ANNUAL REPORT

Prepared by:

CITR Coordinating Center
The EMMES Corporation
Rockville, MD

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

July 1, 2005

NOTICE:

The CITR Annual Report details data received as of April 1, 2005 for all islet transplant recipients registered by December 31, 2004.

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

July 1, 2005

M E M O R A N D U M

TO: CITR 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
Chair, Scientific Advisory Committee

SUBJECT: 2005 CITR Annual Report

The mission of the Collaborative Islet Transplant Registry (CITR) is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America. This report is the compilation of numerous hours of scientific research, patient care and collected information from islet transplant programs in North America. This second Annual Report builds upon the successes of its predecessor and significantly furthers the Registry mission. The report has been prepared by staff of The EMMES Corporation under the leadership of Ms. Nicole Close, CITR Director, with support from a NIDDK contract.

Clearly, the success of this effort depends on the continued interest and efforts of the collaborating islet transplant programs and islet production facilities. We are pleased to present information collectively obtained from nineteen transplant programs. Although data were not always complete in their entirety from each of these sources, the information from 256 processed pancreata, 266 islet infusion procedures and 138 recipients provides the basis for this report. We thank the contributing centers for their efforts and look forward to their continued participation.

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Executive Summary

Background:

The number of transplant centers performing clinical islet transplantation continues to increase, as well as the number of centers participating and reporting to the Collaborative Islet Transplant Registry (CITR). Compiling and analyzing data from all islet transplants facilitates the identification of both critical risk factors and key determinants of success, and thereby guides transplant centers in developing and refining islet/beta cell transplant protocols for the treatment of diabetes. To work toward this end, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) founded CITR. A Coordinating Center, located at The EMMES Corporation, was established in September 2001 to provide support for logistics, data capture, quality control monitoring, statistical design and analysis, and other Registry activities (www.citregistry.org). With this second Annual Report, CITR represents a collaborative effort between islet transplant programs in North America with the mission to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis and communication of comprehensive and current data on all islet/beta cell transplants performed in North America (citr@emmes.com).

Results:

Nineteen North American islet transplant programs have contributed to this CITR Annual Report. There were 118 islet transplant alone recipients, 19 islet after kidney recipients and one autograft transplant recipient included in this year's report (N=138). Islet transplant alone recipient (ITA) median age was 41.6 years (range 23.1 to 64.4), duration of diabetes was 29 years (range 4 to 50) and over 66% of the recipients were female. Median weight of the recipient was 65 kg (range 47 to 97) and median body mass index (BMI) was 23.1 kg/m^2 (range 18.8 to 31.6). All recipients were diagnosed with type 1 diabetes. For islet after kidney recipients (IAK), median age was 47.7 years (range 34.3 to 55.5), duration of diabetes was 31 years (range 15 to 42) and over 63% of the recipients were female.

The median age of the deceased donor for ITA recipients was 44 years (range 8 to 65) and body mass index was 28.3 kg/m^2 (range 13.3 to 59.8). Fifty-three percent of the donors were male and approximately 66% were white. The median serum creatinine of the donors was 1.1 mg/dL, total bilirubin 0.7 mg/dL, AST 39.0 IU/L, ALT 31.0 IU/L, serum lipase 28.0 IU/L and serum amylase 68.5 IU/L. Median time from cross clamp to pancreas recovery was 28 minutes (range 0 to 127) while duration of cold ischemia was 7 hours (range 1.5 to 27.0). UW, Two Layer, and UW Followed by Two Layer preservation were used for pancreas cold storage, and in all but one case Liberase HI was used for collagenase digestion. All of the processing facilities used a density gradient for islet purification and 45.5% of the islet products processed utilized islet cell culture.

One hundred and twelve islet alone recipients have completed at least one follow-up evaluation after their last infusion. Of these 112, 55 (49.1%) are insulin independent, while 39 (34.8%) are insulin dependent at their last follow-up visit post last infusion. A total of 15 (13.4%) participants have experienced graft failure, while three participants have an unknown insulin status. Examining outcomes at six months following the participant's last infusion, 67.0% were insulin independent and at twelve months this percentage decreases to 58.0%. For participants that still require insulin at six months post their last infusion, there was a 56.5% mean reduction in

their required daily insulin units compared to baseline. This ranged from a minimum reduction of 4.8% to an 83.3% reduction in their insulin requirements. At year 1 post last infusion, recipients remaining on insulin experienced a mean reduction of 69.0% in their required daily insulin requirements with a range of 16.7% to 92.4%.

There is a striking decrease in the occurrence of severe hypoglycemic events subsequent to the first infusion. Over 82% of all islet alone participants experienced one or more severe hypoglycemic events in the year prior to their first infusion. However, severe hypoglycemia was observed in only 2.5% of the study participants at 30 days post infusion and was not encountered (0%) in the subsequent 5 months. Only two recipients (2%) experienced one or more severe hypoglycemic events between months 6 and 12 post last infusion, but both of these recipients were on insulin replacement therapy and one had experienced a complete islet graft failure. A similar trend is seen in the IAK recipients. Over 57% of IAK recipients experienced one or more severe hypoglycemic events prior to their first infusion and then this decreases to 5.3% (N=1) up to 30 days and then to 0% for the other intervals.

The majority of the islet alone recipients received Daclizumab for induction and Sirolimus combined with Tacrolimus for maintenance immunosuppression. These regimens are similar to the islet after kidney recipients.

Adverse events have been received from 18 of the 19 centers and these 18 centers comprise the analysis set for adverse events and serious adverse events. Almost 74% (61/83) of the islet alone transplant recipients experienced at least one adverse event in year 1 post their first infusion, while 36% (30/83) experienced one or more serious adverse events in this same period. Of the 235 reported adverse events during this time frame, 34.0% were related to the immunosuppression therapy (probably or definitely related), and 14.5% were related (probably or definitely) to the infusion procedure. Of the 52 reported serious adverse events reported up to year 1 post first infusion, 28.8% were related (probably or definitely) to the immunosuppression therapy and 23.1% were related (probably or definitely) to the islet infusion procedure.

Overall, a total of 77 serious adverse events have been reported to the Registry, with 22% (N=17) of them classified as life threatening and 58% (N=45) requiring an inpatient hospitalization. Almost 69% of the serious adverse events were classified by the reporting CITR investigator as unrelated to the islet infusion procedure, 5.2% unlikely related, 9.1% possibly related, 5.2% probably related and 11.7% as definitely related. Regarding the relationship of these 77 serious adverse events to the immunosuppression therapy, almost 38% were classified as unrelated, 15.6% unlikely related, 16.9% possibly related, 19.5% probably related and 7.8% definitely related. Ninety-five percent (N=73) of the serious adverse events were resolved without residual effects. Most of the reported serious adverse events were related to gastrointestinal disorders, blood and lymphatic system disorders, and infections or infestations as classified by the MedDRA classifications system.

Conclusions:

The second CITR Annual Report provides expanded information from the first report and illustrates the current status of islet transplantation in North America. Caution must be used in the analysis and in the interpretation and conclusions made from the results reported to date. Since reported results are largely derived from small, non-randomized pilot trials, the reader must remember that possible hidden bias may exist concerning a particular outcome of interest (e.g., protocols limiting donor age to <60 years). Nevertheless, the CITR report provides data on a large number of islet transplant recipients, pancreas donors, pancreas preservation, islet processing, islet infusions, recipient treatment, post transplant islet function, and adverse

events. Through its collaboration with the islet transplant community and its interaction with professional societies and federal agencies, CITR provides data on clinically important outcome measures in islet transplantation to transplant professionals, basic scientists, diabetes care teams, other health care providers, funding agencies, payers, and patients. This information will help provide the basis necessary for the development of islet transplantation as a curative therapy for type 1 diabetes.

Methods Summary

CITR implements a set of web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry. These data help characterize and follow trends in safety and efficacy of islet transplantation, with particular emphasis on islet processing, transplant techniques, and treatment protocols. The Registry compiles data that are normally 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. Demographic information is collected 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 collected at six-months post infusion, one-year post infusion, and yearly thereafter. After recipients receive additional infusions, a new follow-up schedule is established such that a recipient is assessed at month 6 and annual anniversaries of the last infusion. Since the last CITR Annual Report, follow-up data has been collected for 6 months and 12 months post first infusion for four main indicators (insulin status, hemoglobin A_{1c}, fasting plasma blood glucose and C-peptide). There are also event driven data collection forms that gather information on adverse events, recipients vital status, non-islet transplant and follow-up, islet graft dysfunction, loss to follow-up, and transfer of the islet transplant recipient to another islet transplant center. A copy of these data collection forms may be requested from the CITR Coordinating Center (citr@emmes.com).

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

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

Time to first insulin use: Time to the first day insulin was required for 14 or more consecutive days.

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

Severe hypoglycemia: Hypoglycemic events requiring the assistance of another person to diagnose symptoms or administer treatment.

Islet graft dysfunction: In an *insulin independent recipient*, after completion of induction immunotherapy, islet graft dysfunction was suspected if the recipient displays, with no evidence of infection or drug toxicity, three consecutive blood glucose readings of 200 mg/dL over any 12-hour period. In an *insulin dependent recipient*, after completion of induction immunotherapy, islet graft dysfunction was suspected if the recipient displays, with no evidence of infection or drug toxicity over any 12-hour period, a 100% increase in the average insulin dose required to maintain pre-prandial blood glucose levels of 120 mg/dL.

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 islet graft dysfunction.

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 islet graft dysfunction.

Adverse event: Grade 3-5 as classified by the Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events (CTCAE), Version 3.0, DCTD, NCI, NIH, DHHS.

Serious Adverse Event: Any AE involving death, life threatening, inpatient hospitalization, prolongation of existing hospitalization, persistent or significant disability/incapacity or congenital anomaly/birth defect.

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

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.

CITR opened participation up to all North American centers early in the fall of 2002. The first Annual Report (2004) contained information on 86 islet transplant recipients, 173 deceased donors and 158 islet infusion procedures from twelve islet transplant centers. This Annual Report summarizes information on 138 islet transplant recipients, 256 deceased donors and 266 islet infusion procedures. This represents a 60% increase in the number of recipients, 48% increase in the number of donors, and a 68% increase in the number of infusion procedures that are reported in this Annual Report.

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 recipients from January 1, 1999 to December 31, 2004. These data were reviewed by the Coordinating Center for quality assurance, errors and data outliers. Any missing follow-up information on these recipients were identified and conveyed back to the site 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, 2005 based on the 138 recipients that had been registered for CITR at the December 31, 2004 closure date.

CITR also collects basic information from all islet transplant centers in North America, regardless of their participation with CITR. Thirty-eight islet transplant programs were sent a questionnaire asking for information. Information collected included the number of islet transplant infusions performed at the islet transplant program as well as the number of

pancreata processed and number of recipients. All 38 programs responded and 27 of the 38 programs had been active during 1999-2004, transplanting at least one patient. The remaining programs had not transplanted yet, or were in the process of setting up their islet transplant program.

The table below displays the data collected from the 27 active islet transplant programs in North America for 1999-2004. To the knowledge of the Registry, this table is inclusive of all active islet transplant programs in North America.

All Islet Transplant Programs in North America	Number of Human Islet Infusion Procedures Conducted	Number of Patients Receiving Their First Infusion
Total	475	257
1999	18	10
2000	33	22
2001	65	45
2002	142	82
2003	106	45
2004	111	53

In summary, this report includes data on 53.7% of all islet transplant recipients in the North America and 56.0% of all islet infusion procedures. The Registry continues to be successful in capturing additional reports, for example as of July 1, 2005, the number of transplant recipients in the CITR database has increased to 211.

Data contained in this report must be interpreted cautiously. Even with the efforts of the 19 participating centers, the total number of reports are still small. As with any registry, a number of potential biases may exist. First, not all islet transplant centers in North America participate in CITR. Second, those Centers reporting information to CITR have not reported on all of the islet transplant recipients at their Center yet or have not reported on all of the infusion procedures of their recipients. Those reported early from the Centers may constitute the successful cases or they may not. Third, there is always the potential of hidden selection bias in a registry database. Since a registry is non randomized and reflects the real world choices of islet transplant centers and physicians, some information may be selective based on the center's protocol (e.g. protocols limiting donor age <60 years). As the Registry progresses these biases may lessen.

Boxplots are used in the report to summarize data. The "star" (★) in the boxplot represents the mean value; and the whiskers represent the minimum and maximum 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). Total islet equivalents in the final product and donor characteristics were also plotted and Pearson correlation coefficients determined.

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 based on the report of 138 islet transplant recipients. Conclusions should recognize that the significance levels control for random variance, but not systematic biases in the data. 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.

This report is divided into four main sections representing a summary of the Registry data (Section 1), islet transplant alone recipient, donor and outcome information (Section 2), islet after kidney recipient, donor and outcome information (Section 3), and Registry data quality (Section 4). The focus of this year's report is the islet transplant alone recipient information and outcome data. As sample size increases for the islet after kidney recipients (N=19), additional tables and outcomes measures will be included for this section of the report.

Section 1
Registry Summary

Registry Summary

As of December 31, 2004, 19 North American islet transplant centers were activated for participation in the Collaborative Islet Transplant Registry (CITR). Exhibit 1 displays the names and locations of these centers. Overall, there has been a steady increase in the number of islet transplant programs joining CITR and contributing information since the last Annual Report (Exhibit 2). There has been a 62% increase in the number of recipients reported to the Registry since the last Annual Report, as well as a 59% increase in the number of islet infusion procedures reported. Exhibit 3 displays the number of centers contributing to this report compared to those that were active islet centers in the field conducting transplants during the same time period. For example, 10 of the 15 (67%) active islet transplant programs in 2003 contributed information to the Registry.

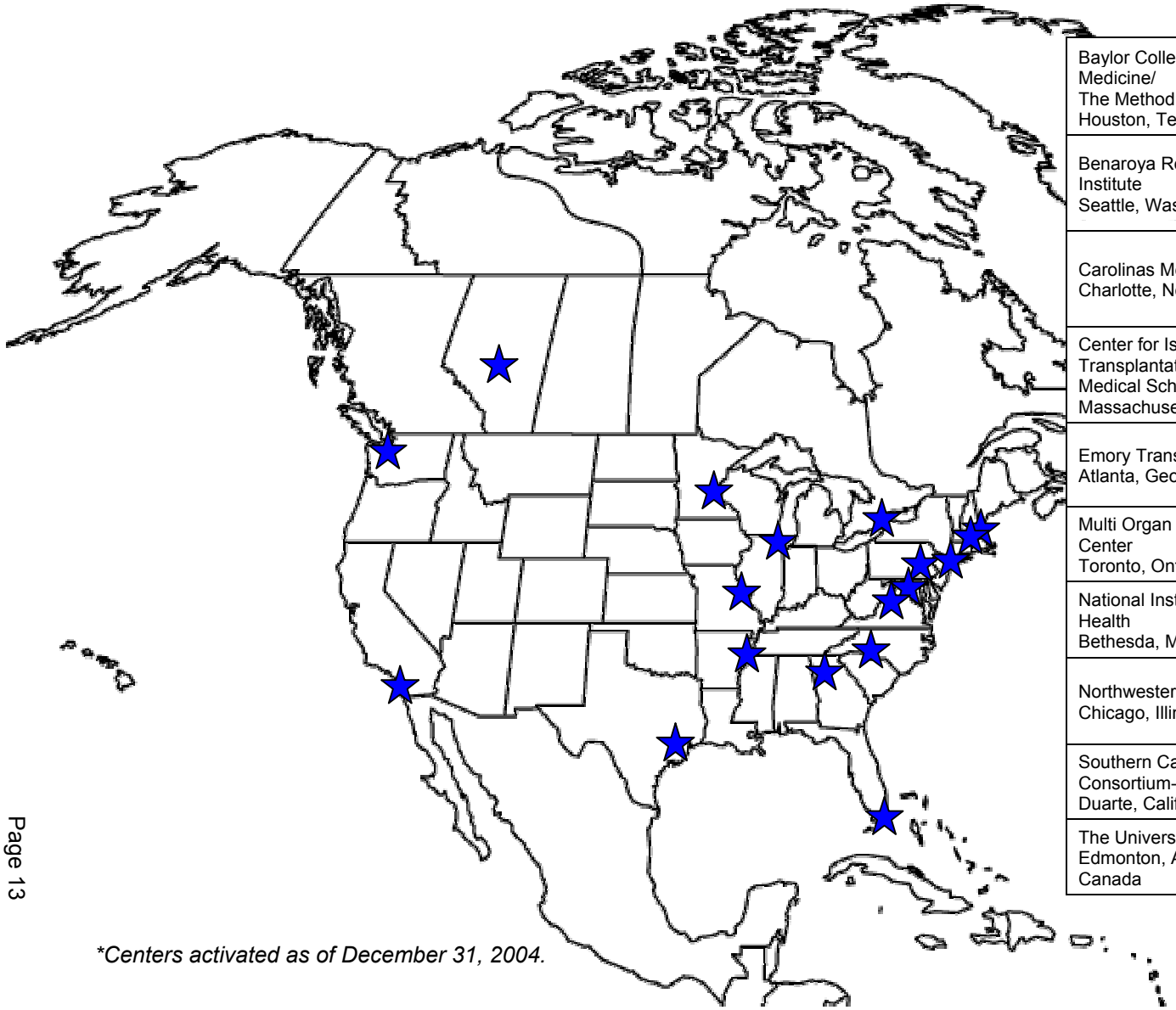
A summary of the number of infusions entered in the Registry by year the islet infusion was performed is included in Exhibit 4. From this summary, there was a large number of first islet infusions conducted by the CITR centers in 2002 (N=48) as well as a large number of recipients receiving their second infusion in 2002 (N=33). In other years, first infusions ranged from 14-30 procedures.

Forty patients (29%) have received just one islet infusion at the time of this report, 69 (50%) received a total of two infusions, 28 (20%) received three infusions, and one participant (1%) received a total of four islet infusions (Exhibit 5). Other sections of the report will not separate the information for the recipient of four infusions, as to assure confidentiality for this one participant and center.

Of the 138 participants represented in this report, 118 (85.5%) are islet transplant alone (ITA) recipients, 19 (13.8%) are islet after kidney recipients (IAK), and 1 recipient (0.7%) received an autograft transplant (Exhibit 6). With data from only one autograft recipient, information for this participant will not be presented in the report. The focus of the report will be centered on the 118 islet transplant alone recipients (Section 2), while a condensed section of analyses for the islet after kidney recipients (Section 3) are presented.

For ITA recipients, there were 215 donors reported for 231 total infusions (Exhibit 7). The discrepancy between the number of donors and total number of infusions (a minimum of one donor is expected per infusion procedure) is due to a lag in data entry of donor information for some of the infusion procedures. Thirty-four of 118 (28.8%) ITA recipients received just one islet infusion, 56 (47.5%) received two infusions, 27 (22.9%) received three infusions, and one received four infusions (0.8%) (Exhibit 8). For IAK recipients, there were 40 donors reported for 34 total infusions (Exhibit 9). In this case, there is a possibility that more than one donor pancreas is used for the islet infusion procedure. Five of 19 (26.3%) IAK recipients received one infusion, 13 (68.4%) received two infusions and one (5.3%) received three infusions.

Exhibit 1
Contributing Islet Transplant Centers*
(N=19)



Baylor College of Medicine/ The Methodist Hospital Houston, Texas	The University of Chicago Chicago, Illinois
Benaroya Research Institute Seattle, Washington	The University of Massachusetts Medical Center Worcester, Massachusetts
Carolinas Medical Center Charlotte, North Carolina	The University of Miami, Diabetes Research Institute Miami, Florida
Center for Islet Transplantation at Harvard Medical School Boston, Massachusetts	The University of Minnesota Minneapolis, Minnesota
Emory Transplant Center Atlanta, Georgia	The University of Pennsylvania Philadelphia, Pennsylvania
Multi Organ Transplant Center Toronto, Ontario, Canada	The University of Tennessee, Memphis Memphis, Tennessee
National Institutes of Health Bethesda, Maryland	The University of Virginia Charlottesville, Virginia
Northwestern University Chicago, Illinois	Washington University, St. Louis St. Louis, Missouri
Southern California Islet Consortium-SCIC Duarte, California	Columbia University New York, New York
The University of Alberta Edmonton, Alberta, Canada	

**Centers activated as of December 31, 2004.*

Exhibit 2
Summary of Information Represented in CITR Annual Reports

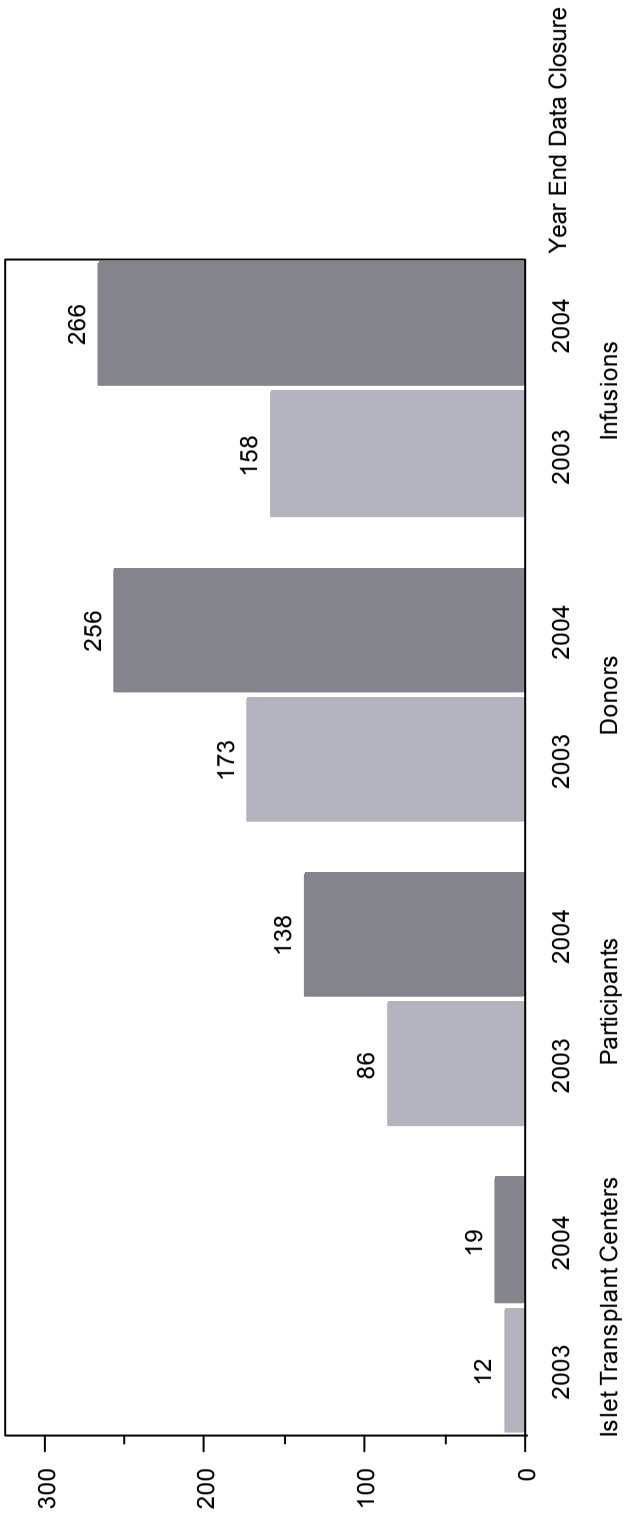


Exhibit 3
Number of Islet Transplant Programs Transplanting and Number Reporting Information to CITR by Year

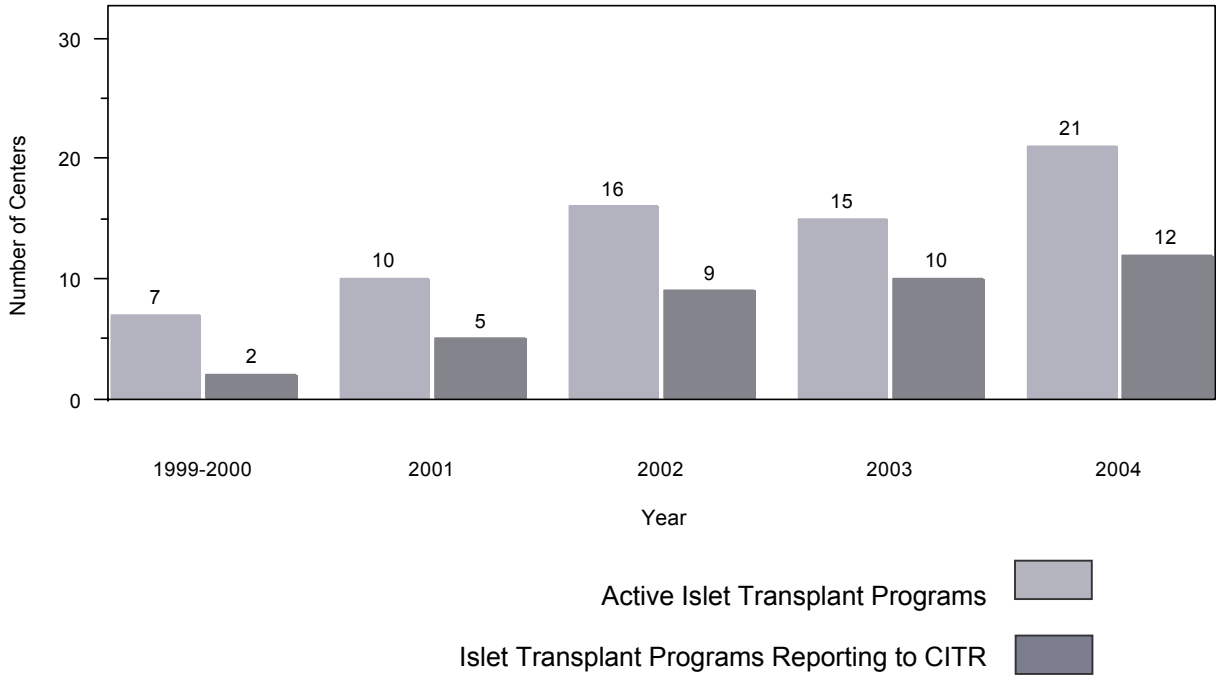
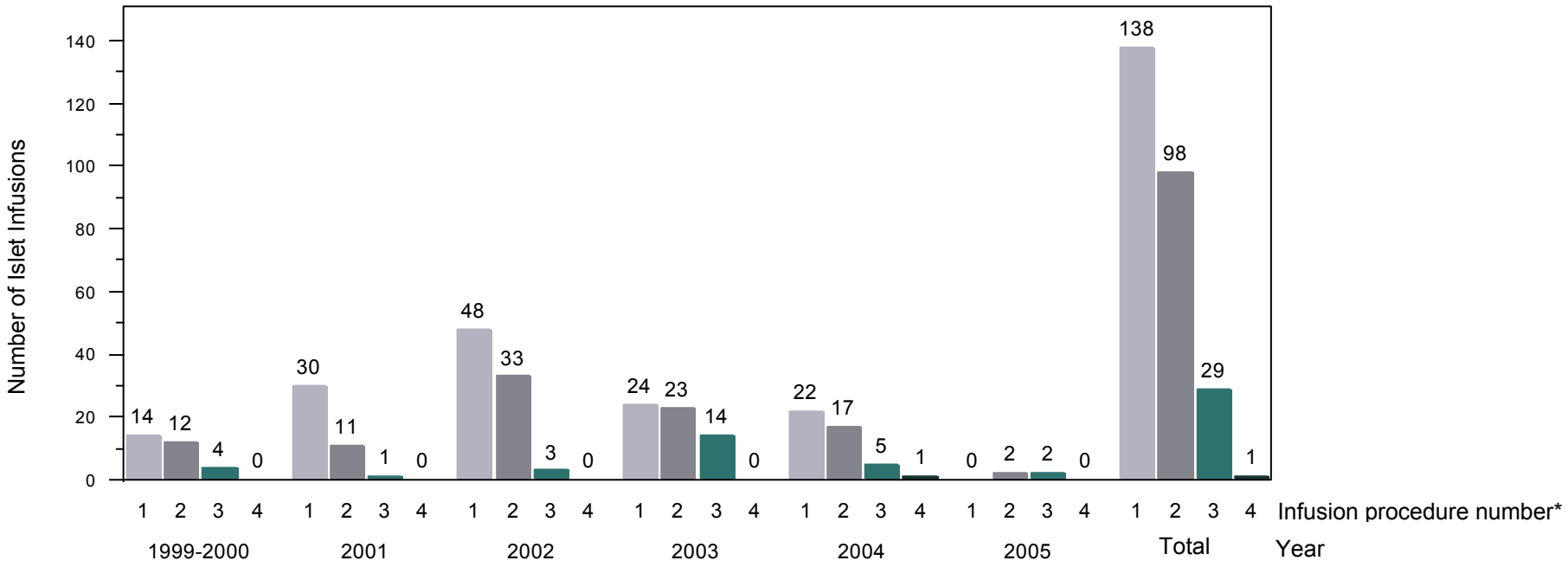


Exhibit 4
Total Number of Infusion Procedures Conducted and Entered in CITR Database by Year and by Infusion Number (All Participants, N=138)



**Infusion procedure number is defined as the sequence number of the total number of infusions received by one recipient. For example, in 2001, 30 individuals received their first infusion while one person received their third infusion.*

Exhibit 5
Total Number of Infusion Procedures Received Per Recipient
(All Participants, N=138)

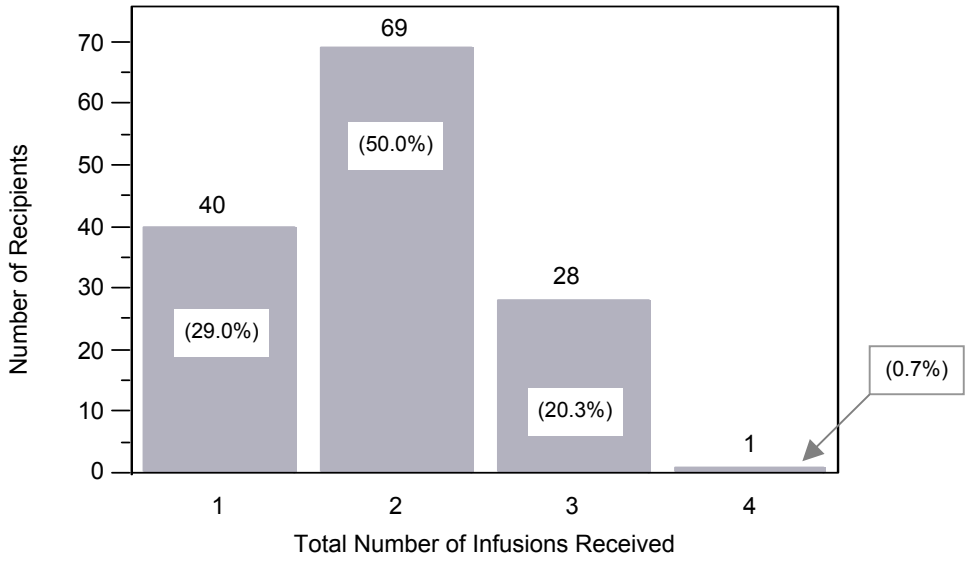


Exhibit 6
Summary of Transplant Types
(All Participants, N=138)

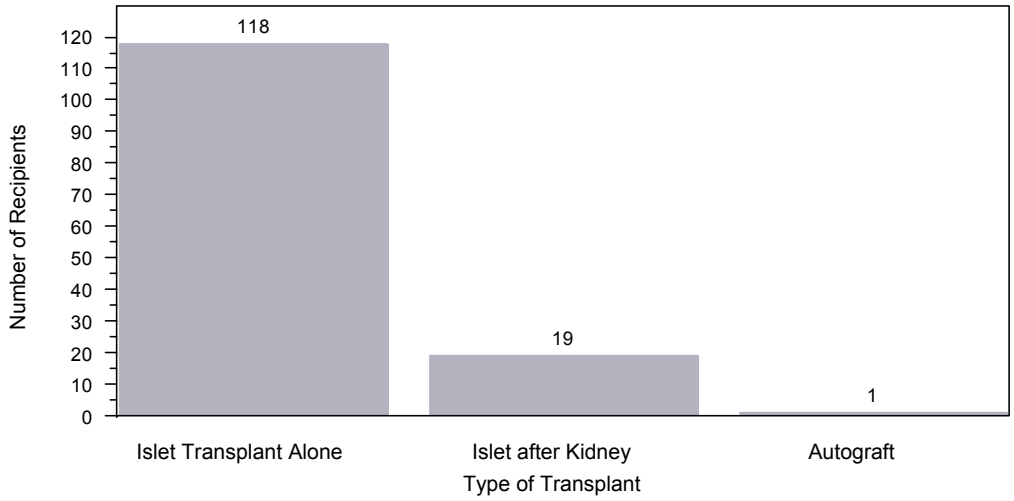


Exhibit 7
Summary of Information for Islet Transplant Alone Recipients

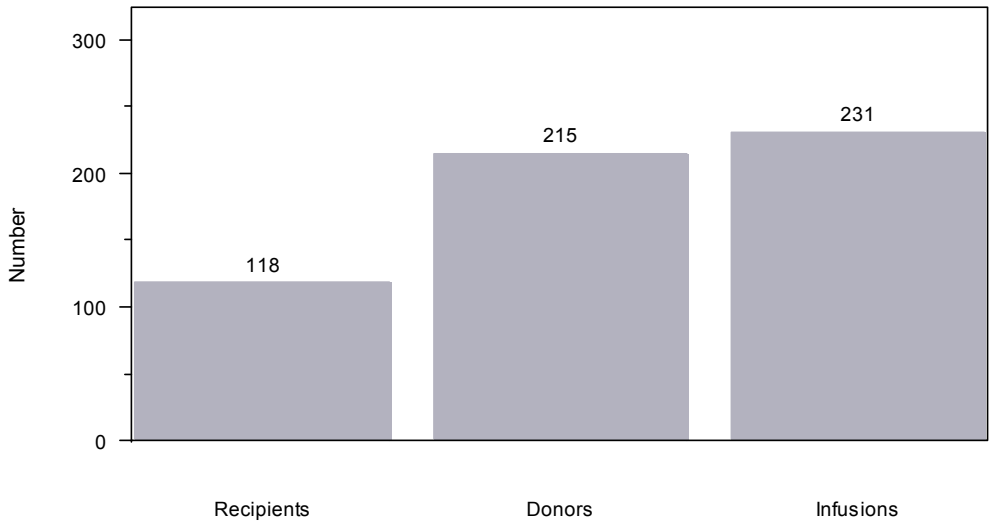


Exhibit 8
Total Number of Islet Infusions Received for Islet Transplant Alone Recipients (N=118)

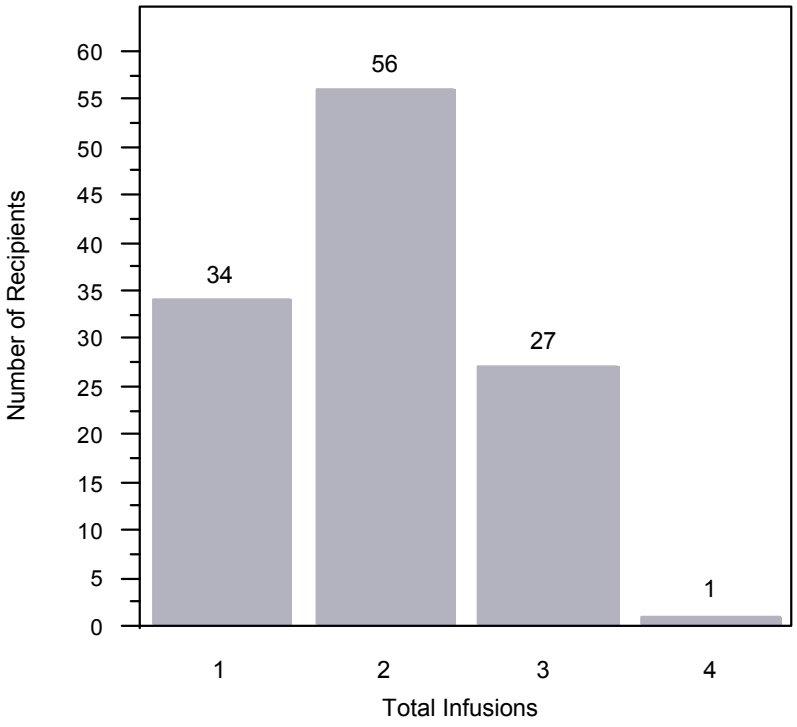


Exhibit 9
Summary of Information for Islet After Kidney Recipients

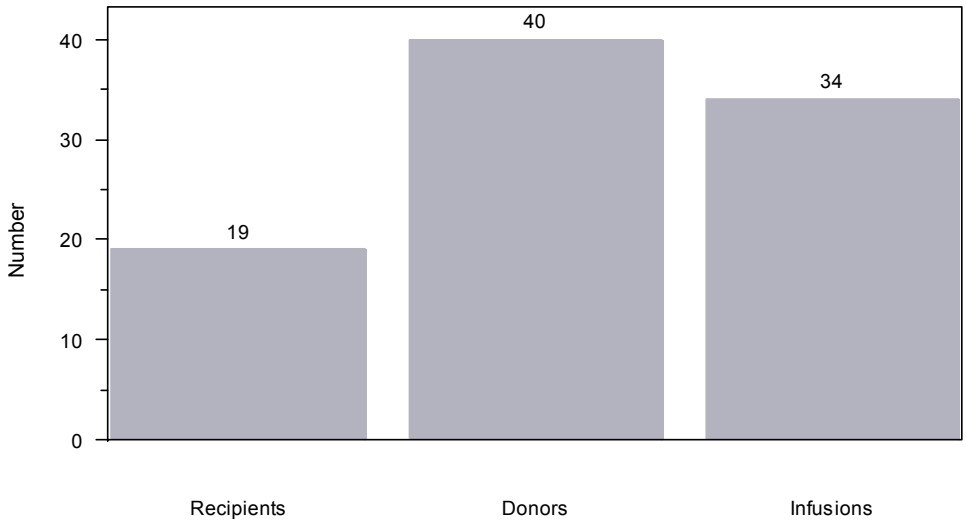
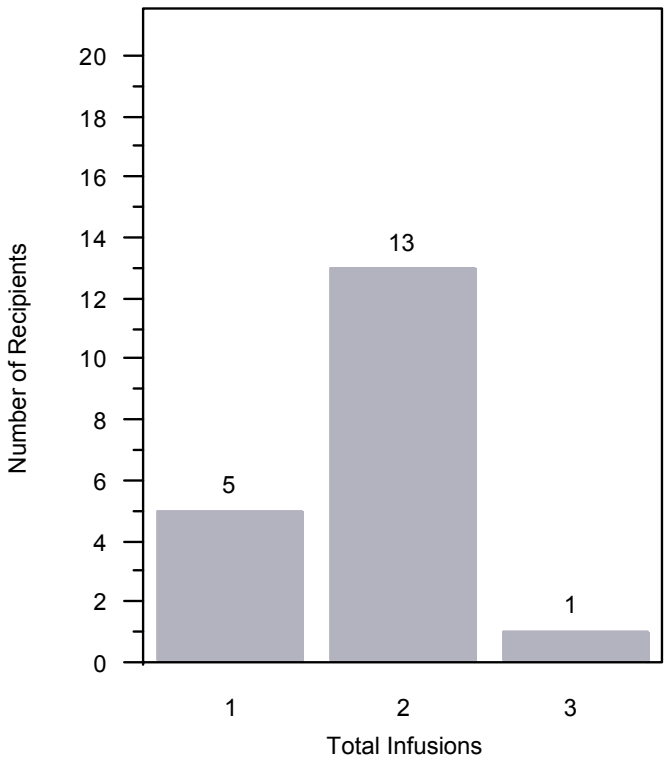


Exhibit 10
Total Number of Islet Infusions Received for Islet After Kidney Recipients (N=19)



Section 2
Islet Transplant Alone Information

Chapter 1
Recipient and Donor Characteristics

Recipient and Donor Characteristics Summary

Registry information collected on islet transplant alone recipients and the deceased donors are summarized in Chapter 1. This Annual Report represents information submitted by the nineteen islet transplant centers trained and activated to conduct CITR registry procedures prior to December 31, 2004.

Recipient Information:

The median age of the islet transplant recipient is 41.6 years (range 23.1 to 64.4) and the median duration of diabetes is 29 years (range 4 to 50). The median weight of the recipient is 65kg (range 47 to 97) and the median body mass index (BMI) is 23.1 kg/m^2 (range 18.8 to 31.6). Over 66% of the recipients are female and the recipients have limited racial diversity (Exhibit 12).

At the time of the first infusion, 59% of the recipients were employed full-time. Approximately 40% of the transplant procedures were funded through non-government research grants and 20% were from a US/State Government agency (Exhibit 13). Approximately, 45% of the islet transplant recipients were on an insulin pump prior to their first infusion and over 92% of the recipients were on the pump or were taking 3 or more insulin injections per day (Exhibit 14). The mean daily insulin requirement of recipients prior to their first infusion procedure was 36.6 units (SD 12.9) and the subset on intensive insulin therapy had received intensive therapy for a mean of 15.1 years (SD 11.1) (Exhibit 15). Their mean fasting plasma glucose for all recipients was 169.8 mg/dL (SD 105.3) and their mean HbA_{1c} was 7.6% (SD 1.3).

Serology tests indicated three recipients tested positive for hepatitis B core antibodies and two recipients tested positive for hepatitis B surface antigen (Exhibit 16).

Islet Infusion Information:

Exhibit 17 summarizes the main infusion procedure characteristics by the infusion number. The mean number of islet equivalents infused was similar (456,130, 437,714 and 448,464, respectively) for each infusion. On average, if a patient received a second infusion, they received this infusion 14.4 weeks following their first infusion, while those receiving a third infusion received this infusion 30.9 weeks after their initial one.

Donor Information:

The median age of the deceased donor was 44 years (range 8 to 65) and the median body mass index was 28.3 kg/m^2 (range 13.3 to 59.8). The median time from cross clamp to pancreas recovery was 28.0 minutes (range 0 to 127) (Exhibit 18). Fifty-three percent of the donors were male, 9.3% were Hispanic and approximately 66% were white. Race is currently missing on a large number of the donors in the database and with the missing removed from the calculation, 87.5% of the donors were white. Over 52% of the donors had a cerebrovascular/stroke as cause of death while 29% experienced a head trauma. Twenty-nine percent of the donors had a history of hypertension and 17% had a history of alcohol dependency.

Thirty-five percent of the donors received a transfusion prior to organ procurement and only 8% received a transfusion during the organ procurement surgery. Approximately 50% of the donors received steroids and almost a quarter of the donors had received insulin (Exhibit 19). Over 86% of the donors received at least one vasopressor during the donor's terminal hospitalization (Exhibit 24).

Deceased donor serology is presented in Exhibit 25. There was report of one donor testing positive for Anti HBC and this donor was used for a hepatitis B immunized recipient.

Deceased donor laboratory data are presented in Exhibit 26. The median serum creatinine of the donors is 1.1 mg/dL, total bilirubin 0.7 mg/dL, AST 39.0 IU/L, ALT 31.0 IU/L, serum lipase 28.0 IU/L and serum amylase 68.5 IU/L. Boxplots are presented for the donor laboratory values (Exhibits 27-35).

Exhibit 11
Recipient Demographics

	Overall			
	N	Median	Min	Max
Age (yrs)	118	41.6	23.1	64.4
Duration of Diabetes (yrs)	118	29.0	4.0	50.0
Weight (kg)	113	65.0	46.8	97.0
Body Mass Index (kg/m^2)	111	23.1	18.8	31.6

Exhibit 12
Recipient Characteristics

	Overall	
	N	%
Gender		
Male	40	33.9
Female	78	66.1
Race		
American Indian or Alaska Native	-	0.0
Asian	-	0.0
Black or African American	-	0.0
Indian Sub-continent	-	0.0
Mideast or Arabian	-	0.0
Native Hawaiian or Other Pacific Islander	-	0.0
White	87	73.7
Missing	31	26.3
Ethnicity		
Non Hispanic or Latino	86	72.9
Hispanic or Latino	2	1.7
Unknown*	30	25.4
Diabetes Type		
Type 1 Diabetes	118	100.0

*Ethnicity is not collected outside of the United States.

Exhibit 13
Recipient's Primary Payer and Employment Status at Time of First Infusion

	Overall	
	N	%
Primary Payer		
US/State Government Agency	24	20.3
Private Insurance	1	0.8
Institutional Commitment	20	16.9
Non-Government Research Grant	47	39.8
Provincial Government	3	2.5
Missing	23	19.5
Employment status		
Working full time	69	58.5
Working part-time by choice	4	3.4
Working part-time due to disease	4	3.4
Working part-time, reason unknown	2	1.7
Not working by choice	7	5.9
Not working due to disease	15	12.7
Not working, unable to find employment	1	0.8
Not working, reason unknown	2	1.7
Student	2	1.7
Retired	7	5.9
Employment status unknown	3	2.5
Missing	2	1.7

Exhibit 14
Recipient Status at First Infusion

	Overall	
	N	%
Total	118	100.0
Use of insulin pump		
Yes	53	44.9
No	64	54.2
Unknown	1	0.8
Number of injections per day		
N/A - on pump	53	44.9
1-2	6	5.1
3-5	56	47.5
Unknown	3	2.5
Intensive therapy (Use of insulin pump or 3 or more injections per day)		
Yes	109	92.4
No	9	7.6
Unknown	-	0.0
Pre transplant autoantibody - GAD 65		
Positive	17	14.4
Negative	34	28.8
Not Done/Unknown	61	51.7
Missing	6	5.1
Pre transplant autoantibody - IA-2		
Positive	21	17.8
Negative	26	22.0
Not Done/Unknown	65	55.1
Missing	6	5.1
Pre transplant autoantibody - Insulin		
Positive	25	21.2
Negative	4	3.4
Not Done/Unknown	82	69.5
Missing	7	5.9

Exhibit 14 *(continued)*
Recipient Status at First Infusion

	Overall	
	N	%
Positive crossmatch for B-Cell	1	0.8
Positive crossmatch for T-Cell	-	0.0

Exhibit 15
Recipient Summary Measures at First Infusion

	Overall		
	N	Mean	SD
Daily insulin requirement prior to infusion (units)	116	36.6	12.9
Duration of intensive therapy (yrs)	77	15.1	11.1
Fasting plasma glucose (mg/dL)	109	169.8	105.3
HbA_{1c} (%)	112	7.6	1.3

Exhibit 16
Recipient Serology at Screening

	Overall	
	N	%
Total	118	100.0
HIV screening		
Positive	-	0.0
Negative	114	96.6
Not Done/Unknown/Missing	4	3.4
CMV IGG		
Positive	50	42.4
Negative	61	51.7
Not Done/Unknown/Missing	7	5.9
CMV IgM		
Positive	-	0.0
Negative	51	43.2
Not Done/Unknown/Missing	67	56.8
HepB core antibody		
Positive	3	2.5
Negative	81	68.6
Not Done/Unknown/Missing	34	28.8
HepB surface antigen		
Positive	2	1.7
Negative	109	92.4
Not Done/Unknown/Missing	7	5.9
HepC antibody		
Positive	-	0.0
Negative	108	91.5
Not Done/Unknown/Missing	10	8.5
EBV IgG		
Positive	100	84.7
Negative	9	7.6
Not Done/Unknown/Missing	9	7.6

Exhibit 17
Infusion Summary by Infusion Sequence

	Infusion 1					
	N	Mean	SD	Median	Min	Max
Islet Equivalents infused	117	456,130	149,445	410,100	200,000	973,133
Islet Equivalents infused/kg	113	6,978	2,385	6,345	2,135	16,142
Packed cell volume	113	4.0	2.2	3.7	1.0	15.0
Pre portal pressure (mmHg)	108	9.1	4.1	9.0	1.0	19.0
Peak portal pressure (mmHg)	106	11.8	4.4	12.0	1.0	25.0
Closure portal pressure (mmHg)	106	10.8	4.7	11.0	0.0	25.0
Time since first infusion (weeks)	0	-	-	-	-	-

	Infusion 2					
	N	Mean	SD	Median	Min	Max
Islet Equivalents infused	80	437,714	155,915	394,422	190,036	1,056,430
Islet Equivalents infused/kg	75	6,958	2,564	6,286	3,061	18,593
Packed cell volume	78	3.7	1.8	3.5	0.8	9.0
Pre portal pressure (mmHg)	76	8.7	4.0	9.0	1.0	19.0
Peak portal pressure (mmHg)	75	12.2	4.8	12.0	4.0	26.0
Closure portal pressure (mmHg)	74	11.4	5.2	11.0	3.0	26.0
Time since first infusion (weeks)	84	14.4	15.8	9.1	0.4	100.6

	Infusion 3					
	N	Mean	SD	Median	Min	Max
Islet Equivalents infused	25	448,464	140,520	420,296	246,000	802,632
Islet Equivalents infused/kg	23	6,704	2,703	6,065	4,000	15,738
Packed cell volume	26	3.5	2.0	2.8	0.7	9.0
Pre portal pressure (mmHg)	25	7.9	4.1	8.0	1.0	14.0
Peak portal pressure (mmHg)	24	11.9	5.9	11.0	3.0	27.0
Closure portal pressure (mmHg)	24	11.0	5.6	11.0	2.0	25.0
Time since first infusion (weeks)	28	30.9	31.5	18.4	3.6	116.0

Exhibit 18
Donor Characteristics

	Overall			
	N	Median	Min	Max
Age (yrs)	200	44.0	8.0*	65.0
Weight (kg)	199	85.0	25.0*	200.0*
Height (m)	197	1.7	1.4	1.9
Body Mass Index (kg/m^2)	197	28.3	13.3	59.8
Time from admission to brain death (hrs)	197	27.0	0.0	484.0
Duration of cardiac arrest where there was a cardiovascular death (mins)	11	20.0	4.0	60.0
Time from cross clamp to pancreas recovery (mins)	137	28.0	0.0	127.0

*Values verified by center as correct.

Exhibit 19
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
Total	215	100.0
Gender		
Female	86	40.0
Male	114	53.0
Missing	15	7.0
Race		
American Indian or Alaska Native	-	0.0
Asian	-	0.0
Black or African American	18	8.4
Indian Sub-continent	1	0.5
Mideast or Arabian	-	0.0
Native Hawaiian or Other Pacific Islander	-	0.0
White	141	65.6
Missing	55	25.6
Ethnicity		
Non Hispanic or Latino	140	65.1
Hispanic or Latino	20	9.3
Unknown*	55	25.6
Body Mass Index		
<25	47	21.9
25-27	42	19.5
28-30	35	16.3
>30	73	34.0
Missing	18	8.4

*Ethnicity is not collected outside of the United States.

Exhibit 19 *(continued)*
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
Donor ABO blood group		
A	77	35.8
A_1	13	6.0
A_2	-	0.0
AB	1	0.5
A_1B	-	0.0
A_2B	-	0.0
B	10	4.7
O	99	46.0
Missing	15	7.0
Cause of death		
Anoxia/cardiac arrest	8	3.7
CNS tumor	2	0.9
Cerebrovascular/stroke	112	52.1
Head trauma	62	28.8
Other	13	6.0
Missing	18	8.4
Mechanism of death		
Asphyxiation	2	0.9
Blunt injury	43	20.0
Cardiovascular	5	2.3
Death from natural causes	1	0.5
Drug intoxication	2	0.9
Gunshot wound	15	7.0
Intracranial hemorrhage/stroke	125	58.1
None of the above	2	0.9
Missing	20	9.3

Exhibit 19 *(continued)*
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
Circumstances of death		
Alleged homicide	8	3.7
Alleged suicide	10	4.7
Death from natural causes	77	35.8
Motor vehicle accident	31	14.4
Non-motor vehicle accident	16	7.4
None of the above	54	25.1
Missing	19	8.8
History of hypertension		
Yes	63	29.3
No	123	57.2
Missing	29	13.5
-Hypertension duration		
0-5 years	27	42.9
6-10 years	5	7.9
>10 years	12	19.0
Missing	19	30.2
-Hypertension control-Diet		
Yes	8	12.7
No	17	27.0
Missing	38	60.3
-Hypertension control-Diuretics		
Yes	11	17.4
No	26	41.3
Missing	26	41.3
-Hypertension control-Other medications		
Yes	32	50.8
No	12	19.0
Missing	19	30.2

Exhibit 19 *(continued)*
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
History of alcohol dependency		
Yes	37	17.2
No	150	69.8
Missing	28	13.0
-Alcohol use in past 6 months		
Yes	23	62.2
No	9	24.3
Missing	5	13.5
History of diabetes		
Yes	-	0.0
No	197	91.6
Missing	18	8.4
Transfusions given prior to surgery		
0 units	115	53.5
0-5 units	55	25.6
6-10 units	11	5.1
>10 units	9	4.2
Missing	25	11.6
Transfusions given intraoperatively		
0 units	170	79.1
0-5 units	15	7.0
6-10 units	2	0.9
Missing	28	13.0
Steroids given		
Yes	107	49.8
No	50	23.3
Missing	58	27.0
Insulin given		
Yes	53	24.7
No	98	45.6
Missing	64	29.8

Exhibit 20
Donor Age (yrs)

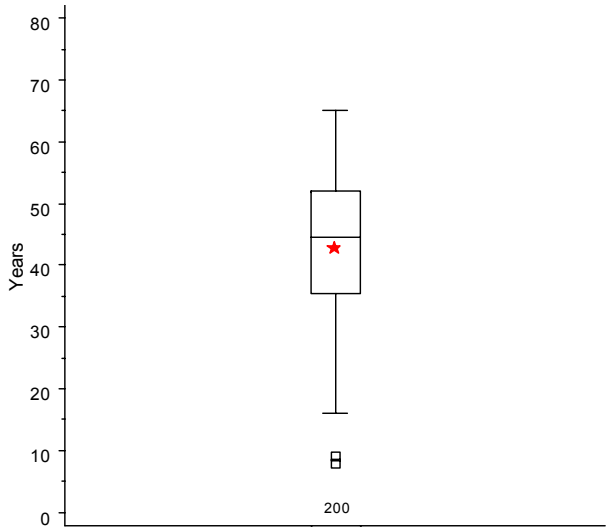


Exhibit 21
Donor Weight (kg)

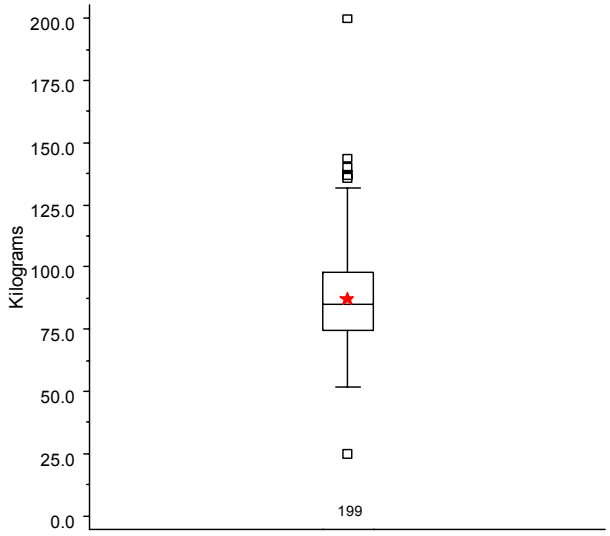


Exhibit 22
Donor Body Mass Index (kg/m^2)

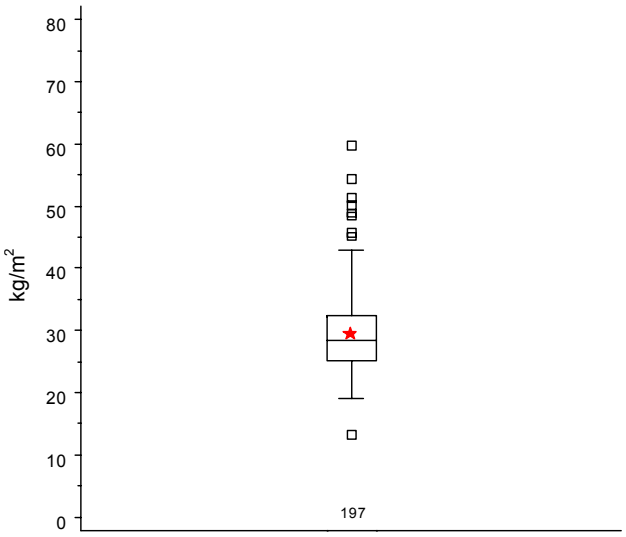


Exhibit 23
Time from Cross Clamp to Pancreas Recovery (mins)

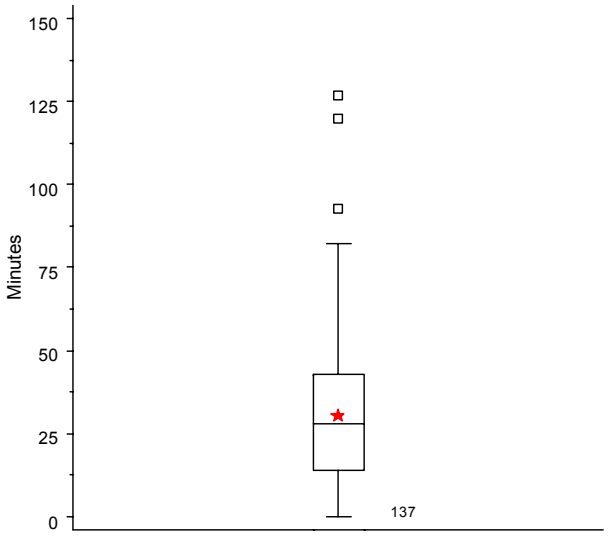


Exhibit 24
Donor Characteristics: Use of Vasopressors

	Overall	
	N	%
Total	215	100.0
Vasopressors used		
Yes	185	86.0
No	8	3.7
Missing	22	10.2
Number of vasopressors used		
None	8	3.7
One	51	23.7
Two	90	41.9
Three	37	17.2
Four	7	3.3
Missing	22	10.2

Exhibit 25
Donor Serology

	Overall	
	N	%
Total	215	100.0
Anti HIV I/II		
Positive	-	0.0
Negative	198	92.1
Not Done/Unknown/Missing	17	7.9
Anti HTLV I/II		
Positive	-	0.0
Negative	191	88.8
Not Done/Unknown/Missing	24	11.2
RPR VDRL		
Positive	-	0.0
Negative	189	87.9
Not Done/Unknown/Missing	26	12.1
Anti CMV		
Positive	106	49.3
Negative	92	42.8
Not Done/Unknown/Missing	17	7.9
HBsAg		
Positive	-	0.0
Negative	196	91.2
Not Done/Unknown/Missing	19	8.8
Anti HBC		
Positive	1*	0.5
Negative	193	89.8
Not Done/Unknown/Missing	21	9.8
Anti HCV		
Positive	-	0.0
Negative	194	90.2
Not Done/Unknown/Missing	21	9.8

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

Exhibit 26
Donor Laboratory Data

	Overall					
	N	Mean	SD	Median	Min	Max
Serum creatinine (mg/dL)	172	1.2	0.7	1.1	0.4	6.9
BUN (mg/dL)	164	14.8	8.5	13.0	3.0	55.0
Total bilirubin (mg/dL)	164	0.9	0.7	0.7	0.1	4.3
AST (IU/L)	164	97.2	320.1	39.0	11.0	3,886.0*
ALT (IU/L)	164	72.5	264.0	31.0	5.0	3,318.0*
Serum lipase (IU/L)	174	67.5	107.2	28.0	0.0	785.0
Serum amylase (IU/L)	176	160.5	366.8	68.5	9.0	3,875.0*
Minimum pre-insulin blood glucose (mg/dL)	187	127.0	40.5	120.0	63.0	317.0
Maximum blood glucose (mg/dL)	175	268.9	97.0	248.5	84.0	700.0

*Values verified by center as correct.

Exhibit 27
Donor Serum Creatinine (mg/dL)

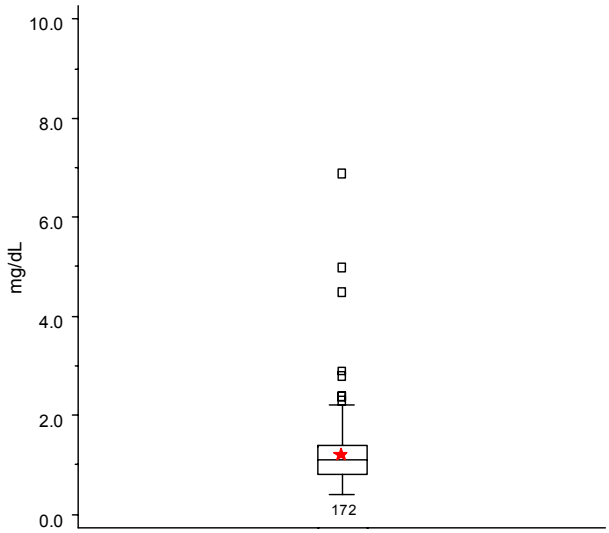


Exhibit 28
Donor BUN (mg/dL)

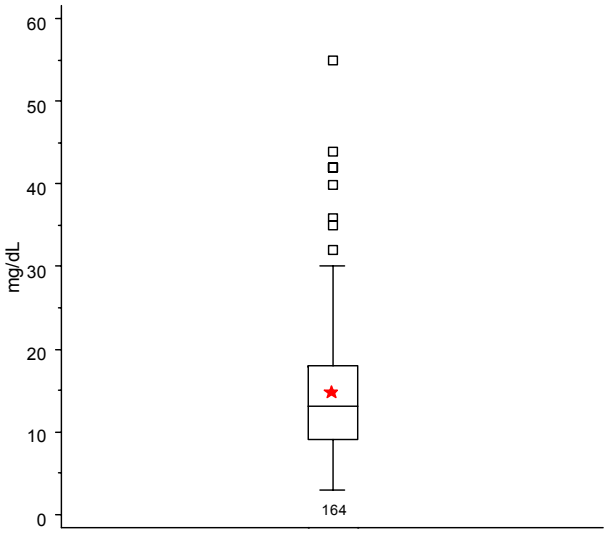


Exhibit 29
Donor Total Bilirubin (mg/dL)

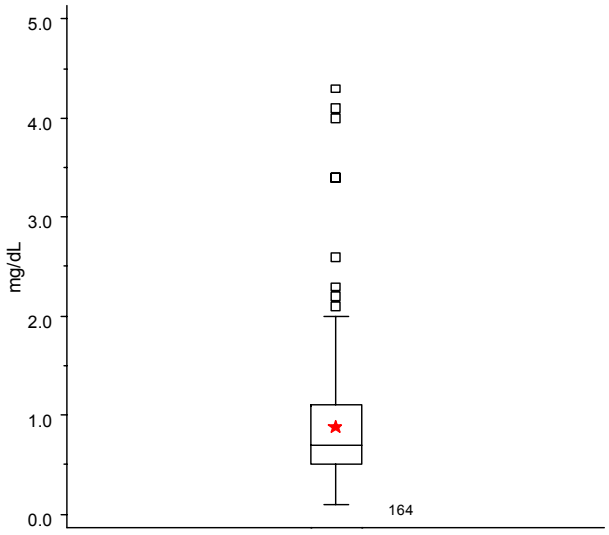
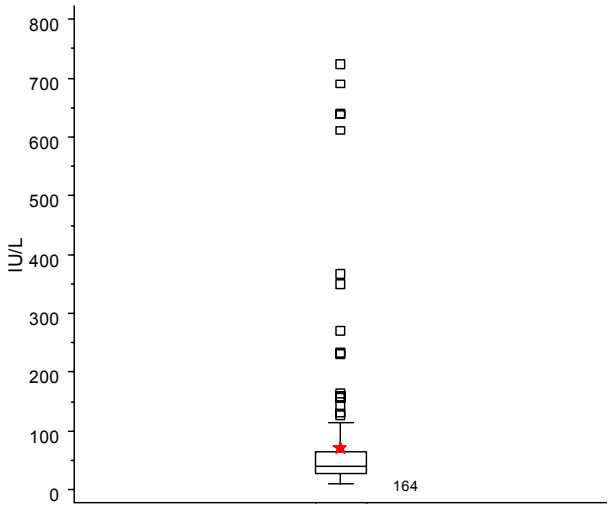
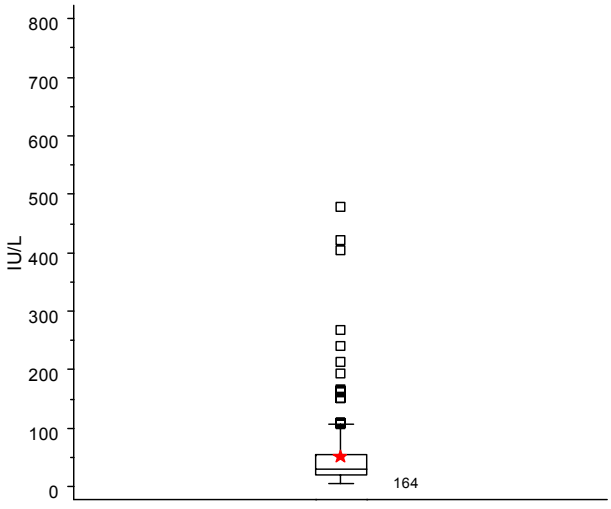


Exhibit 30
Donor AST (IU/L)



Data point 3886 IU/L excluded from graph for presentation, verified correct by center.

Exhibit 31
Donor ALT (IU/L)



Data point 3318 IU/L excluded from graph for presentation, verified correct by center.

Exhibit 32
Donor Serum Lipase (IU/L)

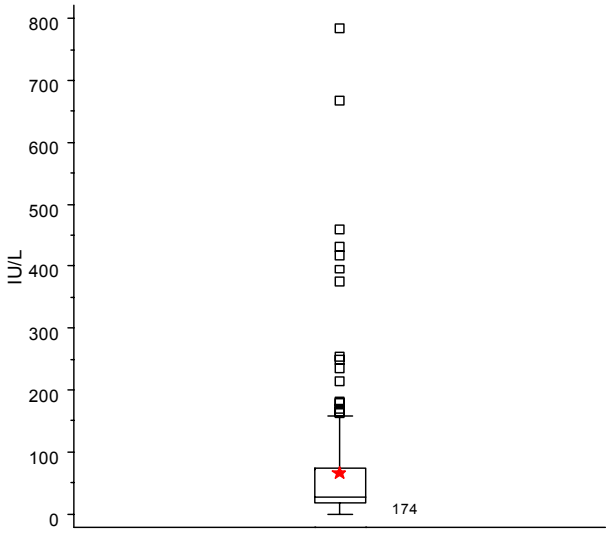
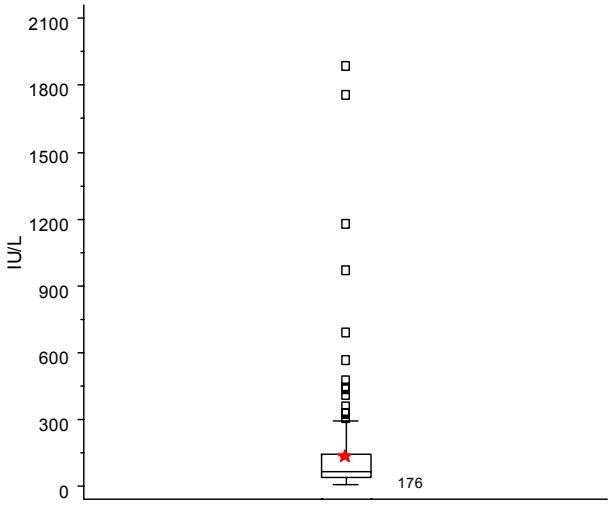


Exhibit 33
Donor Serum Amylase (IU/L)



Data point 3875 IU/L excluded from graph for presentation, verified correct by center.

Exhibit 34
Donor Pre-Insulin Blood Glucose (mg/dL)

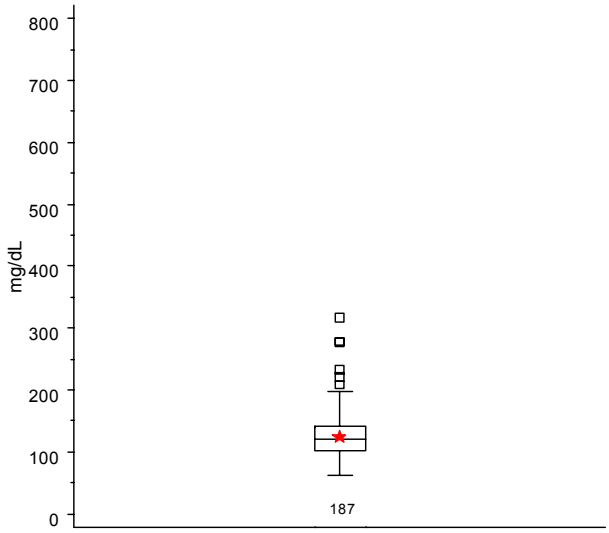
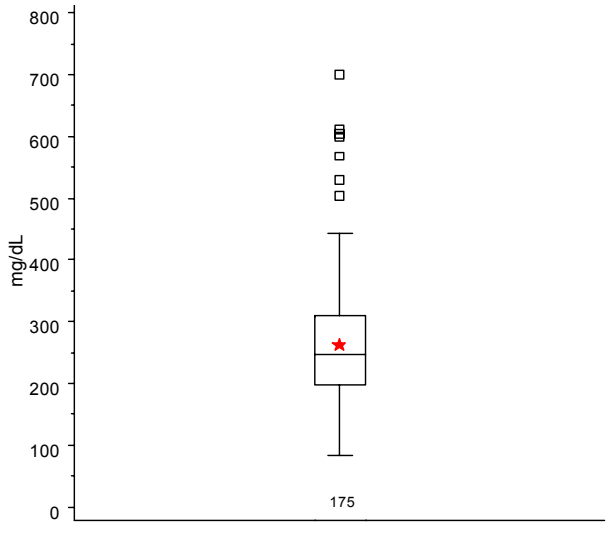


Exhibit 35
Donor Maximum Blood Glucose (mg/dL)



Chapter 2
Pancreas Procurement and Islet Processing

Pancreas Procurement and Islet Processing Summary

Summarized in this chapter are pancreas procurement and islet processing data reported to the Registry. In over 60% of the procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team (Exhibit 36), while 81% of the processing procedures took place at the same institution as the islet transplant center. The median duration of cold ischemia was 7 hours (range 1.5 to 27.0) (Exhibit 37). UW, Two Layer (Top Layer UW, Bottom Layer PFC), and UW Followed by Two Layer methods were used for pancreas preservation (Exhibit 36). In all but one case where Serva was used, Liberase HI was the collagenase type used during islet processing. All of the processing facilities use a density gradient for islet purification, while 45.5% of the islet products processed utilized islet cell culture (Exhibit 36). Of the 215 preparations reported to CITR, five showed a positive aerobic culture (2.5%), three showed a positive anaerobic culture (1.5%) and two showed a positive fungal culture (1.0%).

An islet product characterization summary is located in Exhibit 39. Total islet equivalents in the final product were plotted versus cold ischemic time (Exhibit 40), donor body mass index (Exhibit 41), and donor age (Exhibit 42). Of these three correlations, there is indication that donor body mass index has a statistically significant correlation with the total number of islet equivalents in the final product (Pearson correlation coefficient: $r=0.2983$, $p<0.0001$).

Exhibits 43 through 47 show the results of a series of contrasts for islet cell characteristics and preparation and donor characteristics. The percent viability ($p=0.007$) significantly decreased as the time from cross clamp to pancreas recovery increased (Exhibit 43), but other endpoints were not correlated to this recovery time measure. In Exhibit 44, there was higher viability (95.5%) for pancreata preserved with a Two Layer method only as opposed to pancreata preserved with UW only (91.6%) ($p=0.001$) and DNA content increased with use of a Two Layer method as opposed to using UW (13,741 and 5,601, respectively; $p=0.006$). When examining cold ischemic time subgroups, none of the measures were significant at the $p<0.01$ level and none of the islet characteristics varied significantly with donor age. As expected, there was a significant increase in the mean number of islet equivalents infused as the body mass index of the donor increased ($p=0.002$). Exhibit 48 provides a summary of the total number of islet equivalents/kg for recipients who received only one infusion (N=29), for those who received a total of two infusions (N=42) and for those who received a total of three islet infusions (N=17). Thirty recipients are excluded from this Exhibit, as they did not have islet equivalents reported and/or were missing a reported weight.

Exhibit 36
Islet Processing Summary

	Overall	
	N	%
Total	200	100.0
Pancreas procurement team		
Unrelated to processing/infusion team	121	60.5
Related to processing/infusion team	74	37.0
Missing	5	2.5
Islet processing/testing center		
CITR center, where infusion took place	162	81.0
Another facility not located or affiliated with the transplant center	38	19.0
Missing	-	0.0
Pancreas preservation		
UW	101	50.5
Two layer	88	44.0
UW followed by two layer	11	5.5
Collagenase Type: Liberase HI		
Yes	199	99.5
No	1	0.5
Collagenase Type: Serva		
Yes	1	0.5
No	199	99.5
Islet purification		
None	-	0.0
Density gradient	178	89.0
Missing	22	11.0
Islet pretreatment		
None	105	52.5
Culture	91	45.5
Missing	4	2.0

Exhibit 36 *(continued)*
Islet Processing Summary

	Overall	
	N	%
Gram stain		
Positive	-	0.0
No organism seen	198	99.0
Missing	2	1.0
Aerobic culture		
Positive	5	2.5
No Growth	170	85.0
Not Done	18	9.0
Missing	7	3.5
Anaerobic culture		
Positive	3	1.5
No Growth	172	86.0
Not Done	17	8.5
Missing	8	4.0
Fungal culture		
Positive	2	1.0
No Growth	176	88.0
Not Done	19	9.5
Missing	3	1.5
Mycoplasma		
Positive	-	0.0
Gram negative	158	79.0
Not Done	-	0.0
Missing	42	21.0

Exhibit 37
Cold Ischemia Information

	Overall					
	N	Mean	SD	Median	Min	Max
Duration of cold ischemia (hrs)	188	7.5	3.4	7.0	1.5	27.0

Exhibit 38
Summary of Islet Equivalents and Timing of Count

	Total Islet Equivalents					
	N	Mean	SD	Median	Min	Max
Islet Equivalents (IEQ) measured at:						
Post Digestion	3	839,013	194,663	779,708	680,900	1,056,430
Post Purification (Pre culture/cryo)	147	434,614	153,867	404,135	84,615	973,133
Post culture/cryo	33	396,019	142,702	377,217	234,300	875,583
Timing Missing	8	386,300	97,649	350,145	310,075	608,594

Exhibit 39
Islet Product Characterization

	Overall					
	N	Mean	SD	Median	Min	Max
Total packed cell volume infused (mL)	188	3.7	1.8	3.5	0.7	10.5
Islet count	160	365,382	155,110	351,750	106,333	996,000
Embedded islets (%)	82	14.0	15.0	10.0	0.0	70.0
Islet equivalents/kg	177	5,068	1,779	4,872	1,143	14,551
Islet equivalents planned for infusion	191	470,064	155,047	444,617	190,036	1,056,430
Islet equivalents infused	190	470,632	155,171	442,913	190,036	1,056,430
Beta cells ($x10^6$)	26	222.3	200.0	178.0	4.0	735.0
Beta cells/kg	26	2.3	2.0	1.9	0.0	7.4
Insulin content (µgrams)	60	2,818	2,068	2,348	67	9,999
DNA content (µgrams)	54	8,164	10,375	5,360	83	51,854
Endotoxin units (EU)	176	26.0	56.2	9.4	0.0	540.6*
Endotoxin units/kg (EU/kg)	163	0.3	0.7	0.1	0.0	6.6
Islet purity: Dithizone positive cells (%)	170	65.1	16.3	68.0	30.0	100.0*
Islet potency: Stimulation index	159	2.9	3.6	2.0	0.5	28.8
Islet viability (%)						
Fluorescein Diacetate/Propidium Iodide	134	93.2	5.8	95.0	75.0	100.0*
Trypan Blue	26	95.3	3.0	95.0	90.0	100.0*
Other	15	86.3	6.9	86.0	72.0	96.0

*Values verified by center as correct.

Exhibit 40
Total Islet Equivalents by Cold Ischemic Time

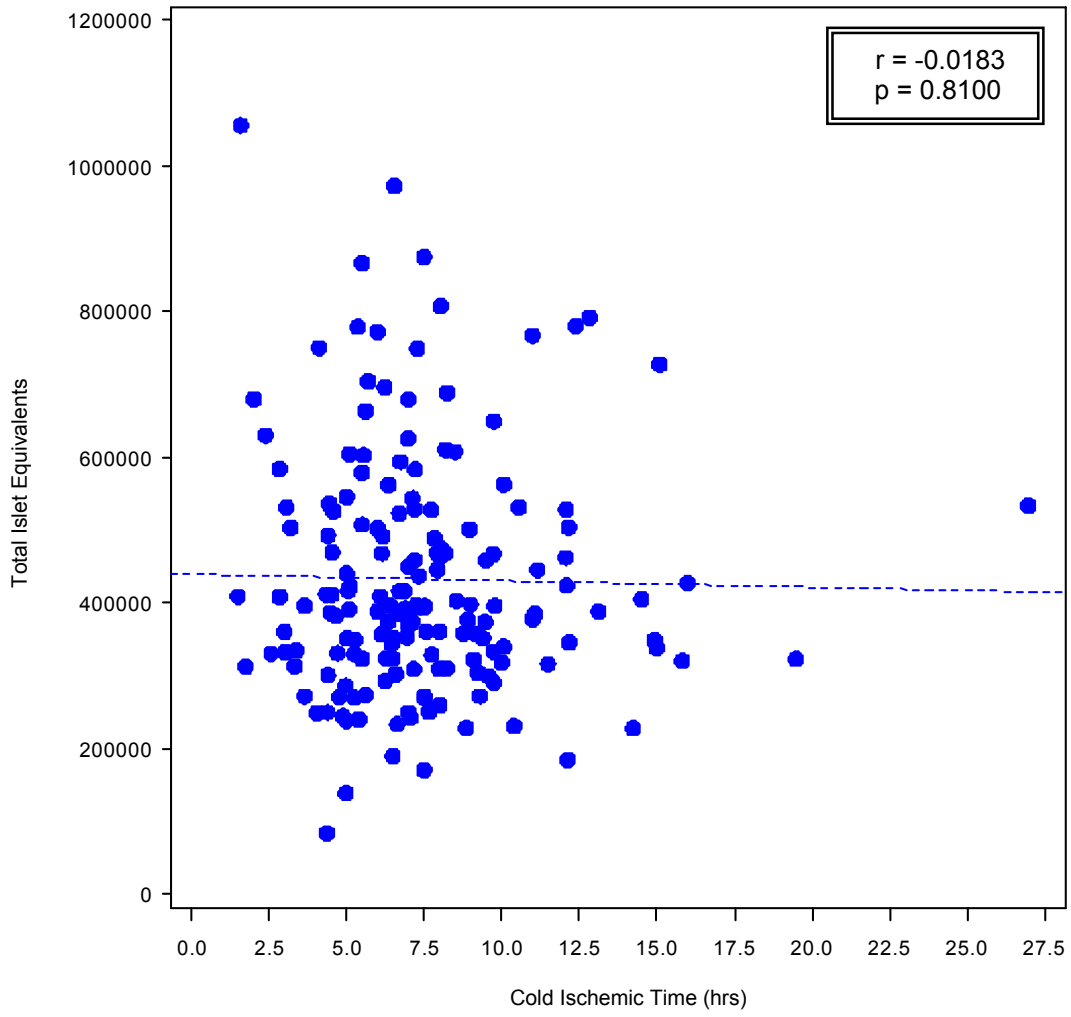


Exhibit 41
Total Islet Equivalents by Donor Body Mass Index

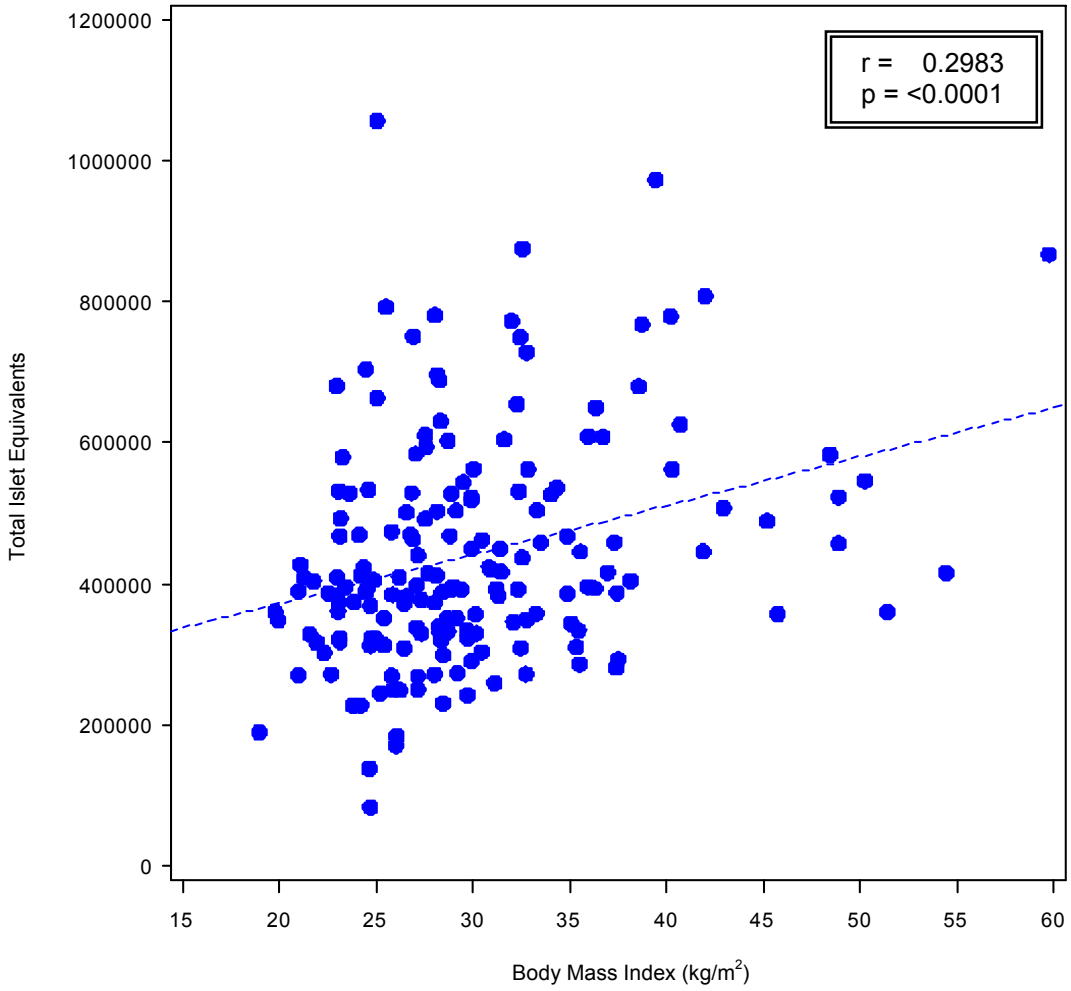


Exhibit 42
Total Islet Equivalents by Donor Age

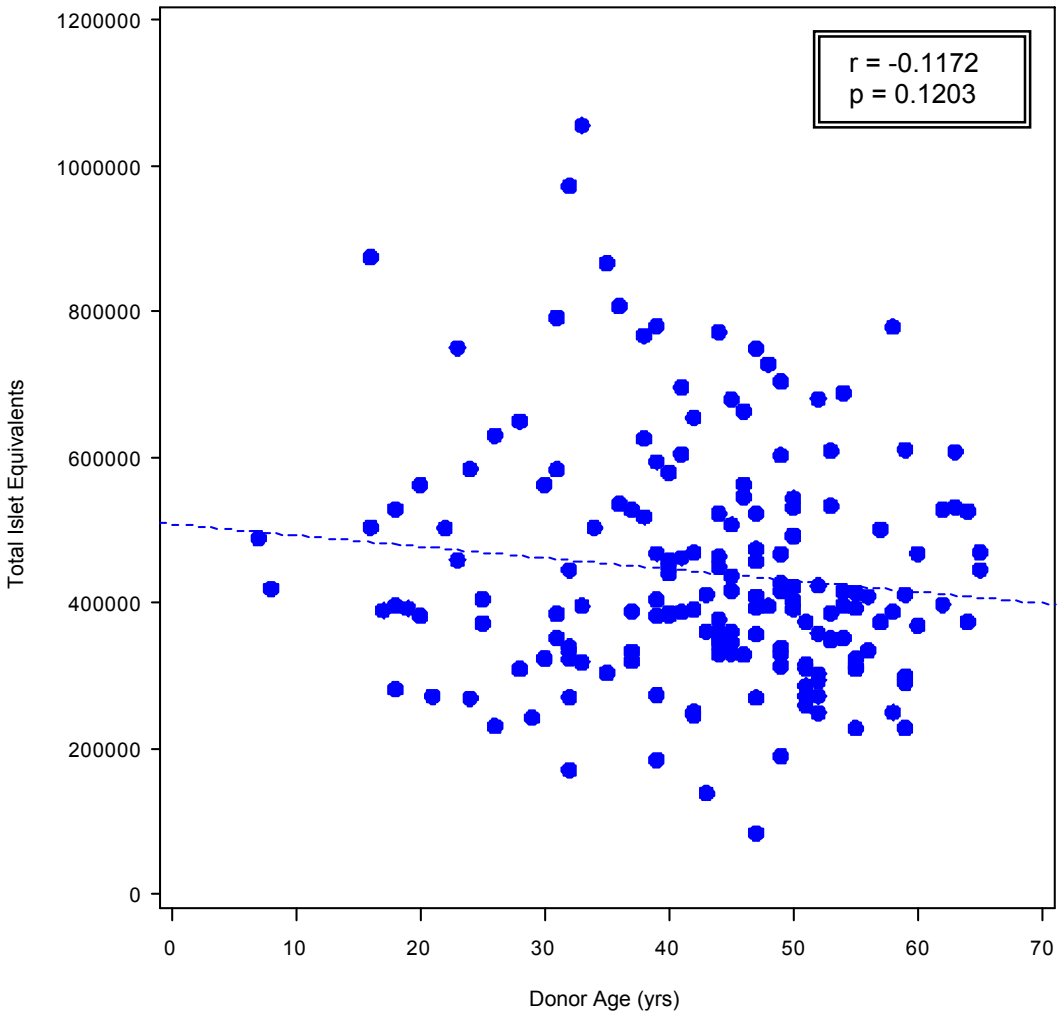


Exhibit 43
Islet Characteristics by Time from Cross Clamp to Pancreas Recovery

	Cross Clamp to Pancreas Recovery Time									p value
	<45 Minutes			45-60 Minutes			>60 Minutes			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Total packed cell volume infused (mL)	93	3.5	1.7	16	3.6	2.2	16	3.8	2.1	0.839
Islet count	72	359,983	188,251	10	356,385	177,0889	17	333,545	121,303	0.859
Embedded islets (%)	43	15.2	16.1	8	12.4	8.3	9	20.9	21.6	0.530
Islet equivalents/kg	89	5,047	1,555	17	4,974	2,721	15	4,529	1,484	0.572
Islet equivalents planned for infusion	94	480,132	163,510	17	450,196	185,345	15	433,303	121,929	0.503
Islet equivalents infused	94	480,923	164,369	16	450,723	191,867	16	428,574	119,304	0.436
Beta cells ($x10^6$)	19	223.7	185.6	2	545.0	268.7	2	114.0	12.7	0.062
Beta cells/kg	19	2.4	2.0	2	4.7	1.1	2	1.3	0.2	0.227
Insulin content (µgrams)	37	2,863	2,266	9	1,860	1,475	4	3,187	1,346	0.399
DNA content (µgrams)	32	8,115	10,011	7	14,044	16,442	4	8,543	11,796	0.461
Endotoxin units (EU)	93	21.3	34.4	15	39.4	65.3	15	21.1	50.8	0.281
Endotoxin units/kg (EU/kg)	85	0.3	0.4	15	0.4	0.5	14	0.3	0.7	0.660
Islet purity: Dithizone positive cells (%)	90	67.3	15.1	16	63.2	17.9	14	57.0	20.1	0.072
Islet viability: Fluorescein Diacetate/Propidium Iodide	73	95.1	5.1	9	90.4	8.4	10	90.5	5.4	0.007
Islet potency: Stimulation index	82	2.9	3.7	16	3.8	6.7	13	2.3	1.5	0.600

Exhibit 44
Islet Characteristics by Pancreas Preservation Method

	Pancreas Preservation Method						p value
	UW Only			Two Layer Only			
	N	Mean	SD	N	Mean	SD	
Total packed cell volume infused (mL)	97	3.7	1.8	88	3.7	1.9	0.901
Islet count	90	331,789	177,289	73	356,131	153,961	0.357
Embedded islets (%)	45	11.5	13.0	39	17.3	16.8	0.076
Islet equivalents/kg	100	5,027	1,898	77	5,122	1,622	0.726
Islet equivalents planned for infusion	100	457,377	148,191	88	484,005	161,922	0.237
Islet equivalents infused	100	459,016	148,273	88	483,540	162,348	0.278
Beta cells ($x10^6$)	15	139.7	115.2	11	334.8	239.3	0.011
Beta cells/kg	15	1.5	1.3	11	3.4	2.3	0.011
Insulin content (µgrams)	44	2,638	2,119	16	3,315	1,894	0.266
DNA content (µgrams)	37	5,601	5,582	17	13,741	15,434	0.006
Endotoxin units (EU)	101	31.3	70.9	77	18.4	24.2	0.130
Endotoxin units/kg (EU/kg)	95	0.4	0.8	68	0.2	0.3	0.151
Islet purity: Dithizone positive cells (%)	99	64.0	18.0	73	66.7	13.6	0.286
Islet viability: Fluorescein Diacetate/Propidium Iodide	68	91.6	6.1	66	95.0	4.9	0.001
Islet potency: Stimulation index	96	3.1	3.9	65	2.8	3.7	0.595

Exhibit 45
Islet Characteristics by Cold Ischemic Time

	Cold Ischemic Time												p value
	<4 Hours			4-8 Hours			9-12 Hours			>12 Hours			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Total packed cell volume infused (mL)	17	3.5	2.2	112	3.8	1.8	25	3.6	1.6	20	3.9	2.3	0.876
Islet count	13	424,943	178,194	99	324,998	178,032	25	331,156	122,944	18	371,516	151,703	0.189
Embedded islets (%)	13	12.9	18.3	43	14.6	12.9	9	6.9	10.0	8	12.8	11.9	0.450
Islet equivalents/kg	16	5,551	2,936	106	5,104	1,639	21	4,665	1,212	18	5,662	1,993	0.282
Islet equivalents planned for infusion	17	460,164	197,092	112	471,762	153,558	26	473,387	162,812	20	490,765	145,188	0.946
Islet equivalents infused	17	458,987	197,346	112	471,489	152,666	26	478,338	165,193	20	490,765	145,188	0.935
Beta cells ($x10^6$)	5	273.2	258.0	20	214.5	193.3	0	-	-	1	123.0	-	0.756
Beta cells/kg	5	3.0	2.8	20	2.2	1.8	0	-	-	1	1.4	-	0.679
Insulin content (µgrams)	10	2,686	2,385	38	2,436	1,591	6	4,661	3,642	5	3,755	1,626	0.067
DNA content (µgrams)	9	12,836	16,572	34	7,838	9,669	6	5,432	4,931	4	4,979	2,016	0.468
Endotoxin units (EU)	15	42.1	65.3	108	21.1	37.7	25	46.3	112.9	16	27.7	28.9	0.180
Endotoxin units/kg (EU/kg)	15	0.5	0.8	97	0.3	0.4	21	0.7	1.5	16	0.3	0.3	0.102
Islet purity: Dithizone positive cells (%)	15	64.9	20.5	104	63.8	15.1	22	68.0	18.4	16	66.6	15.6	0.685
Islet viability: Fluorescein Diacetate/Propidium Iodide	10	95.1	4.4	76	93.7	5.1	19	91.7	5.6	15	91.4	6.8	0.173
Islet potency: Stimulation index	15	5.1	6.9	103	2.8	3.4	20	2.7	2.8	16	2.1	1.2	0.114

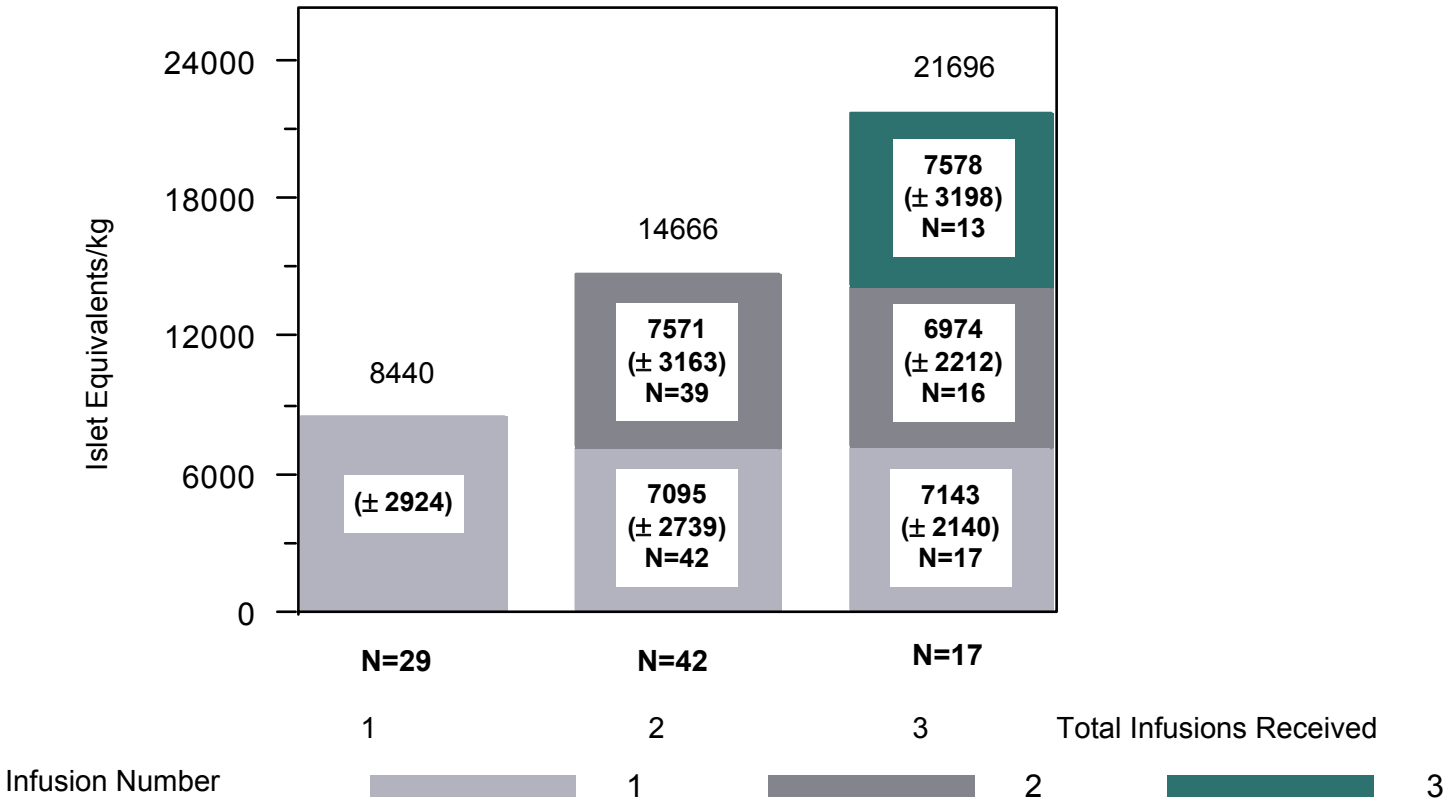
Exhibit 46
Islet Characteristics by Donor Age

	Donor Age												p value
	<41 Years			41-50 Years			51-60 Years			>60 Years			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Total packed cell volume infused (mL)	65	3.8	2.0	61	3.8	1.9	45	3.5	1.7	7	3.9	1.6	0.773
Islet count	47	317,396	175,999	56	354,608	147,919	37	346,046	183,635	8	430,819	174,580	0.319
Embedded islets (%)	26	13.3	15.2	30	13.4	14.6	22	16.8	16.3	3	11.7	10.4	0.827
Islet equivalents/kg	66	5,167	1,966	61	5,119	1,684	42	4,729	1,708	8	5,654	1,048	0.452
Islet equivalents planned for infusion	67	496,944	186,558	61	476,787	139,211	45	429,356	134,142	8	510,377	104,916	0.139
Islet equivalents infused	67	499,725	186,980	62	473,903	138,868	45	432,068	130,742	8	509,903	105,236	0.142
Beta cells ($x10^6$)	10	281.8	280.9	10	207.0	141.1	6	148.5	89.5	0	-	-	0.432
Beta cells/kg	10	2.8	2.6	10	2.4	1.6	6	1.5	0.8	0	-	-	0.458
Insulin content (µgrams)	19	2,751	2,440	22	2,991	1,862	16	2,242	1,356	3	5,051	3,443	0.178
DNA content (µgrams)	19	11,557	15,510	19	6,147	6,106	13	6,468	4,796	3	6,790	6,661	0.377
Endotoxin units (EU)	63	25.2	45.1	54	37.0	82.5	39	21.9	34.5	7	18.5	27.8	0.561
Endotoxin units/kg (EU/kg)	63	0.3	0.4	54	0.4	1.0	39	0.2	0.3	7	0.2	0.3	0.396
Islet purity: Dithizone positive cells (%)	61	67.9	16.9	53	63.8	17.1	37	60.2	16.0	6	67.5	16.4	0.156
Islet viability: Fluorescein Diacetate/Propidium Iodide	54	93.7	5.6	46	93.8	6.2	28	91.3	5.4	4	96.0	1.6	0.184
Islet potency: Stimulation index	59	3.5	5.3	46	2.6	1.8	37	1.9	0.9	5	1.8	0.8	0.173

Exhibit 47
Islet Characteristics by Donor Body Mass Index

	Body Mass Index												p value
	<26			26-30			31-35			>35			
	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Total packed cell volume infused (mL)	55	3.8	2.2	65	3.2	1.7	34	4.1	1.8	24	4.3	1.4	0.036
Islet count	45	314,619	154,379	55	323,223	134,238	27	382,650	215,186	21	417,109	189,055	0.053
Embedded islets (%)	21	15.1	15.7	32	12.6	13.6	18	15.1	16.7	10	15.9	16.1	0.887
Islet equivalents/kg	53	5,691	2,175	63	4,945	1,536	34	4,817	1,625	27	4,452	1,294	0.012
Islet equivalents planned for infusion	56	457,424	159,328	65	442,094	131,500	36	504,880	165,989	24	552,326	178,679	0.013
Islet equivalents infused	56	459,033	156,409	66	440,188	130,992	35	506,622	167,333	25	555,834	175,794	0.002
Beta cells ($x10^6$)	3	93.7	83.4	13	239.0	209.8	5	146.6	128.5	5	331.6	250.2	0.329
Beta cells/kg	3	1.3	1.2	13	2.7	2.3	5	1.6	1.4	5	2.8	1.9	0.541
Insulin content (µgrams)	15	2,855	1,674	27	2,582	1,711	12	2,653	2,536	6	4,122	3,289	0.429
DNA content (µgrams)	12	8,497	7,816	24	7,970	10,931	12	5,691	6,192	6	13,221	18,076	0.558
Endotoxin units (EU)	49	24.6	37.4	58	31.1	77.9	32	22.0	29.3	24	35.8	66.0	0.775
Endotoxin units/kg (EU/kg)	49	0.3	0.5	58	0.4	0.9	32	0.2	0.3	24	0.3	0.6	0.843
Islet purity: Dithizone positive cells (%)	47	63.7	15.9	55	68.5	17.0	32	62.7	17.0	23	60.5	17.7	0.187
Islet viability: Fluorescein Diacetate/Propidium Iodide	41	92.9	5.6	47	93.5	4.4	29	93.7	6.8	15	93.1	7.9	0.943
Islet potency: Stimulation index	47	2.9	4.2	53	2.7	3.6	28	3.3	3.7	19	1.9	0.9	0.655

Exhibit 48
Mean Number of Islet Equivalents/kg (± SD) by Total Number of Infusions Received
(Recipients with a Total of 1 Infusion, 2 Infusions and 3 Infusions)*



*30 Recipients missing information on islet equivalents and/or weight.

Chapter 3
Immunosuppressive and Other Medications

Immunosuppressive and Other Medications Summary

Immunosuppressive, anti-hypertensive, and lipid lowering medications, and a summary of the administration of adjunctive therapies used by the islet transplant recipients are included in this chapter of the report. The majority of the islet alone recipients at the time of first infusion were on a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen (61.9%). A number of other immunosuppression regimens have been used by the islet transplant centers and are listed in Exhibit 49. Dosing for the immunosuppressive medications at induction (dosing by mg/day and the mean total dose) are located in Exhibits 50 and 51. A summary of T-cell antibodies used for induction at the first infusion is included in Exhibit 52. In over 82% of the first infusions, Daclizumab alone was used. Maintenance therapy regimens and dosing information are located in Exhibits 53 and 54. Sirolimus and Tacrolimus trough levels at Day 30 for each infusion (1, 2, and 3), as well as trough levels at Month 6 and Year 1 post last infusion are presented as boxplots in Exhibits 55 and 56. There is one extreme Sirolimus trough level at Day 30 for the third infusion (61.8 ng/mL) that is explained by the center as the participant taking Sirolimus shortly before having labs drawn.

Prior to the first infusion, 32% of the recipients were on at least one anti-hypertensive medication (Exhibits 57 and 58) and 16% were on a lipid lowering medication (Exhibits 59 and 60). By year 1 post last infusion, these rates increased to 46% and 54%, respectively. For adjunctive therapies, at the time of their first infusion (Exhibit 61), over 91% of recipients used an antibiotic, 81% used Heparin (including Heparin used during the infusion), 81% used vitamin supplements, and 80% used antivirals.

Exhibit 49
Immunosuppression Regimen at Time of First Infusion

	Overall	
	N	%
Total	118	100.0
Sirolimus + Tacrolimus + Daclizumab	73	61.9
Sirolimus + Tacrolimus + Daclizumab + Infliximab	12	10.2
Sirolimus + Tacrolimus + Basiliximab + Etanercept	5	4.2
Sirolimus + Tacrolimus + MMF + Methylprednisolone + Anti-thymocyte Globulin + Daclizumab + Infliximab + Etanercept	5	4.2
Sirolimus + Tacrolimus + 15-deoxyspergualin + Daclizumab	5	4.2
Sirolimus + Tacrolimus + hOKT3γ-1(Ala-Ala)	3	2.5
Sirolimus + Tacrolimus + MMF + Daclizumab	2	1.7
Sirolimus + Tacrolimus + MMF + Methylprednisolone + Anti-thymocyte Globulin + Daclizumab + Etanercept	2	1.7
Neoral Cyclosporine + Methylprednisolone + Everolimus + Anti-thymocyte Globulin + Infliximab + Etanercept	2	1.7
Sirolimus + MMF + Anti-thymocyte Globulin + Daclizumab	1	0.8
Neoral Cyclosporine + Methylprednisolone + Anti-thymocyte Globulin + Etanercept	1	0.8
Missing Information on Immunosuppression	7	5.9

Exhibit 50
Immunosuppression Dosing (mg/day) at Time of Infusion by Infusion Sequence

	Infusion Sequence								
	1			2			3		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	104	11.5	3.4	67	8.2	3.3	23	9.1	3.3
Tacrolimus (mg/day)	102	2.2	1.3	69	4.1	2.1	23	4.5	2.1
MMF (mg/day)	10	1300.0	752.8	6	1166.7	683.1	7	1000.0	707.1
Methylprednisolone (mg/day)	10	68.0	23.1	0	-	-	0	-	-
Neoral Cyclosporine (mg/day)	3	250.0	86.6	0	-	-	0	-	-
15-deoxyspergualin (mg/day)	5	117.6	9.5	3	114.7	15.0	0	-	-
Everolimus (mg/day)	2	3.0	0.0	0	-	-	0	-	-

Exhibit 51
Induction Therapy (mg) at Time of Infusion by Infusion Sequence

	Infusion Sequence								
	1			2			3		
	N	Mean Total Dose	SD	N	Mean Total Dose	SD	N	Mean Total Dose	SD
Anti-thymocyte Globulin (mg)	11	374.1	37.2	0	-	-	0	-	-
Basiliximab (mg)	5	32.0	11.0	0	-	-	0	-	-
Daclizumab (mg)	92	284.4	108.7	65	289.8	92.6	22	303.9	100.3
hOKT3γ-1 (Ala-Ala) (mg)	3	48.7	5.5	0	-	-	0	-	-
Infliximab (mg)	12	563.9	225.2	0	-	-	1	510.0	-
Etanercept (mg)	14	119.6	31.3	3	191.7	94.6	2	87.5	53.0

Exhibit 52
Percentage (%) of First Infusions Using T Cell Antibodies for Induction Therapy

	N	%
Total	111	100.0
Anti-thymocyte Globulin Alone	3	2.7
Basiliximab Alone	5	4.5
Daclizumab Alone	92	82.9
hOKT3γ-1 (Ala-Ala) Alone	3	2.7
Anti-thymocyte Globulin and Daclizumab	8	7.2

Exhibit 53
Immunosuppression Therapy Use Post Last Infusion

	Follow-Up			
	1-6 Months		6-12 Months	
	N	%	N	%
Total	112	100.0	102	100.0
Sirolimus + Tacrolimus	68	60.7	49	48.0
Sirolimus + Tacrolimus + MMF	14	12.5	13	12.7
Sirolimus + Tacrolimus + Daclizumab	12	10.7	11	10.8
Tacrolimus + MMF	6	5.4	5	4.9
Sirolimus + MMF	3	2.7	3	2.9
Neoral Cyclosporine + Everolimus	2	1.8	1	1.0
Tacrolimus	1	0.9	-	0.0
Sirolimus + MMF + Anti-thymocyte globulin + Daclizumab	1	0.9	-	0.0
Islet Graft Failure	2	1.8	5	4.9
Missing Information on Immunosuppression	3	2.7	15	14.7

Exhibit 54
Immunosuppression Dosing (mg/day) Post Last Infusion

	Follow-Up								
	Day 30			Month 6			Year 1		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	95	8.3	4.6	95	7.5	3.4	75	6.9	3.2
Tacrolimus (mg/day)	94	3.7	1.7	97	3.9	1.6	77	3.7	1.6
Neoral Cyclosporine (mg/day)	3	175.0	152.1	2	225.0	35.4	1	100.0	-
MMF (mg/day)	17	941.2	747.5	24	1291.7	610.9	20	1550.0	535.6
Methylprednisolone (mg/day)	9	0.0	0.0	0	-	-	0	-	-
15-deoxyspergualin (mg/day)	5	0.0	0.0	0	-	-	0	-	-
Everolimus (mg/day)	2	4.0	1.4	2	3.3	2.5	1	2.5	-
Daclizumab (mg/day)	0	-	-	13	86.5	65.8	10	70.5	13.9
Anti-thymocyte Globulin (mg/day)	0	-	-	1	437.0	-	0	-	-

Exhibit 55
Sirolimus Trough Level (ng/mL) Post Last Infusion

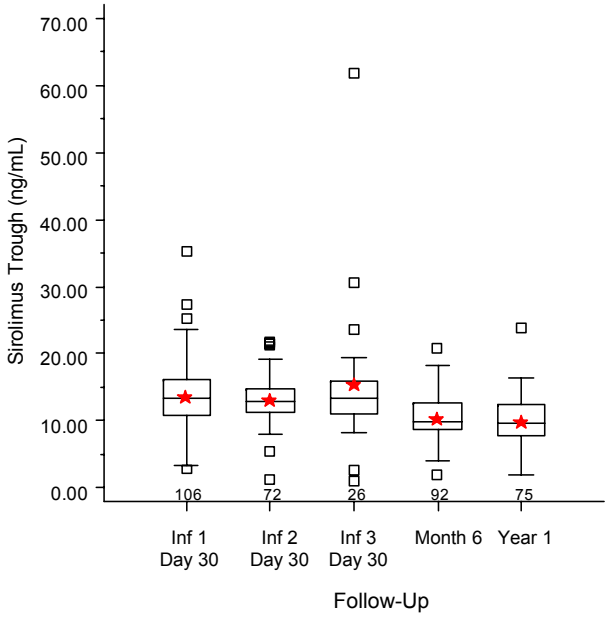


Exhibit 56
Tacrolimus Trough Level (ng/mL) Post Last Infusion

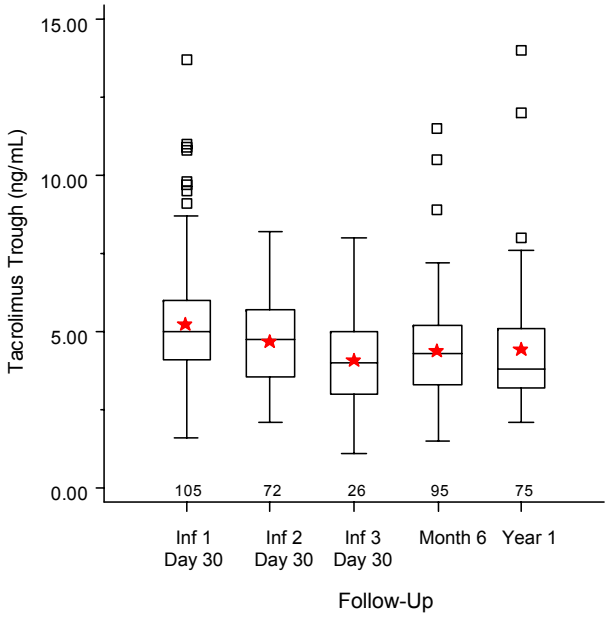


Exhibit 57
Use of Anti-Hypertensive Medications at Pre Infusion and Post Last Infusion

	Follow-Up					
	Pre Infusion 1		Month 6		Year 1	
	N	%	N	%	N	%
Total	118	100.0	112	100.0	102	100.0
ACE Inhibitors	31	26.3	31	27.7	28	27.5
Angiotensin II Receptor Blockers	4	3.4	7	6.3	9	8.8
Beta Adrenergic Blockers	1	0.8	2	1.8	6	5.9
Calcium Channel Blockers	3	2.5	3	2.7	4	3.9
Diuretics	4	3.4	9	8.0	14	13.7
Missing Information on Medications	5	4.2	7	6.3	15	14.7

Exhibit 58
Percent of Participants Using Anti-Hypertensive Medications at Pre Infusion and Post Last Infusion

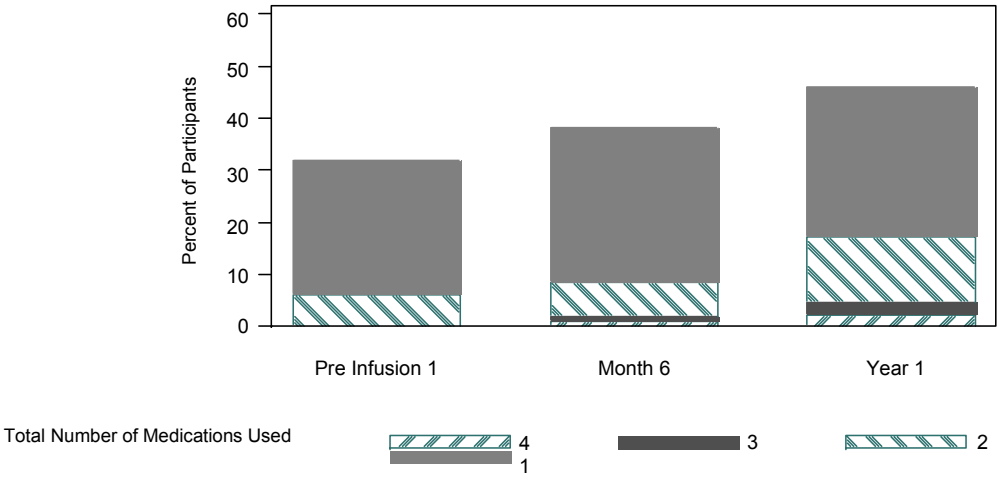


Exhibit 59
Use of Lipid Lowering Medications Pre Infusion and Post Last Infusion

	Follow-Up					
	Pre Infusion 1		Month 6		Year 1	
	N	%	N	%	N	%
Total	118	100.0	112	100.0	102	100.0
Bile Acid Sequestrants	-	0.0	1	0.9	1	1.0
Cholesterol Absorption Inhibitors	-	0.0	-	0.0	2	2.0
HMG CoA Reductase Inhibitors	18	15.3	43	38.4	45	44.1
Nicotinic Acid	1	0.8	3	2.7	-	0.0
Missing Information on Medications	6	5.1	7	6.3	15	14.7

Exhibit 60
Percent of Participants Using Lipid Lowering Medications at Pre Infusion and Post Last Infusion

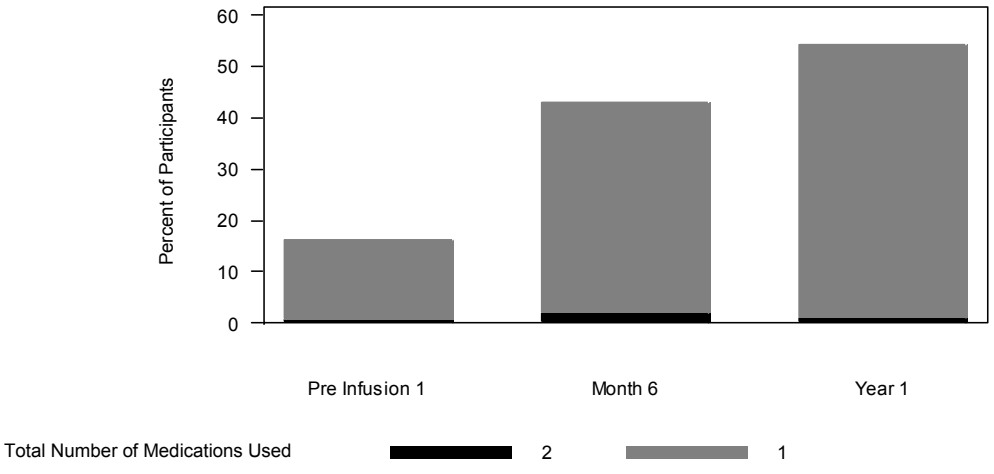


Exhibit 61
Adjunctive Therapy at Time of First Infusion

	Overall	
	N	%
Total	118	100.0
Antibiotics	108	91.5
Anticoagulants	60	50.8
Antifungals	42	35.6
Antivirals	94	79.7
Aspirin	49	41.5
Heparin	95	80.5
Iron Supplements	12	10.2
Metformin	4	3.4
Nicotinamide	17	14.4
Pentamidine	2	1.7
Pentoxifylline	44	37.3
Pioglitazone	6	5.1
Protonix® (pantoprazole)	10	8.5
Vitamins	95	80.5
Zofran® (ondansetron hydrochloride)	15	12.7
Missing Information on Therapies	2	1.7

Chapter 4
Graft Function

Graft Function Summary

Chapter 4 includes information on the analysis of graft function for the 118 islet transplant alone recipients reported to the Registry.

Insulin Independence:

Insulin independence status and insulin dosing is evaluated at the time of CITR follow-up schedules post last infusion. Insulin independence (yes or no) is also collected at month 6 and at year 1 post the first infusion procedure. This chapter evaluates insulin independence both post first infusion and post last infusion in several different ways including:

- Status at the recipient's last follow-up visit (Exhibit 62),
- By the total number of islet infusions a recipient received (Exhibit 63),
- By follow-up visit post last infusion (Exhibit 64),
- To the time of a recipient's first occurrence of insulin use post their last infusion (Exhibit 65),
- To the time of a recipient's first occurrence of insulin use post their last infusion by the total number of islet infusions they received (Exhibit 66),
- By an insulin independence rate each day post last infusion (Exhibit 67),
- By following a cohort of recipients over time post their first infusion and tracking changes in their Month 6 insulin independence status at Year 1 (Exhibit 68),
- By following a cohort of recipients over time post their last infusion and tracking changes in their Month 6 insulin independence status at Year 1 (Exhibit 69),
- By calculating the percent reduction from baseline in their mean total daily units of insulin required post their last infusion, for recipients still requiring insulin (Exhibit 70),
- By summarizing the average daily insulin units required post last infusion, for recipients still requiring insulin (Exhibit 71),
- Summarizing and identifying any differences in insulin independence rates by the recipient's age, duration of diabetes, weight, body mass index, and average daily insulin use (Exhibits 72-77), and
- By examining Sirolimus and Tacrolimus trough levels at month 6 and year 1 post last infusion by insulin status (Exhibits 79 and 80).

One hundred and twelve recipients have completed at least one follow-up visit post their last infusion. Of these 112 recipients, 55 (49.1%) are insulin independent while 39 (34.8%) are insulin dependent. A total of 15 participants have experienced total islet graft failure as reported on their last follow-up form (Exhibit 62). At month 6 post last infusion, 63.3% of the recipients receiving one islet infusion were insulin independent, 75.0% receiving two islet infusions were insulin independent and 54.2% were insulin independent with three islet infusions (Exhibit 63). Rates for all three groups decline at year 1, but for recipients with one and two infusions, rates

remain over 50% (57.1%, 63.4% and 47.4%, respectively). Exhibit 64 contains information reported on the CITR follow-up assessment form. From Exhibit 64, at six months post the recipient's last infusion, 67.0% were insulin independent and at twelve months this drops to 58.0%. By six months, 2.8% of the recipients experienced a total islet graft failure. This percentage increases to a total of 9.1% of the recipients at the one-year period (includes new and previous reports of islet graft failure).

A cohort of recipients was followed for insulin status at both post first infusion in Exhibit 68 and by post last infusion in Exhibit 69. At month 6 post first infusion, 58% of the cohort (61/105) were insulin independent, 37% were insulin dependent, and 5% experienced an islet graft failure. Of the 61 recipients that were insulin independent at month 6, 75.4% remained insulin independent at year 1 post first infusion. For those insulin dependent at month 6, 23.1% (9/39) achieved insulin independence at year 1.

Following a cohort post last infusion (Exhibit 69), at month 6, 67.3% of the cohort (70/104) were insulin independent, 26.9% were insulin dependent, and 5.8% experienced an islet graft failure. Of the 70 recipients that were insulin independent at month 6, 72.9% remained insulin independent at year 1 post last infusion. For those insulin dependent at month 6, none of the 28 recipients achieved insulin independence at year 1 post last infusion.

From Exhibits 72-77, a statistically significant difference in insulin independence rates occurred only for the recipient's age categories ($p=0.0383$). For recipients <35 years of age their insulin independence rate was 40.9%, 35-50 years was 71.4% and for >50 years it was 70.0%.

Exhibits 79 and 80 summarize Sirolimus and Tacrolimus trough levels at month 6 and year 1 post the recipient's last islet infusion procedure by their insulin status. No large differences are seen between the insulin independent and insulin dependent groups.

Time to Initiation of Insulin Therapy:

Exhibits 65 and 66 displays the Kaplan-Meier (KM) estimates for time to initiation of insulin. Although KM estimates are usually used for well-defined endpoints and non-recurrent events, it was used here to estimate the percentage of insulin-free recipients over time. Specifically, recipients could receive ≥14 days of insulin therapy, but be insulin independent at their month six visit post last infusion. In order to construct this estimate, it is assumed that at the recipient's last infusion day they did not require insulin (Day 0). Recipients were identified as having an event when they initiated insulin for a period of 14 or more days or if they reported insulin use at the CITR anniversary visits, but failed to complete the insulin administration report. Exhibit 64 displays the survival distribution for this endpoint and it decreased every time an individual began with ≥14 days of insulin use. At one-year post last infusion, 37.8% of recipients were insulin free. When comparing KM curves in Exhibit 66, there is a statistically significant difference between estimates for recipients of one infusion, two infusions and three infusions ($\chi^2=15.7$, $p=0.0004$).

Exhibit 67 examines the time to initiation of insulin therapy differently. This exhibit summarizes the insulin independence rates on each and every day post the recipient's last infusion and plots this rate. For example, in the 84 recipients at day 350 post their last infusion, 71.4% are insulin independent on that day.

Changes in Insulin Dosing:

Exhibits 70 and 71 show the changes in insulin dosing at 6 and 12 months. For participants remaining on insulin at 6 months and at 12 months post last infusion, calculations for mean

reduction in daily insulin units from baseline at these two time points were conducted (Exhibit 70). Only participants with a CITR insulin administration form were included in the analyses. For participants on insulin at 6 months, there was a 56.5% mean reduction in their daily insulin units as compared to their baseline daily insulin units. This ranged from a minimum mean reduction of 4.8% to 83.3%. Average daily insulin units taken for participants remaining on insulin at 6 months were 15.2 units (Exhibit 71). At 12 months, there was a mean reduction of 69.0% with a minimum of 16.7% and a maximum of 92.4%. Average daily insulin units taken for participants remaining on insulin at 12 months were 12.3 units.

Severe Hypoglycemic Events:

A striking decrease in the number of severe hypoglycemic events occured subsequent to the first infusion (Exhibit 78). Over 82% of participants experienced one or more severe hypoglycemic events prior to their first infusion. This decreased to 2.5% up to 30 days post their first infusion and then to 0% between month 1 and 6. Only 2 recipients (2%) experienced one or more hypoglycemic events between months 6 and 12 post their first infusion. Both of these recipients were on insulin replacement and one experienced a complete islet graft failure.

Metabolic Measures:

Presented in this chapter are the recipient's fasting plasma glucose, HbA_{1c}, and basal plasma C-peptide values at pre infusion 1 (all recipients), pre infusion 2 (for those with a total of two infusions), pre infusion 3 (for those with a total of three infusions), month 6 and year 1 post last infusion (Exhibits 81-92).

Overall, as expected, fasting plasma glucose values and HbA_{1c} decrease over time, while basal plasma C-peptide values increase. This trend is seen within each of the cohort group of recipients (one infusion, two infusions and three infusions). Note that patterns differ when recipients are categorized by insulin requirement status. For example, fasting plasma glucose values decrease over time for insulin independent recipients, but for insulin dependent recipients, pre infusion and post infusion values were similar. Hemoglobin A_{1c} values decrease over time for both insulin independent and insulin dependent recipients. A greater increase between C-peptide values for insulin independent recipients pre and post infusion was seen, than for the difference between these same time points from insulin dependent recipients. A complete set of laboratory values may be seen (by infusion sequence) in Exhibit 99. Additional metabolic test summaries are located in Exhibits 100-102. The choice of which metabolic tests to perform varies from center to center.

Islet Graft Dysfunction:

Exhibit 103 describes the number of islet graft dysfunction episodes reported to the Registry. In addition, there have been no reports of participant death for the Registry for this time period. A complete listing of islet graft dysfunctions reported is listed in Exhibit 104. Within this table information on the total number of islet equivalents/kg infused as well as the number of days from the last infusion procedure to the date of the islet graft dysfunction are presented. The shortest time from infusion to dysfunction was 30 days following the recipient's first infusion. A total of 19 islet graft failures have been reported, with 8 reported after the first infusion, 8 reported after the second infusion and 3 reported after the third infusion. A laboratory summary for the recipients experiencing an islet graft failure is located in Exhibit 105.

Diabetes Related Secondary Complications:

At the end of the chapter is a review of the diabetes related secondary complications experienced by the recipients prior to their first infusion and then at month 6 and year 1 post their last infusion (Exhibit 106). Ocular complications are summarized in Exhibit 107.

Exhibit 62
Insulin Status (%) at Recipient's Last Follow-Up Post Last Infusion

	N	%
Total	112	100.0
Insulin Use		
Insulin Independent	55	49.1
Insulin Dependent	39	34.8
Complete Islet Graft Failure	15	13.4
Missing	3	2.7

Exhibit 63
Insulin Independence Rates (%) by Total Number of Infusions and Follow-Up Post Last Infusion

	Insulin Independent			
	Month 6		Year 1	
	N	%	N	%
Total	71	67.0	51	58.0
Total Infusions				
1	19	63.3	16	57.1
2	39	75.0	26	63.4
3	13	54.2	9	47.4

Exhibit 64
Insulin Status (%) by Follow-Up Visit
Post Last Infusion

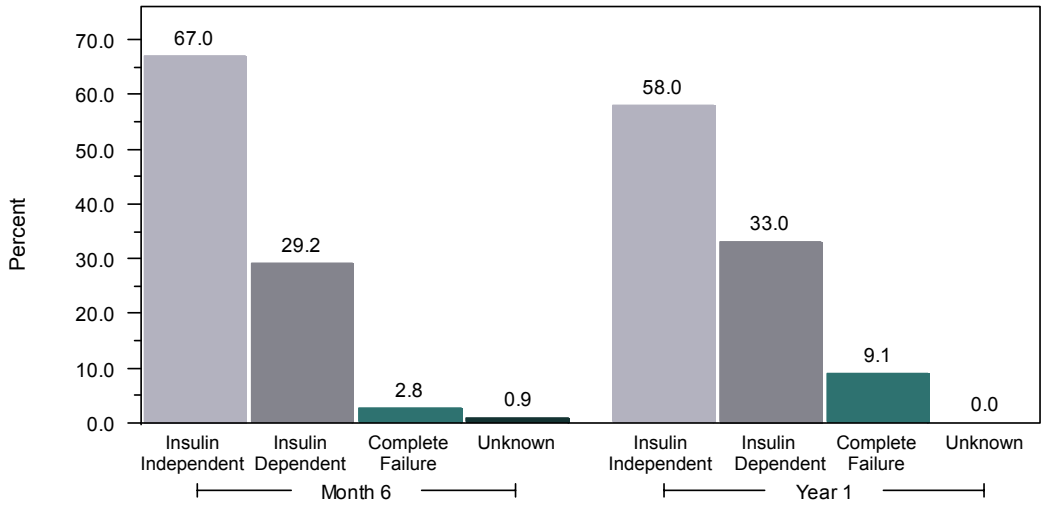
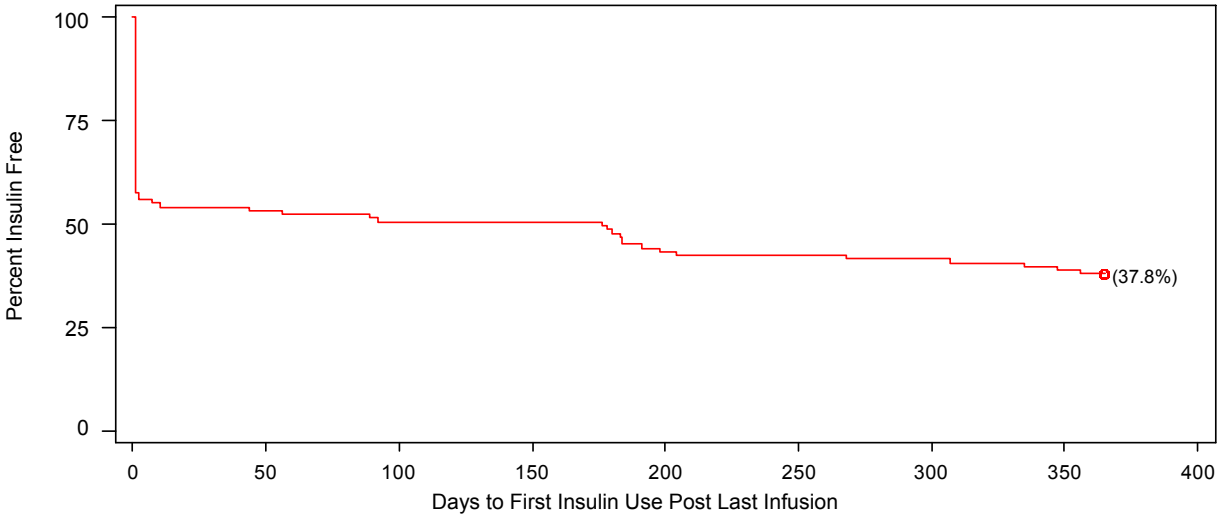
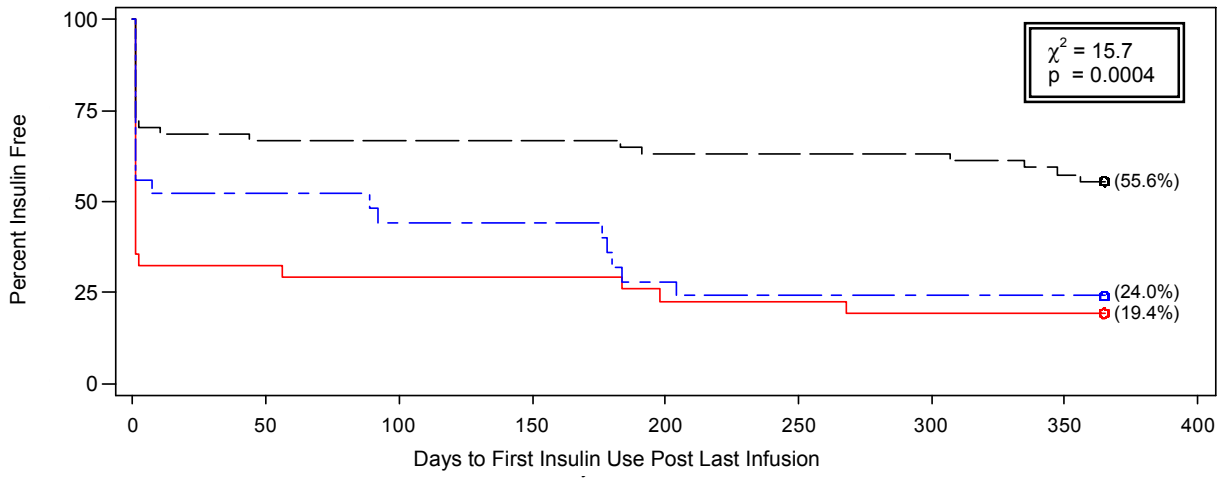


Exhibit 65
Time to First Occurrence of Insulin Use Post Last Infusion



N	111	59	56	56	48	47	46	43

Exhibit 66
Time to First Occurrence of Insulin Use Post Last Infusion by Total Number of Infusions



N_1	31	10	9	9	7	7	6	6
N_2	54	36	36	36	34	34	34	31
N_3	25	13	11	11	7	6	6	6

Exhibit 67
Percent of Insulin Independent Participants Post Last Infusion

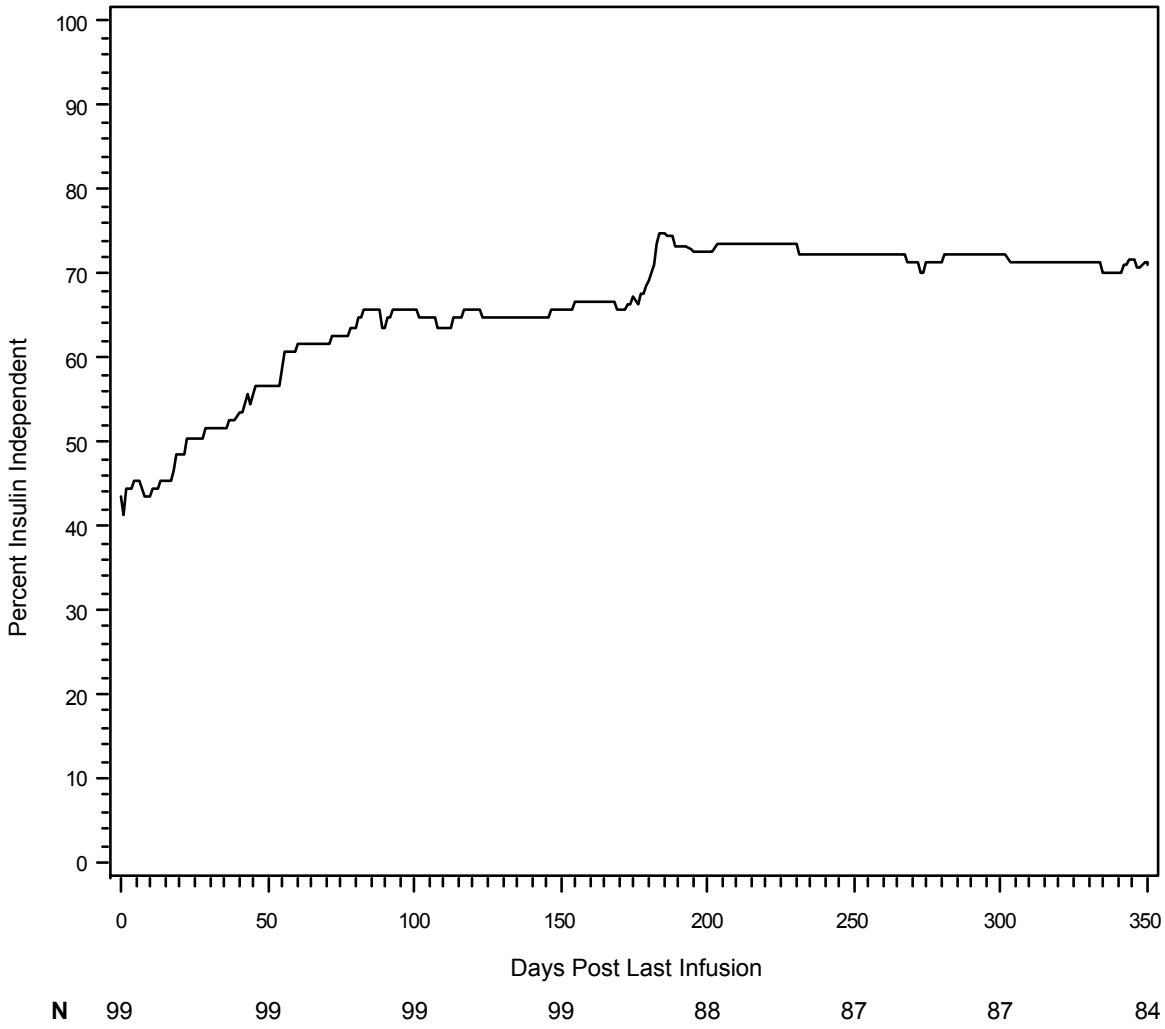


Exhibit 68
Cohort of Recipients Followed by Insulin Status
Post First Infusion

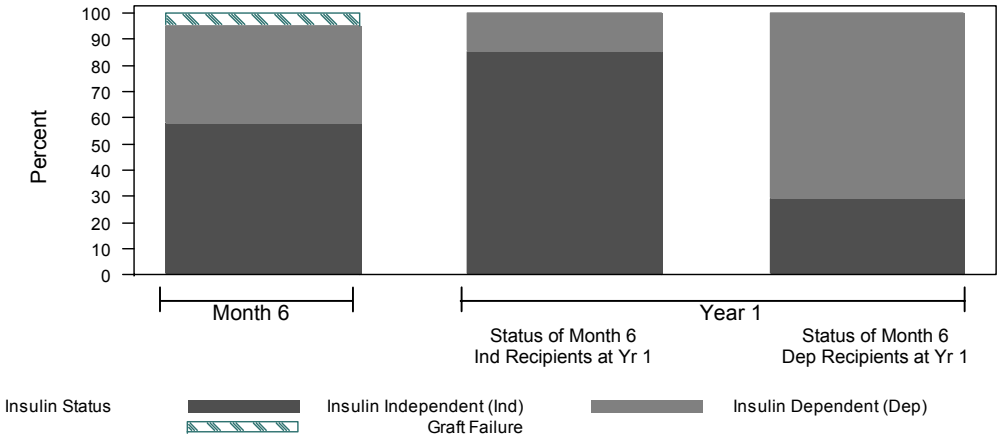


Exhibit 69
Cohort of Recipients Followed by Insulin Status
Post Last Infusion

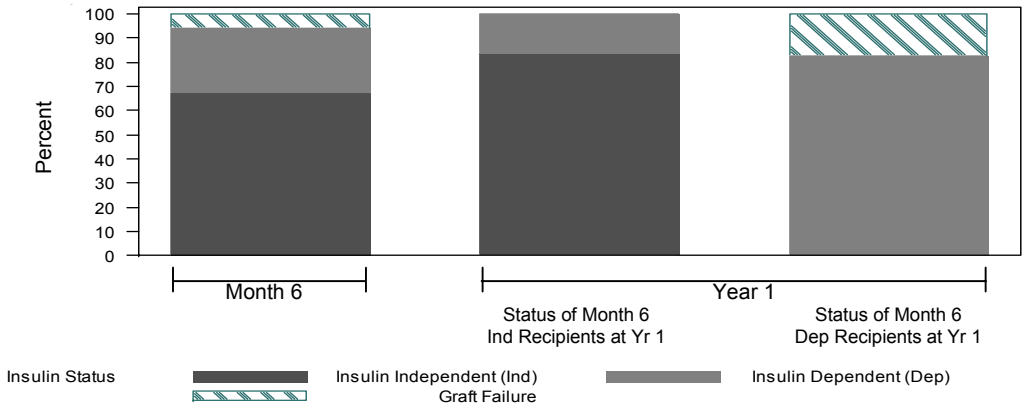


Exhibit 70
Reduction of Insulin (%) Pre Infusion to Follow-Up Post Last Infusion
Participants on Insulin

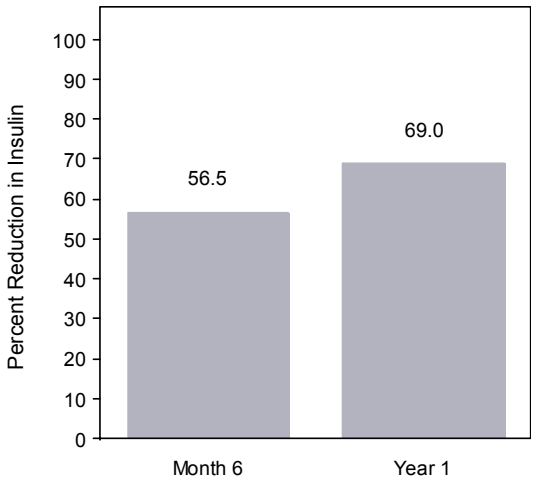


Exhibit 71
Average Daily Insulin Use (Units) at Follow-Up Post Last Infusion
Participants on Insulin

	Average Daily Insulin Use (Units)					
	N	Mean	SD	Median	Min	Max
Follow-Up						
Month 6	16	15.2	7.6	14.4	4.5	32.0
Year 1	14	12.3	9.5	7.5	3.7	28.0

Exhibit 72
Insulin Independence (%) Month 6 Post First Infusion
by Participant's Age (yrs)

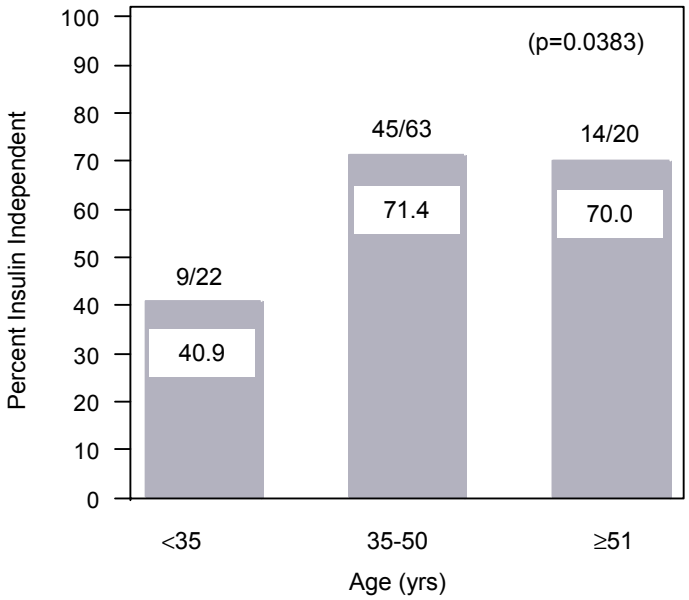


Exhibit 73
Insulin Independence (%) Month 6 Post First Infusion
by Participant's Duration of Diabetes (yrs)

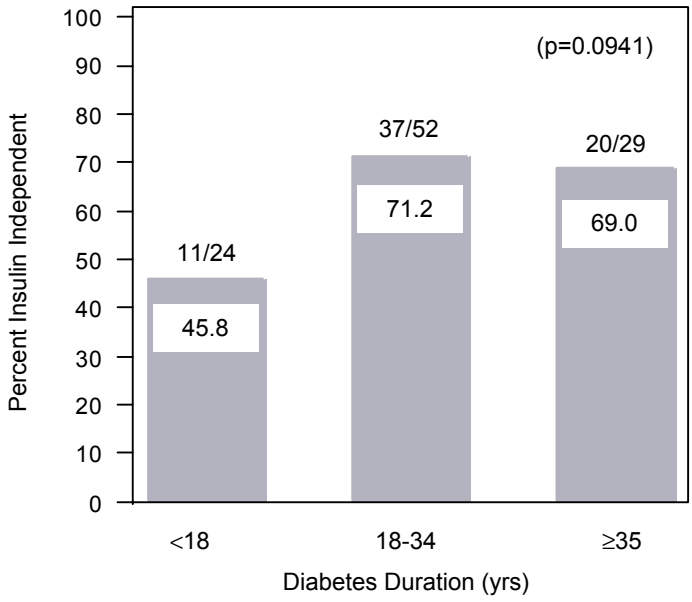


Exhibit 74
Insulin Independence (%) Month 6 Post First Infusion
by Participant's Weight (kg)

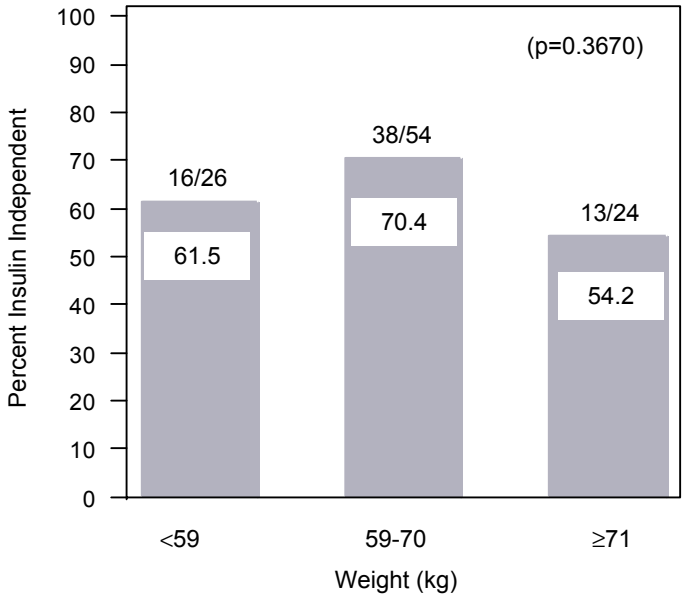


Exhibit 75
Insulin Independence (%) Month 6 Post First Infusion
by Participant's Body Mass Index (kg/m^2)

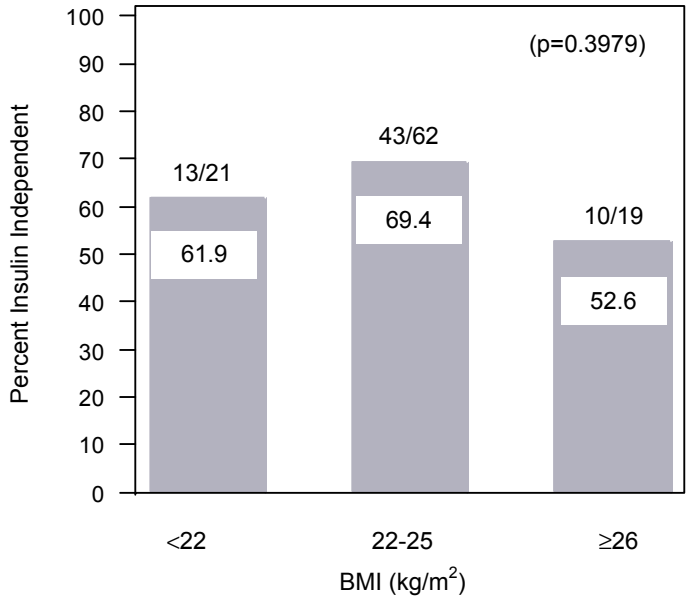


Exhibit 76
Insulin Independence (%) Month 6 Post First Infusion
by Participant's Average Daily Insulin Use (Units/Day)

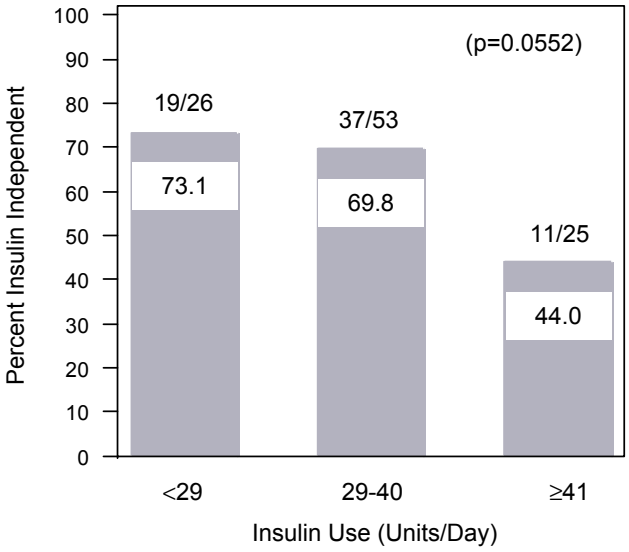


Exhibit 77
Insulin Independence (%) Month 6 Post First Infusion
by Participant's Average Daily Insulin Use (Units/Day/kg)

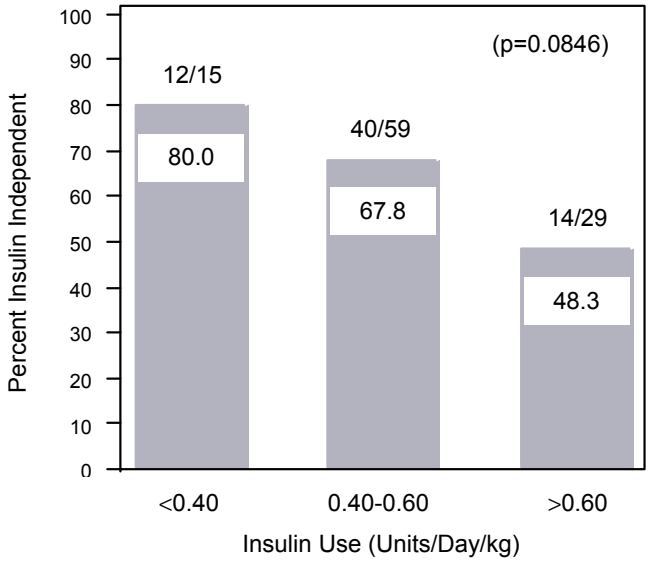


Exhibit 78
Summary of Severe Hypoglycemic Events Pre First Infusion and Follow-Up Post Last Infusion

	Follow-Up							
	Pre First Infusion		Days 0-30 Post First Infusion		Months 1-6 Post Last Infusion		Months 6-12 Post Last Infusion	
	N	%	N	%	N	%	N	%
Total	118	100.0	118	100.0	112	100.0	102	100.0
Any Severe Hypoglycemic Episodes								
Yes	97	82.2	3	2.5	-	0.0	2*	2.0
No	16	13.6	106	89.8	103	92.0	84	82.4
Missing	5	4.2	9	7.6	9	8.0	16	15.7
Frequency of Severe Hypoglycemic Episodes								
None	16	13.6	106	89.8	103	92.0	84	82.4
1-2	7	5.9	1	0.8	-	0.0	1	1.0
3-5	8	6.8	1	0.8	-	0.0	-	0.0
6 or more	71	60.2	-	0.0	-	0.0	-	0.0
Unknown	10	8.5	1	0.8	-	0.0	1	1.0
Missing	6	5.1	9	7.6	9	8.0	16	15.7

*One recipient with insulin use and reported islet graft failure and one recipient with continued insulin use since infusion.

Exhibit 79
Insulin Status at Post Last Infusion Follow-Up and Sirolimus Trough Levels (ng/mL)

	Sirolimus Trough Level (ng/mL)											
	Month 6						Year 1					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Total	83	10.6	3.4	10.4	2.0	20.9	67	10.0	3.6	9.6	2.7	23.9
Insulin Independent	60	10.3	3.4	10.0	2.0	20.9	45	10.2	3.5	9.8	2.7	23.9
Insulin Dependent	23	11.5	3.4	11.3	6.7	18.3	22	9.7	3.9	9.5	3.0	15.7

Exhibit 80
Insulin Status at Post Last Infusion Follow-Up and Tacrolimus Trough Levels (ng/mL)

	Tacrolimus Trough Level (ng/mL)											
	Month 6						Year 1					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Total	85	4.5	1.6	4.4	1.5	11.5	67	4.6	2.1	4.0	2.1	14.0
Insulin Independent	63	4.6	1.7	4.6	1.5	11.5	45	4.9	2.3	4.3	2.8	14.0
Insulin Dependent	22	4.1	1.3	3.8	2.8	7.2	22	3.9	1.6	3.6	2.1	7.2

Exhibit 81
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion

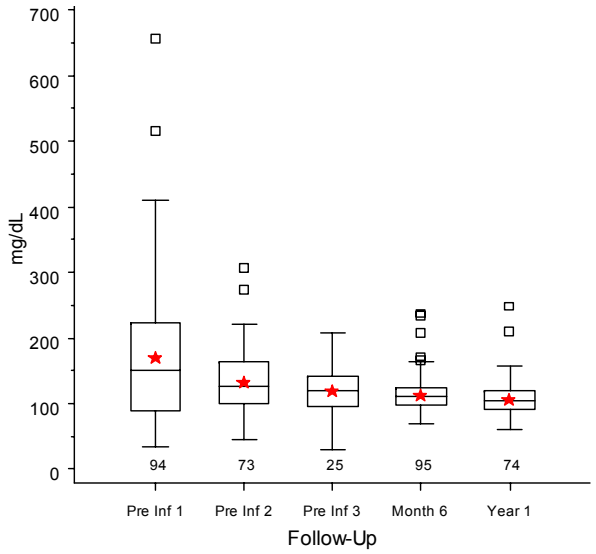


Exhibit 82
HbA_{1c} (%)
Pre Infusion and Post Last Infusion

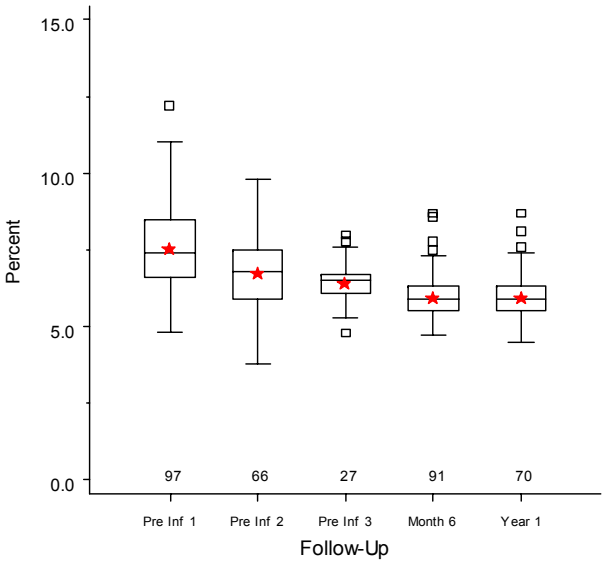


Exhibit 83
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion

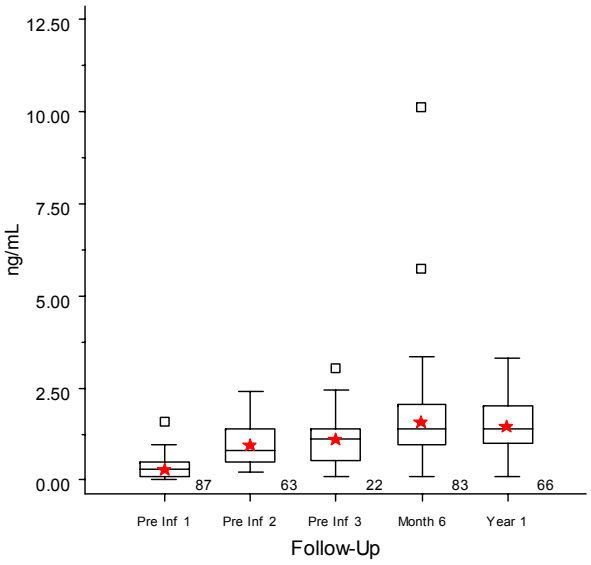


Exhibit 84
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Participants with One Infusion

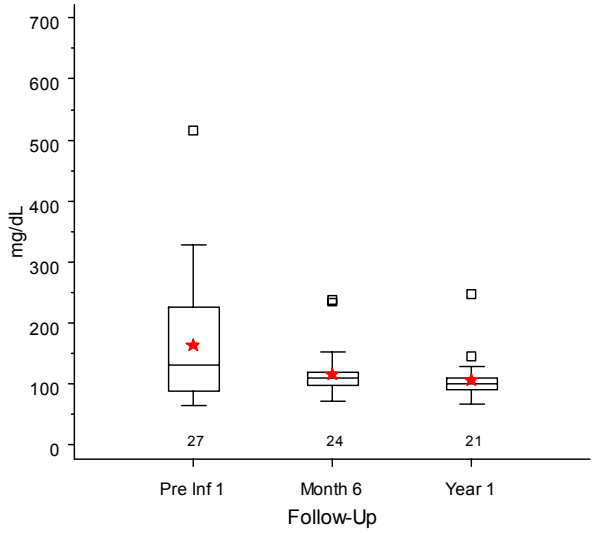


Exhibit 85
HbA_{1c} (%)
Pre Infusion and Post Last Infusion
Participants with One Infusion

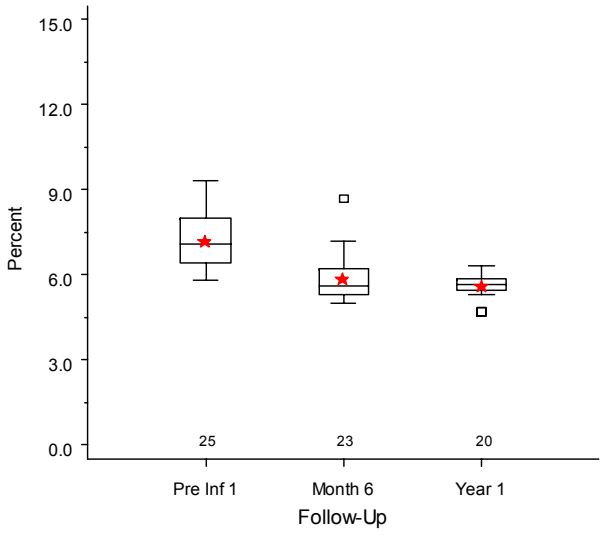


Exhibit 86
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion
Participants with One Infusion

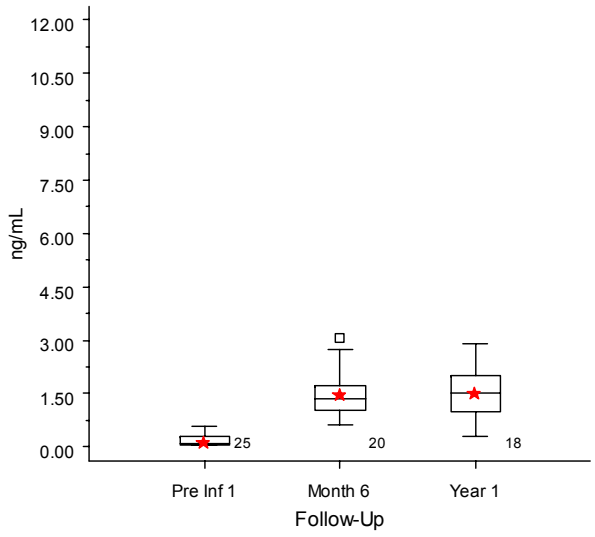


Exhibit 87
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Participants with Two Infusions

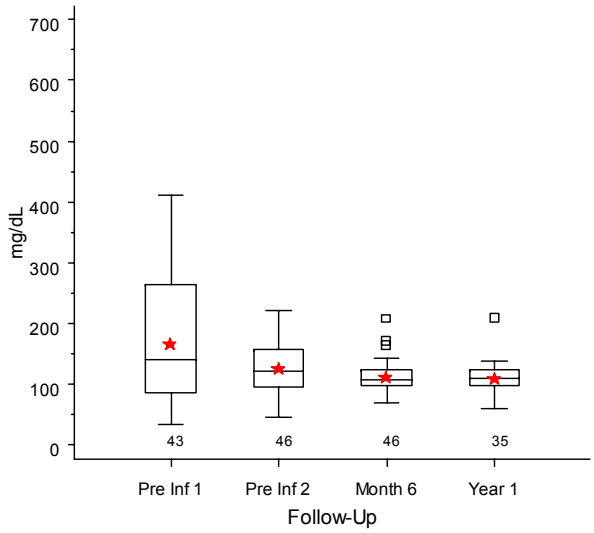


Exhibit 88
HbA_{1c} (%)
Pre Infusion and Post Last Infusion
Participants with Two Infusions

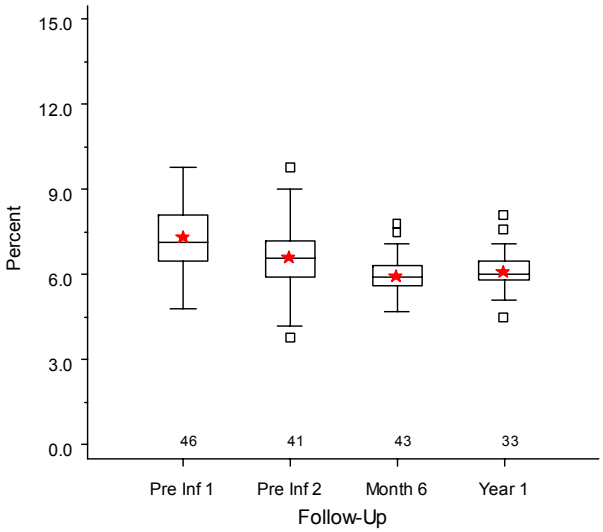


Exhibit 89
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion
Participants with Two Infusions

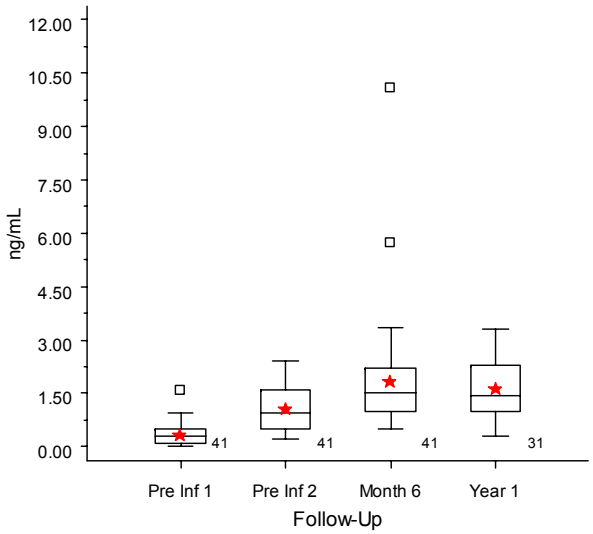


Exhibit 90
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion
Participants with Three Infusions

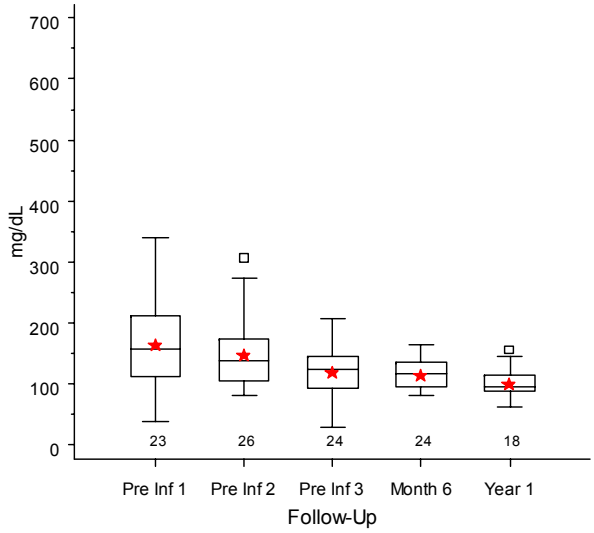


Exhibit 91
HbA_{1c} (%)
Pre Infusion and Post Last Infusion
Participants with Three Infusions

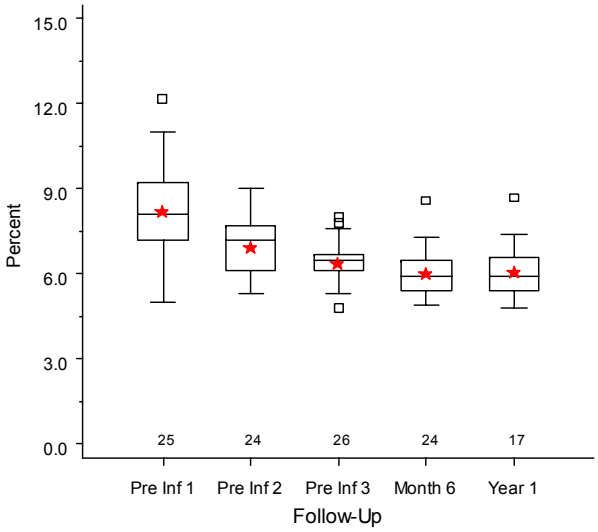


Exhibit 92
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion
Participants with Three Infusions

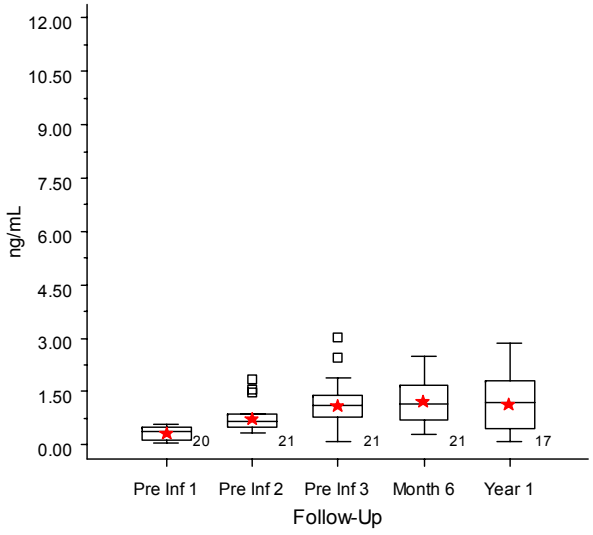


Exhibit 93
Fasting Plasma Glucose (mg/dL) Pre First Infusion to Post First Infusion
Insulin Independent Participants

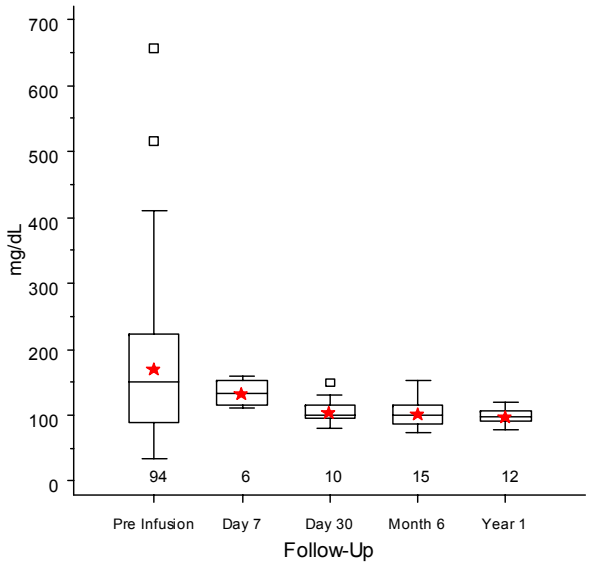


Exhibit 94
Fasting Plasma Glucose (mg/dL) Pre First Infusion to Post First Infusion
Insulin Dependent Participants

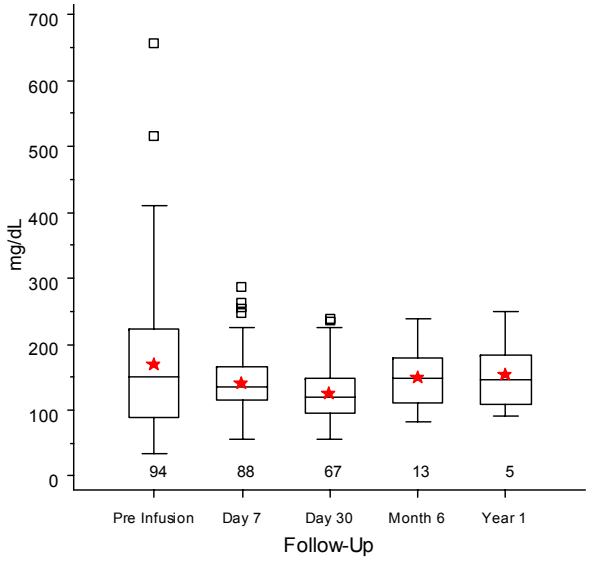


Exhibit 95
HbA_{1c} (%) Pre First Infusion and Post First Infusion
Insulin Independent Participants

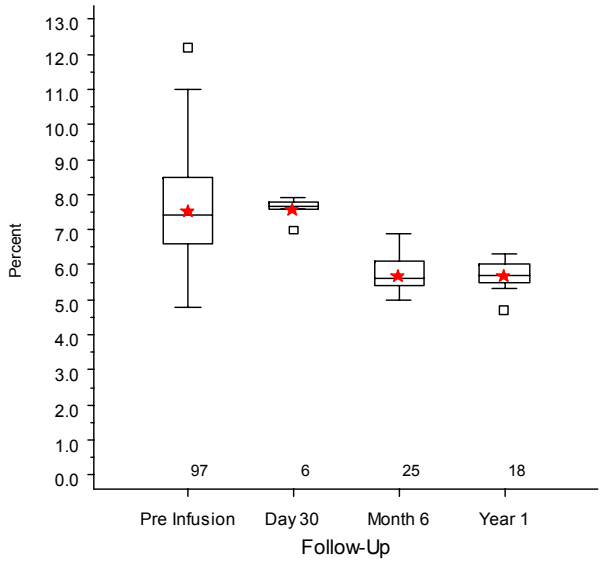


Exhibit 96
HbA_{1c} (%) Pre First Infusion and Post First Infusion
Insulin Dependent Participants

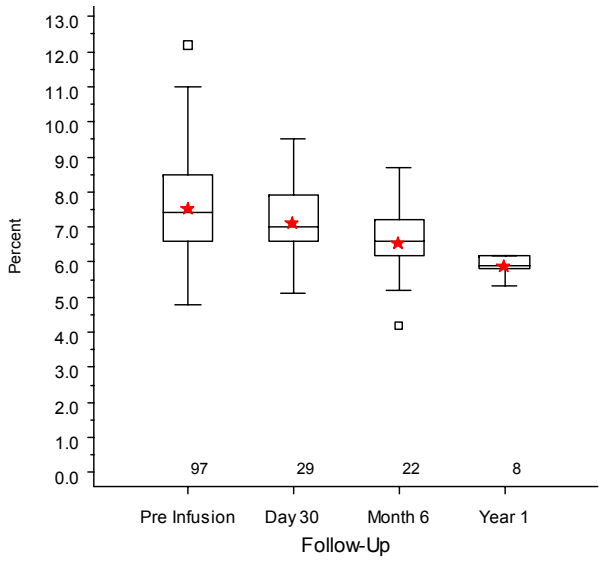


Exhibit 97
Basal Plasma C-peptide (ng/mL) Pre First Infusion and Post First Infusion Insulin Independent Participants

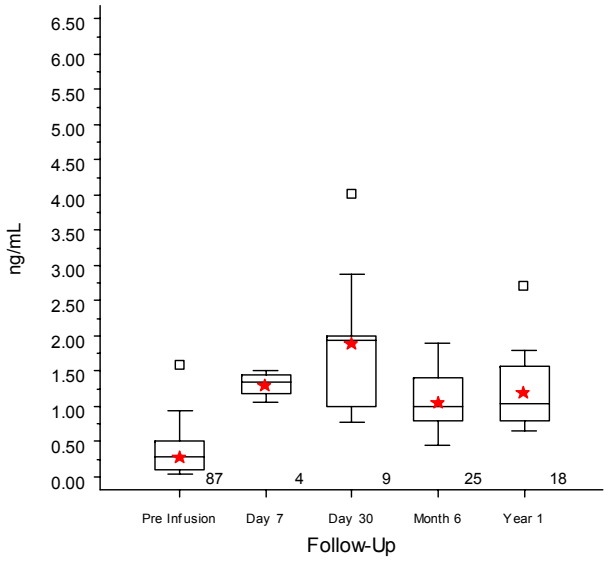


Exhibit 98
Basal Plasma C-peptide (ng/mL) Pre First Infusion and Post First Infusion Insulin Dependent Participants

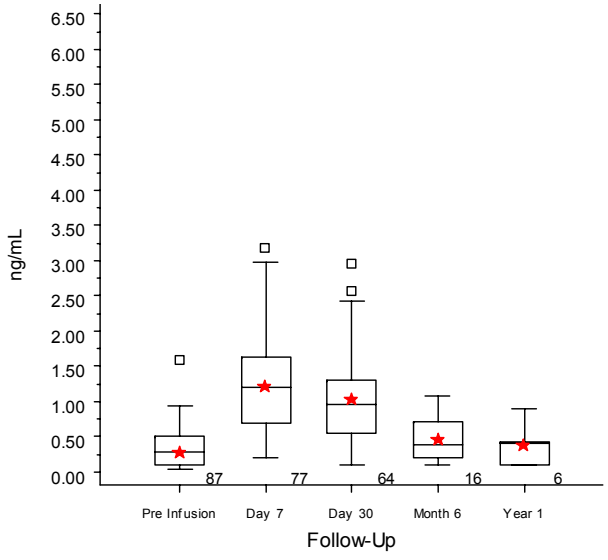


Exhibit 99
Pre Infusion Recipient Lab Summary by Infusion Sequence

	Infusion Sequence																	
	1						2						3					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	94	171.8	106.0	151.5	35.0	658.0	73	133.8	48.0	127.0	45.0	308.1	25	120.1	37.6	120.0	30.0	207.0
HbA_{1c} (%)	97	7.6	1.3	7.4	4.8	12.2	66	6.8	1.1	6.8	3.8	9.8	27	6.4	0.7	6.5	4.8	8.0
ALT (IU/L)	94	20.3	9.1	18.0	3.0	62.0	64	41.3	23.3	37.0	11.0	131.0	23	41.8	22.0	35.0	21.0	121.0
AST (IU/L)	99	24.2	9.1	23.0	6.0	80.0	72	35.8	15.9	32.0	17.0	97.0	26	37.5	11.6	34.5	21.0	64.0
Alkaline Phosphatase (IU/L)	73	69.1	22.7	63.0	28.0	150.0	56	75.6	29.0	70.5	32.0	190.0	24	91.3	30.5	96.0	43.0	175.0
Total Bilirubin (mg/dL)	93	0.6	0.4	0.5	0.1	2.7	70	0.4	0.2	0.4	0.1	1.6	25	0.4	0.2	0.4	0.1	1.2
Total Cholesterol (mg/dL)	100	171.1	30.0	169.9	96.0	247.1	63	191.6	31.2	196.0	119.0	243.0	26	185.2	32.7	188.5	115.8	278.0
HDL (mg/dL)	98	64.3	16.0	62.5	31.0	123.0	63	62.4	16.4	62.0	36.0	101.5	26	58.4	17.0	59.2	24.0	103.0
LDL (mg/dL)	99	93.8	24.2	93.0	41.0	173.4	64	109.9	27.3	112.0	50.0	158.0	25	110.7	42.8	106.6	50.2	268.0
Triglycerides (mg/dL)	100	64.1	32.4	53.6	16.0	177.0	62	98.2	51.9	86.5	34.0	345.2	25	107.7	43.3	103.0	50.0	203.6
Serum Creatinine (mg/dL)	101	0.9	0.2	0.8	0.1	1.8	73	0.9	0.2	0.8	0.6	1.6	27	0.9	0.2	0.9	0.7	1.3
Calculated Creatinine Clearance ($mL/min/1.73m^2$)	84	107.3	27.2	101.5	57.0	196.0	34	101.4	27.0	95.5	59.0	169.0	12	115.0	49.6	99.0	69.0	227.0
Basal Plasma C-peptide (ng/mL)	87	0.3	0.3	0.3	0.0	1.6	63	1.0	0.6	0.8	0.2	2.4	22	1.1	0.7	1.1	0.1	3.0

Exhibit 100
Metabolic Summary by Follow-Up Post Last Infusion

	Month 6						Year 1					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	66	112.5	30.5	106.0	70.0	238.0	46	103.5	27.9	100.5	62.0	249.0
HbA_{1c} (%)	91	6.0	0.7	5.9	4.7	8.7	70	6.0	0.8	5.9	4.5	8.7
Basal Plasma C-peptide (ng/mL)	83	1.1	0.6	1.0	0.1	3.3	66	1.0	0.6	0.9	0.1	3.3
Peak Stimulated C-peptide After Meal (ng/mL)	26	3.0	1.3	2.8	0.8	5.8	21	3.0	1.4	3.3	0.2	5.2
Basal Plasma C-peptide before IV Glucagon (ng/mL)	2	1.7	0.8	1.7	1.1	2.3	1	2.8	-	2.8	2.8	2.8
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	3	3.4	0.4	3.4	3.0	3.8	1	6.1	-	6.1	6.1	6.1
Basal Plasma C-peptide Before IV Arginine (ng/mL)	17	1.5	0.8	1.4	0.2	3.2	20	1.6	0.8	1.6	0.4	4.1
Peak Stimulated C-peptide After IV Arginine (ng/mL)	35	2.5	0.9	2.4	0.3	4.4	33	2.5	0.8	2.4	0.8	4.5
Acute C-peptide Response to IV Arginine (ng/mL)	34	0.9	0.4	0.8	0.1	2.0	34	1.1	0.6	0.9	0.4	3.1
Acute Insulin Response to IV Arginine (µU/mL)	33	18.8	8.6	16.5	6.0	35.8	29	17.3	8.7	14.9	7.0	38.6
Basal Plasma C-peptide Before IV Glucose (ng/mL)	15	1.1	0.4	1.0	0.7	1.9	13	1.1	0.6	1.0	0.5	2.4
Peak Stimulated C-peptide After IV Glucose (ng/mL)	26	2.6	0.9	2.3	1.3	4.2	24	2.5	0.9	2.3	0.5	4.2
Acute C-peptide Response to IV Glucose (ng/mL)	25	1.0	0.6	1.0	0.0	2.5	23	0.9	0.6	0.8	0.0	2.0
Acute Insulin Response to IV Glucose (µU/mL)	24	20.5	11.9	19.8	3.0	43.9	24	15.0	11.3	14.3	0.0	38.7
AUC Insulin derived from 0.5 g/kg IVGTT (µU/mL x min)	0	-	-	-	-	-	0	-	-	-	-	-
KG-value derived from 0.5 g/kg IVGTT (KG Value)	19	-0.6	1.1	-0.9	-2.0	1.2	19	-0.2	1.0	-0.5	-1.4	1.2
2-hr 75g OGTT Plasma Glucose (mg/dL)	20	182.5	73.4	163.0	117.0	370.0	23	158.2	50.0	143.0	81.0	290.0
AUC C-peptide OGTT (ng/mL x min)	1	472.5	-	472.5	472.5	472.5	0	-	-	-	-	-
AUC C-peptide MMTT (ng/mL x min)	9	602.7	155.8	597.8	327.4	811.5	13	439.9	208.4	347.0	227.0	867.8
Mixed Meal Stimulation Index (pmol/mg)	12	0.9	0.8	0.7	0.2	3.2	15	1.0	0.9	0.6	0.2	3.1

Exhibit 101
Metabolic Summary Month 6 Post Last Infusion
by Insulin Status

	Insulin Independent						Insulin Dependent					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	46	104.6	18.2	100.5	73.0	152.0	19	130.6	44.6	119.0	70.0	238.0
HbA_{1c} (%)	65	5.7	0.5	5.7	4.7	7.5	24	6.7	0.8	6.5	5.2	8.7
Basal Plasma C-peptide (ng/mL)	62	1.2	0.6	1.1	0.3	3.3	21	0.6	0.4	0.5	0.1	1.7
Peak Stimulated C-peptide After Meal (ng/mL)	16	3.5	1.3	3.2	1.2	5.8	10	2.2	0.9	2.1	0.8	4.0
Basal Plasma C-peptide before IV Glucagon (ng/mL)	2	1.7	0.8	1.7	1.1	2.3	0	-	-	-	-	-
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	3	3.4	0.4	3.4	3.0	3.8	0	-	-	-	-	-
Basal Plasma C-peptide Before IV Arginine (ng/mL)	14	1.5	0.6	1.5	0.6	2.6	3	1.5	1.5	1.1	0.2	3.2
Peak Stimulated C-peptide After IV Arginine (ng/mL)	30	2.6	0.8	2.5	1.0	4.4	5	1.9	1.3	1.8	0.3	3.9
Acute C-peptide Response to IV Arginine (ng/mL)	30	0.9	0.4	0.9	0.4	2.0	4	0.6	0.4	0.6	0.1	1.1
Acute Insulin Response to IV Arginine (µU/mL)	30	19.7	8.5	19.2	6.0	35.8	3	9.9	3.4	11.8	6.0	11.9
Basal Plasma C-peptide Before IV Glucose (ng/mL)	13	1.1	0.4	1.0	0.7	1.9	2	1.3	0.6	1.3	0.9	1.7
Peak Stimulated C-peptide After IV Glucose (ng/mL)	23	2.7	0.8	2.4	1.6	4.2	3	2.1	1.1	1.6	1.3	3.4
Acute C-peptide Response to IV Glucose (ng/mL)	22	1.0	0.6	1.0	0.2	2.5	3	0.8	0.7	1.2	0.0	1.2
Acute Insulin Response to IV Glucose (µU/mL)	22	20.7	11.5	19.8	5.8	43.9	2	18.4	21.8	18.4	3.0	33.8
AUC Insulin derived from 0.5 g/kg IVGTT (µU/mL x min)	0	-	-	-	-	-	0	-	-	-	-	-
KG-value derived from 0.5 g/kg IVGTT (KG Value)	17	-0.5	1.2	-0.9	-2.0	1.2	2	-1.1	0.6	-1.1	-1.5	-0.7
2-hr 75g OGTT Plasma Glucose (mg/dL)	16	156.8	48.4	138.5	117.0	305.0	4	285.5	68.7	280.0	212.0	370.0
AUC C-peptide OGTT (ng/mL x min)	1	472.5	-	472.5	472.5	472.5	0	-	-	-	-	-
AUC C-peptide MMTT (ng/mL x min)	7	597.8	170.7	597.8	327.4	811.5	2	619.7	136.6	619.7	523.1	716.3
Mixed Meal Stimulation Index (pmol/mg)	10	1.0	0.8	0.7	0.5	3.2	2	0.5	0.4	0.5	0.2	0.7

Exhibit 102
Metabolic Summary Year 1 Post Last Infusion
by Insulin Status

	Insulin Independent						Insulin Dependent					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	29	101.0	11.5	101.0	79.0	124.0	16	109.3	44.9	99.0	62.0	249.0
HbA_{1c} (%)	47	5.8	0.5	5.8	4.5	6.6	22	6.5	0.9	6.4	4.8	8.7
Basal Plasma C-peptide (ng/mL)	45	1.1	0.6	1.0	0.5	3.3	21	0.6	0.5	0.4	0.1	1.4
Peak Stimulated C-peptide After Meal (ng/mL)	11	3.8	1.0	3.9	2.1	5.2	10	2.2	1.4	2.0	0.2	4.4
Basal Plasma C-peptide before IV Glucagon (ng/mL)	1	2.8	-	2.8	2.8	2.8	0	-	-	-	-	-
Peak Stimulated C-peptide After IV Glucagon (ng/mL)	1	6.1	-	6.1	6.1	6.1	0	-	-	-	-	-
Basal Plasma C-peptide Before IV Arginine (ng/mL)	15	1.7	0.8	1.5	0.9	4.1	4	1.4	1.1	1.4	0.4	2.3
Peak Stimulated C-peptide After IV Arginine (ng/mL)	27	2.5	0.6	2.4	1.6	3.9	5	2.0	1.3	1.3	0.8	3.5
Acute C-peptide Response to IV Arginine (ng/mL)	28	1.1	0.6	0.9	0.5	3.1	5	0.8	0.3	0.8	0.4	1.2
Acute Insulin Response to IV Arginine (µU/mL)	25	17.1	8.3	14.9	7.0	38.6	4	18.5	12.1	18.1	7.9	29.7
Basal Plasma C-peptide Before IV Glucose (ng/mL)	10	1.2	0.6	0.9	0.6	2.4	3	0.9	0.4	1.0	0.5	1.3
Peak Stimulated C-peptide After IV Glucose (ng/mL)	20	2.6	0.8	2.5	1.6	4.2	4	1.6	1.0	1.6	0.5	2.6
Acute C-peptide Response to IV Glucose (ng/mL)	19	1.0	0.6	0.8	0.2	2.0	4	0.6	0.4	0.7	0.0	1.0
Acute Insulin Response to IV Glucose (µU/mL)	20	16.1	11.5	15.9	0.9	38.7	4	9.7	9.5	8.3	0.0	22.1
AUC Insulin derived from 0.5 g/kg IVGTT (µU/mL x min)	0	-	-	-	-	-	0	-	-	-	-	-
KG-value derived from 0.5 g/kg IVGTT (KG Value)	16	-0.2	1.1	-0.5	-1.4	1.2	3	-0.6	0.1	-0.5	-0.7	-0.5
2-hr 75g OGTT Plasma Glucose (mg/dL)	19	157.9	52.6	142.0	81.0	290.0	3	147.3	41.4	154.0	103.0	185.0
AUC C-peptide OGTT (ng/mL x min)	0	-	-	-	-	-	0	-	-	-	-	-
AUC C-peptide MMTT (ng/mL x min)	11	461.2	220.7	430.1	227.0	867.8	2	322.7	34.4	322.7	298.4	347.0
Mixed Meal Stimulation Index (pmol/mg)	12	1.1	1.0	0.7	0.5	3.1	3	0.6	0.4	0.6	0.2	0.9

Exhibit 103
Islet Graft Dysfunction and Recipient Survival Summary
Post Last Infusion

	Month 6		Year 1	
	N	%	N	%
Islet Graft Dysfunction Episodes				
None Reported	95	90.0	69	78.0
One or More Partial Graft Dysfunctions Reported	3	2.8	2	2.3
Total Islet Graft Failure	2	1.9	6	6.8
Unknown or Not Reported on Islet Graft Dysfunction Form	6	5.7	11	13.0
Missing	-	0.0	-	0.0
Patient Death				
Yes	-	0.0	-	0.0
No	106	100.0	88	100.0

Exhibit 104
Islet Graft Dysfunction (IGD) Summary

Recipient	Infusion Sequence	Total IEQs/kg to date	Days From Infusion to IGD	Primary Reason for IGD	Outcome*	Were any Adverse Events Associated
1	1	7,745	30	Rejection	Partial recovery	No
2	1	7,921	173	Rejection	Partial recovery	No
	2	15,842	230	Recipient discont. meds	Unknown	Unknown
3	3	20,351	92	Islet exhaustion	Islet graft failure	No
4	1	13,049	66	Unknown	Islet graft failure	No
5	2	18,399	256	Unknown	Partial recovery	No
	3	24,923	196	Unknown	Unknown	No
6	2	13,018	380	Unknown	Islet graft failure	Unknown
7	3	25,060	493	Missing	Islet graft failure	Missing
8	1	10,665	454	Islet exhaustion	Islet graft failure	No
9	4	33,124	164	Rejection	Partial recovery	No
10	1	5,262	301	Rejection	Islet graft failure	No
11	2	11,905	119	Unknown	Islet graft failure	No
12	2	14,553	564	Islet exhaustion	Islet graft failure	No
13	2	13,125	307	Islet exhaustion	Islet graft failure	No
14	2	13,962	769	Missing	Islet graft failure	Missing
15	3	18,187	576	Missing	Islet graft failure	Missing
16	1	.	888	Recipient discont. meds	Islet graft failure	No
17	2	13,369	240	Tx center discont. meds	Islet graft failure	No
18	2	13,228	445	Islet exhaustion	Islet graft failure	No
19	1	9,815	117	Primary nonfunction	Islet graft failure	No
20	1	4,464	275	Rejection	Islet graft failure	No
21	2	16,569	194	Other	Islet graft failure	No
22	1	8,283	268	Islet exhaustion	Islet graft failure	No
23	1	.	92	Missing	Islet graft failure	Missing
24	1	11,988	36	Primary nonfunction	Partial recovery	No
	2	30,587	31	Rejection	Partial recovery	No

*Definitions of outcome are included in the Methods section of the report.

Exhibit 105
Pre Infusion Recipient Lab Summary by Infusion Sequence
Participants with Islet Graft Dysfunction

	Infusion Sequence																	
	1						2						3					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	15	157.5	104.1	110.0	46.0	406.0	8	172.6	66.0	195.0	88.0	252.0	1	224.0	-	224.0	224.0	224.0
HbA_{1c} (%)	15	7.9	1.3	8.0	4.8	10.7	7	7.8	1.2	7.5	6.2	10.0	1	6.1	-	6.1	6.1	6.1
ALT (IU/L)	15	22.4	12.1	19.0	8.0	47.0	8	42.0	22.0	32.5	24.0	85.0	1	76.0	-	76.0	76.0	76.0
AST (IU/L)	15	23.7	12.4	19.0	14.0	61.0	8	30.4	12.8	26.0	19.0	56.0	1	67.0	-	67.0	67.0	67.0
Alkaline Phosphatase (IU/L)	12	73.4	25.6	65.0	44.0	133.0	6	90.2	45.7	82.0	44.0	160.0	0	-	-	-	-	-
Total Bilirubin (mg/dL)	15	0.4	0.2	0.4	0.1	0.7	8	0.4	0.2	0.3	0.1	0.9	1	0.1	-	0.1	0.1	0.1
Total Cholesterol (mg/dL)	15	172.5	32.7	175.0	113.0	231.0	5	160.0	34.8	162.0	122.0	209.0	1	159.0	-	159.0	159.0	159.0
HDL (mg/dL)	15	66.2	14.4	67.0	37.0	99.0	3	63.3	18.6	72.0	42.0	76.0	1	40.0	-	40.0	40.0	40.0
LDL (mg/dL)	15	91.9	26.9	95.0	42.0	150.0	3	108.3	17.5	113.0	89.0	123.0	1	96.0	-	96.0	96.0	96.0
Triglycerides (mg/dL)	15	83.1	34.6	76.0	31.0	149.0	5	65.0	29.5	56.0	35.0	113.0	1	117.0	-	117.0	117.0	117.0
Serum Creatinine (mg/dL)	15	0.8	0.2	0.8	0.5	1.4	8	0.9	0.2	0.9	0.6	1.1	1	0.8	-	0.8	0.8	0.8
Calculated Creatinine Clearance ($mL/min/1.73m^2$)	14	103.0	29.3	109.0	25.0	145.0	3	93.7	30.6	96.0	62.0	123.0	0	-	-	-	-	-
Basal Plasma C-peptide (ng/mL)	15	0.5	0.3	0.5	0.1	0.9	6	0.5	0.1	0.5	0.4	0.8	1	0.8	-	0.8	0.8	0.8

Exhibit 106
Summary of Secondary Complications Pre First Infusion and Post Last Infusion

	Follow-Up					
	Pre First Infusion		Month 6		Year 1	
	N	%	N	%	N	%
Total	118	100.0	112	100.0	102	100.0
Hypoglycemia						
No occurrence	1	0.8	86	76.8	66	64.7
Reduced awareness	21	17.8	6	5.4	8	7.8
Unawareness	89	75.4	-	0.0	2	2.0
Unknown	7	5.9	20	17.9	26	25.5
Peripheral Neuropathy						
No occurrence	72	61.0	69	61.6	57	55.9
Asymptomatic	5	4.2	7	6.3	7	6.9
Symptomatic	34	28.8	12	10.7	10	9.8
Disabling	1	0.8	-	0.0	-	0.0
Unknown	6	5.1	24	21.4	28	27.5
Autonomic Neuropathy						
No occurrence	77	65.3	74	66.1	56	54.9
Asymptomatic	6	5.1	5	4.5	4	3.9
Symptomatic	24	20.3	11	9.8	9	8.8
Disabling	-	0.0	-	0.0	1	1.0
Unknown	11	9.3	22	19.6	32	31.4
Nephropathy						
No occurrence	92	78.0	70	62.5	55	53.9
Microalbuminuria	18	15.3	13	11.6	11	10.8
Macroalbuminuria	-	0.0	2	1.8	5	4.9
Stable allograft	-	0.0	-	0.0	-	0.0
Unknown	8	6.8	27	24.1	31	30.4
CAD						
Yes	4	3.4	1	0.9	1	1.0
No	110	93.2	95	84.8	78	76.5
Unknown	4	3.4	16	14.3	23	22.5

Exhibit 106 *(continued)*
Summary of Secondary Complications Pre First Infusion and Post Last Infusion

	Follow-Up					
	Pre First Infusion		Month 6		Year 1	
	N	%	N	%	N	%
CVA						
Yes	-	0.0	-	0.0	-	0.0
No	112	94.9	96	85.7	81	79.4
Unknown	6	5.1	16	14.3	21	20.6
PVD						
Yes	1	0.8	1	0.9	-	0.0
No	110	93.2	93	83.0	78	76.5
Unknown	7	5.9	18	16.1	24	23.5
Treated Hypertension						
Yes	27	22.9	35	31.3	34	33.3
No	83	70.3	63	56.3	47	46.1
Unknown	8	6.8	14	12.5	21	20.6
Foot Ulcers						
Yes	5	4.2	-	0.0	2	2.0
No	79	66.9	84	75.0	67	65.7
Unknown	34	28.8	28	25.0	33	32.4
Lower Limb Amputation						
Yes	-	0.0	-	0.0	-	0.0
No	94	79.7	89	79.5	70	68.6
Unknown	24	20.3	23	20.5	32	31.4
Foot Deformity						
Yes	1	0.8	2	1.8	2	2.0
No	90	76.3	84	75.0	67	65.7
Unknown	27	22.9	26	23.2	33	32.4
Dysesthesia						
Yes	8	6.8	2	1.8	3	2.9
No	72	61.0	75	67.0	62	60.8
Unknown	38	32.2	35	31.3	37	36.3

Exhibit 106 *(continued)*
Summary of Secondary Complications Pre First Infusion and Post Last Infusion

	Follow-Up					
	Pre First Infusion		Month 6		Year 1	
	N	%	N	%	N	%
Orthostatic Hypotension						
Yes	7	5.9	3	2.7	1	1.0
No	62	52.5	66	58.9	59	57.8
Unknown	49	41.5	43	38.4	42	41.2
Gastroparesis						
Yes	7	5.9	4	3.6	4	3.9
No	73	61.9	78	69.6	64	62.7
Unknown	38	32.2	30	26.8	34	33.3
Constipation						
Yes	8	6.8	6	5.4	4	3.9
No	76	64.4	77	68.8	64	62.7
Unknown	34	28.8	29	25.9	34	33.3
Diabetic Diarrhea						
Yes	2	1.7	3	2.7	4	3.9
No	81	68.6	76	67.9	58	56.9
Unknown	35	29.7	33	29.5	40	39.2
Fecal Incontinence						
Yes	-	0.0	-	0.0	-	0.0
No	83	70.3	83	74.1	68	66.7
Unknown	35	29.7	29	25.9	34	33.3
Diabetic Bladder Dysfunction						
Yes	1	0.8	-	0.0	-	0.0
No	81	68.6	81	72.3	68	66.7
Unknown	36	30.5	31	27.7	34	33.3
Sexual Dysfunction						
Yes	8	6.8	2	1.8	4	3.9
No	74	62.7	65	58.0	51	50.0
Unknown	36	30.5	45	40.2	47	46.1

Exhibit 107
Summary of Ocular Complications Post Last Infusion

	Follow-Up					
	Pre First Infusion		Month 6		Year 1	
	N	%	N	%	N	%
Total	118	100.0	112	100.0	102	100.0
Retinopathy						
None	58	49.2	47	42.0	38	37.3
Non Proliferative	27	22.9	23	20.5	18	17.6
Proliferative	27	22.9	9	8.0	7	6.9
Unknown	6	5.1	33	29.5	39	38.2
Diabetic Macular Edema						
None	106	89.8	79	70.5	63	61.8
Mild	1	0.8	-	0.0	-	0.0
Moderate	1	0.8	-	0.0	-	0.0
Severe	-	0.0	-	0.0	-	0.0
Unknown	10	8.5	33	29.5	39	38.2
Laser photocoagulation surgery performed for proliferative retinopathy						
Yes	34	28.8	2	1.8	1	1.0
No	78	66.1	95	84.8	74	72.5
Unknown	6	5.1	15	13.4	27	26.5
Laser photocoagulation surgery performed for diabetic macular edema						
Yes	4	3.4	-	0.0	1	1.0
No	105	89.0	97	86.6	74	72.5
Unknown	9	7.6	15	13.4	27	26.5
Vitrectomy						
Yes	7	5.9	-	0.0	-	0.0
No	104	88.1	97	86.6	76	74.5
Unknown	7	5.9	15	13.4	26	25.5
Other surgery						
Yes	4	3.4	1	0.9	2	2.0
No	80	67.8	78	69.6	60	58.8
Unknown	34	28.8	33	29.5	40	39.2

Chapter 5
Recipient's Laboratory Data

Recipient's Laboratory Data Summary

This chapter provides a summary of reported abnormal laboratory liver function tests (Exhibit 108), abnormal lipid tests (Exhibit 113), and the percent of participants with a marked increase in serum creatinine from baseline (Exhibit 118). Abnormal has been defined as one or greater times the upper limit of normal to up to two times the upper limit of normal for the test and two or greater times the upper limit of normal for the test.

Reports at the two times or greater than the upper limit of normal at any time since the time of the recipient's first infusion were minimal for ALT (3.7%), AST (4.5%), alkaline phosphatase (4.2%) and for total bilirubin (0.9%). There were no reports at this level for total cholesterol and only 2 reports (1.8%) for triglycerides. In addition, there were only 5 reports (4.7%), of a recipient with an increase in their serum creatinine of 0.5mg/dL or greater than their baseline level.

Summary measures for each laboratory value are also constructed prior to their first infusion and by month 6 and year 1 post the recipient's last infusion procedure. For each of these laboratory tests, boxplots are displayed (Exhibits 109-112, 114-117, and 119-120). For a boxplot the "star" (★) represents the mean value. The whiskers of the plot represent the minimum value and the maximum value, while the lower line of the box represents the 25th percentile, the upper line of the box the 75th percentile and the middle line in the box represent the median (50th percentile).

Exhibit 108
Participants with Abnormal Liver Function Tests Post Infusion

	1-2X ULN		≥ 2X ULN	
	N	%	N	%
ALT	19	17.6	4	3.7
AST	39	35.1	5	4.5
Alkaline Phosphatase	26	27.1	4	4.2
Total Bilirubin	-	0.0	1	0.9

Upper Limit of Normal (ULN)

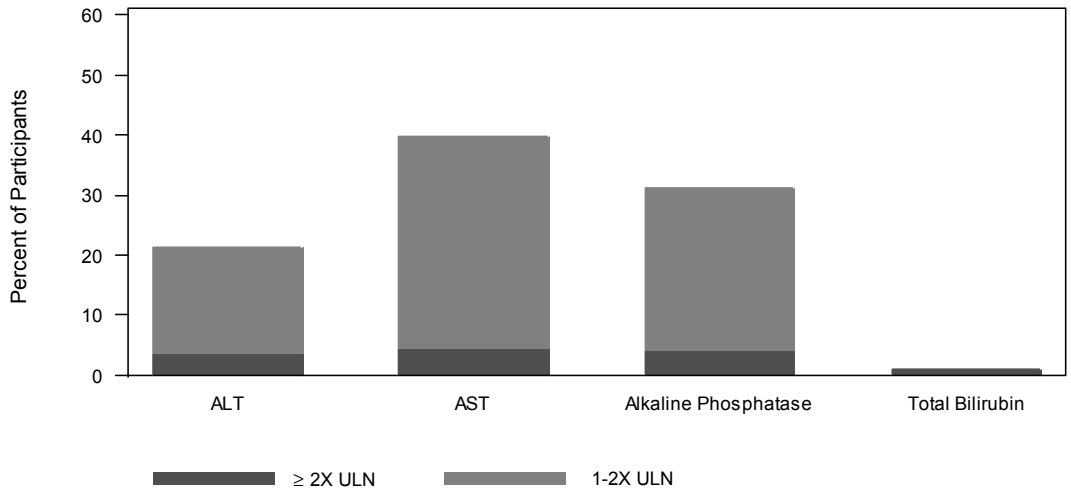


Exhibit 109
ALT (IU/L) Pre Infusion and Post Last Infusion

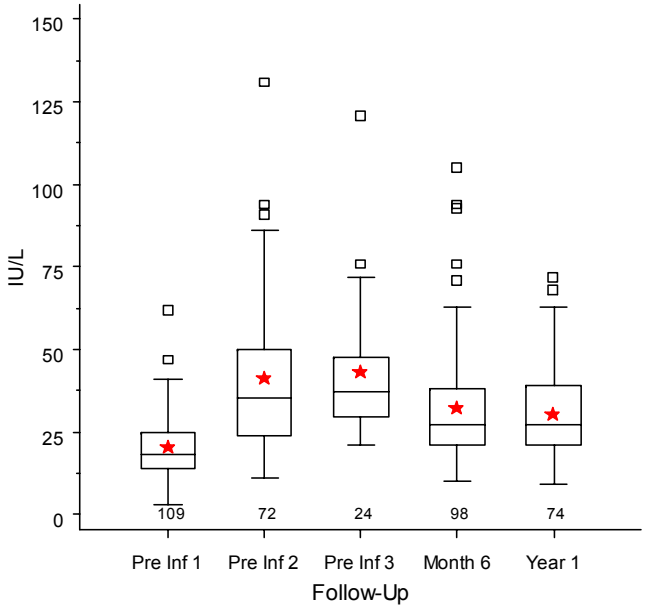


Exhibit 110
AST (IU/L) Pre Infusion and Post Last Infusion

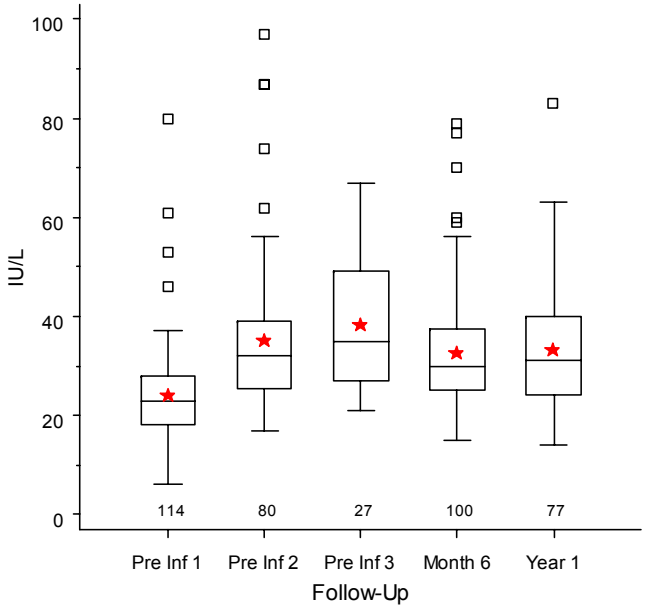


Exhibit 111
Alkaline Phosphatase (IU/L) Pre Infusion and Post Last Infusion

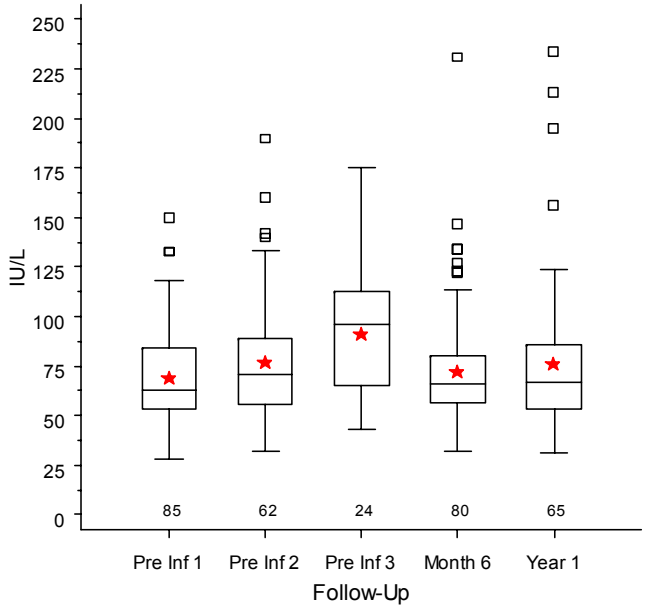


Exhibit 112
Total Bilirubin (mg/dL) Pre Infusion and Post Last Infusion

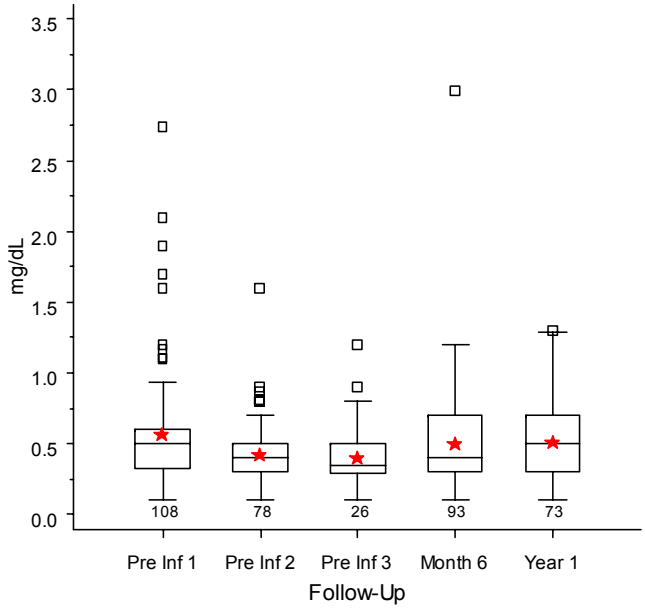


Exhibit 113
Participants with Abnormal Lipid Tests Post Infusion

	1-2X ULN		≥ 2X ULN	
	N	%	N	%
Total Cholesterol	12	10.9	-	0.0
Triglycerides	27	24.8	2	1.8

Upper Limit of Normal (ULN)

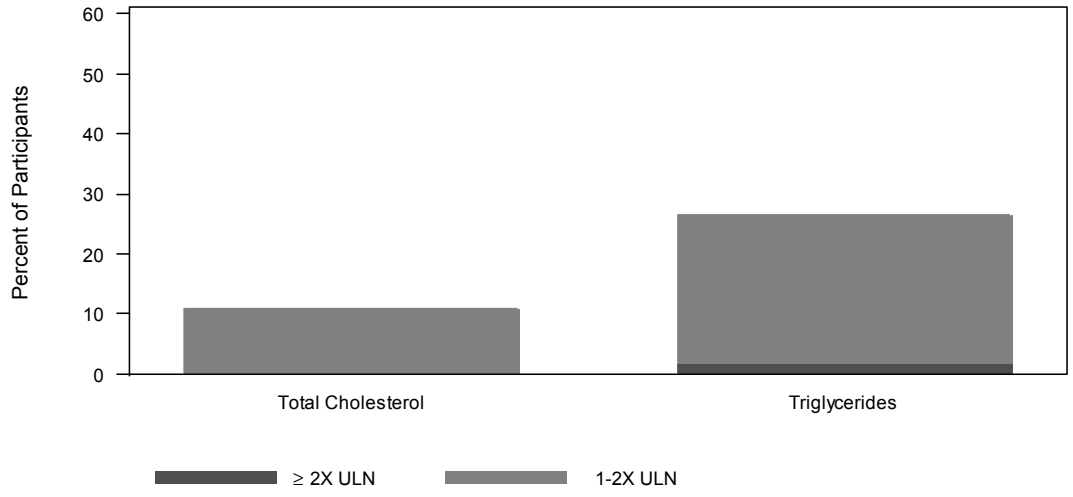


Exhibit 114
Total Cholesterol (mg/dL) Pre Infusion and Post Last Infusion

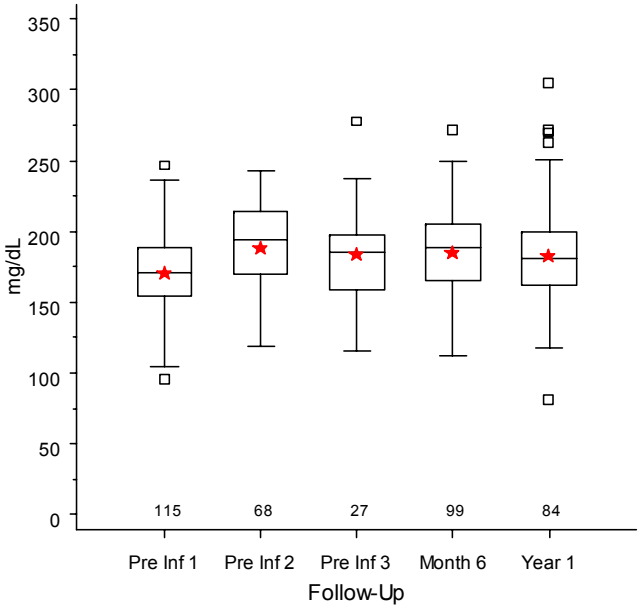


Exhibit 115
HDL (mg/dL) Pre Infusion and Post Last Infusion

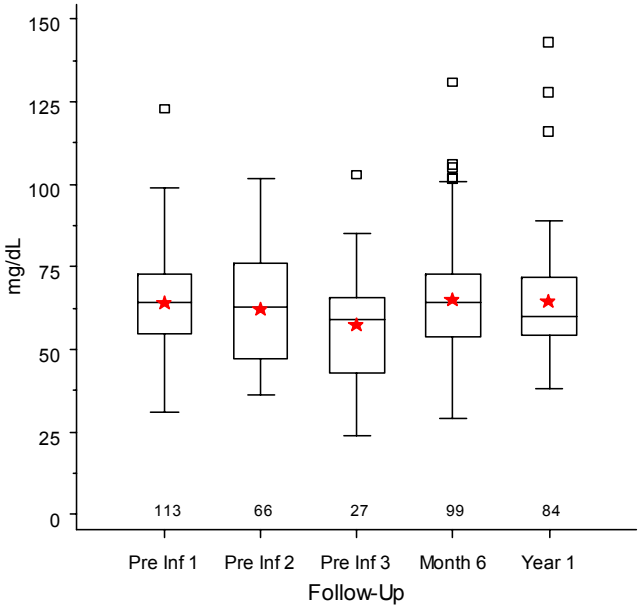


Exhibit 116
LDL (mg/dL) Pre Infusion and Post Last Infusion

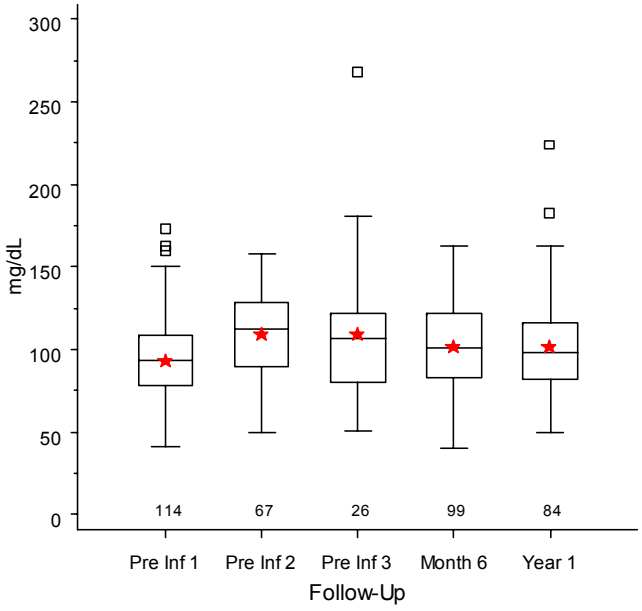


Exhibit 117
Triglycerides (mg/dL) Pre Infusion and Post Last Infusion

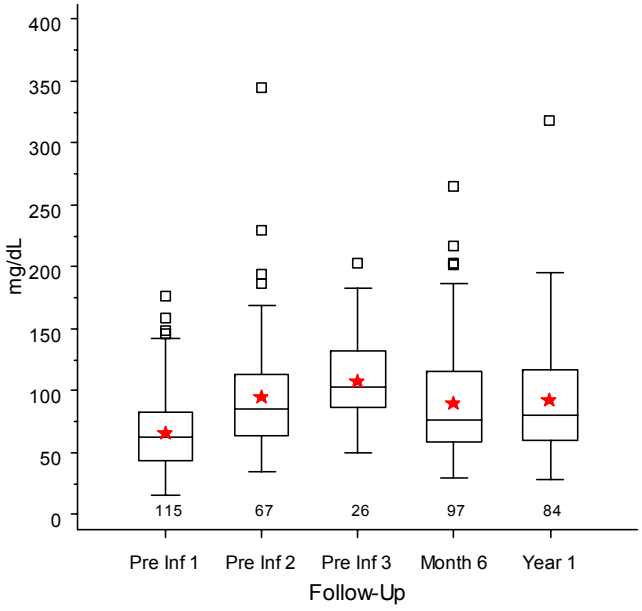


Exhibit 118
Percent of Participants with an Increase in Serum Creatinine (mg/dL) Greater than 0.5 from Baseline

	Increase in Serum Creatinine >0.5 mg/dL	
	N	%
Serum Creatinine	5	4.7

Exhibit 119
Serum Creatinine (mg/dL) Pre Infusion and Post Last Infusion

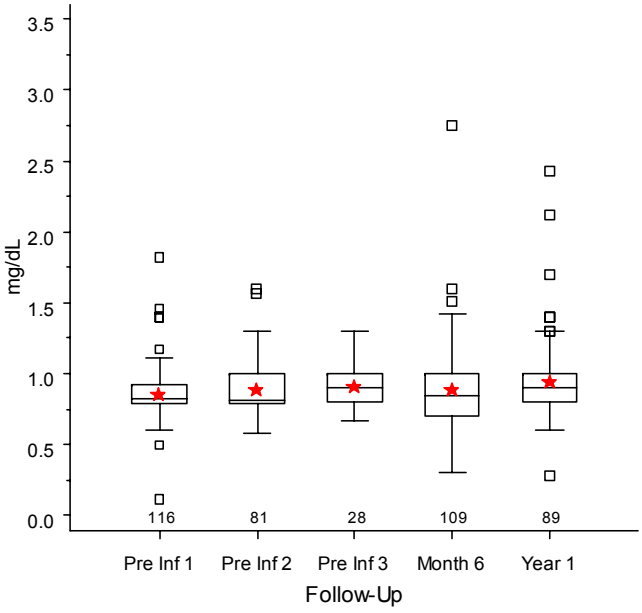
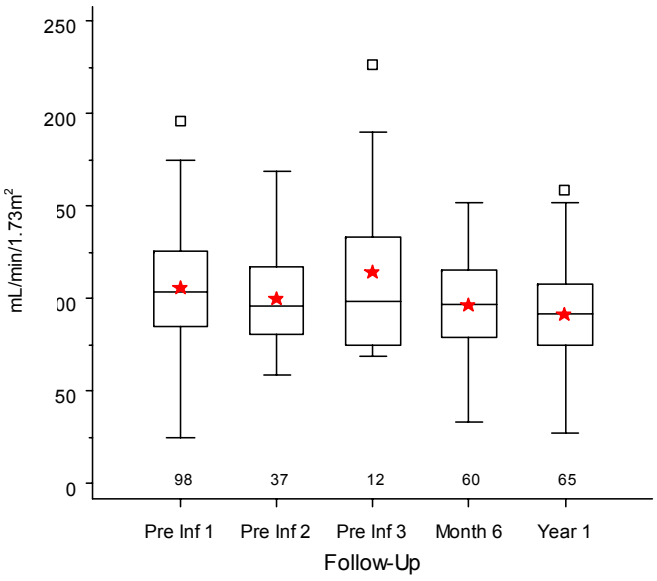


Exhibit 120
Calculated Creatinine Clearance (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion



Chapter 6
Adverse Events

Adverse Events Summary

All grade 3, 4 and 5 adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, are reported to CITR. Respective CITR Principal Investigators determine the relationship of the adverse event to the immunosuppression therapy and to the islet infusion procedure at the time adverse event forms are completed. It is noteworthy for this chapter that one islet transplant program has not reported any adverse events to the Registry. Since data from this center are not included in the analyses for this chapter, calculated rates and percentages may under represent true occurrences.

Exhibit 121 presents the overall adverse event and serious adverse event rate for islet alone transplant recipients in year 1 post their first islet infusion. Almost 74% of the recipients experienced at least one adverse event in year 1, while 36% experienced one or more serious adverse events in this same period. Of the 235 reported adverse events, 34.0% were related to the immunosuppression therapy and 14.5% were related to the infusion procedure. Of the 52 reported serious adverse events, 28.8% were related to the immunosuppression therapy and 23.1% were related to the islet infusion procedure.

In Exhibit 122, adverse and serious adverse events are summarized by time periods following the recipient's first infusion procedure (<1 month, 1-6 months, and 6-12 months). In the first month following infusion, 45.0% of the recipients reported at least one adverse event following their first infusion procedure, with 48.8% reporting an event in months 1-6, decreasing to 39.1% in months 6-12. For serious adverse events reported during the same time period, the percentages are lower with 6.2% serious adverse events within one month of the infusion, 24.4% between months 1-6 and 17.2% reported between months 6 and 12 post first infusion.

Overall, a total of 77 serious adverse events were reported to the Registry, with 22% of them classified as life threatening and 58% requiring an inpatient hospitalization (Exhibit 123). Almost 69% of the serious adverse events were classified by the reporting CITR investigator as unrelated to the islet infusion procedure (Exhibit 124) and 38% unrelated to the immunosuppression therapy (Exhibit 125). Ninety-five percent of the serious adverse events resolved with no residual effects (Exhibit 126). Most of the reported serious adverse events were categorized as gastrointestinal disorders (27.3%), blood and lymphatic system disorders (18.2%) and infections or infestations (10.4%) as classified by the MedDRA classifications system (Exhibit 127).

A summary of all serious adverse events reported to the Registry is listed in alphabetical order in Exhibit 128. This Exhibit contains information regarding the serious adverse event year, when it occurred related to the last infusion date, its relationship to the islet infusion procedure, treatment required and the final outcome of the event.

Duration of hospitalization for the infusion procedure is presented in Exhibit 129 and in Exhibit 130 hospitalizations experienced post the recipient's last infusion procedure are summarized. Portal pressures and changes in portal pressures are summarized in Exhibit 131 and presented in boxplots in Exhibits 132-136.

Exhibit 121
Summary of Adverse Events and Serious Adverse Events in Year 1 Post First Infusion (Participants, N=83)

	Adverse Events			Serious Adverse Events		
		Related to Immunosuppression Therapy	Related to Infusion Procedure		Related to Immunosuppression Therapy	Related to Infusion Procedure
Number of Events	235	80 (34.0%)	34 (14.5%)	52	15 (28.8%)	12 (23.1%)
Number of Participants with 1 or More Events	61 (73.5%)	33 (39.8%)	23 (27.7%)	30 (36.1%)	8 (9.6%)	9 (10.8%)

Exhibit 122
Number of Recipients with Reported Adverse Events and Serious Adverse Events Following First Infusion by Visit Month

	Visit Month					
	<1 Month		1-6 Months		6-12 Months	
	N	%	N	%	N	%
Total Recipients	80	100.0	82	100.0	64	100.0
Total Adverse Events Reported per Recipient (Grade 3, 4, or 5)*						
0	44	55.0	42	51.2	39	60.9
1	18	22.5	16	19.5	13	20.3
2	10	12.5	13	15.9	4	6.3
3	5	6.3	4	4.9	1	1.6
4	1	1.3	5	6.1	2	3.1
5 or More	2	2.5	2	2.4	5	7.8
Total Serious Adverse Events Reported per Recipient						
0	75	93.8	62	75.6	53	82.8
1	3	3.8	12	14.6	8	12.5
2	2	2.5	7	8.5	1	1.6
3	-	0.0	1	1.2	2	3.1

*Based on the Cancer Therapy Evaluation Program, Common Terminology Criteria For Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS.

Exhibit 123
Summary of All Serious Adverse Events (SAEs) Reported by Type of SAE

Type of Serious Adverse Event*	N	%
All Serious Adverse Events	77	100.0
Death	-	0.0
Life Threatening	17	22.1
Inpatient Hospitalization	45	58.4
Prolongation of Existing Hospitalization	12	15.6
Persistent or Significant Disability/Incapacity	5	6.5

*Categories are not mutually exclusive.

Exhibit 124
Summary of All Serious Adverse Events (SAEs) Reported and Relationship to Islet Infusion Procedure

Relationship of Serious Adverse Event	N	%
All Serious Adverse Events	77	100.0
Unrelated	53	68.8
Unlikely Related	4	5.2
Possibly Related	7	9.1
Probably Related	4	5.2
Definitely Related	9	11.7

Exhibit 125
Summary of All Serious Adverse Events (SAEs) Reported and Relationship to Immunosuppression Therapy

Relationship of Serious Adverse Event	N	%
All Serious Adverse Events	77	100.0
Unrelated	29	37.7
Unlikely Related	12	15.6
Possibly Related	13	16.9
Probably Related	15	19.5
Definitely Related	6	7.8

Exhibit 126
Summary of All Serious Adverse Events (SAEs) Reported and Outcome

Outcome of Serious Adverse Event	N	%
All Serious Adverse Events	77	100.0
Resolved with No Residual Effects	73	94.8
Resolved with sequelae	1	1.3
Persistent condition, Recipient Alive	1	1.3
Missing Information	2	2.6

Exhibit 127
Summary of All Serious Adverse Events (SAEs) Reported by System Organ Class

System Organ Class*	N	%
All Serious Adverse Events	77	100.00
Gastrointestinal disorders	21	27.3
Blood and lymphatic system disorders	14	18.2
Infections and infestations	8	10.4
General disorders and administration site conditions	5	6.5
Investigations	5	6.5
Metabolism and nutrition disorders	5	6.5
Injury, poisoning and procedural complications	4	5.2
Hepatobiliary disorders	3	3.9
Nervous system disorders	3	3.9
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2	2.6
Psychiatric disorders	2	2.6
Surgical and medical procedures	2	2.6
Eye disorders	1	1.3
Musculoskeletal and connective tissue disorders	1	1.3
Respiratory, thoracic and mediastinal disorders	1	1.3

*MedDRA Classification (http://www.meddramsso.com/NewWeb2003/index.htm).

Exhibit 128
All Serious Adverse Events (SAEs) Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Abdominal haematoma	2002	Inpatient hospitalization	2 days post 2nd Infusion	Unknown	Missing	Probable	Missing	Missing	Missing
Abdominal hernia	2003	Inpatient hospitalization	299 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects
Abdominal hernia repair	2003	Inpatient hospitalization	39 days post 3rd Infusion	Yes	Severe (Grade 3)	Unrelated	Possible	No treatment or modification of treatment required for AE	Resolved, no residual effects
Abdominal pain	2002	Inpatient hospitalization	5 days post 1st Infusion	No	Severe (Grade 3)	Possible	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Abdominal pain	2002	Inpatient hospitalization	23 days post 1st Infusion	No	Severe (Grade 3)	Possible	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects
Abdominal pain	2002	Inpatient hospitalization	30 days post 2nd Infusion	No	Severe (Grade 3)	Possible	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Abdominal pain	2002	Inpatient hospitalization	52 days post 2nd Infusion	No	Severe (Grade 3)	Possible	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects
Abdominal pain	2004	Inpatient hospitalization	23 days post 2nd Infusion	Yes	Severe (Grade 3)	Unlikely	Possible	Required additional treatment for AE	Resolved, no residual effects
Abdominal pain	2004	Inpatient hospitalization	565 days post 2nd Infusion	No	Severe (Grade 3)	Possible	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects
Abdominal pain	2005	Inpatient hospitalization	1 days post 2nd Infusion	No	Severe (Grade 3)	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Alanine aminotransferase increased	2002	Prolongation of existing hospitalization	1 days post 2nd Infusion	Yes	Severe (Grade 3)	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Alanine aminotransferase increased	2002	Prolongation of existing hospitalization	2 days post 2nd Infusion	Yes	Severe (Grade 3)	Probable	Unlikely	No treatment or modification of treatment required for AE	Resolved, no residual effects
Anaemia	2002	Life threatening	0 days post 3rd Infusion	No	Life threatening (Grade 4)	Unlikely	Possible	Required additional treatment for AE	Resolved, no residual effects
Appendicitis	2003	Inpatient hospitalization	54 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Possible	No treatment or modification of treatment required for AE	Resolved, no residual effects
Aspartate aminotransferase increased	2002	Prolongation of existing hospitalization	1 days post 2nd Infusion	Yes	Severe (Grade 3)	Probable	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Aspartate aminotransferase increased	2002	Prolongation of existing hospitalization	1 days post 2nd Infusion	Yes	Severe (Grade 3)	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Back pain	2002	Inpatient hospitalization	119 days post 2nd Infusion	No	Severe (Grade 3)	Unlikely	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Benign neoplasm	2002	Inpatient hospitalization	1 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Cellulitis	2003	Inpatient hospitalization	58 days post 2nd Infusion	No	Severe (Grade 3)	Probable	Probable	Required additional treatment for AE	Resolved, no residual effects
Chest pain	2002	Inpatient hospitalization	437 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Chest pain	2004	Inpatient hospitalization	711 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects
Cholecystitis	2002	Inpatient hospitalization	211 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Cholecystitis	2003	Life threatening + Prolongation of existing hospitalization	0 days post 2nd Infusion	No	Life threatening (Grade 4)	Possible	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Cholelithiasis	2004	Inpatient hospitalization	438 days post 1st Infusion	No	Severe (Grade 3)	Unlikely	Unlikely	Surgery	Resolved, no residual effects
Confusional state	2003	Inpatient hospitalization	114 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Dehydration	2002	Inpatient hospitalization	214 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Diarrhoea	2002	Inpatient hospitalization	30 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Possible	No treatment or modification of treatment required for AE	Resolved, no residual effects
Diarrhoea	2004	Inpatient hospitalization	621 days post 3rd Infusion	Yes	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Missing
Diarrhoea	2004	Inpatient hospitalization	697 days post 3rd Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Current treatment modified based on AE	Resolved, no residual effects
Drug toxicity	2002	Persistent or significant disability/incapacity	244 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Current treatment modified based on AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Febrile neutropenia	2001	Inpatient hospitalization	62 days post 1st Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Gastroenteritis viral	2002	Inpatient hospitalization	44 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Gastrointestinal disorder	2003	Inpatient hospitalization	183 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Gastrointestinal disorder	2003	Inpatient hospitalization	510 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Haemorrhoids	2003	Inpatient hospitalization	19 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Hepatic haematoma	2003	Prolongation of existing hospitalization	0 days post 3rd Infusion	Yes	Severe (Grade 3)	Definite	Missing	Required additional treatment for AE	Resolved, no residual effects
Hip fracture	2003	Inpatient hospitalization	396 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Hypereosinophilic syndrome	2003	Persistent or significant disability/incapacity	647 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Hypoglycaemia	2002	Life threatening	59 days post 3rd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Hypoglycaemia	2002	Life threatening	230 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Hypoglycaemia	2004	Life threatening	296 days post 2nd Infusion	No	Life threatening (Grade 4)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Hypoglycaemia	2004	Life threatening	360 days post 3rd Infusion	No	Life threatening (Grade 4)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Inflammation	2003	Inpatient hospitalization	33 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Influenza	2003	Inpatient hospitalization	869 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Insomnia	2003	Life threatening	392 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Definite	Current treatment modified based on AE	Resolved, no residual effects
Intra-abdominal haemorrhage	2002	Prolongation of existing hospitalization	0 days post 1st Infusion	No	Severe (Grade 3)	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Intra-abdominal haemorrhage	2002	Prolongation of existing hospitalization	0 days post 2nd Infusion	No	Severe (Grade 3)	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Leukopenia	2004	Prolongation of existing hospitalization	2 days post 1st Infusion	Yes	Severe (Grade 3)	Definite	Definite	Required additional treatment and current treatment modified based on AE	Persistent condition, Alive
Memory impairment	2002	Persistent or significant disability/incapacity	193 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Current treatment modified based on AE	Resolved, no residual effects
Meningitis aseptic	2002	Inpatient hospitalization	102 days post 1st Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Neutropenia	2001	Life threatening	17 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Neutropenia	2002	Life threatening	42 days post 1st Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Neutropenia	2002	Life threatening	52 days post 1st Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Neutropenia	2002	Life threatening	75 days post 1st Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Neutropenia	2003	Life threatening	32 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Definite	No treatment or modification of treatment required for AE	Resolved, no residual effects
Neutropenia	2003	Life threatening	83 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Definite	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Neutropenia	2003	Life threatening	96 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Definite	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Neutropenia	2003	Life threatening	109 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Definite	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Neutropenia	2004	Life threatening	764 days post 2nd Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Pancreatitis	2003	Inpatient hospitalization	542 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Parvovirus infection	2002	Inpatient hospitalization	94 days post 1st Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2003	Prolongation of existing hospitalization	1 days post 3rd Infusion	No	Severe (Grade 3)	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Pneumonia	2002	Inpatient hospitalization	164 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	No treatment or modification of treatment required for AE	Resolved, no residual effects
Pneumonia aspiration	2001	Inpatient hospitalization	101 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Current treatment modified based on AE	Resolved, no residual effects
Post procedural haemorrhage	2004	Prolongation of existing hospitalization	1 days post 2nd Infusion	Yes	Severe (Grade 3)	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Postoperative infection	2004	Inpatient hospitalization	972 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Pyrexia	2004	Prolongation of existing hospitalization	-2 days post 1st Infusion	Yes	Missing	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Pyrexia	2004	Inpatient hospitalization	960 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects
Retinal detachment	2002	Persistent or significant disability/incapacity	334 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Somnolence	2001	Inpatient hospitalization	101 days post 1st Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Required additional treatment for AE	Resolved, no residual effects

Exhibit 128 *(continued)*
All Serious Adverse Events Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Squamous cell carcinoma of skin	2004	Persistent or significant disability/incapacity	591 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects
Surgery	2003	Inpatient hospitalization	133 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Unrelated	No treatment or modification of treatment required for AE	Resolved, with sequelae
Thrombocytopenia	2003	Inpatient hospitalization	14 days post 1st Infusion	Yes	Severe (Grade 3)	Unrelated	Possible	Current treatment modified based on AE	Resolved, no residual effects
Tremor	2004	Inpatient hospitalization	8 days post 2nd Infusion	Yes	Missing	Unrelated	Possible	Current treatment modified based on AE	Resolved, no residual effects
Vomiting	2003	Inpatient hospitalization	2 days post 3rd Infusion	No	Severe (Grade 3)	Possible	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Vomiting	2004	Inpatient hospitalization	1135 days post 2nd Infusion	Yes	Missing	Unrelated	Probable	No treatment or modification of treatment required for AE	Resolved, no residual effects
White blood cell count decreased	2002	Life threatening + Inpatient hospitalization	28 days post 2nd Infusion	No	Life threatening (Grade 4)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects

*Based on the Cancer Therapy Evaluation Program, Common Terminology Criteria For Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS.
**Based on classification by local CITR Investigator.

Exhibit 129
Number of Days Hospitalized at Infusion (Admission to Discharge)
by Infusion Sequence

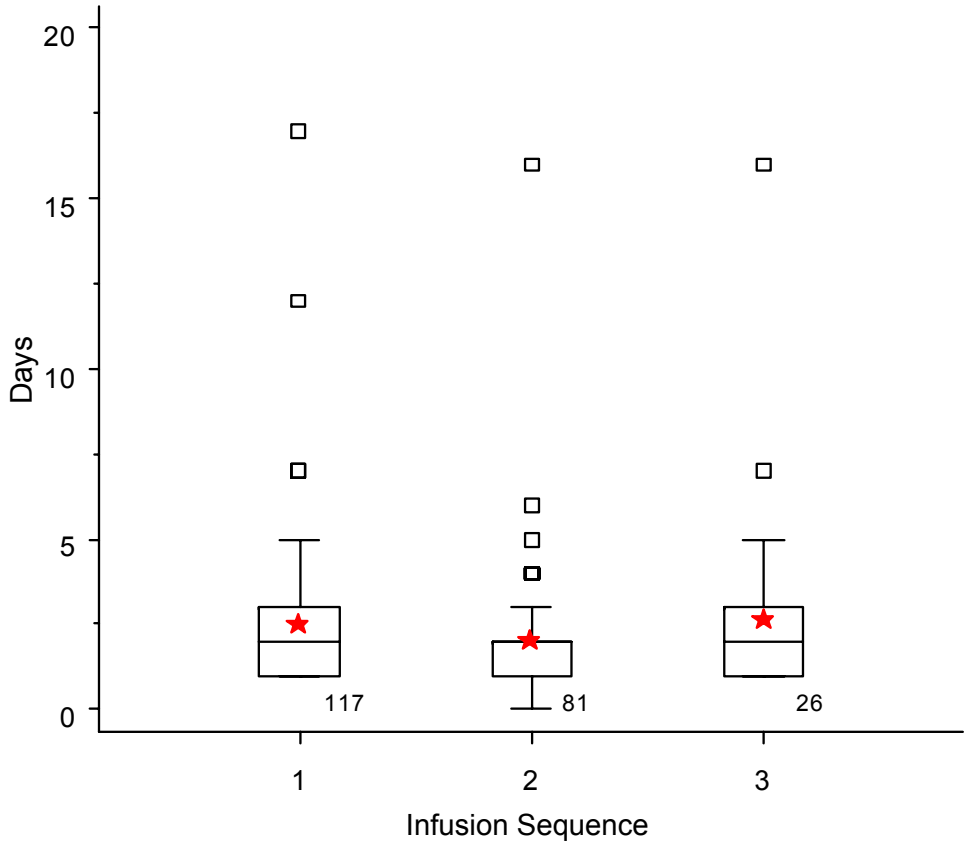


Exhibit 130
Hospitalizations Experienced Post Last Infusion by Total Number of Infusions Received

	Total Infusions Received											
	1				2				3			
	Month 6		Year 1		Month 6		Year 1		Month 6		Year 1	
	N	%	N	%	N	%	N	%	N	%	N	%
Total	46	100.0	32	100.0	64	100.0	45	100.0	25	100.0	20	100.0
Participants Requiring at Least One Hospitalization	5	10.9	-	0.0	16	25.0	8	17.8	3	12.0	2	10.0
Number of Hospitalizations												
0	39	84.8	29	90.6	44	68.8	36	80.0	22	88.0	18	90.0
1	5	10.9	-	0.0	12	18.8	7	15.6	3	12.0	2	10.0
2	-	0.0	-	0.0	3	4.7	1	2.2	-	0.0	-	0.0
3	-	0.0	-	0.0	1	1.6	-	0.0	-	0.0	-	0.0
Missing	2	4.3	3	9.4	4	6.3	1	2.2	-	0.0	-	0.0

Exhibit 131
Changes in Portal Pressure (mmHg) and Infusion Summary by Infusion Sequence

	Infusion 1					
	N	Mean	SD	Median	Min	Max
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure (mmHg)	111	2.5	2.7	2.0	-1.0	16.0
Change in Portal Pressure from Pre to Post Infusion (mmHg)	111	1.6	3.0	1.0	-5.0	16.0
Islet Equivalents Infused	117	456,130	149,445	410,100	200,000	973,133
Islet Packed Cell Volume (mL)	113	4.0	2.2	3.7	1.0	15.0

	Infusion 2					
	N	Mean	SD	Median	Min	Max
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure (mmHg)	77	3.5	2.8	3.0	0.0	15.0
Change in Portal Pressure from Pre to Post Infusion (mmHg)	76	2.5	2.9	2.0	-5.0	15.0
Islet Equivalents Infused	80	437,714	155,915	394,422	190,036	1,056,430
Islet Packed Cell Volume (mL)	78	3.7	1.8	3.5	0.8	9.0

	Infusion 3					
	N	Mean	SD	Median	Min	Max
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure (mmHg)	25	3.8	3.8	3.0	0.0	16.0
Change in Portal Pressure from Pre to Post Infusion (mmHg)	25	2.9	3.2	2.0	-1.0	12.0
Islet Equivalents Infused	25	448,464	140,519	420,296	246,000	802,632
Islet Packed Cell Volume (mL)	26	3.5	2.0	2.8	0.7	9.0

Exhibit 132
Pre Infusion Portal Pressure (mmHg) by Infusion Sequence

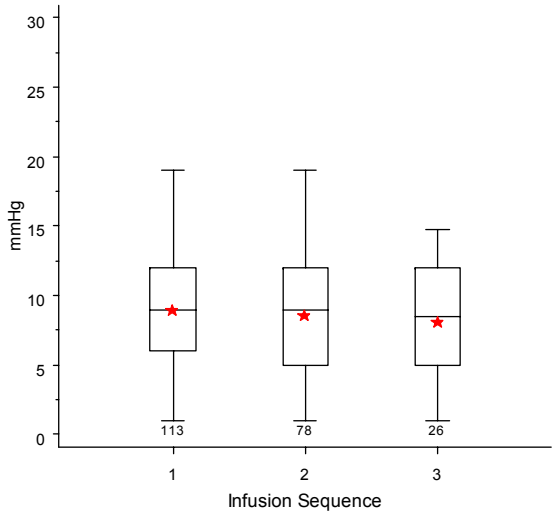


Exhibit 133
Peak Portal Pressure (mmHg) by Infusion Sequence

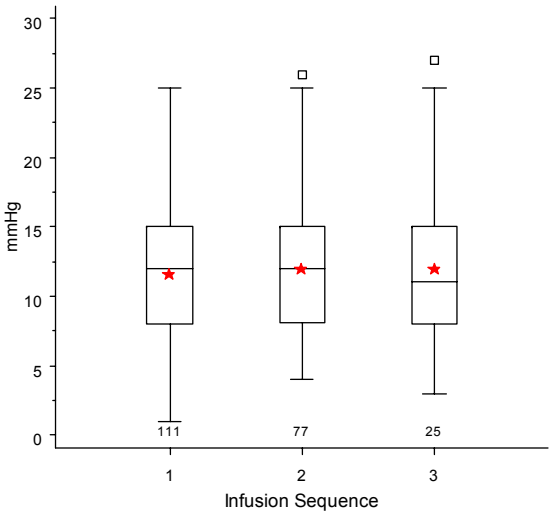


Exhibit 134
Closure Portal Pressure (mmHg) by Infusion Sequence

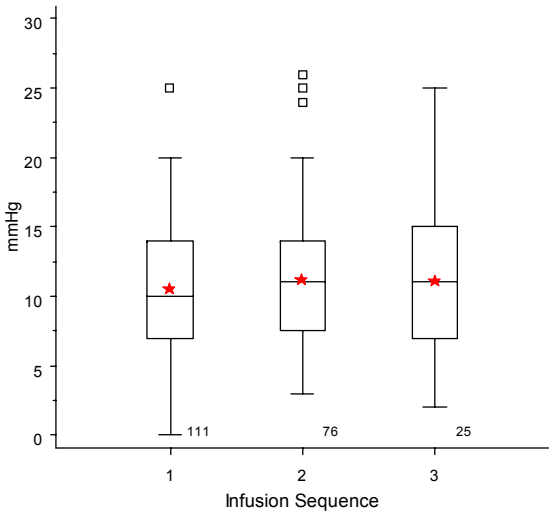


Exhibit 135
Change from Pre Infusion to Closure Portal Pressure (mmHg)
by Infusion Sequence

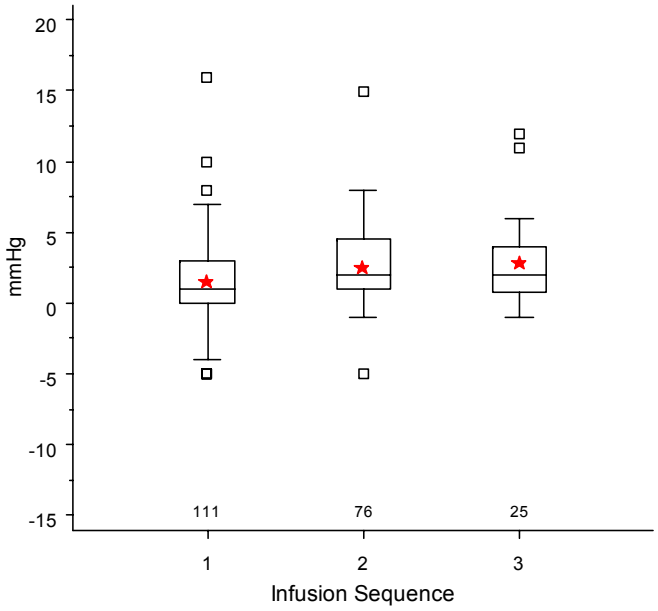
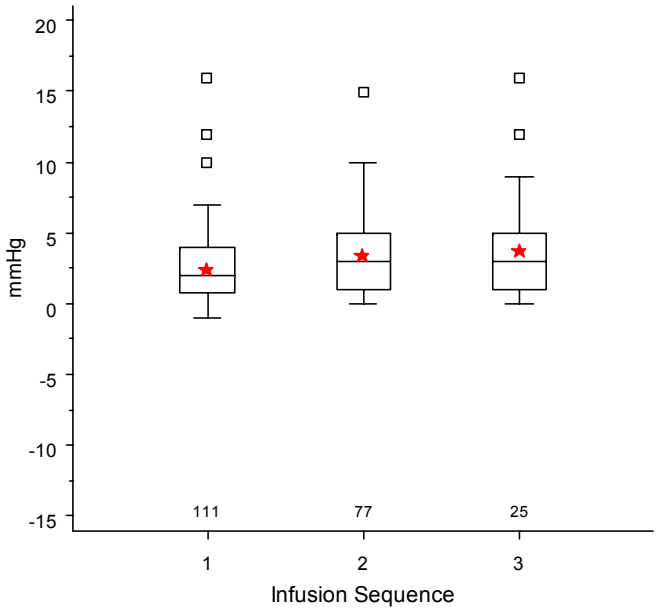


Exhibit 136
Change from Pre Infusion to Peak Portal Pressure (mmHg)
by Infusion Sequence



Section 3
Islet After Kidney Transplant Information

Islet After Kidney Transplant Information Summary

Registry information collected on islet after kidney transplant recipients are included in this section. Currently, 19 recipients from three islet transplant programs were entered with initial infusions prior to December 31, 2004 and this report provides the initial Registry description of islet after kidney transplants. As only one recipient received three islet infusions, information from this infusion has been omitted from the tables and figures in this section where data are presented by infusion sequence.

Recipient Information:

The median age of the islet after kidney transplant recipient was 47.7 years (range 34.3 to 55.5) and the median duration of diabetes was 31 years (range 15 to 42). The median weight of the recipient was 60.0 kg (range 46.8 to 89.4) and the median body mass index (BMI) was 22.7 kg/m^2 (range 15.4 to 25.9) (Exhibit 137). Over 63% of the recipients are female (Exhibit 138). Compared to islet alone recipients, islet after kidney recipients are older, weigh less and have a lower BMI.

At the time of the first infusion, 52.6% of the recipients were employed full-time and for approximately 79% of the transplant procedures the primary funding was through non-government research grants (Exhibit 139). Approximately, 26% of the islet transplant recipients were on an insulin pump prior to their first infusion. Almost 90% of the recipients were either on an insulin pump or were taking 3 or more insulin injections per day (Exhibit 140). The mean daily insulin requirement of recipients prior to their first infusion procedure was 35.3 units (SD 14.7). Their mean fasting plasma glucose was 189.1 mg/dL (SD 123.4) and their mean HbA_{1c} was 7.7% (SD 1.1) (Exhibit 141).

Islet Infusion Information:

Exhibit 143 summarizes the main infusion procedure characteristics by infusion sequence. On average, second infusions were administered 17 weeks following first infusion (N=14).

Donor Information:

The median age of the deceased donor was 46 years (range 19 to 64) and the median body mass index was 28.4 kg/m^2 (range 20.2 to 68.9). The median time from cross clamp to pancreas recovery was 40 minutes (range 5 to 64) (Exhibit 144). Median time for islet alone recipients was 28.0 minutes (range 0 to 127). Fifty percent of the donors were male, 12.5% were Hispanic and approximately 88% were white. Over 72% of the donors had a cerebrovascular/stroke as cause of death while almost 18% experienced a head trauma. Thirty percent of the donors had a history of hypertension and almost 23% had a history of alcohol dependency.

Almost 18% of the donors received a transfusion prior to organ procurement and only one donor received a transfusion during the organ procurement surgery. Approximately 63% of the donors received steroids and almost a third of the donors had received insulin (Exhibit 145). All of the donors received at least one vasopressor during the hospitalization leading to death (Exhibit 150).

Donor serology is presented in Exhibit 151. None of the serology tests (except for Anti CMV) were positive. Donor laboratory data are presented in Exhibit 152. The median serum creatinine of the donors was 0.9 mg/dL, total bilirubin 0.8 mg/dL, AST 34.0 IU/L, ALT 33.0 IU/L, serum lipase 31.0 IU/L and serum amylase 56.0 IU/L. The median minimum pre-insulin blood glucose was 101.5 mg/dL and the median maximum blood glucose was 231.5 (mg/dL). Boxplots are presented for the donor laboratory values (Exhibits 153-161).

Pancreas Procurement and Islet Processing Information:

Also summarized in this section are pancreas procurement and islet processing data reported to the Registry. In half of the pancreas removal procedures, the procurement team was not related/affiliated with the processing/infusion team (Exhibit 162). In every case, islet processing occurred at the same institution where the islet infusion procedure was conducted. In all but three cases, Liberase HI was the collagenase preparation used, all used a density gradient for purification and 27.5% of the islet products processed utilized islet cell culture. Two were gram stain positive (5.0%), while one aerobic test (2.5%) and one anaerobic test (2.5%) were positive (Exhibit 162).

Of the preparations, the median time from cross clamp to pancreas recovery was 40 minutes and the median duration of cold ischemia was 6.9 hours (Exhibit 163). An islet product characterization summary is located in Exhibit 165 and a summary of the mean number of islet equivalents/kg infused is summarized in Exhibit 166.

Immunosuppression Medications:

In 42% of the cases, the islet after kidney recipients were on the Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen. This same regimen was used for 61.9% of the islet alone recipients. A complete list of all immunosuppression regimens is included in Exhibit 167. Dosing for the immunosuppressive medications at the time of infusion is located in Exhibits 168 and 169. Maintenance therapies are listed in Exhibit 170 and 171. Sirolimus and Tacrolimus trough levels at Day 30 for each infusion (1 and 2), as well as trough levels at month 6 and year 1 post last infusion are presented as boxplots in Exhibits 172 and 173.

Graft Function:

As indicated in section 2 of this report, analyses for graft function includes only the most complete data. Given the small sample size and this initial look at islet after kidney transplant, analyses are limited this year.

Exhibits 174 and 175 examine insulin status by a cohort analysis, following a group of recipients from 6 months to year 1 post first infusion and a cohort analysis following the group of recipients at month 6 to year 1 post their last infusion. At month 6 post first infusion, 53.8% (7/13) were insulin independent. Of those recipients insulin independent at month 6, at year 1, four remained insulin independent (57.1%). In contrast, of the 6 insulin dependent participants at month 6, four (66.6%) became insulin independent at year 1 post first infusion (Exhibit 174).

At month 6 post last infusion, 71.4% (10/14) were insulin independent. Of these 10 participants, five (50%) remained insulin independent at year 1. None of the insulin dependent recipients at month 6 achieved insulin independence by year 1 (Exhibit 175).

For participants remaining on insulin at 6 and 12 months post last infusion, the mean reduction in required daily insulin units from baseline were conducted (Exhibit 176). Only participants with a CITR insulin administration form were included in the analyses. Overall, if participants did remain on insulin, there was a 76.2% mean reduction in their daily insulin units as compared to

their baseline daily insulin units at month 6. This ranged from a minimum mean reduction of 66.0% to 83.3%. Islet alone recipients remaining on insulin experienced a 56.5% reduction from baseline for the same time period. Average daily insulin units required for participants remaining on insulin at 6 months were 9.8 units (Exhibit 177). At 12 months, there was a mean reduction of 83.8% (69% reduction for islet alone recipients) with a minimum of 78.0% and a maximum of 91.7%. Average daily insulin required, administered at one year for participants remaining on insulin, was 5.2 (units).

Severe Hypoglycemic Events:

Similar to the islet transplant alone recipients, there was a sharp decrease in the number of hypoglycemic events post first infusion from baseline (Exhibit 178). Over 57% of participants experienced one or more hypoglycemic events prior to their first infusion. This decreases to 5.3% (N=1) up to 30 days post infusion and to 0% at later intervals during the first year post infusion.

Laboratory Tests:

Exhibits 179-181 present summary data for fasting plasma glucose, HbA_{1c}, and basal plasma C-peptide values at pre infusion and post infusion and Exhibit 182 presents a summary of all laboratory values collected just prior to infusion 1 and infusion 2.

Also included are a summary of reported abnormal laboratory liver function tests (Exhibit 183), abnormal lipid tests (Exhibit 188), and the percent of participants with a marked increase in serum creatinine from baseline (Exhibit 193). Abnormal has been defined as one or greater times the upper limit of normal to up to two times the upper limit of normal for the test and two or greater times the upper limit of normal for the test.

There were reports at the two times or greater than the upper limit of normal for ALT (N=1) and AST (N=2), but no reports for alkaline phosphatase or for total bilirubin (Exhibit 183). There were no reports at two times or greater than the upper limit of normal for total cholesterol or for triglycerides (Exhibit 188). When examining LDL, two of the recipients had reported receiving a result between 130-150 mg/dL and 12 had reported obtaining a result of <130 mg/dL. In addition, there were 2 reports (14.3%), of a recipient with an increase in their serum creatinine of 0.5mg/dL or greater than their baseline level.

Summary measures for each laboratory value are also constructed prior to their first infusion and by month 6 and year 1 post the recipient's last infusion procedure. For each of these laboratory tests, boxplots are displayed (Exhibits 184-187, 189-192, and 194-195). For a boxplot the "star" (★) represents the mean value. The whiskers of the plot represent the minimum value and the maximum value, while the lower line of the box represents the 25th percentile, the upper line of the box the 75th percentile and the middle line in the box represent the median (50th percentile).

Adverse Events:

All grade 3, 4 and 5 adverse events, according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute, are reported to CITR. Respective CITR Principal Investigators determine the relationship of the adverse event to the immunosuppression therapy and to the islet infusion procedure at the time the adverse event forms are completed.

Exhibit 196 presents the overall adverse event and serious adverse event rate for islet after kidney transplant recipients in year 1 post their first islet infusion. Almost 58% (N=11) of the recipients experienced at least one adverse event in year 1, while only 26% (N=5) experienced one or more serious adverse events in this same period. Of the 21 reported adverse events, 23.8% were related to the immunosuppression therapy and 52.4% were related to the infusion procedure. Of the 9 reported serious adverse events, 1 (11%) was related to the immunosuppression therapy and 4 (44.4%) were related to the islet infusion procedure.

In Exhibit 197, adverse events are summarized by time periods following the recipient's first infusion procedure (<1 month, 1-6 months, and 6-12 months). In the first month following infusion, 44.4% of the recipients reported at least one adverse event following their first infusion procedure, while during months 1-6, 35.3% reported at least one adverse event, and between 6 and 12 months, 16.7% reported an adverse event. For serious adverse events reported during the same time period, the percentages were 16.7% within one month of the infusion, 17.6% reported between the first month and the sixth month, and 16.7% reported between month 6 and year 1 post first infusion.

At the time of this report, 16 serious adverse events have been reported for the 19 participants, with 56.3% of the serious adverse events requiring an inpatient hospitalization (Exhibit 198). Almost 63% of the serious adverse events were classified as unrelated to the islet infusion procedure (Exhibit 199) with 38% unrelated to the immunosuppression therapy (Exhibit 200). Approximately 88% of the serious adverse events resolved with no residual effects (Exhibit 201). The most common serious adverse events were related to gastrointestinal disorders (18.8%) as classified by the MedDRA classifications system (Exhibit 202).

Exhibit 203 lists serious adverse events, the year when it occurred related to the last infusion date, its relationship to the islet infusion procedure, treatment required and the final outcome of the event. The number of hospitalization days for the islet infusion procedure is summarized in this section (Exhibit 204), as well as hospitalizations occurring during the post infusion follow-up period (Exhibit 205). Portal pressures and changes in portal pressures are summarized in Exhibit 206.

Exhibit 137
Recipient Demographics

	Overall			
	N	Median	Min	Max
Age (yrs)	19	47.7	34.3	55.5
Duration of Diabetes (yrs)	19	31.0	15.0	42.0
Weight (kg)	19	60.0	46.8	89.4
Body Mass Index (kg/m^2)	19	22.7	15.4	25.9

Exhibit 138
Recipient Characteristics

	Overall	
	N	%
Gender		
Male	7	36.8
Female	12	63.2
Race		
American Indian or Alaska Native	-	0.0
Asian	-	0.0
Black or African American	-	0.0
Indian Sub-continent	-	0.0
Mideast or Arabian	-	0.0
Native Hawaiian or Other Pacific Islander	-	0.0
White	19	100.0
Ethnicity		
Non Hispanic or Latino	19	100.0
Hispanic or Latino	-	0.0
Diabetes Type		
Type 1 Diabetes	19	100.0
Pancreatectomy Induced	-	0.0

Exhibit 139
Recipient's Primary Payer and Employment Status at Time of First Infusion

	Overall	
	N	%
Primary Payer		
US/State Government Agency	4	21.1
Private Insurance	-	0.0
Institutional Commitment	-	0.0
Non-Government Research Grant	15	78.9
Provincial Government	-	0.0
Missing	-	0.0
Employment status		
Working full time	10	52.6
Working part-time by choice	2	10.5
Working part-time due to disease	1	5.3
Working part-time, reason unknown	-	0.0
Not working by choice	1	5.3
Not working due to disease	4	21.1
Not working, unable to find employment	-	0.0
Not working, reason unknown	-	0.0
Student	-	0.0
Retired	-	0.0
Employment status unknown	1	5.3
Missing	-	0.0

Exhibit 140
Recipient Status at First Infusion

	Overall	
	N	%
Total	19	100.0
Use of insulin pump		
Yes	5	26.3
No	13	68.4
Unknown	1	5.3
Number of injections per day		
N/A - on pump	5	26.3
1-2	1	5.3
3-5	11	57.9
6 or more	1	5.3
Unknown	1	5.3
Intensive therapy (Use of insulin pump or 3 or more injections per day)		
Yes	17	89.5
No	2	10.5
Unknown	-	0.0
Pre transplant autoantibody - GAD 65		
Positive	-	0.0
Negative	4	21.1
Not Done/Unknown	15	78.9
Pre transplant autoantibody - IA-2		
Positive	-	0.0
Negative	4	21.1
Not Done/Unknown	15	78.9
Pre transplant autoantibody - Insulin		
Positive	3	15.8
Negative	-	0.0
Not Done/Unknown	16	84.2

Exhibit 140 *(continued)*
Recipient Status at First Infusion

	Overall	
	N	%
Positive crossmatch for B-Cell		
Yes	-	0.0
No	19	100.0
Positive crossmatch for T-Cell		
Yes	-	0.0
No	19	100.0

Exhibit 141
Recipient Summary Measures at First Infusion

	Overall		
	N	Mean	SD
Daily insulin requirement prior to infusion (units)	18	35.3	14.7
Duration of intensive therapy (yrs)	1	10.0	-
Fasting plasma glucose (mg/dL)	18	189.1	123.4
HbA_{1c} (%)	17	7.7	1.1

Exhibit 142
Recipient Serology at Screening

	Overall	
	N	%
Total	19	100.0
HIV screening		
Positive	-	0.0
Negative	18	94.7
Not Done/Unknown/Missing	1	5.3
CMV IGG		
Positive	7	36.8
Negative	10	52.6
Not Done/Unknown/Missing	2	10.5
CMV IgM		
Positive	-	0.0
Negative	6	31.6
Not Done/Unknown/Missing	13	68.4
HepB core antibody		
Positive	-	0.0
Negative	6	31.6
Not Done/Unknown/Missing	13	68.4
HepB surface antigen		
Positive	-	0.0
Negative	18	94.7
Not Done/Unknown/Missing	1	5.3
HepC antibody		
Positive	-	0.0
Negative	18	94.7
Not Done/Unknown/Missing	1	5.3
EBV IgG		
Positive	16	84.2
Negative	-	0.0
Not Done/Unknown/Missing	3	15.8

Exhibit 143
Infusion Summary by Infusion Sequence

	Infusion 1					
	N	Mean	SD	Median	Min	Max
Islet Equivalents infused	18	509,764	128,220	492,925	318,000	800,000
Islet Equivalents infused/kg	18	8,568	2,311	8,581	5,274	15,532
Packed cell volume	13	4.2	1.6	5.0	1.0	6.0
Pre portal pressure (mmHg)	16	8.1	4.3	7.5	1.0	15.0
Peak portal pressure (mmHg)	14	9.7	4.1	9.0	3.0	16.0
Closure portal pressure (mmHg)	17	9.7	4.5	9.0	2.0	19.0
Time since first infusion (weeks)	0	-	-	-	-	-

	Infusion 2					
	N	Mean	SD	Median	Min	Max
Islet Equivalents infused	11	440,155	86,910	408,300	298,200	600,000
Islet Equivalents infused/kg	11	7,383	1,690	6,920	5,646	10,926
Packed cell volume	9	3.8	1.3	3.8	1.6	5.0
Pre portal pressure (mmHg)	11	8.9	4.1	10.0	2.0	16.0
Peak portal pressure (mmHg)	10	10.1	3.9	10.0	4.0	16.0
Closure portal pressure (mmHg)	11	9.4	4.7	9.0	2.0	17.0
Time since first infusion (weeks)	14	17.0	19.7	9.9	3.3	73.3

Exhibit 144
Donor Characteristics

	Overall			
	N	Median	Min	Max
Age (yrs)	39	46.0	19.0	64.0
Weight (kg)	39	84.0	55.0	199.6
Height (m)	39	1.7	1.5	1.9
Body Mass Index (kg/m^2)	37	28.4	20.2	68.9
Time from admission to brain death (hrs)	34	40.5	2.0	172.0
Duration of cardiac arrest where there was a cardiovascular death (mins)	3	11.0	1.0	25.0
Time from cross clamp to pancreas recovery (mins)	31	40.0	5.0	64.0

Exhibit 145
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
Total	40	100.0
Gender		
Female	19	47.5
Male	20	50.0
Missing	1	2.5
Race		
American Indian or Alaska Native	-	0.0
Asian	1	2.5
Black or African American	2	5.0
Indian Sub-continent	-	0.0
Mideast or Arabian	-	0.0
Native Hawaiian or Other Pacific Islander	-	0.0
White	35	87.5
Missing	2	5.0
Ethnicity		
Non Hispanic or Latino	34	85.0
Hispanic or Latino	5	12.5
Missing	1	2.5
Body Mass Index		
<25	7	17.5
25-27	9	22.5
28-30	8	20.0
>30	15	37.5
Missing	1	2.5

Exhibit 145 *(continued)*
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
Donor ABO blood group		
A	14	35.0
A_1	3	7.5
A_2	1	2.5
AB	-	0.0
A_1B	-	0.0
A_2B	-	0.0
B	2	5.0
O	19	47.5
Missing	1	2.5
Cause of death		
Anoxia/cardiac arrest	2	5.0
CNS tumor	1	2.5
Cerebrovascular/stroke	29	72.5
Head trauma	7	17.5
Other	-	0.0
Missing	1	2.5
Mechanism of death		
Asphyxiation	-	0.0
Blunt injury	5	12.5
Cardiovascular	1	2.5
Death from natural causes	-	0.0
Drug intoxication	-	0.0
Gunshot wound	1	2.5
Intracranial hemorrhage/stroke	31	77.5
Seizure	1	2.5
None of the above	-	0.0
Missing	1	2.5

Exhibit 145 *(continued)*
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
Circumstances of death		
Alleged homicide	-	0.0
Alleged suicide	1	2.5
Death from natural causes	7	17.5
Motor vehicle accident	3	7.5
Non-motor vehicle accident	2	5.0
None of the above	26	65.0
Missing	1	2.5
History of hypertension		
Yes	12	30.0
No	26	65.0
Missing	2	5.0
-Hypertension duration		
0-5 years	7	58.3
6-10 years	2	16.7
>10 years	1	8.3
Missing	2	16.7
-Hypertension control-Diet		
Yes	2	16.7
No	4	33.3
Missing	6	50.0
-Hypertension control-Diuretics		
Yes	1	8.3
No	7	58.4
Missing	4	33.3
-Hypertension control-Other medications		
Yes	8	66.6
No	2	16.7
Missing	2	16.7

Exhibit 145 *(continued)*
Donor Characteristics and Hospitalization Summary Information

	Overall	
	N	%
History of alcohol dependency		
Yes	9	22.5
No	23	57.5
Missing	8	20.0
-Alcohol use in past 6 months		
Yes	5	55.6
No	4	44.4
Missing	0	0.0
History of diabetes		
Yes	-	0.0
No	39	97.5
Missing	1	2.5
Transfusions given prior to surgery		
0 units	27	67.5
0-5 units	7	17.5
6-10 units	-	0.0
>10 units	-	0.0
Missing	6	15.0
Transfusions given intraoperatively		
0 units	33	82.5
0-5 units	1	2.5
6-10 units	-	0.0
Missing	6	15.0
Steroids given		
Yes	25	62.5
No	9	22.5
Missing	6	15.0
Insulin given		
Yes	13	32.5
No	20	50.0
Missing	7	17.5

Exhibit 146
Donor Age (yrs)

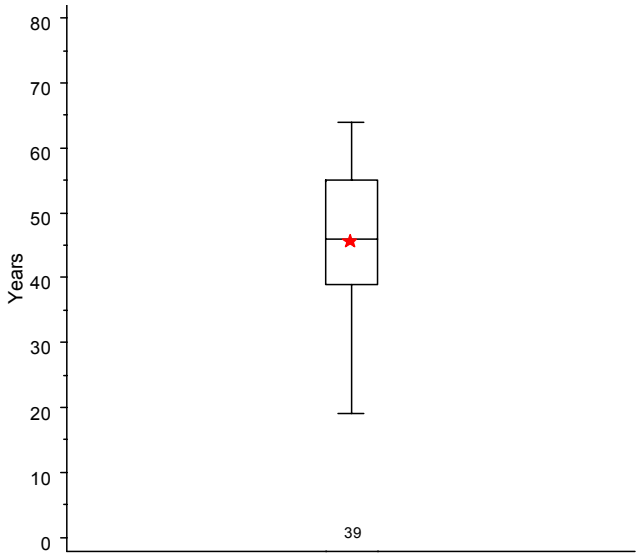


Exhibit 147
Donor Weight (kg)

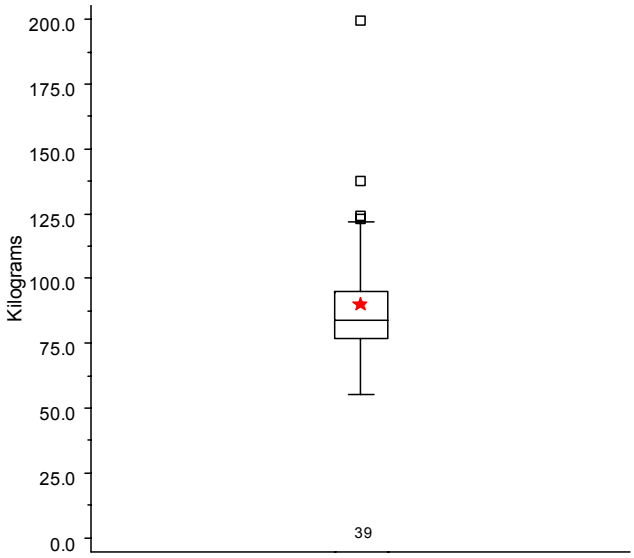


Exhibit 148
Donor Body Mass Index (kg/m^2)

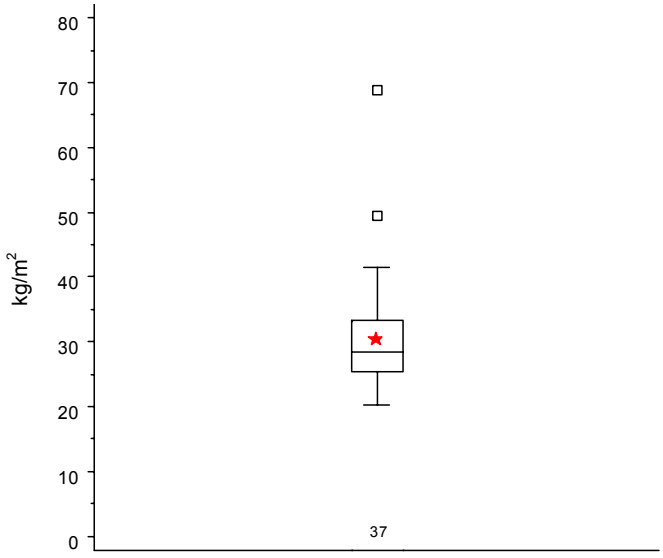


Exhibit 149
Time from Cross Clamp to Pancreas Recovery (mins)

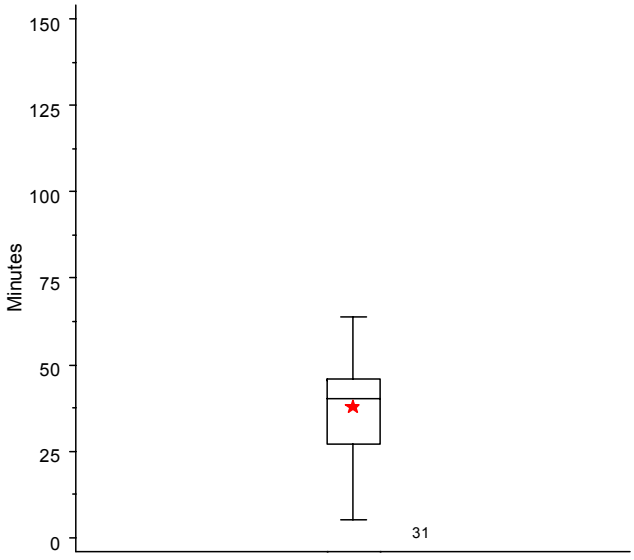


Exhibit 150
Donor Characteristics: Use of Vasopressors

	Overall	
	N	%
Total	40	100.0
Vasopressors used		
Yes	34	85.0
No	-	0.0
Missing	6	15.0
Number of vasopressors used		
None	-	0.0
One	10	25.0
Two	15	37.5
Three	6	15.0
Four	3	7.5
Missing	6	15.0

Exhibit 151
Donor Serology

	Overall	
	N	%
Total	40	100.0
Anti HIV I/II		
Positive	-	0.0
Negative	38	95.0
Not Done/Unknown/Missing	2	5.0
Anti HTLV I/II		
Positive	-	0.0
Negative	38	95.0
Not Done/Unknown/Missing	2	5.0
RPR VDRL		
Positive	-	0.0
Negative	38	95.0
Not Done/Unknown/Missing	2	5.0
Anti CMV		
Positive	18	45.0
Negative	20	50.0
Not Done/Unknown/Missing	2	5.0
HBsAg		
Positive	-	0.0
Negative	38	95.0
Not Done/Unknown/Missing	2	5.0
Anti HBC		
Positive	-	0.0
Negative	38	95.0
Not Done/Unknown/Missing	2	5.0
Anti HCV		
Positive	-	0.0
Negative	38	95.0
Not Done/Unknown/Missing	2	5.0

Exhibit 152
Donor Laboratory Data

	Overall					
	N	Mean	SD	Median	Min	Max
Serum creatinine (mg/dL)	39	0.9	0.3	0.9	0.4	1.5
BUN (mg/dL)	39	12.3	5.8	11.0	4.0	27.0
Total bilirubin (mg/dL)	39	0.9	0.5	0.8	0.2	2.2
AST (IU/L)	39	46.4	46.4	34.0	17.0	269.0
ALT (IU/L)	39	41.7	40.4	33.0	16.0	262.0
Serum lipase (IU/L)	39	55.1	75.8	31.0	2.0	394.0
Serum amylase (IU/L)	39	133.7	202.4	56.0	18.0	797.0
Minimum pre-insulin blood glucose (mg/dL)	34	114.2	31.5	101.5	67.0	216.0
Maximum blood glucose (mg/dL)	34	256.5	102.0	231.5	117.0	581.0

Exhibit 153
Donor Serum Creatinine (mg/dL)

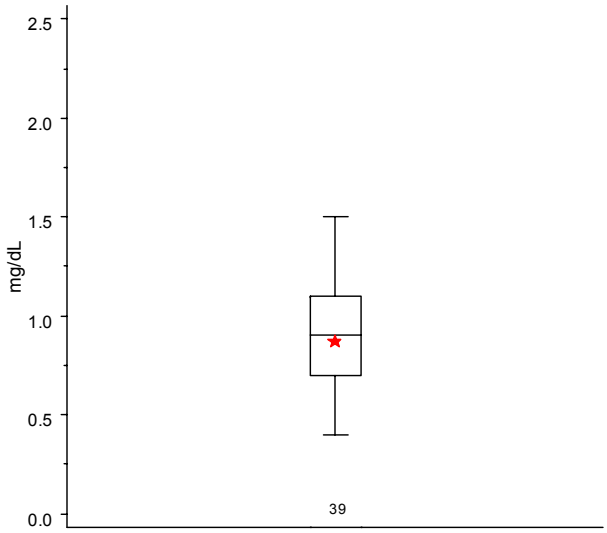


Exhibit 154
Donor BUN (mg/dL)

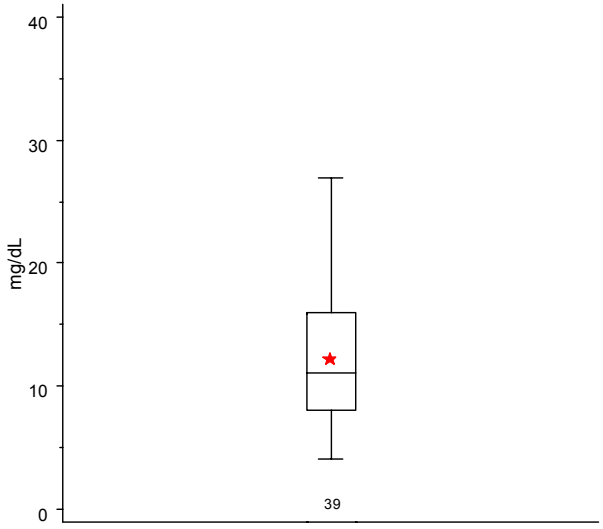


Exhibit 155
Donor Total Bilirubin (mg/dL)

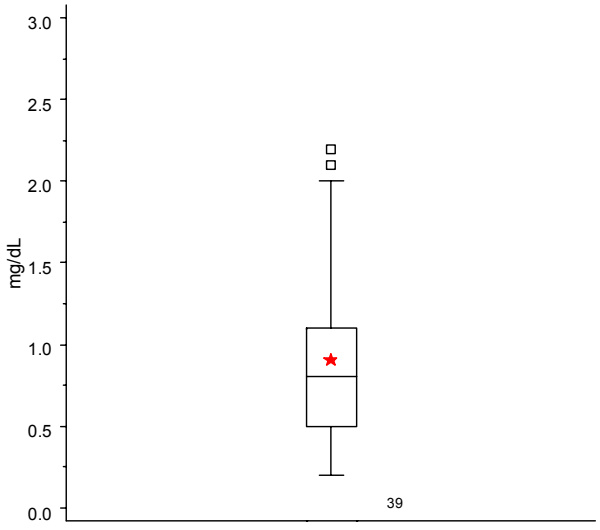


Exhibit 156
Donor AST (IU/L)

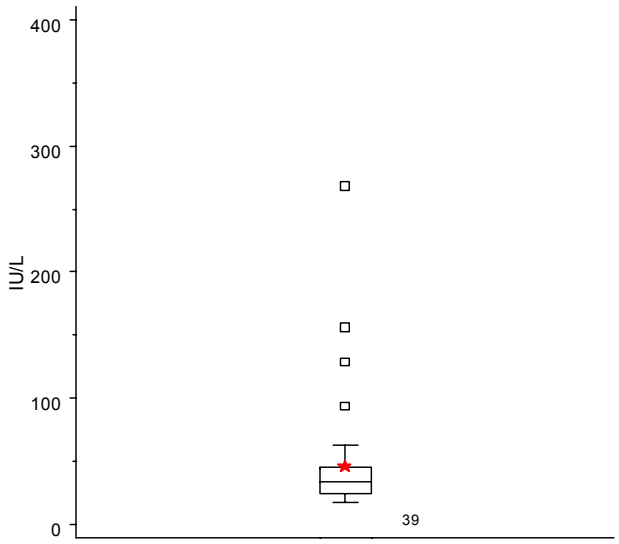


Exhibit 157
Donor ALT (IU/L)

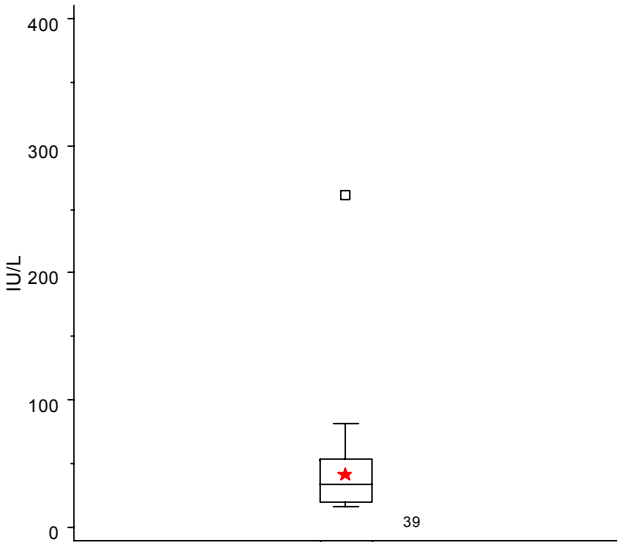


Exhibit 158
Donor Serum Lipase (IU/L)

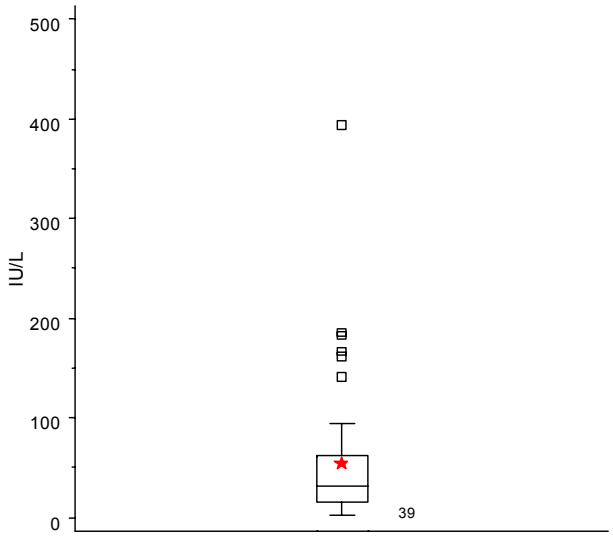


Exhibit 159
Donor Serum Amylase (IU/L)

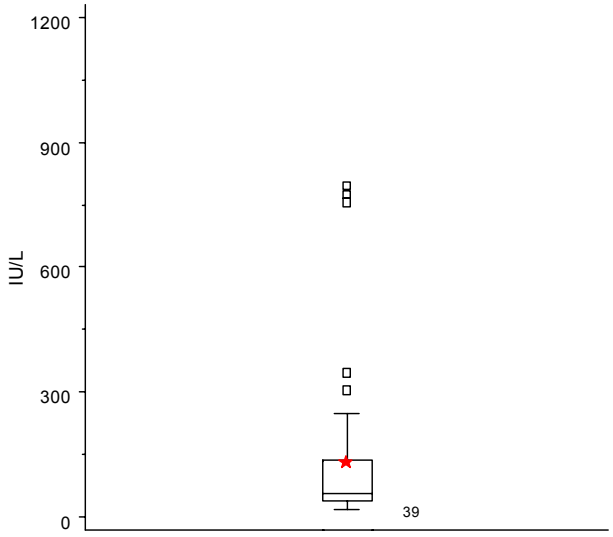


Exhibit 160
Donor Pre-Insulin Blood Glucose (mg/dL)

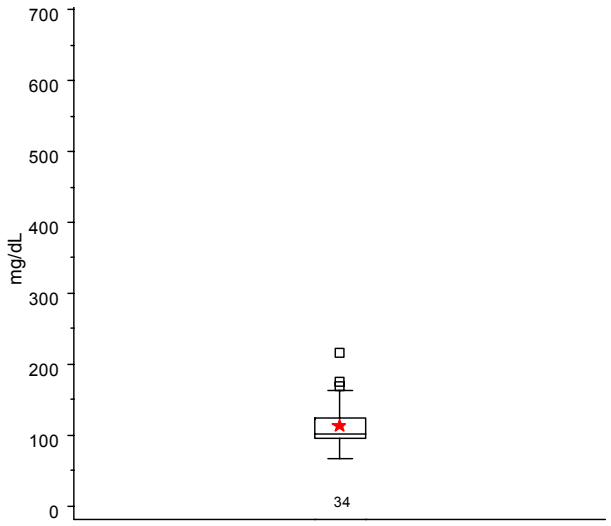


Exhibit 161
Donor Maximum Blood Glucose (mg/dL)

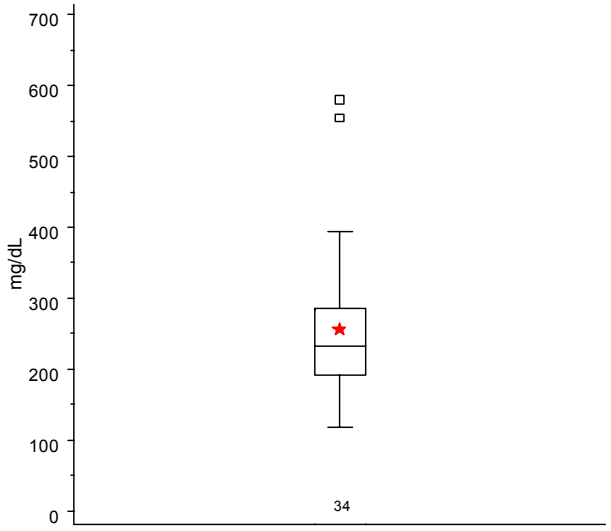


Exhibit 162
Islet Processing Summary

	Overall	
	N	%
Total	40	100.0
Pancreas procurement team		
Unrelated to processing/infusion team	18	45.0
Related to processing/infusion team	18	45.0
Missing	4	10.0
Islet processing/testing center		
CITR center, where infusion took place	33	82.5
Another facility not located or affiliated with the transplant center	-	0.0
Missing	7	17.5
Pancreas preservation		
UW	30	75.0
Two layer	5	12.5
UW followed by two layer	1	2.5
Other	4	10.0
Collagenase Type: Liberase HI		
Yes	37	92.5
No	3	7.5
Collagenase Type: Serva		
Yes	-	0.0
No	40	100.0
Islet purification		
None	-	0.0
Density gradient	37	92.5
Islet pretreatment		
None	26	65.0
Culture	11	27.5
Missing	3	7.5

Exhibit 162 *(continued)*
Islet Processing Summary

	Overall	
	N	%
Gram stain		
Positive	2	5.0
No organism seen	33	82.5
Missing	5	12.5
Aerobic culture		
Positive	1	2.5
No Growth	24	60.0
Not Done	9	22.5
Missing	6	15.0
Anaerobic culture		
Positive	1	2.5
No Growth	25	62.5
Not Done	8	20.0
Missing	6	15.0
Fungal culture		
Positive	-	0.0
No Growth	24	60.0
Not Done	9	22.5
Missing	7	17.5
Mycoplasma		
Positive	-	0.0
Gram negative	18	45.0
Not Done	-	0.0
Missing	22	55.0

Exhibit 163
Pancreas Procurement Information

	Overall					
	N	Mean	SD	Median	Min	Max
Time from cross clamp to pancreas recovery (mins)	31	37.9	14.8	40.0	5.0	64.0
Duration of cold ischemia (hrs)	37	7.5	3.0	6.9	3.5	15.7

Exhibit 164
Summary of Islet Equivalents and Timing of Count

	Total Islet Equivalents					
	N	Mean	SD	Median	Min	Max
Islet Equivalents (IEQ) measured at:						
Post Digestion	1	479,583	-	479,583	479,583	479,583
Post Purification (Pre culture/cryo)	28	414,516	107,591	417,184	193,417	576,000
Post culture/cryo	8	422,435	70,277	434,521	289,833	537,500

Exhibit 165
Islet Product Characterization

	Overall					
	N	Mean	SD	Median	Min	Max
Total packed cell volume infused (mL)	27	4.0	1.5	5.0	1.0	6.0
Islet count	35	386,540	129,985	383,917	102,500	728,333
Embedded islets (%)	10	21.0	18.1	17.5	0.0	50.0
Islet equivalents/kg	37	4,854	1,522	4,786	2,156	9,879
Islet equivalents planned for infusion	28	544,615	137,093	505,546	381,383	800,000
Islet equivalents infused	34	516,045	141,558	492,925	298,200	800,000
Beta cells ($x10^6$)	5	426.0	164.8	374.0	250.0	667.0
Beta cells/kg	5	5.1	2.3	5.3	2.6	7.6
Insulin content (µgrams)	7	1,124	1,406	336	19	3,192
DNA content (µgrams)	6	22,007	15,714	16,470	7,257	42,265
Endotoxin units (EU)	32	10.6	21.8	5.0	0.1	114.0
Endotoxin units/kg (EU/kg)	32	0.1	0.2	0.1	0.0	0.9
Islet purity: Dithizone positive cells (%)	34	65.9	17.4	70.0	30.0	90.0
Islet potency: Stimulation index	21	3.1	2.2	2.3	1.0	9.0
Islet viability (%)						
Fluorescein Diacetate/Propidium Iodide	19	91.8	6.1	94.0	76.0	98.0
Trypan Blue	1	80.0	-	80.0	80.0	80.0
Other	12	93.2	2.8	95.0	88.0	95.0

Exhibit 166
Mean Number of Islet Equivalents/kg (±SD) by Total Number of Infusions Received
(Recipients with a Total of 1 Infusion and 2 Infusions)

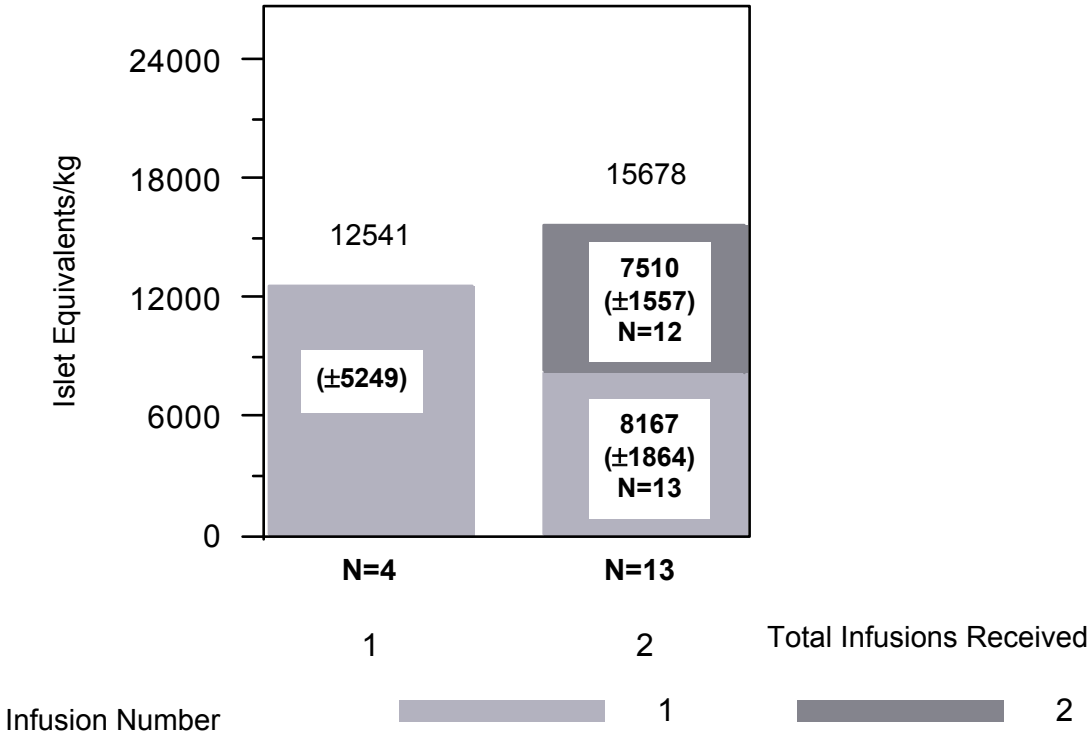


Exhibit 167
Immunosuppression Regimen at Time of First Infusion

	Overall	
	N	%
Total	19	100.0
Sirolimus + Tacrolimus + Daclizumab	8	42.1
Tacrolimus + MMF + Prednisone + Daclizumab	4	21.1
Sirolimus + Tacrolimus + Daclizumab + Infliximab	2	10.5
Sirolimus + Tacrolimus + Prednisone + Daclizumab	2	10.5
Sirolimus + Tacrolimus + MMF + Daclizumab	1	5.3
Sirolimus + Tacrolimus + MMF + Daclizumab + Etanercept	1	5.3
Missing Information on Immunosuppression	1	5.3

Exhibit 168
Immunosuppression Dosing (mg/day) at Time of Infusion by Infusion Sequence

	Infusion Sequence					
	1			2		
	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	14	5.2	2.8	12	8.3	2.0
Tacrolimus (mg/day)	18	3.2	1.7	14	3.6	1.3
MMF (mg/day)	6	666.7	302.8	3	750.0	250.0
Prednisone (mg/day)	6	5.0	0.0	4	5.0	0.0

Exhibit 169
Induction Therapy (mg) at Time of Infusion by Infusion Sequence

	Infusion Sequence					
	1			2		
	N	Mean Total Dose	SD	N	Mean Total Dose	SD
Daclizumab (mg)	15	304.5	132.6	11	225.3	97.4
Infliximab (mg)	2	630.0	42.4	1	520.0	-
Etanercept (mg)	1	150.0	-	1	150.0	-

Exhibit 170
Immunosuppression Therapy Use Post Last Infusion

	Follow-Up			
	1-6 Months		6-12 Months	
	N	%	N	%
Total	15	100.0	11	100.0
Sirolimus + Tacrolimus	7	46.7	4	36.4
Sirolimus + Tacrolimus + Prednisone	2	13.3	1	9.1
Tacrolimus + MMF + Prednisone	2	13.3	1	9.1
Sirolimus + Tacrolimus + Daclizumab	1	6.7	1	9.1
Sirolimus + Tacrolimus + Prednisone + Daclizumab	1	6.7	1	9.1
Tacrolimus + Prednisone	1	6.7	1	9.1
Tacrolimus + MMF	-	0.0	1	9.1
Neoral Cyclosporine + MMF + Prednisone	-	0.0	1	9.1
Missing Information on Immunosuppression	1	6.7	-	0.0

Exhibit 171
Immunosuppressive Dosing (mg/day) Post Last Infusion

	Follow-Up								
	Day 30			Month 6			Year 1		
	N	Mean	SD	N	Mean	SD	N	Mean	SD
Sirolimus (mg/day)	13	7.6	3.2	10	7.5	1.9	6	6.0	1.1
Tacrolimus (mg/day)	16	3.9	1.3	12	3.5	1.2	9	4.1	1.5
Neoral Cyclosporine (mg/day)	0	-	-	0	-	-	1	250.0	-
MMF (mg/day)	5	900.0	418.3	2	1250.0	353.6	3	1000.0	500.0
Prednisone (mg/day)	5	5.0	0.0	6	5.0	0.0	5	5.0	0.0
Daclizumab (mg/day)	0	-	-	2	60.0	1.4	2	61.0	2.8

Exhibit 172
Sirolimus Trough Level (ng/mL) Post Last Infusion

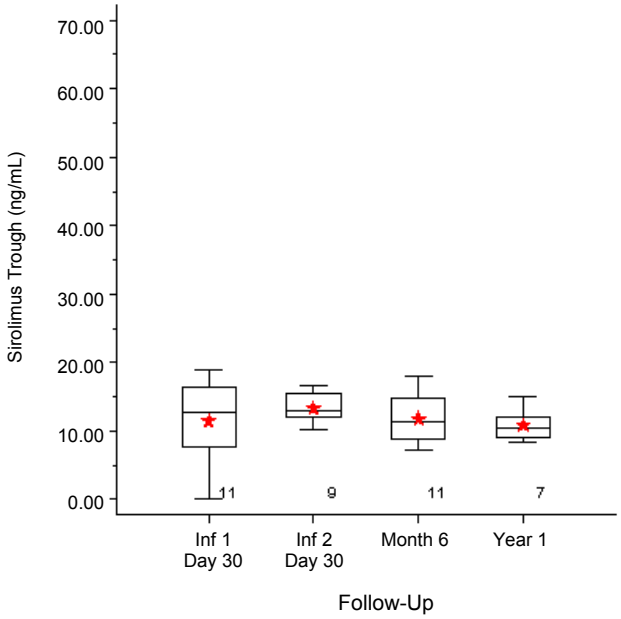


Exhibit 173
Tacrolimus Trough Level (ng/mL) Post Last Infusion

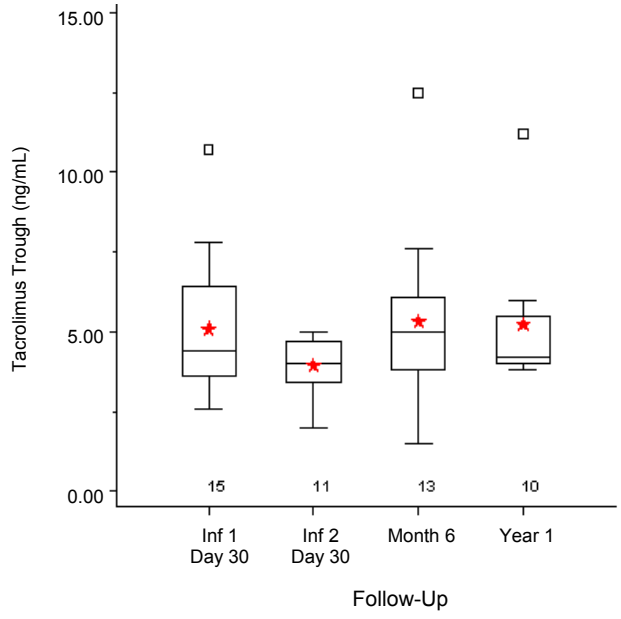


Exhibit 174
Cohort of Recipients Followed by Insulin Status
Post First Infusion

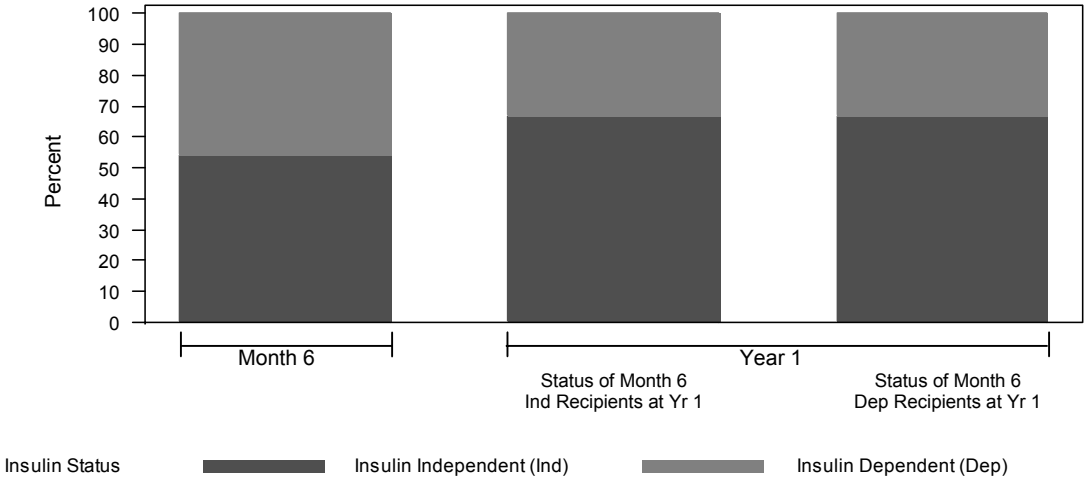


Exhibit 175
Cohort of Recipients Followed by Insulin Status
Post Last Infusion

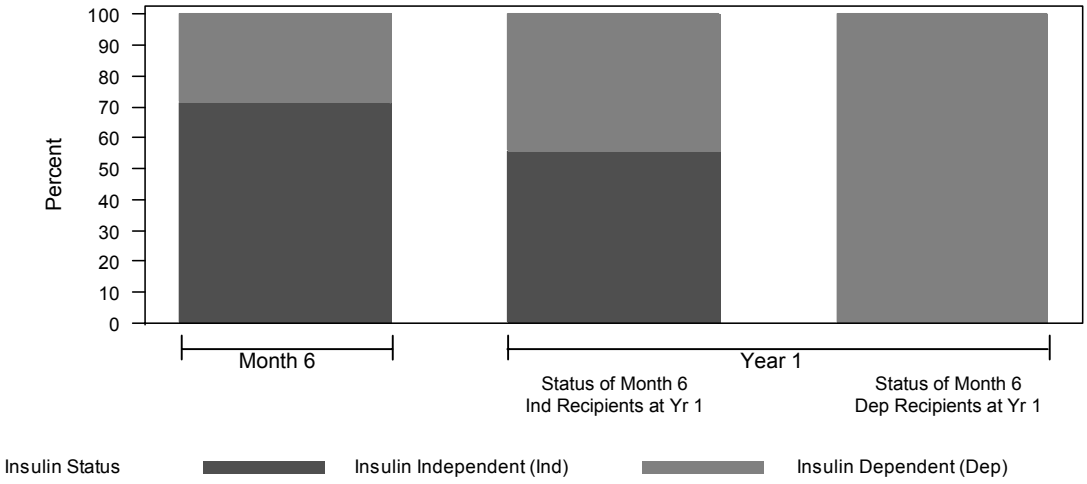


Exhibit 176
Reduction of Insulin (%) from Pre Infusion to Follow-Up Post Last Infusion
Participants on Insulin

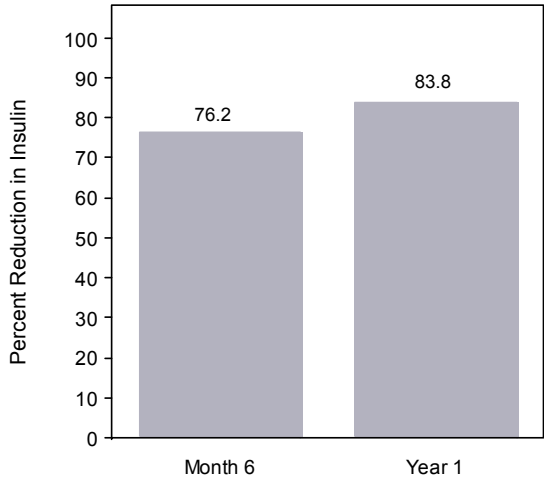


Exhibit 177
Average Daily Insulin Use (Units) at Follow-Up Post Last Infusion
Participants on Insulin

	Average Daily Insulin Use (Units)					
	N	Mean	SD	Median	Min	Max
Follow-Up						
Month 6	4	9.8	5.4	9.0	4.0	17.0
Year 1	5	5.2	2.9	5.0	2.0	9.0

Exhibit 178
Summary of Severe Hypoglycemic Events by Pre First Infusion and Follow-Up Post Last Infusion

	Follow-Up							
	Pre First Infusion		Days 0-30 Post First Infusion		Months 1-6 Post Last Infusion		Months 6-12 Post Last Infusion	
	N	%	N	%	N	%	N	%
Total	19	100.0	19	100.0	15	100.0	11	100.0
Any Hypoglycemic Episodes								
Yes	11	57.9	1	5.3	-	0.0	-	0.0
No	8	42.1	18	94.7	14	93.3	11	100.0
Missing	-	0.0	-	0.0	1	6.7	-	0.0
Frequency of Hypoglycemic Episodes								
None	8	42.1	18	94.7	14	93.3	11	100.0
1-2	3	15.8	1	5.3	-	0.0	-	0.0
3-5	1	5.3	-	0.0	-	0.0	-	0.0
6 or more	4	21.1	-	0.0	-	0.0	-	0.0
Unknown	3	15.8	-	0.0	-	0.0	-	0.0
Missing	-	0.0	-	0.0	1	6.7	-	0.0

Exhibit 179
Fasting Plasma Glucose (mg/dL)
Pre Infusion and Post Last Infusion

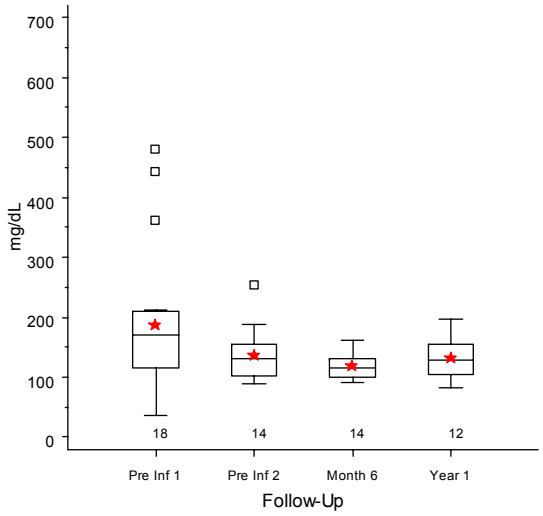


Exhibit 180
HbA_{1c} (%)
Pre Infusion and Post Last Infusion

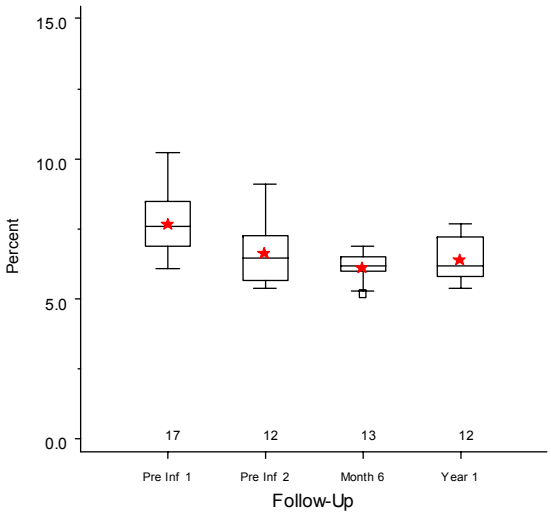


Exhibit 181
Basal Plasma C-peptide (ng/mL)
Pre Infusion and Post Last Infusion

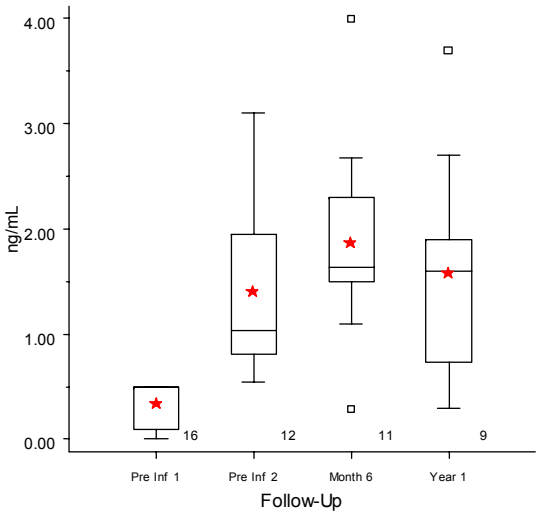


Exhibit 182
Pre Infusion Recipient Lab Summary by Infusion Sequence

	Infusion Sequence											
	1						2					
	N	Mean	SD	Median	Min	Max	N	Mean	SD	Median	Min	Max
Fasting Plasma Glucose (mg/dL)	18	189.1	123.4	169.5	36.0	481.0	14	138.9	45.0	130.5	89.0	255.0
HbA_{1c} (%)	17	7.7	1.1	7.6	6.1	10.2	12	6.7	1.1	6.5	5.4	9.1
ALT (IU/L)	18	28.4	15.8	23.5	13.0	64.0	14	46.8	41.7	35.5	20.0	183.0
AST (IU/L)	18	32.1	14.9	26.0	16.0	80.0	14	42.8	26.1	31.0	17.0	113.0
Alkaline Phosphatase (IU/L)	17	78.6	24.1	75.0	44.0	134.0	14	67.4	26.4	61.5	40.0	144.0
Total Bilirubin (mg/dL)	18	0.5	0.3	0.4	0.1	1.2	14	0.4	0.2	0.4	0.1	0.9
Total Cholesterol (mg/dL)	17	185.4	20.5	179.0	155.0	234.0	8	181.8	20.3	180.5	154.0	206.0
HDL (mg/dL)	17	64.6	20.5	62.0	42.0	112.0	8	64.0	16.5	61.5	44.0	98.0
LDL (mg/dL)	17	95.1	18.5	90.0	66.0	136.0	8	96.8	15.7	104.0	75.0	114.0
Triglycerides (mg/dL)	17	115.6	47.8	109.0	34.0	217.0	8	104.3	49.3	105.0	38.0	188.0
Serum Creatinine (mg/dL)	18	1.2	0.4	1.1	0.5	2.0	14	1.3	0.4	1.4	0.7	2.0
Calculated Creatinine Clearance (mL/min/1.73m^2)	12	79.3	35.2	75.0	41.0	176.0	4	51.5	12.0	47.5	42.0	69.0
Basal Plasma C-peptide (ng/mL)	16	0.3	0.2	0.5	0.0	0.5	12	1.4	0.9	1.0	0.5	3.1

Exhibit 183
Participants with Abnormal Liver Function Tests Post Infusion

	1-2X ULN		≥ 2X ULN	
	N	%	N	%
ALT	5	31.3	1	6.3
AST	7	43.8	2	12.5
Alkaline Phosphatase	4	25.0	-	0.0
Total Bilirubin	-	0.0	-	0.0

Upper Limit of Normal (ULN)

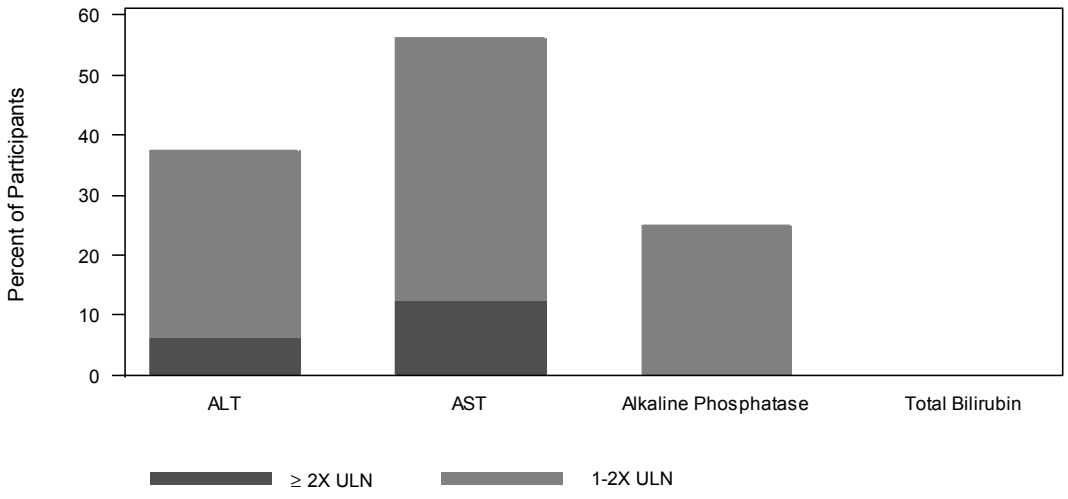


Exhibit 184
ALT (IU/L) Pre Infusion and Post Last Infusion

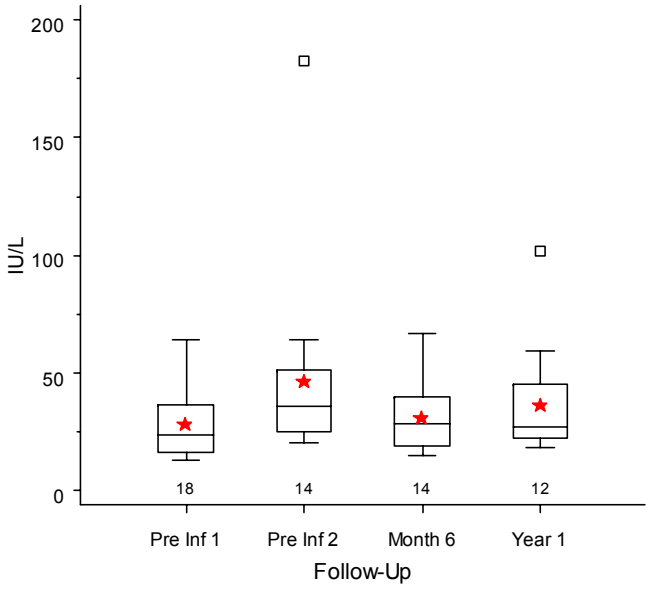


Exhibit 185
AST (IU/L) Pre Infusion and Post Last Infusion

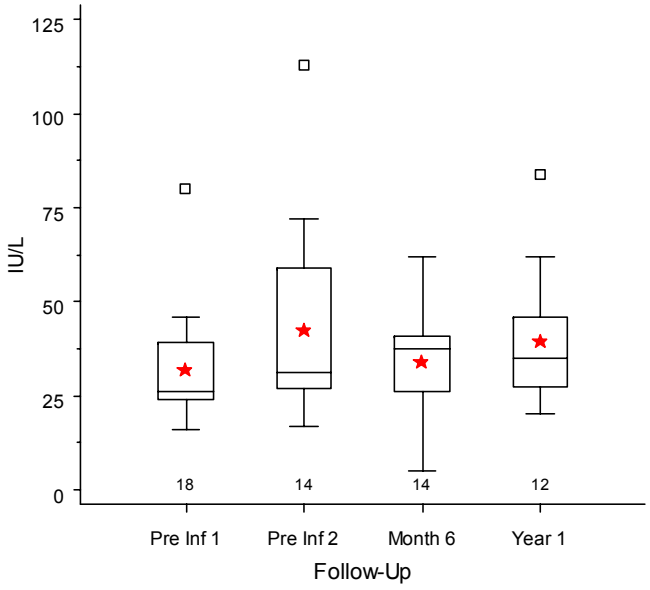


Exhibit 186
Alkaline Phosphatase (IU/L) Pre Infusion and Post Last Infusion

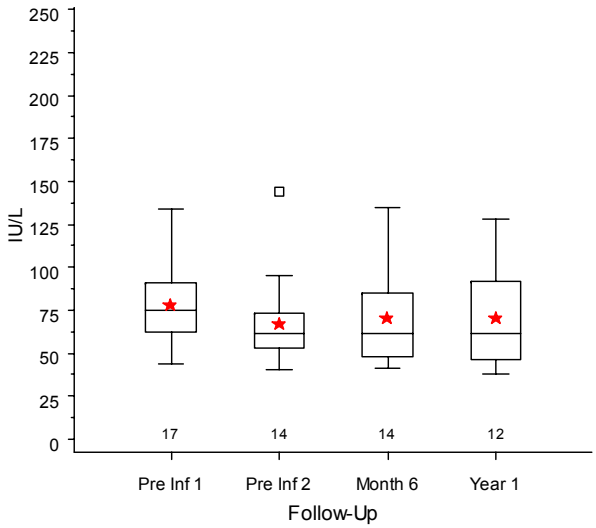


Exhibit 187
Total Bilirubin (mg/dL) Pre Infusion and Post Last Infusion

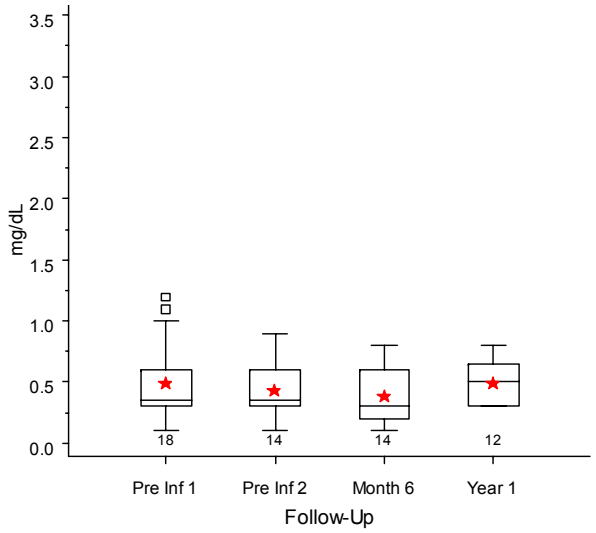


Exhibit 188
Participants with Abnormal Lipid Tests Post Infusion

	1-2X ULN		≥ 2X ULN	
	N	%	N	%
Total Cholesterol	-	0.0	-	0.0
Triglycerides	1	7.1	-	0.0

Upper Limit of Normal (ULN)

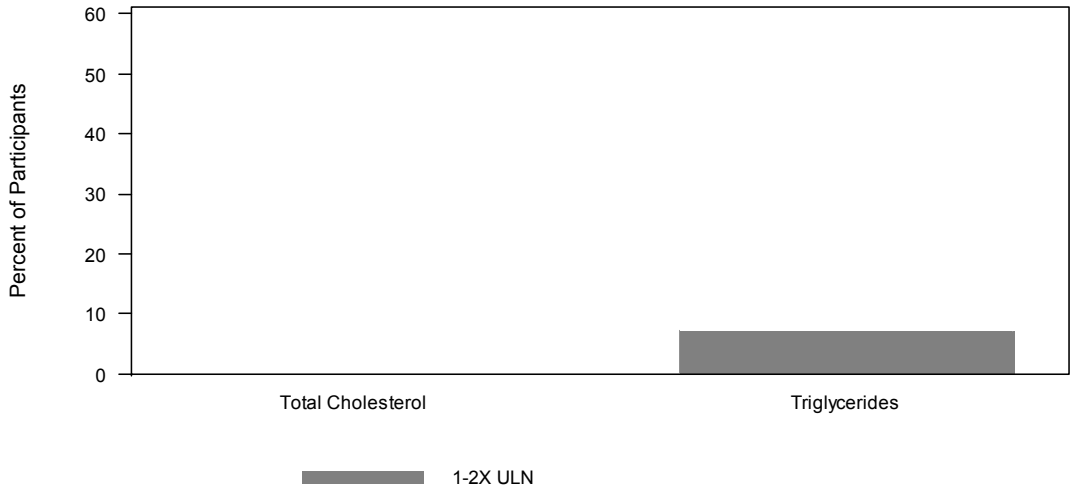


Exhibit 189
Total Cholesterol (mg/dL) Pre Infusion and Post Last Infusion

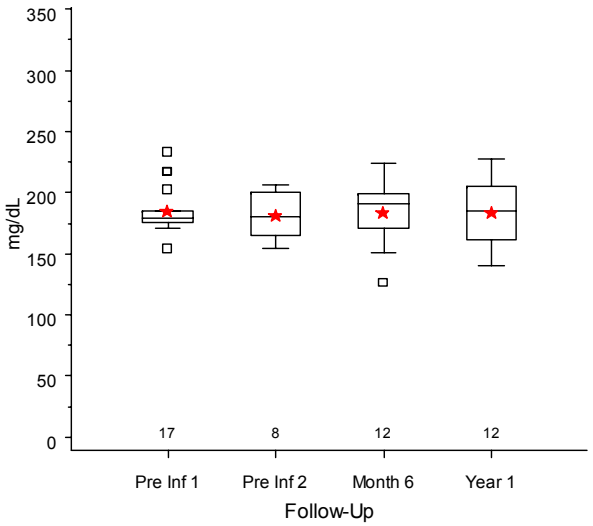


Exhibit 190
HDL (mg/dL) Pre Infusion and Post Last Infusion

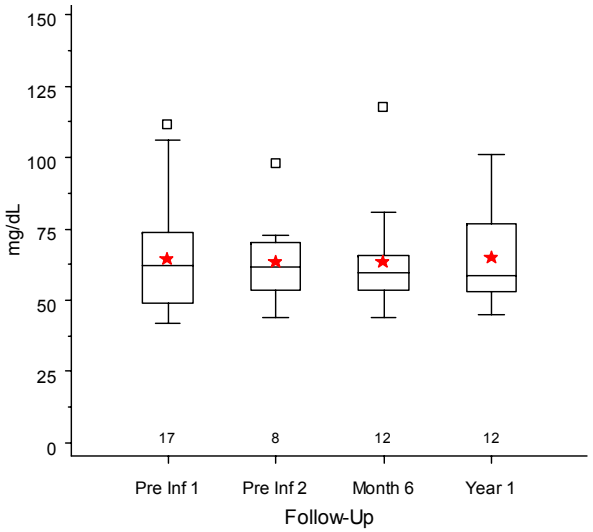


Exhibit 191
LDL (mg/dL) Pre Infusion and Post Last Infusion

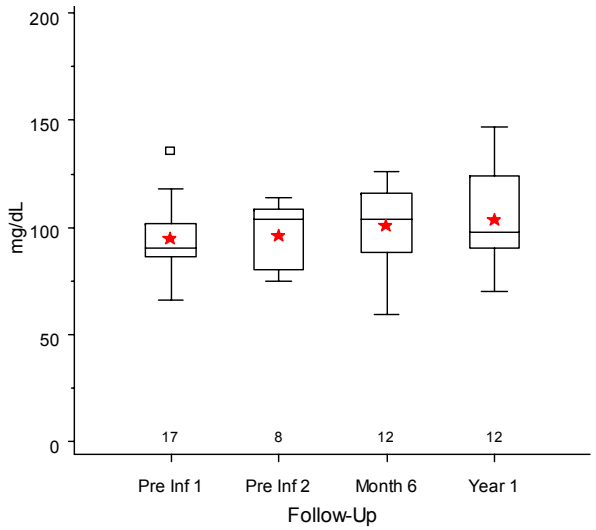


Exhibit 192
Triglycerides (mg/dL) Pre Infusion and Post Last Infusion

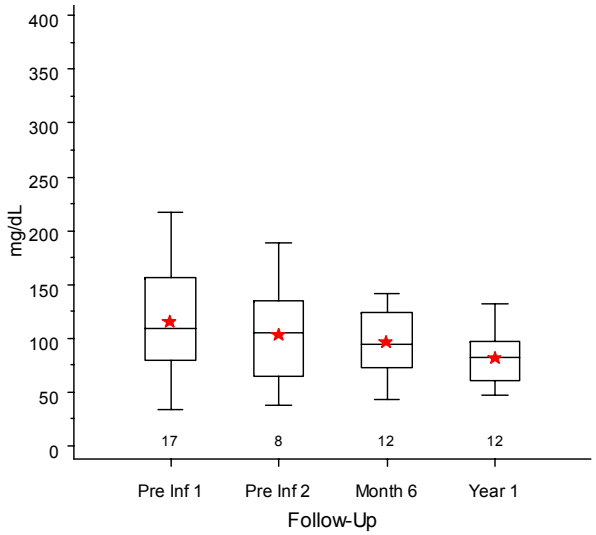


Exhibit 193
Percent of Participants with an Increase in Serum Creatinine (mg/dL) Greater than 0.5 from Baseline

	Increase in Serum Creatinine >0.5 mg/dL	
	N	%
Serum Creatinine	2	14.3

Exhibit 194
Serum Creatinine (mg/dL) Pre Infusion and Post Last Infusion

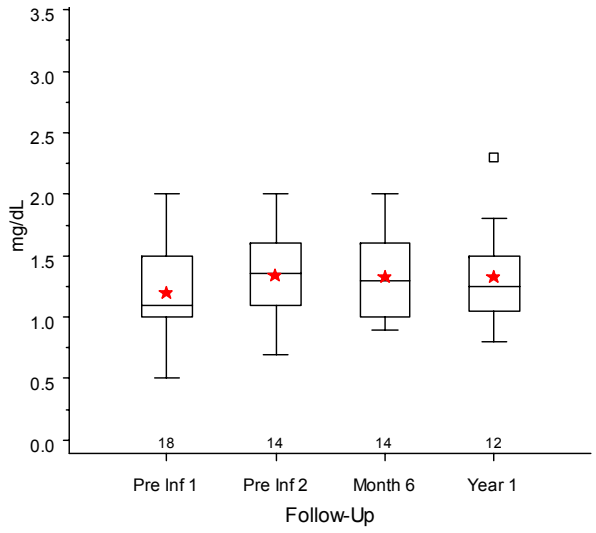


Exhibit 195
Calculated Creatinine Clearance (mL/min/1.73m^2)
Pre Infusion and Post Last Infusion

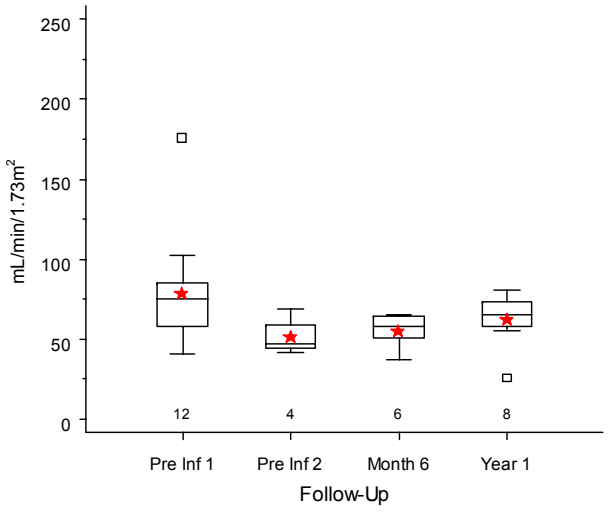


Exhibit 196
Summary of Adverse Events and Serious Adverse Events in Year 1 Post First Infusion (Participants, N=19)

	Adverse Events			Serious Adverse Events		
		Related to Immunosuppression Therapy	Related to Infusion Procedure		Related to Immunosuppression Therapy	Related to Infusion Procedure
Number of Events	21	5 (23.8%)	11 (52.4%)	9	1 (11.1%)	4 (44.4%)
Number of Participants with 1 or More Events	11 (57.9%)	3 (15.8%)	8 (42.1%)	5 (26.3%)	1 (5.3%)	3 (15.8%)

Exhibit 197
Number of Recipients with Reported Adverse Events and Serious Adverse Events Following First Infusion by Visit Month

	Visit Month					
	<1 Month		1-6 Months		6-12 Months	
	N	%	N	%	N	%
Total	18	100.0	17	100.0	12	100.0
Total Adverse Events Reported for Recipient (Grade 3, 4, or 5)*						
0	10	55.6	11	64.7	10	83.3
1	5	27.8	5	29.4	2	16.7
2	2	11.1	1	5.9	-	0.0
3	1	5.6	-	0.0	-	0.0
Total Serious Adverse Events Reported for Recipient						
0	15	83.3	14	82.4	10	83.3
1	2	11.1	3	17.6	2	16.7
2	1	5.6	-	0.0	-	0.0

*Based on the Cancer Therapy Evaluation Program, Common Terminology Criteria For Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS.

Exhibit 198
Summary of All Serious Adverse Events (SAEs) by Type of SAE

Type of Serious Adverse Event*	N	%
All Serious Adverse Events	16	100.0
Death	0	0.0
Life Threatening	5	31.3
Inpatient Hospitalization	9	56.3
Prolongation of Existing Hospitalization	4	25.0
Persistent or Significant Disability/Incapacity	-	0.0

*Categories are not mutually exclusive.

Exhibit 199
Summary of All Serious Adverse Events (SAEs) and Relationship to Islet Infusion Procedure

Relationship of Serious Adverse Event	N	%
All Serious Adverse Events	16	100.0
Unrelated	10	62.5
Unlikely Related	-	0.0
Possibly Related	1	6.3
Probably Related	3	18.8
Definitely Related	2	12.5

Exhibit 200
Summary of All Serious Adverse Events (SAEs) and Relationship to Immunosuppression Therapy

Relationship of Serious Adverse Event	N	%
All Serious Adverse Events	16	100.0
Unrelated	6	37.5
Unlikely Related	3	18.8
Possibly Related	3	18.8
Probably Related	4	25.0
Definitely Related	-	0.0

Exhibit 201
Summary of All Serious Adverse Events (SAEs) and Outcome

Outcome of Serious Adverse Event	N	%
All Serious Adverse Events	16	100.0
Resolved with No Residual Effects	14	87.5
Resolved with sequelae	-	0.0
Persistent condition, Recipient Alive	2	12.5
Missing Information	-	0.0

Exhibit 202
Summary of All Serious Adverse Events (SAEs)
by System Organ Class

System Organ Class*	N	%
All Serious Adverse Events	16	100.00
Gastrointestinal disorders	3	18.8
Blood and lymphatic system disorders	2	12.5
Hepatobiliary disorders	2	12.5
Injury, poisoning and procedural complications	2	12.5
Investigations	2	12.5
Cardiac disorders	1	6.3
Infections and infestations	1	6.3
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1	6.3
Respiratory, thoracic and mediastinal disorders	1	6.3
Vascular disorders	1	6.3
Eye disorders	-	0.0
General disorders and administration site conditions	-	0.0
Metabolism and nutrition disorders	-	0.0
Musculoskeletal and connective tissue disorders	-	0.0
Nervous system disorders	-	0.0
Psychiatric disorders	-	0.0
Surgical and medical procedures	-	0.0

*MedDRA Classification (http://www.meddramsso.com/NewWeb2003/index.htm).

Exhibit 203
All Serious Adverse Events (SAEs) Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Blood creatinine increased	2004	Inpatient hospitalization	515 days post 1st Infusion	Yes	Missing	Unrelated	Probable	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Cholecystitis	2003	Inpatient hospitalization	7 days post 2nd Infusion	Yes	Severe (Grade 3)	Possible	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Colitis	2004	Inpatient hospitalization	138 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Current treatment modified based on AE	Resolved, no residual effects
Colitis	2004	Inpatient hospitalization	180 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects
Cough	2004	Inpatient hospitalization	319 days post 2nd Infusion	Yes	Severe (Grade 3)	Unrelated	Possible	Required additional treatment and current treatment modified based on AE	Resolved, no residual effects
Haematoma	2003	Prolongation of existing hospitalization	0 days post 2nd Infusion	No	Severe (Grade 3)	Definite	Unrelated	No treatment or modification of treatment required for AE	Resolved, no residual effects
Haemoglobin decreased	2003	Life threatening + Prolongation of existing hospitalization	0 days post 2nd Infusion	No	Life threatening (Grade 4)	Probable	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Haemothorax	2003	Prolongation of existing hospitalization	0 days post 2nd Infusion	No	Severe (Grade 3)	Probable	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Neutropenia	2003	Life threatening	94 days post 1st Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	No treatment or modification of treatment required for AE	Resolved, no residual effects
Neutropenia	2004	Life threatening	515 days post 1st Infusion	Yes	Life threatening (Grade 4)	Unrelated	Probable	Required additional treatment for AE	Persistent condition, Alive

Exhibit 203 *(continued)*
All Serious Adverse Events (SAEs) Reported in Alphabetical Order

Serious Adverse Event (SAE)	SAE Year	Reason for Serious Adverse Event Classification	Timing	Expected	Severity*	SAE Related to Infusion Procedure/ Infusion of Islets**	SAE Related to Immunosuppression Therapy**	Treatment Required	Outcome
Pericardial effusion	2005	Inpatient hospitalization	351 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unlikely	Required additional treatment for AE	Resolved, no residual effects
Peritoneal haemorrhage	2001	Life threatening + Prolongation of existing hospitalization	0 days post 1st Infusion	Yes	Life threatening (Grade 4)	Definite	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Portal vein thrombosis	2004	Inpatient hospitalization	35 days post 1st Infusion	No	Severe (Grade 3)	Probable	Unrelated	Required additional treatment for AE	Persistent condition, Alive
Squamous cell carcinoma of skin	2004	Life threatening	640 days post 1st Infusion	Yes	Severe (Grade 3)	Unrelated	Probable	Required additional treatment for AE	Resolved, no residual effects
Upper limb fracture	2004	Inpatient hospitalization	660 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Unrelated	Required additional treatment for AE	Resolved, no residual effects
Urinary tract infection	2004	Inpatient hospitalization	285 days post 2nd Infusion	No	Severe (Grade 3)	Unrelated	Possible	Required additional treatment for AE	Resolved, no residual effects

*Based on the Cancer Therapy Evaluation Program, Common Terminology Criteria For Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS.
**Based on classification by local CITR Investigator.

Exhibit 204
Number of Days Hospitalized at Infusion (Admission to Discharge)
by Infusion Sequence

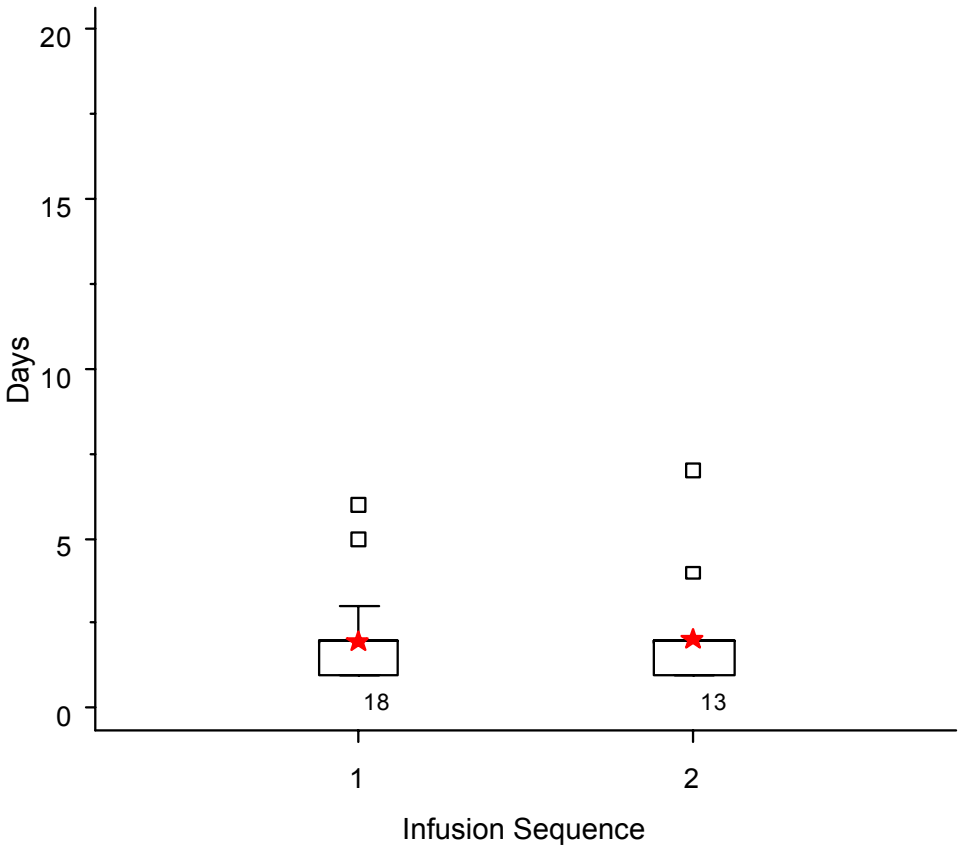


Exhibit 205
Hospitalizations Experienced Post Last Infusion
by Total Number of Infusions Received

	Total Infusions Received							
	1				2			
	Month 6		Year 1		Month 6		Year 1	
	N	%	N	%	N	%	N	%
Total	4	100.0	4	100.0	12	100.0	9	100.0
Participants Requiring at Least One Hospitalization	4	100.0	4	100.0	11	91.7	6	66.7
Number of Hospitalizations								
0	4	100.0	4	100.0	1	91.7	6	66.6
1	-	0.0	-	0.0	-	0.0	1	11.1
2	-	0.0	-	0.0	1	8.3	1	11.1
3	-	0.0	-	0.0	-	0.0	1	11.1
Missing	-	0.0	-	0.0	-	0.0	-	0.0

Exhibit 206
Changes in Portal Pressure (mmHg) and Infusion Summary by Infusion Sequence

	Infusion 1					
	N	Mean	SD	Median	Min	Max
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure (mmHg)	14	2.3	1.5	2.0	0.0	5.0
Change in Portal Pressure from Pre to Post Infusion (mmHg)	16	1.4	2.1	1.5	-4.0	5.0
Islet Equivalents Infused	18	509,764	128,220	492,925	318,000	800,000
Islet Packed Cell Volume (mL)	13	4.2	1.6	5.0	1.0	6.0

	Infusion 2					
	N	Mean	SD	Median	Min	Max
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure (mmHg)	11	1.8	1.5	2.0	0.0	5.0
Change in Portal Pressure from Pre to Post Infusion (mmHg)	12	0.5	2.4	0.4	-4.0	5.0
Islet Equivalents Infused	11	440,155	86,910	408,300	298,200	600,000
Islet Packed Cell Volume (mL)	9	3.8	1.3	3.8	1.6	5.0

Section 4
Registry Data Quality Review

Registry Data Quality Review Summary

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. Each center is also visited and trained by CITR Coordinating Center staff. This training includes a detailed review of data collection forms, definitions, and CITR standards. Initial and continued training in data entry and navigation of the Internet based data collection system is conducted and monitored frequently. Real time quality control and assurance programs and reports are implemented during data entry and monthly reports are generated and reviewed by the participating islet transplant centers. Each center is audited on-site with respect to their source documentation after 10 islet transplant recipients are entered in the CITR database or after the center has been participating for 2 years, whichever occurs first.

Included in this section are summaries of the data collected and reported on for this Annual Report. Exhibit 207 is a summarization for all 138 recipients and the number of CITR required forms that were submitted to the CITR Coordinating Center by the time of the final data lock on April 1, 2005. This summarization is separated by infusion sequence (1, 2 or 3) and an overall summary is provided. Submission form rates ranged from 81.4% to 99.6%. 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 recipient had to have at least one infusion form submitted to be included in the analysis database). For expected and submitted forms, form submission rates were 93.2% for post first infusion forms, 93.4% for post last infusion follow-up and 93.4% for post infusion follow-up laboratory forms (Exhibit 208). At the time of data closure, 14 participants had been lost to CITR follow-up. Time of the recipient's last follow-up visit ranged from 6.3 months to 32.7 months post last infusion (Exhibit 209). CITR Coordinating Center staff continues to work with each islet transplant center to follow-up and re-initiate CITR follow-up for these recipients, as well as to prevent further loss to follow-up.

Within the past year, six CITR islet transplant centers have had an on-site data audit. 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. From the six audits, 14,794 individual data fields were reviewed which produced 584 queries (3.9%) (Exhibit 210). These queries included potential conflicts between source documentation and the CITR database, as well as errors that were identified on-site with data entry. CITR Coordinating Center staff has worked with each of the six centers and at the time of this report, five of the six center reviews have been completed and all identified action items from the reviews have been completed. In addition, the Registry sponsor reviews all audit reports.

Exhibit 207
Expected and Submitted Forms by Infusion Sequence
(All Participants, N=138)

	Infusion Sequence									Overall		
	1			2			3					
	Expected	Submitted	%	Expected	Submitted	%	Expected	Submitted	%	Expected	Submitted	%
Donor Forms	159	142	89.3	100	87	87.0	32	26	81.2	291	255	87.6
Processing Forms	159	134	84.3	100	81	81.0	32	22	68.8	291	237	81.4
Pre Infusion Forms	138	138	100.0	98	93	94.9	29	26	89.7	265	257	97.0
Pre Infusion Lab Forms	138	137	99.3	98	98	100.0	29	29	100.0	265	264	99.6
Infusion Forms	138	138	100.0	98	98	100.0	29	29	100.0	265	265	100.0
Induction Forms	138	137	99.3	98	98	100.0	29	29	100.0	265	264	99.6

Exhibit 208
Expected and Submitted Follow-Up Forms Post First and Last Infusion
(All Participants, N=138)

	Follow-Up						Overall		
	Month 6			Year 1					
	Expected	Submitted	%	Expected	Submitted	%	Expected	Submitted	%
Follow-Up Forms Post First Infusion	132	124	93.9	117	108	92.3	249	232	93.2
Follow-Up Forms Post Last Infusion	128	125	97.7	113	100	88.5	241	225	93.4
Follow-Up Lab Forms Post Last Infusion	128	125	97.7	113	100	88.5	241	225	93.4

Exhibit 209
Date of Last CITR Contact
All Participants Reported as Lost to CITR Follow-Up

Random Participant ID	Time Participant Reported Lost to CITR Follow-up
1	13.5 months post last infusion
2	25.8 months post last infusion
3	32.7 months post last infusion
4	16.2 months post last infusion
5	14.9 months post last infusion
6	25.2 months post last infusion
7	28.3 months post last infusion
8	18.9 months post last infusion
9	30.6 months post last infusion
10	17.8 months post last infusion
11	24.0 months post last infusion
12	12.0 months post last infusion
13	24.0 months post last infusion
14	6.3 months post last infusion

Exhibit 210
Data Queries from Source Document Reviews
(CITR Islet Transplant Center On-Site Data Reviews, N=6)

	Fields Reviewed	Queries*	%
Demographics	187	3	1.6
Registration	246	9	3.7
Donor Forms	1935	94	4.9
Processing Forms	1422	38	2.7
Pre Infusion Forms	2538	128	5.0
Pre Infusion Lab Forms	1423	78	5.5
Infusion Forms	1104	67	6.1
Induction Forms	2514	52	2.1
Follow-Up and Follow-Up Lab Info	1381	35	2.5
Insulin Administration	315	3	1.0
Adverse Event	1582	75	4.7
Islet Graft Dysfunction	122	2	1.6
Non Islet Transplant	25	0	0.0
Total	14,794	584	3.9

**Queries are defined as a potential conflict between source documentation and the CITR database.*

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