5
No Growth	757	83.6	99.5
Unknown	47	5.2	
Not Done	23	2.5	
Missing	74	8.2	
Mycoplasma			
Positive	1	0.1	0.2
Negative	488	53.9	99.8
Unknown	40	4.4	
Not Done	306	33.8	
Missing	70	7.7	

**Culture is defined as ≥ 6 hrs spent in a specially prepared nutrient medium.
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)	547	43.9	22.3	40.0	3.0	188.0
Duration of cold ischemia (hrs)	799	7.3	3.4	6.8	1.0	27.0
Time from brain death to pancreas recovery (hrs)	543	20.2	11.4	18.0	1.0	91.0
Culture time (hrs)	448	29.8	16.6	27.0	6.0	95.8

Time of brain death is defined as the physician-confirmed time documented in the medical chart. Time of cross clamp is defined as the time of aorta cross-clamp prior to organ retrieval. Duration of cold ischemia is defined as the time from pancreas placement in cold preservation solution to the heating up of the organ at the start of the digestion process. Culture is defined as $\geq$ 6 hrs spent in a specially prepared nutrient medium. Islet preparations placed in a nutrient medium for less than six hours (N=109) are not defined as "cultured."

Exhibit 3 – 3
Islet Equivalents and Timing of Count

	Total Islet Equivalents ($x10^3$)					
	N	Mean	SD	Median	Min	Max
Islet equivalents (IEQ) measured at:						
Post Digestion	9	617	307	580	260	1,122
Post Purification (Pre culture)	403	384	156	355	85	973
Post Culture	294	385	160	370	54	1,080

Exhibit 3-3 represents the total Islet Equivalents (IEQs x 10^3) measured from each individual pancreas at specified times of the count (eg., Post Digestion). Multiple pancreata are sometimes used for a single infusion procedure and will account for some of the counts in this Exhibit to be <100 x 10^3 IEQs.

Exhibit 3 – 4A
Islet Product Characterization

	N	Mean	SD	Median	Min	Max
Total cell volume (mL)	805	3.5	2.1	3.0	0.1	16.0
Islet particle count ($x10^3$)	683	364	158	341	63	996
Embedded islets (%)	492	16.0	19.4	9.5	0.0	95.0*
Islet equivalents ($x10^3$)	721	388	162	361	54	1,122
Islet equivalents/kg donor weight ($x10^3$)	700	4.62	1.92	4.35	0.72	17.0
Beta cells ($x10^6$)	266	21	179	166	4*	947
Beta cells ($x10^6$) / kg donor weight	256	2.8	3.1	2.1	0.0	37.8
Insulin content (micrograms $x10^3$)	295	3.2	2.1	2.9	0.2	9.9
DNA content (micrograms** $x10^3$)	317	8.0	9.5	5.3	0.8*	89.1
Endotoxin units	677	23.4	53.2	5.0	0.0	540.6*
Endotoxin units/kg donor weight	659	0.3	0.6	0.1	0.0	6.6
Islet purity: Dithizone positive cells (%)	734	63.3	17.6	63.0	10.0	100.0*
Islet potency: Stimulation index	710	3.3	3.3	2.2	0.1	28.8

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

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

Islet viability data is not shown. Data quality is being assessed.

Exhibit 3 – 4B
Islet Product and Infusion Characteristics by Infusion Sequence

	Islet Alone								
	1			2			3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Islet Equivalents Infused ($x10^3$)	334	447	155	234	415	164	77	412	160
Islet Equivalents Infused ($x10^3$) / kg recipient body weight	330	6.8	2.53	223	6.45	2.58	74	6.50	2.79
Embedded islets (%)	212	14.9	17.9	162	16.6	19.3	51	18.3	21.2
Cell volume (mL)	302	4.1	2.2	218	3.7	1.9	74	3.4	1.8
Time since first infusion (weeks)	0	-	-	252	27.8	42.1	87	81.4	97.1
Time since second infusion (weeks)	0	-	-	0	-	-	87	69.0	96.6
	Islet after Kidney								
	1			2			3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Islet Equivalents Infused ($x10^3$)	61	429	153	46	407	143	13	330	104
Islet Equivalents Infused ($x10^3$) / kg recipient body weight	59	7.11	2.73	43	7.00	2.94	11	5.163	1.56
Embedded islets (%)	12	15.8	16.7	12	11.8	13.3	3	37.0	23.1
Cell volume (mL)	44	4.2	2.6	40	4.2	2.6	11	4.6	1.4
Time since first infusion (weeks)	0	-	-	53	19.7	24.5	16	53.2	65.6
Time since second infusion (weeks)	0	-	-	0	-	-	16	38.3	63.7

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

	Pancreas Preservation Method						
	UW Only			Two Layer Only			Statistically Significant at p<0.05
	N	Mean	SE	N	Mean	SE	
Total cell volume	406	3.6	0.1	228	3.4	0.1	
Islet particle count (x10^3)	363	363	7.50	180	343	11.6	
Embedded islets (%)	252	15.2	1.2	120	17.5	1.9	
Islet equivalents (x10^3)	377	385	7.67	182	378	12.7	
Islet equivalents/kg donor weight (x10^3)	363	4.67	0.10	180	4.34	0.13	✓
Beta cells (X10E6)	152	185.9	14.4	83	236.7	20.3	✓
Beta cells (X10E6) / kg donor weight	143	2.7	0.3	82	2.8	0.2	
Insulin content (micrograms x10^3)	181	3.3	0.16	91	3.2	0.20	
DNA content (micrograms x10^3)*	185	6.8	0.66	95	10.6	1.15	✓
Endotoxin units	340	24.8	3.2	192	28.8	3.8	
Endotoxin units/kg donor weight	328	0.3	<0.1	191	0.3	<0.1	
Islet purity: Dithizone positive cells (%)	360	64.6	1.0	219	62.1	1.2	
Islet potency: Stimulation index	380	3.3	0.2	196	3.2	0.2	

*Method of measurement unspecified.

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Exhibit 3 – 6
Significant Relationships (p<0.05) between Islet Outcomes and Categorical Predictors
Univariate Analysis

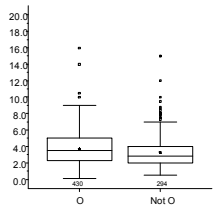
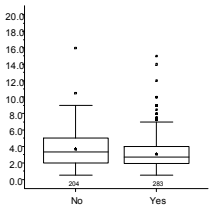
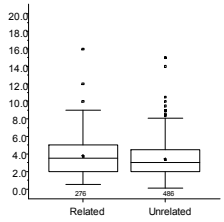
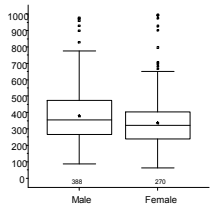
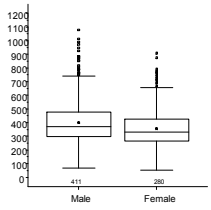
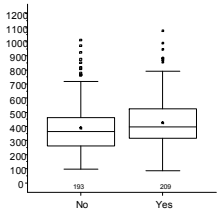
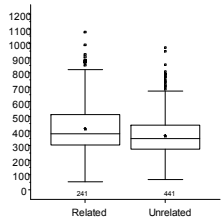
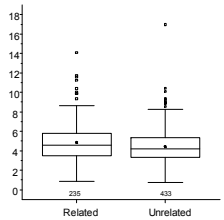
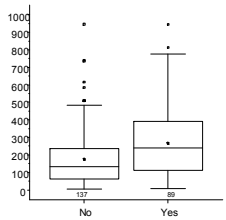
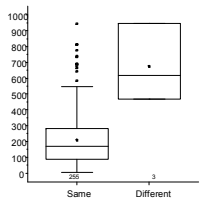
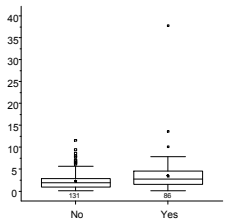
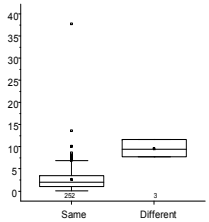
	Donor Gender	Blood Group	Donor Given Steroids	Donor Given Insulin	Procure/Infusion Teams	Processing/ Infusion Teams
Cell Volume (mL)						
Islet Count (x10^3)						
IEQs (x10^3)						
IEQs/kg donor						
Beta Cells (x10E6)						
Beta Cells (x10E6)/kg						

Exhibit 3 – 6 (continued)
Significant Relationships (p<0.05) between Islet Outcomes and Categorical Predictors
Univariate Analysis

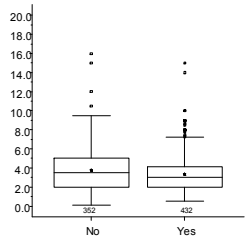
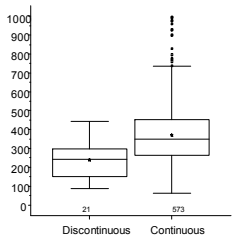
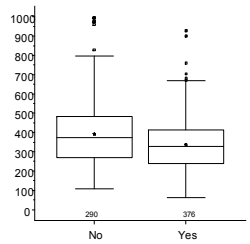
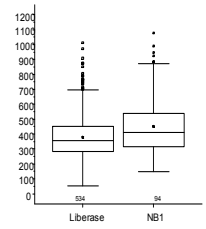
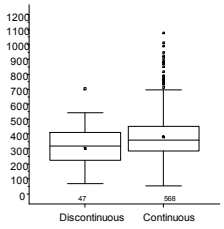
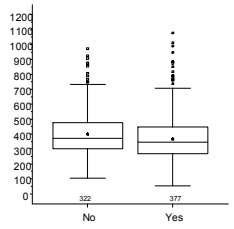
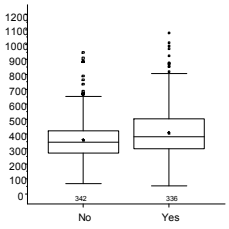
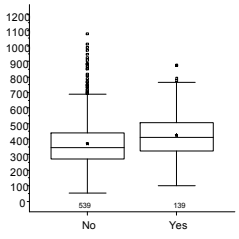
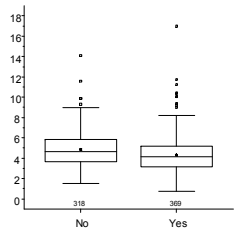
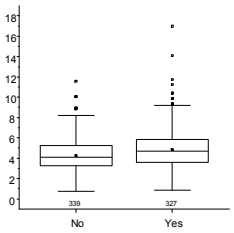
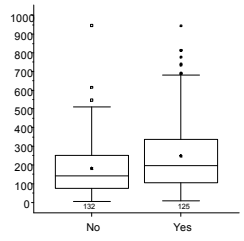
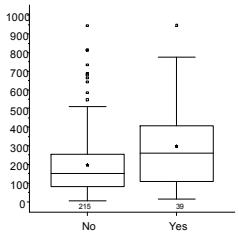
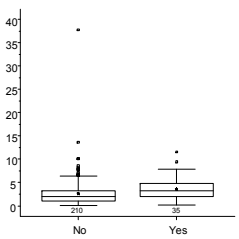
	Collagenase	Density Gradient Type	Islets Cultured	Donor Given Dopamine	Donor Given Phenylephrine
Cell Volume (mL)					
Islet Count (x10^3)					
IEQs (x10^3)					
IEQs/kg donor					
Beta Cells (x10E6)					
Beta Cells (x10E6)/kg					

Exhibit 3 – 6 (continued)
Significant Relationships (p<0.05) between Islet Outcomes and Categorical Predictors
Univariate Analysis

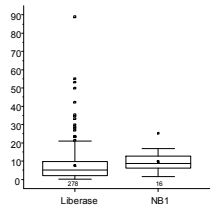
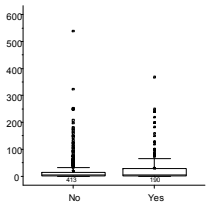
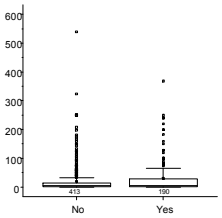
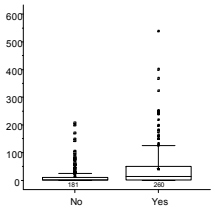
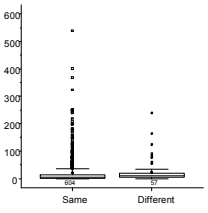
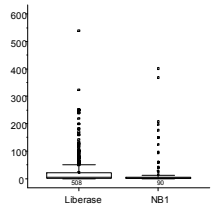
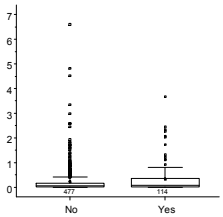
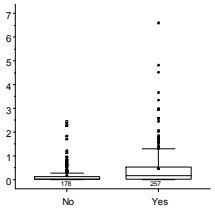
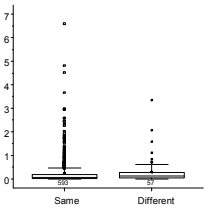
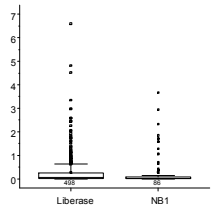
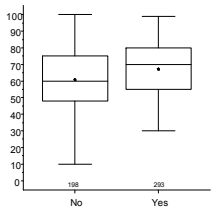
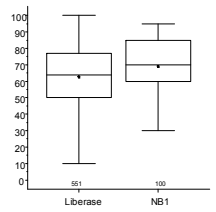
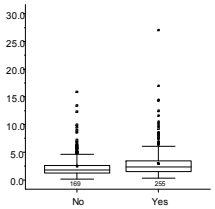
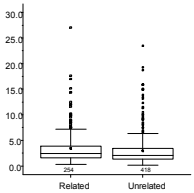
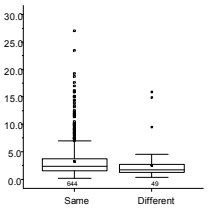
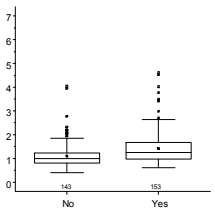
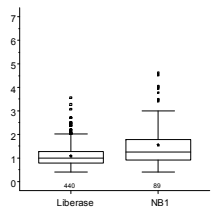
	Donor Alcohol Dependence	Pre-op Blood Transfusion	Donor Given Steroids	Procure/Infusion Teams	Processing/ Infusion Teams	Collagenase
DNA content (micrograms)						
Endotoxin Units						
Endotoxin Units/kg donor						
Dithizone Positive Cells (%)						
Stimulation Index						
IEQs/Islet Count						

Exhibit 3 – 6 (continued)
Significant Relationships (p<0.05) between Islet Outcomes and Categorical Predictors
Univariate Analysis

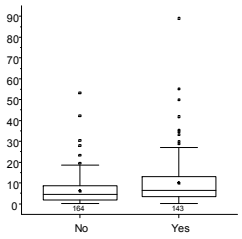
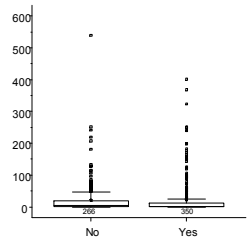
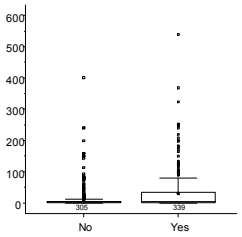
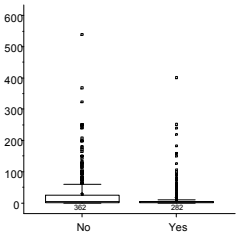
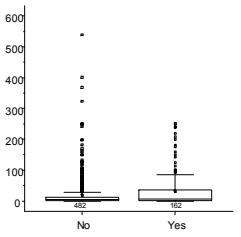
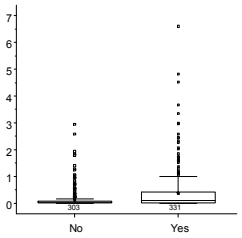
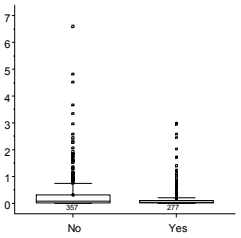
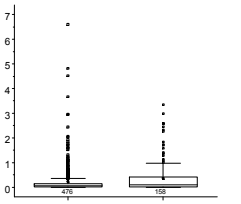
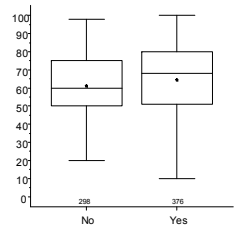
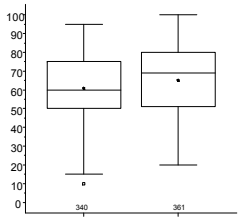
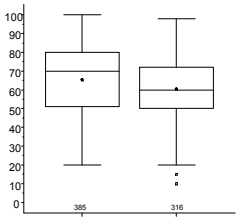
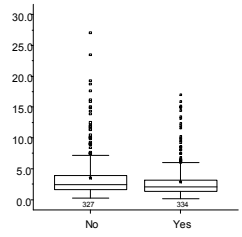
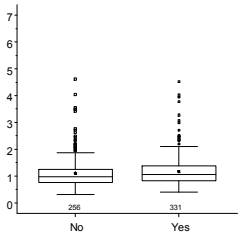
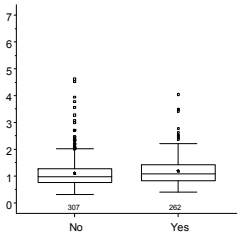
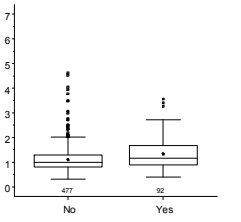
	Pulmozyme Use	Islets Cultured	Donor Given Dopamine	Donor Given Norephinephrine	Donor Given Phenylephrine
DNA content (micrograms)					
Endotoxin Units					
Endotoxin Units/kg donor					
Dithizone positive Cells (%)					
Stimulation Index					
IEQs/Islet Count					

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

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations								
		Total Cell Volume	**Embedded Islets**	**Islet Particle Count**	**Islet Equivalents**	**Islet Equivalents/kg Donor**	**Endotoxin Units**	**Endotoxin Units/kg donor**
Donor Age	r p N	-0.15196 <.0001 782	**-0.24826** **<.0001** **477**	0.03489 0.3694 664	-0.09135 0.0159 697	-0.05416 0.1559 688	-0.01536 0.6950 654	-0.00925 0.8143 648
Donor Weight (kg)	r p N	0.11501 0.0013 776	0.02031 0.6609 469	0.12778 0.0010 658	**0.35994** **<.0001** **691**	**-0.21884** **<.0001** **691**	0.15381 <.0001 650	0.04025 0.3056 650
Donor Height (cm)	r p N	0.09638 0.0076 767	0.00586 0.9003 460	0.16302 <.0001 650	0.16829 <.0001 682	-0.08982 0.0190 682	-0.01294 0.7429 645	-0.06229 0.1140 645
Donor Body Surface Area	r p N	0.12557 0.0005 767	0.02197 0.6384 460	0.14579 0.0002 650	**0.35166** **<.0001** **682**	**-0.20846** **<.0001** **682**	0.13010 0.0009 645	0.01999 0.6124 645
Donor Body Mass Index (kg/m2)	r p N	0.05850 0.1055 767	0.01089 0.8159 460	0.05094 0.1946 650	**0.31063** **<.0001** **682**	-0.17702 <.0001 682	0.16615 <.0001 645	0.06971 0.0769 645
Donor Minimum Pre-Insulin Blood Glucose Level (mg/dL)	r p N	-0.00268 0.9444 679	0.05204 0.3053 390	-0.02044 0.6269 568	-0.06553 0.1106 594	-0.04075 0.3264 582	0.02450 0.5601 568	0.03883 0.3599 558
Donor Maximum Blood Glucose Level (mg/dL)	r p N	0.00244 0.9503 655	-0.00547 0.9173 363	0.01551 0.7181 544	0.10167 0.0151 571	0.08125 0.0547 560	0.16665 <.0001 580	0.17903 <.0001 570
Donor HbA_{1c} (%)	r p N	0.11010 0.1784 151	0.09643 0.4559 62	-0.00562 0.9480 137	0.07945 0.3579 136	-0.02003 0.8169 136	0.01025 0.9033 143	-0.03122 0.7113 143
Donor Serum creatinine (mg/dL)	r p N	0.05908 0.1286 663	0.04683 0.3750 361	0.07499 0.0795 548	**0.20864** **<.0001** **578**	0.04084 0.3278 576	0.04685 0.2559 590	0.01711 0.6789 588
Donor BUN (mg/dL)	r p N	0.06566 0.1379 512	0.02347 0.7341 212	0.01965 0.6960 398	0.10225 0.0347 427	0.01135 0.8153 426	-0.01899 0.6837 463	-0.03319 0.4767 462
Donor Total bilirubin (mg/dL)	r p N	0.05829 0.1734 547	0.07926 0.2117 250	0.01242 0.7969 432	0.12631 0.0066 462	0.00032 0.9945 461	0.04167 0.3549 495	0.02519 0.5765 494
Donor AST (IU/L)	r p N	0.03530 0.4031 563	0.05199 0.3992 265	-0.02651 0.5757 448	0.00985 0.8299 478	0.02527 0.5824 476	0.01776 0.6878 514	0.01549 0.7266 512
Donor ALT (IU/L)	r p N	0.02927 0.4883 563	-0.03885 0.5289 265	0.02525 0.5940 448	0.10710 0.0192 478	0.07789 0.0896 476	0.03044 0.4910 514	0.01769 0.6897 512

The rank correlation coefficient (r) measures the strength of a rank relationship between two variables.
Negative values represent an inverse correlation.
Notable results (|r| > 0.20 and p <0.01) are highlighted.

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

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations								
		Total Cell Volume	**Embedded Islets**	**Islet Particle Count**	**Islet Equivalents**	**Islet Equivalents/kg Donor**	**Endotoxin Units**	**Endotoxin Units/kg donor**
Donor Serum lipase (IU/L)	r p N	0.03545 0.3844 604	-0.06280 0.2510 336	0.02238 0.6209 491	0.04859 0.2678 522	0.05306 0.2275 519	0.04500 0.2993 534	0.03590 0.4086 532
Donor Serum amylase (IU/L)	r p N	0.03720 0.3440 649	-0.00459 0.9313 356	-0.02470 0.5686 535	-0.06437 0.1268 564	-0.02861 0.4985 562	-0.05837 0.1662 564	-0.05499 0.1926 563
Time from cross clamp to pancreas recovery (mins)	r p N	-0.01391 0.7531 514	-0.04085 0.4876 291	0.04397 0.3664 424	-0.18538 <.0001 458	-0.14968 0.0013 457	**-0.25601 <.0001 444**	**-0.25552 <.0001 443**
Time from brain death to pancreas recovery (hrs)	r p N	-0.03679 0.4169 489	-0.07255 0.2288 277	-0.03098 0.5372 399	0.16133 0.0007 436	0.00732 0.8790 435	0.12454 0.0099 428	0.10031 0.0383 427
Duration of cardiac arrest (mins)	r p N	-0.02134 0.5830 664	0.09814 0.0510 396	-0.02343 0.5790 563	-0.01184 0.7751 585	0.00557 0.8934 581	0.00394 0.9260 557	0.01275 0.7644 555
Cold ischemic time (hrs)	r p N	-0.10924 0.0027 751	-0.11564 0.0134 457	0.04062 0.2989 656	-0.00273 0.9439 668	-0.00502 0.8984 650	0.02904 0.4633 640	0.01706 0.6703 625
Culture time (hrs)	r p N	-0.13679 0.0044 432	-0.00921 0.8809 267	0.01311 0.7999 376	0.09342 0.0700 377	0.04071 0.4356 369	**0.24558 <.0001 380**	**0.26263 <.0001 372**

The rank correlation coefficient (r) measures the strength of a rank relationship between two variables.
Negative values represent an inverse correlation.
Notable results (|r| > 0.20 and p <0.01) are highlighted.

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

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations								
		Total Beta Cells*	**Beta Cells/kg donor***	**Insulin Content**	**DNA Content**	**Islet purity: Dithizone positive cells**	**Islet potency: Stimulation index**	**IEQ to Islet Particle Number ratio**
Donor Age	r p N	-0.12125 0.0522 257	-0.09238 0.1420 254	-0.00923 0.8765 286	-0.14988 0.0088 305	0.00267 0.9433 712	-0.07057 0.0647 686	-0.14428 0.0005 585
Donor Weight (kg)	r p N	0.03242 0.6064 255	**-0.20640** **0.0009** **255**	0.04570 0.4429 284	-0.03597 0.5321 304	0.07199 0.0554 709	0.05787 0.1308 683	**0.21106** **<.0001** **579**
Donor Height (cm)	r p N	-0.06579 0.2982 252	-0.16968 0.0069 252	0.09282 0.1206 281	-0.01060 0.8547 301	0.03039 0.4212 703	0.07238 0.0594 679	-0.01164 0.7814 571
Donor Body Surface Area	r p N	0.00975 0.8776 252	**-0.21817** **0.0005** **252**	0.06856 0.2520 281	-0.03326 0.5654 301	0.06633 0.0789 703	0.06989 0.0687 679	0.18633 <.0001 571
Donor Body Mass Index (kg/m2)	r p N	0.05285 0.4035 252	-0.14876 0.0181 252	0.02905 0.6278 281	-0.03971 0.4925 301	0.08801 0.0196 703	0.04001 0.2978 679	**0.24882** **<.0001** **571**
Donor Minimum Pre-Insulin Blood Glucose Level (mg/dL)	r p N	-0.08666 0.1913 229	-0.03653 0.5900 220	0.02923 0.6338 268	-0.01042 0.8639 273	0.01406 0.7259 624	0.05097 0.2068 615	-0.01910 0.6726 492
Donor Maximum Blood Glucose Level (mg/dL)	r p N	0.17925 0.0115 198	0.17440 0.0161 190	-0.03553 0.5960 225	-0.01791 0.7812 243	0.02402 0.5461 634	-0.00297 0.9426 589	0.05443 0.2404 467
Donor HbA_{1c} (%)	r p N	0.10460 0.4224 61	-0.03452 0.7917 61	0.08715 0.5006 62	-0.04957 0.6644 79	-0.04196 0.6090 151	**-0.22042** **0.0086** **141**	0.04559 0.6108 127
Donor Serum creatinine (mg/dL)	r p N	0.07018 0.3617 171	0.01864 0.8088 171	-0.01180 0.8690 198	0.08448 0.2152 217	0.03635 0.3525 656	0.05035 0.2248 583	0.15346 0.0009 469
Donor BUN (mg/dL)	r p N	-0.02580 0.8093 90	-0.02509 0.8144 90	-0.02997 0.7321 133	0.00429 0.9606 135	-0.02824 0.5214 518	0.09865 0.0346 459	0.08679 0.1219 319
Donor Total bilirubin (mg/dL)	r p N	0.21350 0.0265 108	0.18734 0.0522 108	0.19885 0.0218 133	0.02417 0.7668 153	0.02861 0.5019 553	0.11629 0.0102 487	0.09066 0.0890 353
Donor AST (IU/L)	r p N	-0.02765 0.7743 110	-0.03483 0.7179 110	0.12430 0.1479 137	0.06048 0.4532 156	-0.04750 0.2584 568	-0.01364 0.7596 506	0.05068 0.3317 369
Donor ALT (IU/L)	r p N	0.01325 0.8892 113	-0.00524 0.9561 113	0.09650 0.2567 140	-0.01027 0.8977 159	0.05916 0.1595 567	0.05942 0.1816 507	0.07690 0.1404 369

*Method of measurement unspecified.
The rank correlation coefficient (r) measures the strength of a rank relationship between two variables.
Negative values represent an inverse correlation.
Notable results (|r| > 0.20 and p <0.01) are highlighted.

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

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations								
		Total Beta Cells*	**Beta Cells/kg donor***	**Insulin Content**	**DNA Content**	**Islet purity: Dithizone positive cells**	**Islet potency: Stimulation index**	**IEQ to Islet Particle Number ratio**
Serum lipase IU (mg/dL)	r p N	-0.09639 0.2071 173	-0.09504 0.2149 172	0.05193 0.4641 201	0.01564 0.8192 216	0.03182 0.4487 569	0.05535 0.1970 545	0.06382 0.1944 415
Serum amylase IU (mg/dL)	r p N	-0.09733 0.2027 173	-0.07977 0.2982 172	0.04356 0.5372 203	0.00965 0.8874 218	-0.02862 0.4766 621	0.01208 0.7734 570	-0.06009 0.1998 457
Time from cross clamp to pancreas recovery (mins)	r p N	-0.03919 0.6045 177	-0.06297 0.4050 177	-0.00536 0.9412 192	-0.00403 0.9543 205	-0.14229 0.0016 490	0.05633 0.2295 457	**-0.20631** **<.0001** **372**
Time from brain death to pancreas recovery (hrs)	r p N	0.09338 0.2300 167	0.05473 0.4824 167	-0.10050 0.1820 178	-0.07299 0.3169 190	**0.23346** **<.0001** **466**	0.10458 0.0285 439	0.16420 0.0021 350
Duration of cardiac arrest (mins)	r p N	0.14887 0.0236 231	0.14033 0.0338 229	-0.12794 0.0433 250	0.10157 0.0964 269	-0.00967 0.8127 603	-0.02640 0.5226 589	-0.00065 0.9886 493
Cold ischemic time (hrs)	r p N	-0.09768 0.1126 265	-0.08252 0.1890 255	0.00415 0.9442 288	-0.07564 0.1870 306	0.04324 0.2588 684	0.02838 0.4613 676	-0.06055 0.1453 580
Culture time (hrs)	r p N	**0.22510** **0.0116** **125**	0.19815 0.0268 125	-0.17357 0.0539 124	0.13529 0.1072 143	0.11748 0.0150 428	0.12181 0.0191 370	0.15776 0.0040 331

*Method of measurement unspecified.
The rank correlation coefficient (r) measures the strength of a rank relationship between two variables.
Negative values represent an inverse correlation.
Notable results (|r| > 0.20 and p <0.01) are highlighted.

Exhibit 3 – 8A
Pre Infusion Portal Pressure by Infusion Sequence

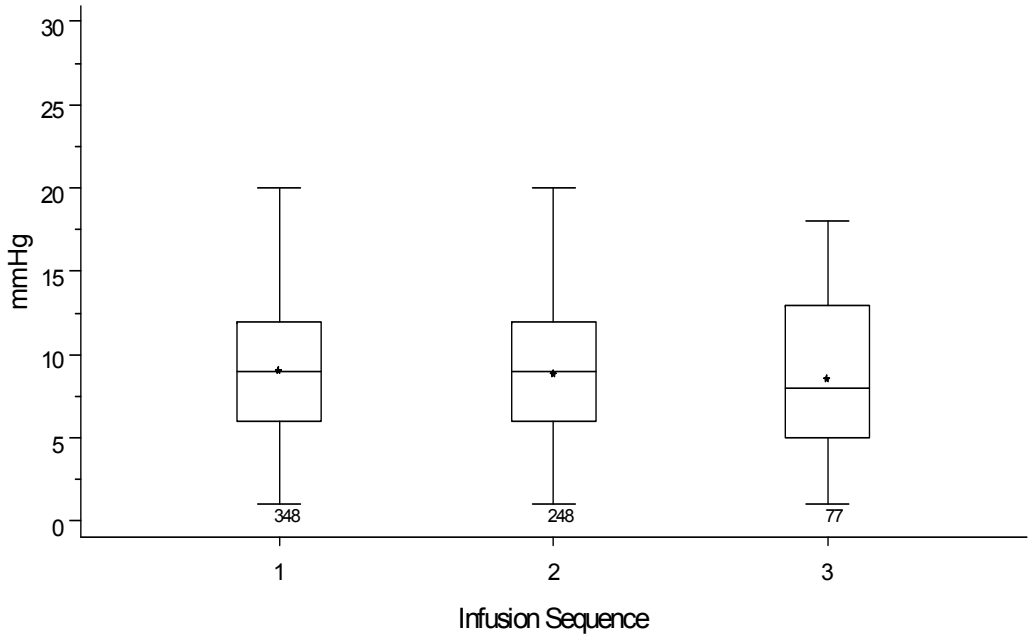


Exhibit 3 – 8B
Peak Portal Pressure by Infusion Sequence

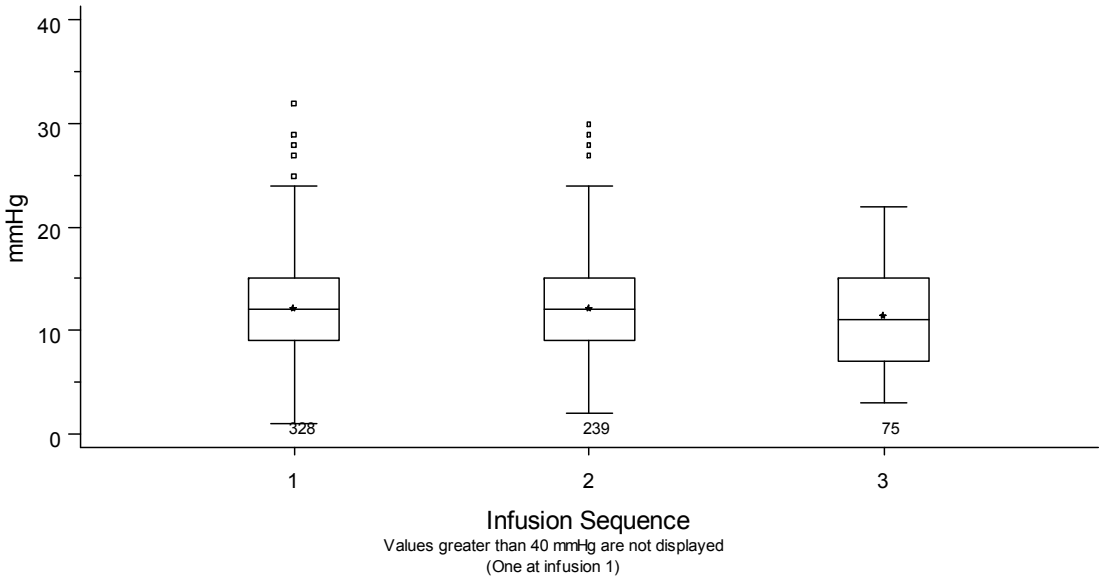


Exhibit 3 – 8C
Closure Portal Pressure by Infusion Sequence

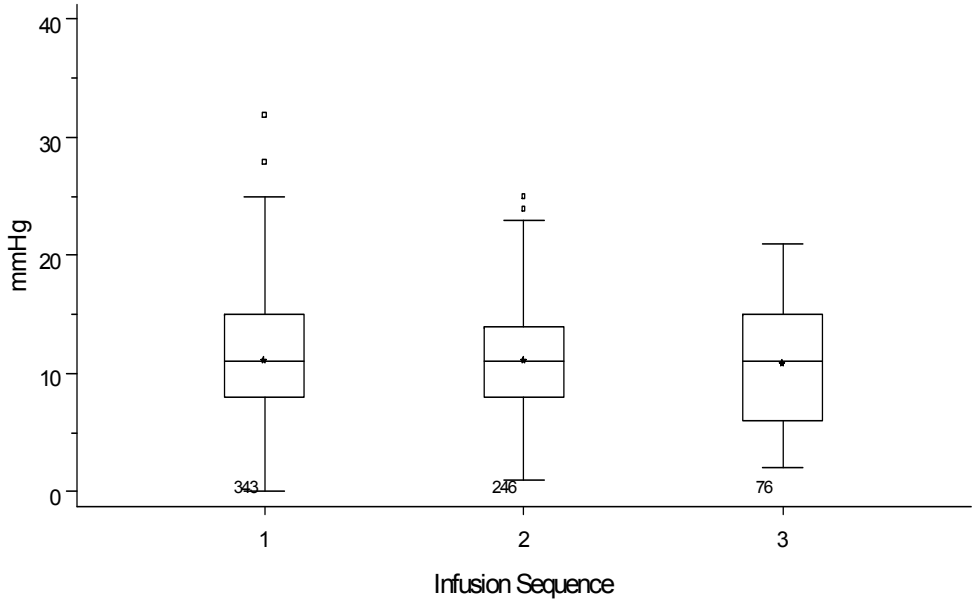


Exhibit 3 – 8D
Change from Pre Infusion to Closure Portal Pressure by Infusion Sequence

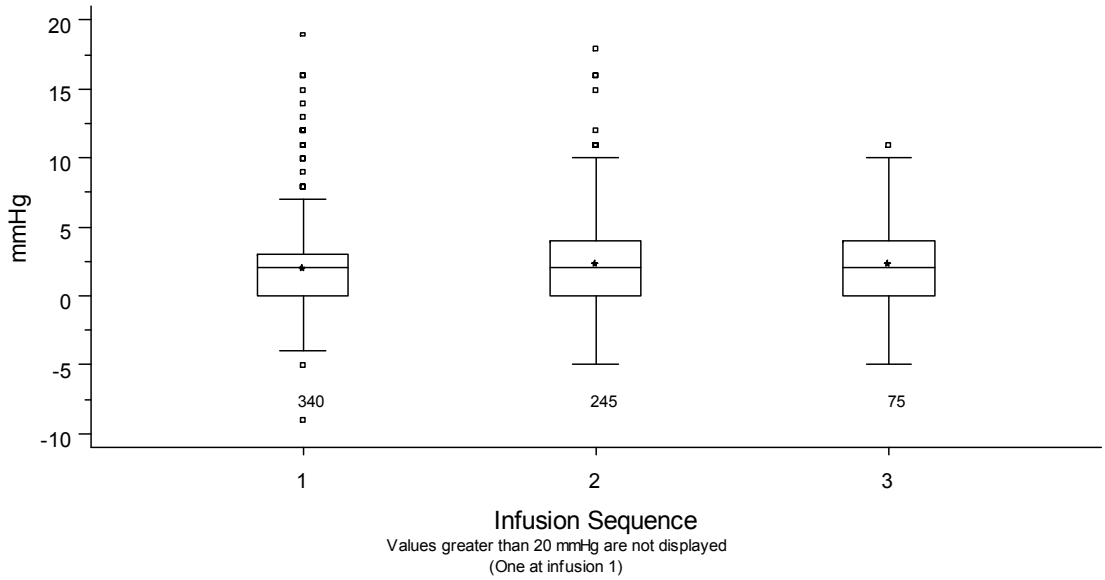


Exhibit 3 – 8E
Change from Pre Infusion to Peak Portal Pressure by Infusion Sequence

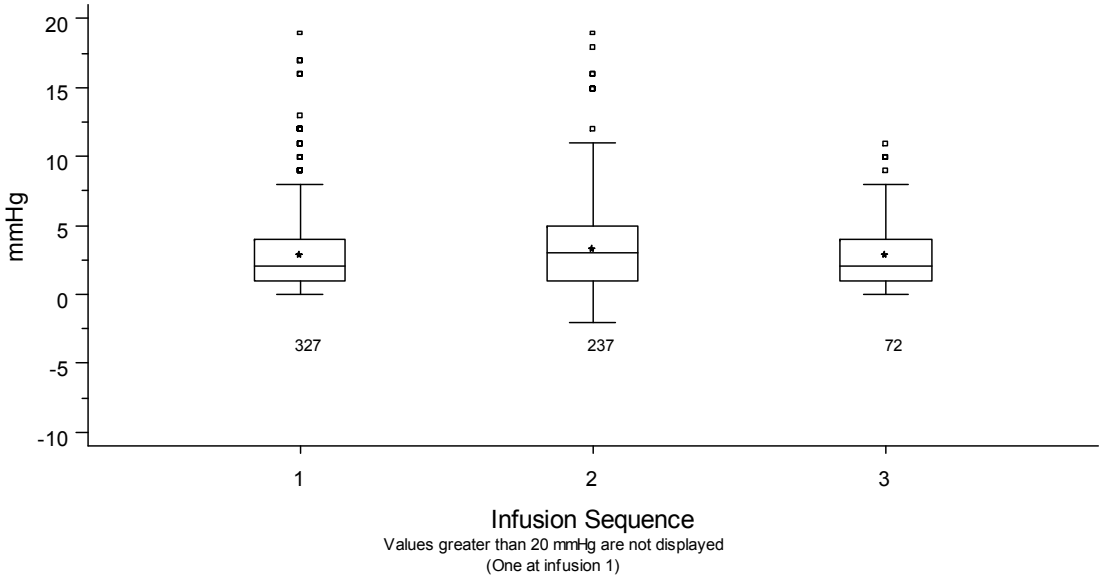
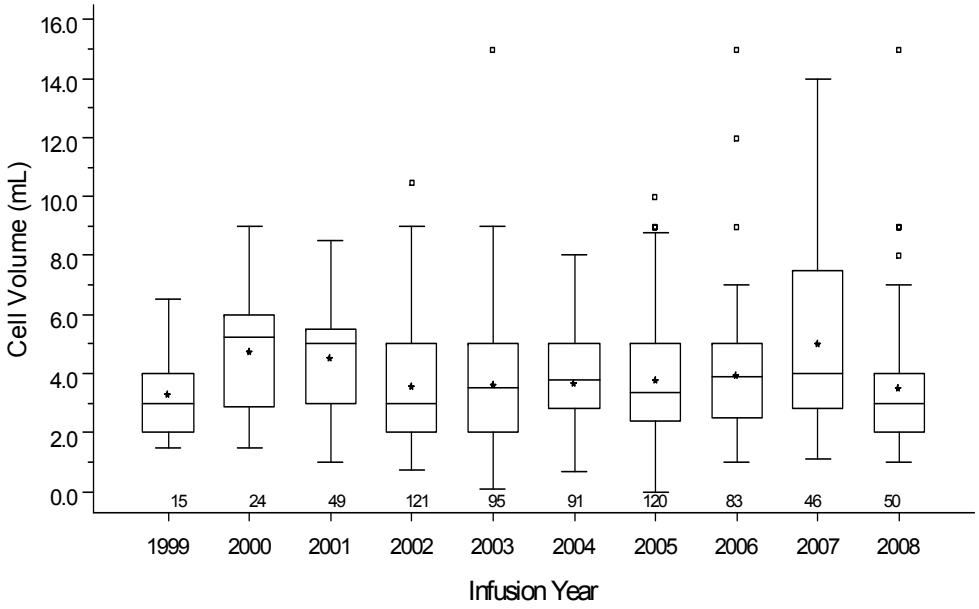
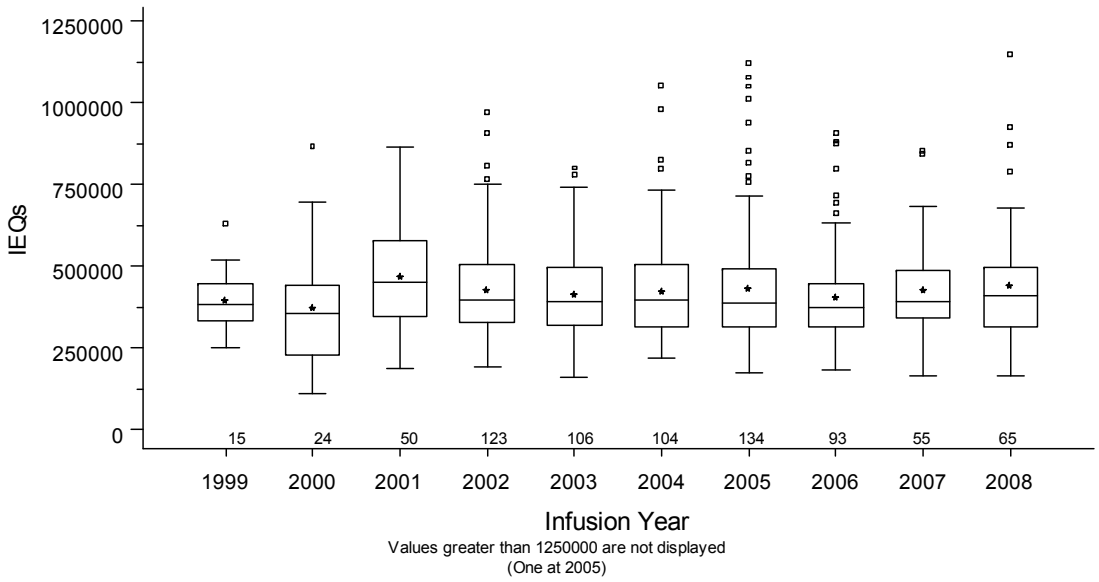


Exhibit 3 – 9
Cell Volume Infused per Infusion by Infusion Year



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

Exhibit 3 – 10
IEQs 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 following table classifies the induction and maintenance therapies used in CITR allograft recipients. Multiple induction and maintenance agents may have been administered peri- and post- several infusions in the same recipient.

Category	Medications Included
Polyclonal T-cell depleting antibodies	Rabbit-anti-human anti-thymocyte globulin (rATG) Horse-anti-human anti-thymocyte globulin (hATG) Anti-lymphocyte globulin (ALG)
Monoclonal T-cell depleting antibodies	Alemtuzumab (Campath)
Monoclonal Anti-IL2R antibodies	Daclizumab, Basiliximab
Monoclonal Anti-CD3 antibodies	hOKT3g1 (Ala-Ala)
TNF-α antagonists	Infliximab, Etanercept
Anti-inflammatory	Deoxyspergualin
Calcineurin inhibitors	Tacrolimus, Cyclosporine
mTOR Inhibitors	Sirolimus, Everolimus
Inosine monophosphate dehydrogenase inhibitors	MMF, Mycophenolate Sodium
Corticosteroids	Prednisone, Methylprednisolone, others

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 (52%). A number of other immunosuppression regimens (N=53) were used and are listed in Exhibit 4-1. A summary of biologic agents used for the participant's first infusion is displayed in Exhibit 4-2. Daclizumab was the sole T-cell antibody used in 59% of first infusions for IA recipients. Maintenance therapy regimens are located in Exhibit 4-3. 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 4-4 and 4-5.

Prior to the first infusion, 43% of the recipients were on at least one anti-hypertensive medication (Exhibits 4-6 and 4-7) and 34% were on a lipid lowering medication (Exhibits 4-8 and 4-9). By Year 1 post last infusion, these rates increased to 53% and 61%, respectively, based on participants with complete medication information. For adjunctive therapies, at the time of their first infusion (Exhibit 4-10), 99% of recipients used an antibiotic, 88% used antivirals, and 71% used vitamin supplements. The most common adjunctive therapies used during follow-up (Exhibit 4-11) included vitamin supplements (17% at Month 6 and 15% at Year 1) and Pentoxifylline (12% at Month 6).

Exhibit 4 – 1
Immunosuppression Regimen at Time of First Infusion

	Allograft Type			
	Islet Alone		IAK	
	N	N	N	N
Total	347	100.0	65	100.0
Anti-thymocyte Globulin + Daclizumab + Etanercept + Methylprednisolone + Sirolimus + Tacrolimus	1	0.3	-	0.0
Anti-thymocyte Globulin + Daclizumab + Etanercept + Methylprednisolone + Sirolimus + Tacrolimus + MMF	7	2.0	-	0.0
Anti-thymocyte Globulin + Daclizumab + Etanercept + Sirolimus + Tacrolimus	1	0.3	-	0.0
Anti-thymocyte Globulin + Daclizumab + Sirolimus + MMF	1	0.3	-	0.0
Anti-thymocyte Globulin + Daclizumab + Sirolimus + Tacrolimus	4	1.2	1	1.5
Anti-thymocyte Globulin + Daclizumab + Cyclosporine + Sirolimus + Tacrolimus + Mycophenolic Acid	-	0.0	1	1.5
Anti-thymocyte Globulin + Efalizumab + Methylprednisolone + Sirolimus	5	1.4	-	0.0
Anti-thymocyte Globulin + Etanercept + Cyclosporine + Prednisone + Methylprednisolone	-	0.0	1	1.5
Anti-thymocyte Globulin + Etanercept + IL-1 Antagonist + Tacrolimus + MMF	2	0.6	-	0.0
Anti-thymocyte Globulin + Etanercept + Methylprednisolone + Sirolimus + Tacrolimus + MMF	-	0.0	1	1.5
Anti-thymocyte Globulin + Etanercept + Cyclosporine + Everolimus	1	0.3	-	0.0
Anti-thymocyte Globulin + Etanercept + Cyclosporine + Methylprednisolone + Everolimus	5	1.4	-	0.0
Anti-thymocyte Globulin + Etanercept + Prednisone + Sirolimus + MMF	1	0.3	-	0.0
Anti-thymocyte Globulin + Etanercept + Prednisone + Tacrolimus + MMF	-	0.0	1	1.5
Anti-thymocyte Globulin + Etanercept + Sirolimus + Tacrolimus	3	0.9	-	0.0
Anti-thymocyte Globulin + Etanercept + Tacrolimus + MMF	5	1.4	-	0.0
Anti-thymocyte Globulin + IL-1 Antagonist + Prednisone + Methylprednisolone + Sirolimus + MMF	1	0.3	-	0.0
Anti-thymocyte Globulin + IL-1 Antagonist + Prednisone + Methylprednisolone + Tacrolimus + MMF	1	0.3	-	0.0
Anti-thymocyte Globulin + Intravenous Immunoglobulin + Sirolimus + Tacrolimus	1	0.3	-	0.0
Anti-thymocyte Globulin + Methylprednisolone + Sirolimus + MMF	4	1.2	-	0.0
Anti-thymocyte Globulin + Methylprednisolone + Sirolimus + Belatacept	1	0.3	-	0.0
Anti-thymocyte Globulin + Cyclosporine + Prednisone + MMF	-	0.0	1	1.5
Anti-thymocyte Globulin + Tacrolimus + MMF	4	1.2	-	0.0
Anti-Lymphocyte Globulin + IL-1 Antagonist + Prednisone + Methylprednisolone + Sirolimus + MMF	3	0.9	-	0.0
Anti-Lymphocyte Globulin + Sandimmune + Methylprednisolone + MMF	-	0.0	1	1.5

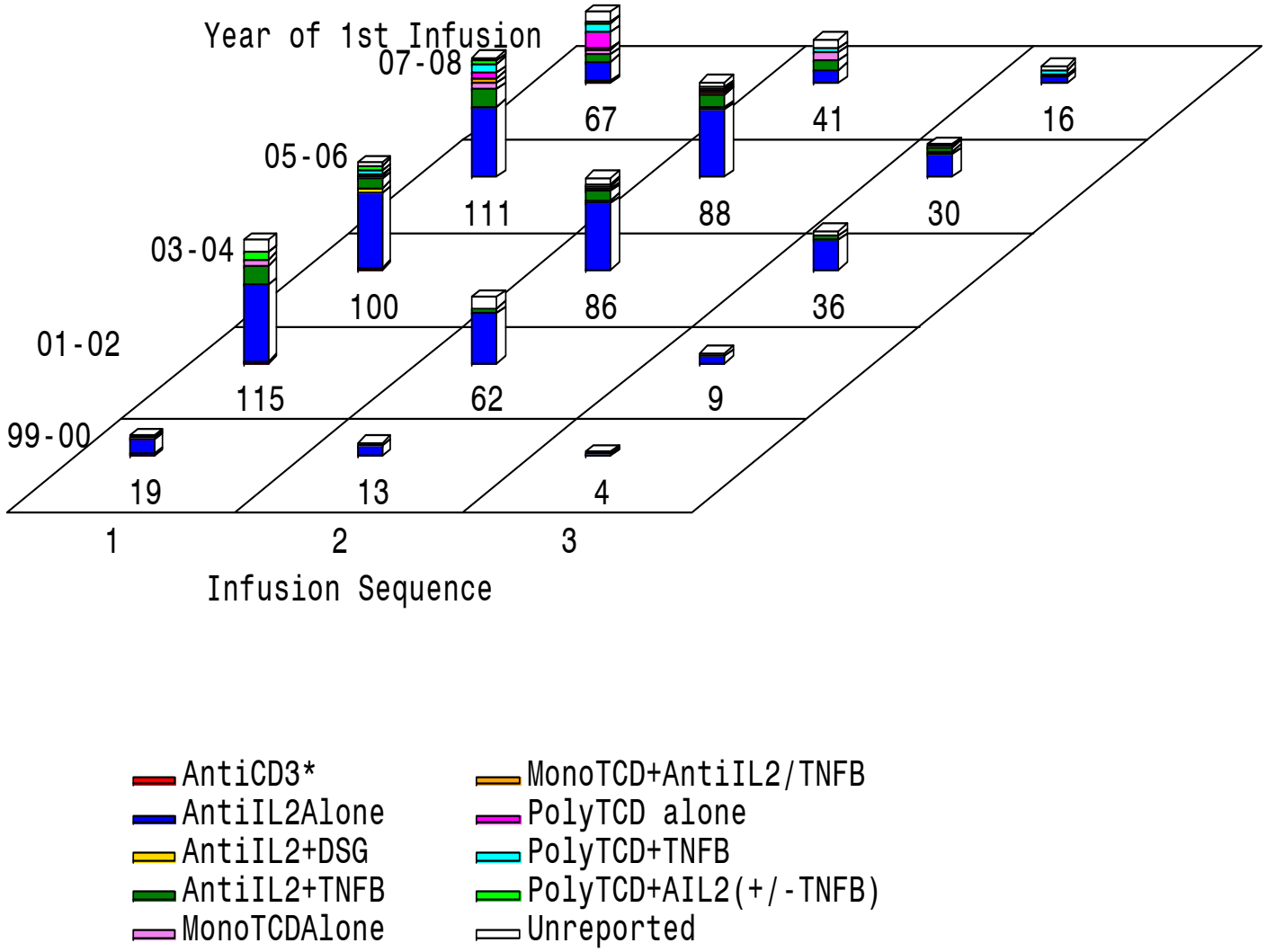
Exhibit 4 – 1 (continued)
Immunosuppression Regimen at Time of First Infusion

	Allograft Type			
	Islet Alone		IAK	
	N	N	N	N
Alemtuzumab + Etanercept + Sirolimus + Tacrolimus	6	1.7	-	0.0
Alemtuzumab + Infliximab + Sirolimus + Tacrolimus	1	0.3	-	0.0
Alemtuzumab + Sirolimus + Tacrolimus	9	2.6	-	0.0
Alemtuzumab + Sirolimus + Tacrolimus + Steroid	1	0.3	-	0.0
Alemtuzumab + Tacrolimus + MMF	10	2.9	-	0.0
hOKT3 γ -1 (Ala-Ala) + Sirolimus + Tacrolimus	6	1.7	-	0.0
hOKT3 γ -1 (Ala-Ala)+ Etanercept + Sirolimus + Tacrolimus	2	0.6	-	0.0
Daclizumab + 15-deoxyspergualin + Sirolimus + Tacrolimus	5	1.4	-	0.0
Daclizumab + Efalizumab + Tacrolimus + MMF	3	0.9	-	0.0
Daclizumab + Etanercept + Methylprednisolone + Sirolimus + Tacrolimus + MMF	-	0.0	1	1.5
Daclizumab + Etanercept + Sirolimus + Tacrolimus	11	3.2	1	1.5
Daclizumab + Etanercept + Sirolimus + Tacrolimus + MMF	-	0.0	1	1.5
Daclizumab + Etanercept + Tacrolimus + MMF	1	0.3	1	1.5
Daclizumab + Infliximab + Sirolimus + Tacrolimus	18	5.2	2	3.1
Daclizumab + Cyclosporine + Prednisone + MMF	-	0.0	1	1.5
Daclizumab + Prednisone + Sirolimus + Tacrolimus	-	0.0	3	4.6
Daclizumab + Prednisone + Sirolimus + Tacrolimus + MMF + Hydrocortisone	-	0.0	1	1.5
Daclizumab + Prednisone + Sirolimus + Tacrolimus + Azathioprine	-	0.0	1	1.5
Daclizumab + Prednisone + Tacrolimus + MMF	-	0.0	4	6.2
Daclizumab + Sirolimus + Tacrolimus	181	52.2	31	47.7
Daclizumab + Sirolimus + Tacrolimus + MMF	5	1.4	3	4.6
Daclizumab + Sirolimus + Tacrolimus + Steroid	1	0.3	-	0.0
Daclizumab + Tacrolimus + MMF	-	0.0	1	1.5
Basiliximab + Etanercept + Cyclosporine + MMF + Mycophenolic Acid	-	0.0	1	1.5
Basiliximab + Etanercept + Sirolimus + Tacrolimus	12	3.5	-	0.0
Basiliximab + IL-1 Antagonist + Prednisone + Methylprednisolone + Sirolimus + MMF	1	0.3	-	0.0
Basiliximab + Sirolimus + Tacrolimus	1	0.3	-	0.0
Efalizumab + Tacrolimus + MMF	1	0.3	-	0.0
Sirolimus	1	0.3	-	0.0
Missing Information on Immunosuppression	20	5.8	6	9.2

Exhibit 4 – 2A
Biologic Agents Used Peri First Infusion for Induction Therapy

	Allograft Type			
	Islet Alone		Islet After Kidney	
	N	%	N	%
Total	327	100.0	59	100.0
Daclizumab Alone	192	58.7	45	76.3
Daclizumab + Anti-Thymocyte Globulin	5	1.5	2	3.4
Daclizumab + Anti-Thymocyte Globulin + Etanercept	9	2.8	-	0.0
Daclizumab + Etanercept	12	3.7	4	6.8
Daclizumab + Infliximab	18	5.5	2	3.4
Daclizumab + Efalizumab	3	0.9	-	0.0
Anti-Thymocyte Globulin Alone	11	3.4	1	1.7
Anti-Thymocyte Globulin + Etanercept	17	5.2	3	5.1
Anti-Thymocyte Globulin + Efalizumab	5	1.5	-	0.0
Anti-Thymocyte Globulin + Belatacept	1	0.3	-	0.0
Alemtuzumab Alone	20	6.1	-	0.0
Alemtuzumab + Etanercept	6	1.8	-	0.0
Alemtuzumab + Infliximab	1	0.3	-	0.0
Basiliximab Alone	2	0.6	-	0.0
Basiliximab + Etanercept	12	3.7	1	1.7
hOKT3γ-1(Ala-Ala) Alone	6	1.8	-	0.0
hOKT3γ-1(Ala-Ala) + Etanercept	2	0.6	-	0.0
Anti-Lymphocyte Globulin	3	0.9	1	1.7
Efalizumab Alone	1	0.3	-	0.0
None	1	0.3	-	0.0

Exhibit 4 – 2B
Biologic Agents Used for Induction Therapy Peri- Each Infusion
by Transplantation Era



Induction immunosuppression combinations given to allograft recipients, according to infusion sequence (horizontal axis), and transplantation era (1999-2000, 01-02. etc, perspective axis). Substantial shifts away from Anti-IL2 alone (blue) to other combinations is evident in recent time periods.

Exhibit 4 – 3A
Immunosuppression Therapy Use at Specified Times Post Last Infusion
Allograft Recipients without Reported Graft Failure at the Time of Follow-Up

	Allograft Type															
	Islet Alone								Islet After Kidney							
	Follow-Up								Follow-Up							
	6 Months		12 Months		2 Years		3 Years		6 Months		12 Months		2 Years		3 Years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	285	100.0	249	100.0	190	100.0	142	100.0	56	100.0	50	100.0	34	100.0	28	100.0
Daclizumab + Methylprednisolone + Sirolimus + Tacrolimus + MMF	-	0.0	-	0.0	-	0.0	-	0.0	1	1.8	-	0.0	-	0.0	-	0.0
Daclizumab + MMF	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Prednisone + Sirolimus + Tacrolimus	-	0.0	-	0.0	-	0.0	-	0.0	1	1.8	1	2.0	-	0.0	-	0.0
Daclizumab + Sirolimus + MMF	2	0.7	-	0.0	1	0.5	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus	13	4.6	9	3.6	1	0.5	-	0.0	2	3.6	2	4.0	-	0.0	-	0.0
Daclizumab + Sirolimus + Tacrolimus + MMF	1	0.4	-	0.0	-	0.0	-	0.0	1	1.8	-	0.0	-	0.0	-	0.0
Daclizumab + Tacrolimus + MMF	-	0.0	3	1.2	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Daclizumab + Tacrolimus + Mycophenolic Acid	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Efalizumab + MMF	1	0.4	1	0.4	1	0.5	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Efalizumab + Sirolimus + MMF	3	1.1	2	0.8	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Efalizumab + Tacrolimus + MMF	2	0.7	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Cyclosporine*	6	2.1	6	2.4	6	3.2	5	3.5	2	3.6	2	4.0	1	2.9	1	3.6
Tacrolimus	3	1.1	-	0.0	4	2.1	1	0.7	-	0.0	-	0.0	-	0.0	1	3.6
Tacrolimus + MMF	33	11.6	38	15.3	30	15.8	29	20.4	4	7.1	5	10.0	4	11.8	3	10.7
Tacrolimus + MMF + Abatacept	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus + Mycophenolic Acid	1	0.4	3	1.2	4	2.1	3	2.1	-	0.0	-	0.0	-	0.0	-	0.0
Tacrolimus + Azathioprine	1	0.4	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0

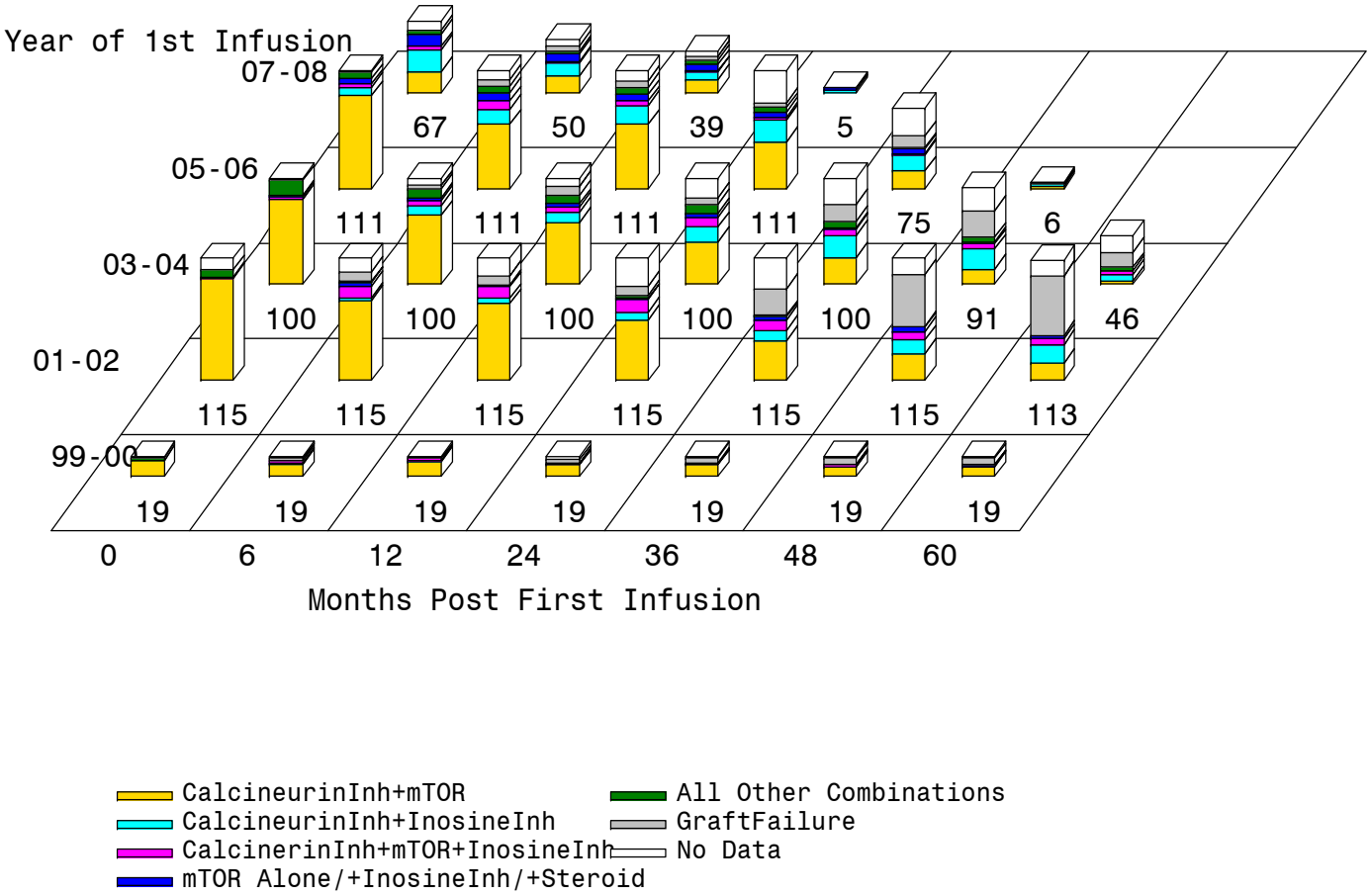
* Cyclosporine used in conjunction with Sirolimus, Everolimus, MMF, Mycophenolic Acid, and/or Prednisone.

Exhibit 4 – 3A (continued)
Immunosuppression Therapy Use at Specified Times Post Last Infusion
Allograft Recipients without Reported Graft Failure at the Time of Follow-Up

	Allograft Type															
	Islet Alone								Islet After Kidney							
	Follow-Up								Follow-Up							
	6 Months		12 Months		2 Years		3 Years		6 Months		12 Months		2 Years		3 Years	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Prednisone	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	2.0	-	0.0	1	3.6
Prednisone + Sirolimus + MMF	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Prednisone + Sirolimus + Azathioprine	-	0.0	1	0.4	1	0.5	1	0.7	-	0.0	-	0.0	-	0.0	-	0.0
Prednisone + Sirolimus + Tacrolimus	-	0.0	-	0.0	-	0.0	-	0.0	3	5.4	2	4.0	1	2.9	2	7.1
Prednisone + Tacrolimus	-	0.0	-	0.0	-	0.0	-	0.0	1	1.8	2	4.0	-	0.0	-	0.0
Prednisone + Tacrolimus + MMF	-	0.0	-	0.0	-	0.0	-	0.0	4	7.1	3	6.0	2	5.9	-	0.0
Sirolimus	-	0.0	2	0.8	1	0.5	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + MMF	13	4.6	9	3.6	3	1.6	6	4.2	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Mycophenolic Acid	2	0.7	2	0.8	2	1.1	1	0.7	1	1.8	1	2.0	1	2.8	1	3.6
Sirolimus + Azathioprine	-	0.0	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Tacrolimus	159	55.8	125	50.2	88	46.3	53	37.3	28	50.0	22	44.0	15	44.1	11	39.3
Sirolimus + Tacrolimus + MMF	23	8.1	19	7.6	17	8.9	10	7.0	3	5.4	4	8.0	3	8.8	1	3.6
Sirolimus + Tacrolimus + Mycophenolic Acid	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Sirolimus + Tacrolimus + Steroid	1	0.4	2	0.8	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
MMF	-	0.0	-	0.0	1	0.5	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Mycophenolic Acid + Efalizumab	-	0.0	1	0.4	-	0.0	1	0.7	-	0.0	-	0.0	-	0.0	-	0.0
Mycophenolic Acid + Efalizumab + Sirolimus	1	0.4	1	0.4	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0
Missing Information on Immunosuppression	12	4.2	20	8.0	30	15.8	32	22.5	5	8.9	5	10.0	7	20.6	6	21.4
No Immunosuppressant Medications Taken	3	1.1	2	0.8	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	1	3.6

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

Exhibit 4 – 3B
Maintenance Immunosuppression Therapy Use Post Initial Infusion
by Transplantation Era



Maintenance immunosuppression combinations given to allograft recipients, according to time (months from initial infusion, horizontal axis), and transplantation era (1999-2000, 01-02. etc, perspective axis). The total number expected at each follow-up time point is accounted for. Complete graft loss trumps any immunosuppression. Substantial shifts away from the Calcineurin+mTOR combination (yellow) to other combinations is evident from the start in recent time periods)2007-2008), as well as among those infused in earlier eras (e.g., 2001-2006) and still on immunosuppression at long-term follow-up (2-5 years).

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

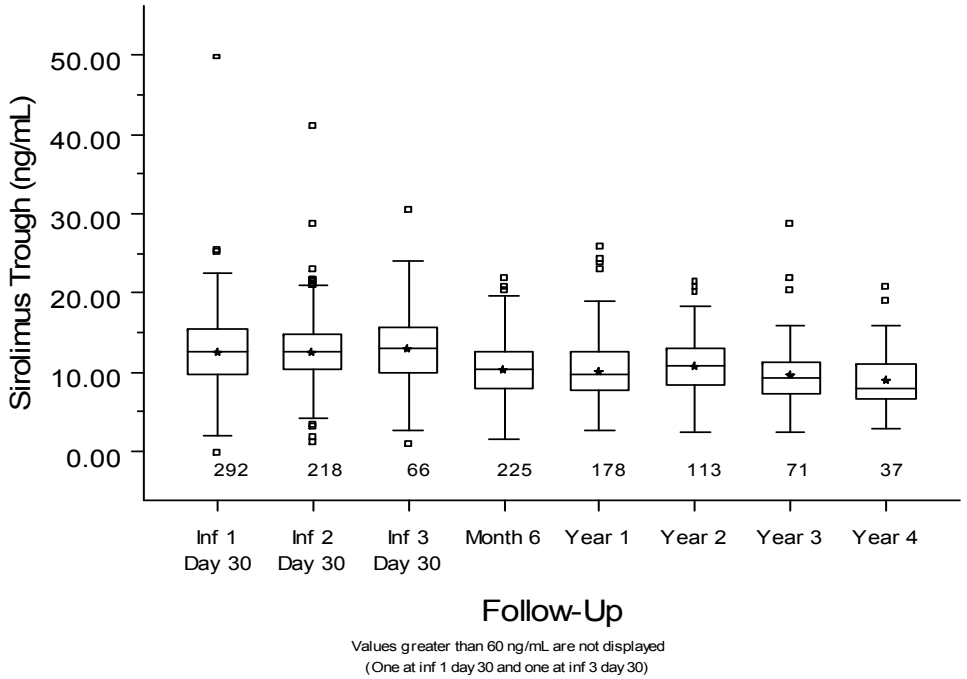


Exhibit 4 – 5
Tacrolimus Recipient Trough Level (ng/mL) Post Last Infusion
All Allograft Recipients

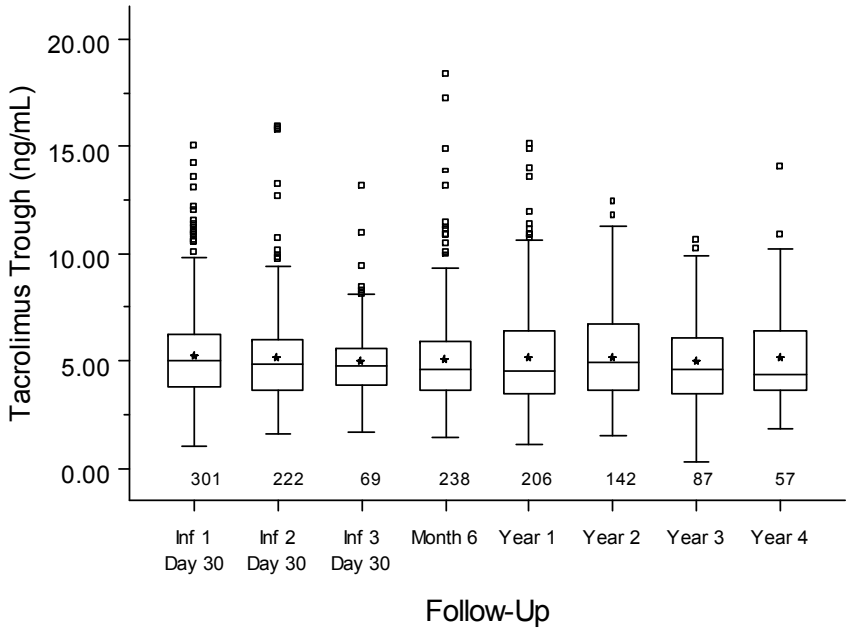


Exhibit 4 – 6
Anti-Hypertensive Medications Pre Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up											
	Pre Infusion 1		Month 6		Year 1		Year 2		Year 3		Year 4	
	N	% of known	N	% of known	N	% of known	N	% of known	N	% of known	N	% of known
Total	391	100.0	322	100.0	281	100.0	194	100.0	127	100.0	73	100.0
No Anti-Hypertensive Medications Taken	224	57.3	164	50.9	132	47.0	82	42.3	53	41.7	29	39.7
ACE Inhibitors	122	31.2	108	33.5	108	38.4	74	38.1	49	38.6	26	35.6
Alpha Adrenergic Blockers	2	0.5	4	1.2	5	1.8	3	1.5	1	0.8	2	2.7
Angiotensin II Receptor Blockers	30	7.7	26	8.1	31	11.0	26	13.4	18	14.2	9	12.3
Beta Adrenergic Blockers	28	7.2	30	9.3	27	9.6	23	11.9	14	11.0	13	17.8
Calcium Channel Blockers	29	7.4	29	9.0	26	9.3	20	10.3	15	11.8	8	11.0
Centrally Acting Agents	3	0.8	4	1.2	1	0.4	1	0.5	2	1.6	-	0.0
Diuretics	21	5.4	36	11.2	36	12.8	17	8.8	16	12.6	7	9.6
Vasodilators	3	0.8	1	0.3	3	1.1	1	0.5	3	2.4	1	1.4

*Recipients may take multiple agents.

Exhibit 4 – 7
Total Number of Anti-Hypertensive Medications
Pre Infusion and Post Last Infusion
All Allograft Recipients

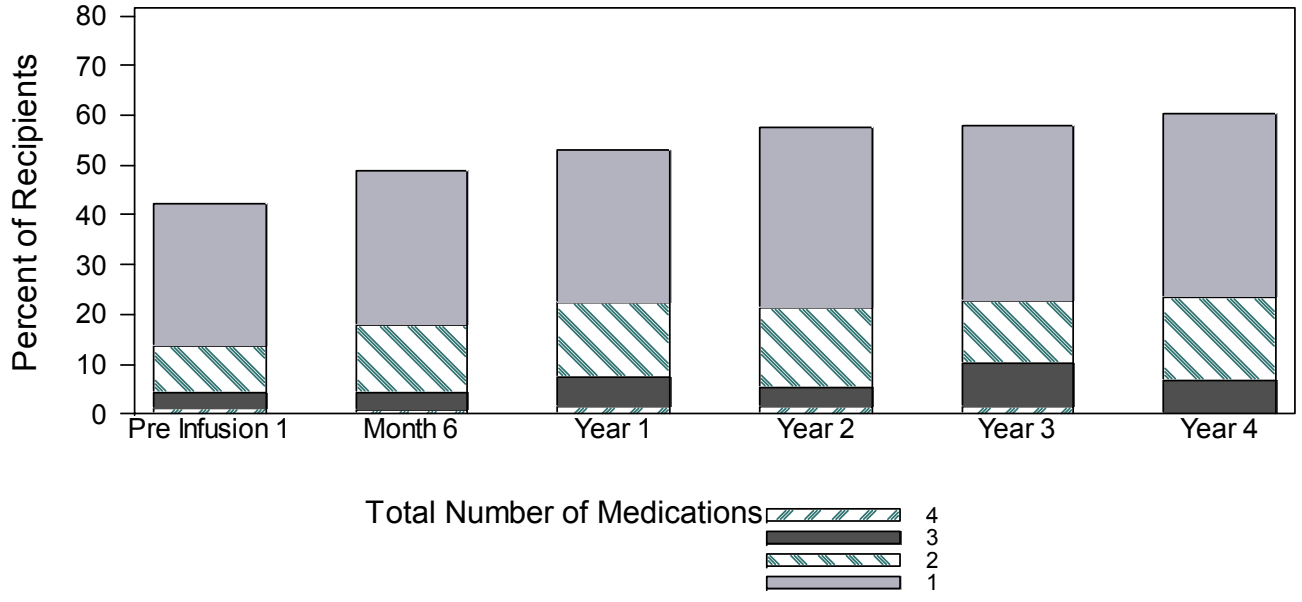


Exhibit 4 – 8
Lipid Lowering Medications Pre Infusion and Post Last Infusion
All Allograft Recipients

	Follow-Up											
	Pre Infusion 1		Month 6		Year 1		Year 2		Year 3		Year 4	
	N	% of known	N	% of known	N	% of known	N	% of known	N	% of known	N	% of known
Total	391	100.0	325	100.0	282	100.0	199	100.0	128	100.0	74	100.0
No Lipid Lowering Medications Taken	258	66.0	148	45.5	110	39.0	69	34.7	49	38.3	29	39.2
Bile Acid Sequestrants	3	0.8	3	0.9	1	0.4	1	0.5	-	0.0	-	0.0
Cholesterol Absorption Inhibitors	12	3.1	12	3.7	12	4.3	10	5.0	6	4.7	4	5.4
Fibric Acid Derivatives	1	0.3	1	0.3	3	1.1	1	0.5	2	1.6	-	0.0
HMG CoA Reductase Inhibitors	125	32.0	162	49.8	152	53.9	117	58.8	72	56.3	41	55.4
Nicotinic Acid	3	0.8	12	3.7	9	3.2	7	3.5	1	0.8	-	0.0

*Recipients may take multiple agents.

Exhibit 4 – 9
Total Number of Lipid Lowering Medications
Pre Infusion and Post Last Infusion
All Allograft Recipients

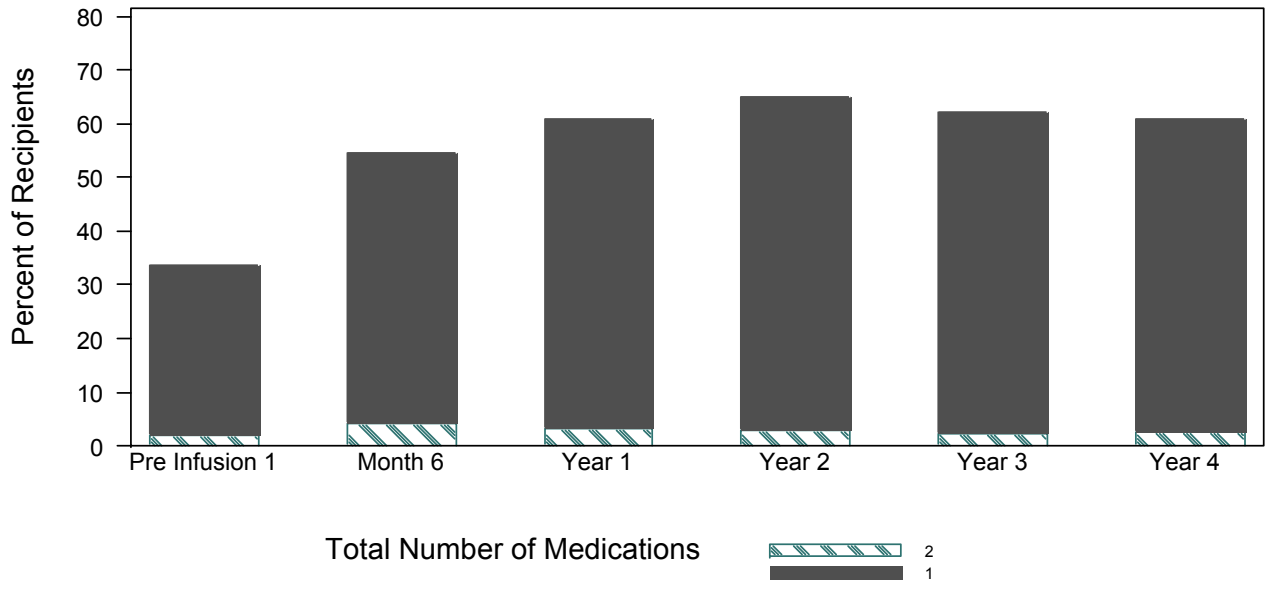


Exhibit 4 – 10
Adjunctive Therapy Used at Time of First Infusion
All Allograft Recipients

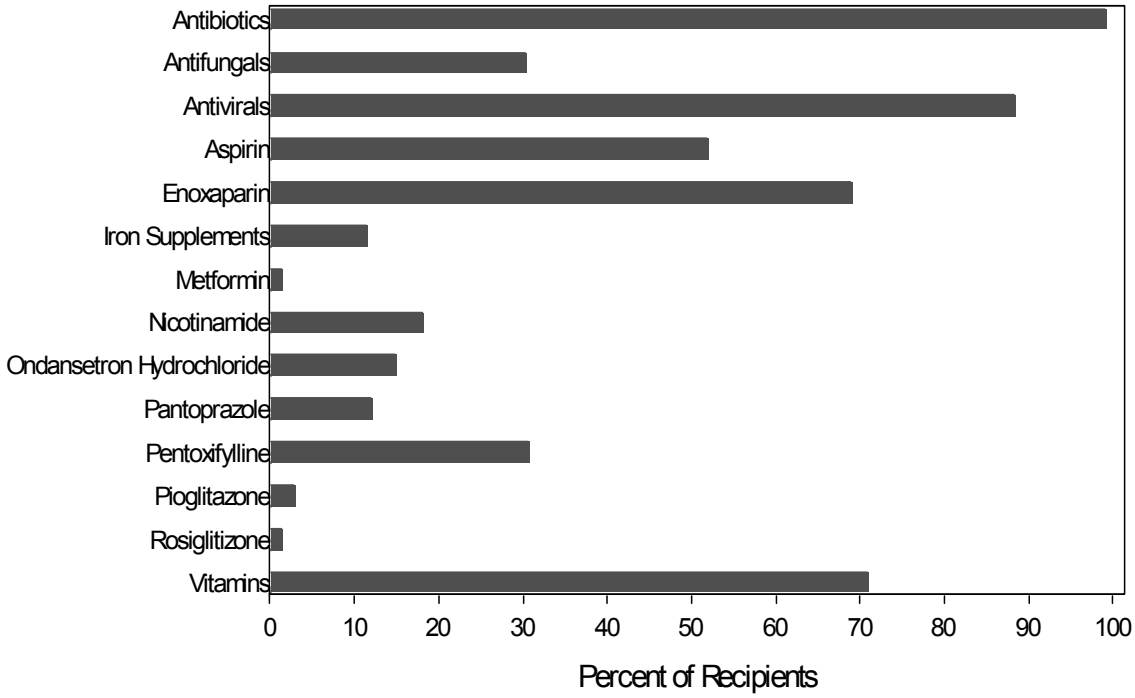


Exhibit 4 – 11
Adjunctive Therapy Post Last Infusion
All Allograft Recipients

	Follow-Up									
	Month 6		Year 1		Year 2		Year 3		Year 4	
	N	%	N	%	N	%	N	%	N	%
Overall	328	100.0	285	100.0	209	100.0	139	100.0	79	100.0
None	245	74.7	218	76.5	168	80.4	116	83.5	66	83.5
Pentoxifylline	41	12.5	6	2.1	2	1.0	-	0.0	-	0.0
Metformin	13	4.0	11	3.9	6	2.9	3	2.2	1	1.3
Exenatide	8	2.4	9	3.2	4	1.9	5	3.6	3	3.8
Rosiglitazone	4	1.2	5	1.8	3	1.4	3	2.2	2	2.5
Pioglitazone	5	1.5	5	1.8	5	2.4	4	2.9	1	1.3
Acarbose	3	0.9	2	0.7	1	0.5	-	0.0	-	0.0
Repaglinide	5	1.5	2	0.7	3	1.4	5	3.6	2	2.5
Chromium picolinate	2	0.6	1	0.4	1	0.5	1	0.7	-	0.0
Iron	5	1.5	7	2.5	6	2.9	-	0.0	-	0.0
Magnesium	-	0.0	1	0.4	-	0.0	-	0.0	-	0.0
Vitamins	56	17.1	44	15.4	15	7.2	3	2.2	2	2.5

*Patients may be counted in multiple categories.

Chapter 5
Graft Function

Graft Function

Chapter 5 summarizes results on graft function for the 412 allogeneic islet transplant alone (IA) or islet after kidney (IAK) recipients reported to the Registry from 1999 through 2008.

Insulin Independence and Graft Function

As discussed in Detailed Methods, insulin independence, insulin dependence and islet graft failure are treated as mutually exclusive states. They are reported as

- prevalence at scheduled visits (e.g., Exh 5-1), in which case status post first infusion is reported up to re-infusion for all recipients, with missing data accounted for, or
- daily prevalence from diaries, in which case missing data is either considered as shown as best-case or worst-case (Exh 5-4), or missing at random (Exh 5-5).
- time to event or durability, i.e., Kaplan-Meier rates of achieving insulin independence (Exhibit 5-6), durability of insulin independence (Exh 5-7) or persistence of graft function (Exh 5-12).

Because individuals can achieve insulin independence, subsequently lose and perhaps re-gain it, Kaplan-Meier cumulative event rates and prevalence rates do not estimate exactly the same quantities. Prevalences are estimated at fixed timepoints, either explicitly counting missing data or treating missing data is missing at random. Kaplan-Meier loss of insulin independence post achievement is measured from achievement (not from infusion). Achievement and loss pertain to the longest period of insulin independence the patient achieved, while prevalence also takes into account intermittent periods of insulin independence/dependence.

It should be noted that events/prevalence for all recipients post first infusion are distinct from events/prevalence for those receiving only one infusion, whether by local protocol or by patient/doctor decision. The denominators for each Exhibit will distinguish between these two scenarios: for analyses of post first-infusion, all recipients are included, e.g., 347 islet-alone or 56 islet-after-kidney, clearly noted as censored at re-infusion or not; for analyses stratified by total infusions received, the denominators will be as in Exhibit 1-6.

Additionally, analyses done post first infusion are of two types:

- those that censor cases at re-infusion (e.g., Exh 5-1, 5-14, 5-16), namely, cases which are re-infused prior to the follow-up time point are not counted after the reinfusion, or
- those that count all events over all follow-up regardless of re-infusion, but measured as time from first infusion (e.g., Exh 5-6 & 5-12).

Some imputation for missing data was done, as follows.

If function loss is reported with no further infusion:

- all subsequent missing values for C-peptide are imputed as 0;
- all subsequent missing values for insulin use, HbA_{1c}, fasting BG, revert to baseline;
- all subsequent missing values for hypoglycemia severity are left missing.

Otherwise (no reported function loss and C-peptide>=0.1ng/mL):

- if the patient was insulin independent, then a missing C-peptide is imputed as 0.6;
- otherwise, if the preceding and subsequent visits have reported values for C-Peptide, HbA_{1c}, or fasting BG, the respective mean is imputed.

Of the data at 1-, 2-, 3- and 4- years post last infusion, these imputation rules reduced the missing data to 4%, 9%, 14%, and 17%, respectively.

After the first infusion (Exhibit 5-1), increasing proportions of islet-alone (IA) recipients are re-infused: 11% by Day 30, 33% by Day 75, 54% by Month 6, and 65% by Year 1. The proportion that is insulin independent without re-infusion remains fairly constant at 11-15% throughout the first year. An additional 8-12% retains detectable C-peptide for one year with insulin dependence and no re-infusion. Of all 347 IA recipients, 74% have at least three years of follow up post first infusion, at which time, regardless of the total number of infusions received, about 27% are insulin independent, 30% are insulin dependent with detectable C-peptide, 27% have no detectable C-peptide and 16% have missing data (required but not yet reported).

Analyzed from last infusion (Exhibit 5-2), the percentage of all IA recipients that is insulin independent declined steadily from 55% at Month 6 to 27% at Year 3 and 16% at Year 4. The proportion with loss of islet function (reported graft failure or no detectable C-peptide) increased steadily from 12% at Month 6 to 35% at Year 3, and 42% at Year 4 (Exhibit 5-2). A stable 19-31% retained graft function with exogenous insulin over the four years; the percentage of missing data increases over time. These trends of increasing prevalence of graft loss and decreasing prevalence of insulin independence over time post last infusion prevail regardless of the total number of infusions given (Exhibit 5-3), although the three groups are not comparable because of the different factors that influence reinfusion.

When all islet recipients are stratified by total number of infusions, graft loss appears highest with one infusion and lowest with two infusions, while insulin independence appears highest with 2-3 infusions and lowest with one infusion. This is likely due to the mixture of earlier and more recent recipients: those who have had only one infusion as of the report cut-off date comprise those transplanted early who experienced graft loss and chose not to be re-infused, as well as those transplanted more recently who either have good function or may have lost function and are awaiting re-infusion.

Focusing only on the insulin independence status (available from submitted daily diaries), the prevalence of insulin independence from last infusion declined from 59% at Month 4 to about 31% at Year 3 post last infusion (Exhibit 5-4). Two or three infusions (Exhibit 5-5) exhibit higher prevalence of insulin independence in the first year to a peak of about 65%, with a subsequent decline to levels that are comparable to those with a single infusion. However, this type of post-hoc stratification by total infusions received is difficult to interpret since the decision to reinfuse islets is often dependent upon the outcome of previous islet infusions. 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 347 IA recipients post last infusion.

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 5-6) follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. Overall, about 70% of all recipients are estimated to have achieved insulin independence, for both IA and IAK recipients, which follow very similar cumulative event rates (Exh 5-6). The median time to achievement of insulin independence was 6-7 months after first infusion. After achievement, 70% of IA recipients retained insulin independence one year later, 55% at two years, 45% at 3-years and 36% at 4-years (Exhibit 5-7).

Stratified by era of first infusion (1999-2004 regarded as early and 2005-2008 regarded as recent), attainment of insulin independence has improved slightly (Exhibit 5-6 bottom), while retention of insulin independence has improved substantially (Exhibit 5-7 bottom), even though the more recent cohort has not had equal opportunity for re-infusion. However, retention of graft function (Exhibit 5-12) remains remarkably unchanged.

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 (Exhibits 5-8 to 5-10).

Changes in Islet Graft Function

Graft loss, whether measured by C-peptide levels, or reported by the site, increases steadily over time. At Year 3 post last infusion, 33% of IA recipients lost graft function (Exhibit 5-11). Viewed as Kaplan-Meier estimates (Exhibit 5-12), 35% of IA recipients are estimated to have lost graft function by Year 3 post last infusion.

Factors of Primary Outcomes

Factors of achieving and maintaining insulin independence, and complete islet failure, post first infusion up to reinfusion and post last infusion, are presented in Exhibits 5-14 and 5-15, where they are fully described.

C-peptide

Recipients with pre-infusion basal C-peptide ≥0.5 ng/mL, included in various exhibits of C-peptide and/or graft function in this Chapter, are listed in Appendix B. All but one have other indications for islet transplantation, and all received their first islet infusion prior to 2006.

C-peptide levels are substantially increased by islet transplantation. The percent of IA recipients with C-peptide ≥0.5 ng/mL (censored at re-infusion, Exhibit 5-16), increases from 7% pre-infusion to 77% at Month 6, 66% at Year 1, and 45% at Year 3 post last infusion.

C-peptide ≥0.3 ng/mL is indicative of graft function. The rates for IA post last infusion are 72% at 1-year, 56% at 3-years and 41% at 4-years, assuming missing data is at random (Exhibit 5-16C). The relationship between graft function and insulin independence is characterized in Exhibit 5-18; the higher the C-peptide, the more likely insulin independence ($p<0.01$).

Composite Outcome: Severe Hypoglycemia and HbA_{1c}

Taken as a composite outcome, the percent of IA recipients with HbA_{1c} <6.5% and absence of severe hypoglycemic episodes increases from 2% pre-infusion to 51-63% at Year 1 post last infusion with a subsequent decline to 20-45% by Year 4 post last infusion (Exhibit 5-26). In these ranges, the lower estimate represents the case where all missing data are counted as not achieving the outcome whereas the upper estimate assumes all missing data for recipients with confirmed or unknown graft function do achieve the outcome.

Severe Hypoglycemic Events

There continues to be a striking decrease in the prevalence of severe hypoglycemic events that occur after islet transplantation. In IA, severe hypoglycemia of 81% pre-infusion was reduced to 5% throughout the first year post last infusion, and to <10% at four years post last infusion (Exhibit 5-27 C). Hypoglycemia awareness is also markedly improved and is eroded only by loss of graft function or loss to follow-up (Exhibit 5-27). All participants that experienced a severe hypoglycemic event during follow-up were on insulin at the time of the event.

Enduring protection against severe hypoglycemia after complete graft failure is suggested by Exhibit 5-27F. This observation warrants further investigation.

HbA_{1c}

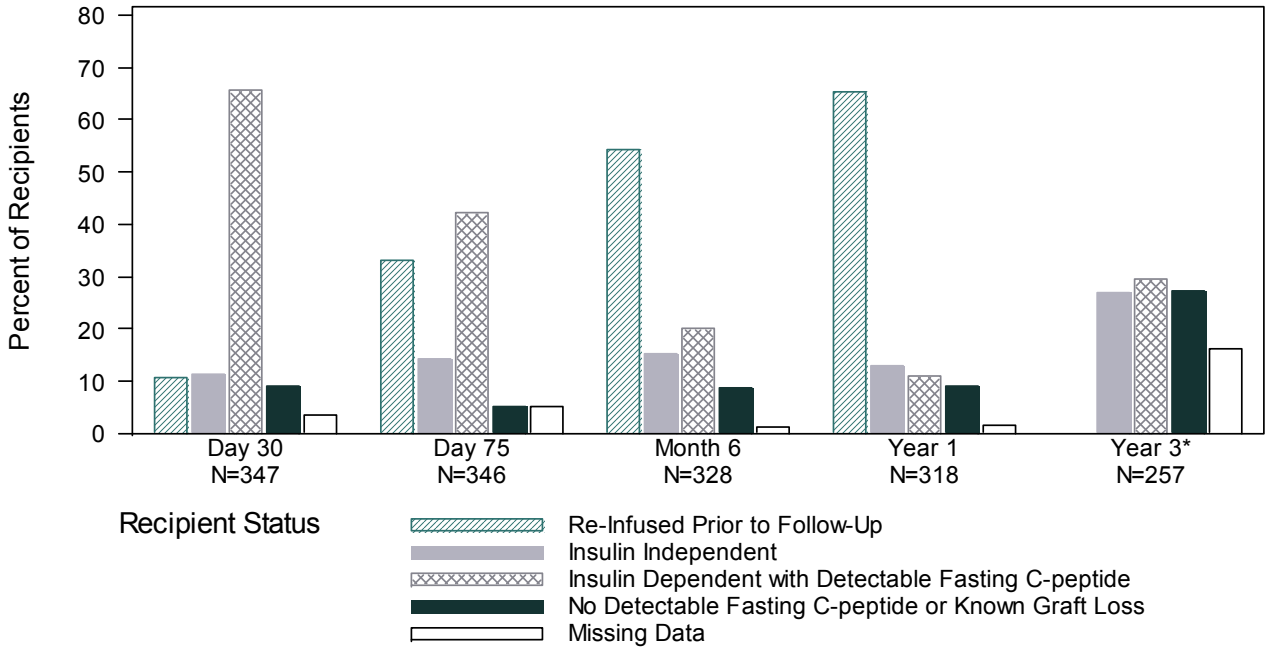
HbA_{1c} levels are improved substantially by islet transplantation. The percent of IA recipients with HbA_{1c} <7.0% increases from 28% pre-infusion to 70% at Month 6 and 66% at Year 1 post first infusion, censored at re-infusion (Exhibit 5-29). Post last infusion; these rates are 78% at Month 6 and 46% at Year 3. Based on available measurements, Exhibit 5-30 shows substantial reduction and long-term maintenance of reduced HbA_{1c} after islet transplantation, with means and medians stabilizing at <7.0% in Years 1-3 post last infusion.

Diabetes Related Secondary Complications

Exhibits 5-34 through 5-57 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, which are excluded from these exhibits. It is the goal of the Registry to continue to track the occurrence of these complications across time to determine any trends.

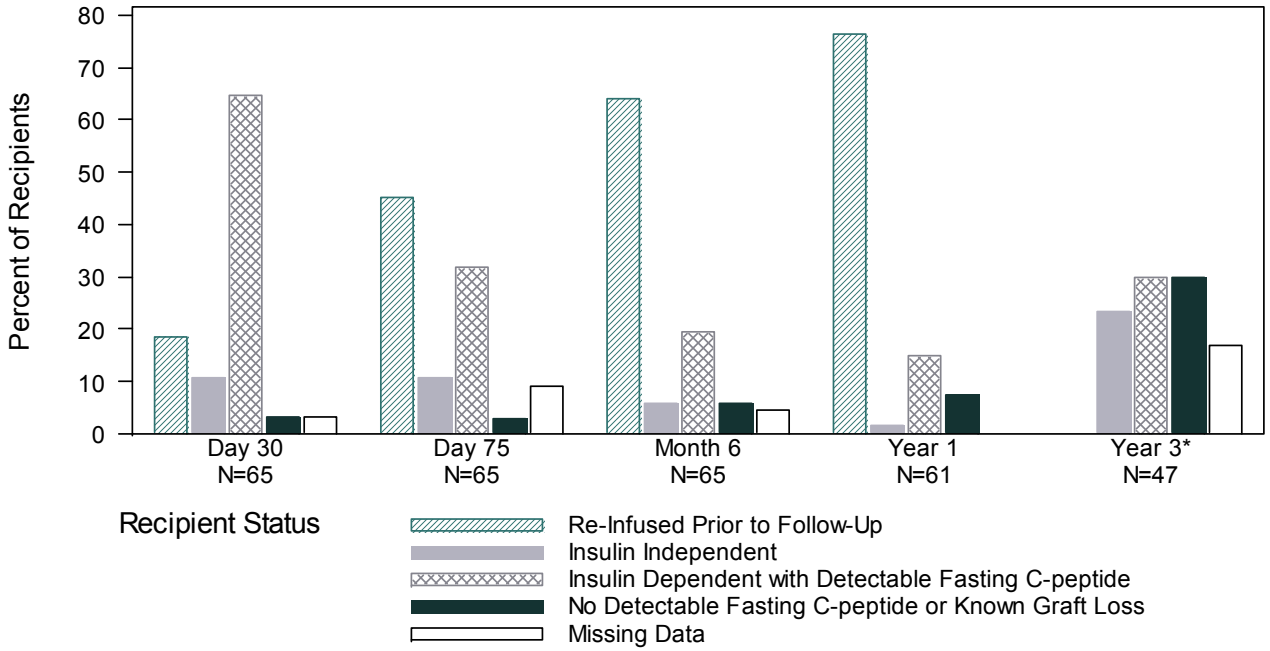
Exhibit 5 – 1
Insulin Independence, Insulin Dependence,
Absence of Fasting C-peptide, or Re-Infusion
Post First Infusion

A. Islet Alone Recipients



*Year 3 status regardless of re-infusion

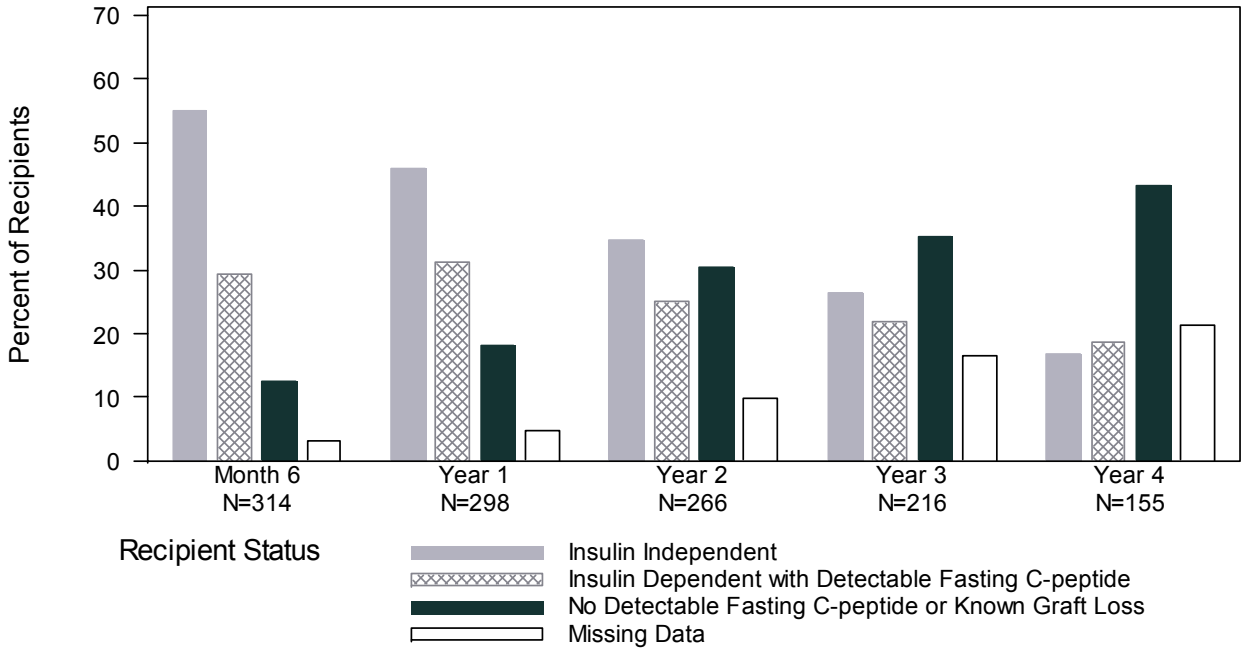
B. Islet After Kidney Recipients



*Year 3 status regardless of re-infusion

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

A. Islet Alone Recipients



B. Islet After Kidney Recipients

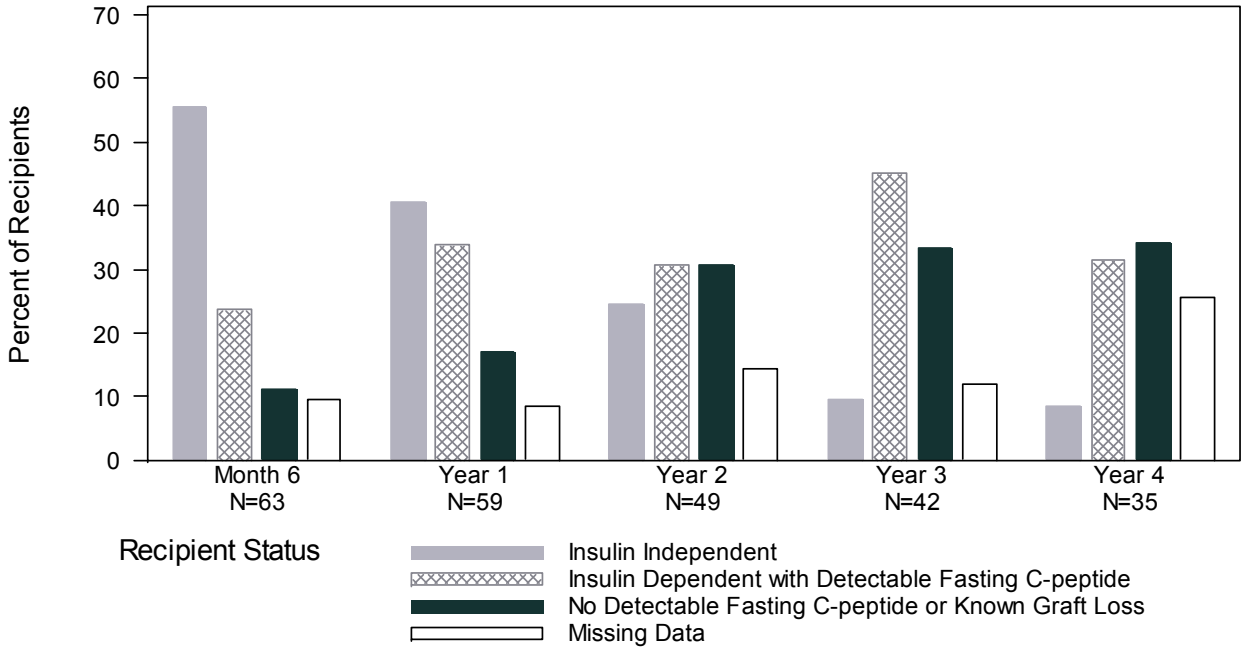
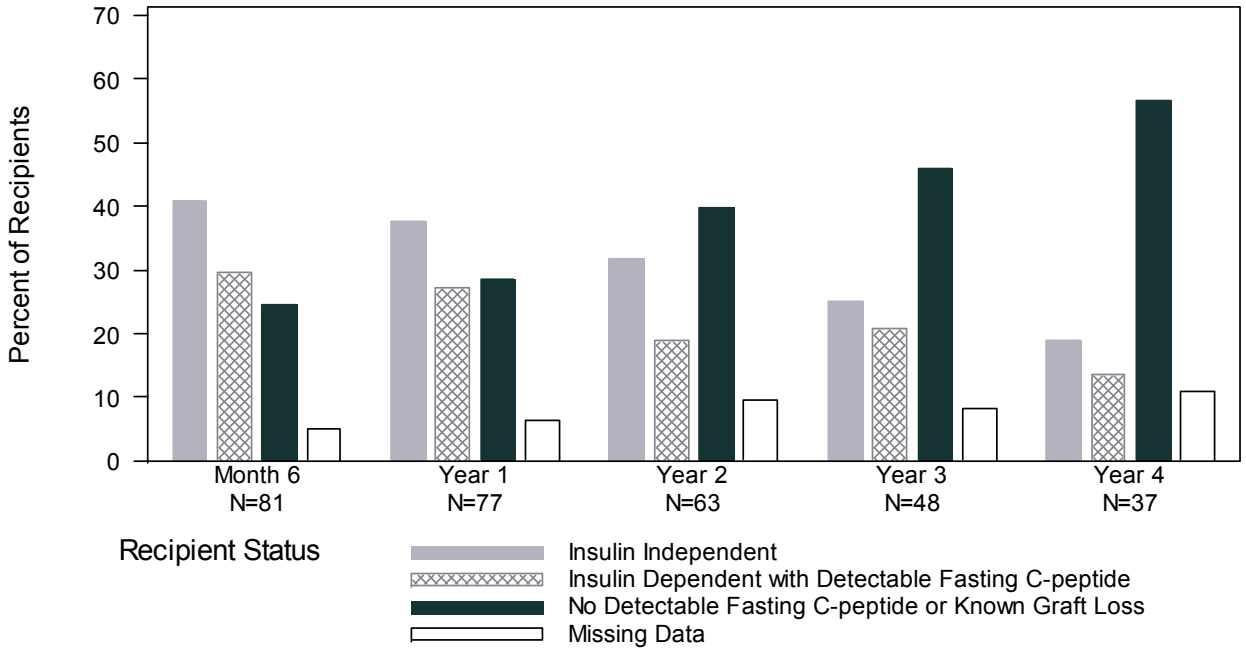


Exhibit 5 – 3
Insulin Independence, Insulin Dependence, or Absence of Fasting C-peptide Post Last Infusion by Total Number of Infusions Received
Islet Alone Recipients

A. Recipients of 1 Infusion



B. Recipients of 2 Infusions

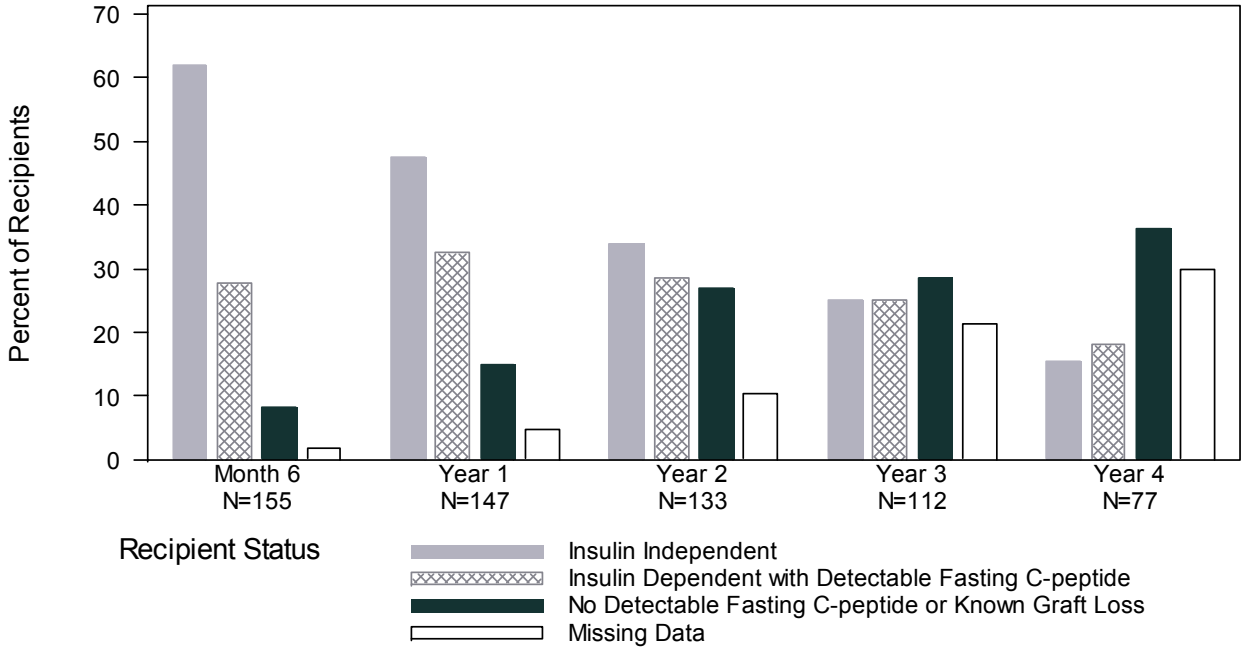


Exhibit 5 – 3(continued)
Insulin Independence, Insulin Dependence, or Absence of Fasting C-peptide Post Last Infusion by Total Number of Infusions Received Islet Alone Recipients

C. Recipients of 3 Infusions

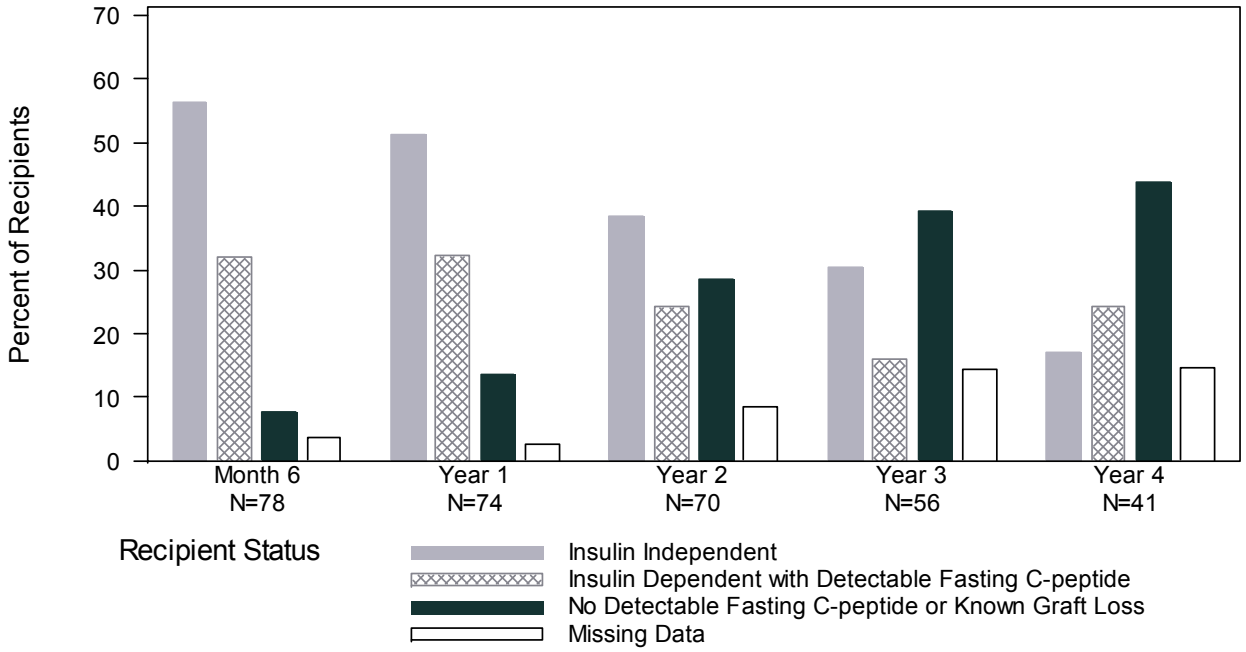
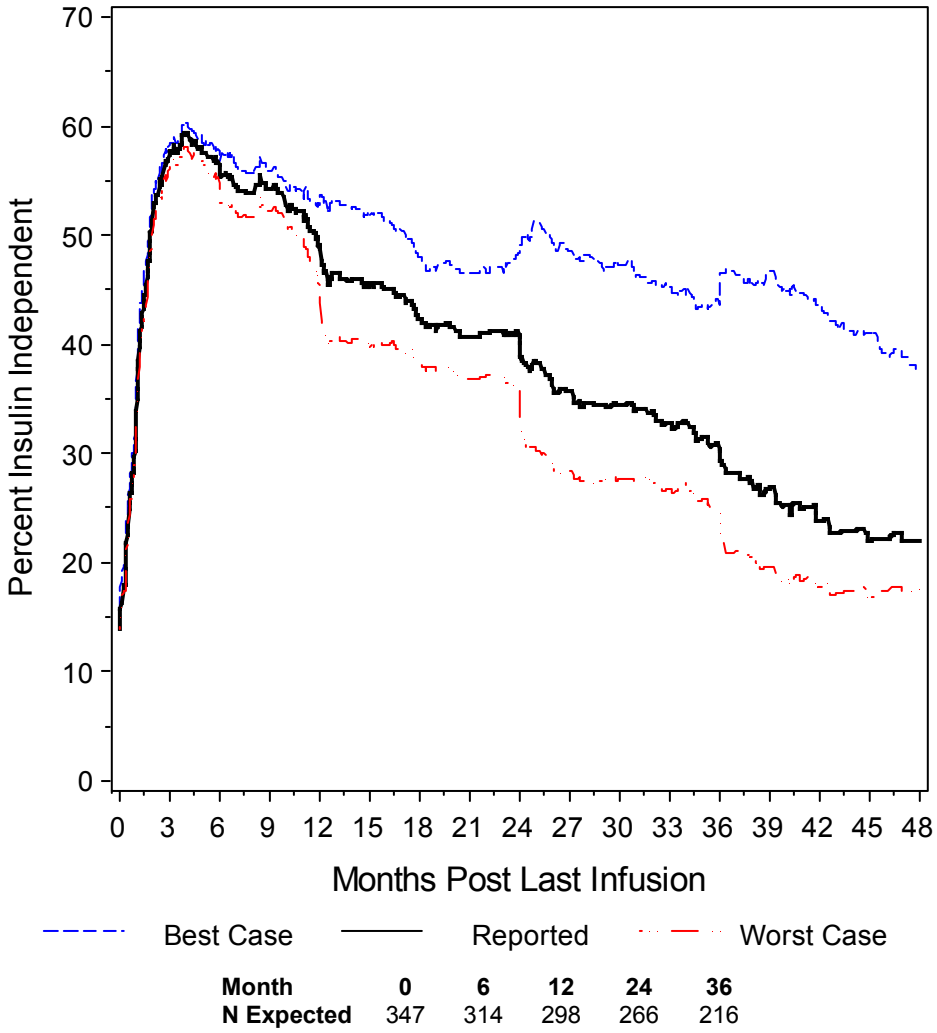


Exhibit 5 – 4
Prevalence of Insulin Independence Post Last Infusion
Islet Alone Recipients



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.

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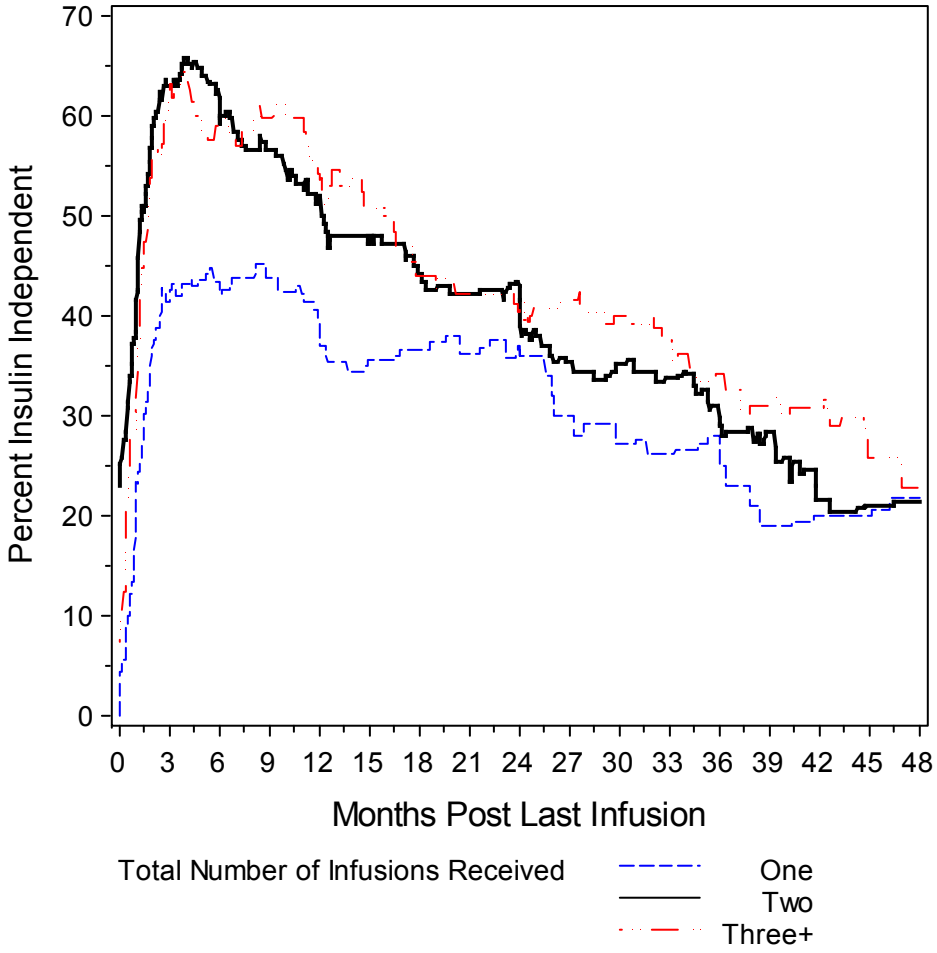
Exhibit 5 – 5
Prevalence of Insulin Independence Post Last Infusion
by Total Number of Infusions Received
Islet Alone Recipients



Month	0	6	12	24	36
N 1 Infusion	95	76	67	53	43
N 2 Infusions	161	149	132	114	84
N 3 Infusions	82	72	70	62	44

This Exhibit summarizes the percent of recipients that are insulin independent by time post their last infusion procedure. Missing data is excluded (i.e., considered missing at random). At Month 4, 65% of participants who received more than one islet infusion were insulin independent, while 43% with one infusion were insulin independent. By Year 2, these rates drop to 43% for those with two infusions, 40% with three or four infusions, and 36% for those with one infusion.

Exhibit 5-6 displays the cumulative percent of recipients who ever achieved insulin independence, measured from first infusion (left column) and from last infusion (right column). An event is the longest-lasting insulin-free period ≥14 days. For example, if a recipient became insulin independent at 1 month post first infusion, then resumed exogenous insulin 3 months later, was re-infused and regained insulin independence for 36 months, it is the longer period that is counted as the event. These long-lasting periods of insulin independence occur later, as measured from first infusion, than the first occurrence of insulin independence ≥ 14 days. Censoring is at the last time point with data on insulin use, a diary-based data source with more complete ascertainment than laboratory measurements. Note that time from first infusion is through 24 months and time from last infusion is 12 months, reflecting the influence of time intervals between infusions.

Estimated by the Kaplan-Meier method, 69% of the 347 IA recipients and 67% of 65 IAKs achieved insulin independence (II, ≥14 days) at least once.

Achievement of insulin independence by total number of infusions (top panel) is not an ideal comparison, because the total number of infusions recipients have had is largely due to whether they achieved and maintained insulin independence. The total number of infusions given as of the report cut-off is a mixture of earlier recipients who may have had either good or unfavorable results with a single infusion and either did not need a re-infusion or perhaps chose to withdraw from further infusions. In addition, more recent recipients of a single infusion may be waiting for a second infusion but are currently classified as having only one infusion.

Achievement of insulin independence is indistinguishable between islet alone and islet after kidney patients, measured as either from first or last infusion.

Achievement of long-lasting insulin independence has improved by 5-10% in the recent cohort (bottom panel), despite the fact that the recent cohort has had less opportunity for re-infusion.

This Exhibit does not represent durability of insulin independence, which is represented as prevalence in Exhibits 5-1 to 5-5 and durability from achievement in Exhibit 5-7.

	N cases			
Months from Last Infusion	**0**	**6**	**12**	**24**
1 Infusion	101	42	34	23
2 Infusions	197	50	38	34
3 Infusions	98	29	25	21
N Islet Alone	332	105	86	60
N Islet After Kidney	64	17	12	9
1999-2004	230	78	70	64
2005-2009	166	44	28	8

Exhibit 5 – 6
Achievement of Insulin Independence

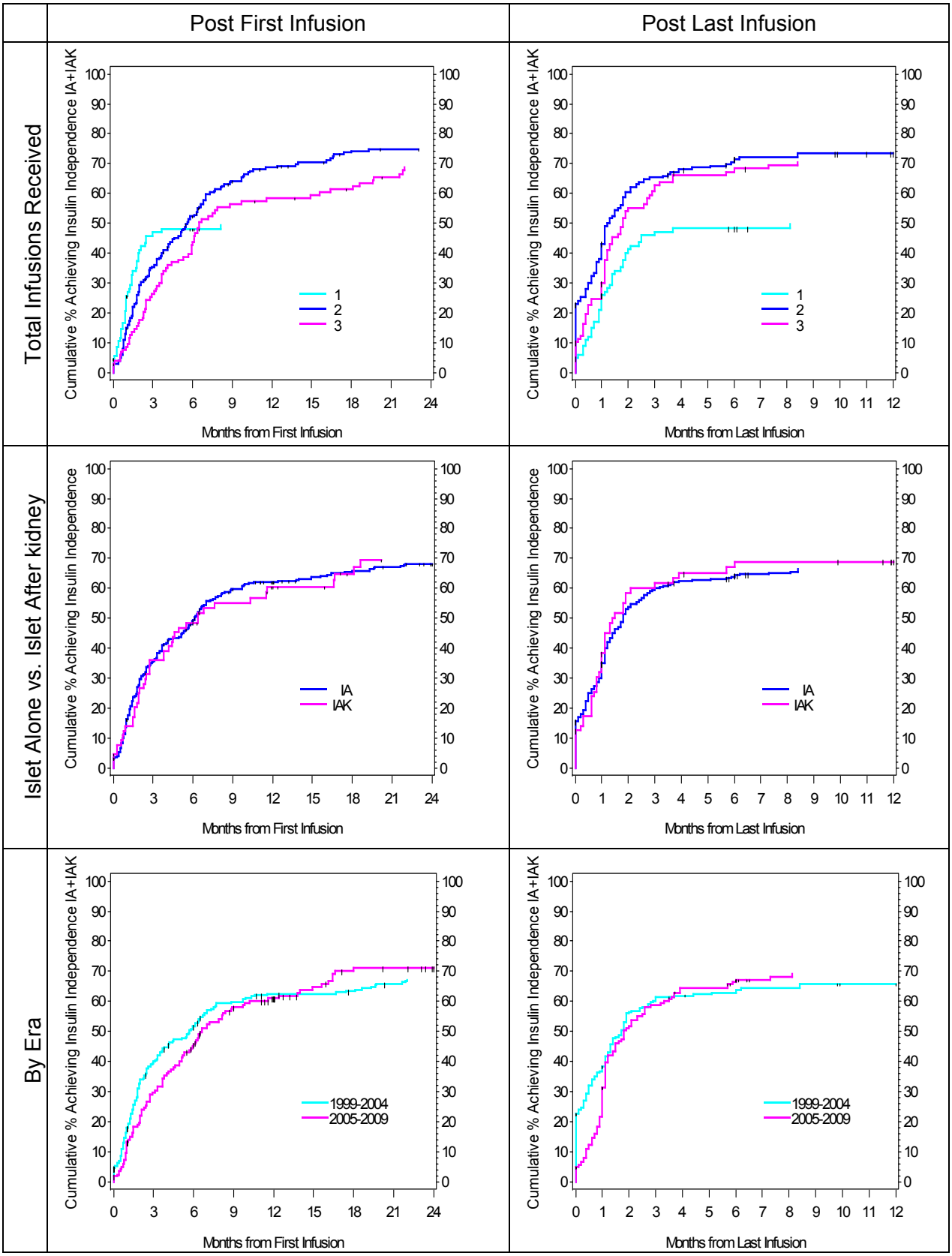


Exhibit 5-7 tracks durability of long-lasting insulin independence for those who achieved it (see previous Exhibit), regardless of the total number of infusions. The cumulative percentage remaining insulin-free (i.e., not returning to insulin use for 14 or more consecutive days) is shown. Censoring is at the last time point with data on insulin use, a diary-based data source with higher ascertainment than laboratory measurements. Known loss of graft function in the absence of insulin data, including reported graft loss or unrecovered loss of C-peptide>0.1 ng/mL, is carried forward though last expected follow-up as insulin dependence.

Estimated by Kaplan-Meier method, of the IAs who achieved insulin independence, 72% retained it at 1 year, 56% at 2 years and 45% at 3 years.

About 12% (51/412) of all allograft recipients were re-infused after achieving insulin independence, some after losing it and then regaining it, others continuing it, after the re-infusion. The median duration of the intermittent period of insulin use was 18 months, during which time recipients took an average of 42% of their pre-infusion insulin.

Again here, stratification by number of infusions received (top panel) is not an ideal comparison (see previous Exhibit). For instance, the single-infusion line is a mixture of early long-term successes (achieved II) and failures (complete graft loss) and more recent recipients who may be waiting for re-infusion or censored insulin-free.

The unadjusted difference between islet alone and islet after kidney is significant at $p<0.05$. However, adjusted for various baseline variables, the difference is accounted for.

There is substantial improvement in the 2- and 3-year rates of durable insulin independence seen in the recently infused era (2005-2008 compared to 1999-2004, $p=0.02$). Of the roughly 70% of allograft recipients who achieved insulin independence, 60-65% of the recent cohort retained insulin independence for 3 years or longer. Nonetheless, there are subgroups from the earlier cohort who had better outcomes attributable to identifiable recipient factors and immunosuppression strategies (see Exhibit 5-14 and 5-15).

	N cases			
Months from Last Infusion	**0**	**12**	**24**	**36**
1 Infusion	46	23	18	10
2 Infusions	140	80	52	25
3 Infusions	66	42	25	15
N Islet Alone	209	125	83	46
N Islet After Kidney	43	20	12	4
1999-2004	148	102	71	41
2005-2009	104	45	24	9

Exhibit 5 – 7
Persistence of Insulin Independence
Allograft Recipients Achieving Insulin Independence

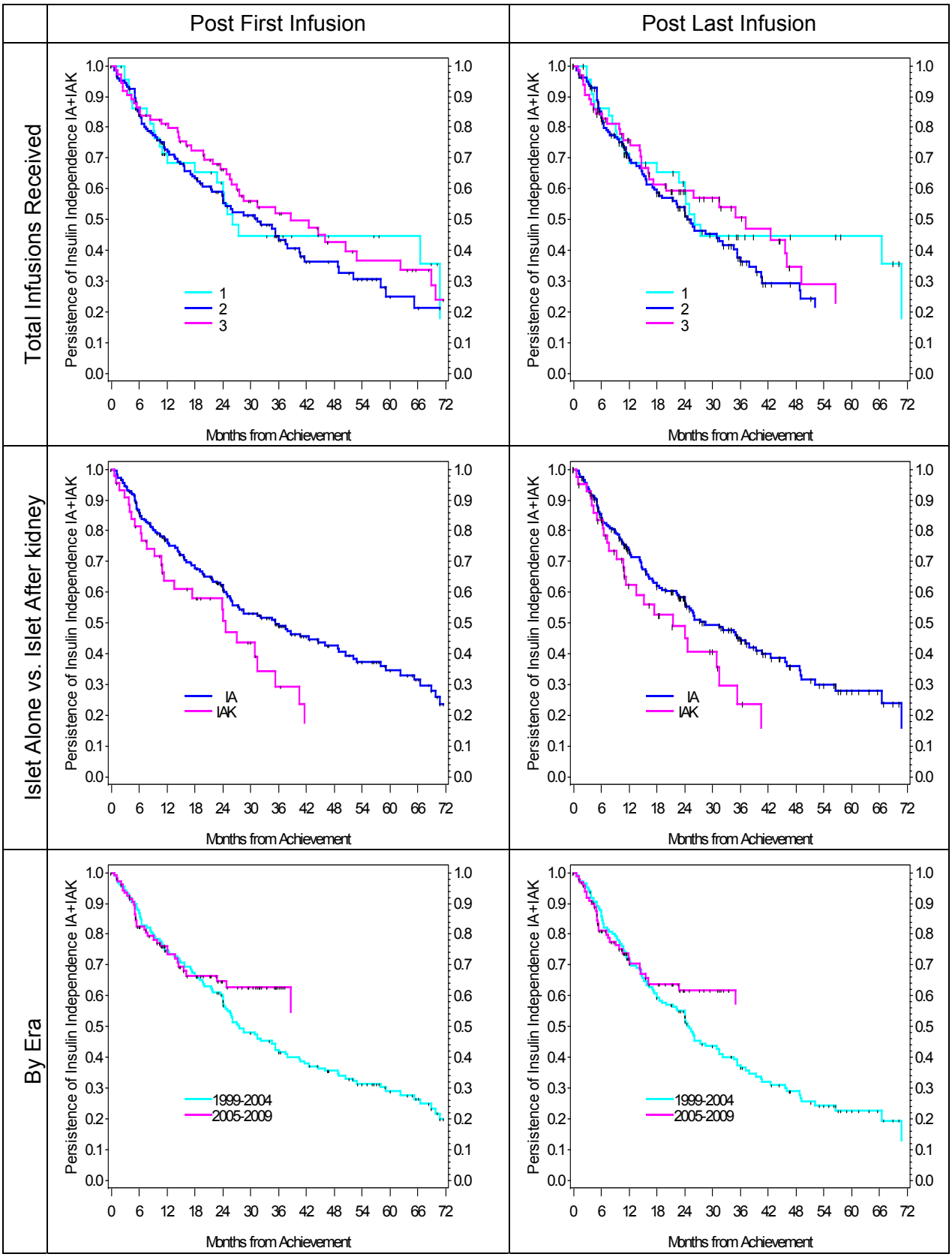
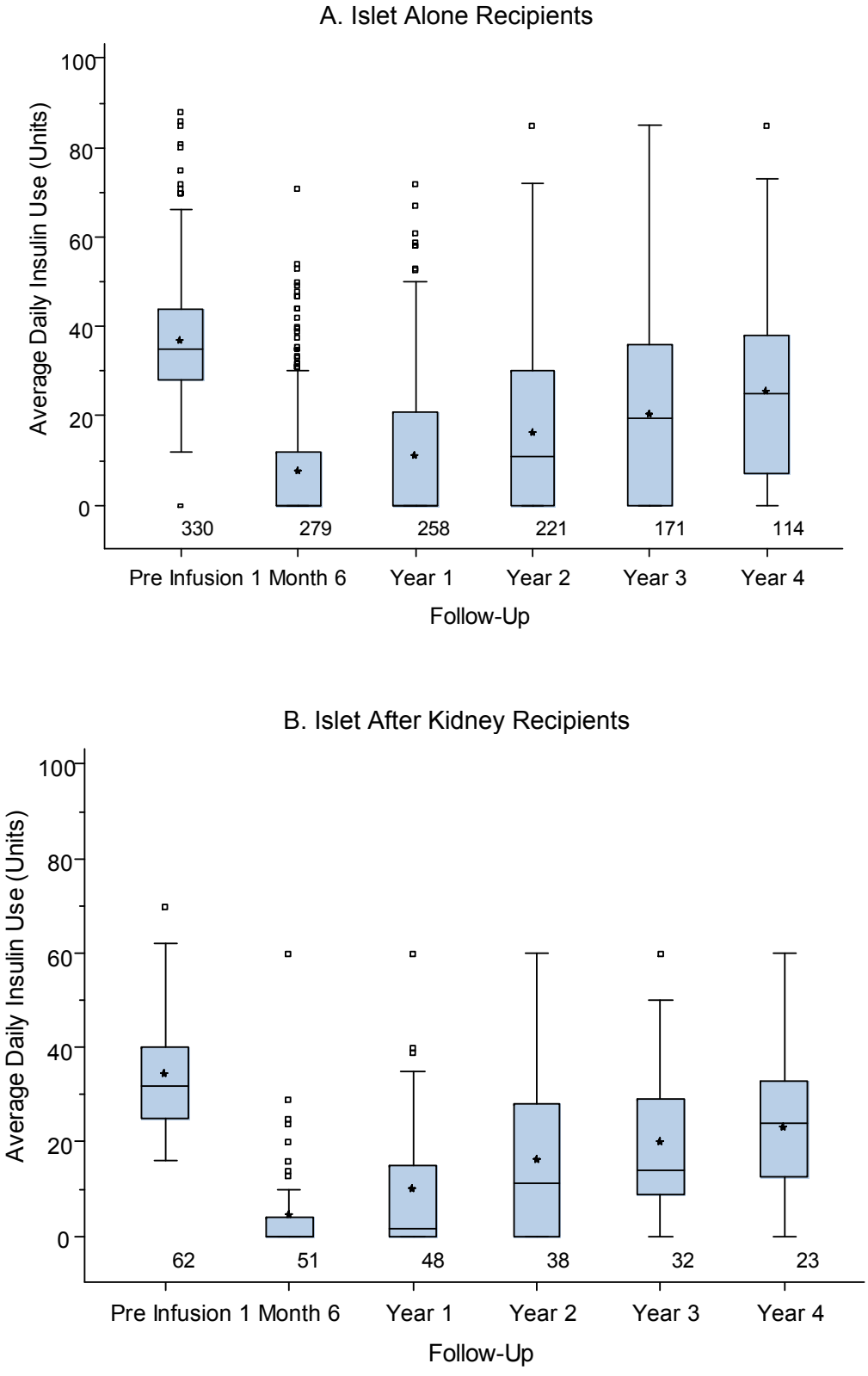
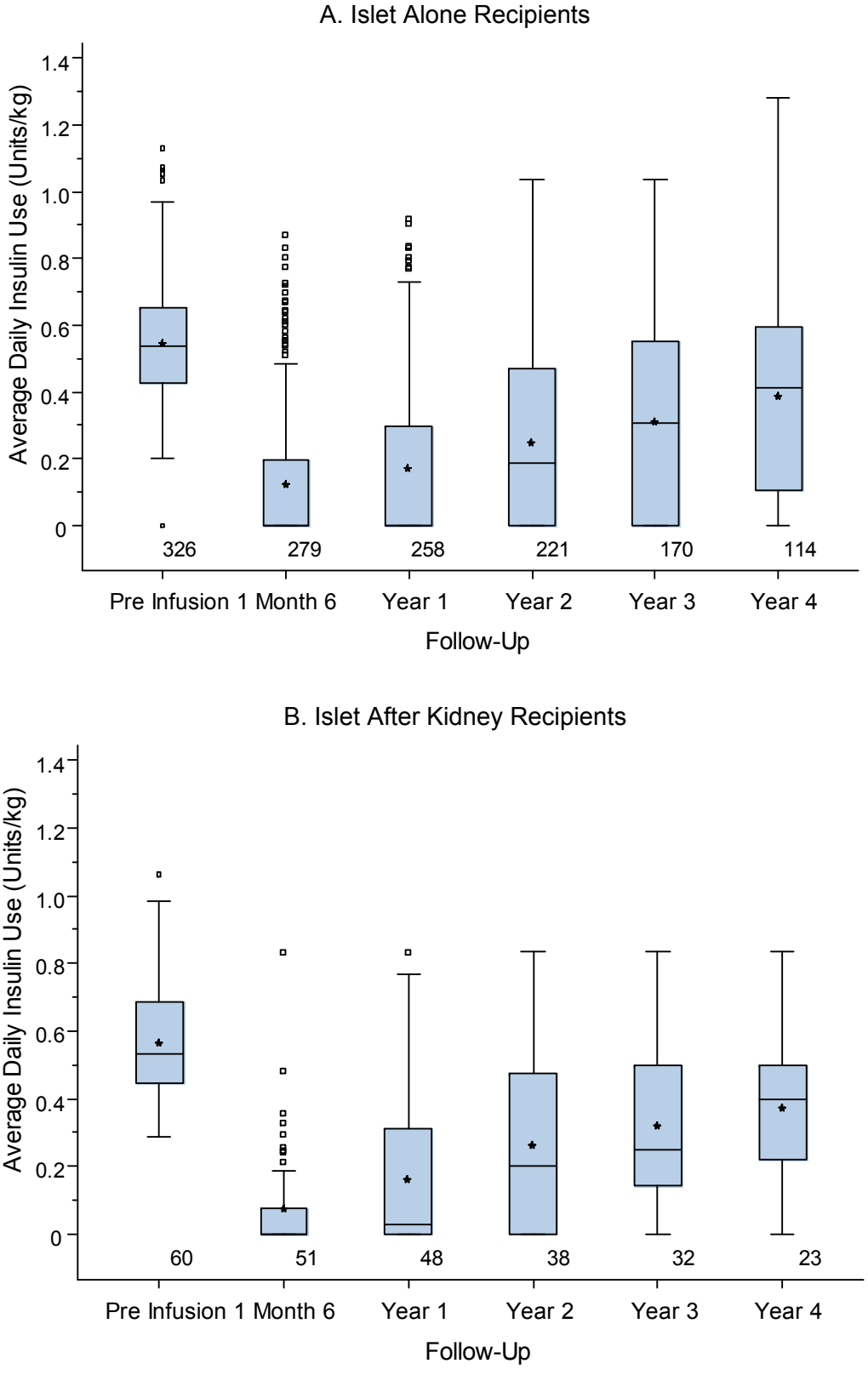


Exhibit 5 – 8
Average Daily Insulin (Units)
Baseline and Post Last Infusion



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

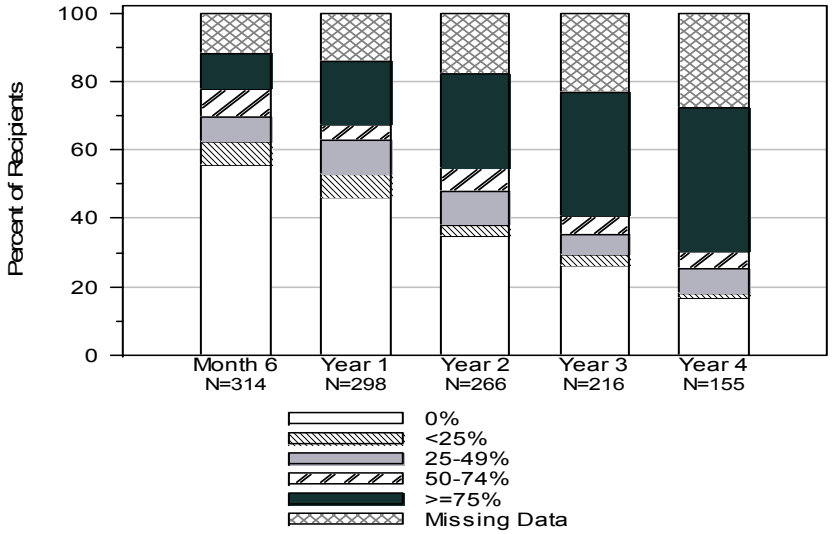
Exhibit 5 – 9
Average Daily Insulin (Units/Kg)
Baseline and Post Last Infusion



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

Exhibit 5 – 10
Percent of Baseline Insulin
Follow-Up Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

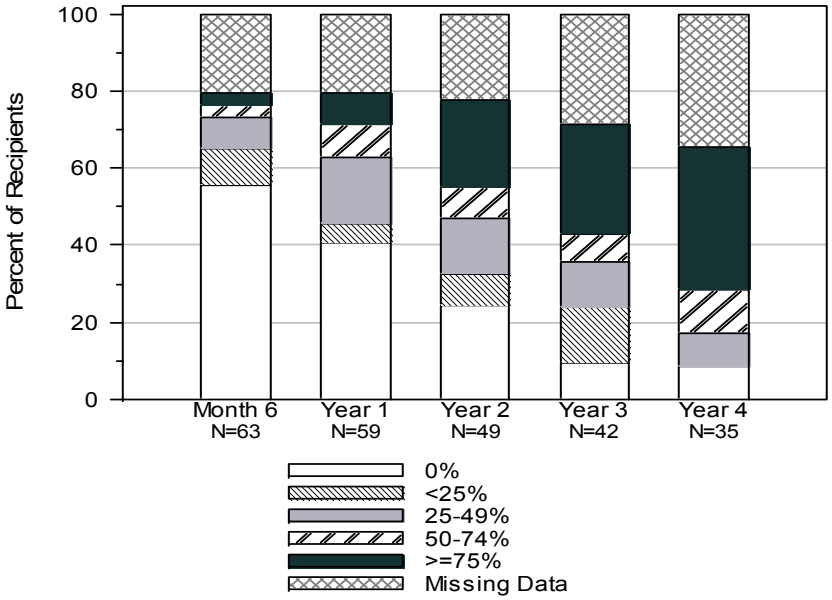
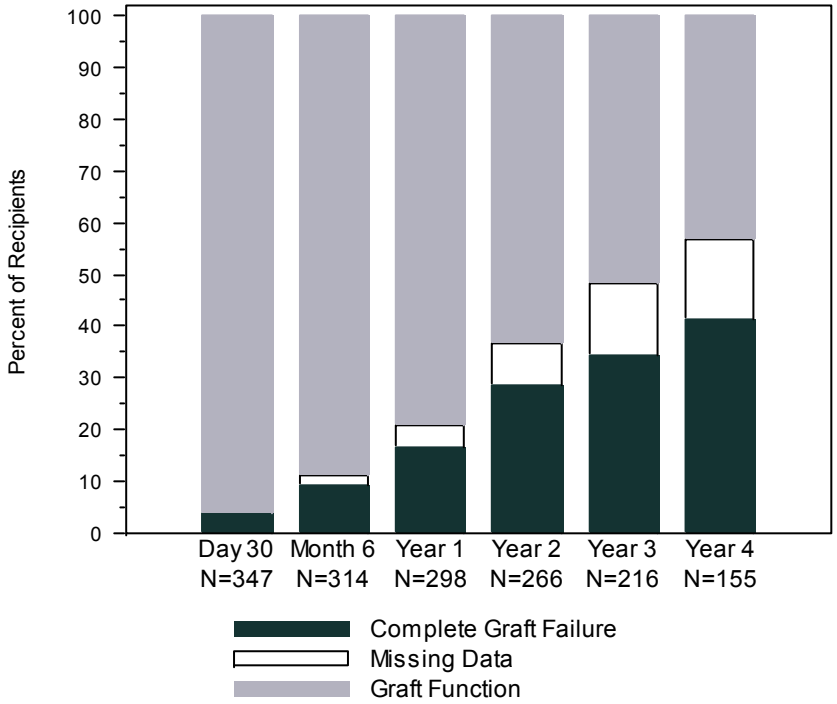
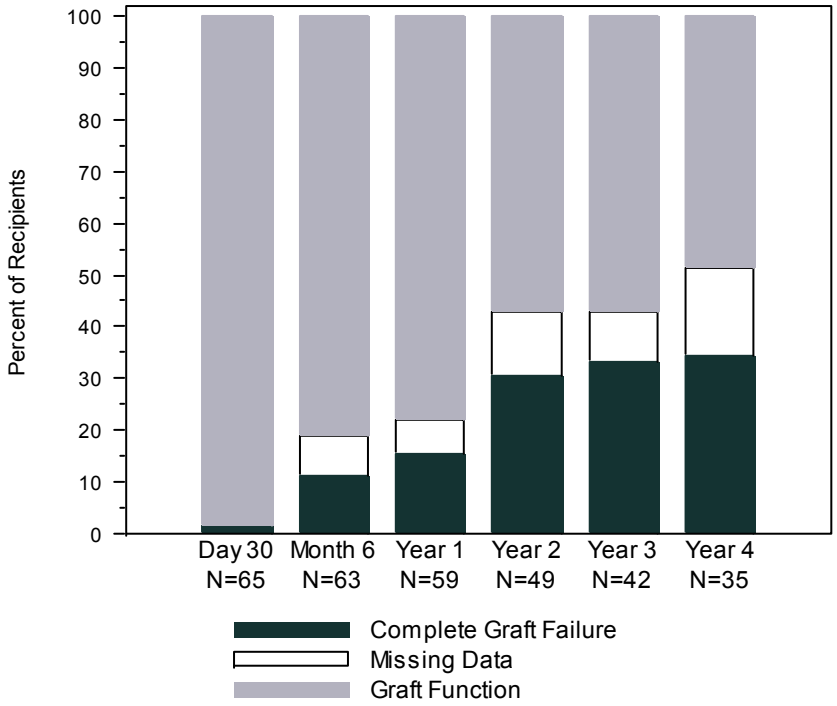


Exhibit 5 – 11
Complete Islet Graft Failure Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients



In Exhibit 5-12, persistence of graft function is shown both post first infusion over all follow-up (not censored at re-infusion, left column), as well as from last infusion (right column). The event is defined as complete graft loss following the last infusion (previous graft loss followed by re-infusion is not counted). Complete graft failure may be reported by the site with or without additional data (C-peptide, HbA_{1c}, etc), or is imputed without a specific report by the site when the patient loses measurable C-peptide (<0.1 ng/mL) without recovery over two consecutive scheduled visits and without subsequent re-infusion. Patients lost to follow-up without a report of complete graft failure are censored in these analyses (i.e., assumed missing at random).

Estimated by Kaplan-Meier method, 13% of IA or IAK lost graft function by 1 year post last transplant, 30% by 2 years and 35% by 3 years.

Again as in Exhibits 5-6 and 5-7, stratification by total number of infusions to date is not an ideal comparison. Recipients of a single infusion seem to exhibit greater graft loss likely resulting from patient decision rather than biological factors.

Persistence of graft function does not differ between IA and IAK. This is related to the lessened ability of IAK to maintain II over time despite good C-peptide levels (See Exhibit 5-18).

There is a trend of improvement in persistence of graft function between early and late cohorts in the decade (bottom panel). However, the most recent cohort has not yet had equal opportunity for re-infusion, so what may be intermittent graft failures before re-infusion are counted as events in the recent cohort.

N cases				
Months from Last Infusion	**0**	**12**	**24**	**36**
1 Infusion	101	48	29	23
2 Infusions	197	141	107	67
3 Infusions	98	71	42	25
N Islet Alone	332	222	153	102
N Islet After Kidney	64	39	26	15
1999-2004	230	172	132	98
2005-2009	166	87	47	14

Exhibit 5 – 12
Persistence of Graft Function
All Allograft Recipients

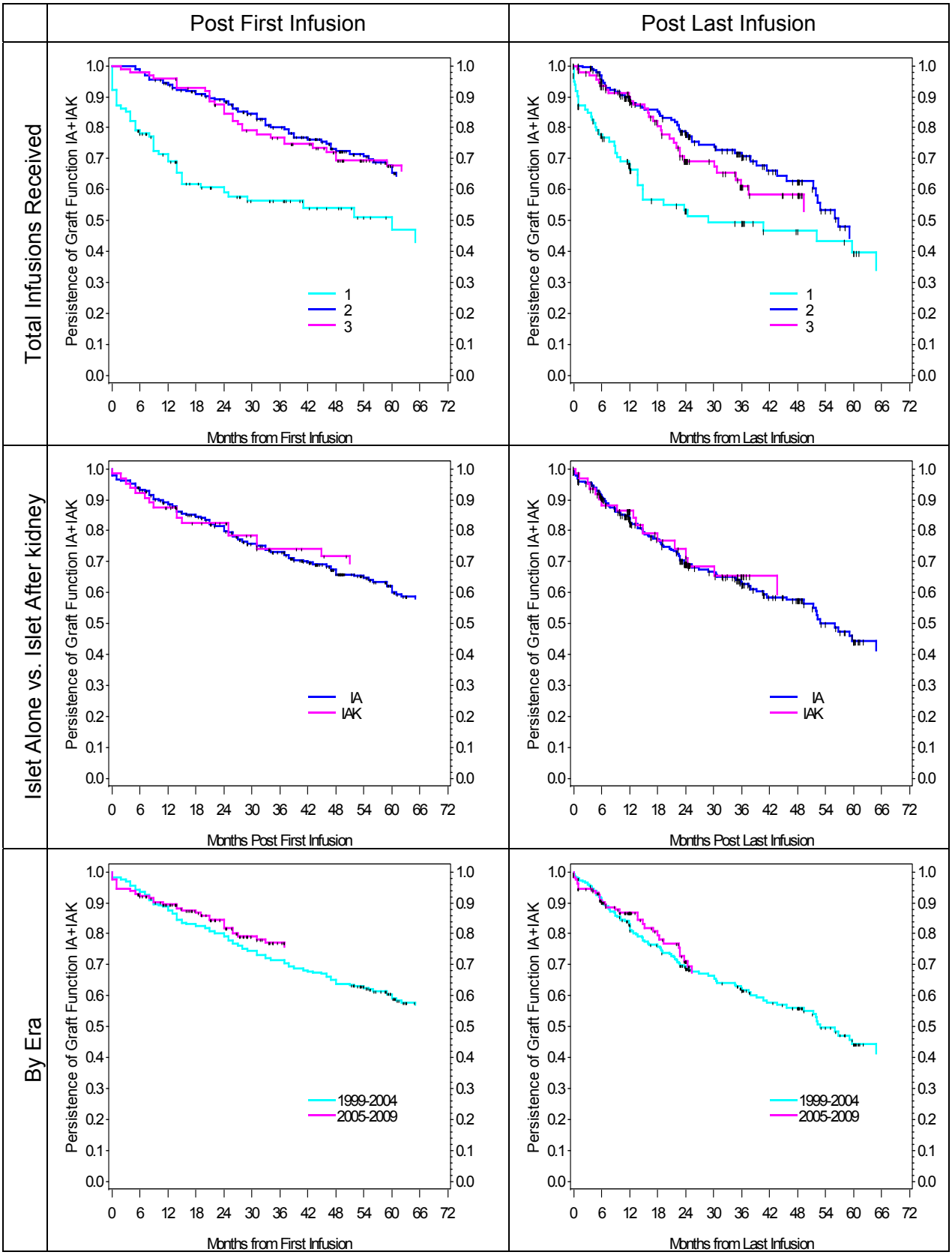
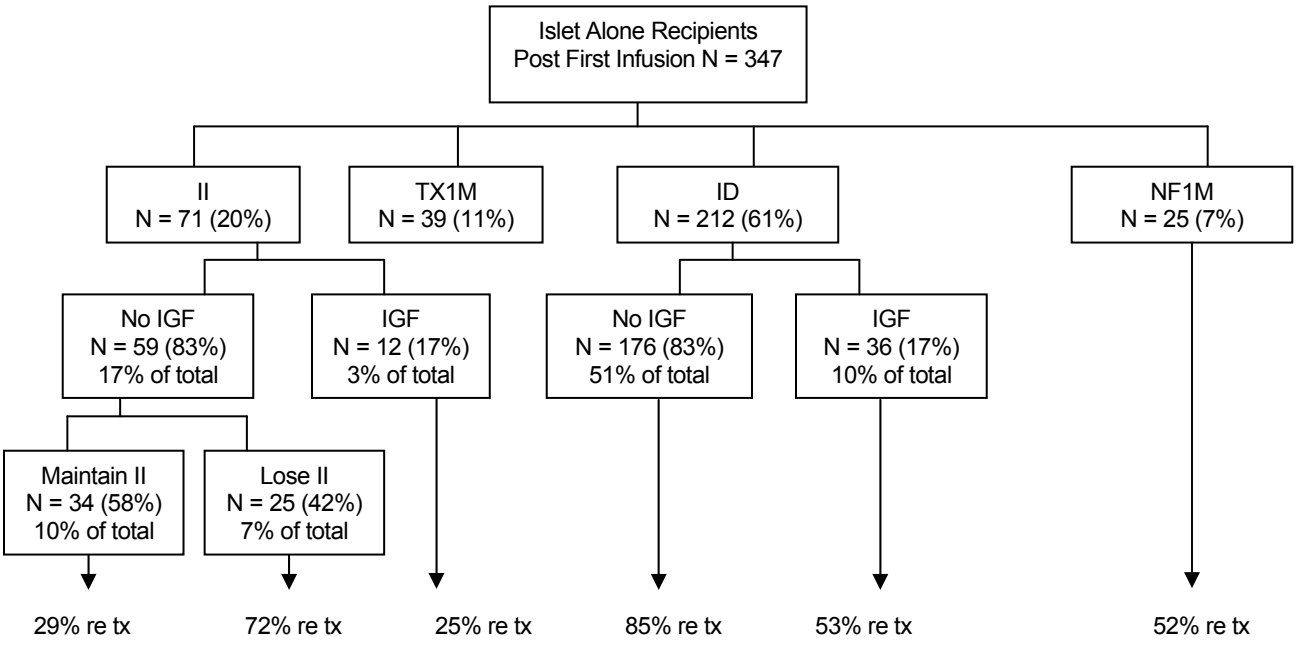
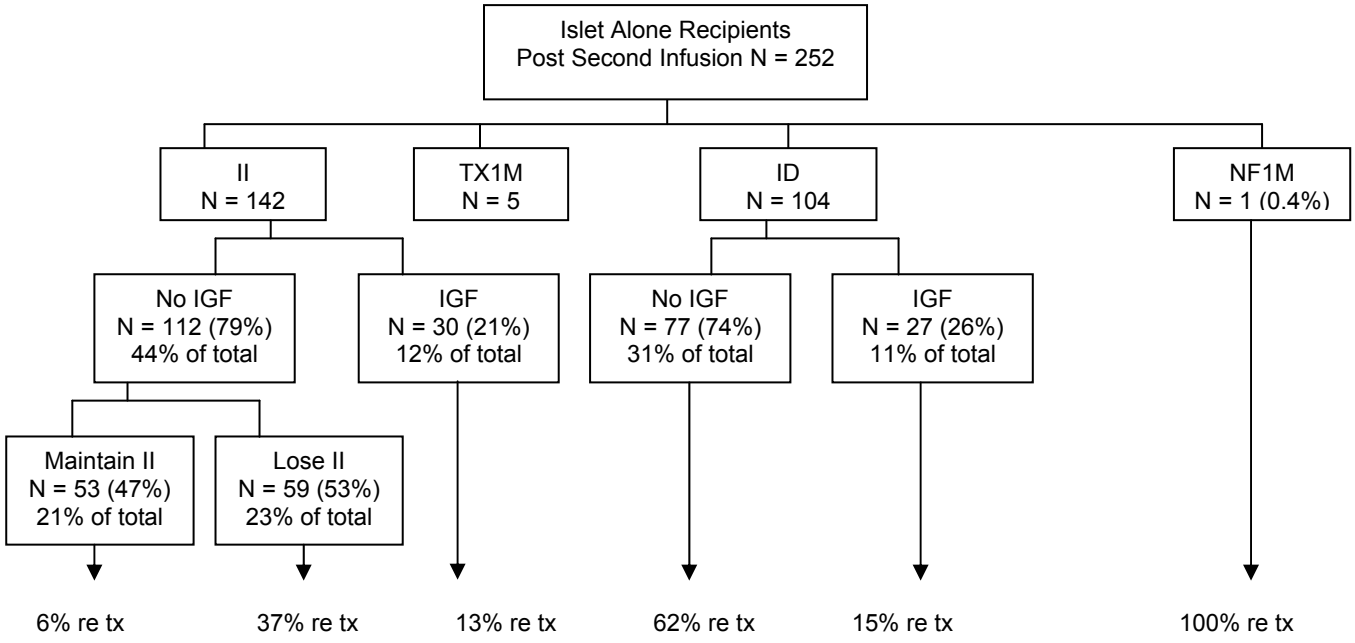


Exhibit 5 – 13A
Outcomes Post Each Infusion
Post First Infusion



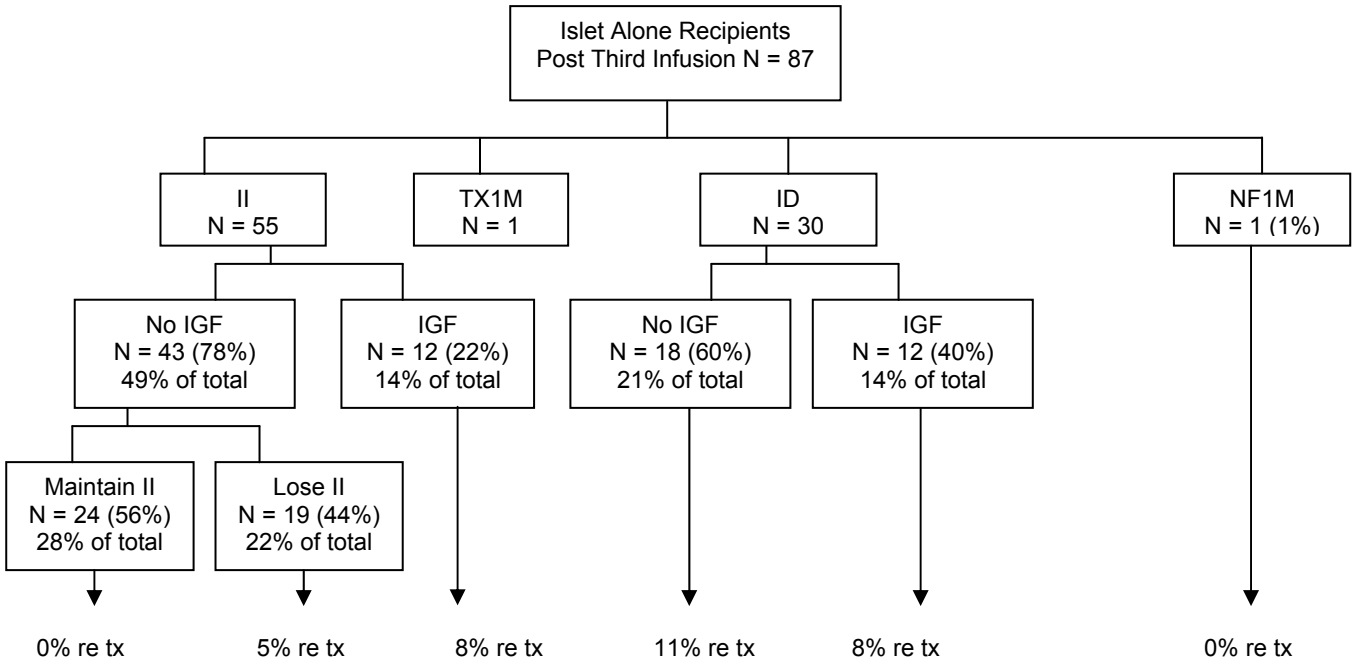
TX1M = Received a subsequent islet infusion prior to one month. Recipient not insulin independent with graft function at the time of the subsequent infusion.
NF1M = Loss or absence of graft function prior to one month post islet infusion.

Exhibit 5 – 13B
Outcomes Post Each Infusion
Post Second Infusion



TX1M = Received a subsequent islet infusion prior to one month. Recipient not insulin independent with graft function at the time of the subsequent infusion.
NF1M = Loss or absence of graft function prior to one month post islet infusion.

Exhibit 5 – 13C
Outcomes Post Each Infusion
Post Third Infusion



TX1M = Received a subsequent islet infusion prior to one month. Recipient not insulin independent with graft function at the time of the subsequent infusion.
NF1M = Loss or absence of graft function prior to one month post islet infusion.

Cox Modeling of Primary Outcomes Post First Infusion (Exhibits 5-14A-E and 5-15A-D)
(Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up)
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics (Factors)
Islet Alone Recipients with Data Available on Key Predictors

All variables describing recipient, donor, islet and immunosuppressant characteristics were included in univariate Cox models to identify factors that influence primary outcomes (achievement of insulin independence, loss after achievement, complete graft failure and re-infusion). Factors that were significant at $p<0.10$ univariately (shown in Tables 5-14A post first infusion and 5-15A post last infusion) were added or withdrawn in multivariate models one at a time, to assess joint effects on the outcomes. Variables not significant at $p<0.10$ are left blank. Variables with data available on only a small subset of the group being analyzed are not included in the multivariate analyses, and thus cannot be precluded as significant.

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

Definitive ascertainment of complete islet failure remains challenging. Cases with unknown outcome status are censored as of their last observed follow-up, to minimize estimation bias.

Univariate results are displayed tabularly (Exhibit 5-14-A for outcomes of first infusion and 5-15-A for outcomes of last infusion), and graphically as forest plots (Exhibits 5-14-B-E and Exhibits 5-15-B-D, respectively).

Exhibit 5 – 14A
Primary Outcomes Post First Infusion Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] >1.0 is favorable			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] <1.0 is favorable			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1] <1.0 is favorable			D. ReInfusion Post First Infusion[2] <1.0 = less likelihood of re-infusion		
Events / Total >>	**72 / 341**			**43 / 72**			**251 / 341**			**73 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**OR**	**p**
Cohort 1999-2004/05-08	.	.		72	0.562	0.09	.	.		341	0.405	<0.001
Recipient gender (0=M 1=F)	341	1.678	0.05	.	.		.	.		341	0.485	0.006
Recipient age (years)	.	.		.	.		341	0.703	0.005	.	.	
Employment impacted by dx	.	.		.	.		.	.		.	.	
Diabetes Duration (years)	.	.		72	0.731	0.03	341	0.777	0.02	.	.	
Months on waitlist	.	.		.	.		.	.		.	.	
Baseline daily insulin use (Units)	330	0.639	<0.001	.	.		.	.		330	1.441	<0.001
Baseline weight (10-kg)	330	0.703	0.006	.	.		.	.		330	1.383	0.009
Baseline PRA (%)	.	.		.	.		.	.		.	.	
Baseline BMI	327	0.905	0.03	.	.		327	0.920	0.06	.	.	
Baseline use of insulin pump (0=N 1=Y)	.	.		.	.		.	.		330	0.546	0.02
Baseline number of daily insulin injections	212	0.749	<0.001	.	.		.	.		.	.	
Baseline use of insulin pump or >=3 insulin inject	.	.		.	.		.	.		.	.	
Years prior to first inf using ins pump or >= 3 in	.	.		.	.		226	0.978	0.03	.	.	
Intensive therapy <10/10-25/>=25 yrs	.	.		.	.		196	0.752	0.09	.	.	
Baseline HbA_{1c} (%)	329	0.763	0.008	72	0.677	0.01	329	1.193	0.07	329	1.189	0.08
Baseline fasting glucose (mg/dL)	316	0.972	0.07	.	.		.	.		.	.	
Baseline C-peptide (ng/mL)	.	.		70	2.891	0.06	.	.		.	.	
Baseline GAD 65 autoantibodies (0,1)	.	.		.	.		217	2.169	0.02	.	.	
Baseline IA-2 autoantibodies (0,1)	.	.		.	.		159	2.313	0.02	.	.	
Baseline insulin autoantibodies (0,1)	.	.		.	.		167	2.535	0.08	.	.	
Baseline total positive autoantobodies (0,1,2,3)	.	.		.	.		234	1.909	0.004	.	.	

Exhibit 5 – 14A (continued)
Primary Outcomes Post First Infusion Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] >1.0 is favorable			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] <1.0 is favorable			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1] <1.0 is favorable			D. ReInfusion Post First Infusion[2] <1.0 = less likelihood of re-infusion		
Events / Total >>	**72 / 341**			**43 / 72**			**251 / 341**			**73 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**OR**	**p**
Total donors	.	.		.	.		.	.		.	.	
Donor gender (1=M 1.5=Mix 2=F)	.	.		.	.		.	.		.	.	
Donor age (x10 yrs)	.	.		.	.		.	.		296	1.022	0.04
Donor(s) Hispanic (0=N 1=Y)	.	.		51	5.703	0.03	.	.		.	.	
Donor race (0=W 1=Non-white)	341	1.749	0.05	.	.		341	0.447	0.06	.	.	
Donor(s) blood type (1=A,B,AB 2=O)	318	0.631	0.06	.	.		.	.		318	1.637	0.05
CVS death(s) (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor CMV (0=- 1=+)	.	.		.	.		.	.		.	.	
Donor(s) hx hypertension (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) ETOH (0=N 1=Y)	.	.		62	2.559	0.02	.	.		281	2.256	0.03
Donor(s) diabetes (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) given vasopressors (0=N 1=Y)	341	0.365	0.02	72	0.261	0.01	.	.		.	.	
Donor transfused prior to hospitalization (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) transfused in hospital (0=N 1=Y)	.	.		.	.		.	.		.	.	
Donor(s) given steroids (0=N 1=Y)	195	0.505	0.02	.	.		.	.		.	.	
Donor(s) insulin (0=N 1=Y)	.	.		62	0.507	0.06	277	1.645	0.06	277	0.576	0.04
Donor(s) weight (10-kg)	317	1.013	0.006	.	.		.	.		317	0.976	<0.001
Donor(s) height (cm)	.	.		.	.		.	.		.	.	
Donor(s) BSA	315	2.576	0.02	.	.		.	.		315	0.168	<0.001
Donor(s) BMI	315	1.054	0.001	.	.		.	.		315	0.928	<0.001
Donor(s) creatinine	.	.		.	.		.	.		.	.	
Donor(s) BUN	.	.		.	.		.	.		.	.	
Donor(s) bilirubin	.	.		.	.		.	.		.	.	
Donor(s) AST	.	.		54	0.991	0.08	.	.		.	.	
Donor(s) ALT	.	.		54	0.988	0.05	.	.		.	.	
Donor(s) serum lipase	.	.		.	.		.	.		254	0.998	0.04

Exhibit 5 – 14A (continued)
Primary Outcomes Post First Infusion Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] >1.0 is favorable			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] <1.0 is favorable			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1] <1.0 is favorable			D. ReInfusion Post First Infusion[2] <1.0 = less likelihood of re-infusion		
Events / Total >>	**72 / 341**			**43 / 72**			**251 / 341**			**73 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**OR**	**p**
Donor(s) pre-insulin glucose	.	.		.	.		.	.		.	.	
Max donor(s) glucose (mg/dL)	.	.		.	.		.	.		.	.	
Any positive crossmatch (0=N 1=Y)	.	.		.	.		.	.		185	0.145	0.07
Procurement/infusion teams (0-Unrelated 1-Related)	308	1.805	0.02	67	0.483	0.02	.	.		.	.	
Processing/infusion center (0-Unrelated 1-Related)	.	.		69	0.209	0.01	315	0.264	<0.001	.	.	
Collagenase (1=Liberase alone 2=Other)	.	.		.	.		.	.		341	0.772	0.02
Pulmozyme	.	.		.	.		.	.		.	.	
Gradient type	301	1.796	0.03	.	.		.	.		.	.	
Cultured >6 hrs (0=N 1=Y)	.	.		72	0.454	0.01	341	0.663	0.08	.	.	
Culture time (hrs)	.	.		67	0.977	0.01	292	0.979	0.007	.	.	
Donor(s)-recipient age difference (x10-yrs)	296	0.843	0.04	.	.		296	1.181	0.05	296	1.175	0.05
Donor(s)-recipient BMI difference (x10)	305	1.769	<0.001	.	.		.	.		305	0.482	<0.001
Genders match (0=N 1=Y)	.	.		72	0.522	0.04	.	.		.	.	
Donor(s) CMV+ / Recipient CMV- (0=N 1=Y)	312	0.475	0.02	.	.		.	.		.	.	
Pancreas preservation (1-UW 2-2L 3-Both)	.	.		.	.		.	.		.	.	
Recipient insulin day 0 (0=N 1=Y)	.	.		.	.		.	.		262	0.315	<0.001
Time from cross clamp to panc recovery (hrs)	.	.		.	.		.	.		.	.	
Time from admission to death (hrs)	.	.		.	.		.	.		.	.	
Death to pancreas recovery (hrs)	208	1.017	0.07	.	.		.	.		208	0.953	<0.001
Recovery to transplant (hrs)	.	.		.	.		.	.		215	0.988	0.09
Death to cross-clamp (hrs)	.	.		.	.		.	.		301	0.977	0.01
Death to transplant (hrs)	.	.		.	.		.	.		308	0.986	0.002
Cold ischemia time (hrs)	307	0.912	0.03	67	1.161	0.02	.	.		.	.	
Embedded islets (%)	.	.		.	.		.	.		.	.	
Stimulation index	.	.		66	0.839	0.02	.	.		.	.	
Stimulation index <2/2-3.5/>=3.5	.	.		66	0.627	0.02	.	.		.	.	

Exhibit 5 – 14A (continued)
Primary Outcomes Post First Infusion, Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] >1.0 is favorable			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] <1.0 is favorable			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1] <1.0 is favorable			D. ReInfusion Post First Infusion[2] <1.0 = less likelihood of re-infusion		
Events / Total >>	**72 / 341**			**43 / 72**			**251 / 341**			**73 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**OR**	**p**
Islet Viability (%)	285	1.042	0.07	.	.		.	.		285	0.949	0.02
Viability > 87% (0=N 1=Y)	285	2.517	0.02	.	.		.	.		285	0.459	0.02
Total beta cells (1000s)	.	.		.	.		.	.		110	0.111	0.03
Total beta cells/kg donor	.	.										
Total insulin content of islets	.	.		22	1.223	0.09	.	.		.	.	
Insulin content <3/3-5/>=5	.	.		.	.		.	.		.	.	
Total endotoxin infused	.	.		60	165.6	0.04	.	.		.	.	
Total endotoxin infused/kg donor	.	.		56	1.050	0.06	.	.		.	.	
Endotoxin/kg <0.6/.06-3.0/>=3.0	.	.		.	.		.	.		254	1.768	0.007
Total IEQs at time of islet count (1000s)	282	7.649	0.001	.	.		.	.		282	0.071	0.001
Total islet particles infused (1000s)	.	.		.	.		.	.		.	.	
Total volume infused over all infusions (ml)	286	0.929	0.05	63	1.236	<0.001	.	.		286	1.708	<0.001
Cumulative IEQs infused (1000s)	328	8.268	<0.001	.	.		.	.		328	0.062	<0.001
Cumulative IEQs infused (1:<400K 2:>=400K)		.		.	.		.	.		.	.	
Cumulative IEQs infused/kg recipient (100s)												
IEQ/islet particle ratio	.	.		.	.		230	1.552	0.01	230	0.518	0.003
Isletsize (0-small 1-large)	.	.		.	.		230	1.687	0.10	.	.	
Poly T-cell depleting	.	.		.	.		.	.		327	0.201	<0.001
Rabbit thymoglobulin	.	.		.	.		.	.		330	0.193	<0.001
Horse thymoglobulin	.	.		.	.		.	.		.	.	
Anti-lymphocyte globulin	.	.		.	.		.	.		.	.	
Mono T-cell depleting	.	.		.	.		.	.		.	.	
Anti-Il2	.	.		70	2.449	0.06	.	.		327	3.752	<0.001
Basiliximab	.	.		.	.		.	.		.	.	
Daclizumab	.	.		70	2.449	0.06	.	.		330	3.134	<0.001
Anti-CD3	327	2.753	0.03	.	.		.	.		327	0.113	0.004
TNF blocker	.	.		.	.		327	0.525	0.04	327	0.500	0.01

Exhibit 5 – 14A (continued)
Primary Outcomes Post First Infusion, Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] >1.0 is favorable			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] <1.0 is favorable			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1] <1.0 is favorable			D. ReInfusion Post First Infusion[2] <1.0 = less likelihood of re-infusion		
Events / Total >>	**72 / 341**			**43 / 72**			**251 / 341**			**73 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**OR**	**p**
Infliximab	.	.		.	.		.	.		327	6.860	0.01
Etanercept	328	1.597	0.08	.	.		328	0.571	0.09	328	0.299	<0.001
DSG	.	.		.	.		.	.		.	.	
Calcineurin inhibitor	.	.		.	.		327	0.301	<0.001	327	6.239	<0.001
Tacrolimus	.	.		.	.		334	0.519	0.07	334	4.310	<0.001
Cyclosporin	.	.		.	.		.	.		.	.	
Sirolimus or Everolimus	.	.		.	.		.	.		327	3.348	0.003
Sirolimus	.	.		71	5.914	0.08	.	.		334	3.109	0.002
Everolimus	.	.		.	.		.	.		.	.	
Inosine: MMF or mycophenolic acid	.	.		.	.		.	.		327	0.260	<0.001
MMF	.	.		.	.		.	.		331	0.252	<0.001
Mycophenolic acid	.	.		.	.		.	.		.	.	
Prednisone, Methylprednisolone, or other steroid	.	.		.	.		.	.		331	0.195	<0.001
Poly or mono T-cell AB + calc inh + (mtor OR inosine)	.	.		72	0.286	0.09	.	.		341	0.502	0.09
Poly or mono T-cell AB + TNF-alpha ant + calc inh + (mtor OR inos	.	.		.	.		.	.		341	0.267	0.005
Monoclonal anti-IL2R + calc inh + (mtor OR inosine)	.	.		72	1.911	0.04	.	.		341	3.079	<0.001
Monoclonal anti-IL2R + TNF-alpha ant + calc inh + (mtor OR inosin	.	.		.	.		341	0.402	0.08	.	.	
Number of A locus mismatches	.	.		.	.		.	.		.	.	
Number of B locus mismatches	.	.		.	.		.	.		.	.	
Number of DR locus mismatches	.	.		.	.		.	.		.	.	
Number of DQ locus mismatches	.	.		.	.		.	.		.	.	
Number of Class I locus mismatches	.	.		.	.		.	.		.	.	
Number of Class II locus mismatches	.	.		.	.		.	.		.	.	
Number of A/B/DR locus mismatches	.	.		.	.		.	.		.	.	
Number of A/B/DR/DQ locus mismatches	.	.		.	.		.	.		.	.	

Exhibit 5 – 14A (continued)
Primary Outcomes Post First Infusion Up to Re-Infusion, Complete Islet Failure, or Last Follow-Up According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics
Islet Alone Recipients

[1]Cox proportional hazard model: Hazard ratio (HR) and p-value [2]Logistic regression model: Odds ratio (OR) and p-value	A. Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] >1.0 is favorable			B. Loss of Insulin Independence Post First Infusion Censored at CIF, Reinfusion or Last Follow-Up[1] <1.0 is favorable			C. Complete Islet Failure (CIF) Post First Infusion Censored at Reinfusion or Last Follow-Up[1] <1.0 is favorable			D. ReInfusion Post First Infusion[2] <1.0 = less likelihood of re-infusion		
Events / Total >>	**72 / 341**			**43 / 72**			**251 / 341**			**73 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**OR**	**p**
Reexposed to A locus mismatch	.	.		.	.		.	.		.	.	
Reexposed to B locus mismatch	.	.		.	.		.	.		.	.	
Reexposed to DR locus mismatch	.	.		.	.		.	.		.	.	
Reexposed to DQ locus mismatch	.	.		.	.		.	.		.	.	
Reexposed to Class I	.	.		.	.		.	.		.	.	
Reexposed to Class II locus mismatch	.	.		.	.		.	.		.	.	
Reexposed to A/B/DR locus mismatch	.	.		.	.		.	.		.	.	
Reexposed to A/B/DR/DQ locus mismatch	.	.		.	.		.	.		.	.	

Exhibit 5 – 14A (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

The final multivariate model for insulin independence (72 events / 341recipients) post first infusion up to reinfusion is:

Variable	HR	p
Baseline daily insulin use (Units)	0.62 higher insulin predicts lower likelihood of achieving II	<0.001
Donor(s) given vasopressors (0=N 1=Y)	0.39 donor vasopressors predict lower likelihood of achieving II	0.04
Cumulative IEQs infused (1000s)	9.27 higher IEQs predict greater likelihood of achieving II	<0.001
Anti-CD3 antagonists (0=N 1=Y)	3.83 Anti-CD3 use predicts greater likelihood of achieving II	0.01
Daclizumab (0=N 1=Y)	1.78 Daclizumab use use predicts greater likelihood of achieving II	0.07

Many relationships exist among the independent variables (see 2009 Annual Report Supplemental Materials at www.CITRegistry.org): baseline daily insulin is substantially correlated with baseline weight, baseline BMI, baseline HbA_{1c}, fasting glucose, and number of daily injections. Any of these measures of initial control suffices to explain its influence on achieving insulin independence: the better the control, the more likely to achieve insulin independence. Greater number of IEQs infused improves the chances of achieving insulin independence as well as reducing the need for re-infusion. When the procurement team is related to the transplant center, insulin independence is more likely. Whether the donor was given steroids cannot be excluded as significantly associated with this outcome. Additionally, there is substantial imbalance between immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of immunosuppressant therapies as yes/no variables in a multivariate model. However, their effects cannot be ruled out. Anti-CD3 antagonists and daclizumab each shows advantage to achieving insulin independence. More-comprehensive modeling of immunosupression regimens are being conducted in focus topic analysis.

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

The final multivariate model for complete islet failure (251 events / 341 recipients) post first infusion up to re-infusion is:

Variable	HR (<1.0 favorable for retaining function)	p
Age	0.64	0.001
Processing/infusion center (0=Unrelated 1=Related)	0.28	<0.001
TNF Blocker (0=No 1=Yes)	0.54	0.06

Older recipient age predicts lower risk of losing the graft. The effect of worse diabetic control does not predict losing the first graft. Related processing and infusion centers substantially reduce the chances of losing the first graft, as does use of TNF blocker. Higher baseline autoantibodies, donor insulin use, IE/count ratio and calcineurin inhibitor use cannot be ruled out as factors of losing the first graft due to sample size issues.

Exhibit 5 – 14B
Achievement of Insulin Independence Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
Of Factors Univariately Significant p <0.10

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

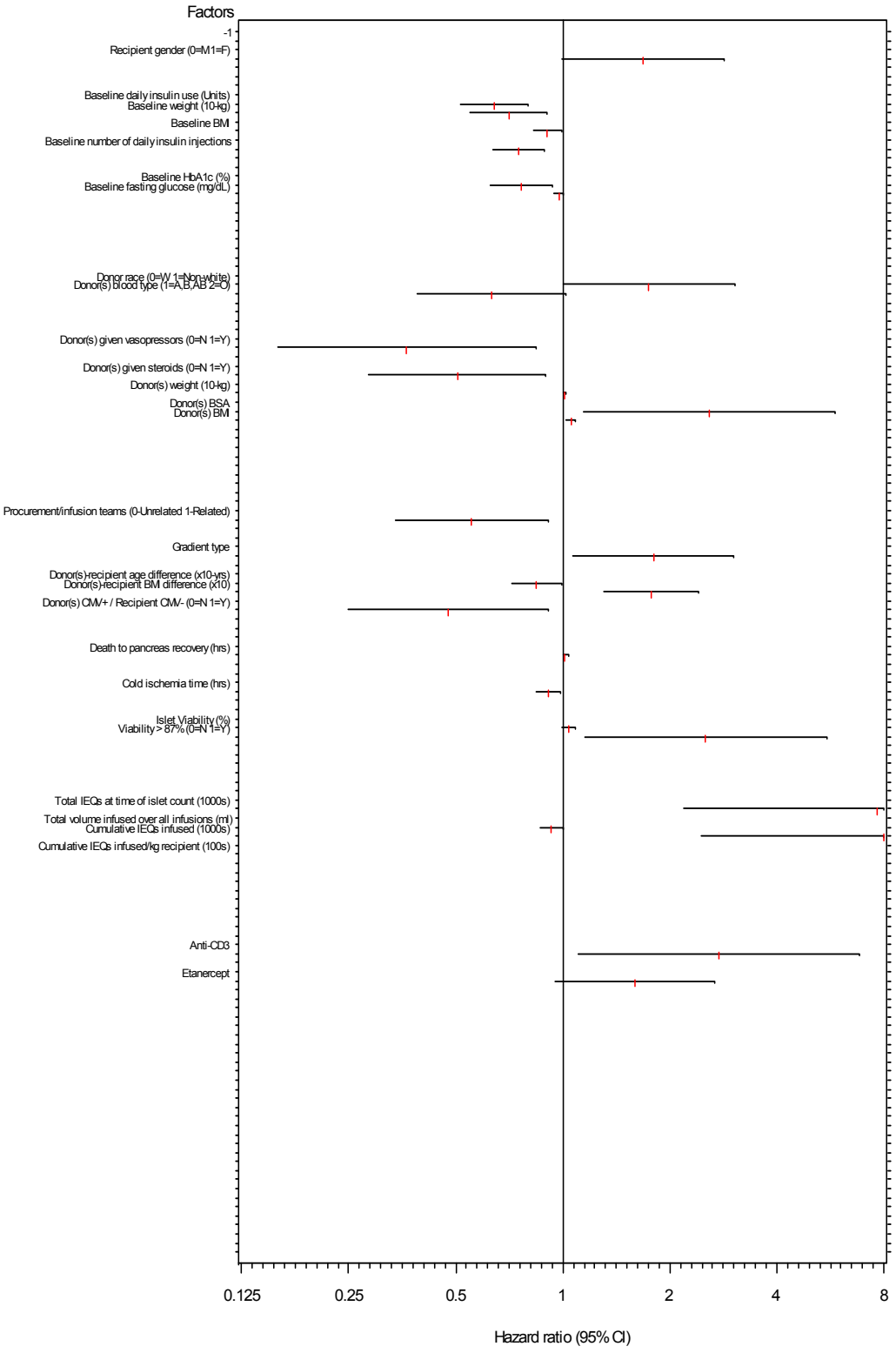


Exhibit 5 – 14C
Loss of Insulin Independence Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
Of Factors Univariately Significant p <0.10

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

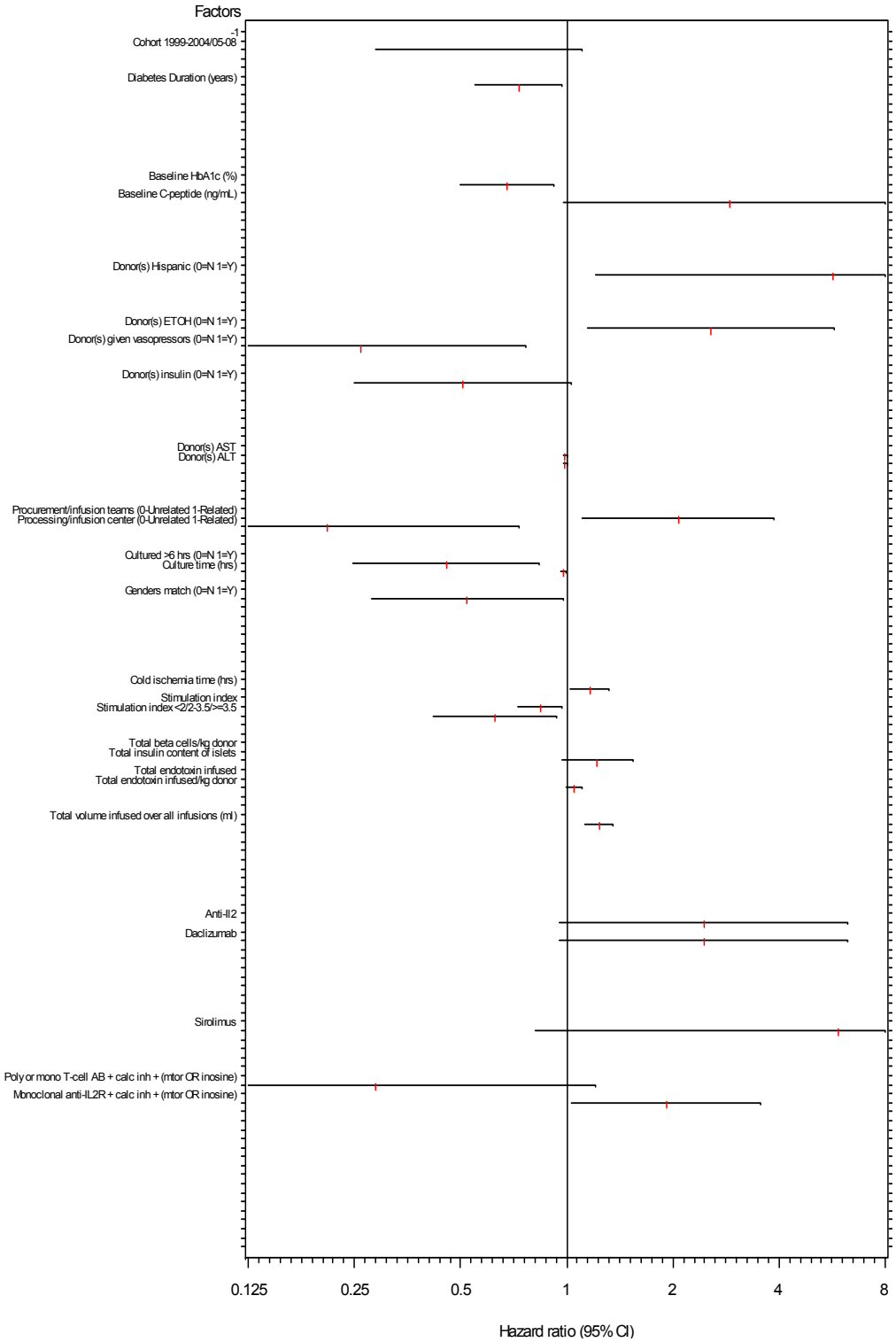


Exhibit 5 – 14D
Complete Islet Failure Post First Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
Of Factors Univariately Significant p <0.10

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

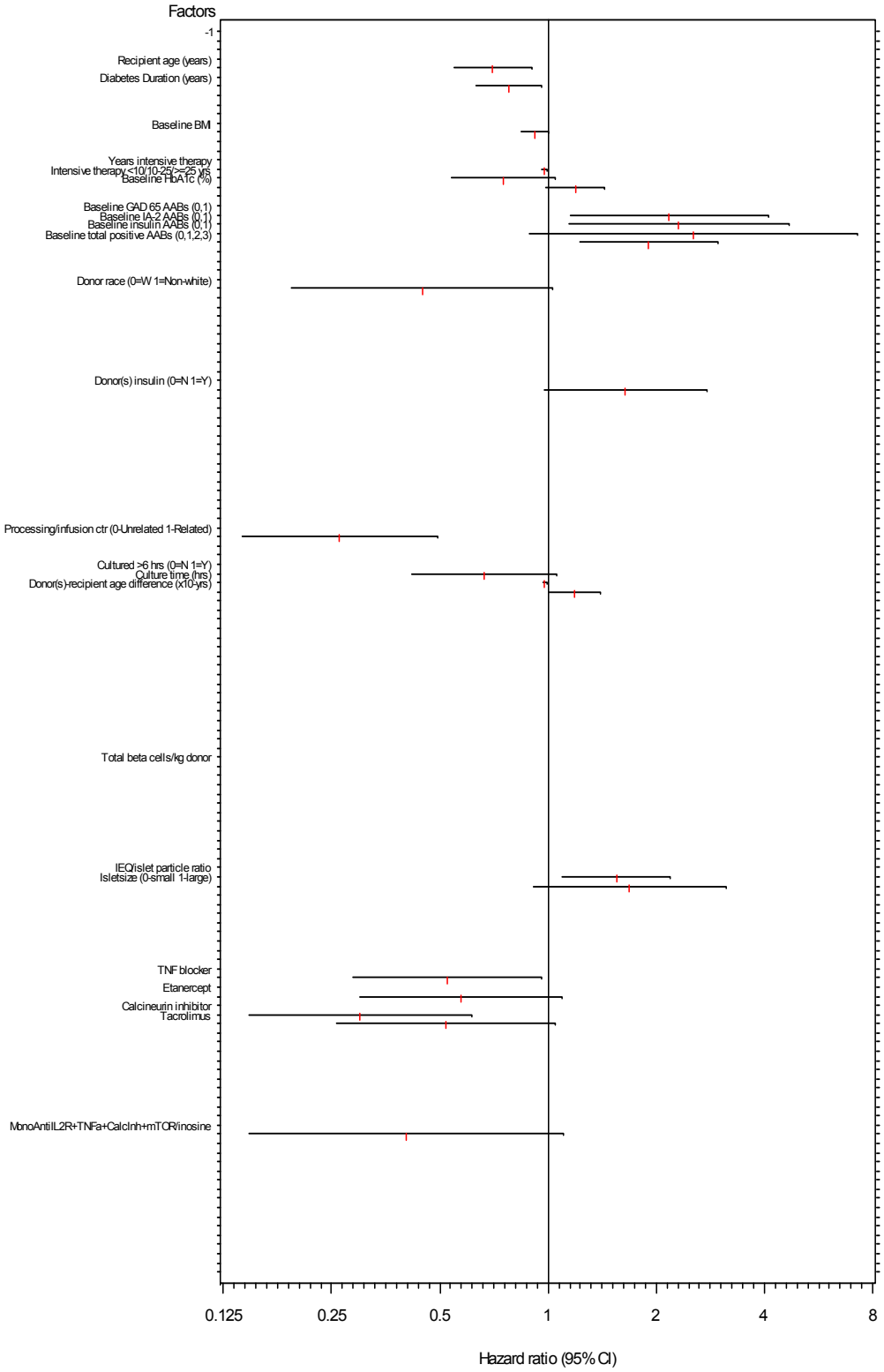


Exhibit 5 – 14E
Reinfusion Post First Infusion
Forest Plot (Odds Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

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

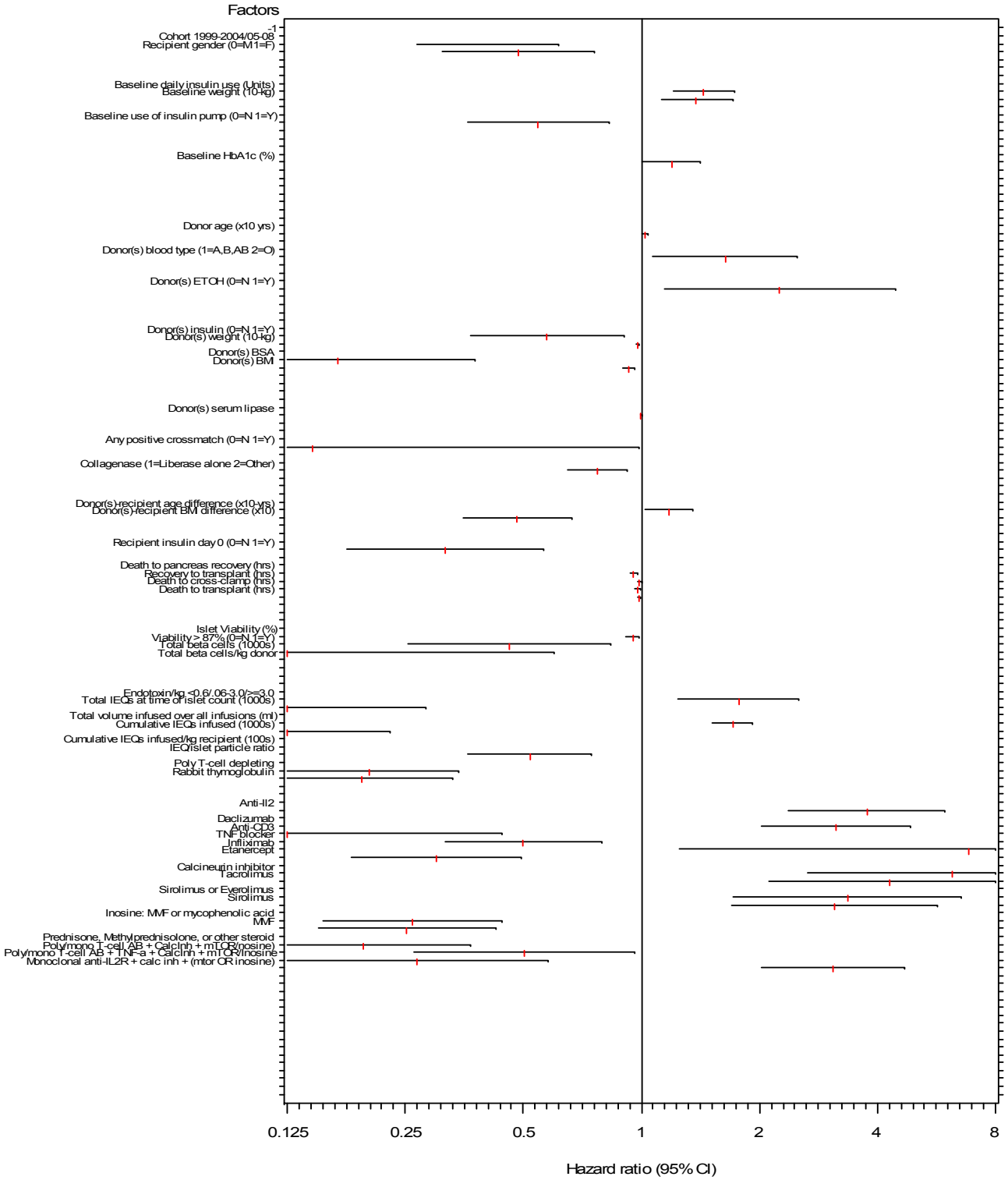


Exhibit 5 – 15A
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

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

Cox proportional hazard model: Hazard ratio (HR) and p-value	A. Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up >1.0 is favorable			B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up <1.0 is favorable			C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up <1.0 indicates less likelihood of reinfusion		
Events / Total >>	**209 / 341**			**109 / 209**			**111 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Cohort 1999-2004/05-08	.	.		.	.		.	.	
Recipient gender (0=M 1=F)	.	.		.	.		.	.	
Recipient age (years)	.	.		.	.		341	0.690	<0.001
Employment impacted by dx	.	.		.	.		298	0.635	0.09
Diabetes Duration (years)	.	.		209	0.750	0.002	341	0.701	<0.001
Months on waitlist	.	.		.	.		.	.	
Baseline daily insulin use (Units)	.	.		202	1.250	0.004	.	.	
Baseline weight (10-kg)	.	.		.	.		.	.	
Baseline PRA (%)	.	.		.	.		.	.	
Baseline BMI	.	.		.	.		.	.	
Baseline use of insulin pump (0=N 1=Y)	.	.		.	.		330	1.394	0.09
Baseline number of daily insulin injections	.	.		.	.		.	.	
Baseline use of insulin pump or >=3 insulin inject	.	.		202	2.401	0.06	.	.	
Years prior to first inf using ins pump or >= 3 in	.	.		.	.		226	0.964	<0.001
Intensive therapy <10/10-25/>=25 yrs	.	.		.	.		196	0.602	0.002
Baseline HbA_{1c} (%)	329	0.864	0.01	.	.		329	1.154	0.06
Baseline fasting glucose (mg/dL)	.	.		.	.		.	.	
Baseline C-peptide (ng/mL)	.	.		200	2.384	0.02	325	1.896	0.10
Baseline GAD 65 autoantibodies (0,1)	.	.		131	1.572	0.07	.	.	
Baseline IA-2 autoantibodies (0,1)	.	.		.	.		159	1.832	0.02
Baseline insulin autoantibodies (0,1)	.	.		.	.		.	.	
Baseline total positive autoantobodies (0,1,2,3)	.	.		.	.		234	1.387	0.04
Total donors	.	.		.	.		341	0.821	0.07
Donor gender (1=M 1.5=Mix 2=F)	.	.		.	.		.	.	
Donor age (x10 yrs)	.	.		193	1.005	0.04	.	.	
Donor(s) Hispanic (0=N 1=Y)	220	0.559	0.01	.	.		.	.	
Donor race (0=W 1=Non-white)	341	1.374	0.05	.	.		341	0.496	0.03

Exhibit 5–15A (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 >1.0 is favorable			B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up <1.0 is favorable			C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up <1.0 indicates less likelihood of reinfusion		
Events / Total >>	**209 / 341**			**109 / 209**			**111 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Donor(s) blood type (1=A,B,AB 2=O)	.	.		.	.		.	.	
CVS death(s) (0=N 1=Y)	.	.		.	.		.	.	
Donor CMV (0=- 1=+)	.	.		.	.		.	.	
Donor(s) hx hypertension (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) ETOH (0=N 1=Y)	285	1.561	0.004	.	.		.	.	
Donor(s) diabetes (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) given vasopressors (0=N 1=Y)	.	.		209	0.118	0.004	.	.	
Donor transfused prior to hospitalization (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) transfused in hospital (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) given steroids (0=N 1=Y)	202	0.646	0.02	.	.		.	.	
Donor(s) insulin (0=N 1=Y)	.	.		183	0.645	0.04	.	.	
Donor(s) weight (10-kg)	.	.		.	.		.	.	
Donor(s) height (cm)	318	1.001	0.06	.	.		.	.	
Donor(s) BSA	.	.		.	.		.	.	
Donor(s) BMI	.	.		.	.		318	0.996	0.09
Donor(s) creatinine	295	1.178	<0.001	.	.		.	.	
Donor(s) BUN	207	1.009	0.06	.	.		.	.	
Donor(s) bilirubin	.	.		143	1.194	0.07	.	.	
Donor(s) AST	.	.		.	.		.	.	
Donor(s) ALT	.	.		.	.		.	.	
Donor(s) serum lipase	.	.		.	.		.	.	
Donor(s) serum amylase	.	.		.	.		.	.	
Donor(s) pre-insulin glucose	.	.		.	.		.	.	
Max donor(s) glucose (mg/dL)	.	.		.	.		.	.	
Any positive crossmatch (0=N 1=Y)	.	.		.	.		.	.	
Procurement/infusion teams (0-Unrelated 1-Related)	313	1.634	0.001	.	.		313	0.591	0.009

Exhibit 5–15A (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** **>1.0 is favorable**			**B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up** **<1.0 is favorable**			**C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up** **<1.0 indicates less likelihood of reinfusion**		
Events / Total >>	**209 / 341**			**109 / 209**			**111 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Processing/infusion center (0-Unrelated 1-Related)	316	3.027	<0.001	198	0.439	0.03	316	0.373	<0.001
Collagenase (1=Liberase alone 2=Other)	.	.		.	.		.	.	
Pulmozyme	.	.		.	.		.	.	
Gradient type	302	1.430	0.02	.	.		.	.	
Cultured >6 hrs (0=N 1=Y)	.	.		.	.		341	0.694	0.06
Culture time (hrs)	.	.		.	.		300	0.993	0.04
Donor(s)-recipient age difference (x10-yrs)	.	.		193	1.098	0.01	307	1.106	0.006
Donor(s)-recipient BMI difference (x10)	.	.		.	.		.	.	
Genders match (0=N 1=Y)	.	.		.	.		.	.	
Donor(s) CMV+ / Recipient CMV- (0=N 1=Y)	.	.		.	.		.	.	
Pancreas preservation (1-UW 2-2L 3-Both)	.	.		.	.		.	.	
Recipient insulin day 0 (0=N 1=Y)	262	0.730	0.05	.	.		.	.	
Time from cross clamp to panc recovery (hrs)	.	.		.	.		.	.	
Time from admission to death (hrs)	261	1.001	0.08	.	.		.	.	
Death to pancreas recovery (hrs)	.	.		.	.		.	.	
Recovery to transplant (hrs)	256	0.997	0.10	.	.		256	0.992	0.02
Death to cross-clamp (hrs)	.	.		.	.		.	.	
Death to transplant (hrs)	.	.		.	.		315	0.997	0.09
Cold ischemia time (hrs)	.	.		.	.		.	.	
Embedded islets (%)	.	.		.	.		.	.	
Stimulation index	.	.		.	.		297	0.958	0.04
Stimulation index <2/2-3.5/>=3.5	.	.		.	.		.	.	
Islet Viability (%)	.	.		.	.		300	0.997	0.08
Viability > 87% (0=N 1=Y)	300	4.581	0.03	.	.		300	0.232	<0.001
Total beta cells (1000s)	.	.		.	.		.	.	
Total beta cells/kg donor (1000s)	.	.		.	.		.	.	
Total insulin content of islets	.	.		.	.		.	.	
Insulin content <3/3-5/>=5	.	.		.	.		.	.	

Exhibit 5–15A (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 >1.0 is favorable			B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up <1.0 is favorable			C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up <1.0 indicates less likelihood of reinfusion		
Events / Total >>	**209 / 341**			**109 / 209**			**111 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Total endotoxin infused	.	.		.	.		.	.	
Total endotoxin infused/kg donor	.	.		.	.		.	.	
Endotoxin/kg <0.6/.06-3.0/>=3.0	.	.		.	.		.	.	
Total IEQs at time of islet count (1000s)	.	.		.	.		.	.	
Total islet particles infused (1000s)	.	.		.	.		.	.	
Total volume infused over all infusions (ml)	.	.		.	.		.	.	
Cumulative IEQs infused (1000s)	.	.		.	.		.	.	
Cumulative IEQs infused (1:<400K 2:>=400K)	.	.		.	.		.	.	
Cumulative IEQs infused/kg recipient (100s)	.	.		.	.		.	.	
IEQ/islet particle ratio	.	.		.	.		.	.	
Isletsize (0-small 1-large)	.	.		157	0.633	0.04	.	.	
Poly T-cell depleting (0=N 1=Y)	313	0.547	0.01	.	.		.	.	
Rabbit thymoglobulin (0=N 1=Y)	327	0.568	0.008	202	0.525	0.10	.	.	
Horse thymoglobulin (0=N 1=Y)	.	.		.	.		326	9.856	0.002
Anti-lymphocyte globulin (0=N 1=Y)	.	.		.	.		.	.	
Mono T-cell depleting (0=N 1=Y)	.	.		.	.		.	.	
Anti-Il2 (0=N 1=Y)	325	1.788	0.007	202	2.575	0.04	325	0.553	0.02
Basiliximab (0=N 1=Y)	.	.		.	.		.	.	
Daclizumab (0=N 1=Y)	328	1.810	0.003	203	2.628	0.02	328	0.646	0.07
Anti-CD3 (0=N 1=Y)	.	.		.	.		.	.	
TNF blocker (0=N 1=Y)	.	.		.	.		325	0.576	0.03
Infliximab (0=N 1=Y)	.	.		200	1.755	0.06	.	.	
Etanercept (0=N 1=Y)	.	.		.	.		325	0.427	0.01
DSG (0=N 1=Y)	.	.		.	.		.	.	
Calcineurin inhibitor (0=N 1=Y)	326	3.183	0.02	.	.		326	0.148	<0.001
Tacrolimus (0=N 1=Y)	331	1.890	0.06	.	.		331	0.502	0.05
Cyclosporin (0=N 1=Y)	.	.		.	.		.	.	
Sirolimus or Everolimus (0=N 1=Y)	.	.		.	.		.	.	
Sirolimus (0=N 1=Y)	.	.		203	7.196	0.05	.	.	
Everolimus (0=N 1=Y)	.	.		.	.		.	.	

Exhibit 5–15A (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 >1.0 is favorable			B. Loss of Insulin Independence Post Last Infusion Censored at CIF or Last Follow-Up <1.0 is favorable			C. Complete Islet Failure (CIF) Post Last Infusion Censored at Last Follow-Up <1.0 indicates less likelihood of reinfusion		
Events / Total >>	**209 / 341**			**109 / 209**			**111 / 341**		
Variable	**N**	**HR**	**p**	**N**	**HR**	**p**	**N**	**HR**	**p**
Inosine: MMF or mycophenolic acid (0=N 1=Y)	324	0.743	0.09	201	0.515	0.04	.	.	
MMF (0=N 1=Y)	326	0.708	0.05	201	0.478	0.03	326	1.501	0.08
Mycophenolic acid	.	.		.	.		.	.	
Prednisone, Methylprednisolone, or other steroid (0=N 1=Y)	.	.		201	0.436	0.07	.	.	
Poly or mono T-cell AB + calc inh + (mtor OR inosine) (0=N 1=Y)	.	.		.	.		.	.	
Poly or mono T-cell AB + TNF-alpha ant + calc inh + (mtor OR inosine) (0=N 1=Y)	335	0.551	0.05	.	.		.	.	
Monoclonal anti-IL2R + calc inh + (mtor OR inosine) (0=N 1=Y)	335	1.491	0.007	206	1.448	0.10	.	.	
Monoclonal anti-IL2R + TNF-alpha ant + calc inh + (mtor OR inosine) (0=N 1=Y)	.	.		.	.		335	0.573	0.06
Number of A locus mismatches	209	1.114	0.04	.	.		.	.	
Number of B locus mismatches	208	1.093	0.07	.	.		.	.	
Number of DR locus mismatches	.	.		.	.		.	.	
Number of DQ locus mismatches	.	.		.	.		.	.	
Number of Class I locus mismatches	203	1.064	0.02	.	.		.	.	
Number of Class II locus mismatches	.	.		.	.		.	.	
Number of A/B/DR locus mismatches	185	1.036	0.09	.	.		.	.	
Number of A/B/DR/DQ locus mismatches	80	1.050	0.04	.	.		.	.	
Reexposed to A locus mismatch	.	.		.	.		129	0.611	0.10
Reexposed to B locus mismatch	130	0.655	0.07	.	.		.	.	
Reexposed to DR locus mismatch	.	.		.	.		.	.	
Reexposed to DQ locus mismatch	.	.		.	.		.	.	
Reexposed to Class I	.	.		.	.		.	.	
Reexposed to Class II locus mismatch	.	.		.	.		.	.	
Reexposed to A/B/DR locus mismatch	.	.		.	.		.	.	
Reexposed to A/B/DR/DQ locus mismatch	.	.		.	.		.	.	

Exhibit 5 – 15A (continued)
Primary Outcomes Post Last Infusion
According to Pre-Infusion Recipient, Donor, Procurement, and Islet Characteristics

The final multivariate model for insulin independence post last infusion (209 events / 341 recipients) is:

Variable	HR		p
Baseline HbA_{1c}	0.89	Lower HbA_{1c} favorable	0.03
Procurement/infusion center (0=unrelated 1=related)	1.32	Related is favorable	0.08
Processing/infusion center (0-unrelated 1=related)	2.88	Related is favorable	0.002
Daclizumab (0=N 1=Y)	1.79	Daclizumab is favorable	0.005

Baseline $HbA_{1c,}$ baseline weight, baseline BMI, baseline daily insulin, fasting glucose, and number of daily injections are substantially mutually correlated: any of these measures of initial control suffices to explain its influence on achieving insulin independence: the better the control, the more likely to achieve insulin independence. The processing center being related to the transplant center is favorable. Daclizumab is favorable. Variables that cannot be excluded as significantly associated with this outcome are donor's given steroids, HLA factors and islet beta cell counts. There is substantial imbalance between most immunosuppressants other than sirolimus and tacrolimus with most measures of procurement and processing and several recipient characteristics as well, thus preventing meaningful assessment of those immunosuppressant therapies in a multivariate model. Their univariate effects cannot be dismissed. Daclizumab is stable in this model and seems to be favorable for insulin independence.

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

The final model for complete islet failure post last infusion (111 events / 341 recipients) is:

Variable	HR		p
Age	0.68	Higher age is favorable	<0.001
Processing/infusion center (0-unrelated 1=related)	0.42	Related is favorable	0.003
Etanercept (0=N 1=Y)	0.47	Etanercept is favorable	0.02
Calcineurin Inhibitor (0=N 1=Y)	0.26	Calcineurin inhibitor is favorable	0.003

Older recipient age predicts lower risk of losing the graft. Related processing and infusion centers substantially reduce the chances of losing the last graft. Etanercept and calcineurin inhibitors are confirmed as favorable for persistent function.

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

Exhibit 5 – 15B
Achievement of Insulin Independence Post Last Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

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

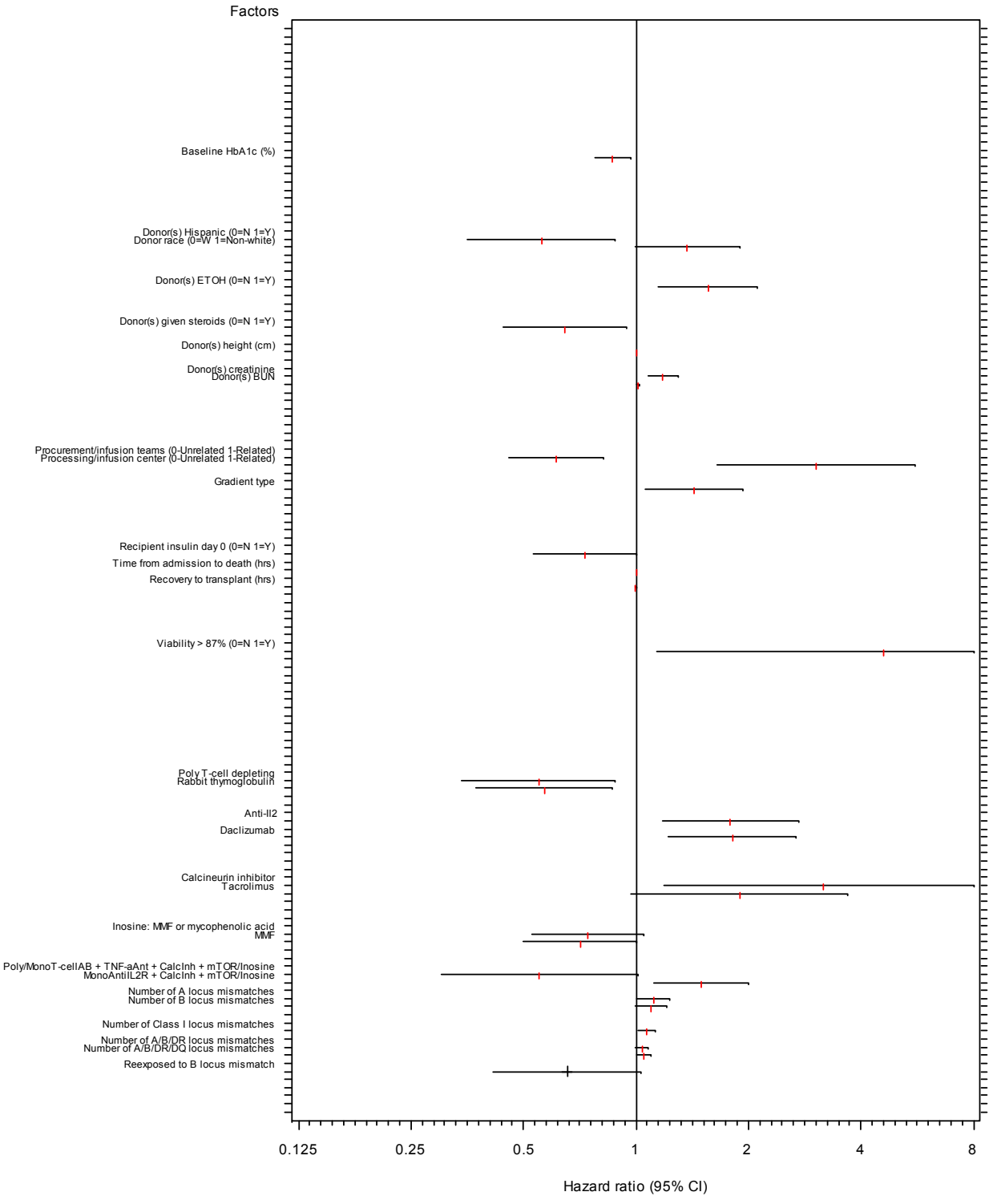


Exhibit 5 – 15C
Loss of Insulin Independence Post Last Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

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

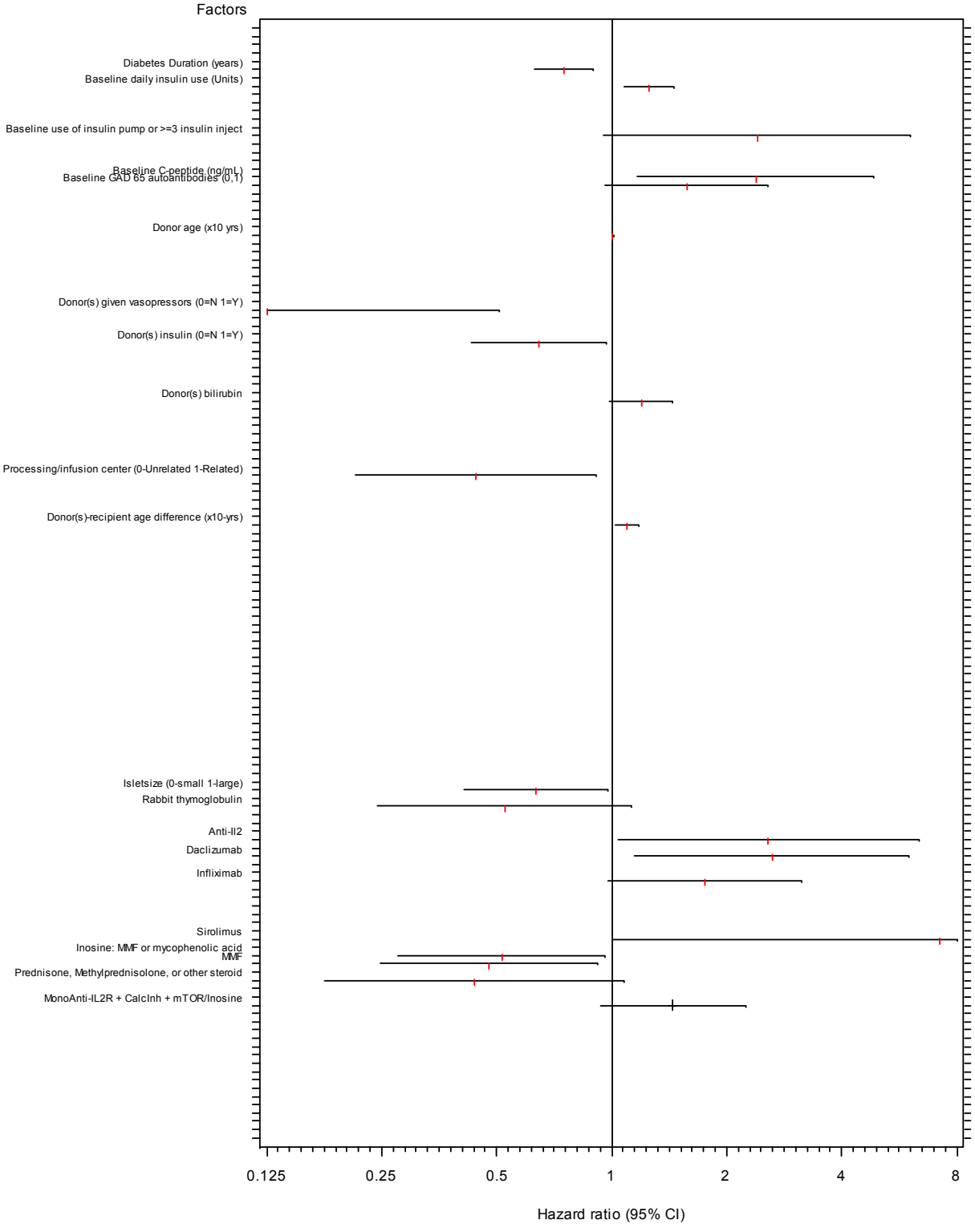


Exhibit 5 – 15D
Complete Islet Failure Post Last Infusion
Forest Plot (Hazard Ratio ± 95% Confidence Interval)
of Factors Univariately Significant p <0.10

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

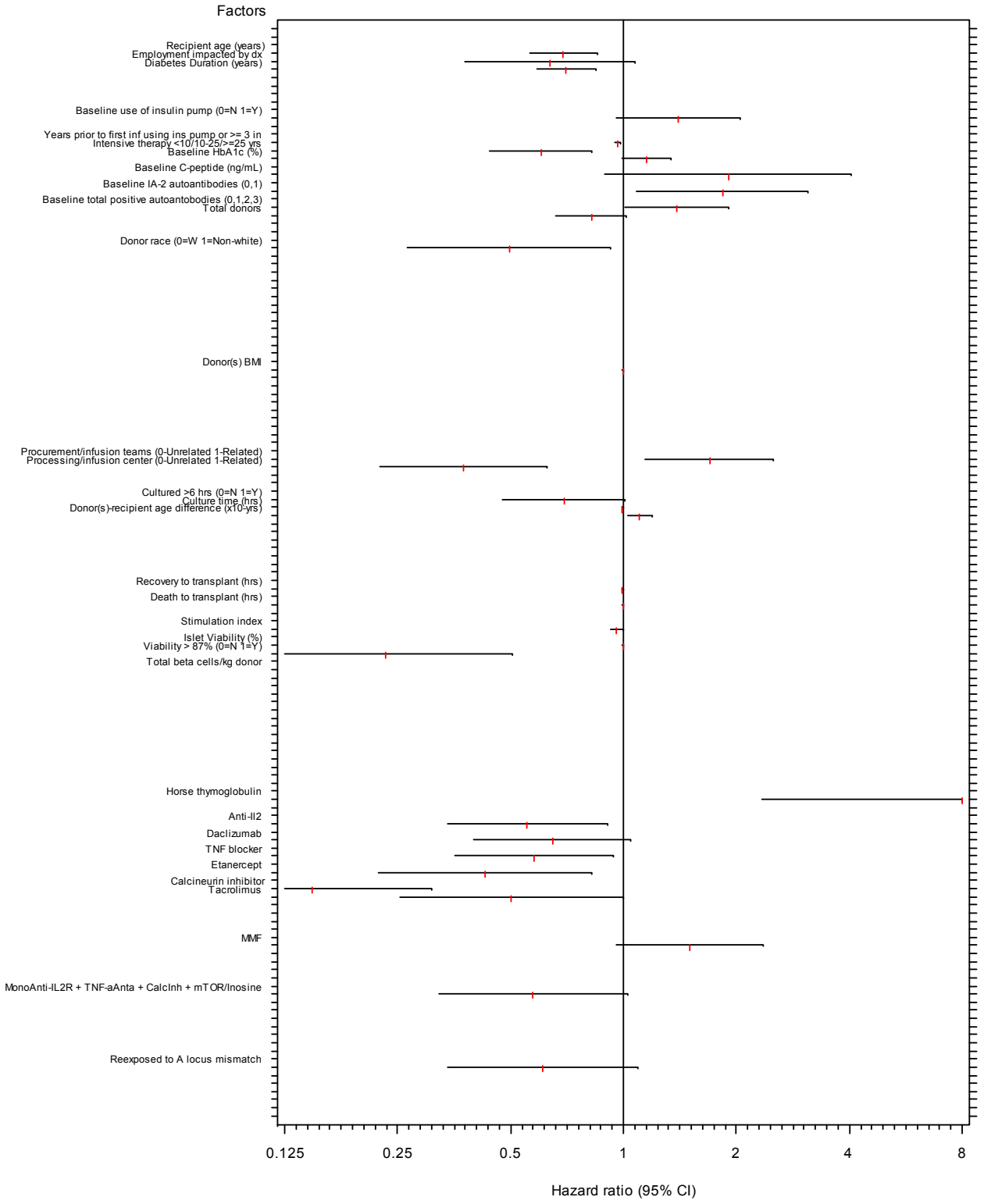
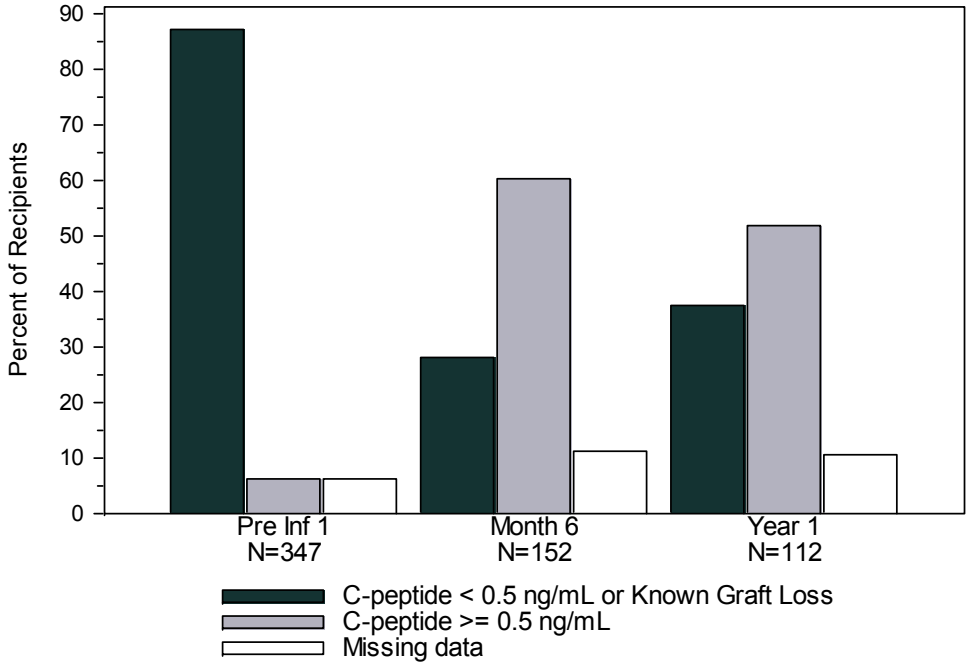


Exhibit 5 – 16
C-peptide ≥ 0.5 ng/mL

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

Islet Alone Recipients



Islet After Kidney Recipients

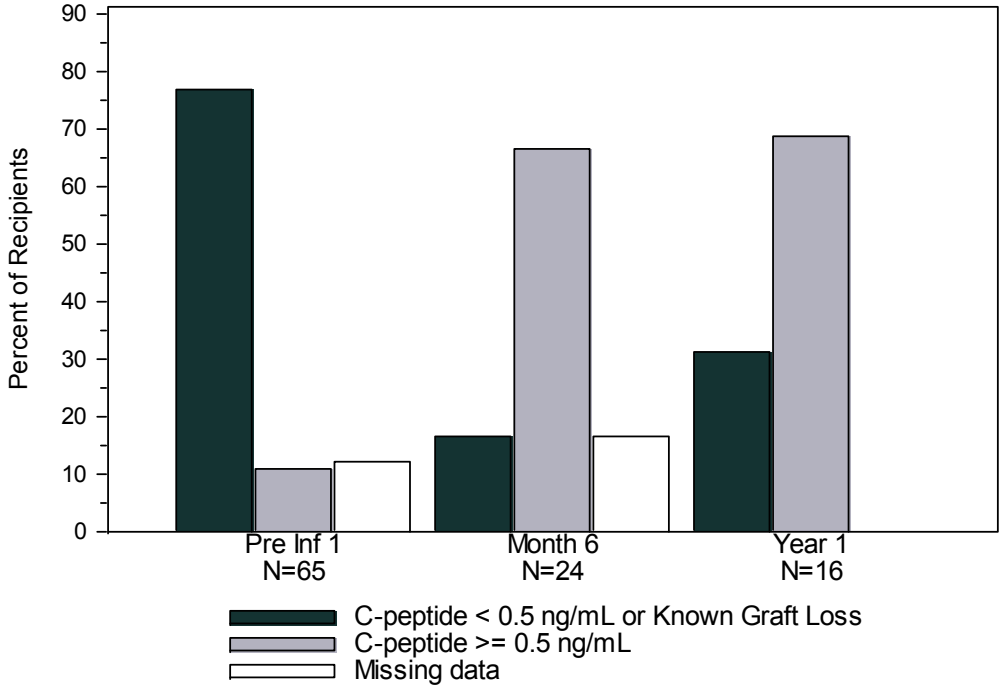
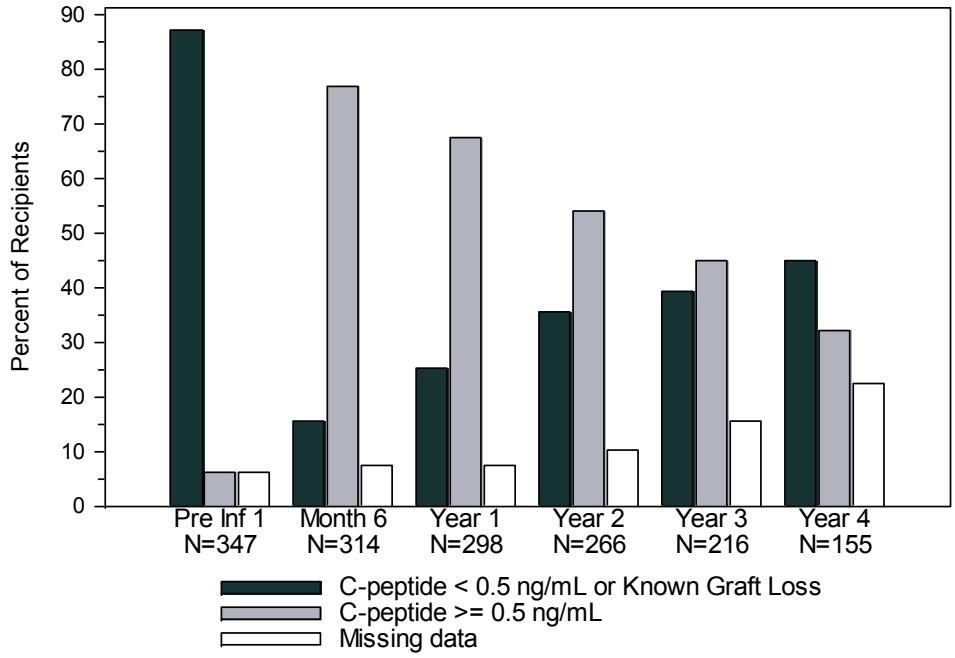


Exhibit 5-16 (continued)
C-peptide ≥ 0.5 ng/mL

B. Post Last Infusion

Islet Alone Recipients



Islet After Kidney Recipients

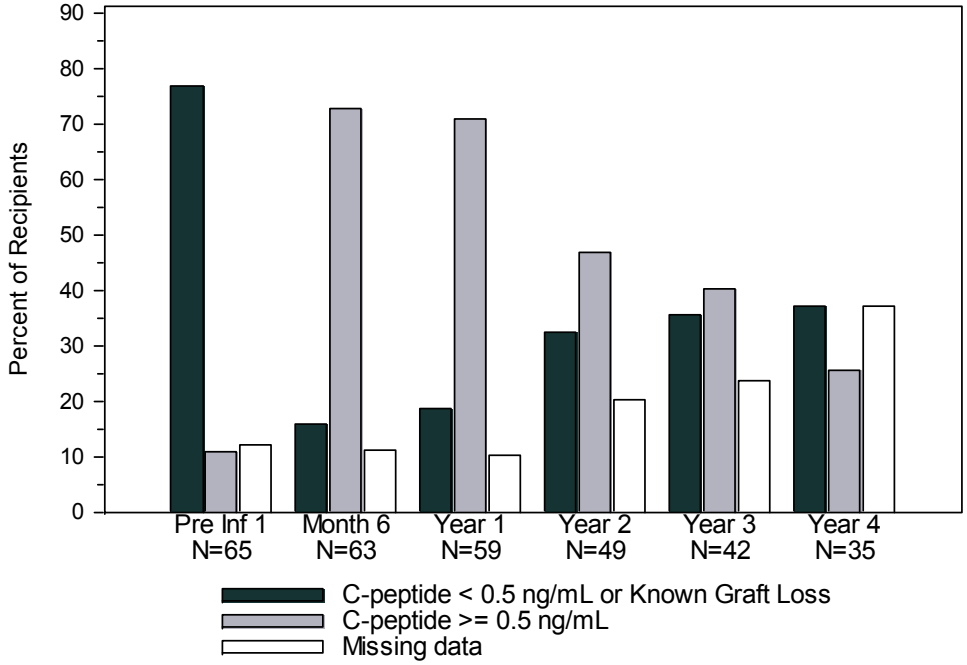


Exhibit 5 – 16 (continued)
C-peptide ≥ 0.3 ng/mL

C. Post Last Infusion
With or without missing data

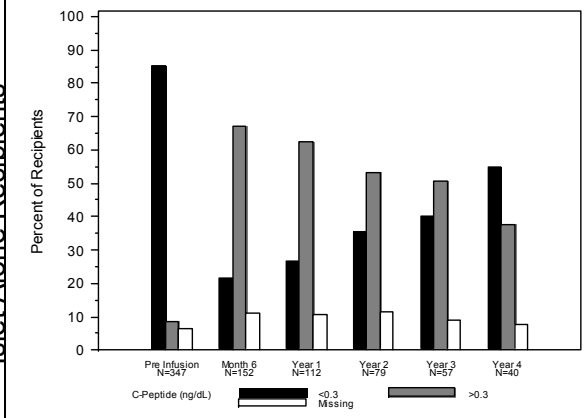
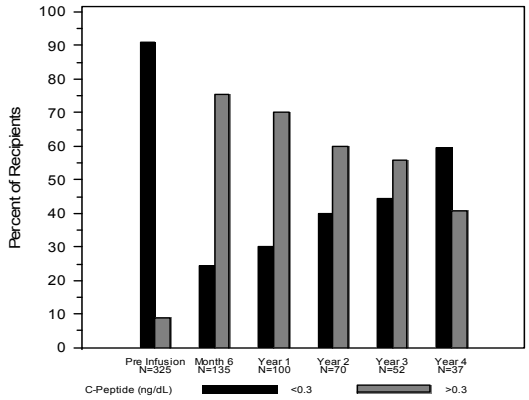
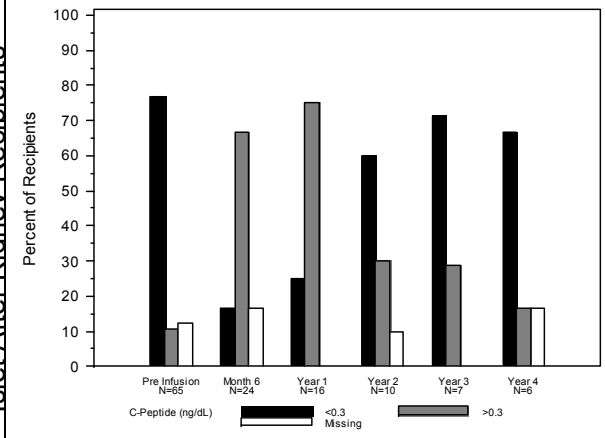
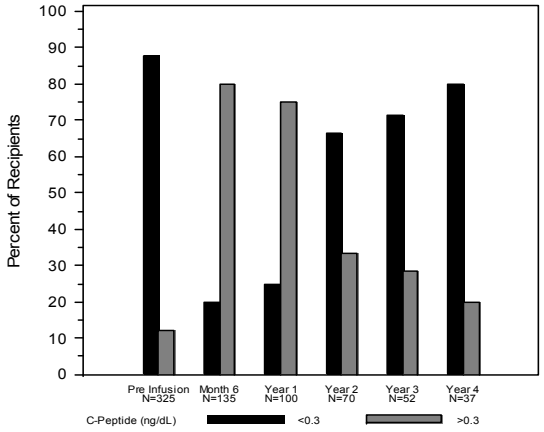
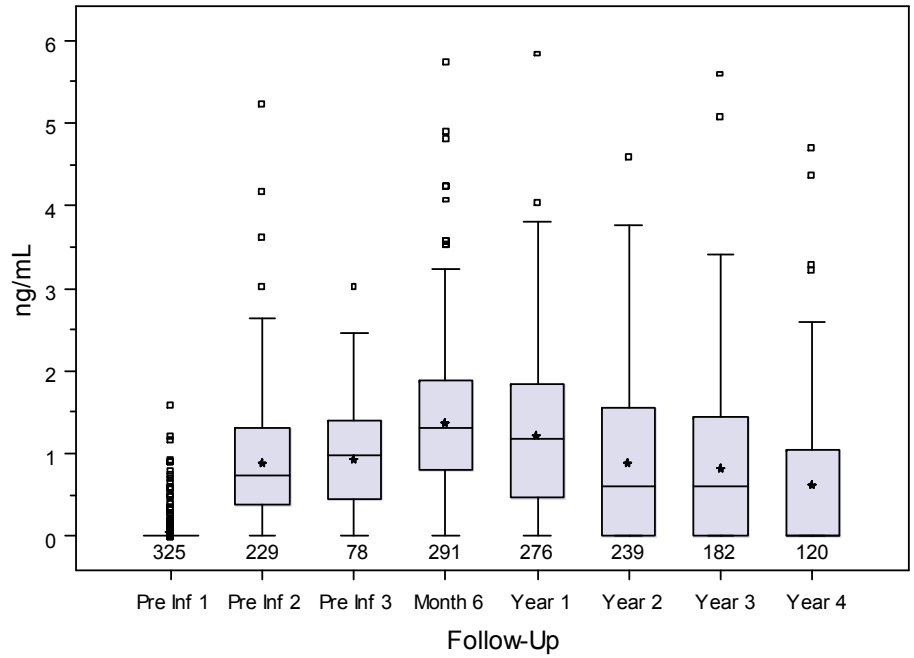
	Missing data included	Missing data excluded (missing assumed at random)
Islet Alone Recipients		
Islet After Kidney Recipients		

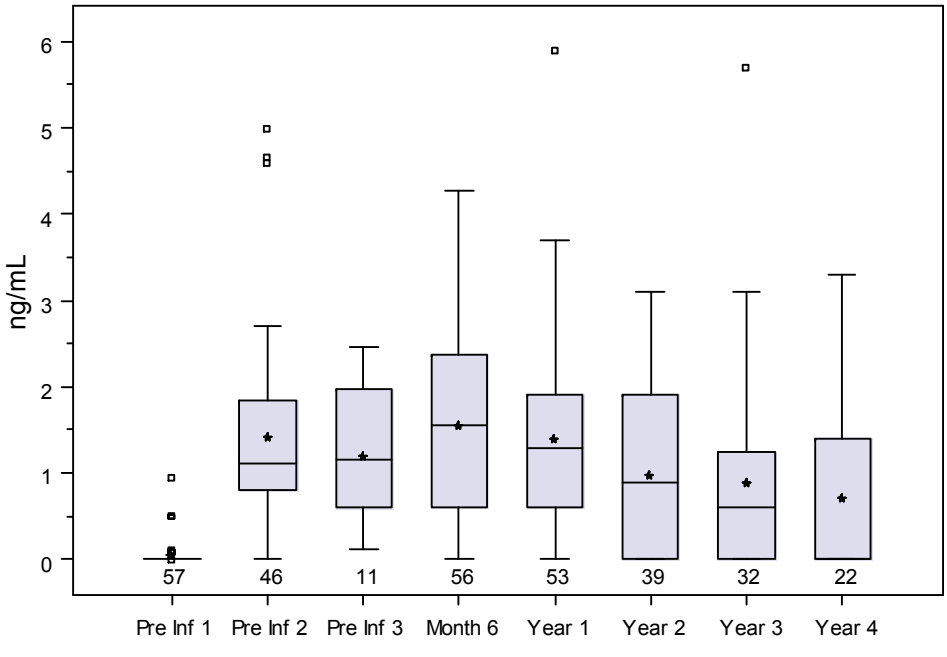
Exhibit 5 – 17
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 6 ng/ml are not displayed or used in boxplot values
(One at pre-inf 2, three at month 6, one at year 1, and one at year 3)

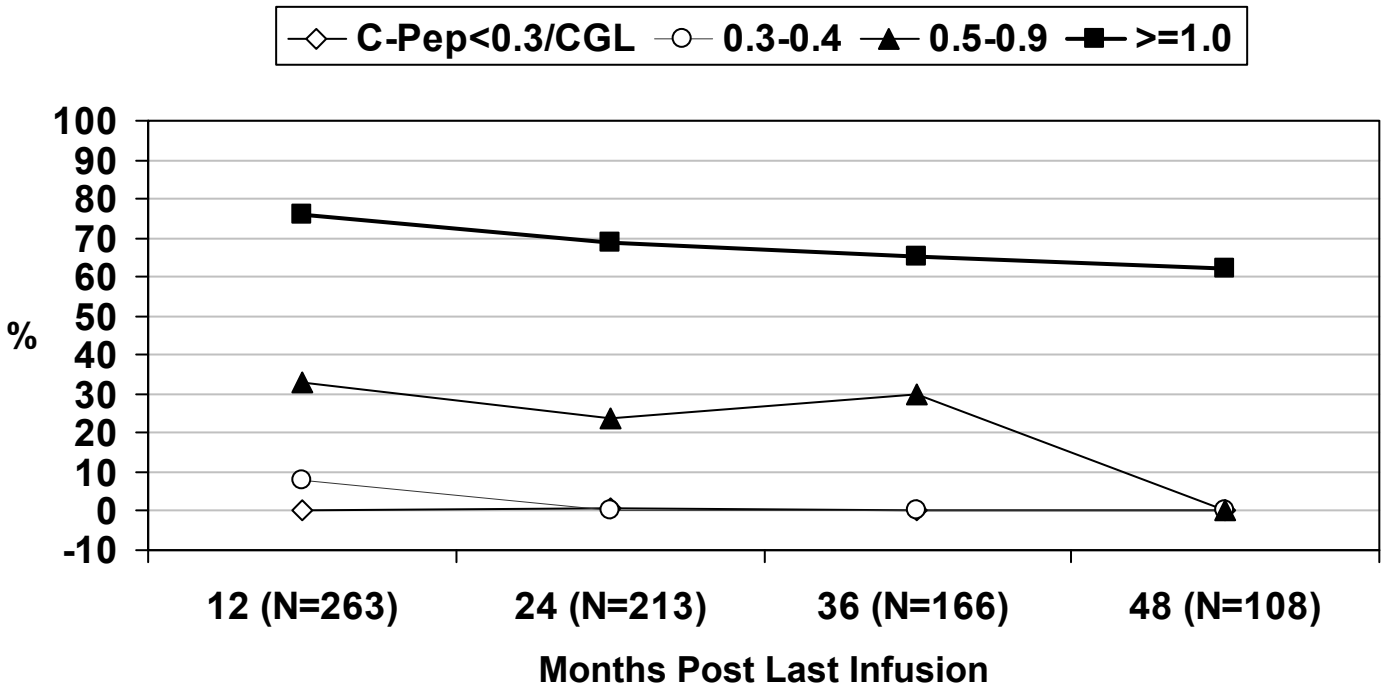
B. Islet After Kidney Recipients



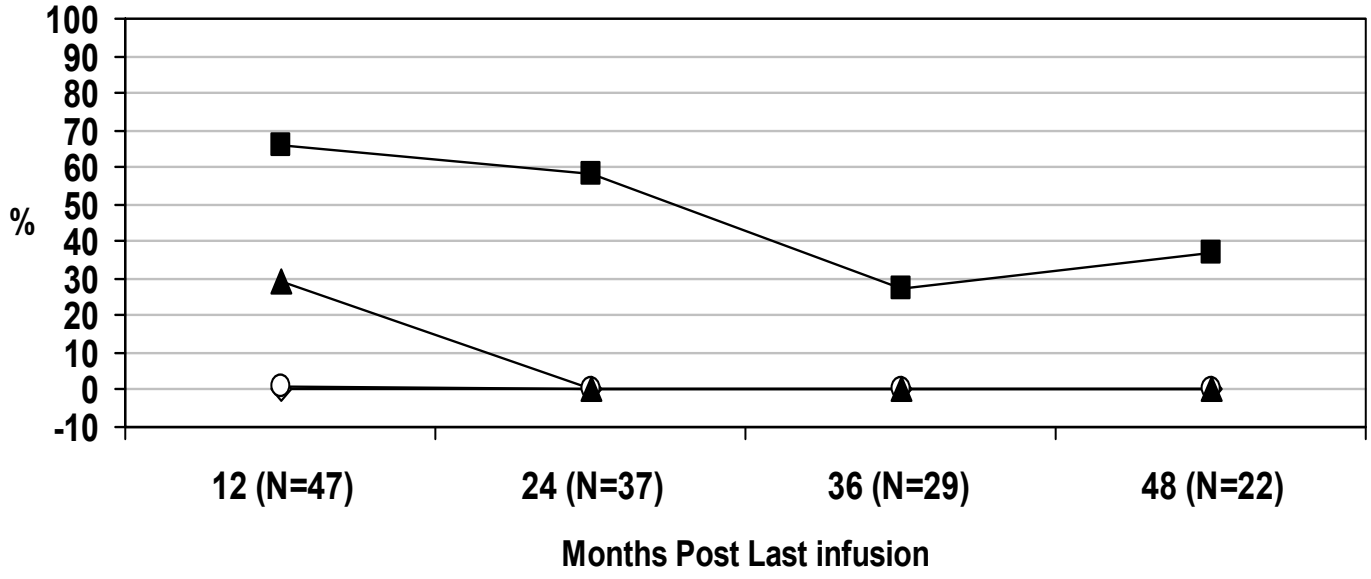
Values greater than 6 ng/ml are not displayed or used in boxplot values
(One at year 2)

Exhibit 5 – 18
Association of Islet Graft Function with Insulin Independence:
Percent Insulin Independent by C-peptide Level Post Last Infusion

A. Islet Alone Recipients



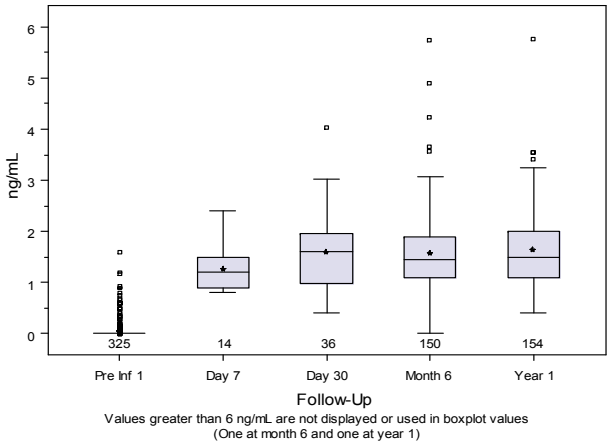
B. Islet After Kidney Recipients



This Exhibit shows the relationship between insulin use and concurrent C-peptide level. At all follow-up post islet transplantation, the higher the C-peptide level, the more likely is the patient to be insulin independent ($p<0.01$), with levels >1.0 ng/mL exhibiting 60-80% insulin independence. This relationship erodes more quickly over time for IAK recipients than for islet alone.

Exhibit 5 – 19
Basal Plasma C-peptide (ng/mL)
Pre and Post First Infusion
Insulin Independent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

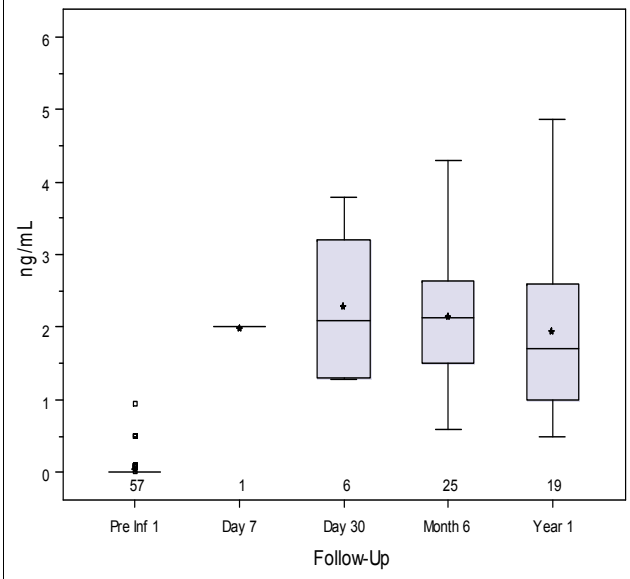
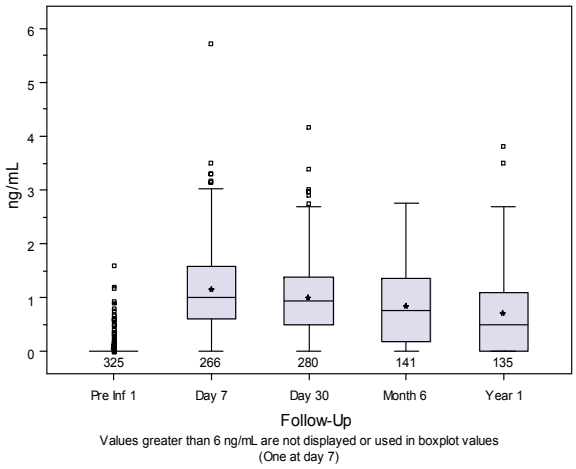


Exhibit 5 – 20
Basal Plasma C-peptide (ng/mL)
Pre and Post First Infusion
Insulin Dependent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

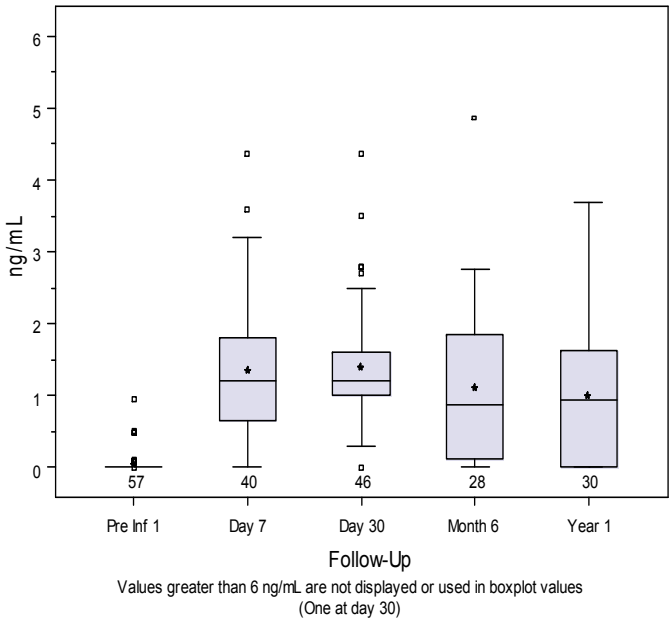
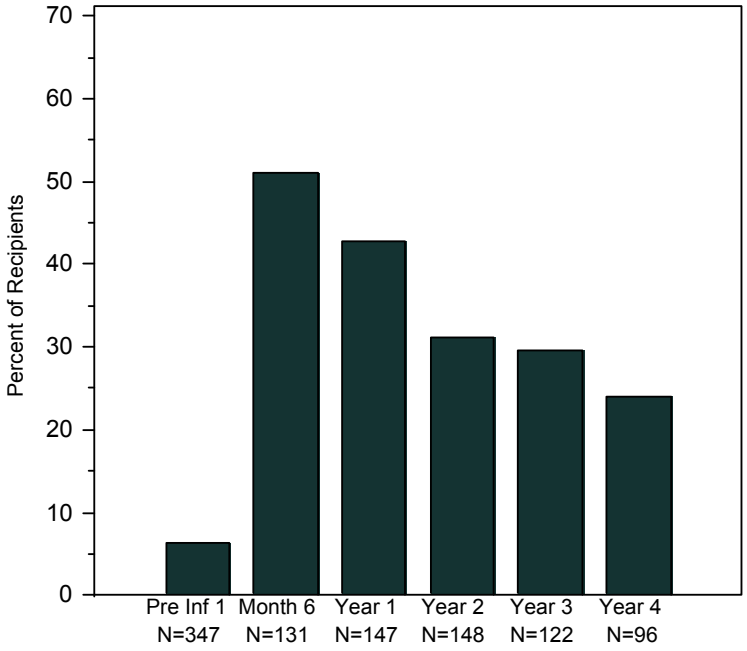


Exhibit 5 – 21
Percent of Insulin Dependent Recipients with Basal C-peptide ≥ 0.5 ng/mL
Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

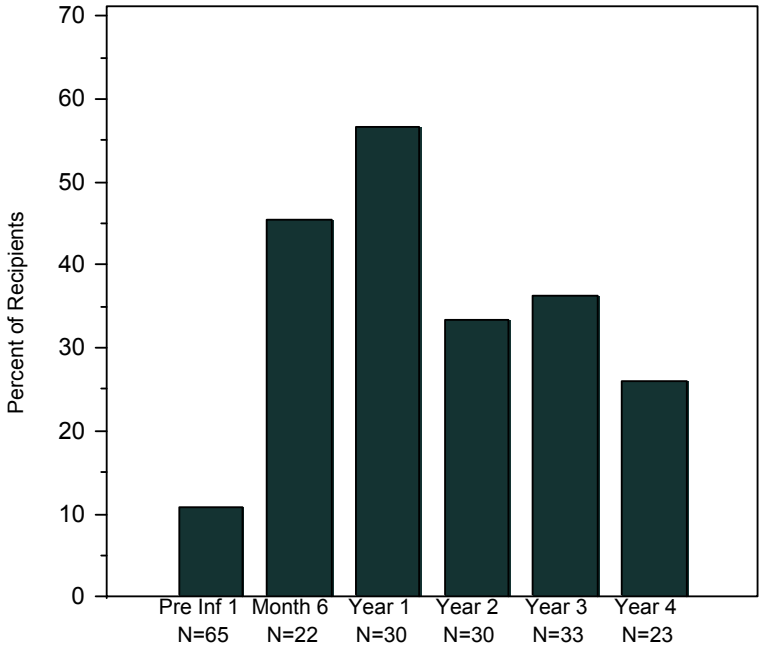
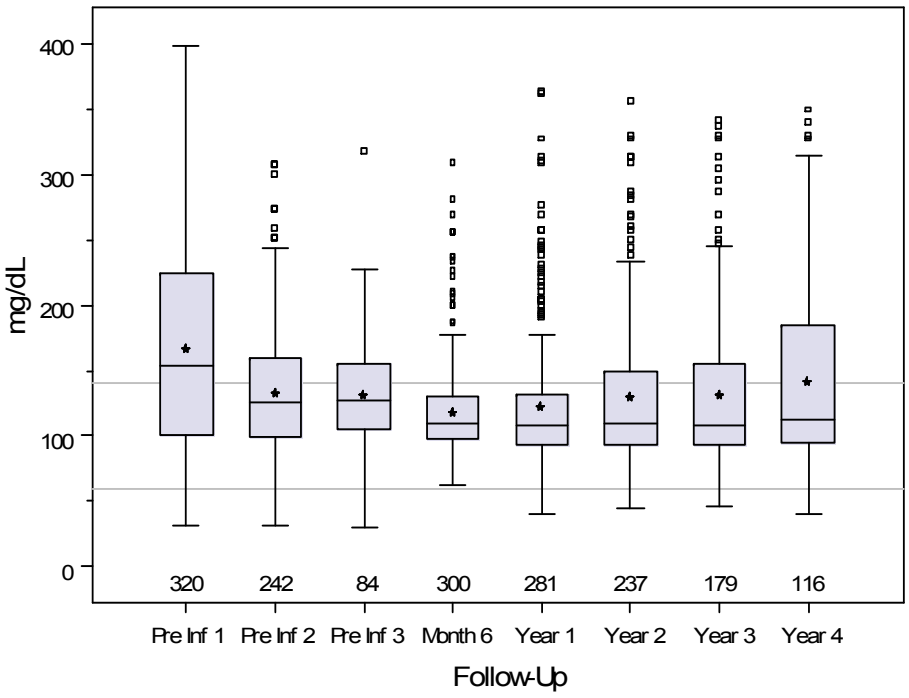


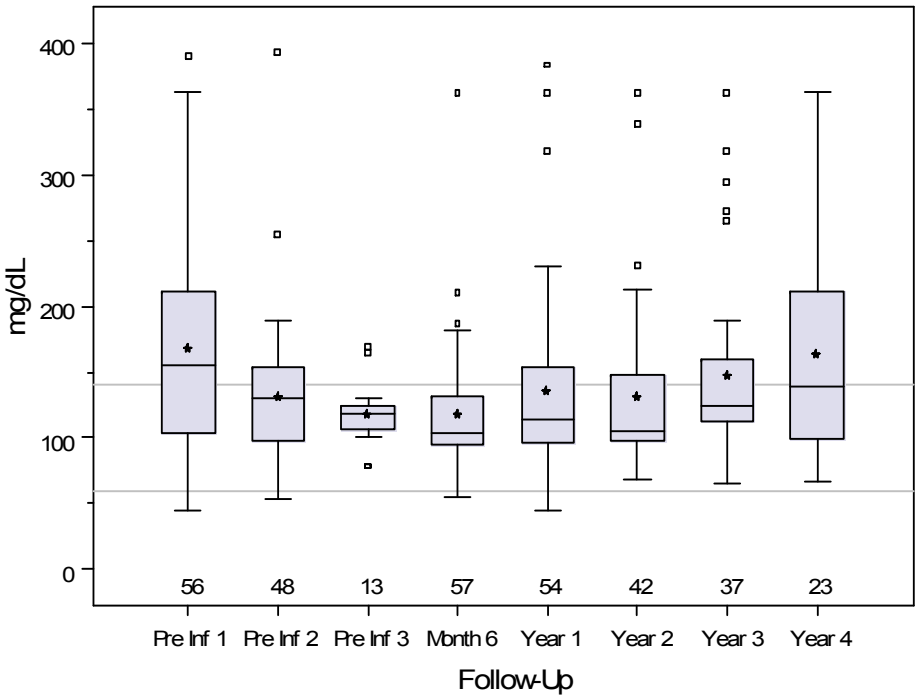
Exhibit 5 – 22
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 400 mg/dL are not displayed or used in boxplot values
(Five at pre-inf 1, one at month 6, one at year 1, two at year 2, one at year 3 and two at year 4)

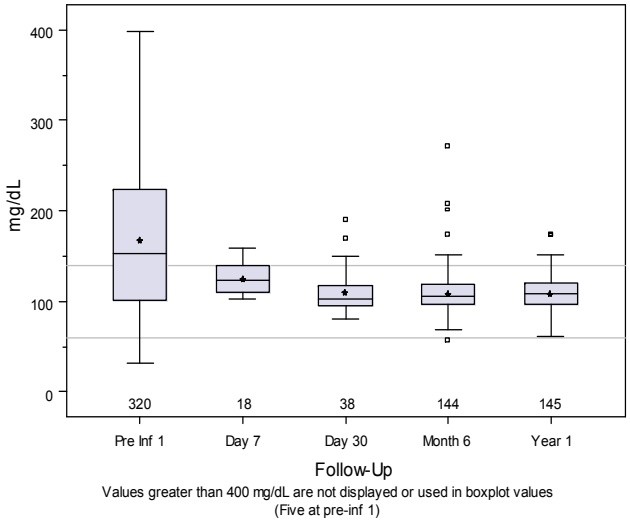
B. Islet After Kidney Recipients



Values greater than 400 mg/dL are not displayed or used in boxplot values
(Two at pre-inf 1, one at year 2 and one at year 4)

Exhibit 5 – 23
Fasting Plasma Glucose (mg/dL)
Pre and Post First Infusion
Insulin Independent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

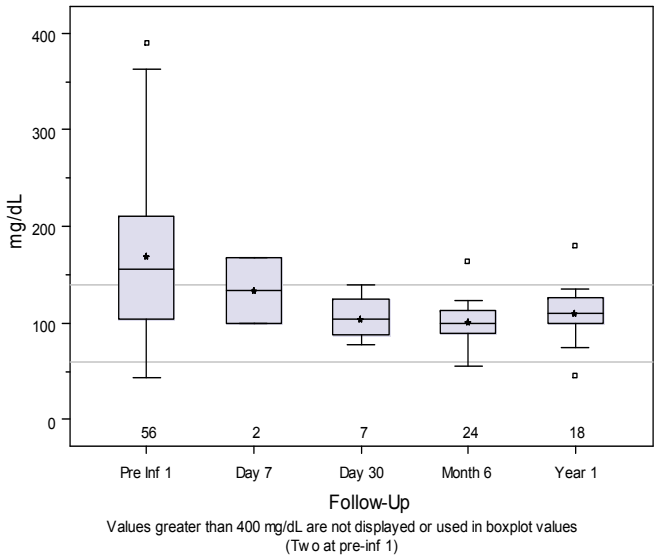
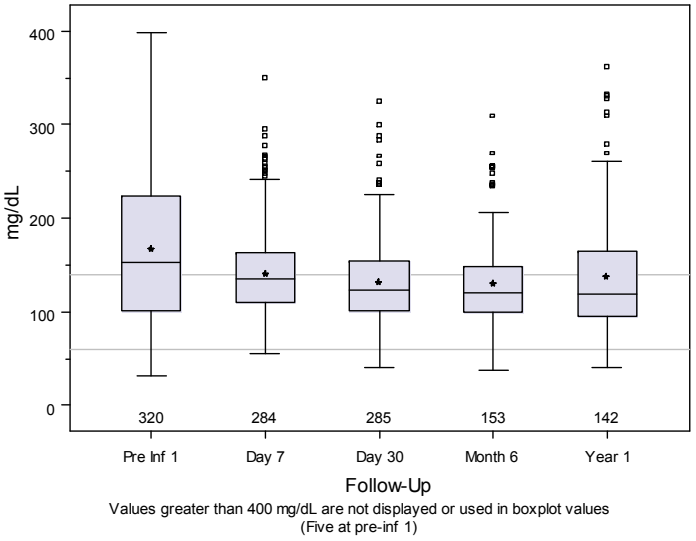


Exhibit 5 – 24
Fasting Plasma Glucose (mg/dL)
Pre and Post First Infusion
Insulin Dependent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

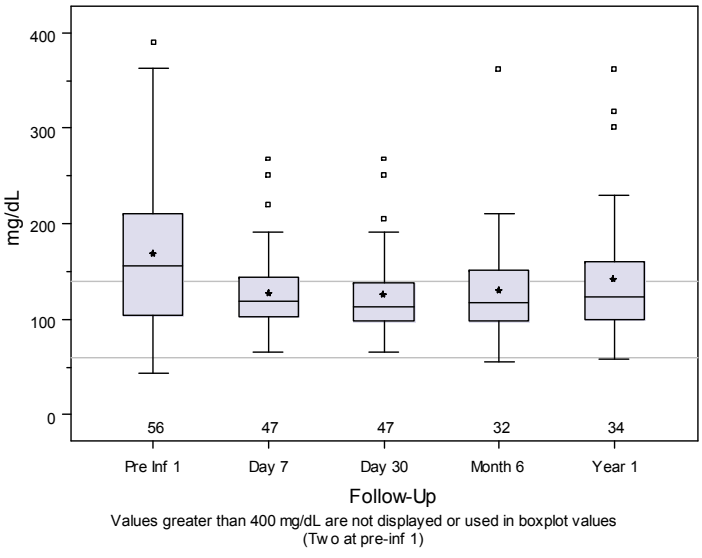
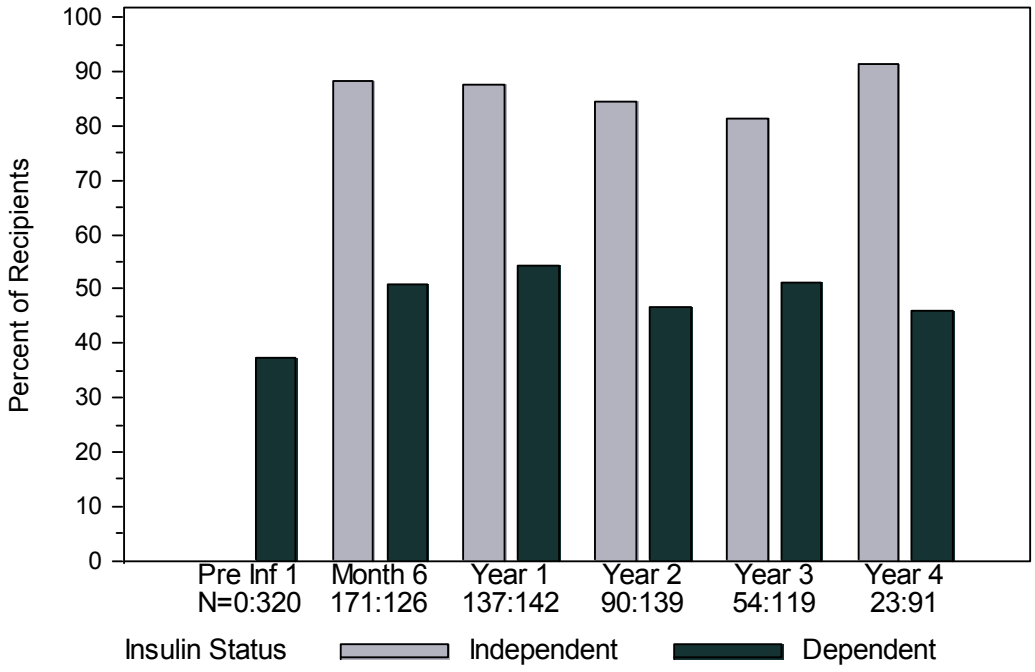


Exhibit 5 – 25
Percent of Recipients with Fasting Blood Glucose < 126 mg/dL
Post Last Infusion by Insulin Status

A. Islet Alone Recipients



B. Islet After Kidney Recipients

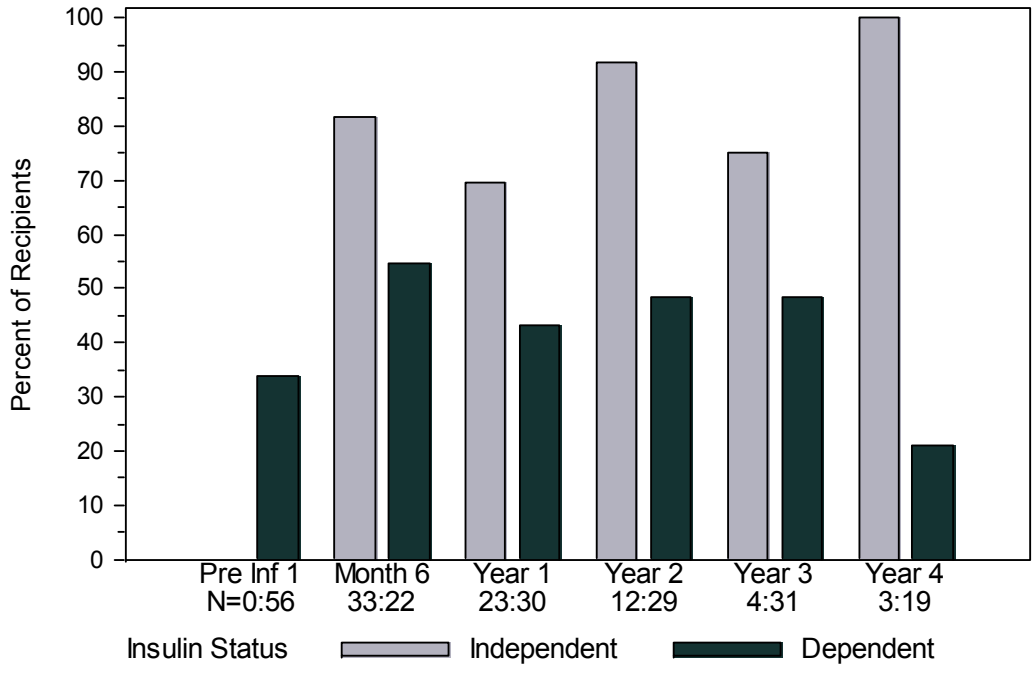
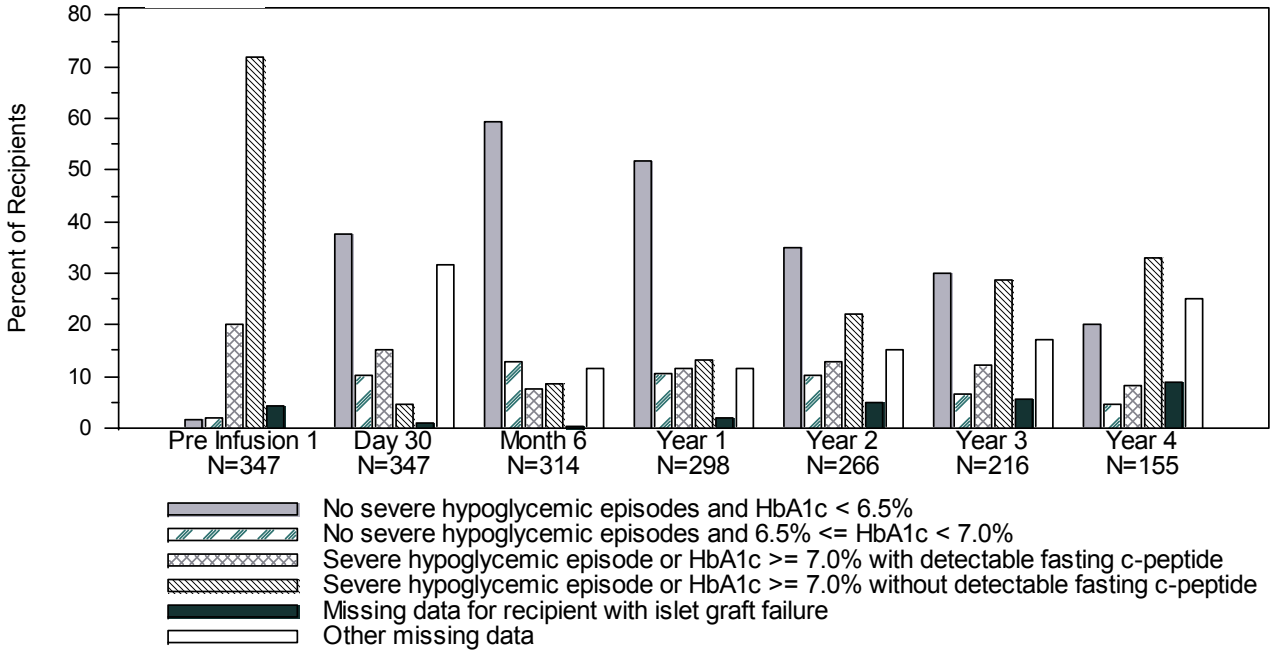


Exhibit 5 – 26
Composite Outcome (Hypoglycemia and HbA_{1c}) Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

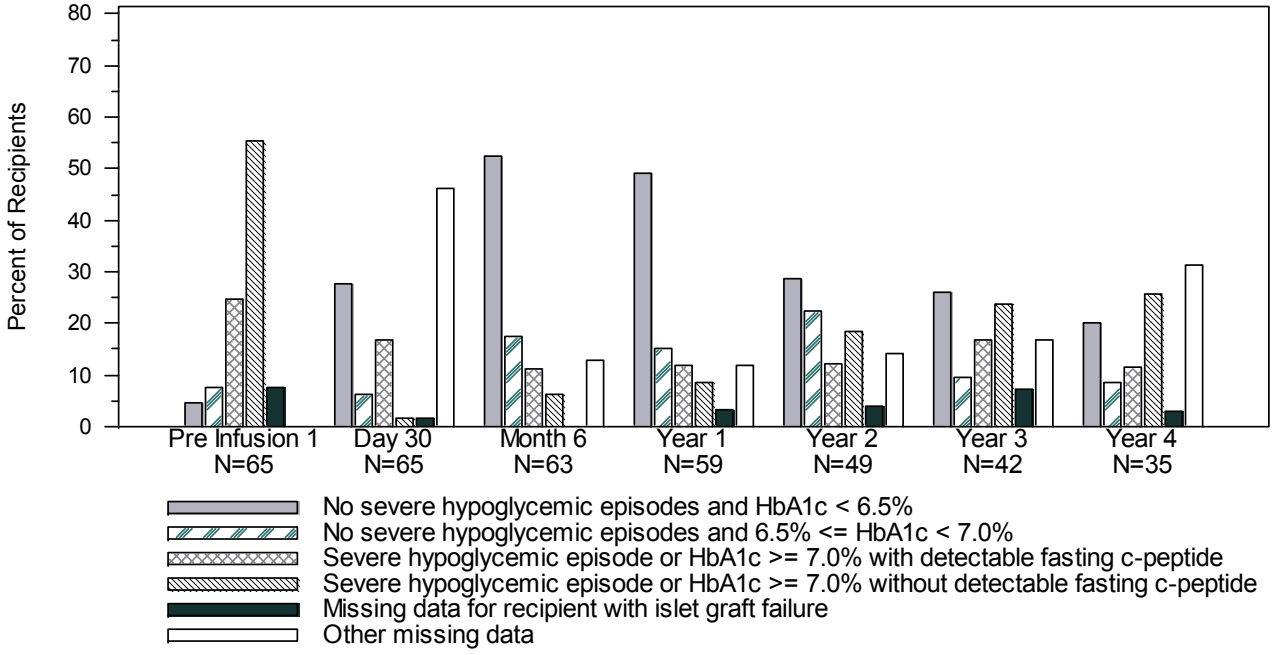
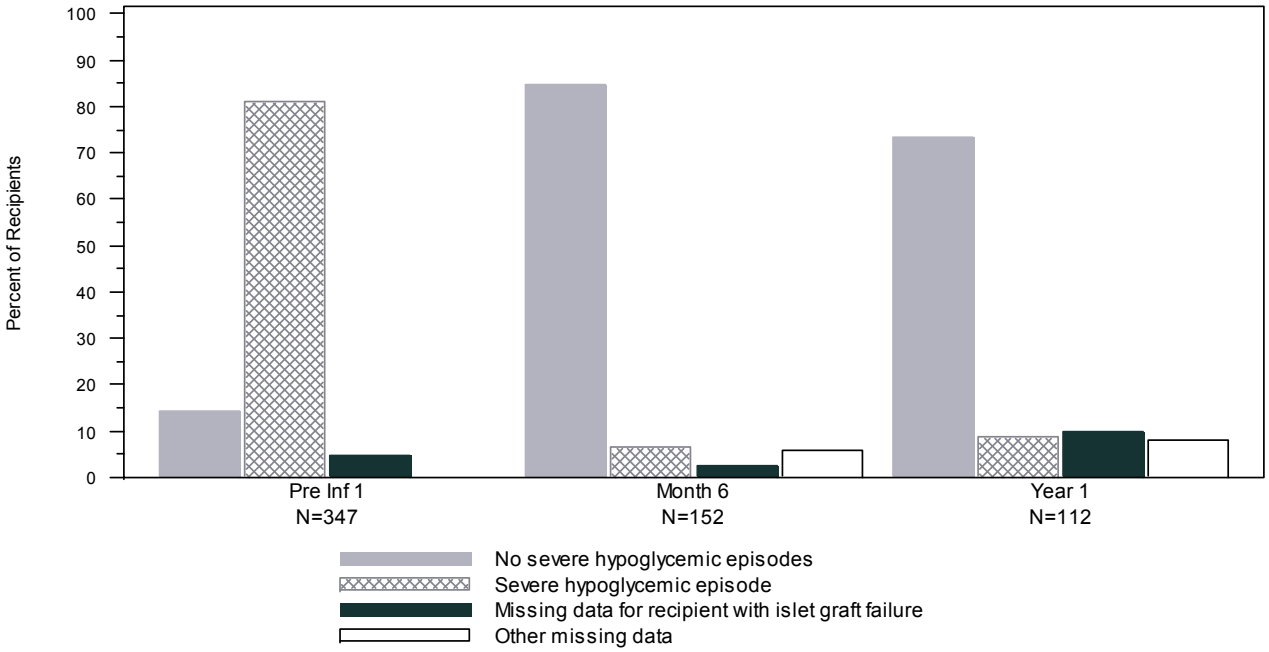


Exhibit 5 – 27
Severe Hypoglycemia

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

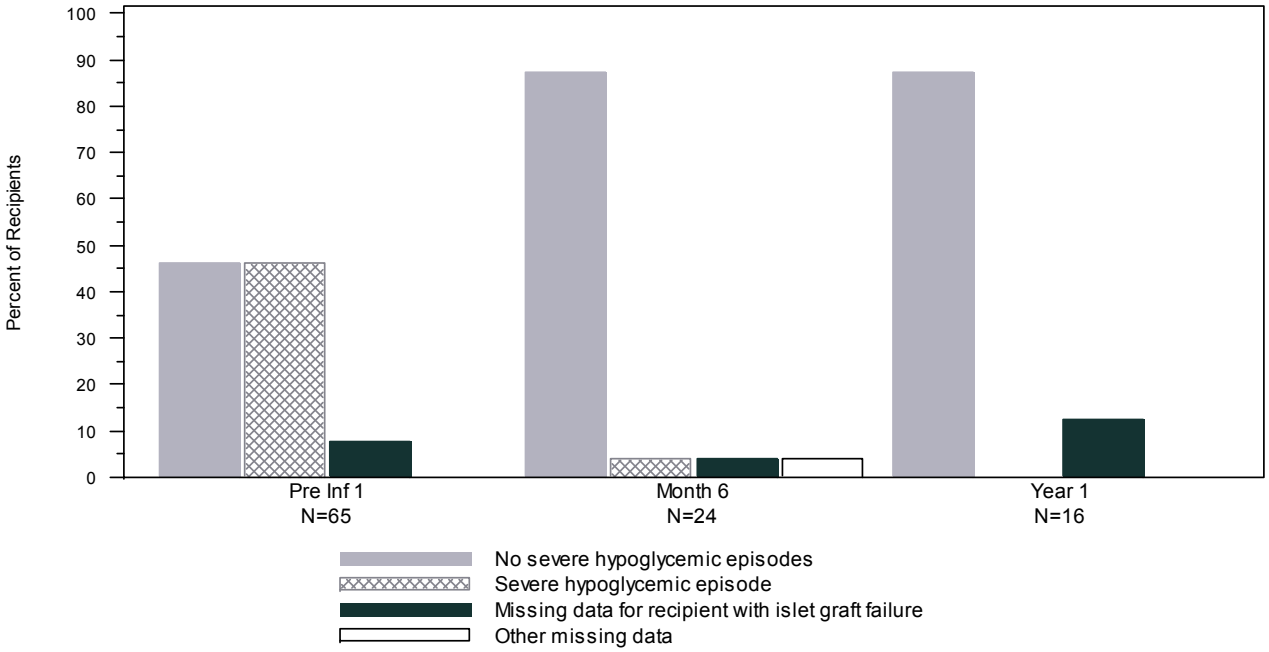
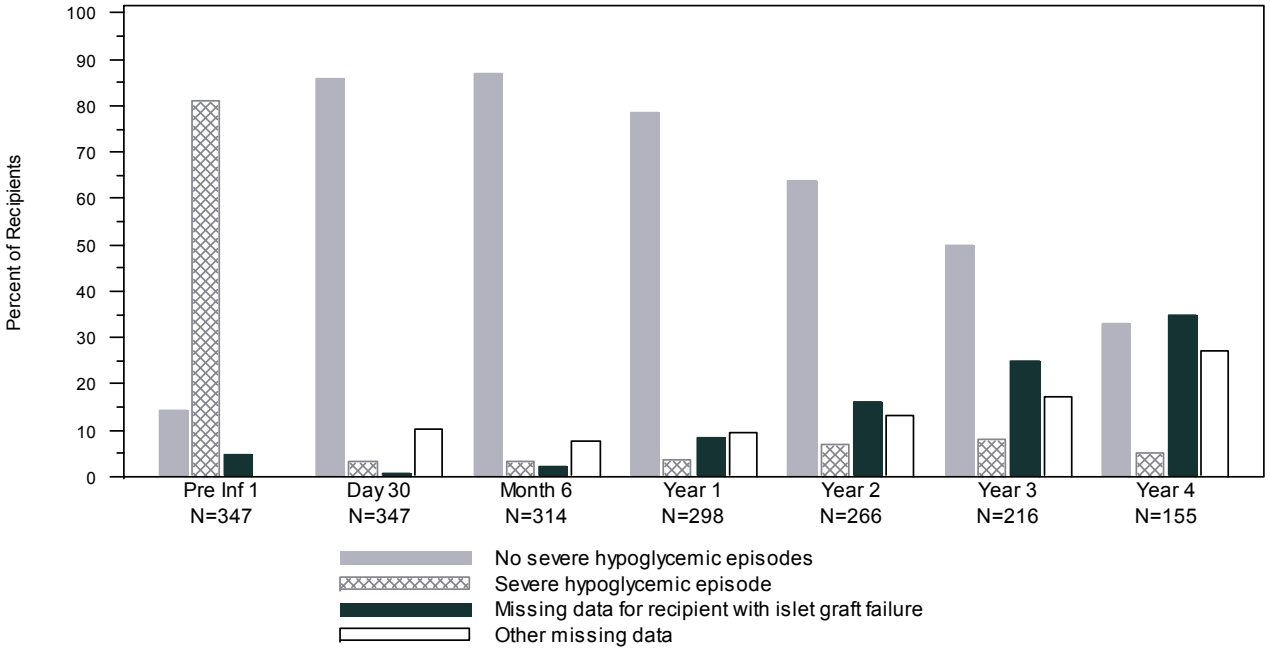


Exhibit 5 – 27 (continued)
Severe Hypoglycemia

C. Post Last Infusion
Islet Alone Recipients



D. Post Last Infusion
Islet After Kidney Recipients

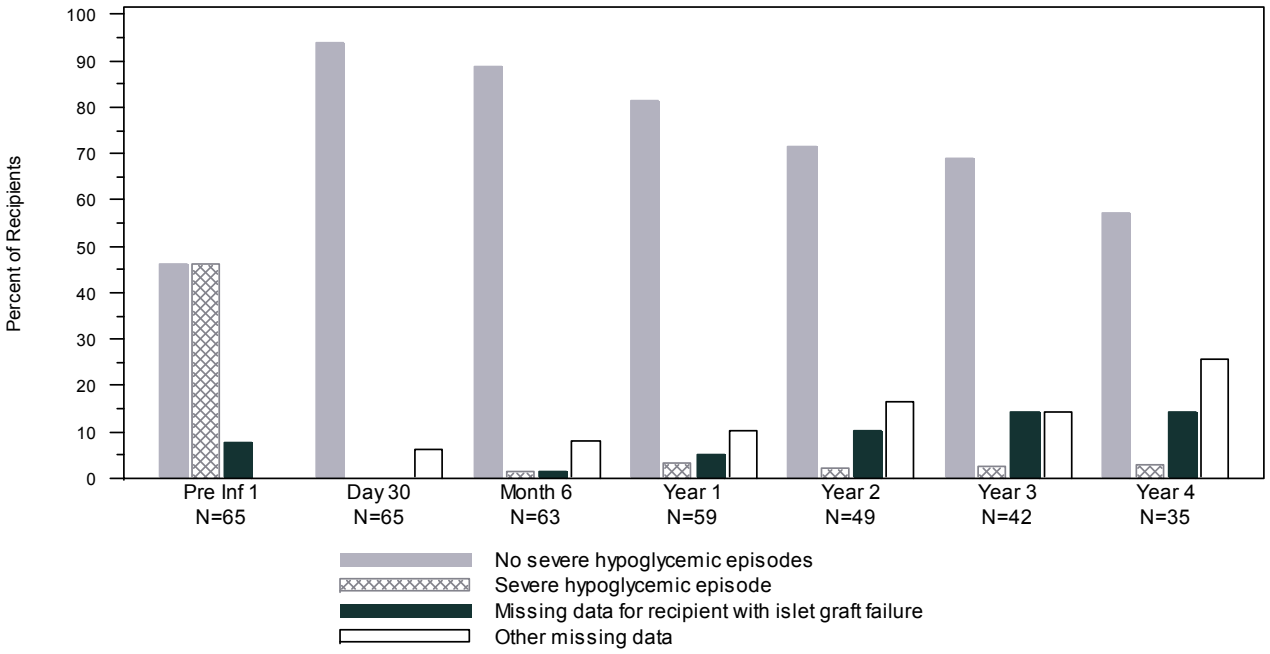
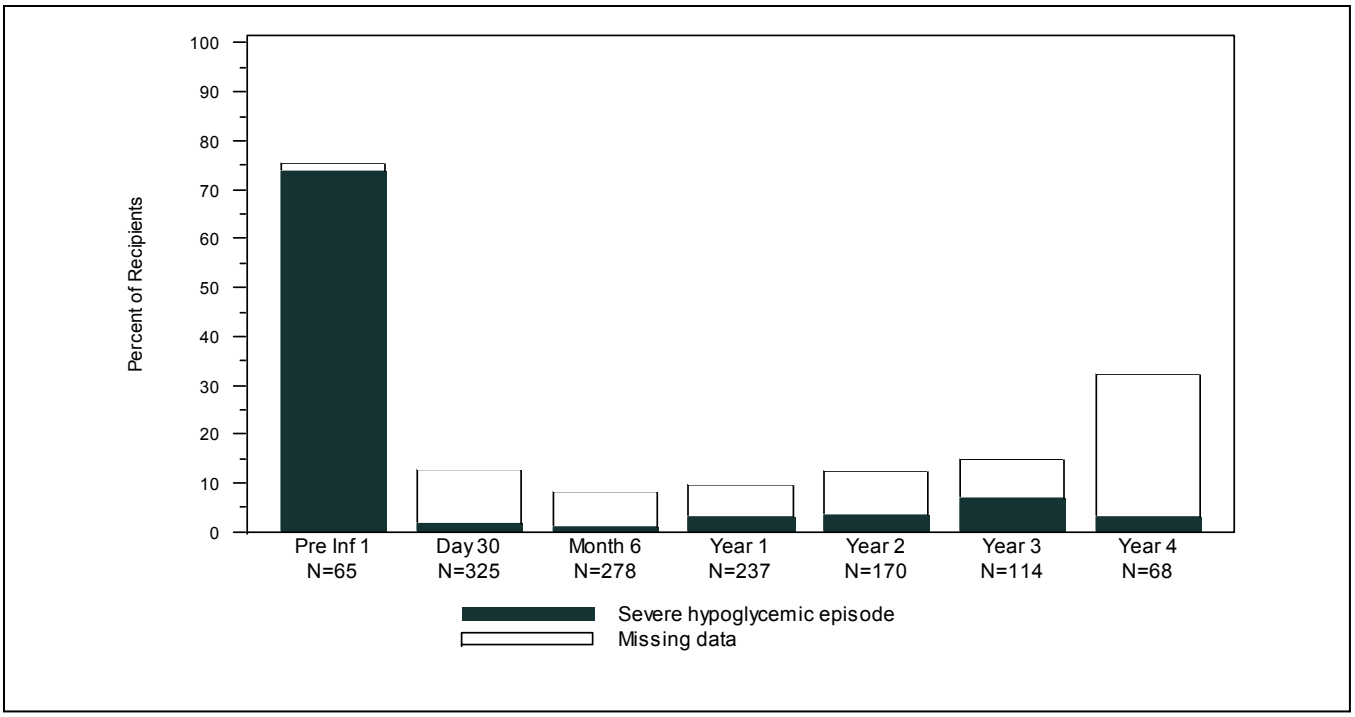


Exhibit 5 – 27 (continued)
Severe Hypoglycemia

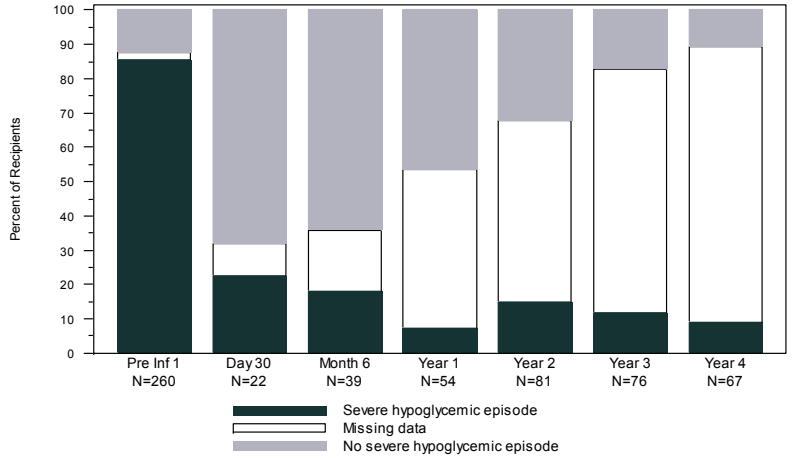
E. Post Last Infusion
Islet Alone Recipients with Detectable Fasting C-peptide



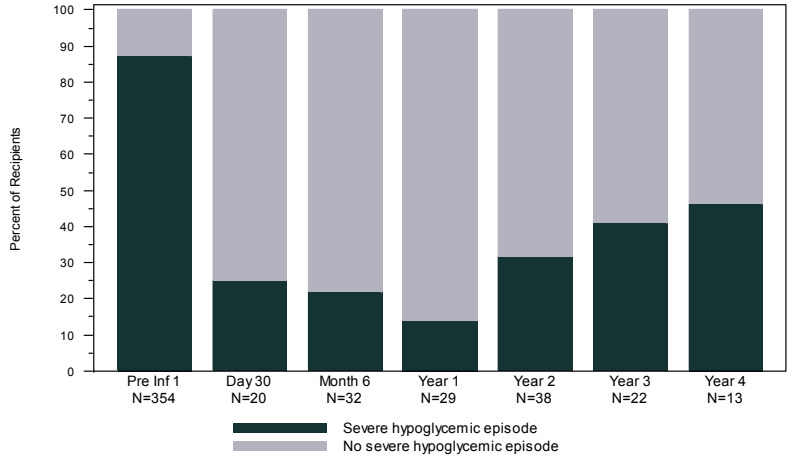
All those experiencing hypoglycemic episodes during follow-up were on insulin at the time of the episode with a mean daily insulin dose of 21 units/day

Exhibit 5-27 (continued)
Severe Hypoglycemia

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



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



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

Exhibit 5 – 28
Hypoglycemia Status Pre First Infusion and Post Last Infusion
All Allograft Recipients

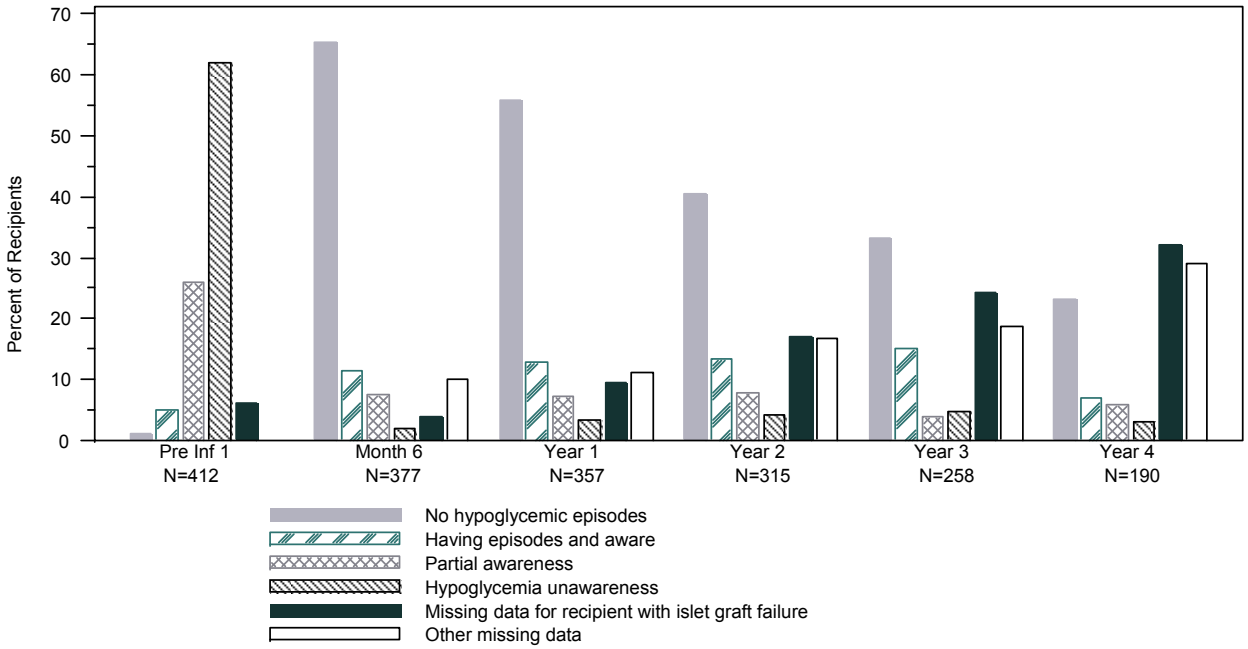
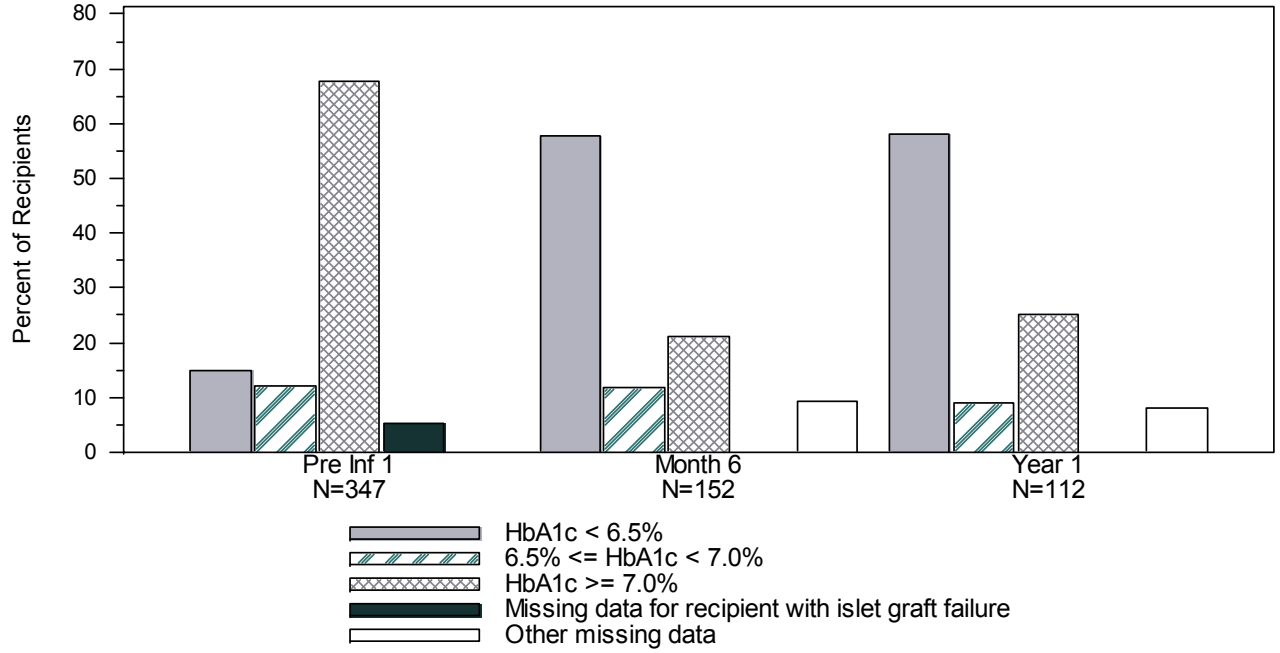


Exhibit 5 – 29
HbA_{1c}

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

Islet Alone Recipients



Islet After Kidney Recipients

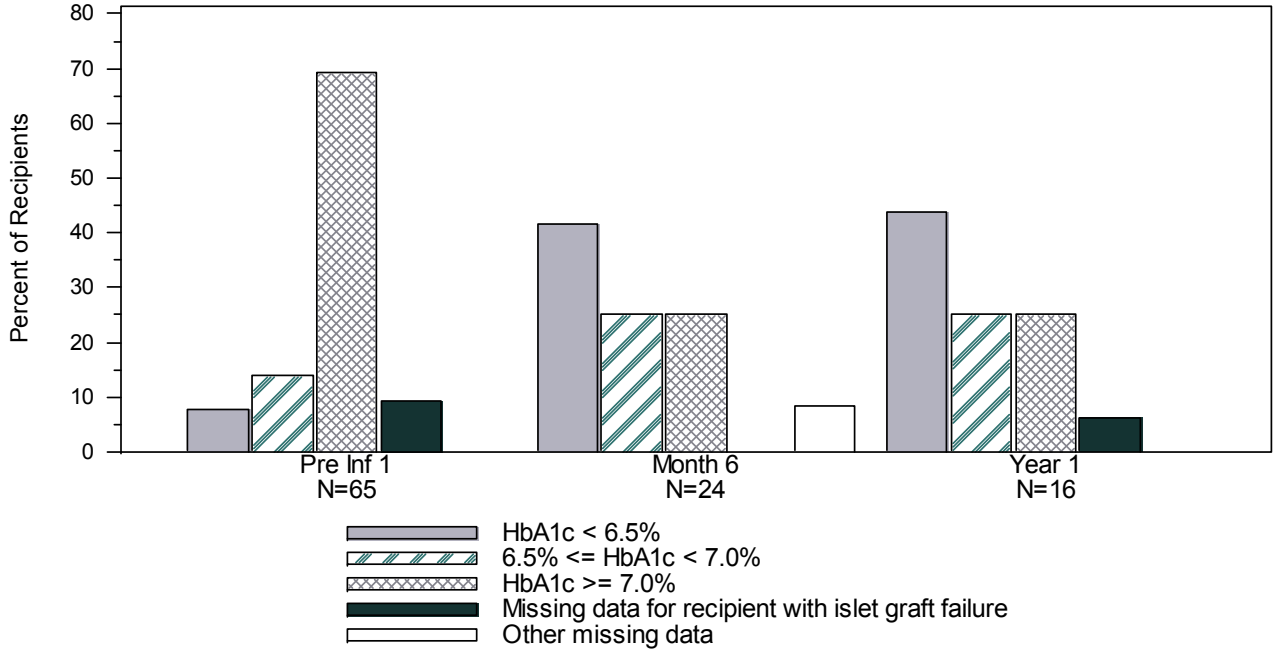
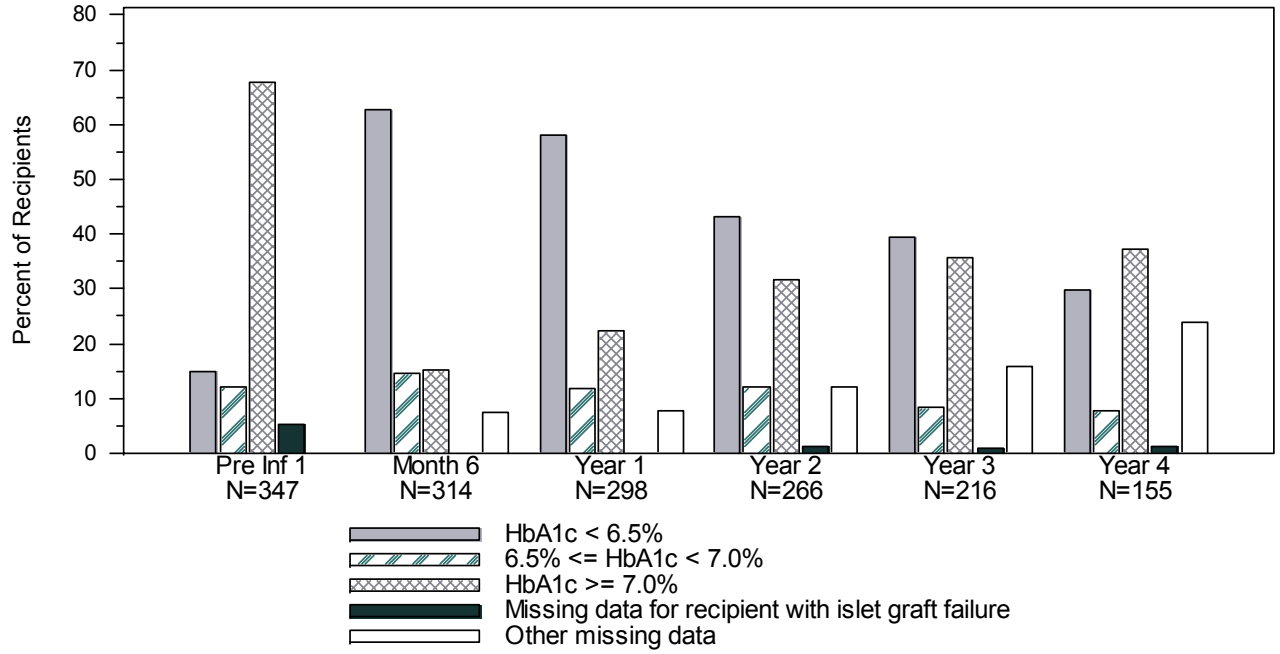


Exhibit 5 – 29 (continued)
HbA_{1c}

B. Post Last Infusion

Islet Alone Recipients



Islet After Kidney Recipients

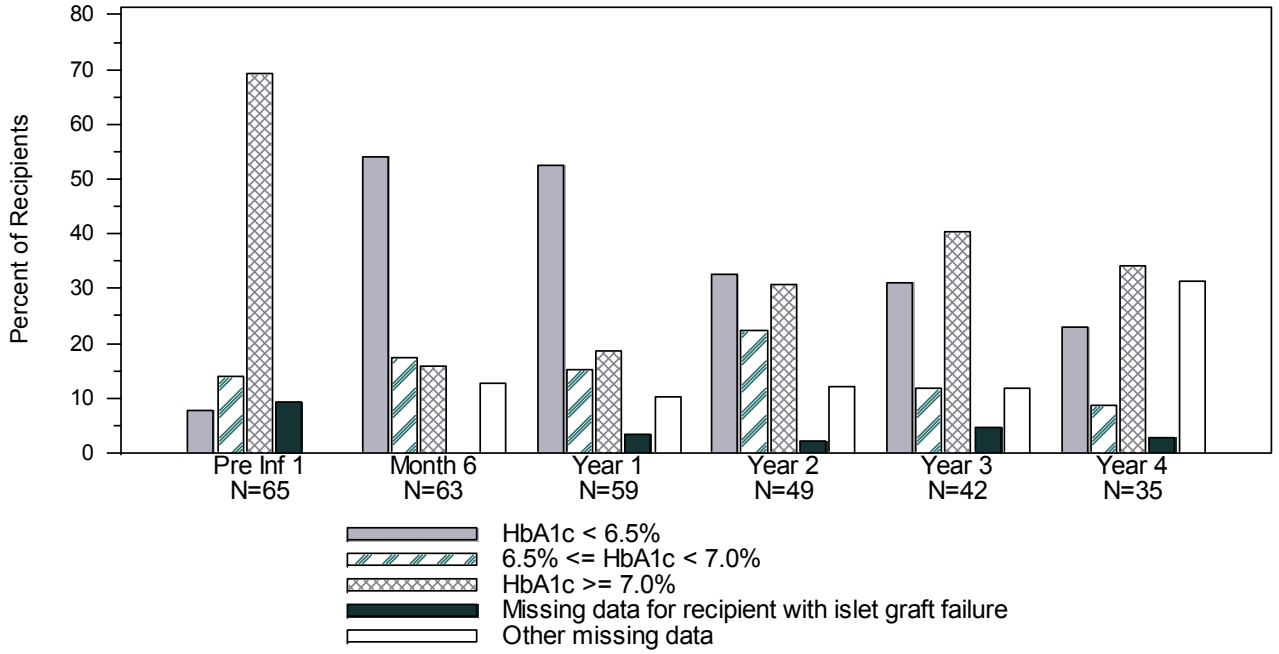


Exhibit 5 – 30
HbA_{1c} (%)
Pre Infusion and Post Last Infusion

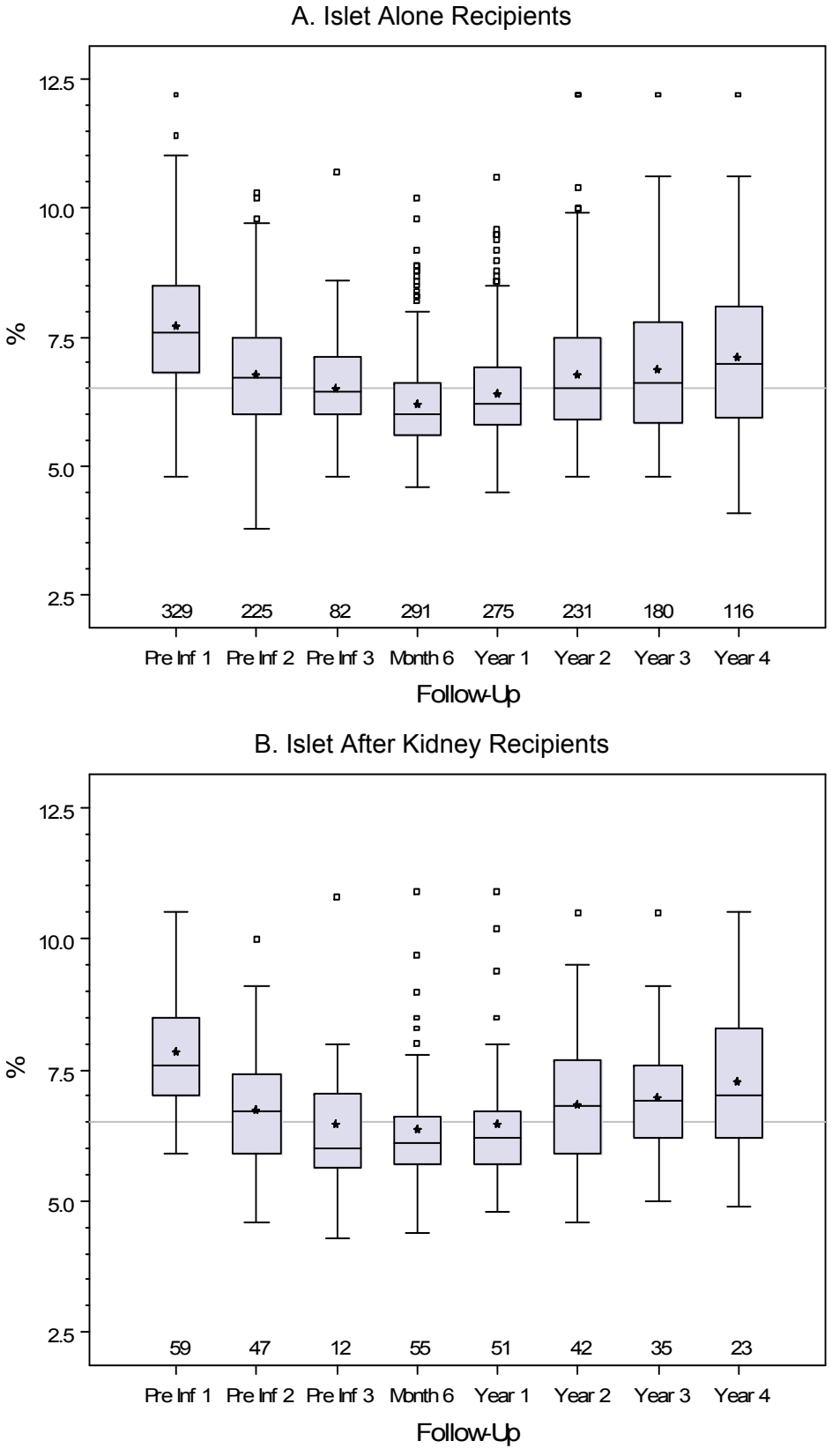
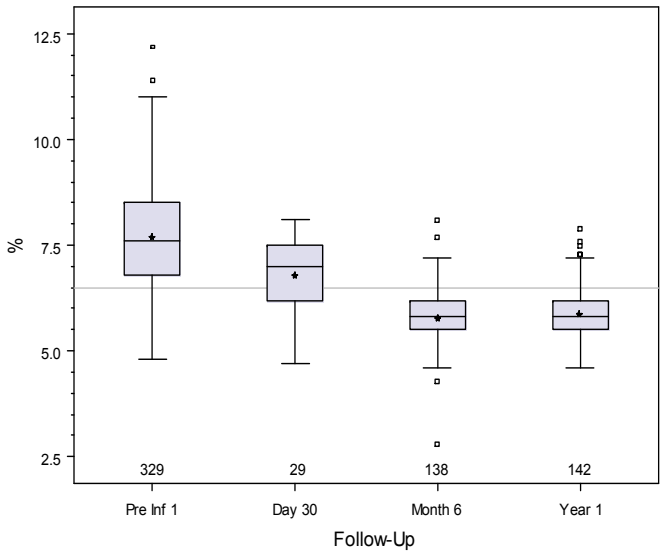


Exhibit 5 – 31
HbA_{1c} (%) Pre and Post First Infusion
Insulin Independent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

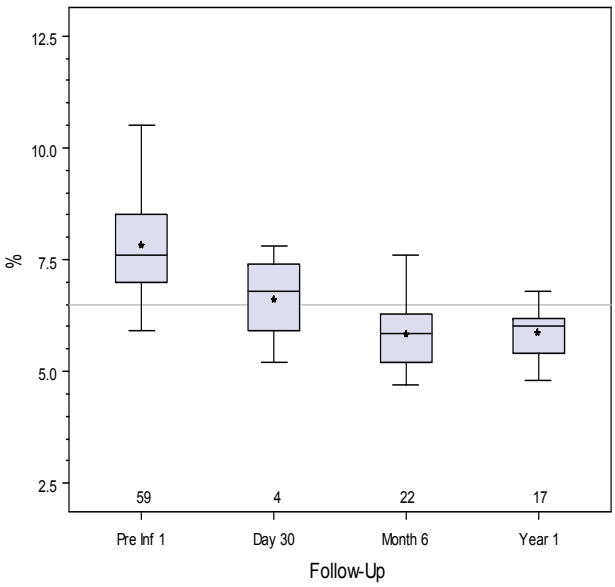
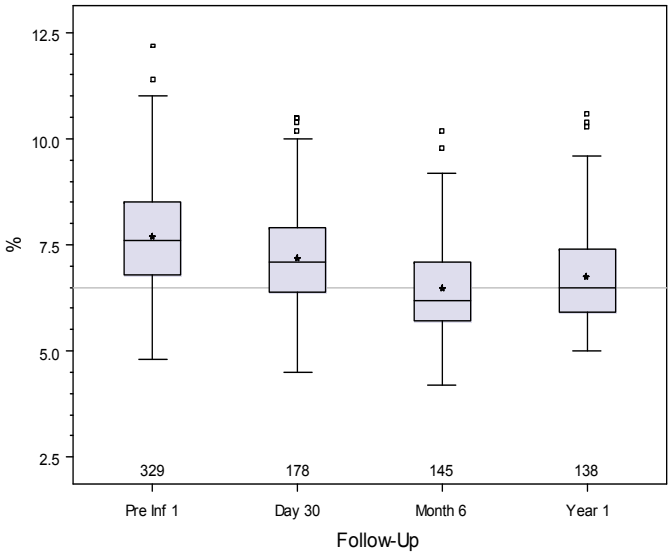


Exhibit 5 –32
HbA_{1c} (%) Pre and Post First Infusion
Insulin Dependent Recipients

A. Islet Alone Recipients



B. Islet After Kidney Recipients

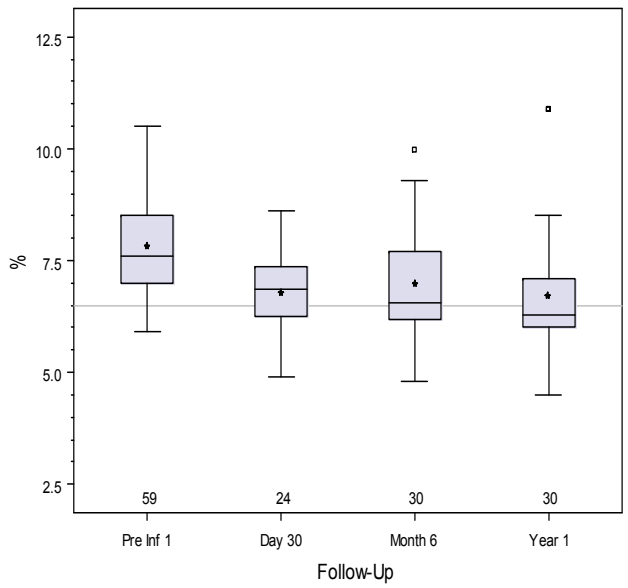
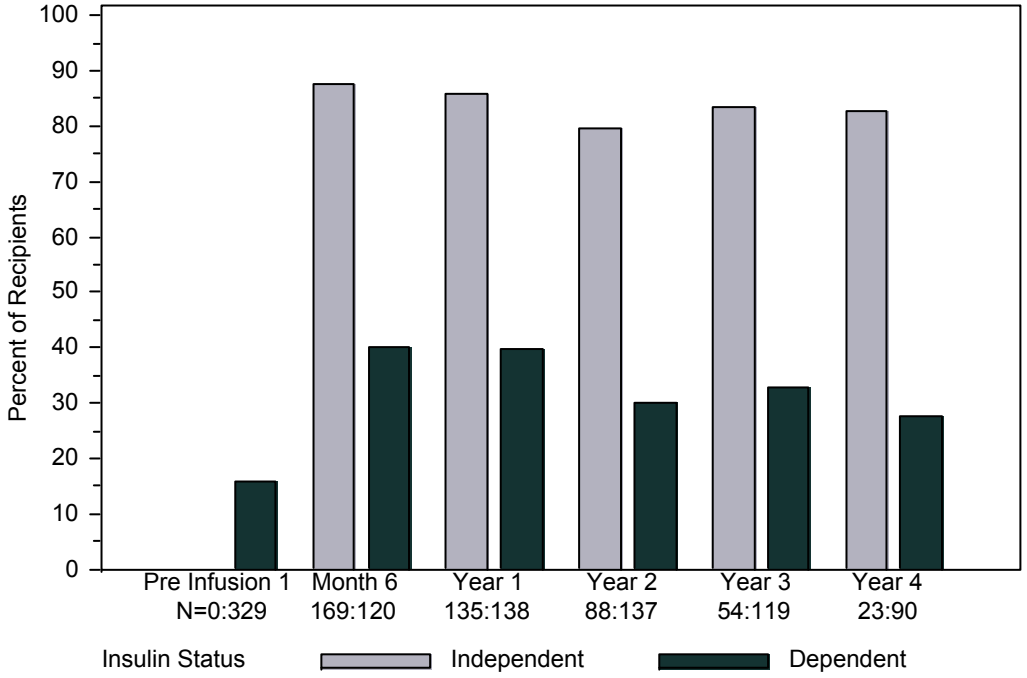


Exhibit 5 – 33
Recipients with HbA_{1c} < 6.5%
Percent of Post Last Infusion by Insulin Status

A. Islet Alone Recipients



B. Islet After Kidney Recipients

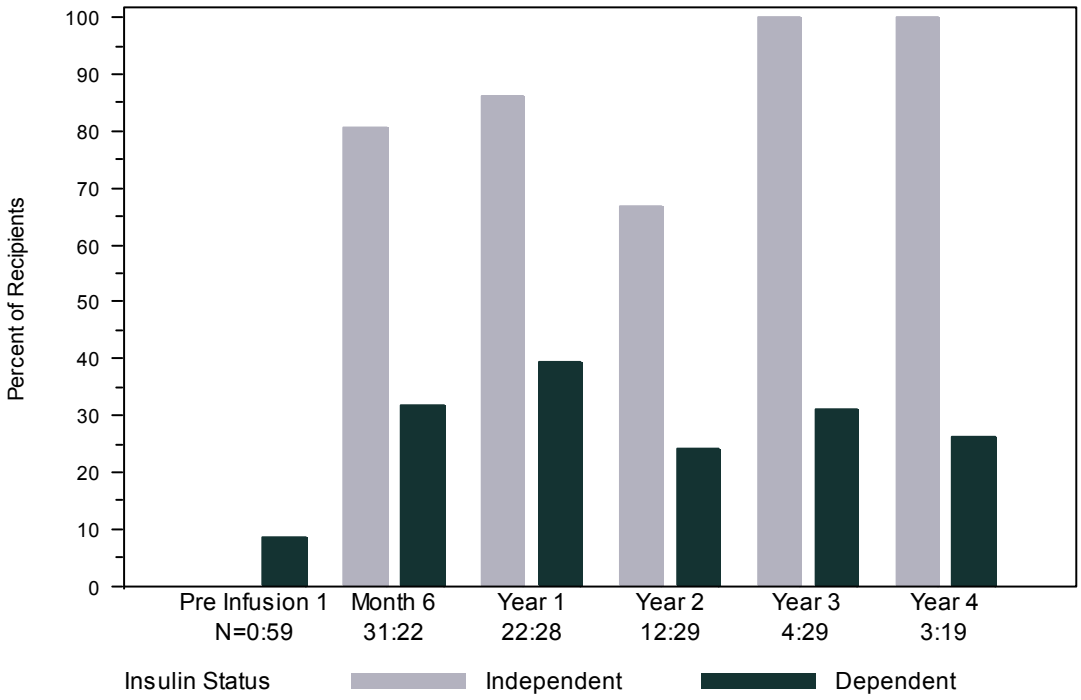


Exhibit 5 – 34
Peripheral Neuropathy
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

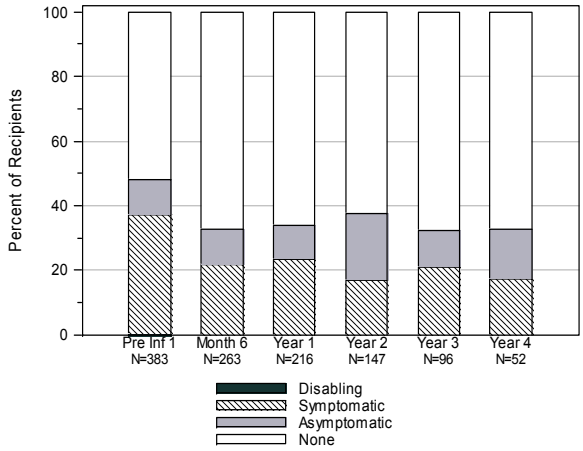


Exhibit 5 – 35
Autonomic Neuropathy
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

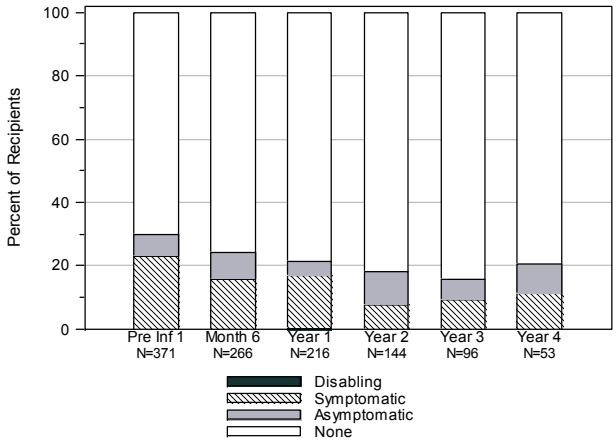


Exhibit 5 – 36
Nephropathy
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

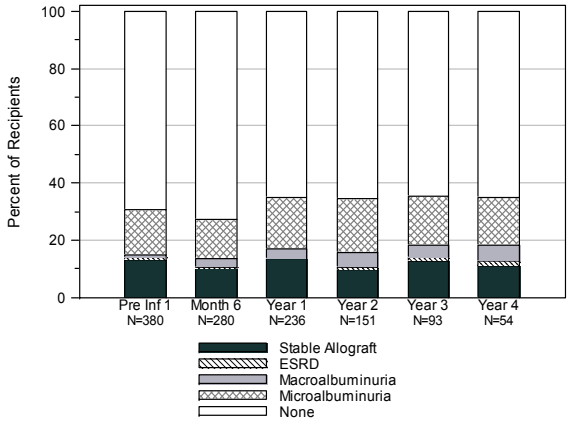


Exhibit 5 – 37
Coronary Artery Disease
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

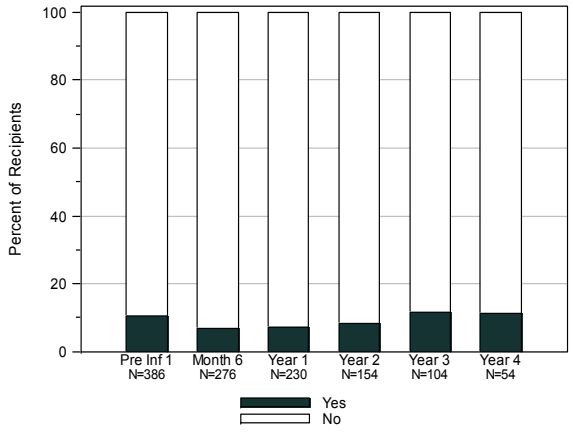


Exhibit 5 – 38
Stroke
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

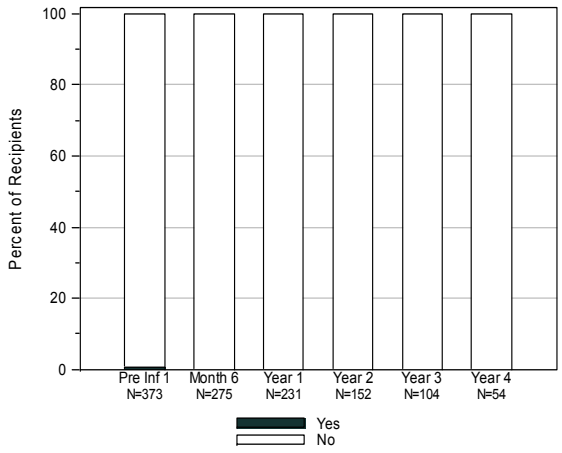


Exhibit 5 – 39
Peripheral Vascular Disease
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

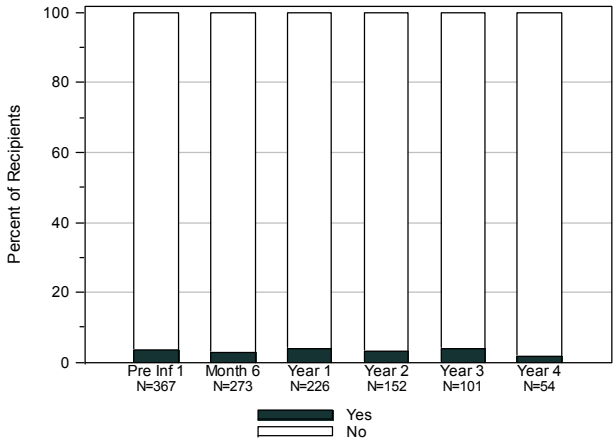


Exhibit 5 – 40
Treated Hypertension
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

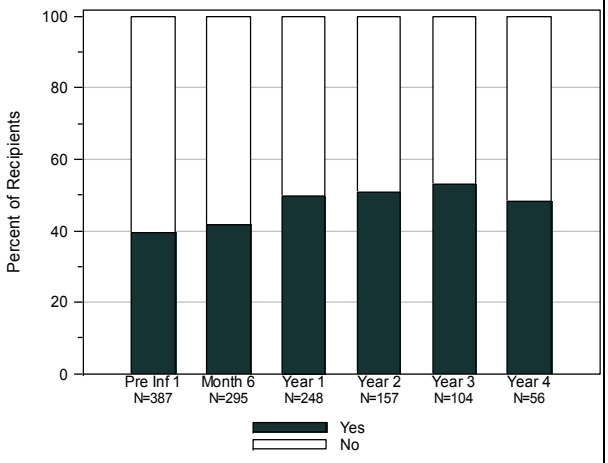


Exhibit 5 – 41
Foot Ulcers
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

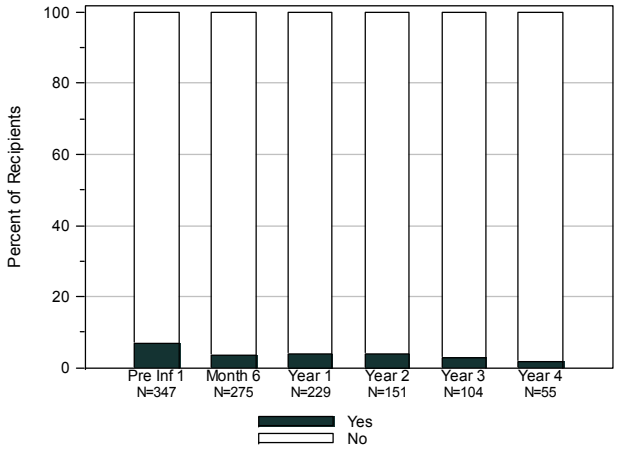


Exhibit 5 – 42
Lower Limb Amputation
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

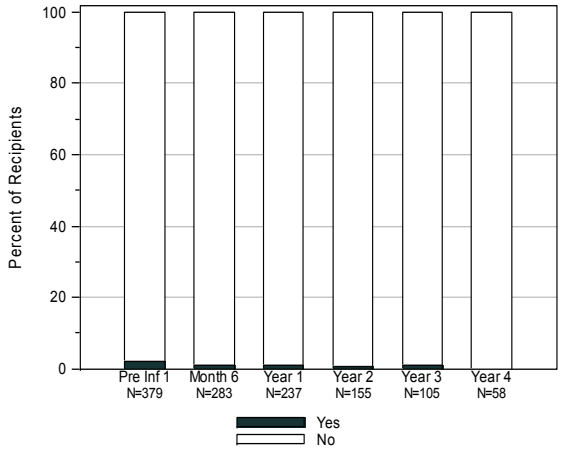


Exhibit 5 – 43
Foot Deformity
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

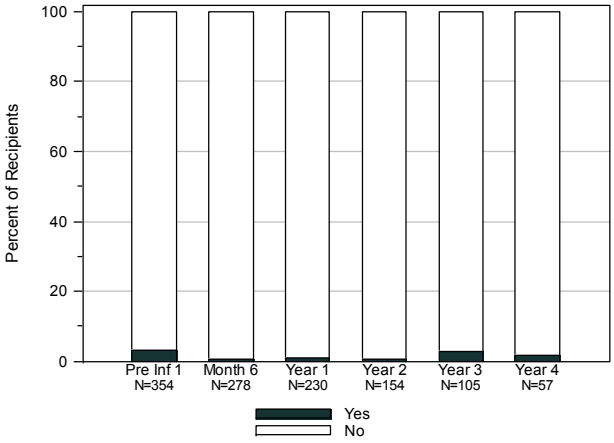


Exhibit 5 – 44
Dysesthesia
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

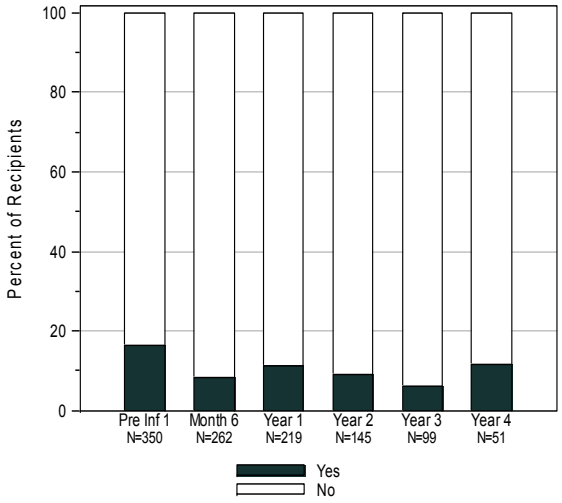


Exhibit 5 – 45
Orthostatic Hypotension
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

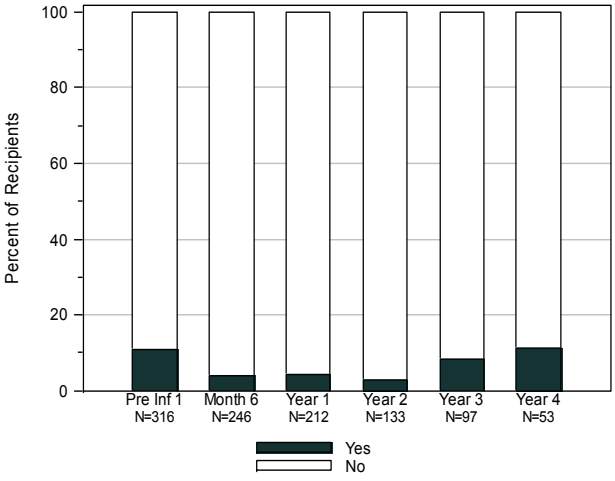


Exhibit 5 – 46
Gastroparesis
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

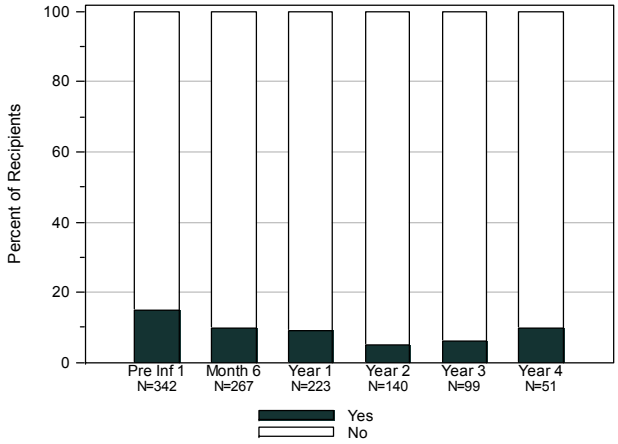


Exhibit 5 – 47
Constipation
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

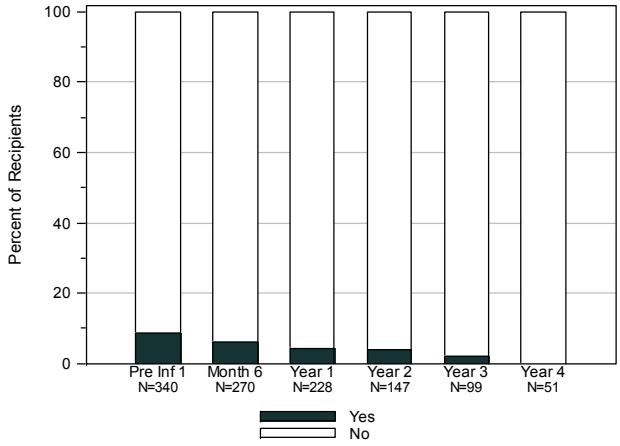


Exhibit 5 – 48
Diabetic Diarrhea
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function with
Documented Graft Function

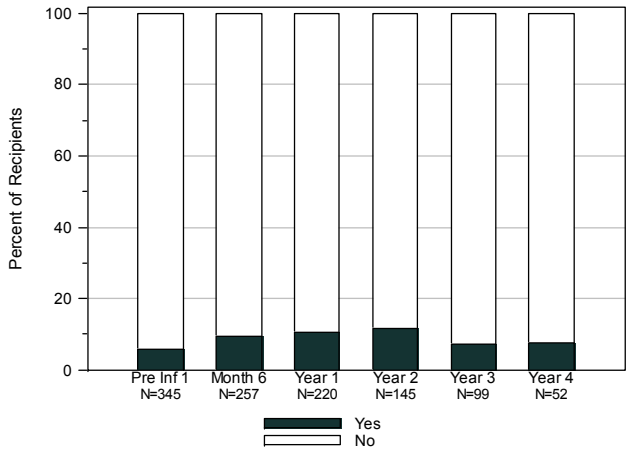


Exhibit 5 – 49
Fecal Incontinence
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function with
Documented Graft Function

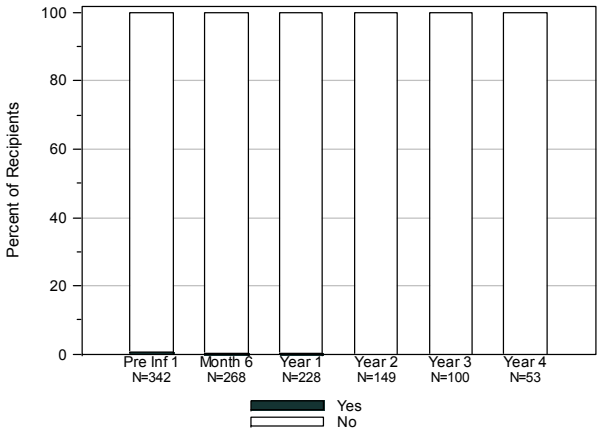


Exhibit 5 – 50
Diabetic Bladder Dysfunction
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

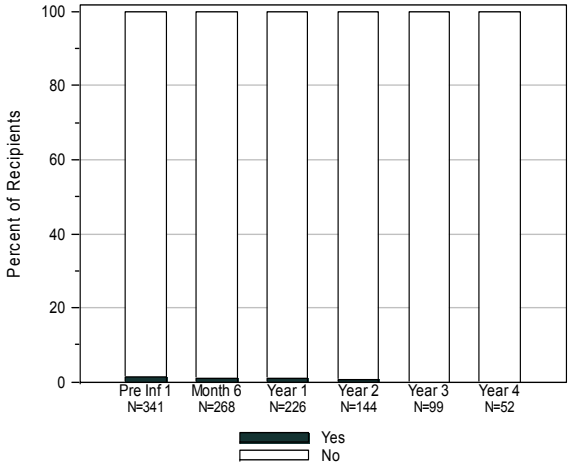


Exhibit 5 – 51
Sexual Dysfunction
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

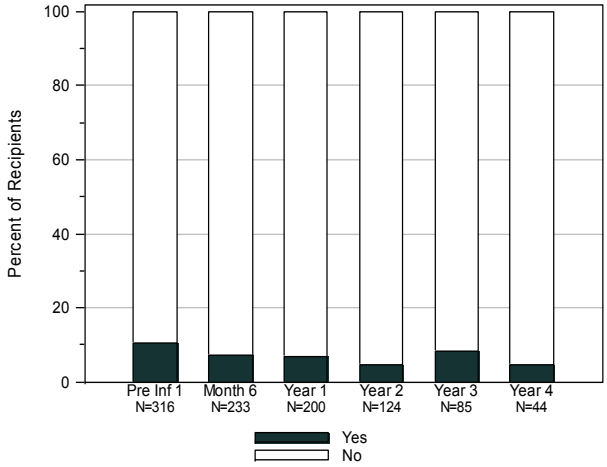


Exhibit 5 – 52
Retinopathy
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

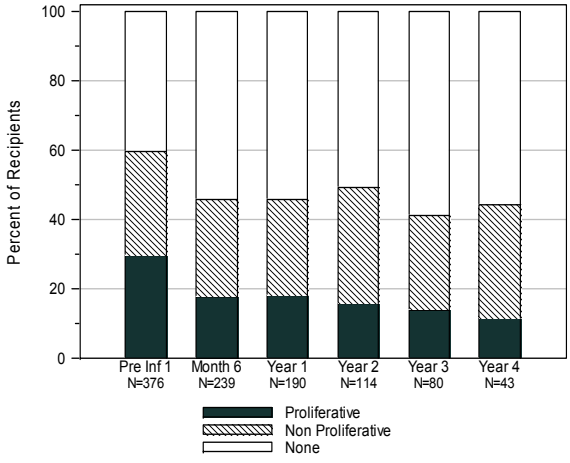


Exhibit 5 – 53
Diabetic Macular Edema
Pre First Infusion and Post Last Infusion
All Allograft Recipients with
Documented Graft Function

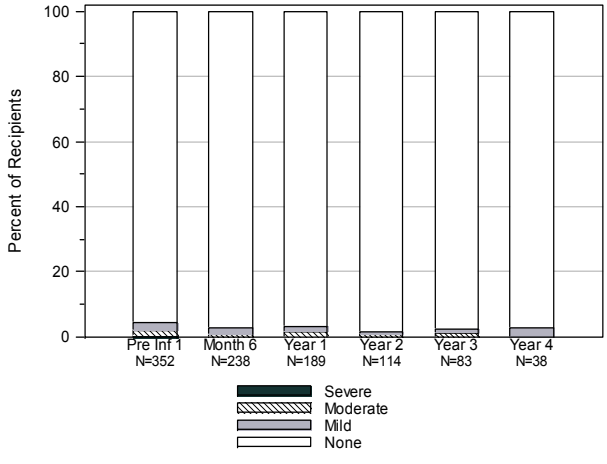


Exhibit 5 – 54
Laser Photocoagulation Surgery for Proliferative Retinopathy
Pre First Infusion and Post Last Infusion
All Allograft Recipients with Documented Graft Function

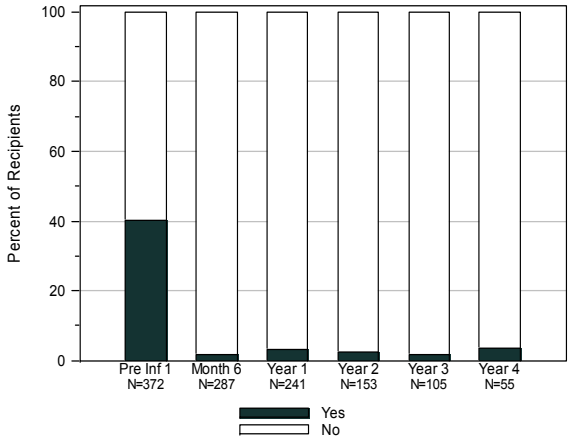


Exhibit 5 – 55
Laser Photocoagulation Surgery for Diabetic Macular Edema
Pre First Infusion and Post Last Infusion
All Allograft Recipients with Documented Graft Function

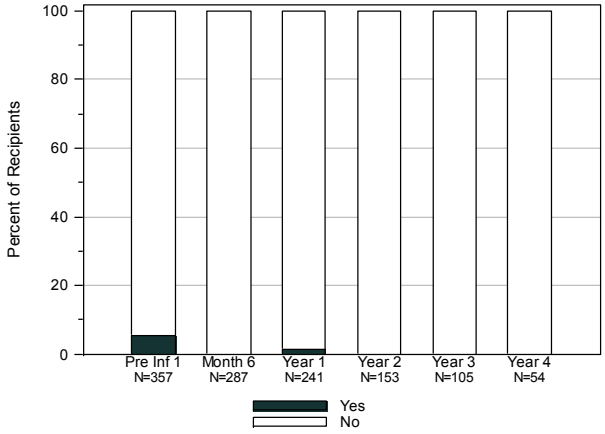


Exhibit 5 – 56
Vitrectomy
Pre First Infusion and Post Last Infusion
All Allograft Recipients with Documented Graft Function

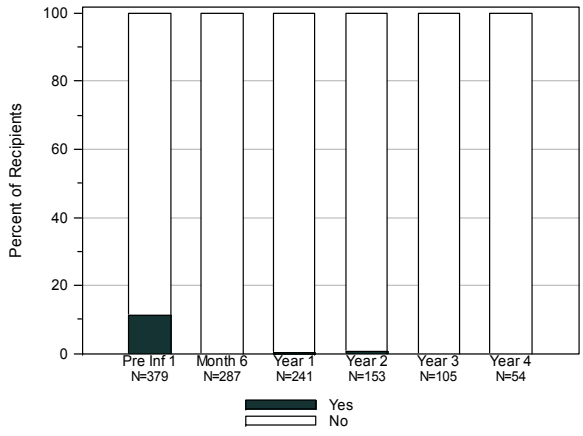
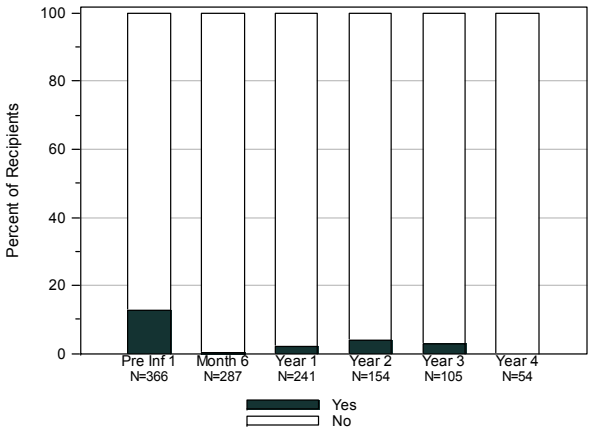


Exhibit 5 – 57
Other Eye Surgery
Pre First Infusion and Post Last Infusion
All Allograft Recipients with Documented Graft Function



Chapter 6
Liver, Kidney, Lipid, and PRA Effects

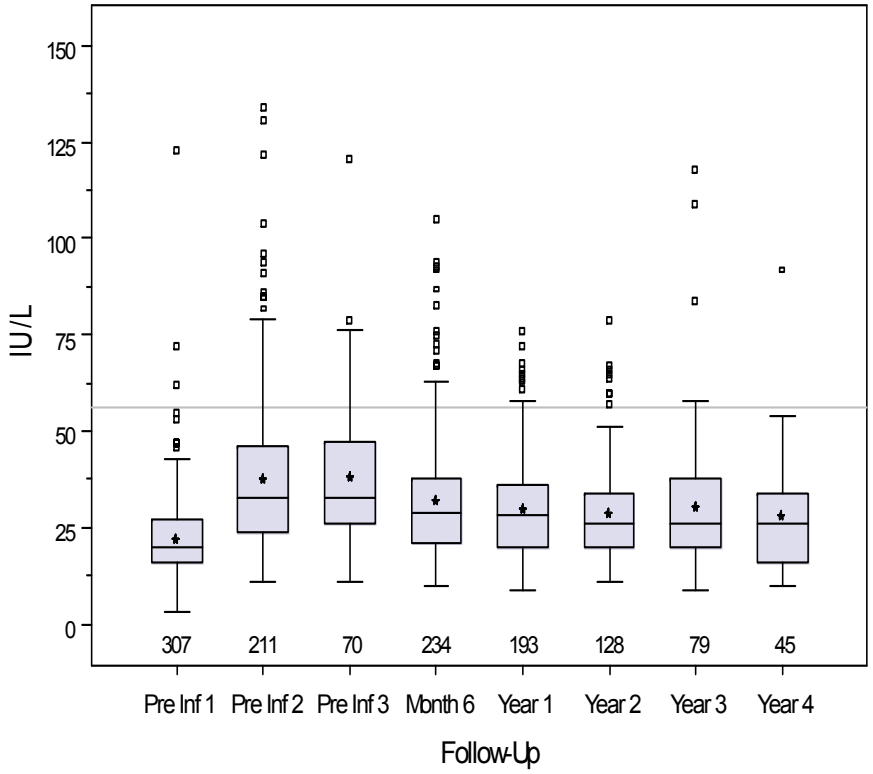
Liver, Kidney, Lipid, and PRA Effects

This chapter provides a summary of liver, kidney, lipid and PRA laboratory tests.

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

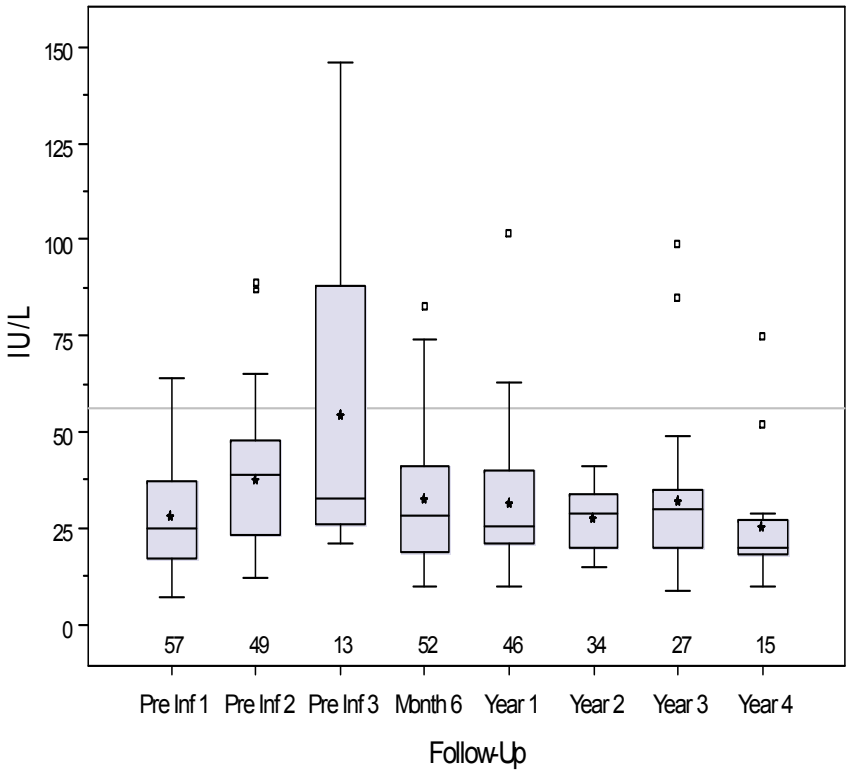
Exhibit 6 – 1
ALT (IU/L) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 150 IU/L are not displayed or used in boxplot values
(Two at pre-inf 2, one at month 6, one at year 1, and one at year 2)

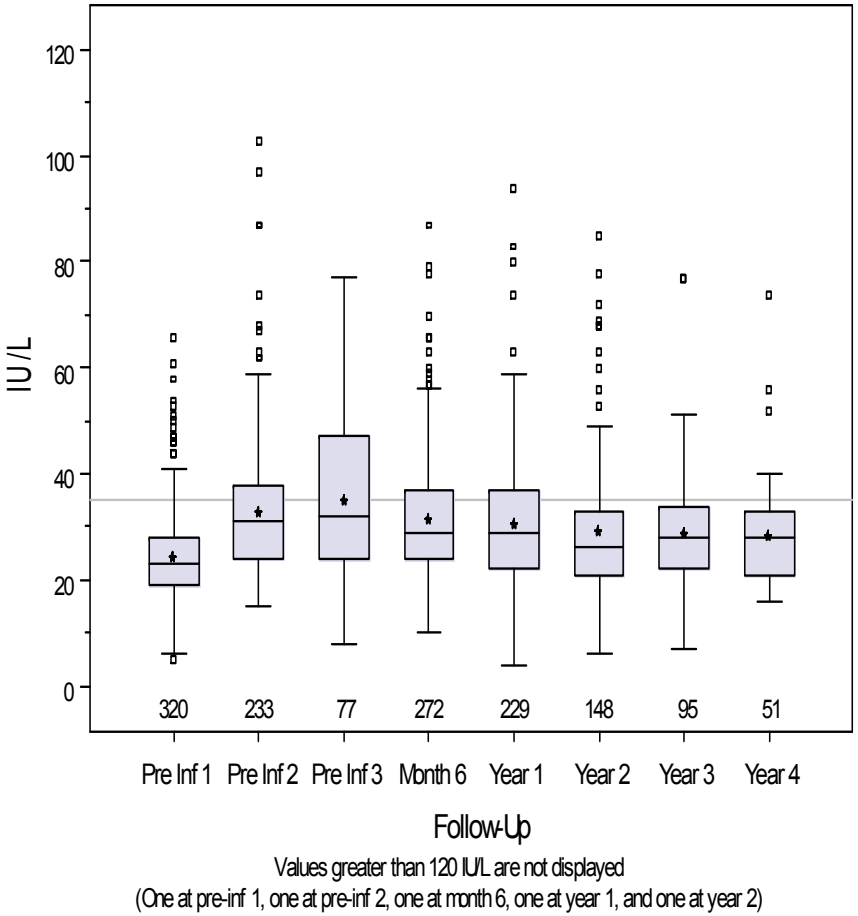
B. Islet After Kidney Recipients



Values greater than 150 IU/L are not displayed or used in boxplot values
(One at pre-inf 2, one at month 6, and one at year 2)

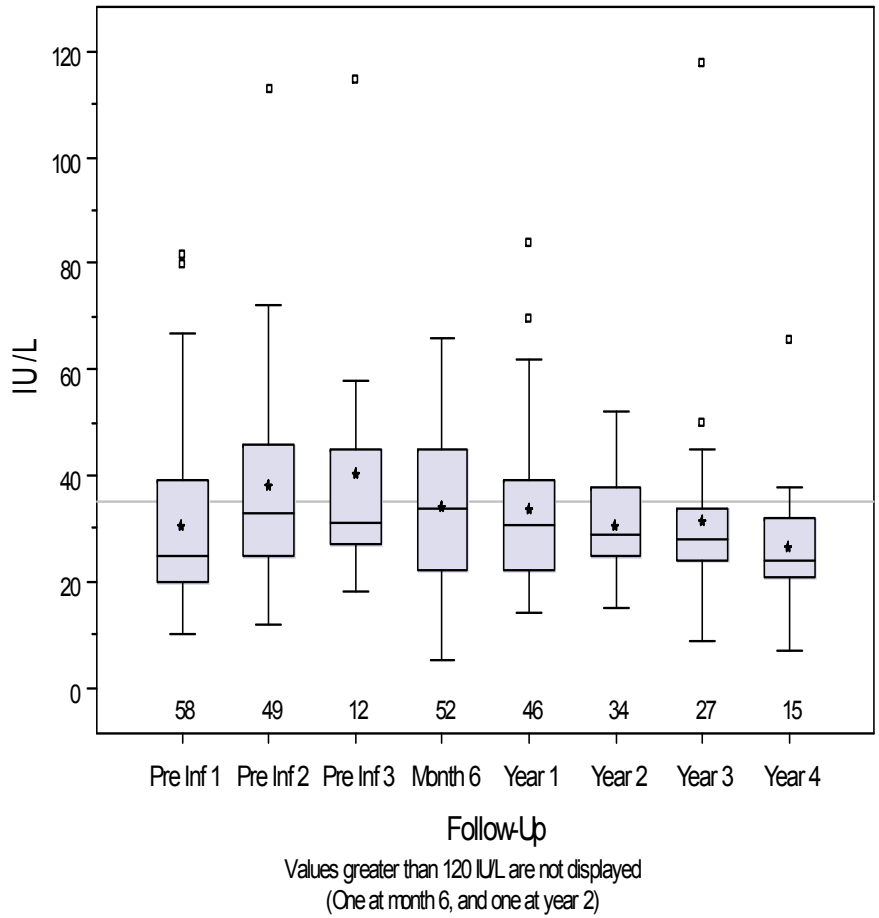
Exhibit 6 – 2
AST (IU/L) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 120 IU/L are not displayed
(One at pre-inf 1, one at pre-inf 2, one at month 6, one at year 1, and one at year 2)

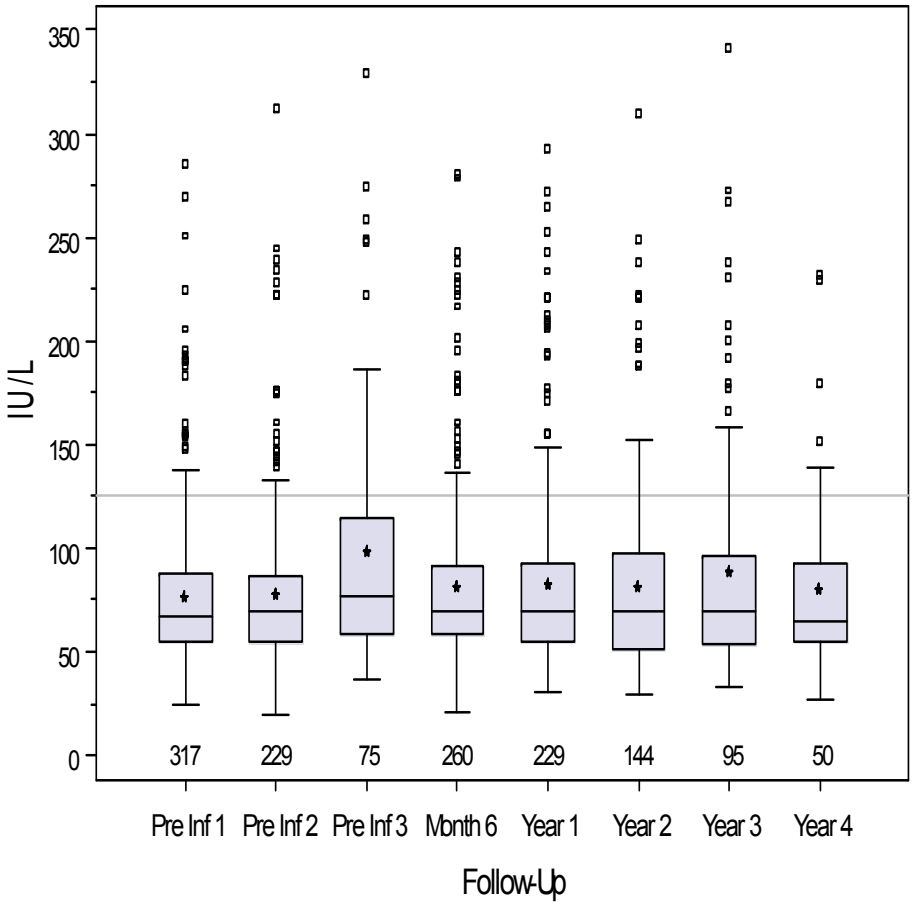
B. Islet After Kidney Recipients



Values greater than 120 IU/L are not displayed
(One at month 6, and one at year 2)

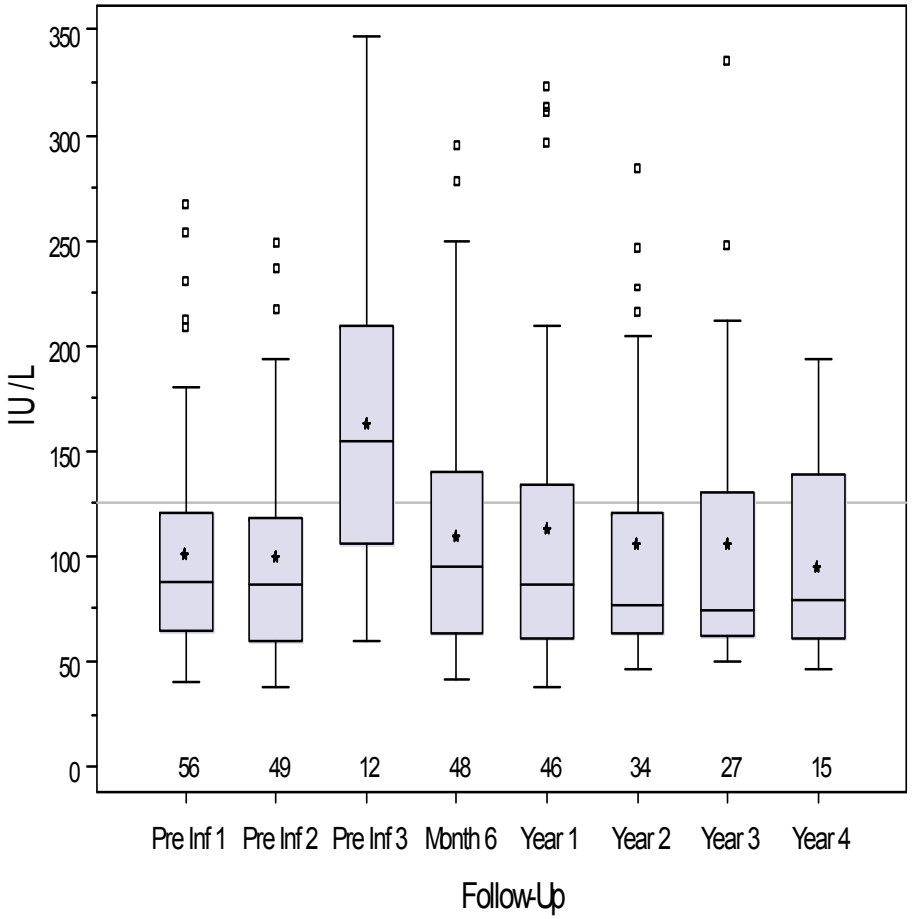
Exhibit 6 – 3
Alkaline Phosphatase (IU/L) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 350 IU/L are not displayed
(Two at pre-inf 2, one at month 6, one at year 1, and one at year 2)

B. Islet After Kidney Recipients



Values greater than 350 IU/L are not displayed
(Four at pre-inf 1, four at pre-inf 2, two at year 1, and one at year 2)

Exhibit 6 – 4
Total Bilirubin (mg/dL) Pre Infusion and Post Last Infusion

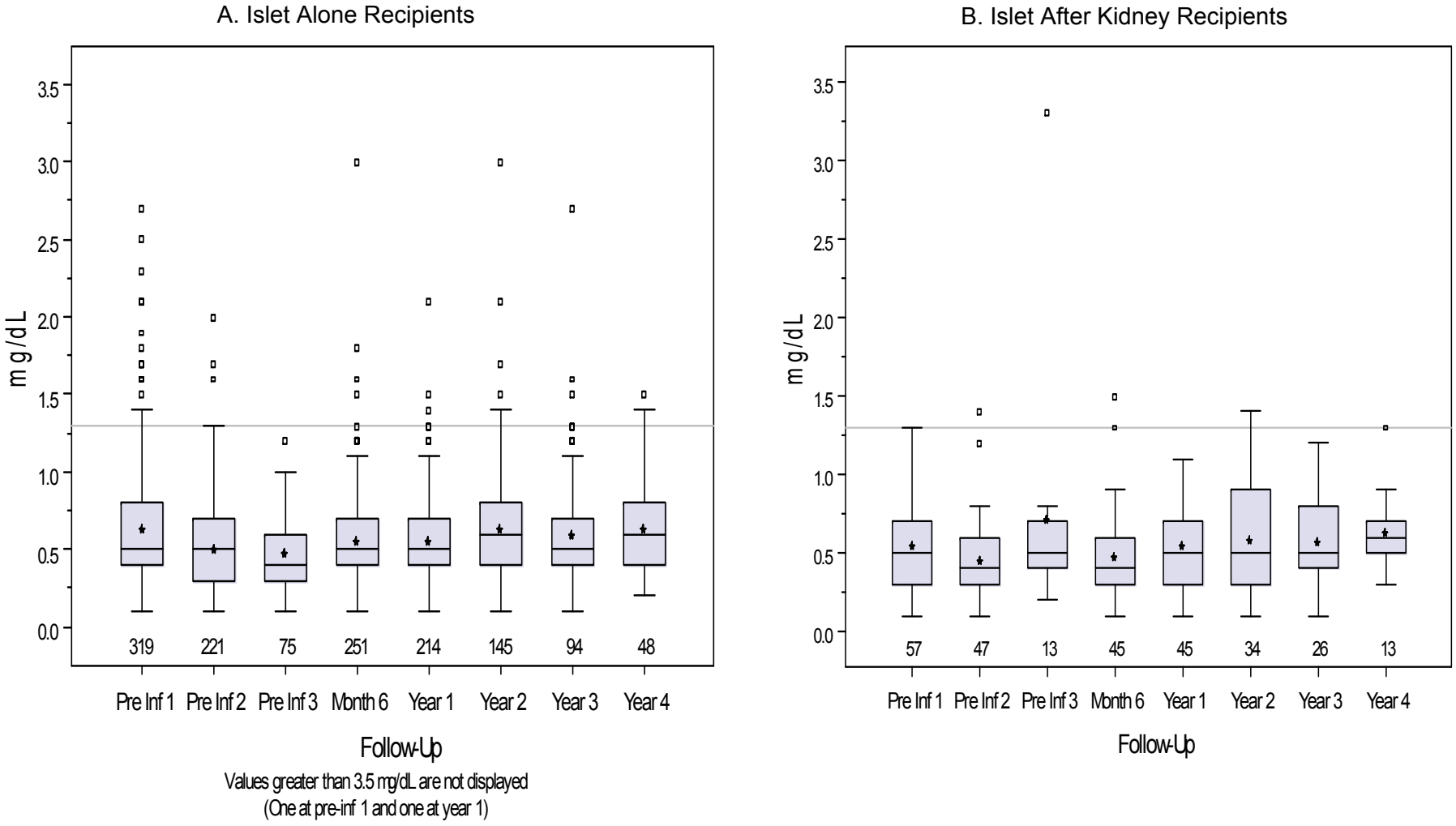


Exhibit 6 – 5
Total Cholesterol (mg/dL) Pre Infusion and Post Last Infusion

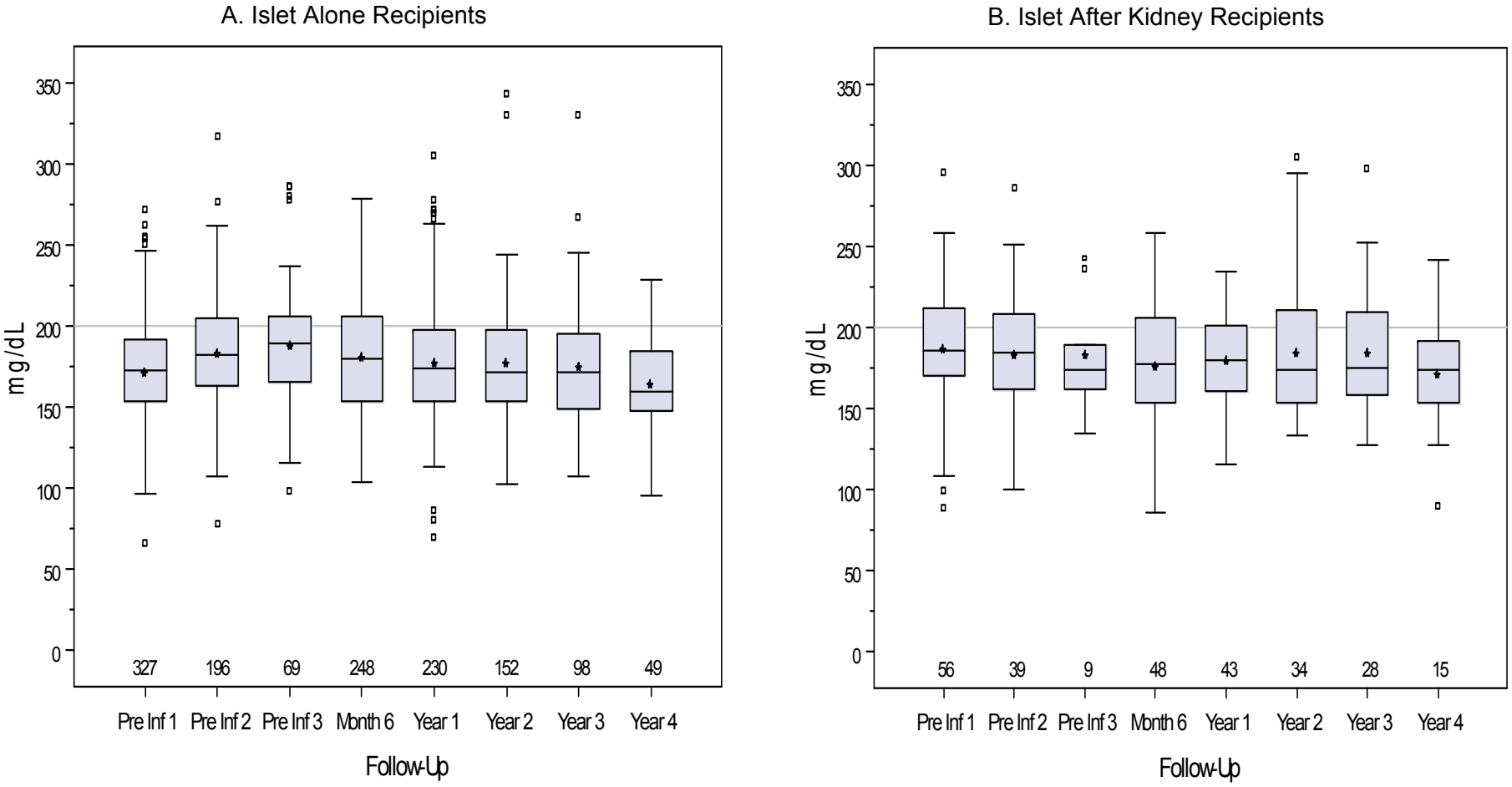
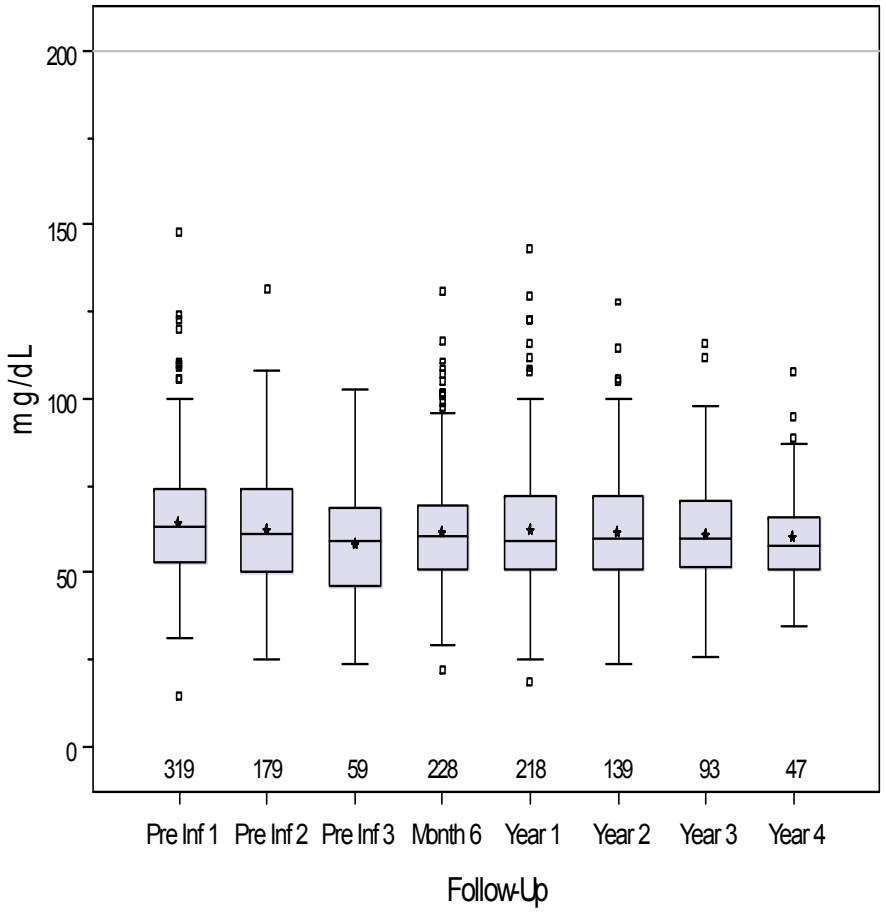


Exhibit 6 – 6
HDL (mg/dL) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

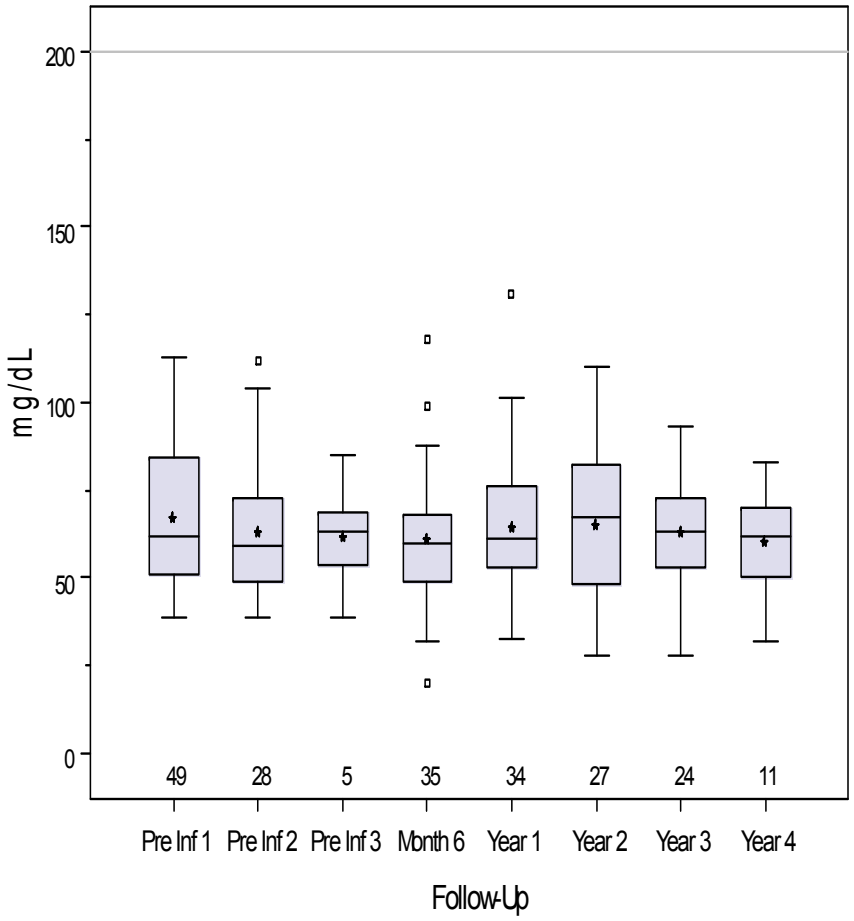


Exhibit 6 – 7
LDL (mg/dL) Pre Infusion and Post Last Infusion

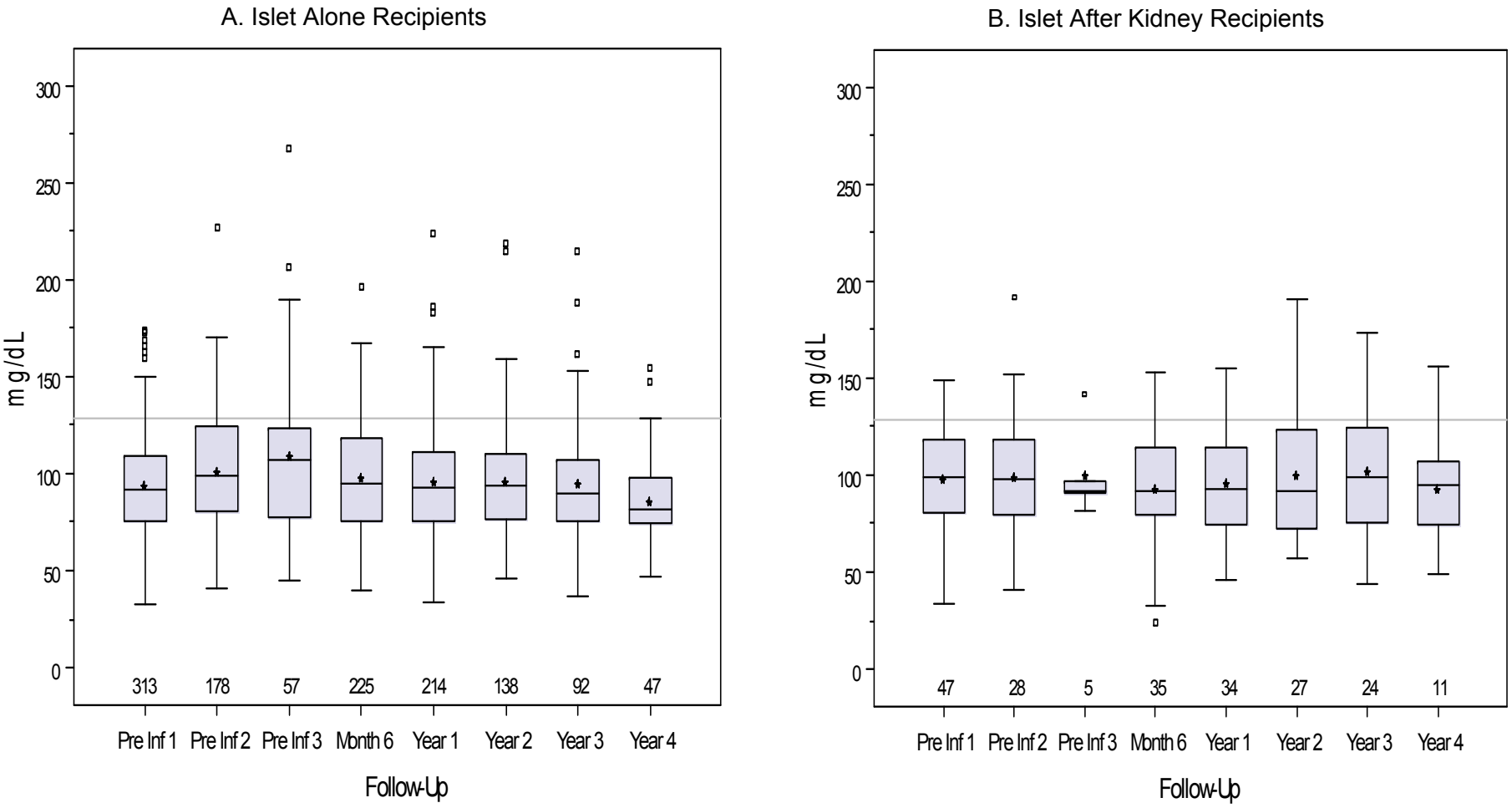
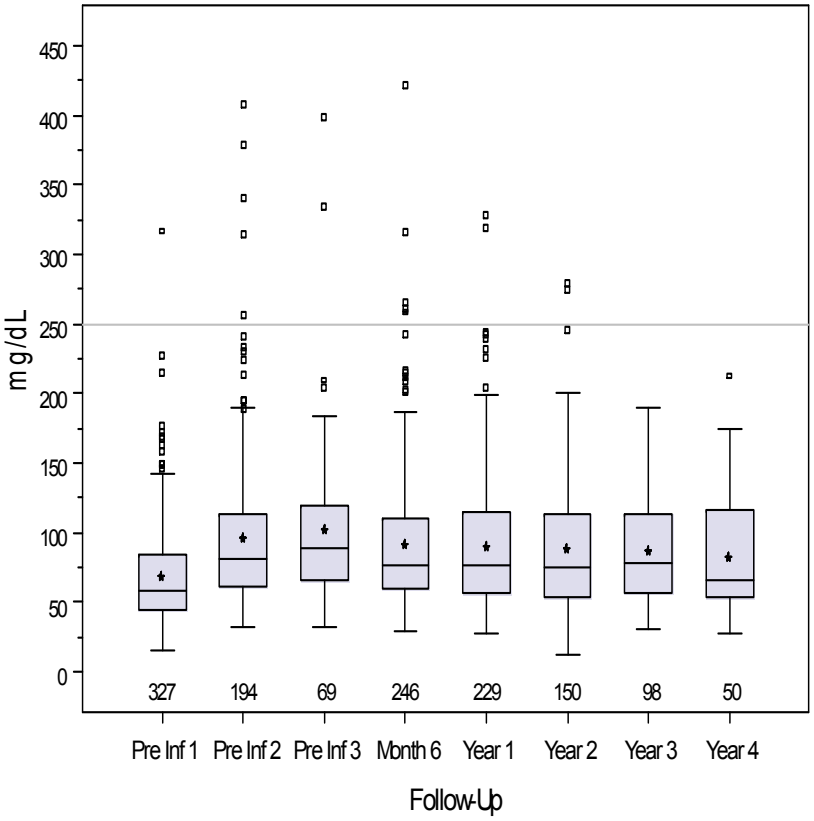


Exhibit 6 – 8
Triglycerides (mg/dL) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



B. Islet After Kidney Recipients

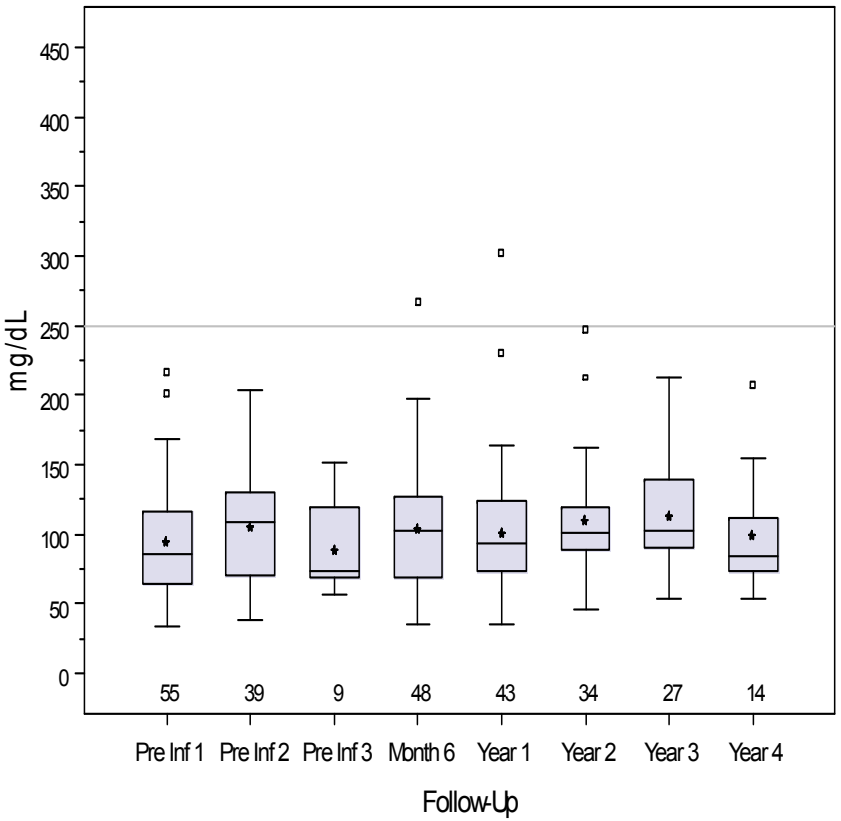
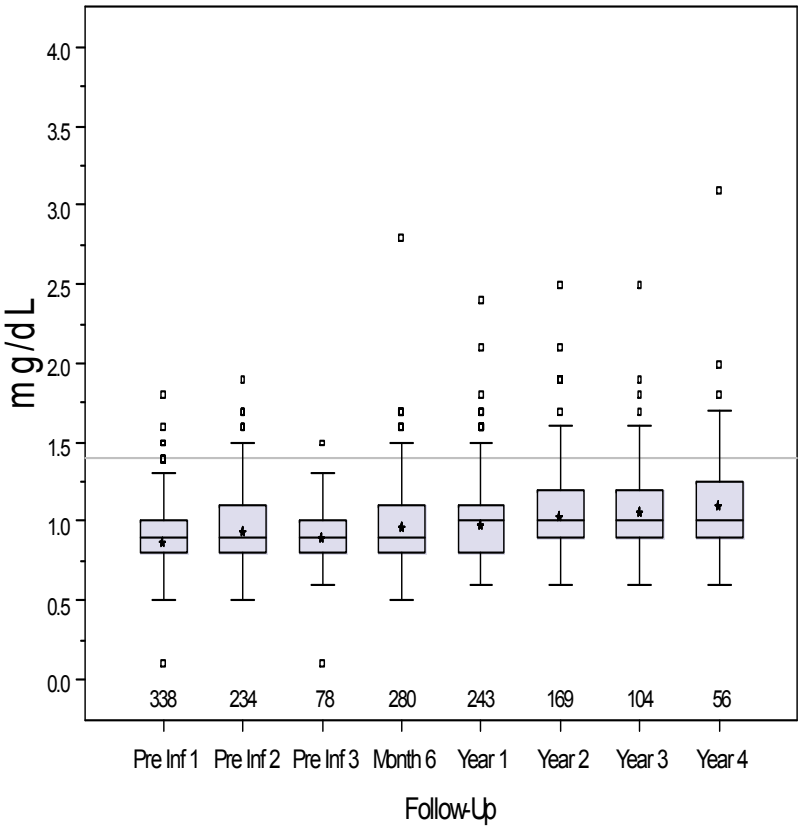
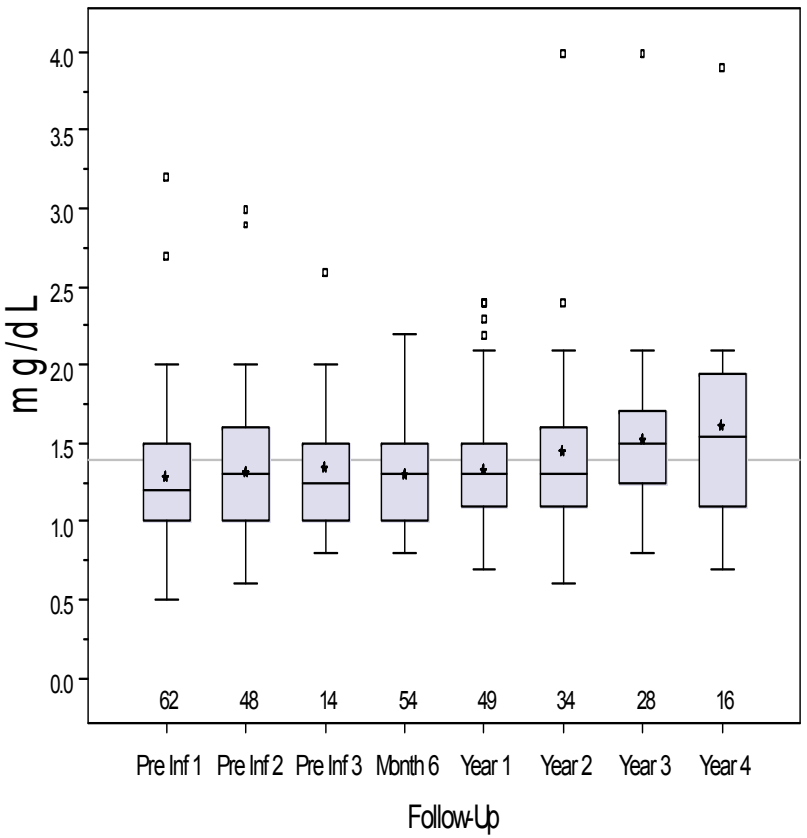


Exhibit 6 – 9
Serum Creatinine (mg/dL) Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



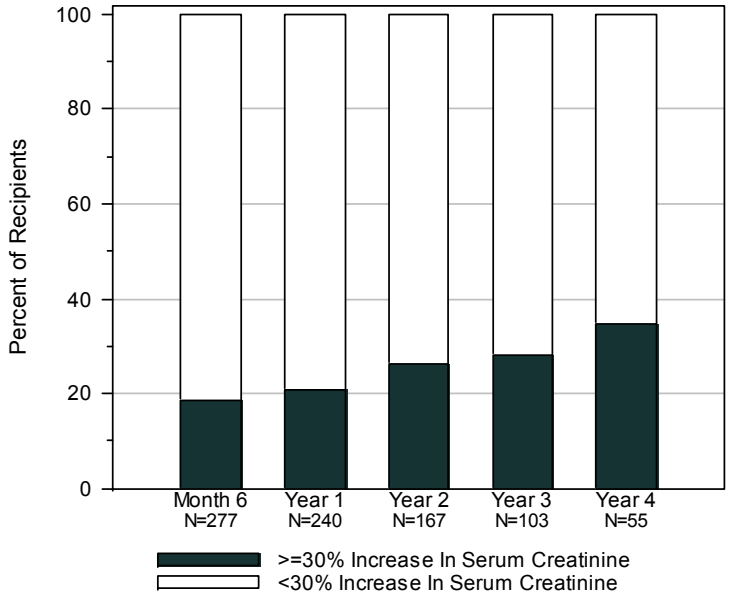
B. Islet After Kidney Recipients



Values greater than 4.0 mg/dL are not displayed
(Two at pre-inf 1, one at month 6 and one at year 2)

Exhibit 6 – 10
Percent of Recipients with a 30% Increase in Serum Creatinine at Each Follow-up Time Point

A. Islet Alone Recipients



B. Islet After Kidney Recipients

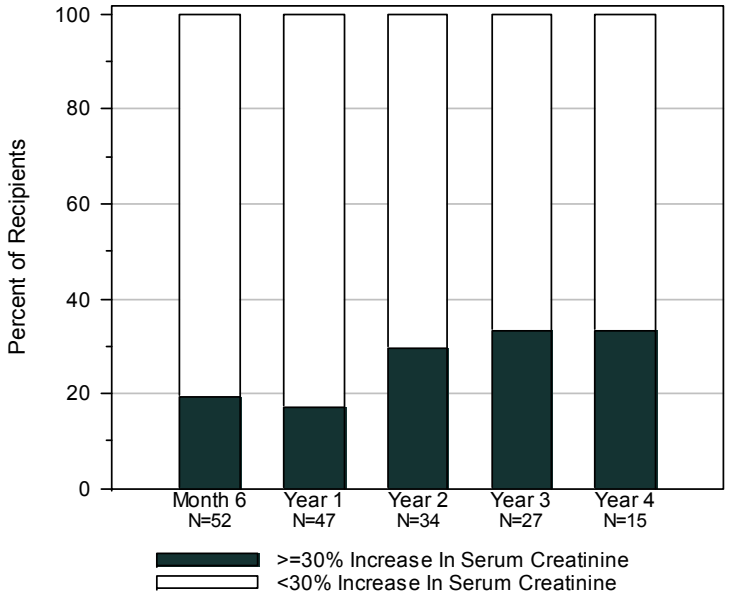


Exhibit 6 – 11
Cockgroft-Gault Calculated Creatinine Clearance (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

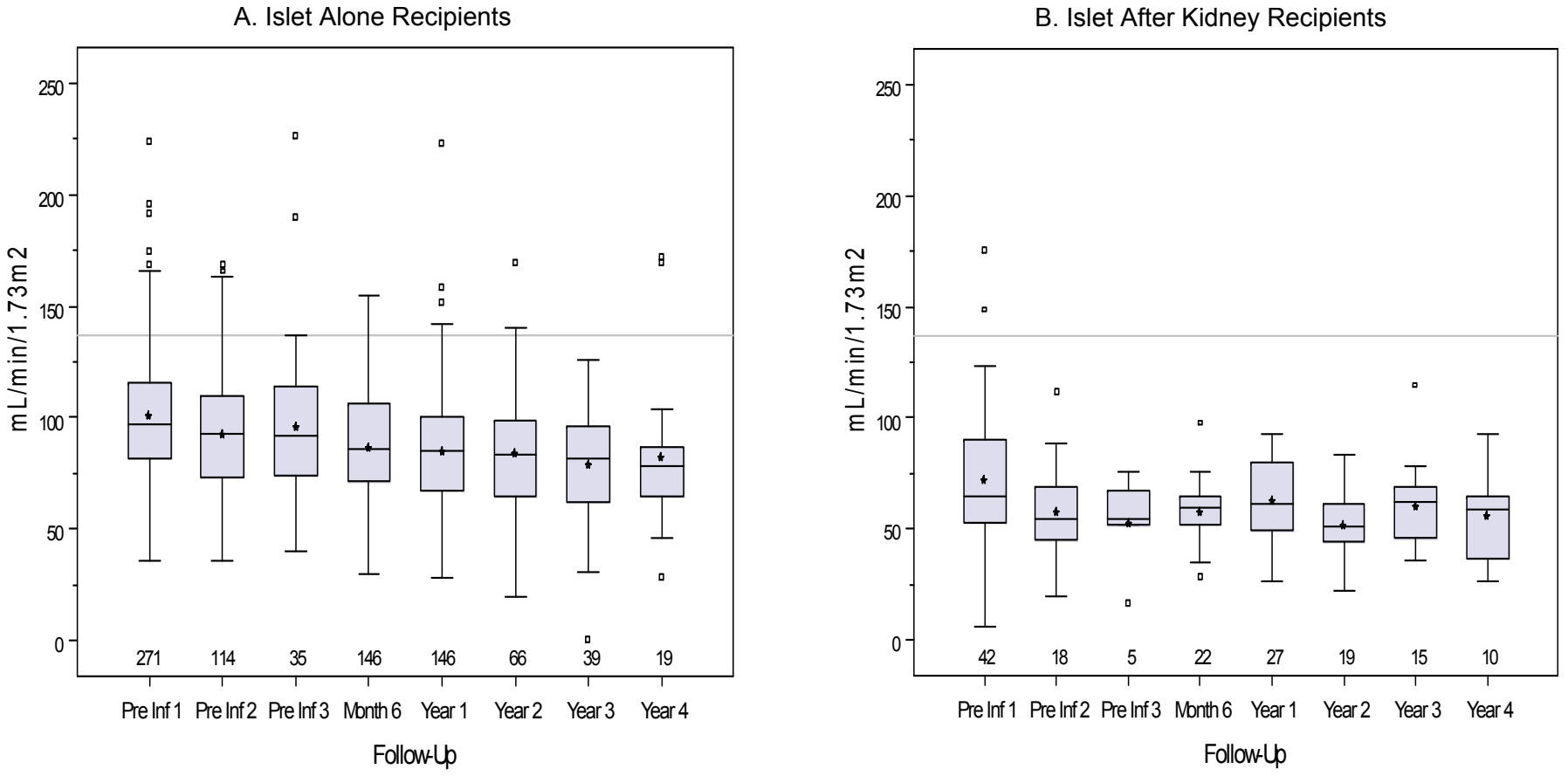
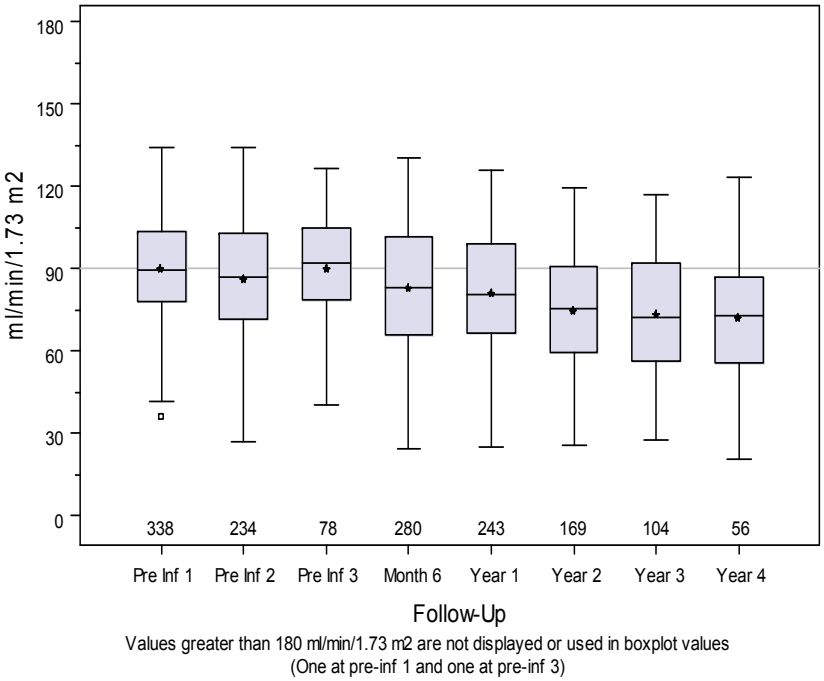


Exhibit 6 – 12
"Chronic Kidney Disease Epidemiology Collaboration" (CKD-EPI) Estimated GFR (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

A. Islet Alone Recipients



Values greater than 180 ml/min/1.73 m2 are not displayed or used in boxplot values
(One at pre-inf 1 and one at pre-inf 3)

B. Islet After Kidney Recipients

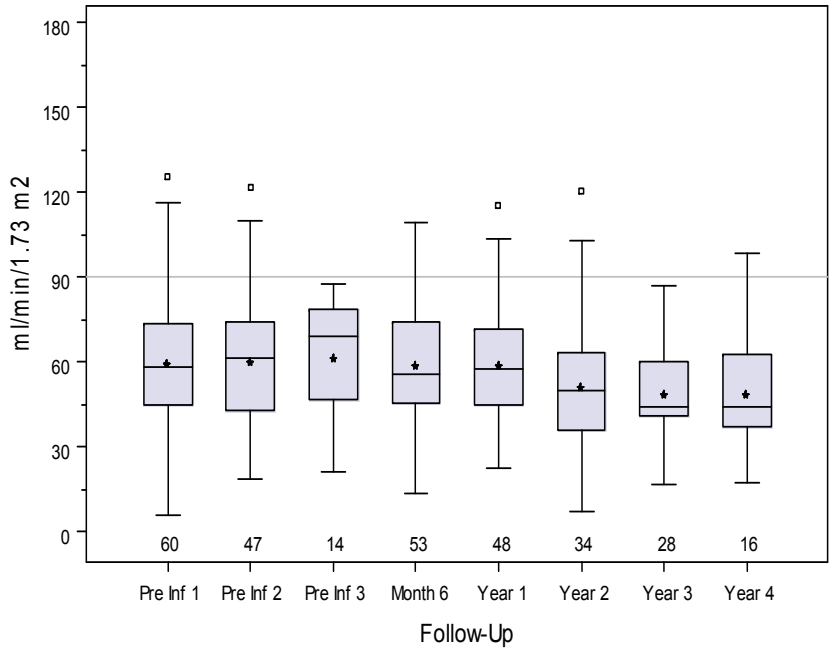


Exhibit 6 – 13
Class I PRA (%)
Pre Infusion and Post Last Infusion

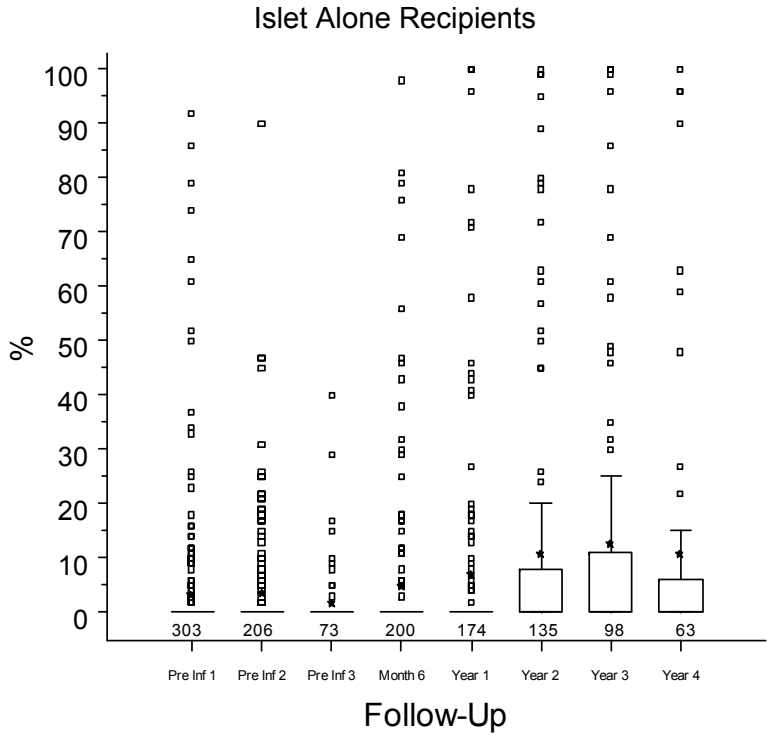
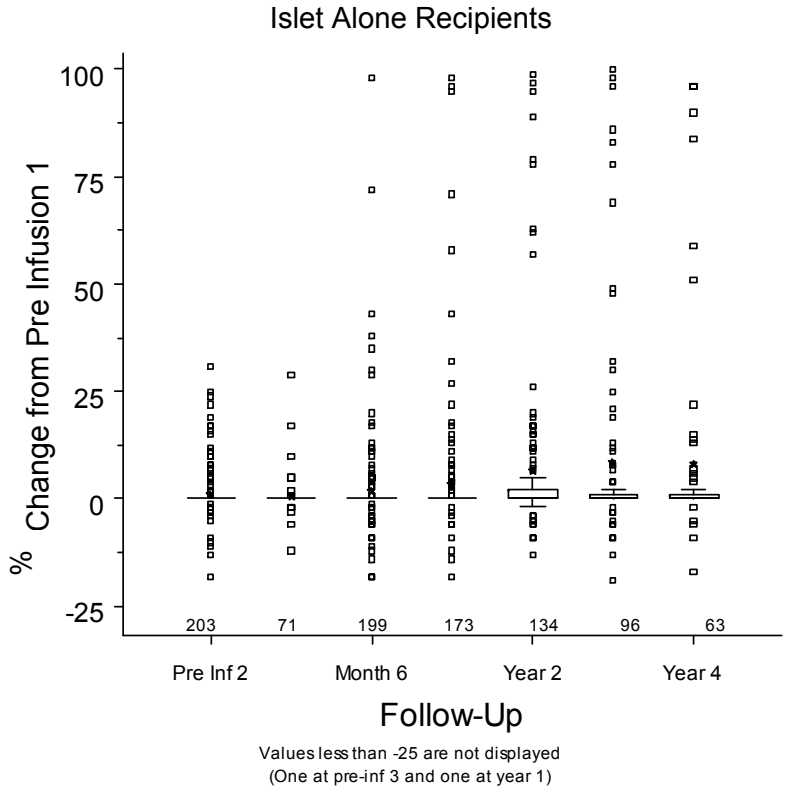


Exhibit 6 – 14
% Change in Class I PRA from Pre First Infusion
Pre Subsequent Infusion and Post Last Infusion



Values less than -25 are not displayed
(One at pre-inf 3 and one at year 1)

Exhibit 6 – 15
Class I PRA Post Last Infusion
Islet Alone Recipients with Complete Graft Loss

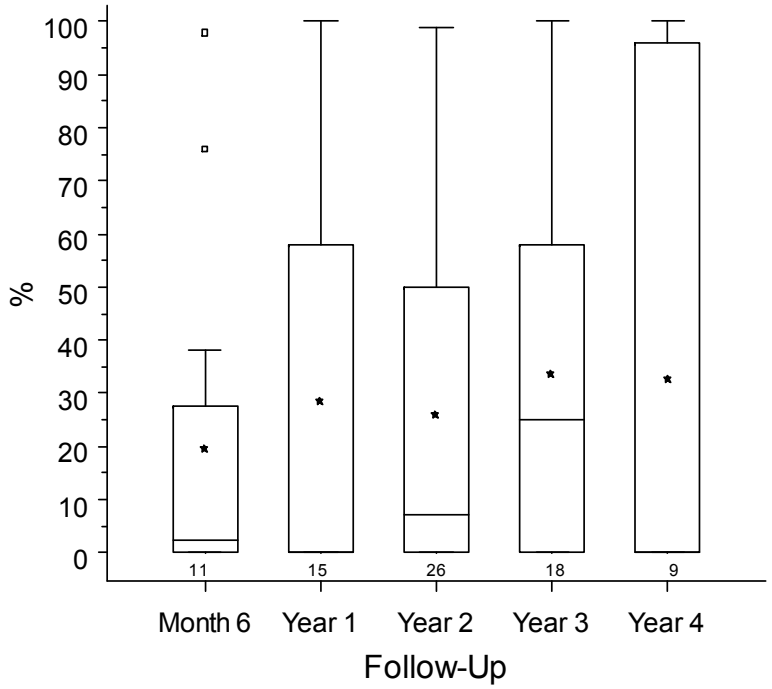


Exhibit 6 – 16
Class I PRA Post Last Infusion
Islet Alone Recipients without Complete Graft Loss

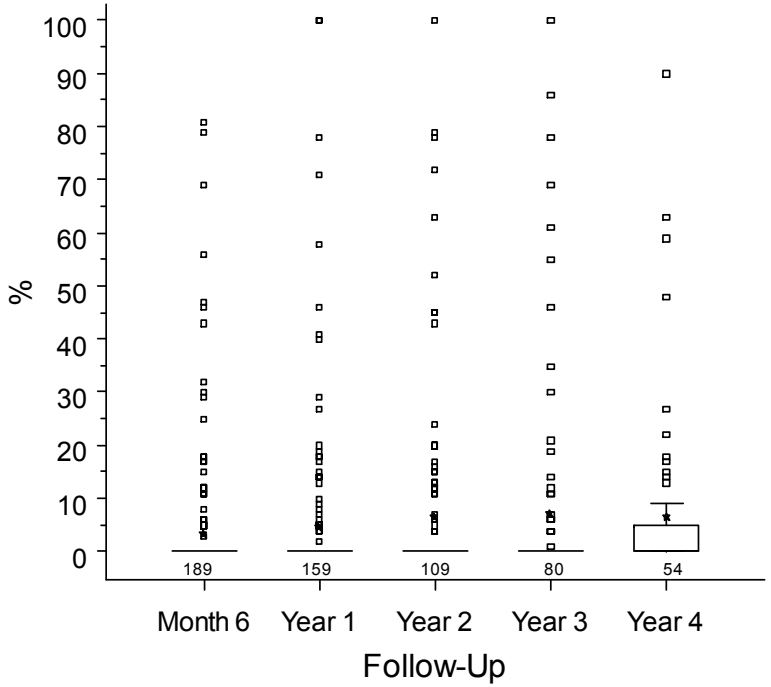


Exhibit 6 – 17
Class I PRA Post Last Infusion
Non-Immunosuppressed Islet Alone Recipients

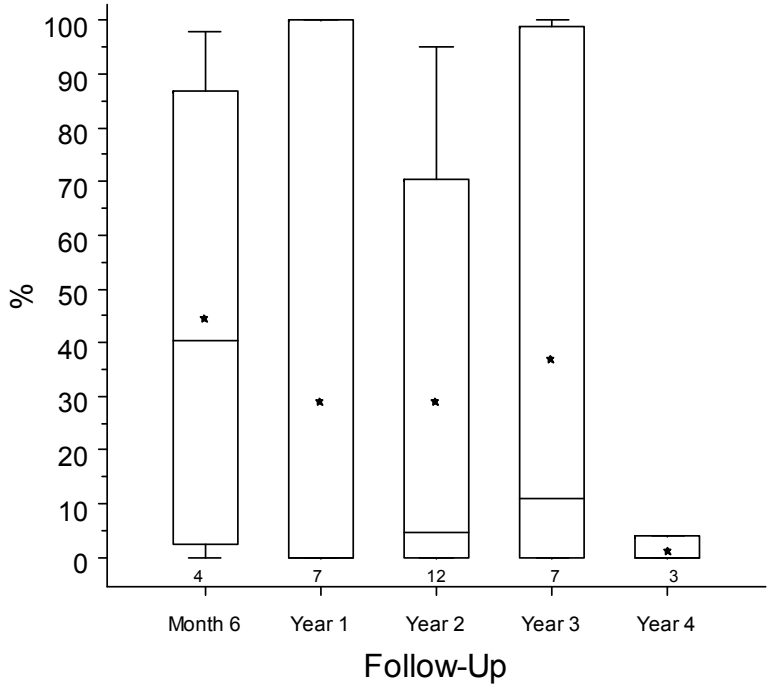
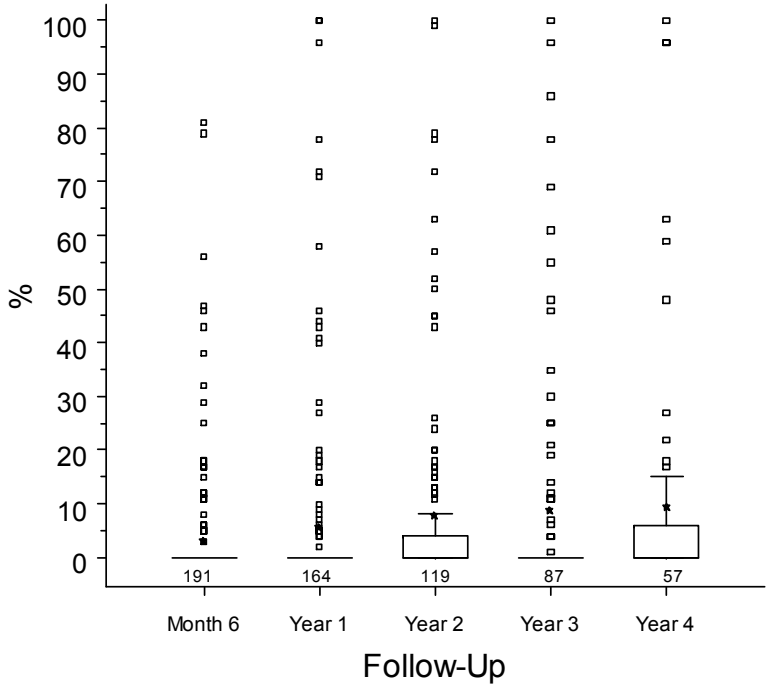


Exhibit 6 – 18
Class I PRA Post Last Infusion
Immunosuppressed Islet Alone Recipients



Chapter 7
Adverse Events

Adverse Events

All grade 3, 4 and 5 adverse events, according to the Clinical Islet Transplantation Consortium (CIT) Terminology Criteria for Adverse Events (TCAE), and all serious adverse events (regardless of grade) are reportable to CITR. CITR site investigators determine the relationship of the adverse event to the immunosuppression therapy and to the islet infusion procedure at the time of adverse event form completion.

Exhibit 7-1 shows the patient-wise incidence of 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-two percent of the islet alone recipients experienced at least one adverse event in Year 1, while 44% experienced one or more serious adverse events in this same period. Of the 594 adverse events reported in Year 1 post first infusion for islet alone recipients, 32% were related to the immunosuppression therapy and 27% were related to the infusion procedure (Exhibit 7-2). Of the 312 serious adverse events reported in Year 1 post first infusion for islet alone recipients, 29% were related to the immunosuppression therapy and 33% were related to the islet infusion procedure (Exhibit 7-2).

Exhibits 7-3 and 7-4 shows the incidence of post-transplant adverse events related to the infusion procedure and the immunosuppression regimen, respectively in islet alone recipients. Exhibits 7-5 and 7-6 show the incidence of post-transplant adverse events related to the infusion procedure and the immunosuppression regimen, respectively in islet-after-kidney recipients. If a patient has a partial year of follow up during the interval, only that portion contributes the person-years of follow-up during the interval. “Person-years of follow-up during the year” approximates the number of recipients at risk of adverse events during the year.

Overall, a total of 592 serious adverse events were reported to the Registry as of datafile closure, with 29% of them classified as life threatening and 52% requiring an inpatient hospitalization (Exhibit 7-8). Sixty-two percent (365 of 592) of serious adverse events occurred in the first year following the participants’ first infusion procedure. Twenty-five percent of the serious adverse events were classified by the reporting CITR investigator as related to the islet infusion procedure and 29% related to the immunosuppression therapy. Adverse event relationships to the infusion procedure and immunosuppression regimen are determined by the local CITR Investigator. Approximately 82% of the serious adverse events resolved with no residual effects (Exhibit 7-9). Most of the reported serious adverse events were categorized as gastrointestinal disorders (17%), investigations (15%) and blood and lymphatic system disorders (13%) as classified by the MedDRA classifications system (Exhibit 7-10). The most common SAEs reported are summarized in Exhibits 7-11 through 7-14.

A listing of reported neoplasms (N=21) is included in Exhibit 7-15. A listing of reported hemorrhages and portal vein thromboses is included in Exhibit 7-16. Duration of hospitalization for the infusion procedure is presented in Exhibits 7-17 and 7-18 and in Exhibits 7-19 and 7-20 hospitalizations experienced post the recipient’s last infusion procedure are tabulated.

Reported Deaths

There have been nine reports of death to the Registry for islet allograft recipients; a viral meningitis attributed death possibly related to the immunosuppressant therapy occurring three years following the person’s last islet infusion, a drug toxicity (acute methadone and diphenhydramine) 70 days post the person’s last infusion, a stroke two years post the person’s last infusion, another stroke three years post the person’s last infusion, a death due to acute respiratory distress syndrome five years post last islet infusion, pneumonia eight years after the person’s last infusion, diabetic ketoacidosis six years after the person’s last infusion, atherosclerotic coronary artery disease 16 months after the person’s last infusion and one death due to unknown causes.

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

	Islet Alone (N=347)				Islet After Kidney (N=65)			
	Recipients with an AE		Recipients with an SAE		Recipients with an AE		Recipients with an SAE	
	N	%	N	%	N	%	N	%
Any Event	214	62%	152	44%	36	55%	31	48%
Related to either the infusion procedure or immunosupression therapy	172	50%	112	32%	27	42%	23	35%
Related to the infusion procedure	104	30%	72	21%	18	28%	14	22%
Related to immunosupression therapy	118	34%	62	18%	14	22%	12	18%

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

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

	Islet Alone				Islet After Kidney			
	Adverse Events		Serious Adverse Events		Adverse Events		Serious Adverse Events	
	N	%	N	%	N	%	N	%
Total	594	100.0	312	100.0	68	100.0	53	100.0
Related to the infusion procedure	163	27.4	103	33.0	23	33.8	16	30.2
Related to immunosupression therapy	192	32.3	90	28.8	22	32.4	19	35.8
Related to both the infusion procedure and immunosupression therapy	25	4.2	9	2.9	2	2.9	1	1.9
Related to neither the infusion procedure nor immunosupression therapy	214	36.0	110	35.3	21	30.9	17	32.1

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

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.9	1	0.34	0.01 - 1.91	1	0.34	0.01 - 1.91
2000	10.0	2	0.20	0.02 - 0.72	2	0.20	0.02 - 0.72
2001	27.6	16	0.58	0.33 - 0.94	5	0.18	0.06 - 0.42
2002	79.3	51	0.64	0.48 - 0.85	32	0.40	0.28 - 0.57
2003	130.3	47	0.36	0.26 - 0.48	23	0.18	0.11 - 0.26
2004	149.9	19	0.13	0.08 - 0.20	9	0.06	0.03 - 0.11
2005	187.5	38	0.20	0.14 - 0.28	25	0.13	0.09 - 0.20
2006	215.0	26	0.12	0.08 - 0.18	21	0.10	0.06 - 0.15
2007	204.6	7	0.03	0.01 - 0.07	5	0.02	0.01 - 0.06
2008	126.4	10	0.08	0.04 - 0.15	7	0.06	0.02 - 0.11

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	321.7	188	0.58	0.50 - 0.67	112	0.35	0.29 - 0.42
2	264.0	14	0.05	0.03 - 0.09	10	0.04	0.02 - 0.07
3	200.8	7	0.03	0.01 - 0.07	2	0.01	0.00 - 0.04
4	142.3	7	0.05	0.02 - 0.10	6	0.04	0.02 - 0.09
5	98.9	1	0.01	0.00 - 0.06	0	0.00	0.00 - 0.04
6	60.8	1	0.02	0.00 - 0.09	1	0.02	0.00 - 0.09
7	23.5	0	0.00	0.00 - 0.16	0	0.00	0.00 - 0.16
8	8.6	0	0.00	0.00 - 0.43	0	0.00	0.00 - 0.43

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

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	1.3	0	0.00	0.00 - 2.80	0	0.00	0.00 - 2.80
2000	2.8	0	0.00	0.00 - 1.33	0	0.00	0.00 - 1.33
2001	4.1	2	0.49	0.06 - 1.76	1	0.24	0.01 - 1.36
2002	7.0	3	0.43	0.09 - 1.26	1	0.14	0.00 - 0.80
2003	20.4	13	0.64	0.34 - 1.09	10	0.49	0.24 - 0.90
2004	32.8	3	0.09	0.02 - 0.27	1	0.03	0.00 - 0.17
2005	39.3	2	0.05	0.01 - 0.18	2	0.05	0.01 - 0.18
2006	42.0	2	0.05	0.01 - 0.17	1	0.02	0.00 - 0.13
2007	41.8	1	0.02	0.00 - 0.13	1	0.02	0.00 - 0.13
2008	22.6	0	0.00	0.00 - 0.16	0	0.00	0.00 - 0.16

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	62.1	25	0.40	0.26 - 0.59	17	0.27	0.16 - 0.44
2	47.8	0	0.00	0.00 - 0.08	0	0.00	0.00 - 0.08
3	38.9	1	0.03	0.00 - 0.14	0	0.00	0.00 - 0.09
4	33.3	0	0.00	0.00 - 0.11	0	0.00	0.00 - 0.11
5	19.3	0	0.00	0.00 - 0.19	0	0.00	0.00 - 0.19
6	7.6	0	0.00	0.00 - 0.48	0	0.00	0.00 - 0.48
7	2.3	0	0.00	0.00 - 1.63	0	0.00	0.00 - 1.63
8	1.0	0	0.00	0.00 - 3.62	0	0.00	0.00 - 3.62

Exhibit 7– 5
IA: Incidence of Post-Transplant Adverse Events Related to Immunosuppression Therapy
Follow-up Based on Completed Scheduled Visits

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.9	1	0.34	0.01 - 1.91	1	0.34	0.01 - 1.91
2000	10.0	1	0.10	0.00 - 0.55	0	0.00	0.00 - 0.37
2001	27.6	13	0.47	0.25 - 0.80	2	0.07	0.01 - 0.26
2002	79.3	57	0.72	0.54 - 0.93	22	0.28	0.17 - 0.42
2003	130.3	24	0.18	0.12 - 0.27	12	0.09	0.05 - 0.16
2004	149.9	43	0.29	0.21 - 0.39	14	0.09	0.05 - 0.16
2005	187.5	63	0.34	0.26 - 0.43	36	0.19	0.13 - 0.27
2006	215.0	39	0.18	0.13 - 0.25	23	0.11	0.07 - 0.16
2007	204.6	16	0.08	0.04 - 0.13	14	0.07	0.04 - 0.11
2008	126.4	23	0.18	0.12 - 0.27	16	0.13	0.07 - 0.21

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	321.7	216	0.67	0.58 - 0.77	98	0.30	0.25 - 0.37
2	264.0	34	0.13	0.09 - 0.18	18	0.07	0.04 - 0.11
3	200.8	16	0.08	0.05 - 0.13	13	0.06	0.03 - 0.11
4	142.3	8	0.06	0.02 - 0.11	6	0.04	0.02 - 0.09
5	98.9	4	0.04	0.01 - 0.10	2	0.02	0.00 - 0.07
6	60.8	0	0.00	0.00 - 0.06	0	0.00	0.00 - 0.06
7	23.5	1	0.04	0.00 - 0.24	0	0.00	0.00 - 0.16
8	8.6	0	0.00	0.00 - 0.43	0	0.00	0.00 - 0.43

Exhibit 7– 6
IAK: Incidence of Post-Transplant Adverse Events Related to Immunosuppression Therapy
Follow-up Based on Completed Scheduled Visits

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	1.3	0	0.00	0.00 - 2.80	0	0.00	0.00 - 2.80
2000	2.8	0	0.00	0.00 - 1.33	0	0.00	0.00 - 1.33
2001	4.1	1	0.24	0.01 - 1.36	1	0.24	0.01 - 1.36
2002	7.0	2	0.29	0.03 - 1.03	1	0.14	0.00 - 0.80
2003	20.4	9	0.44	0.20 - 0.84	8	0.39	0.17 - 0.77
2004	32.8	11	0.33	0.17 - 0.60	8	0.24	0.11 - 0.48
2005	39.3	7	0.18	0.07 - 0.37	5	0.13	0.04 - 0.30
2006	42.0	5	0.12	0.04 - 0.28	4	0.10	0.03 - 0.24
2007	41.8	2	0.05	0.01 - 0.17	2	0.05	0.01 - 0.17
2008	22.6	0	0.00	0.00 - 0.16	0	0.00	0.00 - 0.16

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	62.1	24	0.39	0.25 - 0.58	20	0.32	0.20 - 0.50
2	47.8	5	0.10	0.03 - 0.24	4	0.08	0.02 - 0.21
3	38.9	5	0.13	0.04 - 0.30	3	0.08	0.02 - 0.23
4	33.3	1	0.03	0.00 - 0.17	0	0.00	0.00 - 0.11
5	19.3	2	0.10	0.01 - 0.37	2	0.10	0.01 - 0.37
6	7.6	0	0.00	0.00 - 0.48	0	0.00	0.00 - 0.48
7	2.3	0	0.00	0.00 - 1.63	0	0.00	0.00 - 1.63
8	1.0	0	0.00	0.00 - 3.62	0	0.00	0.00 - 3.62

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

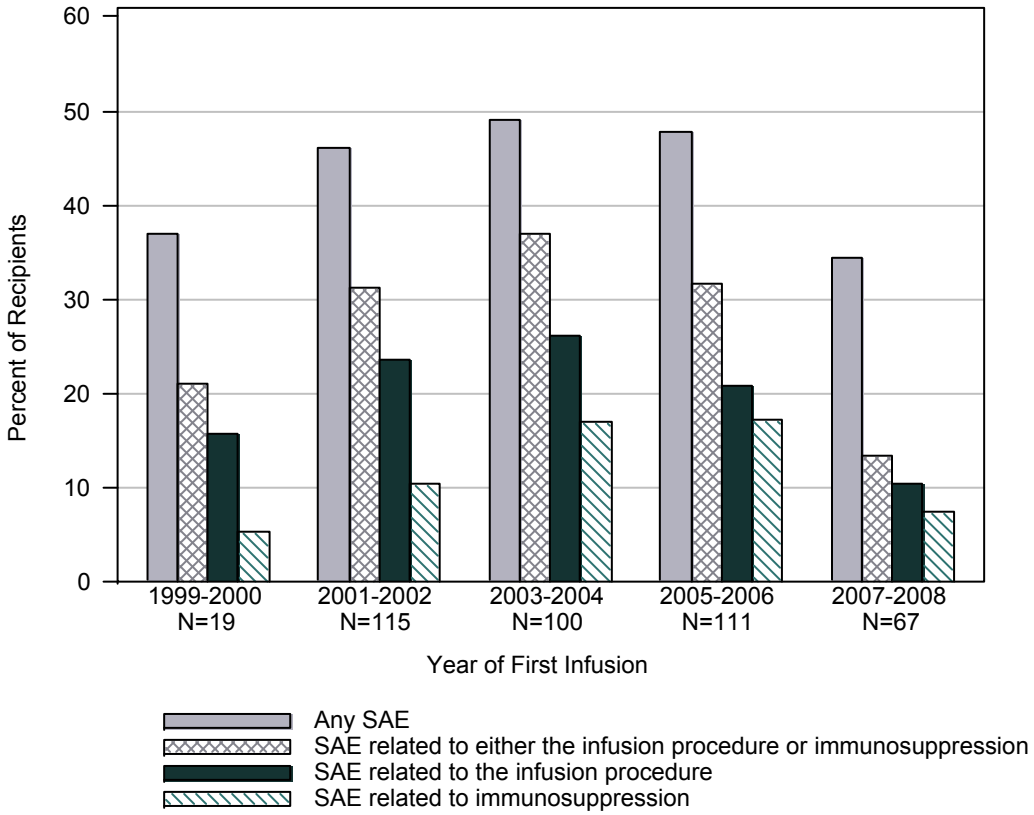


Exhibit 7 – 8
Serious Adverse Event Criteria by Relatedness to Islet Infusion or Immunosuppression

	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	120	100.0	129	100.0	11	100.0	212	100.0	16	100.0	28	100.0	1	100.0	75	100.0	592	100.0
Death*	-	0.0	-	0.0	-	0.0	7	3.3	-	0.0	-	0.0	-	0.0	2	2.7	9	1.5
Life Threatening	63	52.5	41	31.8	5	45.5	36	17.0	6	37.5	10	35.7	-	0.0	12	16.0	173	29.2
Inpatient Hospitalization	22	18.3	65	50.4	4	36.4	143	67.5	4	25.0	19	67.9	1	100.0	53	70.7	311	52.5
Prolongation of Existing Hospitalization	47	39.2	25	19.4	7	63.6	20	9.4	12	75.0	3	10.7	-	0.0	4	5.3	118	19.9
Persistnet or Significant Disability/Incapacity**	1	0.8	6	4.7	-	0.0	5	2.4	-	0.0	2	7.1	-	0.0	2	2.7	16	2.7
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	11	9.2	23	17.8	2	18.2	26	12.3	2	12.5	4	14.3	-	0.0	24	32.0	92	15.5
Missing Information	-	0.0	1	0.8	-	0.0	1	0.5	-	0.0	-	0.0	-	0.0	-	0.0	2	0.3

Serious adverse event categories are not mutually exclusive.
*See chapter summary for details of reported deaths.
**The event related to the infusion procedure was a portal vein thrombosis requiring continued anticoagulation. The six events related to immunosuppression therapy in IA participants were tongue ulceration, memory deficit, tacrolimus induced neurotoxicity, diarrhea, hypokalemia and anxiety attacks. All events have since resolved with no residual side effects. The two events related to immunosuppression in IAK participants were leukopenia and renal graft failure. Both events have resolved with sequelae.

Of the 592 serious adverse events, 365 (62%) occurred in the first year following their first infusion procedure. Relationships to immunosuppression therapy and to the infusion procedure are based on classification of “Probable” or “Definite” by the local CITR Investigator.

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

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	120	100.0	129	100.0	11	100.0	212	100.0	16	100.0	28	100.0	1	100.0	75	100.0	592	100.0
Outcome of Serious Adverse Event																		
Resolved with No Residual Effects	117	97.5	110	85.3	10	90.9	169	79.7	15	93.8	21	75.0	1	100.0	43	57.3	486	82.1
Resolved with Sequelae*	2	1.7	14	10.9	1	9.1	20	9.4	-	0.0	6	21.4	-	0.0	16	21.3	59	10.0
Persistent Condition, ** Recipient Alive	1	0.8	4	3.1	-	0.0	16	7.5	1	6.3	1	3.6	-	0.0	12	16.0	35	5.9
Death caused by Adverse Event ***	-	0.0	-	0.0	-	0.0	7	3.3	-	0.0	-	0.0	-	0.0	2	2.7	9	1.5
Missing Information	-	0.0	1	0.8	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0	2	2.7	3	0.5

*Events related to the protocol include: two hospitalizations for kidney rejection in one participant, four hospitalizations due to complications associated with ovarian cyst removal and heavy menstrual bleeding in one patient resulting in a total abdominal hysterectomy, two myonecrosis episodes in one patient, acute mononucleosis resulting in graft loss, four leucopenia, one lymphopenia, colitis, papillary carcinoma resulting in thyroidectomy, pyelonephritis resulting in kidney graft failure, MRSA infection, kidney nephritis with BK virus, kidney graft failure and pneumonitis resulting in tracheotomy and graft loss..
**Events related to the protocol include: diarrhea, hematoma, pneumonia, portal vein thrombosis and renal graft failure.
***See chapter summary for details.

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

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

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	120	100.0	129	100.0	11	100.0	212	100.0	16	100.0	28	100.0	1	100.0	75	100.0	592	100.0
System Organ Class																		
Blood and lymphatic system disorders	2	1.7	55	42.6	3	27.3	7	3.3	-	0.0	9	32.1	1	100.0	1	1.3	78	13.2
Cardiac disorders	-	0.0	1	0.8	-	0.0	6	2.8	-	0.0	-	0.0	-	0.0	2	2.7	9	1.5
Eye disorders	-	0.0	1	0.8	-	0.0	5	2.4	-	0.0	-	0.0	-	0.0	2	2.7	8	1.4
Gastrointestinal disorders	21	17.5	17	13.2	2	18.2	44	20.8	1	6.3	4	14.3	-	0.0	12	16.0	101	17.1
General disorders and administration site conditions	2	1.7	5	3.9	-	0.0	18	8.5	1	6.3	2	7.1	-	0.0	1	1.3	29	4.9
Hepatobiliary disorders	13	10.8	-	0.0	-	0.0	8	3.8	5	31.3	-	0.0	-	0.0	-	0.0	26	4.4
Immune system disorders	-	0.0	-	0.0	-	0.0	6	2.8	-	0.0	2	7.1	-	0.0	-	0.0	8	1.4
Infections and infestations	-	0.0	16	12.4	1	9.1	23	10.8	-	0.0	7	25.0	-	0.0	15	20.0	62	10.5
Injury, poisoning and procedural complications	16	13.3	-	0.0	-	0.0	11	5.2	2	12.5	3	10.7	-	0.0	3	4.0	35	5.9
Investigations	57	47.5	8	6.2	4	36.4	6	2.8	1	6.3	1	3.6	-	0.0	11	14.7	88	14.9
Metabolism and nutrition disorders	3	2.5	2	1.6	-	0.0	27	12.7	-	0.0	-	0.0	-	0.0	3	4.0	35	5.9
Musculoskeletal and connective tissue disorders	-	0.0	1	0.8	-	0.0	7	3.3	-	0.0	-	0.0	-	0.0	6	8.0	14	2.4
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	-	0.0	4	3.1	-	0.0	5	2.4	-	0.0	-	0.0	-	0.0	1	1.3	10	1.7

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

	Islet Alone								Islet After Kidney								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related		Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Nervous system disorders	-	0.0	3	2.3	-	0.0	7	3.3	-	0.0	-	0.0	-	0.0	4	5.3	14	2.4
Psychiatric disorders	-	0.0	2	1.6	-	0.0	4	1.9	-	0.0	-	0.0	-	0.0	-	0.0	6	1.0
Renal and urinary disorders	1	0.8	5	3.9	-	0.0	4	1.9	-	0.0	-	0.0	-	0.0	2	2.7	12	2.0
Reproductive system and breast disorders	-	0.0	5	3.9	1	9.1	3	1.4	-	0.0	-	0.0	-	0.0	1	1.3	10	1.7
Respiratory, thoracic and mediastinal disorders	-	0.0	-	0.0	-	0.0	11	5.2	1	6.3	-	0.0	-	0.0	4	5.3	16	2.7
Skin and subcutaneous tissue disorders	-	0.0	-	0.0	-	0.0	1	0.5	-	0.0	-	0.0	-	0.0	2	2.7	3	0.5
Surgical and medical procedures	1	0.8	4	3.1	-	0.0	6	2.8	-	0.0	-	0.0	-	0.0	2	2.7	13	2.2
Vascular disorders	4	3.3	-	0.0	-	0.0	3	1.4	5	31.3	-	0.0	-	0.0	3	4.0	15	2.5

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

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

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

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	120	100.0	129	100.0	11	100.0	212	100.0	472	100.0
Elevated Liver Function Tests*	56	46.7	0	0.0	3	27.3	0	0.0	59	12.5
Neutropenia	1	0.8	35	27.1	0	0.0	4	1.9	40	8.5
Hemorrhage**	20	16.7	0	0.0	1	9.1	0	0.0	21	4.4
Hypoglycemia	2	1.7	0	0.0	0	0.0	19	9.0	21	4.4
Diarrhea	0	0.0	7	5.4	1	9.1	9	4.2	17	3.6
Abdominal pain	4	3.3	1	0.8	0	0.0	11	5.2	16	3.4
Anemia	1	0.8	3	2.3	2	18.2	4	1.9	10	2.1
Portal vein thrombosis	9	7.5	0	0.0	0	0.0	0	0.0	9	1.9
Vomiting	0	0.0	2	1.6	0	0.0	7	3.3	9	1.9
Leukopenia	0	0.0	7	5.4	1	9.1	0	0.0	8	1.7
Lymphopenia	0	0.0	8	6.2	0	0.0	0	0.0	8	1.7
Pneumonia	0	0.0	4	3.1	0	0.0	4	1.9	8	1.7
Infection	0	0.0	2	1.6	0	0.0	4	1.9	6	1.3

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

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

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

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	16	100.0	28	100.0	1	100.0	75	100.0	120	100.0
Hemorrhage**	8	50.0	0	0.0	0	0.0	0	0.0	8	6.7
Blood creatinine increased	0	0.0	1	3.6	0	0.0	5	6.7	6	5.0
Neutropenia	0	0.0	6	21.4	0	0.0	0	0.0	6	5.0
Pneumonia	0	0.0	3	10.7	0	0.0	2	2.7	5	4.2
Trigger finger	0	0.0	0	0.0	0	0.0	5	6.7	5	4.2
Gastrointestinal obstruction	0	0.0	1	3.6	0	0.0	3	4.0	4	3.3
Colitis	0	0.0	0	0.0	0	0.0	3	4.0	3	2.5
Lymphopenia	0	0.0	2	7.1	1	100.0	0	0.0	3	2.5

**Hemorrhage includes peritoneal, intra-abdominal, hepatic, operative and post-procedural hemorrhage.

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

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	136	100.0	131	100.0	10	100.0	175	100.0	452	100.0
Elevated Liver Function Tests*	56	41.2	0	0.0	3	30.0	0	0.0	59	13.1
Neutropenia	1	0.7	36	27.5	0	0.0	4	2.3	41	9.1
Hemorrhage**	28	20.6	0	0.0	1	10.0	0	0.0	29	6.4
Abdominal pain	4	2.9	1	0.8	0	0.0	10	5.7	15	3.3
Diarrhea	0	0.0	5	3.8	0	0.0	7	4.0	12	2.7
Lymphopenia	0	0.0	10	7.6	1	10.0	0	0.0	11	2.4
Pneumonia	0	0.0	7	5.3	0	0.0	4	2.3	11	2.4
Hypoglycemia	2	1.5	0	0.0	0	0.0	8	4.6	10	2.2
Portal vein thrombosis	10	7.4	0	0.0	0	0.0	0	0.0	10	2.2
Anemia	1	0.7	3	2.3	2	20.0	3	1.7	9	2.0
Leukopenia	0	0.0	8	6.1	1	10.0	0	0.0	9	2.0

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

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

	Relationship to Protocol								Overall	
	Related to Infusion Procedure		Related to Immunosuppression Therapy		Related to Both		Not Related			
	N	%	N	%	N	%	N	%	N	%
All Serious Adverse Events	0	-	26	100.0	2	100.0	112	100.0	140	100.0
Hypoglycemia	0	-	0	0.0	0	0.0	11	9.8	11	7.9
Diarrhea	0	-	3	11.5	1	50.0	3	2.7	7	5.0
Blood creatinine increased	0	-	1	3.8	0	0.0	5	4.5	6	4.3
Neutropenia	0	-	5	19.2	0	0.0	0	0.0	5	3.6
Hysterectomy	0	-	1	3.8	0	0.0	3	2.7	4	2.9
Infection	0	-	1	3.8	0	0.0	3	2.7	4	2.9
Vomiting	0	-	1	3.8	0	0.0	3	2.7	4	2.9
Abdominal pain	0	-	0	0.0	0	0.0	3	2.7	3	2.1
Gastroenteritis viral	0	-	0	0.0	0	0.0	3	2.7	3	2.1
Hyperglycemia	0	-	0	0.0	0	0.0	3	2.7	3	2.1

Exhibit 7 – 15
Listing of Reported Neoplasms
All Allograft Recipients

Reported Neoplasm	Malignancy?	Timing	Relation to Islet Infusion Procedure	Relation to Immunosupression Therapy	Outcome of Event
Basal Cell Carcinoma	Yes	13 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Skin lesion removed from lower leg. Immunosuppression continued for over two years with no residual effects at which time graft failure occurred and immunosuppression was discontinued.
Basal Cell Carcinoma	Yes	37 months post 2nd Infusion	Unrelated	Probable	Resolved, no residual effects. Skin lesion removed from nose. Immunosuppression continued over two years post event with no additional events.
Basal Cell Carcinoma	Yes	48 months post 3rd Infusion	Unrelated	Probable	Resolved, no residual effects. Skin lesion removed. Immunosuppression continued over one year post event with one additional event. No further details are available.
Basal Cell Carcinoma	No	12 months post 3rd Infusion	Unrelated	Unlikely	Resolved, no residual effects. Non-cancerous skin growth on right cheekbone was removed. No follow-up data has been reported.
Breast Cancer	Yes	4 months post 1st Infusion	Unrelated	Unrelated	Persistent Condition, Recipient Alive. Had invasive ductal carcinoma. Immunosuppression continued through one month post event with no residual effects.
Breast Cancer	Yes	16 months post 3rd Infusion	Unrelated	Probable	Resolved, no residual effects. Invasive focal lobular carcinoma in situ diagnosed on routine screening 16 months post third infusion. Bilateral section performed participant continued immunosuppression. One month later, metastatic carcinoma of lymph nodes identified followed by section and chemotherapy. Participant decided to leave study due to chemotherapy. Immunosuppression was tapered.
Melanocytic Nevus	No	4 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Had surgical excision. Immunosuppression continued through one month post event.
Ovarian Cysts	No	2 months post 3rd infusion	Unlikely	Probable	Participant with a personal and family history of ovarian cysts diagnosed with ovarian hyperstimulation syndrome. Several surgeries performed to remove bilateral cysts and an endometrial polyp. Persistent heavy menses resulted in a total abdominal hysterectomy. Participant continued on immunosuppression through 16 months post hysterectomy with no additional events.
Papillary Thyroid Cancer	Yes	2 month post 1st Infusion	Unrelated	Probable	Resolved, with sequelae. Nodule diagnosed 2 months post infusion. Thyroidectomy performed, immunosuppression continued. Partial thyroidectomy performed about 17 years earlier for adenoma. No residual effects 2 years post thyroidectomy.

Exhibit 7 – 15 (continued)
Listing of Reported Neoplasms
All Allograft Recipients

Reported Neoplasm	Malignancy?	Timing	Relation to Islet Infusion Procedure	Relation to Immunosupression Therapy	Outcome of Event
Papillary Thyroid Cancer	Yes	22 months post 2nd Infusion	Unrelated	Probable	Resolved, no residual effects. Nodule at right of isthmus was removed. Thyroidectomy performed four months after the initial event. No follow-up data has been reported following the surgery.
Pulmonary Nodules	No	25 months post 2nd infusion	Unrelated	Possible	Bronchoscopy cultures indicated a mycobacterial infection. Increased lesions two months later required thoracoscopic surgery. Persistent condition four months post surgery. IAK recipient remains on steroid immunosuppression.
Right Ovarian Mucinous Cystadenoma	No	1 day post 1st infusion	Unrelated	Unrelated	Resolved, no residual effects. Mass was diagnosed at time of first infusion. Removal of adnexal mass and bilateral oopherectomy performed. Immunosuppression continued through five years post event with no residual effects.
Squamous Cell Carcinoma of Skin	Yes	17 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Squamous lesion removed from back. Immunosuppression was continued for another 8 months. No further follow-up available.
Squamous Cell Carcinoma of Skin	Yes	21 months days post 1st Infusion	Unrelated	Probable	Resolved, no residual effects. Immunosuppression continued. Eighteen months later, participant diagnosed with skin basal cell carcinoma. Immunosuppression continued through an additional 18 months with no residual effects.
Squamous Cell Carcinoma of Skin	Yes	6 months post 2nd infusion	Missing	Missing	Missing
Squamous Cell Carcinoma of Skin	Yes	60 months post 2nd Infusion	Unlikely	Possible	Resolved, with sequelae. Squamous lesion removed from chest. Immunosuppression continued.
Squamous Cell Carcinoma of Skin	Yes	36 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Squamous lesion removed from right shoulder. Immunosuppression continued.

Exhibit 7 – 15 (continued)
Listing of Reported Neoplasms
All Allograft Recipients

Reported Neoplasm	Malignancy?	Timing	Relation to Islet Infusion Procedure	Relation to Immunosupression Therapy	Outcome of Event
Squamous Cell Carcinoma of Skin	Yes	21 months post 1st Infusion	Unrelated	Probable	Resolved, no residual effects. Squamous lesion removed from left cheek and right temple. Immunosuppression continued. Eighteen months later, participant diagnosed with skin basal cell carcinoma. Immunosuppression continued through an additional 18 months with no residual effects.
Squamous Cell Carcinoma of Skin	Yes	45 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Squamous lesion removed from right cheek. Immunosuppression continued.
Squamous Cell Carcinoma of Skin	Yes	34 months post 3rd Infusion	Unrelated	Probable	Resolved, no residual effects. Squamous lesion removed from scalp. Immunosuppression continued.
Squamous Cell Carcinoma of Skin	Yes	20 months post 2nd Infusion	Unrelated	Possible	Resolved, no residual effects. Squamous lesion removed from right wrist. Immunosuppression continued.

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

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to 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
Haemorrhage	2002	0 days post 1st Infusion	Life threatening + Prolongation of existing hospitalization + Required intervention to prevent permanent damage	Probable	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects
Intra-abdominal hemorrhage*	2002	0 days post 1st Infusion	Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Intra-abdominal hemorrhage*	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	1 day post 2nd infusion	Prolongation of existing hospitalization	Probable	Unlikely	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
Post procedural hemorrhage	2002	0 days post 2nd Infusion	Life threatening + Prolongation of existing hospitalization	Definite	Possible	Required additional treatment for AE	Resolved, no residual effects

*Same participant experienced both events.

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

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosupression Therapy	Treatment Required	Outcome of Event
Hemorrhage	2003	0 days post 2nd Infusion	Prolongation of existing hospitalization	Probable	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Haemorrhage	2003	1 day post 2nd infusion	Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Hepatic hemorrhage	2003	0 days post 1st Infusion	Inpatient hospitalization	Probable	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Operative hemorrhage**	2003	0 days post 1st Infusion	Prolongation of existing hospitalization	Definite	Unrelated	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 hemorrhage**	2003	0 days post 2nd Infusion	Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Operative hemorrhage	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	0 days post 3rd Infusion	Missing	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 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	Resolved, no residual effects

**Same participant experienced all three events.

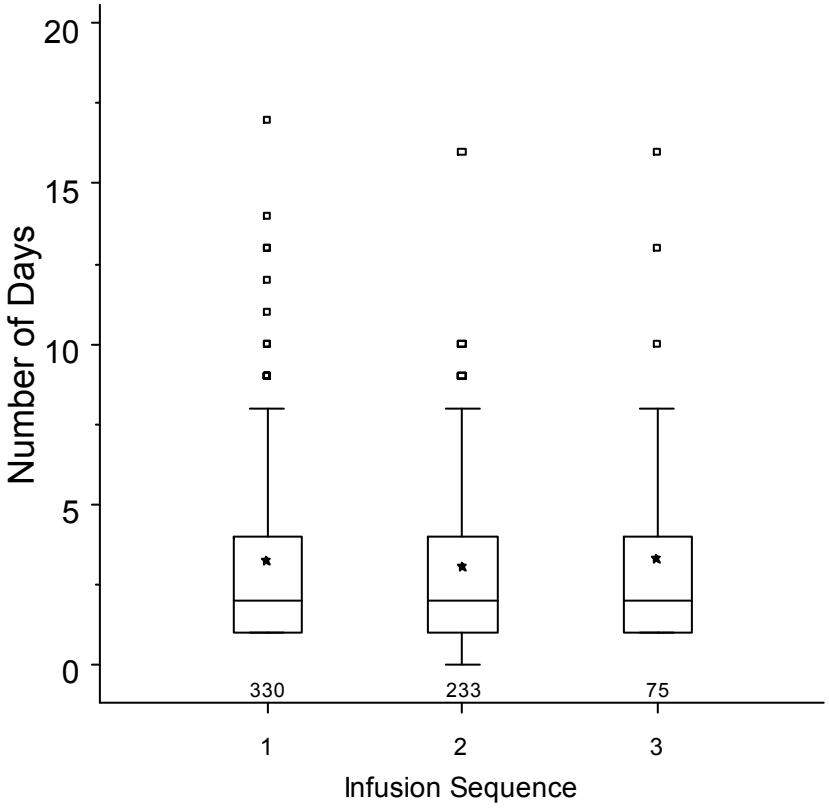
Exhibit 7 – 16 (continued)
Listing of Reported Hemorrhages and Portal Vein Thromboses
All Allograft Recipients

Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to 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
Post procedural hemorrhage	2003	0 days post 3rd Infusion	Life threatening + Prolongation of existing hospitalization + Required intervention to prevent permanent damage	Definite	Unrelated	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
Haemorrhage	2005	0 days post 1st Infusion	Inpatient hospitalization	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Hepatic haemorrhage	2005	1 day post 1st infusion	Life threatening + Prolongation of existing hospitalization	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2005	0 days post 2nd Infusion	Missing	Definite	Unrelated	No treatment or modification of treatment required 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

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

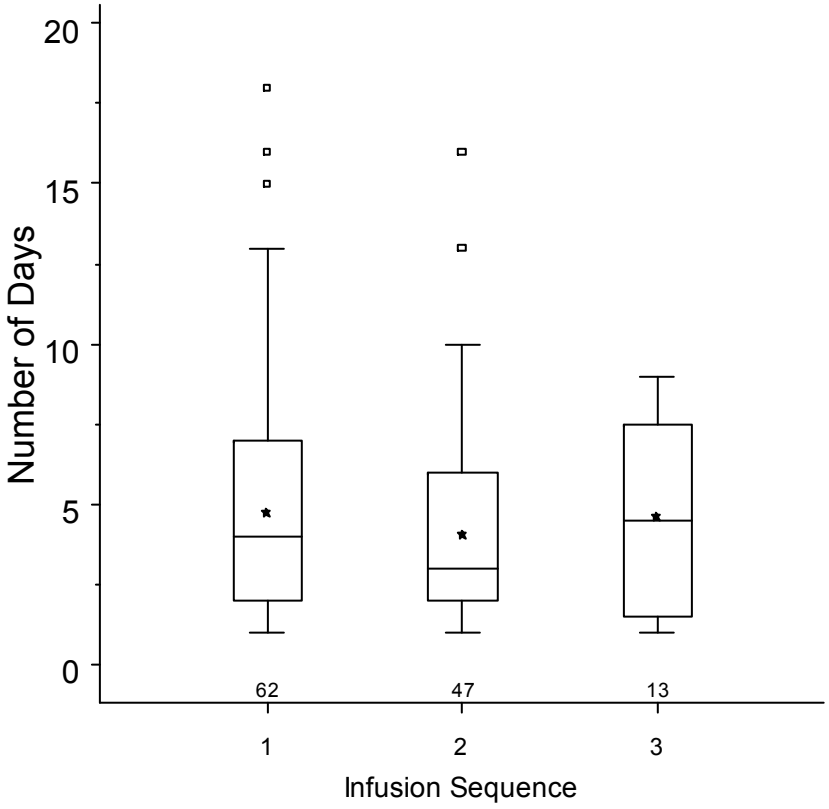
Event	Year	Timing	Classification	Relation to Islet Infusion Procedure	Relation to Immunosupression Therapy	Treatment Required	Outcome of Event
Portal vein thrombosis	2006	0 days post 1st Infusion	Life threatening + Prolongation of existing hospitalization	Definite	Unrelated	Required additional treatment 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	Resolved, no residual effects
Haemorrhage	2007	2 days post 2nd Infusion	Life threatening + Prolongation of existing hospitalization + Required intervention to prevent permanent damage	Definite	Unlikely	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Peritoneal haemorrhage	2007	0 days post 1st Infusion	Prolongation of existing hospitalization	Definite	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects
Peritoneal haemorrhage	2007	0 days post 1st Infusion	Missing	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Peritoneal haemorrhage	2008	0 days post 2nd Infusion	Life threatening + Prolongation of existing hospitalization + Required intervention to prevent permanent damage	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Portal vein thrombosis	2008	1 day post 2nd infusion	Prolongation of existing hospitalization + Required intervention to prevent permanent damage	Definite	Unlikely	Required additional treatment for AE	Resolved, no residual effects

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



Values greater than 20 days are not displayed
(Three at infusion 1 and one at infusion 3)

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



Values greater than 20 days are not displayed
(Three at infusion 1 and one at infusion 3)

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

	Total Infusions Received																							
	1								2								3							
	Follow-Up								Follow-Up								Follow-Up							
	Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	65	100.0	51	100.0	31	100.0	21	100.0	131	100.0	116	100.0	74	100.0	49	100.0	61	100.0	56	100.0	40	100.0	26	100.0
Participants Requiring at Least One Hospitalization	13	20.0	7	13.7	8	25.8	2	9.5	26	19.8	18	15.5	9	12.2	6	12.2	10	16.4	13	23.2	8	20.0	10	38.5
Number of Hospitalizations																								
1	7	10.8	3	5.9	6	19.4	2	9.5	19	14.5	16	13.8	8	10.8	5	10.2	8	13.1	12	21.4	6	15.0	8	30.8
2	3	4.6	1	2.0	2	6.5	0	0	6	4.6	1	0.9	1	1.4	1	2.0	2	3.3	1	1.8	1	2.5	0	0
3	1	1.5	2	3.9	0	0	0	0	1	0.8	1	0.9	0	0	0	0	0	0	0	0	0	0	1	3.8
4	1	1.5	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	2.5	1	3.8
5 or more	1	1.5	1	2.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0

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

	Total Infusions Received																							
	1								2								3							
	Follow-Up								Follow-Up								Follow-Up							
	Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3		Month 6		Year 1		Year 2		Year 3	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	8	100.0	8	100.0	4	100.0	3	100.0	33	100.0	28	100.0	23	100.0	16	100.0	10	100.0	11	100.0	5	100.0	6	100.0
Participants Requiring at Least One Hospitalization	5	62.5	2	25.0	1	25.0	3	100.0	11	33.3	5	17.9	8	34.8	4	25.0	3	30.0	2	18.2	1	20.0	2	33.3
Number of Hospitalizations																								
1	3	37.5	1	12.5	0	0	3	100.0	5	15.2	3	10.7	7	30.4	2	12.5	2	20.0	2	18.2	1	20.0	0	0
2	1	12.5	1	12.5	1	25.0	0	0	5	15.2	1	3.6	1	4.3	1	6.3	1	10.0	0	0	0	0	1	16.7
3	0	0	0	0	0	0	0	0	1	3.0	1	3.6	0	0	1	6.3	0	0	0	0	0	0	1	16.7
4	1	12.5	0	0	0	0	0	0	0	0	0	0	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 North American center is audited on-site with respect to their source documentation after three islet transplant recipients are entered in the CITR database. Subsequent data audits occur after an additional 10 recipients are registered or at the discretion of the Coordinating Center if less than 10 new recipients are registered.

During on-site audits, 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.

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 412 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 March 31, 2009. 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 91% at Month 6 to 86% at Year 1. Post the participant's last infusion procedure rates are similar for Month 6 (95%) and Year 1 (90%). However, the submitted forms for Year 2 drops to 81%, to 67% in Year 3, 58% in Year 4, and 49% in Year 5 (Exhibit 8-2). The low submission rates for Years 2-5 are due in large part to difficulties obtaining information from participants who have completed their protocol and are no longer returning to their transplant center.

Exhibit 8 – 1
Expected and Submitted Forms by Infusion Sequence

A. Islet Alone Recipients

	Infusion Sequence									Overall		
	1			2			3					
	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent
Deceased Donor Forms	384	376	98%	265	260	98%	97	95	98%	746	731	98%
Islet Processing Forms	384	359	93%	265	252	95%	97	92	95%	746	703	94%
Pre Infusion Forms	347	345	99%	252	245	97%	87	84	97%	686	674	98%
Pre Infusion Lab Forms	347	343	99%	252	245	97%	87	84	97%	686	672	98%
Infusion Forms	347	347	100%	252	252	100%	87	87	100%	686	686	100%
Induction Therapy Forms	347	338	97%	252	244	97%	87	84	97%	686	666	97%

B. Islet After Kidney Recipients

	Infusion Sequence									Overall		
	1			2			3					
	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent	Expected	Submitted	Percent
Deceased Donor Forms	78	77	99%	56	55	98%	16	15	94%	150	147	98%
Islet Processing Forms	78	72	92%	56	50	89%	16	15	94%	150	137	91%
Pre Infusion Forms	65	64	98%	53	50	94%	16	14	88%	134	128	96%
Pre Infusion Lab Forms	65	65	100%	53	52	98%	16	16	100%	134	133	99%
Infusion Forms	65	65	100%	53	53	100%	16	16	100%	134	134	100%
Induction Therapy Forms	65	64	98%	53	51	96%	16	15	94%	134	130	97%

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

		Expected	Submitted	Percent Submitted	Lost to Follow up	Data not available	Missing Forms	Percent Missing
Post First Infusion	**Month 6**	407	370	91%	7	2	28	7%
	Year 1	387	334	86%	13	1	39	10%
Post Last Infusion	**Month 6**	375	358	95%	9	0	8	2%
	Year 1	355	319	90%	18	2	16	5%
	Year 2	313	252	81%	36	3	22	7%
	Year 3	257	173	67%	46	5	33	13%
	Year 4	189	109	58%	48	1	31	16%
	Year 5	134	65	49%	46	1	22	16%

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	412	29.8	23.4	24.0	1.0	119.6
Extent of Insulin Log Completion	412	27.5	23.3	24.0	0.0	119.6
Participants Lost to Follow Up	76	24.7	18.3	23.6	0.9	77.2

Appendix A
Islet Transplant Centers, Coordinating Center and CITR Committees

Islet Transplant Centers

(Centers and Staff are listed in alphabetical order)

Baylor College of Medicine/
The Methodist Hospital
Houston, Texas, USA
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Tiffany Zgabay

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Darrell Grimes
Bashoo Naziruddin
Lori Otken
Kerri Purcell

Benaroya Research Institute
Seattle, Washington, USA
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Marli McCulloch-Olson
Marilyn Reeve

Carolinas Medical Center
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Melissa McGraw

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Joan Kelly
Zhuoru Liu
Piotr Witkowski

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Elizabeth Holbrook
Marti Sears

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Elsa Boely
Coralie Brault
Sandrine Demuylder-Mischler
Laure Nasse

Lille University Hospital
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Rimed Ezzouaoui
Valery Gmyr
Julie Kerr-Conte
Violeta Raverdy
Marie Christine Vantyghem

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Jarrett Anderson
LeAnn Batterson
Deborah Dicke-Henslin
Jane Fasbender
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Northwestern University
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Patrice Al-Saden
Angela Hecyk
Elyse Stuart

San Raffaele Institute
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Marina Scavini
Paola Maffi
Paola Magistretti

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Denadra Holland
Jonathan Fisher
Amy Knight
Lynn Dee Knight
Jaime Rullman
Daniel Salomon

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Jeannette Hacker
Lisa Johnson
Jeffrey Longmate
Aria Miller
Keiko Omori
KD Shiang
Cindy Stahl

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Lina Mariana
Kathy Howe

Swedish Medical Center
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Terri Baker

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Dianne Donat
Mark Heslegrave
Gary Levy
Meerna Nsouli
Jill Sheedy
Elizabeth Wright

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Barbara Culbreath

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PI: Juan Luis Contreras
Deborah Seale
Patricia Wilson

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Co-PI: Peter Senior
Parastoo Dinyari
Tatsuya Kin
Janet Wright

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San Francisco
San Francisco, California, USA
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Co-PI: Andrew Posselt
Kristina Johnson
Joan McElroy
Debbie Ramos
Tara Rojas
Greg Szot
Mehdi Tavakol

Islet Transplant Centers *(continued)*

(Centers and Staff are listed in alphabetical order)

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Kathleen Singraber

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Meyer Belzer
Betsy Britz
Susan George
Ron Gill
Heather Sours
Antony Valentine

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

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

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Minneapolis, Minnesota, USA
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Barbara Bland
Dan Fraga
Robin Jevne
Anne Nettles
David Radosevich
Sandra White

University of Nebraska
Omaha, Nebraska, USA
PI: R. Brian Stevens
Kristi DeHaai
Suzanne Miller

University of Pennsylvania
Philadelphia, Pennsylvania, USA
PI: Ali Naji
Chenyang Lu
Eileen M. Markmann
Diane McLaughlin
Maral Palanjian

University of Virginia
Charlottesville, Virginia, USA
PI: Kenneth Brayman
John Angle
Donna Broshek
Jason Freeman
Courtney Garbee
Klaus Hagspiel
Boris Kovatchev
Anthony McCall
Claire McKinley
Timothy Pruett
Robert Sawyer
Julie Straub
Timothy Schmitt

University of Wisconsin
Madison, Wisconsin, USA
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Luis Fernandez
Janice Kalvin
Matthew Hanson
Nancy Radke
Kristi Schneider
Larry Westby

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Martha Behnke
Melissa Thompson
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St. Louis, Missouri, USA
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Mona Awan
Heather Robertson

Westmead Hospital
Wentworthville, NSW, Australia
PI: Philip Oconnell
Patricia Anderson
Lindy William

s

CITR Coordinating Center

PI: Franca Benedicty Barton

Don Stablein
Steve Wease
Yamini Babu
Christina Mandzuk
Andrew Heitman
Ruth Danoff
Jodi DeStefano
Krista Huang

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

Scientific Advisory Committee (SAC)

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

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(2008)

Chair: Rodolfo Alejandro
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Nancy Bridges
Shari Messinger Cayetano
Brian Flanagan
Elizabeth Holbrook
Robert Ketchum
Bashoo Naziruddin
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(2008)

Chair: Fouad Kandeel
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Parastoo Dinyari
Albert Hwa
Carol Kramer
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Marti Sears
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(2008)

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Enrico Cagliero
Marc Garfinkel
Fouad Kandeel
Dixon Kaufman
Robert Ketchum
Francois Pattou
David Sutherland

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

Appendix B
CITR Allografts
Recipients with C-Peptide ≥ 0.3 Pre-Infusion

IA/IAK	Infusion 1 Year	Gender	Weight (kg)	BMI	Fasting C-Peptide (ng/mL)	Stimulated C-Peptide (ng/mL)	HbA1c (%)	Blood Glucose (mg/dL)	Hypoglycemia Status	Insulin (U/day)	Intensive Therapy	List days
IA	1999	Female	64.8	23.8	0.5	0	8.1	243	Unawareness	31	Y	6
IA	2000	Female	76.3	30.2	0.9	0.8	8	350	Unawareness	63	Y	63
IA	2000	Male	69.2	20.4	1.2	1.3	6.7	241	Unawareness	52	Y	113
IA	2001	Female	56.6	20.1	0.5	.	9.9	.	Having Episodes and Aware	32	Y	.
IA	2001	Female	64	26.0	0.6	0.5	8.1	74	Unawareness	36	Y	11
IA	2001	Female	54.7	22.2	0.7	.	7	76	Unknown	35	Y	174
IA	2001	Male	88	28.4	1.2	.	7.9	110	Unawareness	56	Y	165
IA	2002	Female	63	23.5	0.6	0.6	6.9	102	Partial Awareness	40	Y	17
IA	2002	Male	85	29.3	0.6	0	7.8	159	Unawareness	36	Y	280
IA	2002	Male	70	22.8	0.6	.	12.2	157	Partial Awareness	39	Y	89
IA	2002	Female	62	21.0	0.7	0.6	8	270	Partial Awareness	48	N	241
IA	2002	Male	70	22.1	0.9	.	8.1	251	Unawareness	30	Y	486
IA	2002	Male	67	24.6	0.9	0.7	7.1	102	Unawareness	45	Y	226
IA	2002	Female	59	20.8	1.6	.	7.2	130	Unawareness	40	Y	129
IAK	2003	Female	53.8	23.9	0.5	0.4	7.6	171	Unawareness	30	Y	1324
IAK	2003	Female	60.3	25.9	0.5	0.5	7.1	183	Partial Awareness	41	Y	260
IA	2003	Female	56.8	22.3	0.6	0	7.4	88	Unawareness	40	Y	57
IA	2003	Male	50	16.3	0.6	1.7	8.4	142	No Occurrence	25	Y	210
IA	2003	Male	65.2	22.6	0.8	0	7.7	67	Unawareness	47	Y	48
IA	2003	Female	61.3	23.2	0.8	0.7	6.3	272	Unawareness	43	Y	99
IAK	2003	Female	.	.	1.0	.	7.7	.		.	U	.
IA	2005	Female	53.9	20.9	0.5	0.6	7.5	197	Unawareness	30	Y	457
IAK	2005	Female	62	22.2	0.5	0.5	7	187	Having Episodes and Aware	32	N	400

While these recipients had some levels of positive C-peptide pre-infusion, all but one had other indications for islet transplantation (shaded areas) including absence of stimulated c-peptide, HbA1c>7.5%, fasting blood glucose <60 or >140 mg/dL, and hypoglycemia unawareness.

The Collaborative Islet Transplant Registry (CITR) is sponsored by the National Institute of Diabetes & Digestive & Kidney Diseases under contract number N01-DK-6-2868 to The EMMES Corporation. Reprints and additional information may be requested via email to citr@emmes.com or through the CITR website at www.citregistry.org.