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, 2004

NOTICE:

The CITR Annual Report details data received as of April 5, 2004 for all islet transplant recipients registered by November 30, 2003. These data should be considered a privileged communication and may not be used for publication or presentation without prior written permission of the CITR Publications/Presentations Committee.

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

July 1, 2004

M E M O R A N D U M

TO: CITR Islet Transplant Centers

FROM: Thomas Eggerman, MD, PhD
Director, Islet Transplantation Program
NIDDK

Bernhard Hering, MD
CITR Medical Director, SAC Chair

SUBJECT: First 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 initial scientific CITR Annual Report and is a significant step towards furthering project goals. 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 transplant clinics and islet production facilities. We are pleased to report on the combined efforts of twelve transplant programs, processing 173 pancreata and performing 158 islet infusion procedures in 86 recipients. We thank them for their efforts and look forward to their continued participation along with all centers in the islet transplant community of North America.

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Introduction

Background

Type 1 diabetes remains a therapeutic challenge. Failure to prevent hypoglycemia and hyperglycemia, results in acute and chronic diabetes complications, leading to poor quality of life, premature death, and considerable health care costs in 30% to 50% of patients *(1)*. Therefore, establishing safe and effective methods of achieving and maintaining normoglycemia will have substantial implications for the well-being of individuals with diabetes. Intensive insulin has been shown to reduce the risk of chronic complications in patients who achieve near normalization of glycemia *(2)*. However, this therapy is labor intensive, difficult to implement for many patients, and limited by the accompanying increased frequency of severe hypoglycemia *(3)*.

Currently, the only way to reliably restore normoglycemia is a pancreas or islet transplant. Interest in islet transplantation relative to pancreas transplantation is tied to a set of possible advantages including its vantage as a significantly less invasive procedure, the potential of minimizing the need for continuous immunosuppression, and the opportunities presented by alternative cell sources. Pursuing and exploiting these advantages is expected to faciliatate progressively increasing application of cell-based diabetes therapy early in the course of diabetes.

Fewer than 750 islet transplants have been performed in recipients with type 1 diabetes worldwide. The majority of these transplants have been done as part of small, single-center pilot trials. For many years, islets transplants have been much less successful than vascularized pancreas transplants. Of the 267 allografts transplanted worldwide between 1990 and 1999, only 12.4% resulted in insulin independence for periods of more than one week, and only 8.2% have remained insulin-independent for periods of more than one year *(4)*. In the majority of these procedures, islets were transplanted from a single-donor pancreas and the regimen of immunosuppression consisted of antilymphocyte globulin induction therapy combined with cyclosporine, azathioprine, and glucocorticoids for maintenance therapy. The success rate of islet transplants recently increased markedly by transplanting a higher islet mass prepared from two to four donor pancreata and using a glucocorticoid-free immunosuppressive protocol *(5)*. These unprecedented findings by Shapiro et al. have now been confirmed by other investigators *(6-9)* and extended to type 1 diabetic islet recipients with previous kidney transplants *(10)*. In addition, preliminary evidence of the ability to reverse type 1 diabetes with islets prepared from one donor pancreas *(11)* has recently been presented.

The results of these recent clinical trials have been very promising but with them come several questions. What factors determine procedure-related complications such as bleeding and portal vein thrombosis. What are the long-term consequences of islet placement in the liver? What are the long-term risks of immunosuppressive medication? How many donor pancreata need to be processed to reverse diabetes in one recipient? What are the most promising strategies for restoring insulin independence with a much lower islet mass on a consistent basis across centers? Will peritransplant inhibition of innate immune responses increase the post transplant insulin secretory response of a given transplanted islet mass? Do transplanted islets restore physiologic regulation of glycemia? What is the longevity of islet transplants in type 1 diabetes? What are the reasons for late failure of initially successful islet transplants? Will steroid-free and calcineurin inhibitor-sparing immunosuppressive regimens be effective in preventing rejection and autoimmune destruction of islet transplants for prolonged periods in more than 80% of recipients? Will successful islet transplants reverse early microvascular lesions? What is the

long-term risk/benefit ratio of islet transplants versus intensive insulin therapy? What are the costs per quality adjusted life year saved?

Registry Design

In September 2001, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) has established the Collaborative Islet Transplant Registry (CITR). CITR represents a collaborative effort between islet transplant centers 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. A Coordinating Center, located at The EMMES Corporation, provides support for logistics, data capture, quality control monitoring, statistical design and analysis, and other Registry activities. The Coordinating Center also maintains a public website at www.citregistry.org with information about the Registry and the participating islet transplant centers. Participating in the Registry is voluntary but is highly encouraged by the scientific community. The mission of CITR is to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America. Islet/beta cell transplantation is a complex procedure with many factors contributing to outcome. Compiling and analyzing data from all transplant centers in North America will accelerate the identification of both critical risk factors and key determinants of success, and thereby guide transplant centers in developing and refining islet/beta cell transplant protocols, leading to advances in the field of islet transplantation.

As islet/beta cell transplantation has become a rapidly developing field, it is difficult for non-experts to stay abreast of the most recent information. Data communicated by CITR will assist people with diabetes, health care professionals, payers and providers, scientific communities, funding agencies, and governmental institutions in making decisions regarding islet/beta cell transplantation. The inclusion of the term “collaborative” in the name of the Registry emphasizes the importance of collaboration in fulfilling the mission of CITR. Close collaboration with the transplant centers will ensure that relevant questions are addressed, that data submitted are accurate and complete, and that the needs of the transplant community are served. Collaboration with other initiatives, programs, and networks of the National Institutes of Health, (e.g., the Human Pancreatic Islet Cell Resource (HPICR) Consortium, the Immune Tolerance Network (ITN), US Pancreas Transplant Registry), and the Juvenile Diabetes Research Foundation (JDRF), will be instrumental in utilizing established infrastructures and in facilitating ancillary studies.

Collaboration with the diabetes care community, the health insurance industry, the Centers for Medicare and Medicaid Services (CMS), Health Resources and Services Administration (HRSA), and the US Food and Drug Administration (FDA) will ensure that the outcome measures used by CITR are appropriate, standardized, and relevant. Collaboration with United Network for Organ Sharing (UNOS) and the Canadian Organ Replacement Register (CORR) will avoid duplication of efforts with respect to the collection of donor and recipient information. Finally, collaboration with the International Transplant Registry (ITR) in Giessen, Germany will ensure that the worldwide status of islet/beta cell transplantation is regularly updated.

Specific Objectives

To meet these goals CITR has and will continue to encourage all transplant centers in North America that perform islet cell transplants to become a participating center. Specific objectives of the Registry are as follows:

1. To develop and implement standards for reporting islet/beta cell transplants and their outcome.

2. To collect and compile data on all islet/beta cell transplants in human recipients performed in North America.

3. To increase the safety of islet/beta cell transplantation by electronically distributing the pertinent information of submitted adverse event reports to all participating clinical sites in a timely fashion.

4. To perform scientific analysis on islet/beta cell transplant data, with particular emphasis on:

    a. Safety of islet/beta cell transplant product and procedures, and protocol-regulated treatment products.

    b. Number of islet/beta cell transplants and retransplants performed, categorized by transplant institution, donor tissue source and handling, recipient category, transplant technique and site, and recipient treatment protocols.

    c. Efficacy of islet/beta cell transplants as defined by standardized outcome measures and as determined by donor factors, recipient demographics, donor-recipient matching, islet/beta cell processing and product characteristics, transplant technique and site, recipient treatment, and post transplant events.

5. To communicate comprehensive and current information on islet/beta cell transplantation to transplant centers, the diabetes and general health care community, and the interested general public via the CITR web site (http://www.citregistry.org), publications, and presentations.

6. To stimulate prospective and retrospective studies on emerging issues of importance.

For the investigator, the Registry is intended to allow the collection of data in a single format that will facilitate and lessen the effort to prepare reports, manuscripts and presentations. As a group of investigators, the Registry was planned to facilitate safety and efficacy data communication on islet transplantation, so that a limited number of islets would be most safely targeted to the best patient population(s). Long term it is hoped that the Registry would facilitate in the licensing and reimbursement of islet transplantation in the United States. Through this collaborative effort, investigators will be able to contribute to the efforts to have islet transplantation FDA (US Food and Drug Administration) approved and become a reimbursable procedure. Investigators may also request special analyses of data submitted by all centers and have the Registry serve as a hypothesis-generating platform to further scientific investigations.

Islet Transplant Recipient Entry Criteria

Recipient entry criteria include at least one infusion of islet/beta cells (regardless of center specific entry criteria) on or after January 1, 1996, local Institutional Review Board (IRB) or Ethics Review Board (ERB) submission and review, informed consent/assent or a waiver of consent, and for those recipients in the US, HIPAA (Health Insurance Portability and Accountability Act) authorization. There are no other entry criteria restrictions including any restrictions on the age of the recipient or the type of islet transplant (autotransplant, allotransplant, xenotransplant).

Organization

The CITR Executive Committee ensures policies pertaining to the Registry are conducted in an organized and consistent manner. This Committee also oversees the daily functions of CITR, answers Registry specific questions, and coordinates aspects of the Registry with the Scientific Advisory Committee. The Scientific Advisory Committee (SAC) is responsible for the scientific integrity of the Registry and is chaired by Dr. Bernhard Hering from the University of Minnesota. The SAC voting members consist of:

- Dr. Reinhard G. Bretzel *(University of Giessen)*
- Dr. Michael Cecka *(University of California, Los Angeles)*
- Dr. Mary D. Ellison *(United Network for Organ Sharing)*
- Dr. Bernhard J. Hering *(University of Minnesota)*
- Dr. Jerry P. Palmer *(VA Puget Sound Health Care Systems)*
- Dr. Camillo Ricordi *(University of Miami)*
- Dr. James Shapiro *(University of Alberta)*

In addition, Dr. Thomas Eggerman (Project Officer, NIDDK) and Ms. Nicole Close (Director, EMMES) are ex-officio voting members of the SAC. Other invited participants of the SAC include the members of the Executive Committee, the Transplant Coordinators'/Data Managers' Subgroup Chair, and representatives from the following organizations: The National Institute of Allergy and Infectious Diseases (NIAID), the National Center for Research Resources (NCRR), the United States Food and Drug Administration (FDA), Centers for Medicare and Medicaid Services (CMS), Health Resources and Services Administration (HRSA), the Juvenile Diabetes Research Foundation (JDRF), UNOS Kidney and Pancreas Committee member, and the Canadian Organ Replacement Register (CORR). Dr. Hering also serves as the Medical Director for CITR. There are also four standing Committees for CITR: the Compliance Committee, the Transplant Coordinators'/Data Managers' Subgroup Committee, the Data Monitoring Committee and the Publications/Presentations Committee (roster included on page 111).

The collaborative effort between islet transplant researchers and centers and their efforts to collect and report information to CITR is much needed to advance the field. CITR is expected to be a useful tool in providing information to investigators active in the field of islet transplantation. A specific area in CITR anticipated to be useful is its ability to collect safety data. Unlike a pharmaceutical agent being developed by a single entity, academic investigators initiate most islet transplant studies. Thus, all safety and adverse event information is being gathered and reported by many individuals and centers. CITR will bridge this gap by collecting valuable safety data from all investigators performing islet transplantation studies evaluating islets as a

new drug. By compiling this information, CITR will be able to provide safety reports to these investigators in a timely manner as well as presenting this information in the Annual Report. The CITR platform will also facilitate capture of predictors of post transplant function and islet product related information. CITR Annual Reports will be the guide to investigators in developing and designing new protocols, as they will contain current and comprehensive data in the field.

This report is the first CITR Annual Report of the Registry. It represents the efforts of twelve islet transplant centers and islet processing facilities who joined CITR in its first year. Eighty-six islet transplant recipients' data are represented in the report as well as 173 processed pancreata leading to 158 infusion procedures. Average follow-up time from their last infusion for the 86 recipients is 7.5 months. As a multi-center, collaborative registry, CITR will have a sufficient patient population to evaluate potential risk factors for patient morbidity and mortality that is not amenable to single center studies.

CITR will strive to continue to develop standards for the islet transplantation field, which will also facilitate the comparison of data across centers. However, this information will also translate across multiple health care and research settings, providing valuable information to diabetologists, endocrinologists, immunologists, family practitioners, nurses, and other health care providers. Overall, CITR will continue to strive 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.

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Executive Summary

BACKGROUND: The number of transplant centers performing islet transplants continues to increase. Compiling and analyzing data from all islet transplants will accelerate the identification of both critical risk factors and key determinants of success, and thereby guide 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) has founded the Collaborative Islet Transplant Registry (CITR) in September 2001. A Coordinating Center, located at The EMMES Corporation, has been established to provide support for logistics, data capture, quality control monitoring, statistical design and analysis, and other Registry activities. CITR represents a collaborative effort between islet transplant centers 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 (www.citregistry.org).

METHODS: CITR opened participation to all North American centers early in the fall of 2002 with the first center trained and entering data December 2002. In less than one year, this first Annual Report represents the efforts of 12 islet transplant centers that joined CITR during its inaugural year. Eighty-six islet transplant recipient's data are represented in the report as well as 173 processed pancreata leading to 158 islet infusion procedures. Average follow-up time from their last infusion for the 86 recipients is 7.5 months. All data submitted to CITR through its Internet data entry system are reviewed for quality assurance, errors and extremes in the numbers reported (outliers). Islet transplant recipient data for this report were entered by the islet transplant centers by November 30, 2003. Centers were allowed time to review their data, make any corrections and complete any follow-up information prior to the final data closure for these recipients on April 5, 2004.

RESULTS: Recipient median age was 42.2 years (range 24.5 to 64.4), duration of diabetes was 30 years (range 5 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 23.3 kg/m^2 (range 17.7 to 31.6). All recipients were diagnosed with type 1 diabetes. Over 67% of the recipients had experienced at least one hypoglycemic event that required the assistance of another person in the previous 12 months of the islet infusion procedure. Over 41% of the recipients had experienced at least one hypoglycemic event that required assistance of another person and resulted in the loss of consciousness/seizures in the previous 12 months of the islet infusion procedure. The mean daily insulin requirement of recipients prior to their first infusion procedure was 35.4 units (SD 11.5). Almost 47% of the recipients were on an insulin pump prior to their first infusion. The mean fasting plasma glucose was 163.0 mg/dL (SD 91.5) and the mean HbA_{1c} was 7.7% (SD 1.3). Just over half of the recipients were transplanted in the same state as their primary residence.

Only islet allografts were reported to the Registry for this report; no autograft transplants or xenotransplants were submitted to the Registry. The median age of the deceased donor was 44 years (range 7 to 65) and body mass index was 28.2 kg/m^2 (range 13.3 to 68.9). Fifty-four percent of the donors were male and approximately 69% were white. The median serum creatinine of the donors was 1.1 mg/dL, total bilirubin 0.7 mg/dL, AST 37.5 IU/L, ALT 29.0 IU/L, serum lipase 28.5 IU/L and serum amylase 71.5 IU/L. Median time from cross clamp to pancreas recovery was 27 minutes (range 0 to127) while duration of cold ischemia was 7 hours

(range 1.8 to 22.5). UW, Two Layer, and UW Followed by Two Layer preservation were used for pancreas cold storage, and in over 90% of the cases Liberase HI was used as the collagenase type. Over 77% of the processing facilities used a density gradient for islet purification and half of the islet products processed did not have any islet pretreatment, while the other half were subjected to culture pre transplant.

Twenty-eight patients received a total of one islet infusion, 44 received two and 14 received three islet infusions. None of the islet procedures used an immunobarrier device, the site of infusion was always intraportally and in over 80% of the cases the portal vein was accessed via percutaneous transhepatic catheterization. For recipients of only one infusion, 8,665 total islet equivalents/kg were infused. Recipients of two infusions received 14,102 total islet equivalents/kg and recipients of three infusions received 22,922 islet equivalents/kg.

The majority of the islet alone recipients received Daclizumab for induction and Sirolimus combined with Tacrolimus for maintenance immunosuppression. For 1-6 months following a recipient's last infusion, over 35% of islet alone recipients were on a Sirolimus (Mean 8.0 mg/day, SD 2.7) and Tacrolimus (Mean 3.9 mg/day, SD 1.5) regimen (Exhibits 57 and 58). For adjunctive therapies at time of infusion, over 90% of recipients were using an antibiotic, over 82% were using Heparin (including Heparin used during the infusion), and 66% were using vitamins. Overall, 25.7% of the recipients are on an anti-hypertensive medication (Exhibit 61) and 18.6% are on a lipid lowering medication at the time of their first infusion.

For analysis of islet graft function, only the most complete data elements were analyzed for this report. On average, the HbA_{1c}% for the recipients decreased with each subsequent infusion (Infusion 1=7.7% (SD 1.3), Infusion 2=7.0% (SD 1.2), and Infusion 3=6.3% (SD 0.5)). C-peptide (ng/mL) increased with the number of infusions received (Infusion 1=0.31 (SD 0.29), Infusion 2=0.82 (SD 0.51), and Infusion 3=1.01 (SD 0.47). At six months post last infusion, the most reported metabolic tests included fasting plasma glucose (Mean 114.9 mg/dL, SD 35.9), HbA_{1c}% (Mean 6.1, SD 0.6), and basal plasma C-peptide (Mean 1.2 ng/mL, SD 0.7). At six months post last infusion, 61.1% of the recipients were reported insulin-independent and at 12 months post the last infusion 57.9% were reported insulin independent.

All grade 3, 4 and 5 adverse events according to the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute were reported to CITR. There have been no deaths reported to CITR. In the first month following infusion, almost 33% of the recipients experienced at least one grade 3, 4, or 5 adverse event following their first infusion procedure. Typically these were neutropenia and hyperglycemia and were not regarded as serious. Only 3.5% of recipients experienced a serious adverse event in the first month following their first infusion, which increased to 13.8% for one month post the second infusion and 21.4% for one month post the third infusion. As of this report there were a total of 45 serious adverse events reported for the 86 recipients. Almost 58% of the serious adverse events were classified as inpatient hospitalizations and almost 27% were classified as life threatening. The serious adverse events reported were quite varied and include over two-dozen event types. Serious adverse events related to the transplant included elevated ALT, elevated AST, hemoperitoneum, intra-abdominal bleed, low hemoglobin, peripherally inserted catheter line infection/cellulitis, right hemothorax and a subcapsular hematoma of the liver. The 10 serious adverse events related to immunosuppressive medications included anemia, aseptic meningitis, febrile neutropenia, neutropenia, peripherally inserted catheter line infection/cellulitis, and neurotoxicity.

CONCLUSIONS: This first CITR annual report demonstrates the current status of islet transplants in North America. Great care 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 a possible hidden bias to a particular outcome of interest may exist (e.g., protocols limiting donor age to

<60 years). Also, follow-up is limited in this report, as this is the first year of implementation and data entry for the 12 active centers. Nevertheless, this initial CITR report provides data on a large number of islet transplant recipients, deceased pancreas donors, pancreas preservation, islet processing, islet implantation, 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 is positioned to provide data on clinically significant outcome measures in islet transplantation to transplant professionals, basic scientists, diabetes care teams, other health care providers, funding agencies, payers, and patients, and thereby facilitate the integration of islet transplantation into diabetes care.

Methods Summary

CITR has developed a set of web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry. These data will help characterize and follow trends in safety and efficacy of islet transplantation, with particular emphasis on islet processing, transplant techniques, and treatment protocols. Demographic information is collected 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. There are also event driven data collection forms collecting 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).

CITR utilizes an Internet-based approach to data collection and information distribution for the Registry. This approach is well suited to satisfy data needs for quality, timeliness, security, privacy, safety and general user needs for ease of use, responsiveness, and availability. Overall, the Registry intends to compile data that would normally be collected by investigators for scientific evaluations and reporting to the multiple agencies and entities required by FDA regulated trials.

CITR opened participation up to all North American centers early in the fall of 2002. The first activation of a center and participation occurred at the University of Minnesota on December 6, 2002, followed by the University of Miami on January 10, 2003. In the subsequent year, this first Annual Report represents the collaborative efforts of twelve islet transplant centers who joined during CITR's inaugural year (Exhibit 1).

This Annual Report contains information on 86 islet transplant recipients, 173 deceased donors and 158 islet infusion procedures from twelve islet transplant centers. Average follow-up time from their last infusion for the 86 participants is 7.5 months. 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 were entered by the islet transplant centers by the date of November 30, 2003. 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 cleaned and closed for analysis on April 5, 2004 based on the 86 recipients that had been registered for CITR by November 30, 2004.

Data contained in this report must be interpreted cautiously. Even with the great response and data collected prior to the first report, the numbers represented from the twelve islet transplant centers in this report are small. As with any registry, a number of potential biases may exist. First, not all islet transplant centers in North America have been trained to participate in CITR. Second, those Centers reporting information to CITR have not reported on all of the islet

transplant recipients at their Center yet. 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 highly selective based on the center's protocol (e.g. protocols limiting donor age <60 years). As the Registry continues these biases may lessen.

Boxplots are used to summarize data in this Report. 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). Also, pertinent characteristics, the total islet equivalents in the final product and donor characteristics, were plotted and Pearson correlation coefficients determined.

Statistical significance of analyses is shown for a number of the Exhibits. These are provided to the reader for their own interpretation based on the report of 86 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.

The main exhibits of the report display information by two different subgroups. These subgroups are:

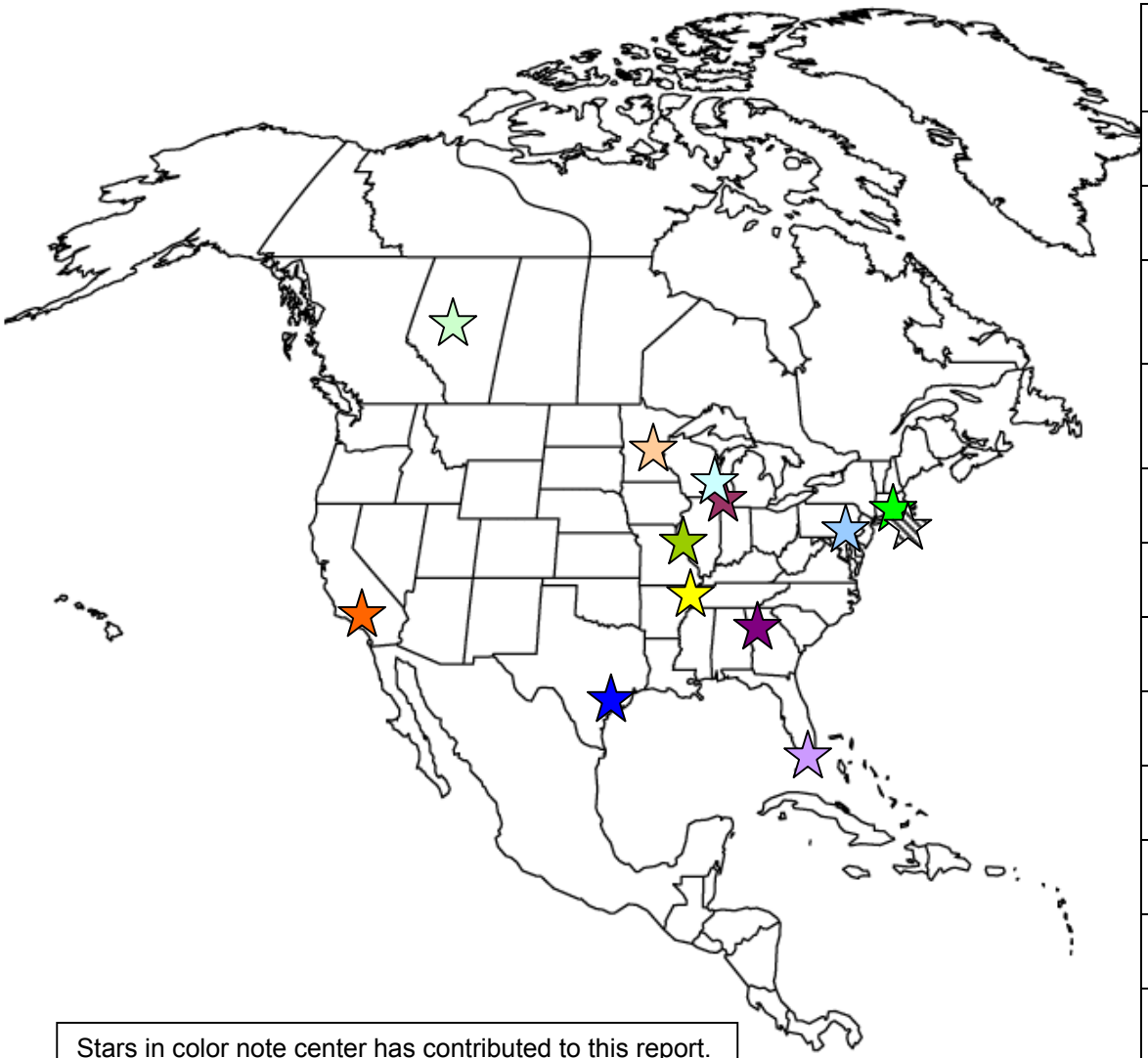
1. the year of the islet transplant recipient's first infusion procedure AND

2. the sequence of the infusion procedures (first infusion procedure, second infusion procedure and third infusion procedure).

Islet characteristics of interest were identified for analyses and subgroups were created for different processing and donor characteristics.

Graft function is cautiously described using that subset of the most complete data reported to the Registry. First, data are described overall as a summary measure of the recipient's HbA_{1c} and C-peptide values. Data are then described grouping recipients by their first infusion, second infusion and their third infusion. Another subgrouping for comparison is all recipients who received a total of just one infusion, those who received a total of two infusions and those who received a total of three infusions. There were no reports of recipients with more than three infusion procedures. Analyses for graft function are also based on the recipient's insulin use following last infusion. Insulin use post last infusion is presented in this Report as a first look at the data. Insulin independence is defined as the recipient being insulin independent at the time of the follow-up assessment.

Exhibit 1: Contributing Islet Transplant Centers



★	Baylor College of Medicine/The Methodist Hospital Houston, Texas
★	Emory Transplant Center Atlanta, Georgia
★	Southern California Islet Consortium-SCIC Duarte, California
★	The University of Massachusetts Medical Center Worcester, Massachusetts
★	The University of Miami, Diabetes Research Institute Miami, Florida
★	The University of Minnesota Minneapolis, Minnesota
★	The University of Pennsylvania Philadelphia, Pennsylvania
★	The University of Tennessee, Memphis Memphis, Tennessee
★	Northwestern University Chicago, Illinois
★	The University of Chicago Chicago, Illinois
★	Washington University, St. Louis St. Louis, Missouri
★	University of Alberta Edmonton, Alberta, Canada
★	Center for Islet Transplantation at Harvard Medical School Boston, Massachusetts

Stars in color note center has contributed to this report.

Stars with stripes note center activation date was subsequent to datafile closure date.

Section 1
Islet Transplant Recipient and Donor Characteristics

Islet Transplant Recipient and Donor Characteristics Data Summary

Registry information collected on islet transplant recipients and the deceased donors are summarized in this section. This first Annual Report represents information submitted by the twelve islet transplant centers trained and activated to conduct CITR registry procedures prior to November 30, 2003. A total of 173 pancreata were processed for islet transplant procedures and reported to CITR. Ninety-nine of these pancreata were used for the recipient's first islet infusion procedure, 59 pancreata were used for the recipient's second infusion procedure and 15 pancreata were used for the recipient's third infusion procedure. Eighty-six recipients are included in this report with a total of 158 infusion procedures. Eighty-six infusion procedures were for a first infusion, 58 infusion procedures for a recipient's second infusion and 14 for a recipient's third infusion (Exhibit 2).

Recipient Information:

The median age of the islet transplant recipient is 42.2 years (range 24.5 to 64.4) and the median duration of diabetes is 30 years (range 5 to 50). The median weight of the recipient is 65.0 kg (range 47 to 97) and the median body mass index (BMI) is 23.3 kg/m^2 (range 17.7 to 31.6). Over 66% of the recipients are female and just over half of the recipients were transplanted in the same state as their primary residence. There are five recipients in the database that received two islet infusions after a kidney transplant and one recipient who received one islet infusion after a kidney transplant. Twenty-seven recipients received a total of one islet infusion, 44 received two islet infusions and 14 received three islet infusions (Exhibit 4). No autograft transplants or xenotransplants were submitted to the Registry for this report.

At the time of the first infusion, over 66% of the recipients were employed full-time and for approximately one-third of the first infusion procedures the primary payer was non-government research funding and another one-third was US/State Government agency (Exhibit 5). Over 67% of the recipients had experienced at least one hypoglycemic event that required the assistance of another person in the previous 12 months of the islet infusion procedure. Over 41% of the recipients had experienced at least one hypoglycemic event that required assistance of another person and resulted in the loss of consciousness/seizures in the previous 12 months of the islet infusion procedure (Exhibit 7). The mean daily insulin requirement of recipients prior to their first infusion procedure was 35.4 units (SD 11.5). Almost 47% of the recipients were on an insulin pump prior to their first infusion. The mean fasting plasma glucose was 163.0 mg/dL (SD 91.5) and the mean HbA_{1c} was 7.7% (SD 1.3). Recipient's body mass index (kg/m^2) at the time of the infusion procedures is presented as a boxplot in Exhibit 8. 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).

Secondary complications of diabetes are being tracked at pre infusion and at post infusion for all of the recipients according to the CITR follow-up schedule. Exhibit 9 lists the secondary complications at the recipient's first infusion. At the time of the first infusion procedure, almost 56% of the recipients had experienced at least one of the CITR secondary complications (peripheral neuropathy, autonomic neuropathy, nephropathy, coronary artery disease,

cerebrovascular accidents, peripheral vascular disease, and hypertension) (Exhibit 10). Retinopathy and diabetic macular edema are two major ocular complications for people with diabetes. Prior to their first infusion, none of the recipients had reported diabetic macular edema in either eye, but 51% of the recipients had experienced either non proliferative or proliferative retinopathy.

Islet Infusion Information:

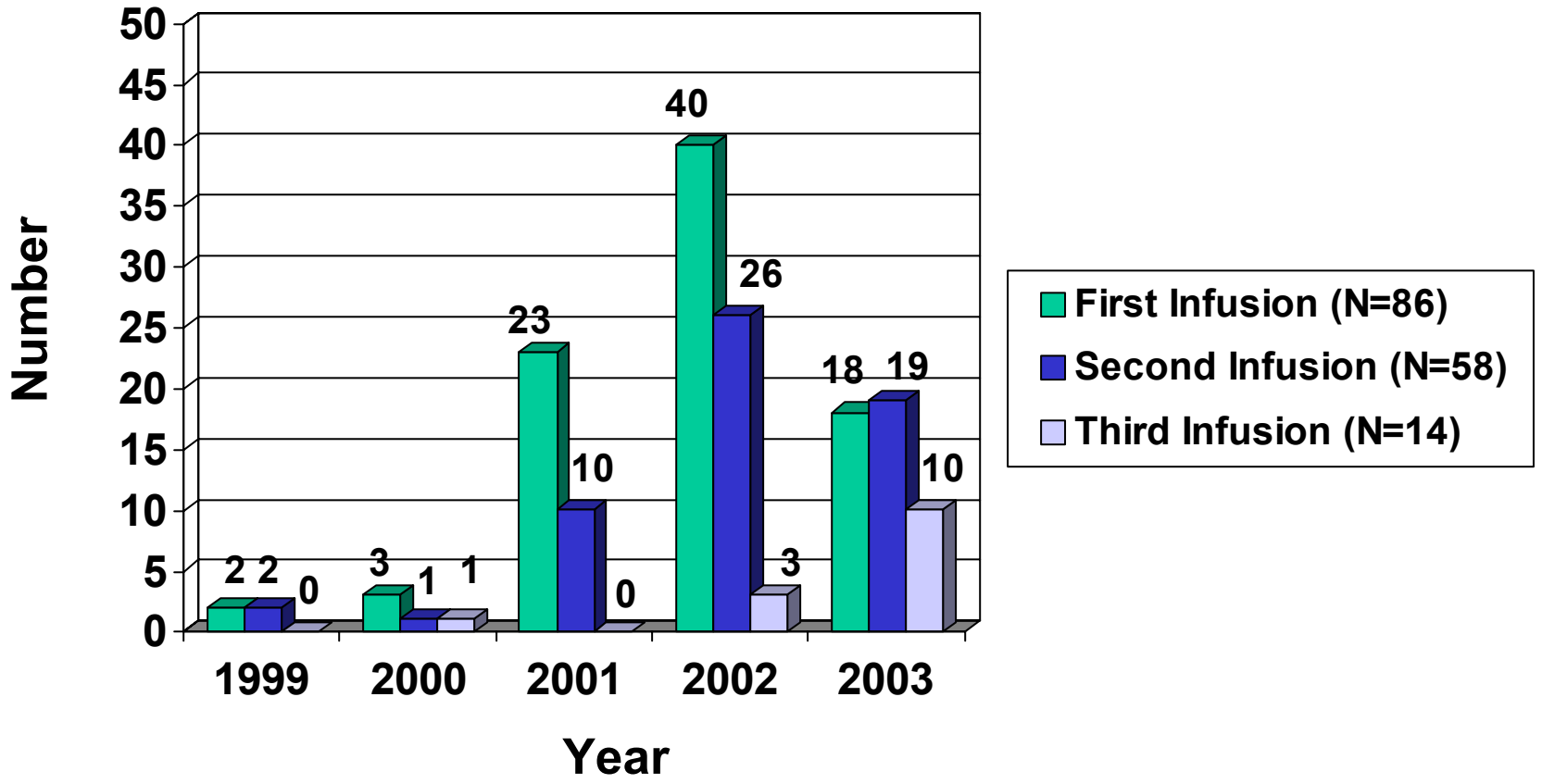
Exhibit 12 and Exhibit 13 summarize the main infusion procedure characteristics by the first infusion, second infusion and third infusion procedure. None of the procedures used an immunobarrier device, the site of infusion was always intraportally and over 80% of the time the portal vein was accessed via percutaneous transhepatic catheterization.

Donor Information:

The median age of the deceased donor was 44 years (range 7 to 65) and the median body mass index was 28.2 kg/m^2 (range 13.3 to 68.9). The median time from cross clamp to pancreas recovery was 27 minutes (range 0 to 127) (Exhibit 14). Fifty-four percent of the donors were male, 10% were Hispanic and approximately 69% were white. Over 54% of the donors had a cerebrovascular/stroke as cause of death while 30% experienced a head trauma. Thirty-one percent of the donors had a history of hypertension and 16% had a history of alcohol dependency.

Thirty-five percent of the donors received a transfusion prior to organ procurement and only 7% received a transfusion during the organ procurement surgery. Approximately 54% of the donors received steroids and just over a quarter of the donors had received insulin (Exhibit 15). Over 50% of the donors received one vasopressor, over 31% received two vasopressors, and almost 10% did not receive any vasopressors during the hospitalization leading to death (Exhibit 22). Deceased donor serology and recipient serology at screening are presented in Exhibits 23-25. Deceased donor laboratory data are presented in Exhibit 26. The median serum creatinine of the donors is 1.2 mg/dL, total bilirubin 0.7 mg/dL, AST 37.5 IU/L, ALT 29.0 IU/L, serum lipase 28.5 IU/L and serum amylase 71.5 IU/L.

Exhibit 2
Total Number of Infusion Procedures Conducted by Year and by Infusion Sequence



99 pancreata were used for first infusion procedures
59 pancreata were used for second infusion procedures
15 pancreata were used for third infusion procedures

Exhibit 3
Recipient Demographics by Year of First Infusion

Characteristic	1999-2001 (N=28)		2002 (N=40)		2003 (N=18)		Overall (N=86)	
	Median	Range	Median	Range	Median	Range	Median	Range
Age (yrs)	37.3	24.7 – 57.9	43.4	24.9 – 64.4	43.3	24.5 – 55.4	42.2	24.5 – 64.4
Duration of Diabetes (yrs)	23.5	5.0 – 50.0	30.0	7.0 – 47.0	32.0	13.0 – 45.0	30.0	5.0 – 50.0
Weight (kg)	66.0	48.9 – 97.0	64.5	47.6 – 90.0	61.0	47.0 – 81.0	65.0	47.0 – 97.0
Body Mass Index	24.2	18.9 – 28.4	23.1	18.8 – 30.1	22.8	17.9 – 31.6	23.3	17.7 – 31.6

Exhibit 4
Recipient Characteristics by Year of First Infusion

Characteristic	1999-2001 (N=28)		2002 (N=40)		2003 (N=18)		Overall (N=86)	
	N	%	N	%	N	%	N	%
Gender								
Female	19	67.9	22	55.0	16	88.9	57	66.3
Male	9	32.1	18	45.0	2	11.1	29	33.7
Race								
White	19	67.9	36	90.0	15	83.3	70	81.4
Unknown	9	32.1	4	10.0	3	16.7	16	18.6
Ethnicity								
Hispanic	1	3.6	0	0.0	0	0.0	1	1.2
Non Hispanic	18	64.3	36	90.0	14	77.8	68	79.1
Unknown	9	32.1	4	10.0	4	22.2	17	19.7
Transplanted in Same State as Primary Residence	10	35.7	26	65.0	9	50.0	45	52.3
Type 1 Diabetes	28	100.0	40	100.0	18	100.0	86	100.0

Exhibit 4 *(continued)*
Recipient Characteristics by Year of First Infusion

Characteristic	1999-2001 (N=28)		2002 (N=40)		2003 (N=18)		Overall (N=86)	
	N	%	N	%	N	%	N	%
Total Number of Islet Infusions Ever Received								
Islet Alone:								
One	10	35.7	10	25.0	7	46.7	27	31.4
Two	12	42.9	22	55.0	5	27.8	39	45.3
Three	6	21.4	7	17.5	1	6.6	14	16.3
More than Three	0	0.0	0	0.0	0	0.0	0	0.0
Islet After Kidney:								
One	0	0.0	1	2.5	0	0.0	1	1.2
Two	0	0.0	0	0.0	5	27.8	5	5.8
Type of Transplant Received								
Allograft	28	100.0	40	100.0	18	100.0	86	100.0
Autograft	0	0.0	0	0.0	0	0.0	0	0.0
Xenograft	0	0.0	0	0.0	0	0.0	0	0.0
Multiple Organ Transplants Ever Received								
Islet after Kidney	0	0.0	1	2.5	5	27.8	6	7.0
Other	0	0.0	0	0.0	0	0.0	0	0.0

Exhibit 5
Recipient's Primary Payer and Employment Status at Time of Infusion by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3	
	N	%	N	%	N	%
Total	86	100.0	58	100.0	14	100.0
Primary Payer						
Medicare	0	0.0	0	0.0	0	0.0
Medicaid	0	0.0	0	0.0	0	0.0
US/State Gov't Agency	26	30.2	20	34.5	5	35.7
Private Insurance	1	1.2	1	1.7	0	0.0
HMO/PPO	0	0.0	0	0.0	0	0.0
Self	0	0.0	2	3.4	0	0.0
Donation	0	0.0	0	0.0	0	0.0
Institutional Contribution	13	15.1	12	20.7	4	28.6
Non-Gov't Research Funding	30	34.9	14	24.1	2	14.3
Dept. of VA	0	0.0	0	0.0	0	0.0
Pending	0	0.0	0	0.0	0	0.0
Provincial Gov't	0	0.0	0	0.0	0	0.0
Non-US/Canada Gov't	0	0.0	0	0.0	0	0.0
Missing	16	18.6	9	15.5	3	21.4
Employment Status						
Full time	57	66.3	31	53.4	7	50.0
Part time – By Choice	5	5.8	4	6.9	2	14.3
Part time – Due to Dx	3	3.5	2	3.4	0	0.0
Part time – Unknown	0	0.0	0	0.0	0	0.0
Not Working by Choice	6	7.0	4	6.9	2	14.3
Not Working due to Dx	9	10.5	5	8.6	0	0.0
Not Working, unable to find work	0	0.0	0	0.0	0	0.0
Not Working, Unknown	1	1.2	0	0.0	0	0.0
Retired	4	4.7	1	1.7	0	0.0
Student	0	0.0	0	0.0	0	0.0
Status Unknown	0	0.0	1	1.7	0	0.0
Missing	1	1.2	10	17.2	3	21.4

Exhibit 6
Recipient's Primary Payer and Employment Status at Time of Infusion by Year of Infusion

	1999-2001		2002		2003	
	N	%	N	%	N	%
Total	42	100.0	69	100.0	47	100.0
Primary Payer						
Medicare	0	0.0	0	0.0	0	0.0
Medicaid	0	0.0	0	0.0	0	0.0
US/State Gov't Agency	18	42.9	18	26.1	15	31.9
Private Insurance	0	0.0	2	2.9	0	0.0
HMO/PPO	0	0.0	0	0.0	0	0.0
Self	0	0.0	0	0.0	0	0.0
Donation	0	0.0	0	0.0	0	0.0
Institutional Contribution	0	0.0	20	29.0	9	19.1
Non-Gov't Research Funding	8	19.0	20	29.0	18	38.3
Dept. of VA	0	0.0	0	0.0	0	0.0
Pending	0	0.0	0	0.0	0	0.0
Provincial Gov't	0	0.0	0	0.0	0	0.0
Non-US/Canada Gov't	0	0.0	0	0.0	0	0.0
Missing	16	38.1	9	13.0	5	10.6
Employment Status						
Full time	25	59.5	42	60.9	28	59.6
Part time – By Choice	3	7.1	3	4.3	5	10.6
Part time – Due to Dx	2	4.8	2	2.9	1	2.1
Part time – Unknown	0	0.0	0	0.0	0	0.0
Not Working by Choice	1	2.4	6	8.7	5	10.6
Not Working due to Dx	3	7.1	6	8.7	5	10.6
Not Working, unable to find work	0	0.0	0	0.0	0	0.0
Not Working, Unknown	0	0.0	0	0.0	1	2.1
Retired	2	4.8	3	4.3	0	0.0
Student	0	0.0	0	0.0	0	0.0
Status Unknown	0	0.0	1	1.4	0	0.0
Missing	6	14.3	6	8.7	2	4.3

Exhibit 7
Recipient Status at First Infusion

	N	%
Total	86	100.0
Recipient experienced any hypoglycemic episode in the past 12 months that required assistance of another person:		
Yes	58	67.4
No	14	16.3
Unknown	14	16.3
If yes,		
Number of episodes		
1	7	12.1
2	2	3.4
3	0	0.0
4	4	6.9
5	2	3.4
>5	43	74.1
Recipient experienced hypoglycemic episode in the past 12 months that required assistance of another person and resulted in the loss of consciousness/seizures:		
Yes	36	41.9
No	26	30.2
Unknown	24	27.9
If yes,		
Number of episodes		
1	11	30.6
2	5	13.9
3	4	11.1
4	5	13.9
5	2	5.6
>5	9	25.0
Daily Insulin Requirement Prior to Infusion, Units (Mean ± SD)	85 (35.4 ± 11.5)	
Number of injections per day		
N/A - on pump	40	46.5
1	1	1.2
2	3	3.5
3	8	9.3
4	24	27.9
5	8	9.3
>5	1	1.2
Unknown	1	1.2

Exhibit 7 *(continued)*
Recipient Status at First Infusion

	N	%
Total	86	100.0
Use of Insulin Pump		
Yes	40	46.5
No	46	53.5
Intensive Therapy (Use of insulin pump or 3 or more injections)	81	94.2
Duration of intensive therapy in years (Mean ± SD)	54 (14.6 ± 11.8)	
Prior Organ Transplant	6	7.0
Pre Transplant autoantibody (positive)		
GAD 65	15	17.4
IA-2	21	24.4
Insulin	13	15.1
ICA, JDF units (Mean ± SD)	9 (20.0 ± 0.0)	
Positive Crossmatches		
B-Cell	1	1.2
T-Cell	0	0.0
Fasting Plasma Glucose, mg/dL (Mean ± SD)	78 (163.0 ± 91.5)	
HbA_{1c} (%) (Mean ± SD)	82 (7.7 ± 1.3)	

Exhibit 8
Recipient's Body Mass Index by Infusion Sequence

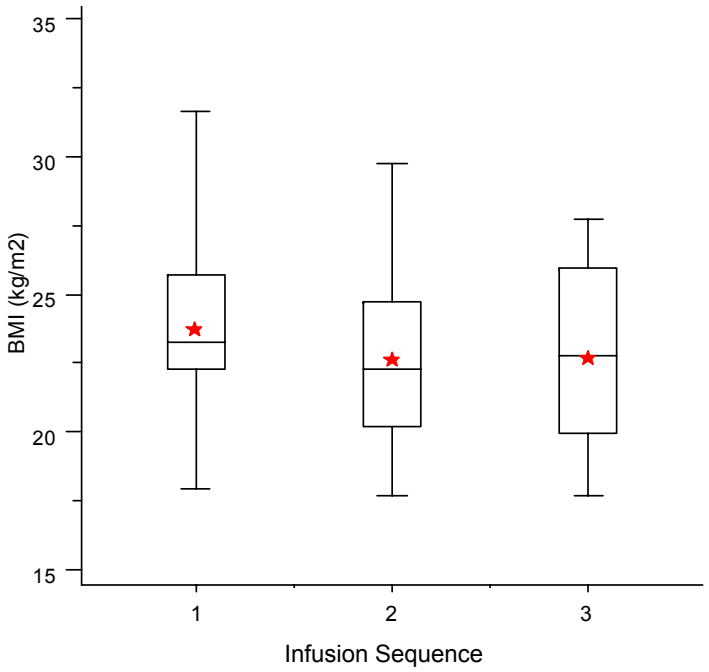


Exhibit 9
Secondary Complications at Recipient's First Infusion

	N	%
Total	86	100.0
Peripheral Neuropathy		
No occurrence	56	65.1
Asymptomatic	4	4.7
Symptomatic	22	25.6
Disabling	2	2.3
Unknown	2	2.3
Autonomic Neuropathy		
No occurrence	62	72.1
Asymptomatic	4	4.7
Symptomatic	17	19.8
Disabling	0	0.0
Unknown	3	3.5
Nephropathy		
No occurrence	68	79.1
Microalbuminuria	14	16.3
Macroalbuminuria	1	1.2
Stable Allograft	2	2.3
Unknown	1	1.2
CAD		
No	84	97.7
Yes	2	2.3
Unknown	0	0.0
CVA		
No	86	100.0
Yes	0	0.0
Unknown	0	0.0
PVD		
No	81	94.2
Yes	2	2.3
Unknown	3	3.5
Hypertension (treated)		
No	68	79.1
Yes	17	19.8
Unknown	1	1.2

Exhibit 10
Number of Secondary Complications Reported at Recipient's First Infusion

	N	%
Number of Secondary Complications Reported per Recipient		
None	38	44.2
1	22	25.6
2	17	19.8
3	8	9.3
4	1	1.2
5 or more	0	0.0

Exhibit 11
Ocular Complications at Recipient's First Infusion

	Left Eye		Right Eye	
	N	%	N	%
Total	86	100.0	86	100.0
Retinopathy				
None	40	46.5	40	46.5
Non Proliferative	21	24.4	20	23.3
Proliferative	23	26.7	24	27.9
Unknown	2	2.3	2	2.3
If present:				
Duration in years (Mean ± SD)	28 (13.1 ± 9.8)		27 (12.9 ± 10.0)	
If Proliferative				
Laser Photocoagulation Surgery Performed:				
No	1	4.3	1	4.2
Yes	22	95.7	23	95.8
Unknown	0	0.0	0	0.0
Diabetic Macular Edema				
None	80	93.0	80	93.0
Mild	0	0.0	0	0.0
Moderate	0	0.0	0	0.0
Severe	0	0.0	0	0.0
Unknown	6	7.0	6	7.0
Laser Photocoagulation Surgery Performed for Diabetic Macular Edema:				
No	78	90.7	78	90.7
Yes	2	2.3	2	2.4
Unknown	6	7.0	6	7.0

Exhibit 12
Infusion Summary by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Total	86		58		14	
Islet Equivalents Infused	86	473,705 (159,592)	57	436,805 (137,883)	14	482,225 (166,894)
Islet Equivalents Infused/kg	86	7268 (2482)	47	7265 (2074)	11	7964 (3306)
Packed Cell Volume Infused, mL	81	4.13 (2.35)	55	3.52 (1.59)	14	2.99 (1.37)
Pre-Infusion Portal Pressure	79	8.5 (3.7)	56	8.2 (3.5)	14	6.9 (4.3)
Peak Portal Pressure	79	11.9 (4.6)	55	11.6 (4.1)	14	10.6 (4.6)
Closure Portal Pressure	79	10.4 (4.4)	54	10.5 (4.4)	14	9.8 (4.6)
Time since first infusion in weeks	0		57	12.4 (12.2)	14	36.5 (33.4)

Exhibit 13
Infusion Characteristics by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3	
	N	%	N	%	N	%
Total	86	100.0	58	100.0	14	100.0
Immunobarrier Device Used	0	0.0	0	0.0	0	0.0
Infusion Site						
Liver	86	100.0	58	100.0	14	100.0
Other	0	0.0	0	0.0	0	0.0
If Site is liver:						
Technique Used						
Mini lap	13	15.1	3	5.2	0	0.0
Percutaneous	70	81.4	51	87.9	14	100.0
Other	3	3.5	3	5.2	0	0.0

Exhibit 14
Deceased Donor Characteristics
(All Donors, N=173)

Characteristic	N	Median	Range
Age (yrs)	168	44.0	7.0 – 65.0
Weight (kg)	171	83.9	25.0 – 200.0
Height (m)	169	1.7	1.4 – 1.9
Body Mass Index	169	28.2	13.3 – 68.9
Time from Admission to Brain Death (hrs)	146	31.1	0.0 – 484.0
Duration of Cardiac Arrest where Cardiovascular Death (mins)	8	22.5	4.0 – 60.0
Time from Cross Clamp to Pancreas Recovery (mins)	105	27.0	0.0 – 127.0

Exhibit 15
Deceased Donor Characteristics

Characteristic	N	%
Total	173	100.0
Female	79	45.7
Male	93	53.8
Unknown	1	0.5
Hispanic	18	10.4
Non Hispanic	116	67.1
Unknown	39	22.5
White	119	68.8
Non White	15	8.7
Unknown	39	22.5
Body Mass Index		
<25	43	24.9
25-27	40	23.1
28-30	30	17.3
>30	60	34.7
ABO Blood Group		
A	68	39.3
A_1	10	5.8
A_2	0	0.0
B	8	4.6
AB	1	0.6
A_1B	0	0.0
A_2B	0	0.0
O	85	49.1
Missing	1	0.6
Cause of Death		
Cerebrovascular/stroke	94	54.3
Head trauma	51	29.5
Anoxia/cardiac arrest	7	4.1
CNS Tumor	2	1.2
Other	15	8.7
Unknown	3	1.7
Missing	1	0.6
Mechanism of Death		
Intracranial hemorrhage/stroke	109	63.0
Blunt injury	36	20.8
Gun shot wound	12	6.9
Drug intoxication	2	1.2
Asphyxiation	2	1.2
Cardiovascular	4	2.3
Natural causes	1	0.6
Unknown	4	2.3
None of the above	2	1.2
Missing	1	0.6

Exhibit 15 *(continued)*
Deceased Donor Characteristics

Characteristic	N	%
Total	173	100.0
Circumstance of Death		
Natural causes	57	33.0
MVA	28	16.2
Non MVA	13	7.5
Alleged homicide	7	4.1
Alleged suicide	8	4.6
None of the above	57	33.0
Unknown	2	1.2
Missing	1	0.6
History of Hypertension		
Yes	54	31.2
No	106	61.3
Unknown	12	6.9
Missing	1	0.6
Duration of Hypertension		
0-5 Years	21	38.9
6-10 Years	4	7.4
>10 Years	10	18.5
Unknown	14	25.9
Missing	5	9.3
Control Method		
Diet	7	13.0
Diuretics	8	14.8
Other Medications	30	55.6
History of Alcohol Dependency		
Yes	28	16.2
Use in Last 6 months	20	71.4
No	132	76.3
Unknown	12	6.9
Missing	1	0.6
History of Diabetes	0	0.0

Exhibit 15 *(continued)*
Deceased Donor Characteristics

Characteristic	N	%
Total	173	100.0
Transfusions Prior to Surgery		
0 Units/No Transfusion	99	57.2
0-5 Units	46	26.6
6-10 Units	10	5.8
>10 Units	5	2.9
Unknown	12	6.9
Missing	1	0.6
Transfusions Given Intraoperatively		
0 Units/No Transfusion	149	86.1
0-5 Units	11	6.7
6-10 Units	1	0.6
>10 Units	0	0.0
Unknown	11	6.4
Missing	1	0.6
Steroids Given	94	54.3
Insulin Given	44	25.4

Exhibit 16
Deceased Donor Age (yrs)

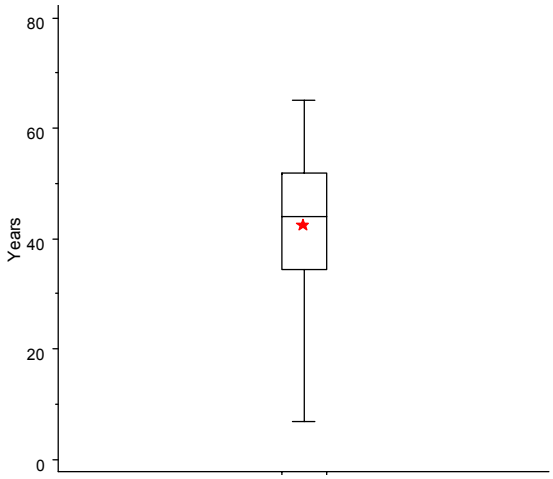


Exhibit 17
Deceased Donor Weight (kg)

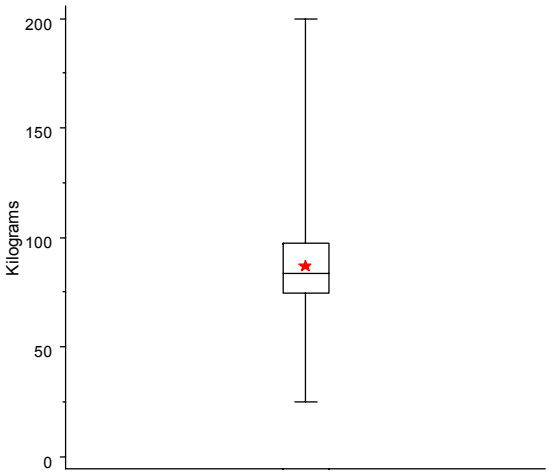


Exhibit 18
Deceased Donor Height (m)

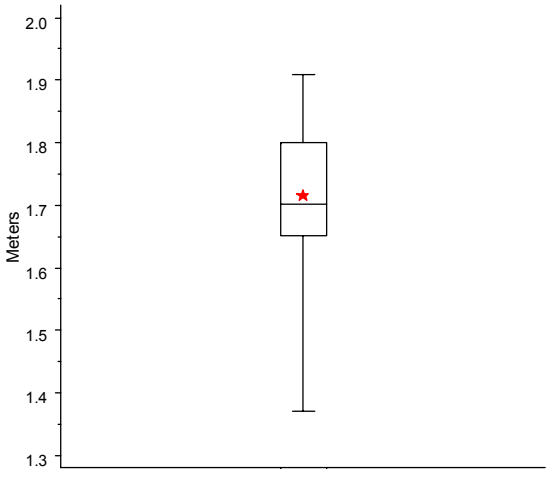


Exhibit 19
Deceased Donor Body Mass Index

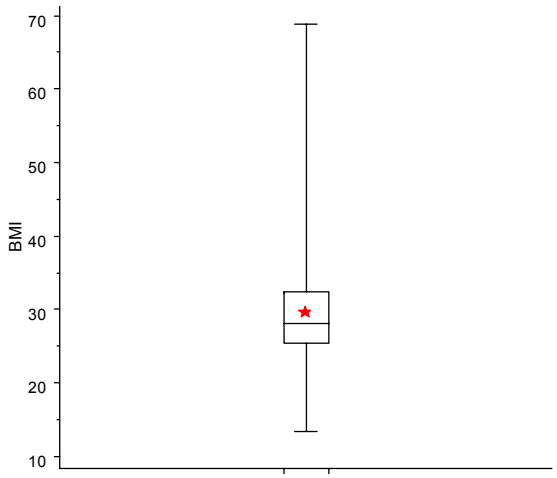


Exhibit 20
Time from Admission to Brain Death (hrs)

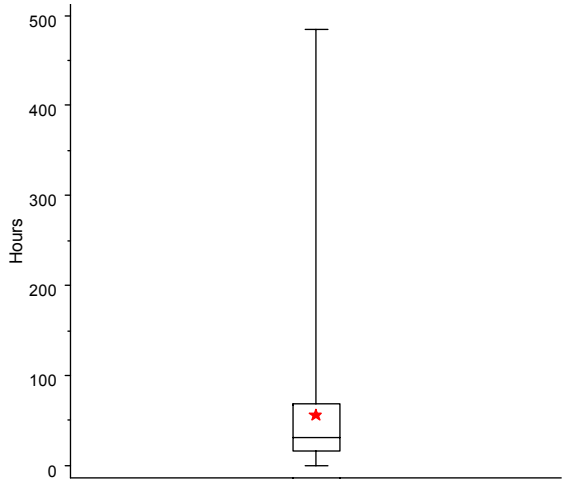


Exhibit 21
Time from Cross Clamp to Pancreas Recovery (mins)

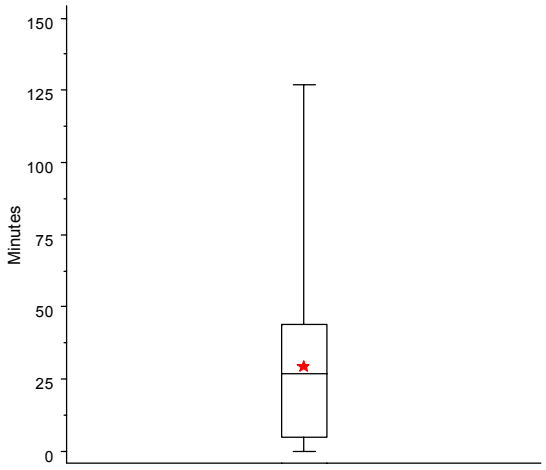


Exhibit 22
Deceased Donor Characteristics: Use of Vasopressors
(All Donors, N=173)

Use of Vasopressors	N	%
None	17	9.8
One	88	50.9
Two	54	31.2
Three	13	7.5
Four	1	0.6

Exhibit 23
Deceased Donor Serology

	Deceased Donors (N=173)		
Serology	Negative (%)	Positive (%)	Not Done/ Unknown/Missing (%)
Anti-HIV I/II	97.7	0.0	2.3
Anti-HTLV I/II	93.6	0.0	6.4
RPR-VDRL	91.9	0.0	8.1
Anti-CMV	46.2	51.5	2.3
HBsAg	94.8	0.6	4.6
Anti-HBC	94.2	0.6	5.8
Anti-HCV	94.8	0.6	5.2

Exhibit 24
Recipient Serology at Screening

	Pre Infusion 1 (N=86)		
Serology	Negative (%)	Positive (%)	Not Done/ Unknown/Missing (%)
HIV Screening	96.5	0.0	3.5
CMV IGG	51.2	44.2	4.6
CMV IGM	34.9	0.0	65.1
Hep B core antibody	75.6	2.3	22.1
Hep B surface antigen	91.9	2.3	5.8
Hep C antibody	95.3	0.0	4.7
EBV IGG	3.5	87.2	9.3
EBV IGM	31.4	25.6	43.0

Exhibit 25
Changes in Serology Results from Screening to Post First Infusion
(N=57)

Serology	N	%	Screening Result	Post First Infusion Result
HIV Screening	0	0.0		
CMV IGG	0	0.0		
CMV IGM	0	0.0		
Hep B core antibody	0	0.0		
Hep B surface antigen	0	0.0		
Hep C antibody	0	0.0		
EBV IGG	1	1.8	Positive	Negative
EBV IGM	1	1.8	Positive	Negative
	1	1.8	Negative	Positive
Total	3	5.3		

Exhibit 26
Deceased Donor Laboratory Data
(All Donors, N=173)

Terminal Lab Test	N	Mean (SD)	Median	Range
Serum Creatinine (mg/dL)	144	1.2 (1.0)	1.1	0.4 – 10.0
BUN (mg/dL)	136	14.6 (8.5)	13.0	3.0 – 55.0
Total Bilirubin (mg/dL)	136	0.9 (0.7)	0.7	0.1 – 4.1
AST (IU/L)	136	97.6 (345.0)	37.5	11.0 – 3886.0
ALT (IU/L)	136	72.6 (286.3)	29.0	5.0 – 3318.0
Serum Lipase (IU/L)	148	68.3 (108.2)	28.5	0.0 – 785.0
Serum Amylase (IU/L)	150	170.3 (395.9)	71.5	9.0 – 3875.0

*There were only three reports for donor HbA_{1c} and these data were omitted from the Exhibit.

Exhibit 27
Deceased Donor Serum Creatinine (mg/dL)

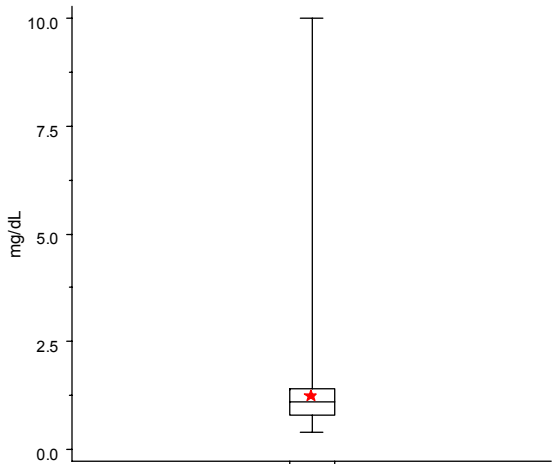


Exhibit 28
Deceased Donor BUN (mg/dL)

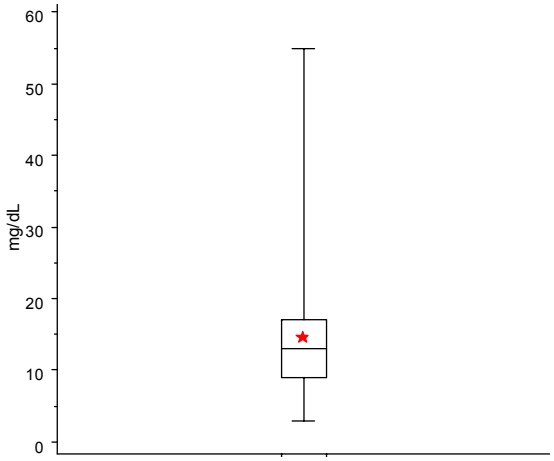


Exhibit 29
Deceased Donor Total Bilirubin (mg/dL)

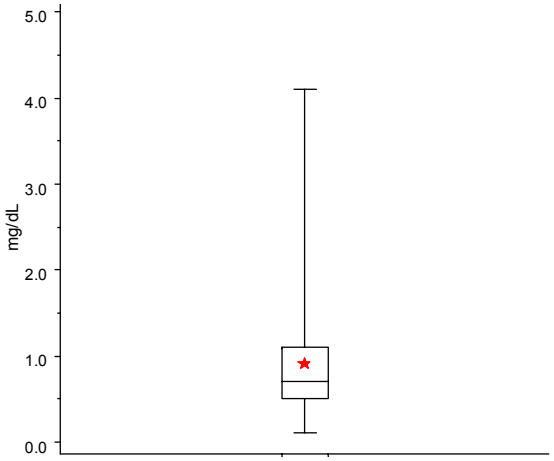


Exhibit 30
Deceased Donor AST (IU/L)

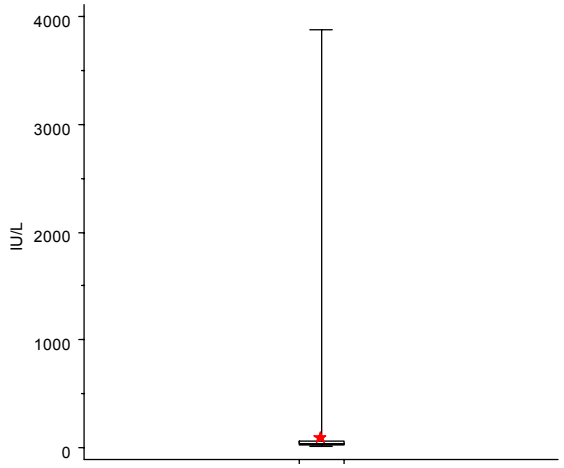


Exhibit 31
Deceased Donor ALT (IU/L)

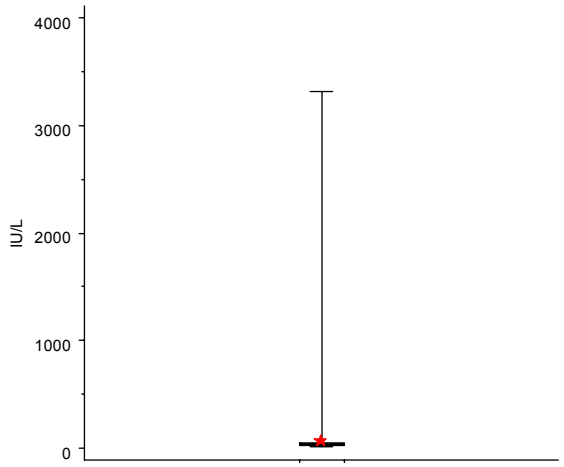


Exhibit 32
Deceased Donor Serum Lipase (IU/L)

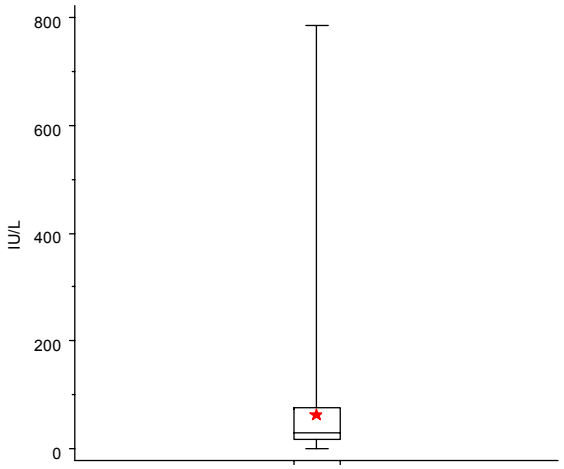
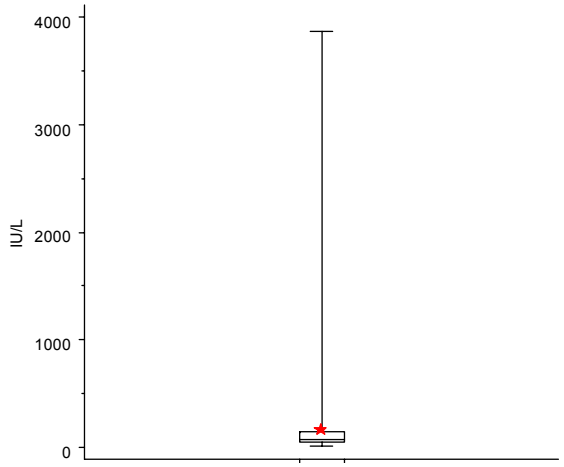


Exhibit 33
Deceased Donor Serum Amylase (IU/L)



Section 2
Pancreas Procurement and Islet Processing

Pancreas Procurement and Islet Processing Data Summary

Summarized in this section are pancreas procurement and islet processing data reported to the Registry. Overall the median time from cross clamp to pancreas recovery was 27 minutes (range 0 to 127) while the duration of cold ischemia was 7 hours (range 1.8 to 22.5) (Exhibit 34). In over 70% of the pancreas removal procedures, the pancreas procurement team was not related/affiliated with the processing/transplant team (Exhibit 35) while over 70% of the processing procedures took place at the same institution as the islet transplant center. UW, Two Layer (Top Layer UW, Bottom Layer PFC), and UW Followed by Two Layer methods are used for pancreas preservation, and in over 90% of the cases Liberase HI was used as the collagenase type. All of the processing facilities use a density gradient for islet purification and half of the pancreata processed did not have any islet pretreatment, while the other half had culture procedures performed (Exhibit 35). Of the 173 pancreata reported to CITR, only five showed a positive aerobic culture (2.9%), three showed a positive anaerobic culture (1.7%) and one showed a positive fungal culture (0.6%).

An islet product characterization summary is located in Exhibit 37. Total islet equivalents in the final product was plotted versus cold ischemic time (Exhibit 38), donor body mass index (Exhibit 39), donor age (Exhibit 40), and donor weight (Exhibit 41). Of these four correlations, there is indication that both deceased donor body mass index and donor weight have a statistically significant correlation with the total number of islet equivalents in the final product (Pearson correlation coefficient: $r=0.306$, $p=0.0002$ and $r=0.421$, $p<0.0001$; respectively).

Exhibits 42 through 47 show the results of a series of contrasts for islet cell characteristics and preparation and donor characteristics. At a conservative alpha of $p<0.01$, the percent of dithizone positive cells ($p=0.0006$) and the percent viability ($p<0.001$) significantly decreased as the time from cross clamp to pancreas recovery increased (Exhibit 42). In Exhibit 43, there was higher viability (95.5%) for pancreata preserved with a Two Layer method as opposed to pancreata not preserved with a Two Layer method (90.7%) ($p<0.0001$). When examining cold ischemic time subgroups, those at <4 hours had a higher endotoxin units/kg (Mean 0.56, SD 0.96), than those at 4-8 hours (Mean 0.30, SD 0.72), at 9-12 hours (Mean 0.05, SD 0.13), and at >12 hours (Mean 0.05, SD 0.09) ($p=0.001$). None of the islet characteristics varied significantly with donor age or donor body mass index. Endotoxin units/kg ($p=0.002$), viability ($p=0.0004$), and stimulation index ($p=0.005$), all varied significantly by year of the infusion procedure (Exhibit 47).

Exhibit 48 provides a summary of the total number of islet equivalents/kg for recipients who received only one infusion (N=25), for those who received a total of two infusions (N=37) and for those who received a total of three islet infusions (N=10).

Exhibit 34
Pancreas Procurement Information by Year of Infusion

	1999-2001 (N=46)			2002 (N=78)			2003 (N=49)			Overall (N=173)		
	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range	Mean (SD)	Median	Range
Time from Cross Clamp to Pancreas Recovery (mins)	32.7 (15.5)	30.0	11.0 – 63.0	27.5 (25.4)	25.0	0.0 – 127.0	31.2 (26.6)	26.5	0.0 – 80.0	29.5 (24.6)	27.0	0.0 – 127.0
Duration of Cold Ischemia (hrs)	8.4 (2.8)	7.6	5.0 – 16.0	7.7 (3.5)	6.9	2.6 – 22.5	6.9 (3.1)	6.4	1.8 – 15.7	7.6 (3.3)	7.0	1.8 – 22.5

Exhibit 35
Islet Processing Summary by Year

	1999-2001 (N=46)		2002 (N=78)		2003 (N=49)		Overall (N=173)	
	N	%	N	%	N	%	N	%
Pancreas Procurement Team								
Related to Processing/ Transplant Team	6	13.0	18	23.1	7	14.3	31	17.9
Unrelated to Processing/ Transplant Team	27	58.7	56	71.8	39	79.6	122	70.5
Missing	13	28.3	4	5.1	3	6.1	20	11.6
Pancreas Processing/Testing Center								
CITR Center where TX- took place	36	78.3	54	69.2	37	75.5	127	73.4
Another facility not located at TX center	0	0.0	21	26.9	9	18.4	30	17.3
Missing	10	21.7	3	3.8	3	6.1	16	9.2
Pancreas Preservation								
UW	19	41.3	34	43.6	21	42.9	74	42.8
Two Layer	23	50.0	43	55.1	25	51.0	91	52.6
UW Followed by Two Layer	4	8.7	1	1.3	3	6.1	8	4.6
Other	0	0.0	0	0.0	0	0.0	0	0.0
Collagenase Type (Multiple Choices Allowed)								
Liberase HI	36	78.3	75	96.2	45	91.8	156	90.2
Serva	0	0.0	0	0.0	1	2.0	1	0.6
Collagenase P	0	0.0	0	0.0	0	0.0	0	0.0
Sigma Blend	0	0.0	0	0.0	0	0.0	0	0.0
Other	0	0.0	0	0.0	0	0.0	0	0.0
Missing	10	21.7	3	3.8	3	6.1	16	9.2
Islet Purification								
None	0	0.0	0	0.0	1	2.0	1	0.6
Density Gradient	29	63.0	64	82.1	41	83.7	134	77.5
Missing	17	37.0	14	17.9	7	14.3	38	22.0
Islet Pretreatment								
None	8	17.4	43	55.1	25	51.0	76	43.9
Culture	26	56.5	30	38.5	21	42.9	77	44.5
Cryopreservation	0	0.0	0	0.0	0	0.0	0	0.0
Irradiation	0	0.0	0	0.0	0	0.0	0	0.0
Gene Transfer	0	0.0	0	0.0	0	0.0	0	0.0
Missing	12	26.1	5	6.4	3	6.1	20	11.6

Exhibit 35 *(continued)*
Islet Processing Summary by Year

	1999-2001 (N=46)		2002 (N=78)		2003 (N=49)		Overall (N=173)	
	N	%	N	%	N	%	N	%
Positive Microbiology Results								
Gram Stain	0	0.0	0	0.0	0	0.0	0	0.0
Aerobic Culture	0	0.0	5	6.4	0	0.0	5	2.9
Anaerobic Culture	0	0.0	3	3.8	0	0.0	3	1.7
Fungal Culture	1	2.2	0	0.0	0	0.0	1	0.6
Mycoplasma	0	0.0	0	0.0	0	0.0	0	0.0

Exhibit 36
Summary of Islet Equivalents and Timing of Count

	N	%	Mean (SD)	Median	Range
Islet Equivalents (IEQ) Measured at:					
Post Purification	125	72.3	434,276 (154,966)	396,867	139,600 - 973,133
Post Culture/Cryo	15	8.7	483,396 (163,694)	417,650	270,032 - 875,583
Missing	33	19.1	---	---	---

Exhibit 37
Islet Product Characterization
(All Pancreata, N=173)

Characteristic	N	Mean (SD)	Median	Range
Total Packed Cell Volume Infused (mL)	132	3.2 (1.8)	2.8	0.7 - 10.5
Islet Count	129	342,767 (156,788)	326,000	202 - 996,000
Embedded Islets (%)	48	15.9 (14.8)	12.0	0.0 - 56.0
Islet Equivalents/kg	146	6815 (2512)	6611	2019 - 16,305
Islet Equivalents Planned for Infusion	172	467,330 (155,980)	442,913	167,126 - 973,133
Islet Equivalents Infused	172	466,688 (155,830)	442,913	167,126 - 973,133
Beta Cells ($x10^6$)	21	246.5 (215.6)	202.0	4.0 - 735.0
Beta Cells/kg	21	3.96 (3.28)	3.41	0.07 - 11.04
Insulin Content (µg)	35	2164 (1702)	1777	67 - 7203
DNA Content (µg)	28	11,443 (12,835)	8088	83.0 - 51,854
Endotoxin Units	135	13.9 (34.6)	5.0	0.03 - 241.0
Endotoxin Units/kg	135	0.24 (0.62)	0.06	0.0004 - 4.92
Purity:				
Dithizone Positive Cells (%)	124	62.8 (15.9)	60.0	30.0 - 95.0
Beta Cells (%)	18	30.6 (7.5)	29.5	18.0 - 46.0
Viability:				
Fluorescein Diacetate/ Propidium Iodide (%)	100	93.7 (5.5)	95.0	76.0 - 100.0
Trypan Blue Positive (%)	7	71.4 (43.8)	95.0	5.0 - 100.0
Potency:				
Stimulation Index (glucose stimulated insulin release)	112	2.58 (2.91)	2.0	0.0 - 27.0

Exhibit 38
Total Islet Equivalents by Cold Ischemic Time
(All Pancreata)

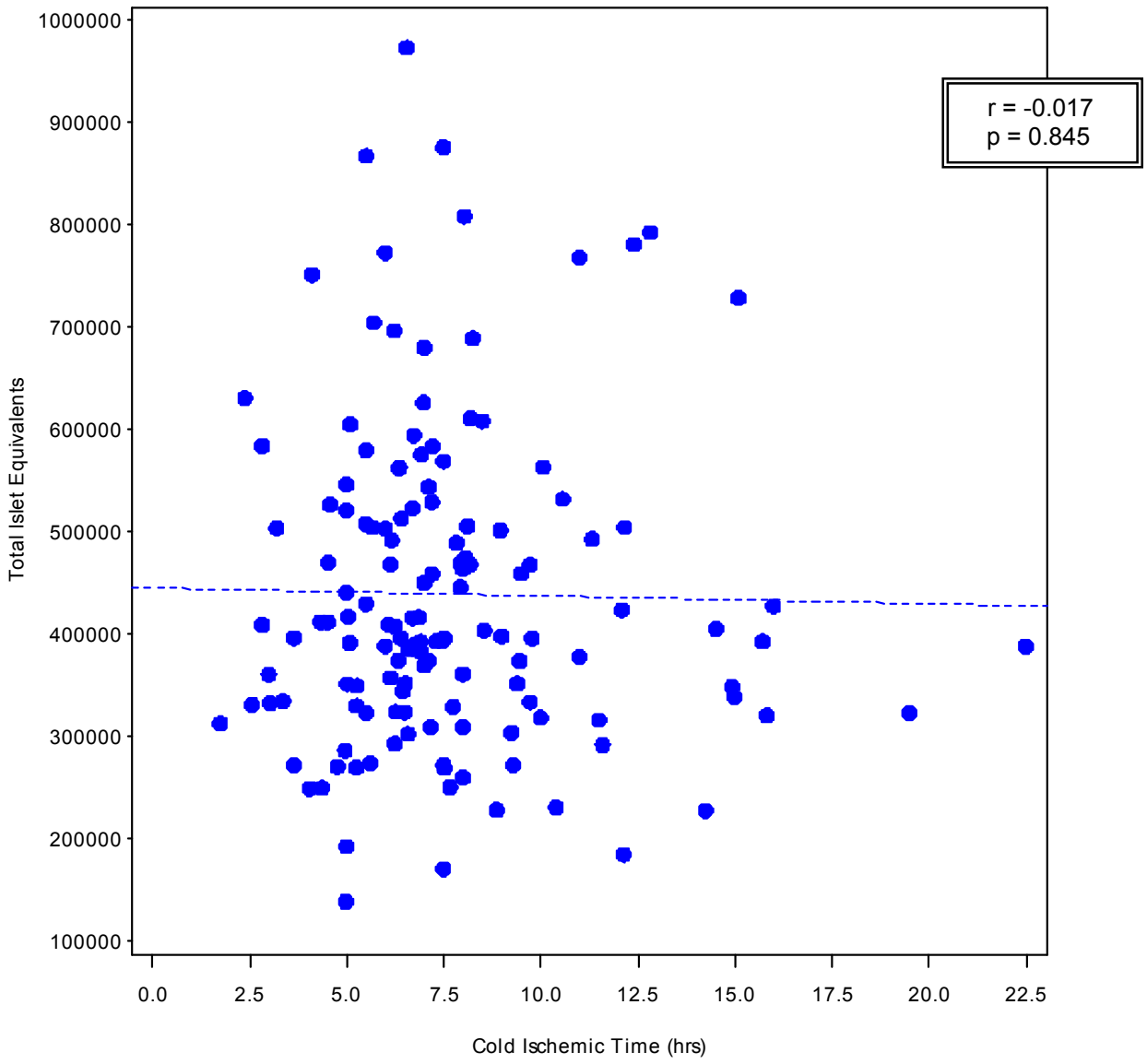


Exhibit 39
Total Islet Equivalents by Deceased Donor Body Mass Index
(All Pancreata)

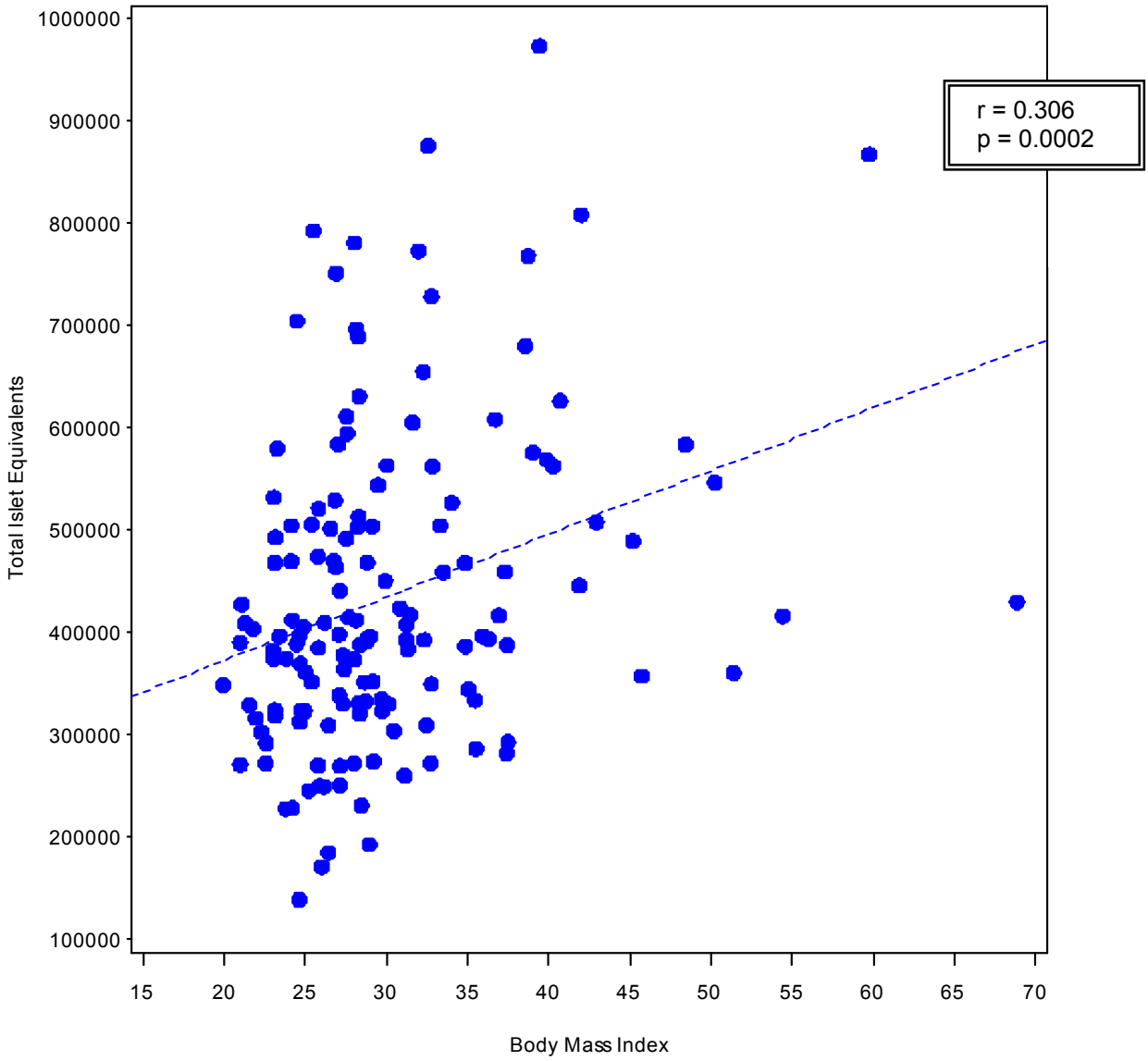


Exhibit 40
Total Islet Equivalents by Deceased Donor Age
(All Pancreata)

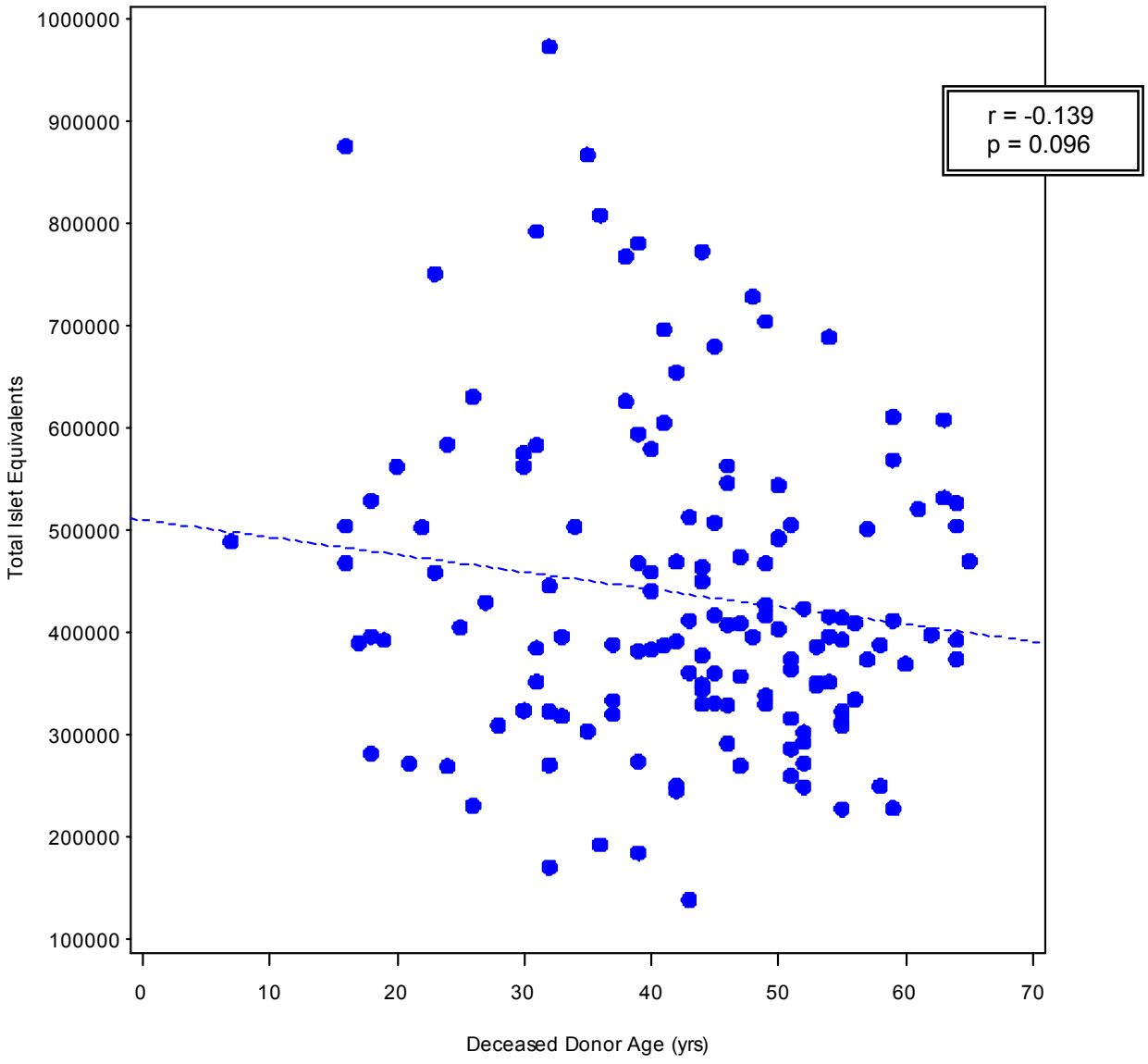


Exhibit 41
Total Islet Equivalents by Deceased Donor Weight
(All Pancreata)

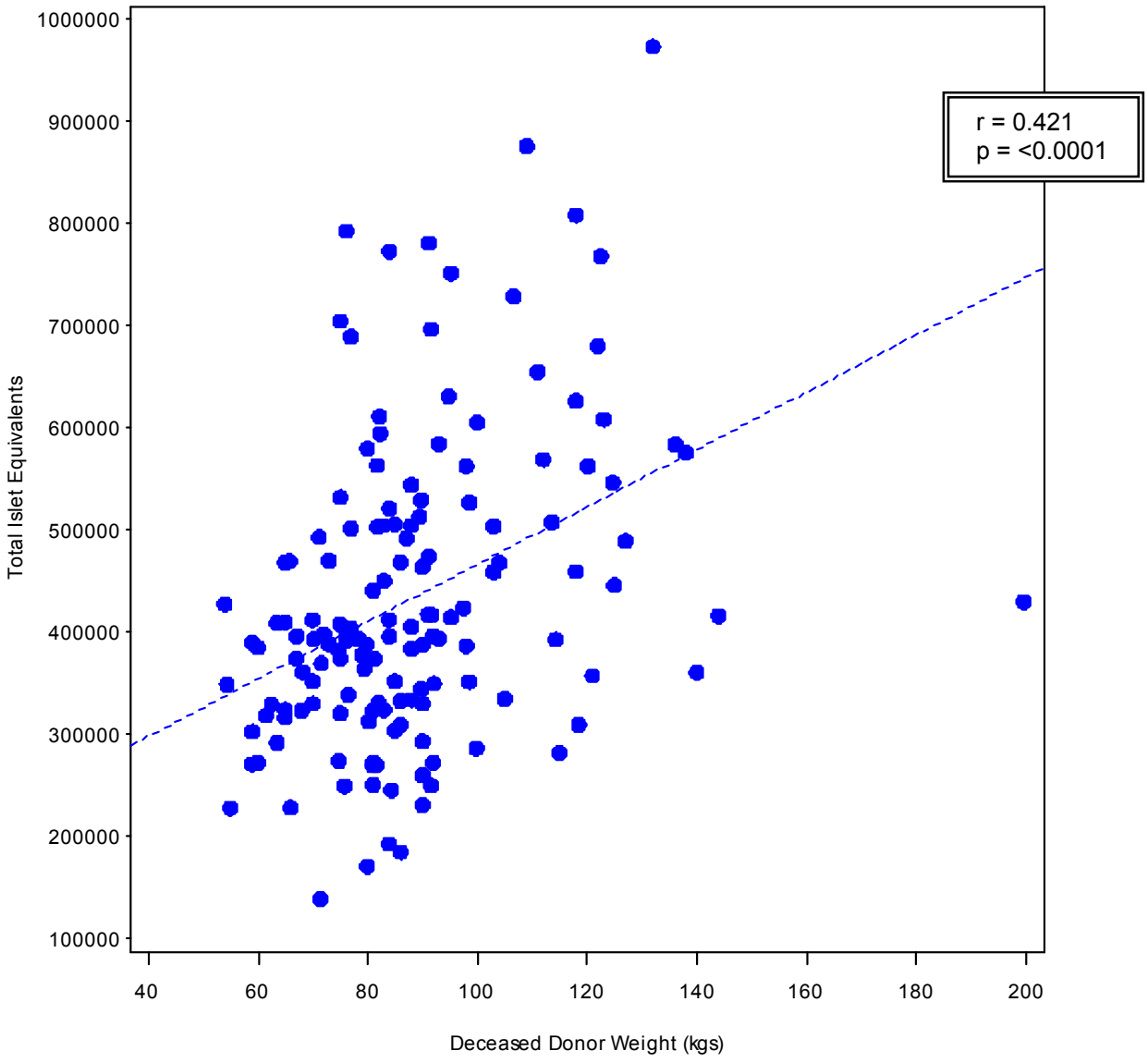


Exhibit 42
Islet Characteristics by Time from Cross Clamp to Pancreas Recovery
(All Pancreata, N=173)

Characteristic	<45 Minutes		45-60 Minutes		>60 Minutes		p value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Total Packed Cell Volume Infused (mL)	62	3.01 (1.64)	12	3.08 (2.08)	13	3.66 (1.84)	0.471
Islet Equivalents Infused	79	478,851 (166,287)	15	394,902 (114,200)	17	505,103 (158,146)	0.116
Islet Equivalents/kg	71	7267 (2502)	15	6400 (1889)	16	6903 (2758)	0.445
Endotoxin Units/kg	66	0.32 (0.60)	13	0.65 (1.39)	15	0.03 (0.06)	0.080
Purity: Dithizone Positive Cells (%)	63	65.4 (14.0)	13	60.8 (18.3)	12	46.8 (14.8)	0.0006
Viability: Fluorescein Diacetate/Propidium Iodide (%)	52	96.2 (4.1)	6	95.3 (2.3)	10	88.5 (6.2)	<0.001
Potency: Stimulation Index (glucose stimulated insulin release)	53	2.8 (3.9)	12	2.4 (0.7)	11	2.5 (2.4)	0.914

Exhibit 43
Islet Characteristics Based on Pancreas Preservation Method
(All Pancreata, N=173)

Characteristic	Two Layer Method Used		Two Layer Method Not Used		p value
	N	Mean (SD)	N	Mean (SD)	
Total Packed Cell Volume Infused (mL)	83	3.27 (1.77)	50	3.04 (1.79)	0.307
Islet Equivalents Infused	98	479,285 (159,487)	76	450,997 (148,808)	0.393
Islet Equivalents/kg	73	6995 (2607)	73	6635 (2418)	0.365
Endotoxin Units/kg	67	0.18 (0.33)	68	0.29 (0.81)	0.801
Purity: Dithizone Positive Cells (%)	63	66.3 (14.1)	61	59.3 (17.0)	0.021
Viability: Fluorescein Diacetate/Propidium Iodide (%)	63	95.5 (4.4)	37	90.7 (6.0)	<0.0001
Potency: Stimulation Index (glucose stimulated insulin release)	55	2.67 (3.88)	57	2.51 (1.51)	0.046

Exhibit 44
Islet Characteristics Based on Cold Ischemic Time
(All Pancreata, N=173)

Characteristic	<4 hours		4-8 hours		9-12 hours		>12 hours		p value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Total Packed Cell Volume Infused (mL)	10	3.03 (1.81)	65	3.28 (1.97)	20	2.76 (1.12)	14	3.30 (2.20)	0.947
Islet Equivalents Infused	11	396,698 (117,070)	87	469,245 (156,524)	21	519,811 (156,839)	14	477,111 (183,523)	0.135
Islet Equivalents/kg	10	7150 (2148)	85	6998 (2563)	18	6113 (2555)	13	6869 (2833)	0.520
Endotoxin Units/kg	9	0.56 (0.96)	79	0.30 (0.72)	18	0.05 (0.13)	13	0.05 (0.09)	0.001
Purity: Dithizone Positive Cells (%)	10	63.9 (19.6)	72	62.0 (15.0)	15	60.4 (14.5)	13	66.4 (17.3)	0.520
Viability: Fluorescein Diacetate/ Propidium Iodide (%)	7	93.9 (4.5)	54	93.8 (5.7)	14	93.1 (5.0)	12	91.9 (6.8)	0.818
Potency: Stimulation Index (glucose stimulated insulin release)	10	2.75 (1.26)	67	2.77 (3.63)	14	2.24 (1.07)	13	2.09 (1.24)	0.368

Exhibit 45
Islet Characteristics Based on Donor Age
(All Pancreata, N=173)

Characteristic	<41 years		41-50 years		51-60 years		>60 years		p value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Total Packed Cell Volume Infused (mL)	51	3.30 (1.93)	41	3.29 (1.85)	32	2.87 (1.28)	5	2.88 (1.83)	0.789
Islet Equivalents Infused	64	486,107 (181,773)	52	468,006 (147,910)	42	433,758 (125,200)	9	502,639 (103,883)	0.292
Islet Equivalents/kg	55	7582 (2938)	44	6638 (2383)	35	5893 (1847)	8	6814 (1724)	0.025
Endotoxin Units/kg	53	0.30 (0.75)	38	0.20 (0.54)	32	0.23 (0.61)	8	0.04 (0.04)	0.527
Purity: Dithizone Positive Cells (%)	49	65.6 (14.9)	38	61.9 (16.9)	28	59.6 (15.2)	6	60.0 (13.8)	0.372
Viability: Fluorescein Diacetate/ Propidium Iodide (%)	45	94.1 (5.4)	31	93.9 (6.0)	20	92.4 (5.3)	3	96.7 (1.2)	0.362
Potency: Stimulation Index (glucose stimulated insulin release)	47	3.04 (4.19)	32	2.40 (1.67)	25	2.03 (0.97)	4	1.80 (1.02)	0.797

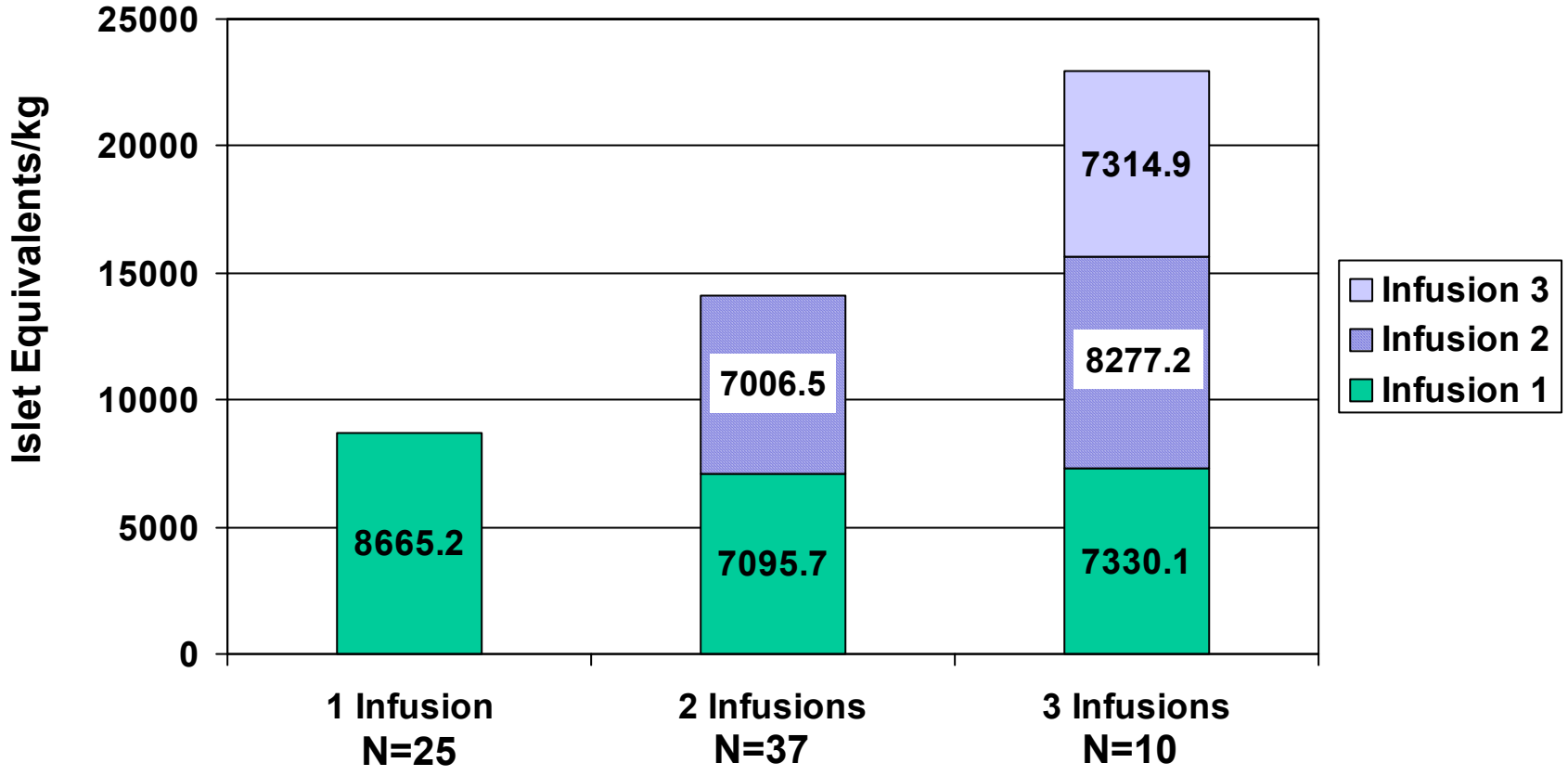
Exhibit 46
Islet Characteristics by Donor Body Mass Index
(All Pancreata, N=173)

Characteristic	<26		26-27		28-30		31-35		≥36		p value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Total Packed Cell Volume Infused (mL)	35	4.41 (2.06)	18	2.84 (1.92)	35	2.72 (1.52)	28	3.29 (1.64)	16	3.86 (1.57)	0.107
Islet Equivalents Infused	39	425,590 (129,426)	24	426,869 (162,018)	46	448,195 (131,163)	33	503,910 (173,058)	26	551,602 (170,161)	0.015
Islet Equivalents/kg	33	5961 (2192)	20	6390 (2570)	40	6649 (2360)	28	7232 (2667)	24	8108 (2565)	0.018
Endotoxin Units/kg	32	0.08 (0.15)	18	0.24 (0.36)	35	0.21 (0.55)	27	0.14 (0.19)	22	0.62 (1.26)	0.043
Purity: Dithizone Positive Cells (%)	30	61.7 (16.8)	18	65.9 (14.8)	33	65.4 (17.3)	25	60.8 (13.2)	18	59.8 (16.9)	0.487
Viability: Fluorescein Diacetate/ Propidium Iodide (%)	25	92.8 (5.3)	14	93.0 (4.9)	24	93.7 (5.3)	24	94.5 (6.0)	13	95.0 (6.4)	0.299
Potency: Stimulation Index (glucose stimulated insulin release)	30	2.32 (1.68)	16	3.94 (6.23)	29	2.18 (1.38)	20	2.97 (2.97)	16	2.01 (0.88)	0.655

Exhibit 47
Islet Characteristics by Year of Islet Infusion
(All Pancreata, N=173)

Characteristic	1999-2001		2002		2003		p value
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	
Total Packed Cell Volume Infused (mL)	31	3.65 (2.02)	64	3.25 (1.73)	38	2.69 (1.55)	0.082
Islet Equivalents Infused	47	476,585 (170,133)	78	465,371 (151,029)	49	460,150 (148,150)	0.870
Islet Equivalents/kg	32	6894 (3544)	69	6616 (2090)	45	7064 (2251)	0.582
Endotoxin Units/kg	29	0.24 (0.92)	63	0.33 (0.65)	43	0.10 (0.13)	0.002
Purity: Dithizone Positive Cells (%)	26	56.6 (14.6)	58	64.4 (14.4)	40	66.6 (18.0)	0.087
Viability: Fluorescein Diacetate/ Propidium Iodide (%)	26	90.2 (6.0)	44	95.4 (4.5)	30	94.4 (5.2)	0.0004
Potency: Stimulation Index (glucose stimulated insulin release)	28	3.47 (2.82)	58	2.44 (3.45)	26	1.95 (0.81)	0.005

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



*14 recipients missing information

Section 3
Immunosuppressive and Other Medications

Immunosuppressive and Other Medications Data Summary

Immunosuppressive medications, as well as anti-hypertensive medications, lipid lowering medications and administration of adjunctive therapies used by the islet transplant recipients are summarized in this section of the report. For immunosuppressive medications, summaries are presented for islet alone recipients (Exhibit 49) and for islet after kidney recipients (Exhibit 50). Clearly, the majority of the islet alone recipients at the time of infusion were on a Daclizumab, Sirolimus, and Tacrolimus immunosuppression regimen (Infusion 1=53.8%, Infusion 2=69.8%, and Infusion 3=57.1%). Dosing for the immunosuppressive medications at time of infusion for islet alone recipients are located in Exhibits 51 and 53, with trough levels presented in Exhibit 55. Immunosuppression therapy used post last infusion is displayed in Exhibits 57-59. For the 1-6 month period following a recipient's last infusion, over 35% of islet alone recipients were on a Sirolimus (Mean 8.0 mg/day, SD 2.7) and Tacrolimus (Mean 3.9 mg/day, SD 1.5) regimen (Exhibit 57).

At the time of first infusion, 25.7% of the recipients are on an anti-hypertensive medication (Exhibit 61) and 18.6% are on a lipid lowering medication (Exhibit 62). Overall, for adjunctive therapies, over 90% of recipients were using an antibiotic, over 82% were using Heparin (including Heparin used during the infusion), and 66% were using vitamins (Exhibit 63).

Exhibit 49
Immunosuppression Regimen at Time of Infusion by Infusion Sequence for Islet Alone Recipients

	Infusion 1		Infusion 2		Infusion 3	
	N	%	N	%	N	%
Total	80	100.0	53	100.0	14	100.0
Daclizumab + Sirolimus + Tacrolimus	43	53.8	37	69.8	8	57.1
Daclizumab + Infliximab + Sirolimus + Tacrolimus	8	10.0	0	0.0	1	7.1
hOKT3γ1 (Ala-Ala) + Sirolimus + Tacrolimus	3	3.8	0	0.0	0	0.0
Daclizumab + MMF + Sirolimus	0	0.0	0	0.0	1	7.1
Daclizumab + MMF + Sirolimus + Tacrolimus	0	0.0	2	3.8	0	0.0
Daclizumab + MMF + Etanercept + Sirolimus + Tacrolimus	0	0.0	1	1.9	1	7.1
Daclizumab + 15-Deoxyspergualin + Sirolimus + Tacrolimus	3	3.8	1	1.9	0	0.0
Etanercept + Methylprednisolone + Everolimus + Thymoglobulin + Cyclosporine	1	1.3	0	0.0	0	0.0
Daclizumab + MMF + Etanercept + Methylprednisolone + Thymoglobulin + Sirolimus + Tacrolimus	7	8.8	0	0.0	0	0.0
Missing Information on Immunosuppression	15	18.8	12	22.6	3	21.4

Exhibit 50
Immunosuppression Regimen at Time of Infusion by Infusion Sequence for Islet After Kidney Recipients

	Infusion 1		Infusion 2	
	N	%	N	%
Total	6	100.0	5	100.0
Daclizumab + Sirolimus + Tacrolimus	1	16.7	2	40.0
Daclizumab + Infliximab + Sirolimus + Tacrolimus	2	33.3	1	20.0
Sirolimus + Tacrolimus + Prednisone	0	0.0	1	20.0
Daclizumab + Sirolimus + Tacrolimus + Prednisone	2	33.3	1	20.0
Missing Information on Immunosuppression	1	16.7	0	0.0

Exhibit 51
Immunosuppression Dosing at Time of Infusion by Infusion Sequence for Islet Alone Recipients

(mg/day)	Infusion 1			Infusion 2			Infusion 3		
	N	Mean (SD)	Median Day Initiated	N	Mean (SD)	Median Day Initiated	N	Mean (SD)	Median Day Initiated
Sirolimus	64	12.3 (2.9)	0.0	41	8.5 (3.0)	0.0	11	9.7 (2.9)	0.0
Tacrolimus	64	1.8 (0.9)	0.0	41	4.0 (1.7)	0.0	10	4.5 (1.0)	0.0
Everolimus	1	3.0 (---)	-2.0	0	---	---	0	---	---
MMF	7	1571.4 (731.9)	25.0	3	1000.0 (866.0)	-4.5	2	1250.0 (1060.7)	-4.5
Methylprednisolone	8	60.7 (6.1)	-2.0	0	---	---	0	---	---

Exhibit 52
Immunosuppression Dosing at Time of Infusion by Infusion Sequence for Islet After Kidney Recipients

(mg/day)	Infusion 1			Infusion 2		
	N	Mean (SD)	Median Day Initiated	N	Mean (SD)	Median Day Initiated
Sirolimus	5	6.0 (3.4)	0.0	5	8.2 (2.0)	0.0
Tacrolimus	5	3.0 (1.4)	0.0	5	3.5 (0.5)	0.0
Prednisone	2	5.0 (0.0)	0.0	2	5.0 (0.0)	0.0

Exhibit 53
Induction Therapy at Time of Infusion by Infusion Sequence for Islet Alone Recipients

(mg)	Infusion 1				Infusion 2				Infusion 3			
	N	Median Day Initiated	Median Dose Days	Total Dose Mean (SD)	N	Median Day Initiated	Median Dose Days	Total Dose Mean (SD)	N	Median Day Initiated	Median Dose Days	Total Dose Mean (SD)
Thymoglobulin	8	-2.0	5.0	367.8 (36.3)	0	---	---	---	0	---	---	---
Daclizumab	61	0.0	5.0	280.9 (90.3)	41	0.0	5.0	286.8 (94.9)	11	0.0	5.0	323.5 (81.8)
hOKT3γ1 (Ala-Ala)	3	-2.0	12.0	48.7 (5.5)	0	---	---	---	0	---	---	---
Infliximab	8	0.0	1.0	491.9 (244.3)	0	---	---	---	1	0.0	1.0	510.0 (---)
Etanercept	8	0.0	4.0	125.0 (0.0)	1	0.0	4.0	125.0 (---)	1	0.0	4.0	125.0 (---)

Exhibit 54
Induction Therapy at Time of Infusion by Infusion Sequence for Islet After Kidney Recipients

(mg)	Infusion 1				Infusion 2			
	N	Median Day Initiated	Median Dose Days	Total Dose Mean (SD)	N	Median Day Initiated	Median Dose Days	Total Dose Mean (SD)
Daclizumab	5	0.0	4.0	258.4 (116.2)	4	2.0	4.0	200.0 (119.9)
Infliximab	2	0.0	1.0	630.0 (42.4)	1	0.0	1.0	520.0 (---)

Exhibit 55
Immunosuppression Trough Levels at Day 30 Following Infusion by Infusion Sequence for Islet Alone Recipients

(mg/day)	Infusion 1		Infusion 2		Infusion 3	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Sirolimus	58	12.3 (4.2)	38	12.3 (3.0)	10	13.6 (3.6)
Tacrolimus	60	4.9 (1.8)	35	4.4 (1.3)	10	4.1 (0.9)
Cyclosporine	1	563.0 (---)	0	---	0	---

Exhibit 56
Immunosuppression Trough Levels at Day 30 Following Infusion by Infusion Sequence for Islet After Kidney Recipients

(mg/day)	Infusion 1		Infusion 2	
	N	Mean (SD)	N	Mean (SD)
Sirolimus	3	15.5 (2.9)	5	13.5 (1.8)
Tacrolimus	3	4.4 (0.7)	5	4.0 (0.5)

Exhibit 57
Immunosuppression Therapy Use Post Last Infusion for Islet Alone Recipients

	1-6 Months	
	N	%
Total	73	100.0
None	2	2.7
Sirolimus + MMF	1	1.4
Sirolimus + Tacrolimus	26	35.6
MMF + Sirolimus + Tacrolimus	10	13.7
Daclizumab + Sirolimus + Tacrolimus	6	8.2
Missing Information on Immunosuppression	28	38.4

Exhibit 58
Immunosuppression Dosing Post Last Infusion for Islet Alone Recipients

	1-6 Months	
(mg/day)	N	Mean (SD)
Sirolimus	43	8.0 (2.7)
Tacrolimus	42	3.9 (1.5)
MMF	11	818.2 (603.0)
Daclizumab	6	70.4 (18.6)

Exhibit 59
Immunosuppression Trough Levels Post Last Infusion for Islet Alone Recipients

(mg/day)	Day 30				Visit Month 6			
	N	Mean (SD)	Median	Range	N	Mean (SD)	Median	Range
Sirolimus	58	11.8 (3.7)	12.8	1.3 – 19.5	42	10.6 (3.5)	9.8	5.1 – 21.7
Tacrolimus	58	4.7 (1.5)	4.9	1.7 – 10.9	42	4.1 (1.8)	4.0	1.5 – 11.5

Exhibit 60
Immunosuppression Trough Levels Post Last Infusion for Islet After Kidney Recipients

(mg/day)	Day 30			
	N	Mean (SD)	Median	Range
Sirolimus	6	14.4 (2.8)	13.3	12.0 – 19.9
Tacrolimus	6	4.0 (0.5)	4.1	3.4 – 4.7

Exhibit 61
Use of Anti-Hypertensive Medications Prior to Infusion by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3		Overall	
	N	%	N	%	N	%	N	%
Total	86	100.0	58	100.0	14	100.0	158	100.0
ACE Inhibitors	16	18.6	9	15.6	3	21.4	28	17.7
Angiotensin II Receptor Blockers	2	2.3	1	1.7	0	0.0	3	1.9
Beta Adrenergic Blockers	2	2.3	1	1.7	0	0.0	3	1.9
Calcium Channel Blockers	2	2.3	2	3.4	0	0.0	4	2.5
Diuretics	2	2.3	2	3.4	1	7.1	5	3.2
Vasodilators	1	1.2	1	1.7	0	0.0	2	1.3
Total Number of Anti-Hypertensive Medications Used								
0	62	72.1	35	60.3	8	57.1	105	66.5
1	20	23.3	11	19.0	2	14.3	33	20.9
2	1	1.2	1	1.7	1	7.1	3	1.9
3	0	0.0	0	0.0	0	0.0	0	0.0
4	1	1.2	1	1.7	0	0.0	2	1.3
Missing	2	2.3	10	17.2	3	21.4	15	9.5

Exhibit 62
Use of Lipid Lowering Medications Prior to Infusion by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3		Overall	
	N	%	N	%	N	%	N	%
Total	86	100.0	58	100.0	14	100.0	158	100.0
HMG CoA Reductase Inhibitors	16	18.6	13	22.4	5	35.7	34	21.5
Total Number of Lipid Lowering Medications Used								
0	70	81.4	35	60.3	6	42.9	111	70.3
1	16	18.6	13	22.4	5	35.7	34	21.5
Missing	0	0.0	10	17.2	3	21.4	13	8.2

Exhibit 63
Adjunctive Therapy at Time of Infusion by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3		Overall	
	N	%	N	%	N	%	N	%
Total	86	100.0	58	100.0	14	100.0	158	100.0
Antibiotics	79	91.9	51	87.9	13	92.9	143	90.5
Antifungal	34	39.5	17	29.3	5	35.7	56	35.4
Antiviral	24	27.9	18	31.0	6	42.9	48	30.4
Aspirin	22	25.6	4	6.9	2	14.3	28	17.7
Feosol® (Iron Supplement)	7	8.1	6	10.3	2	14.3	15	9.5
Heparin	71	82.6	49	84.5	11	78.6	131	82.9
Lovenox® (Anticoagulant)	40	46.5	24	41.4	7	50.0	71	44.9
Metformin	0	0.0	1	1.7	1	7.1	2	1.3
Nicotinamide	5	5.8	2	3.4	1	7.1	8	5.1
Pentoxifylline	40	46.5	22	37.9	8	57.1	70	44.3
Protonix® (pantoprazole)	10	11.6	8	13.8	2	14.3	20	12.7
Rosiglitazone	0	0.0	1	1.7	0	0.0	1	0.6
Vitamins	57	66.3	34	58.6	10	71.4	101	66.0
Zofran® (ondansetron hydrochloride)	8	9.3	7	12.1	2	14.3	17	10.8
Missing	3	3.5	5	8.6	1	7.1	9	5.7

Section 4
Graft Function

Graft Function
Data Summary

This section is the initial examination of graft function of the 86 islet transplant recipients reported to the Registry. Only the most complete data are presented in this section, so the reader should pay particular note to sample sizes presented with each of the Exhibits. As this is the first report of the Registry, this section represents a glimpse into future analyses when current Centers complete recipient information reports and as more centers join the Registry. It should be clearly noted that this section does not represent all islet transplants performed in North America. It is hopeful that future reports will be more inclusive.

Presented in this section are the recipient's HbA_{1c} values at Infusion 1, Infusion 2 and at Infusion 3 (Exhibit 64). Recipients are then categorized by the total number of infusions received (1, 2, or 3) and their mean HbA_{1c} presented in boxplots. The "star" in the boxplot represents the mean value. The whiskers of the plot 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). Changes in HbA_{1c} from Pre Infusion 1 to Pre Infusion 2 and to Pre Infusion 3 are also presented (Exhibit 68 and Exhibit 69). Basal C-peptide is also evaluated in the same manner as HbA_{1c}. C-peptide increases with the number of infusions (Exhibit 70) and this increase is also consistent with the total number of islet infusions received by each of the recipients (Exhibit 71, Exhibit 72, and Exhibit 73). Changes in C-peptide from Pre Infusion 1 to Pre Infusion 2 and to Pre Infusion 3 are presented in Exhibit 74 and Exhibit 75.

Insulin use is summarized in Exhibit 76 and Exhibit 77. Thirty days following Infusion 1, there were 17 recipients off insulin after Infusion 1 and 36 recipients off insulin after Infusion 2. For those on insulin 30 days after Infusion 1, levels were at 14.6 units (SD 10.3) and decreased to 12.3 units (SD 8.9) 30 days following Infusion 2. At 30 days following Infusion 3, insulin levels averaged 12.1 units (SD 10.0) (Exhibit 76).

CITR collects data on a number of different metabolic tests; with the understanding not all centers perform these tests. Currently, data are collected for the following:

- Fasting Plasma Glucose (mg/dL)
- HbA_{1c} (%)
- Basal Plasma C-peptide (ng/mL)
- Peak Stimulated C-Peptide after meal (ng/mL)
- Peak Stimulated C-Peptide after IV Glucagon (ng/mL)
- Peak Stimulated C-Peptide after IV Arginine (ng/mL)
- Acute C-Peptide response to IV Arginine (ng/mL)
- Acute insulin response to IV Arginine (µU/mL)
- Peak Stimulated C-Peptide after IV Glucose (ng/mL)
- Acute C-Peptide response to IV Glucose (ng/mL)
- Acute insulin response to IV Glucose (µU /mL)
- Kg-Value derived from 0.5 g/kg IVGTT
- 2-hr 75g OGTT Plasma Glucose (mg/dL)
- Mixed meal stimulation index (pmol/mg)

At six months post last infusion, the most reported tests included fasting plasma glucose, HbA_{1c} and basal plasma C-peptide. Exhibit 78 includes summary data for the three most commonly reported tests. There were between 4 and 26 reports for the other metabolic measures. Due to low frequency of reports for these measures, the data will not be included in this Report.

The first glimpse at insulin independence status for the recipients is included in this section. For this report, insulin independence is defined as an insulin independent recipient at the time of the follow-up assessment. Insulin status is evaluated at the last follow-up conducted following their last infusion (Exhibit 79) and at 6 months and 12 months post the recipient's last infusion (Exhibit 80). Because the CITR follow-up schedule collects data at 6 months, 12 months and yearly post the recipient's last infusion procedure, all analyses conducted post the recipient's first infusion cannot be conducted at this time.

Fifty-five recipients have completed at least one follow-up visit post their last infusion. Of these 55 recipients, 28 (50.9%) are currently insulin independent. Only two of these recipients (7%), needed to take insulin 14 or more days prior to this visit. Assessing insulin independence at the follow-up schedule visits, 61.1% (33/54) were insulin independent at 6 months post their last infusion and 57.9% (22/38) were insulin independent at their 12 month visit. Of those insulin independent at their 6 month visit, 16 (48.5%) needed to take insulin 14 or more days prior to the visit and of those insulin independent at the 12 month visit, none needed to take insulin prior to their visit. Also, keep in mind that the Registry does not ask the Centers to indicate if they have further plans to infuse each of their recipients. Thus, recipients may be subsequently re-infused.

Exhibit 64
HbA_{1c} (%) by Infusion Sequence

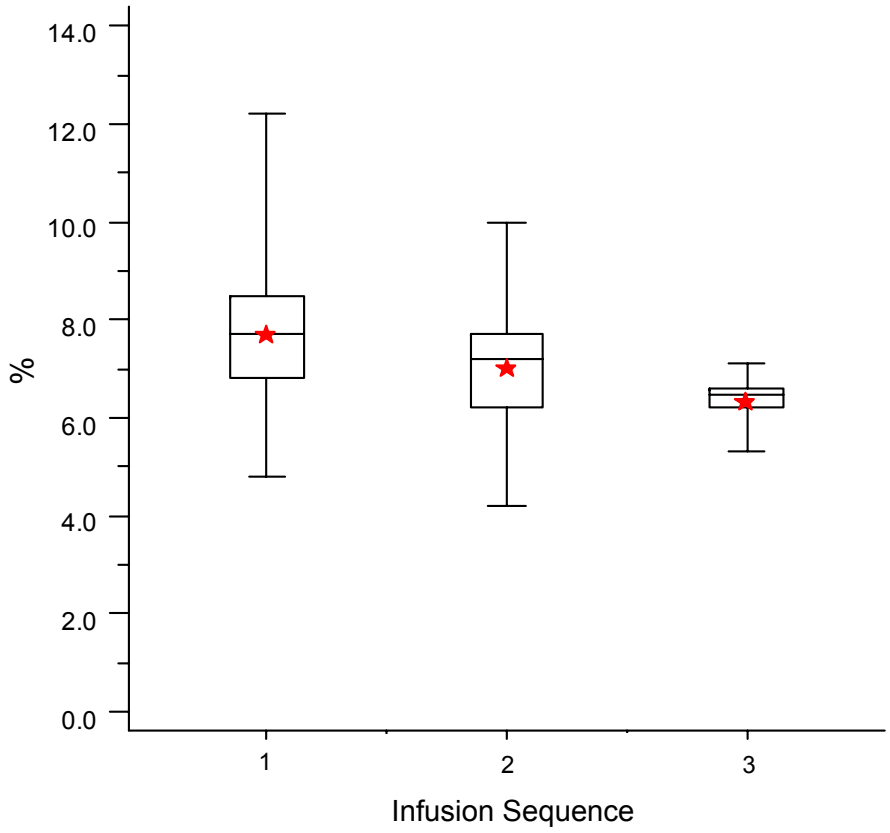


Exhibit 65
HbA_{1c} (%) for Recipients of One Infusion

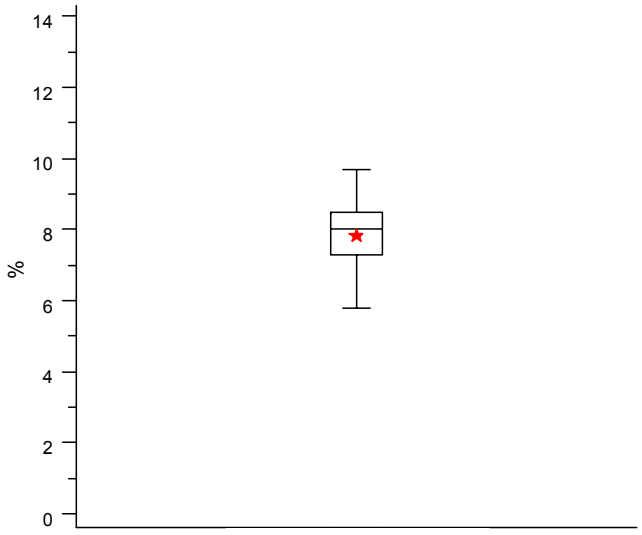


Exhibit 66
HbA_{1c} (%) by Infusion Sequence for Recipients of Two Infusions

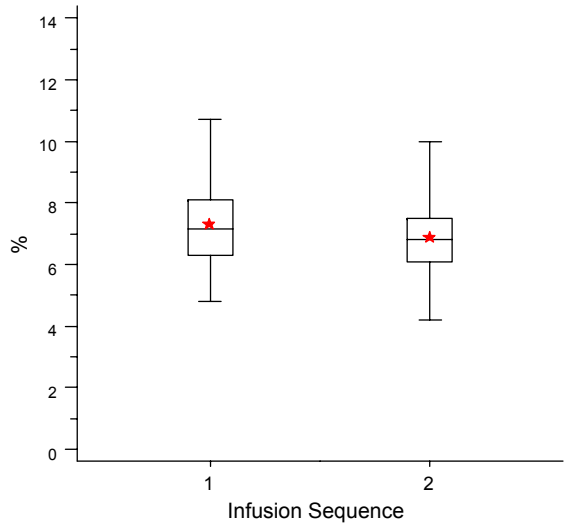


Exhibit 67
HbA_{1c} (%) by Infusion Sequence for Recipients of Three Infusions

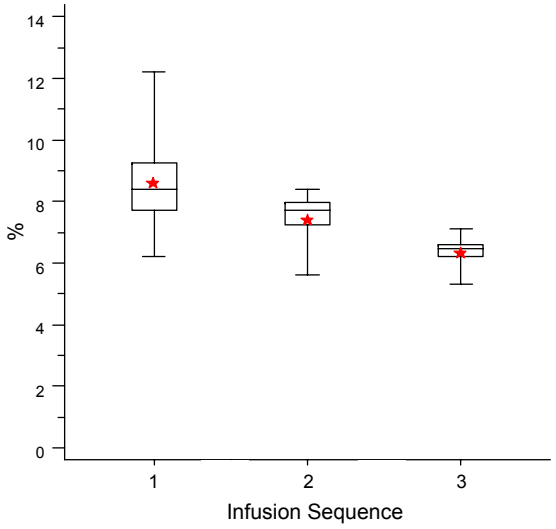


Exhibit 68
Change in HbA_{1c} (%) from Pre Infusion 1 to Pre Infusion 2
for Recipients of Two Infusions

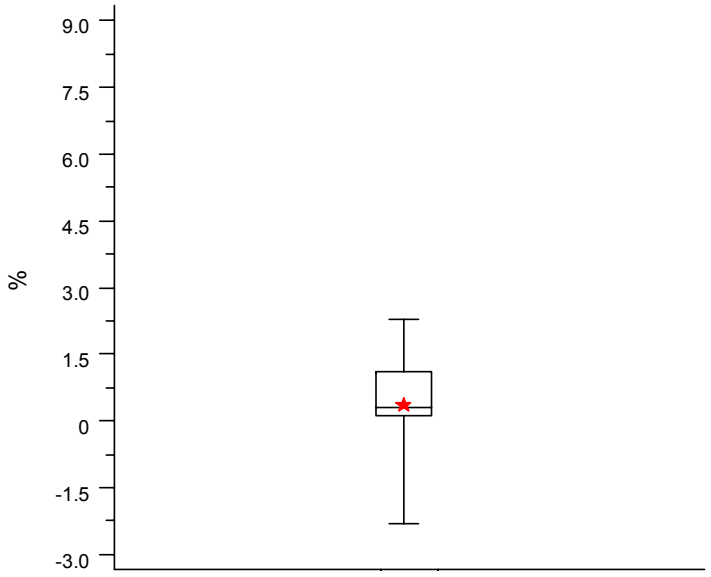


Exhibit 69
Change in HbA_{1c} (%) from Pre Infusion 1 to Pre Infusion 2
and to Pre Infusion 3 for Recipients of Three Infusions

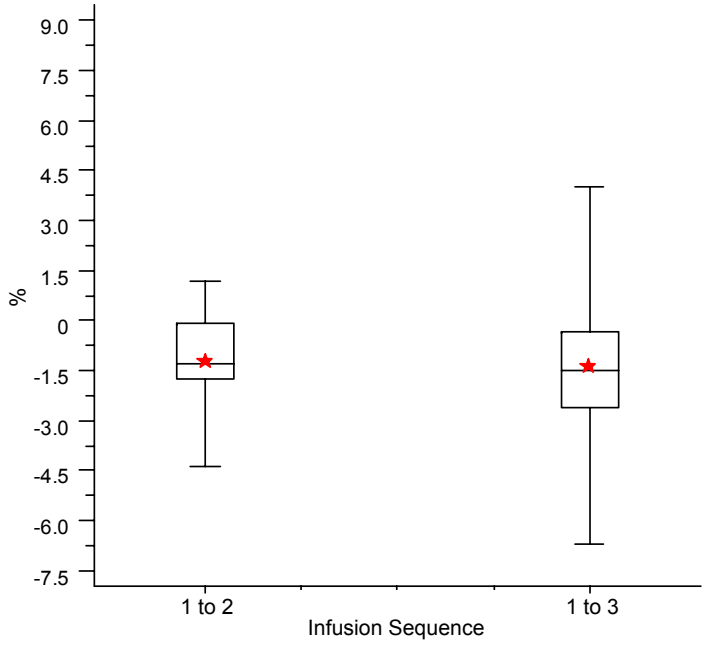


Exhibit 70
Basal C-peptide (ng/mL) by Infusion Sequence

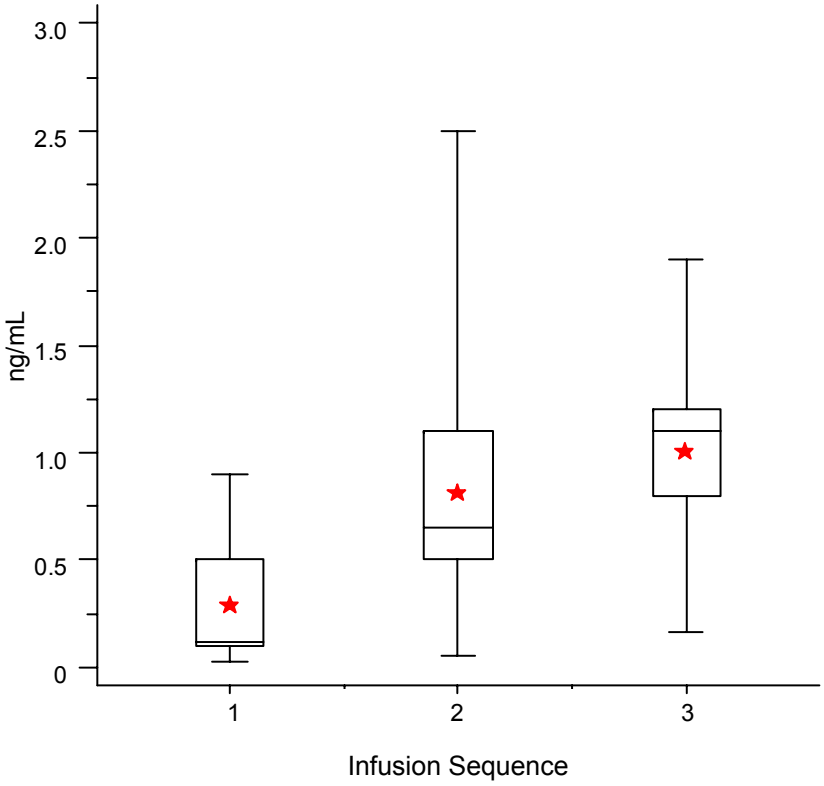


Exhibit 71
Basal C-peptide (ng/mL) for Recipients of One Infusion

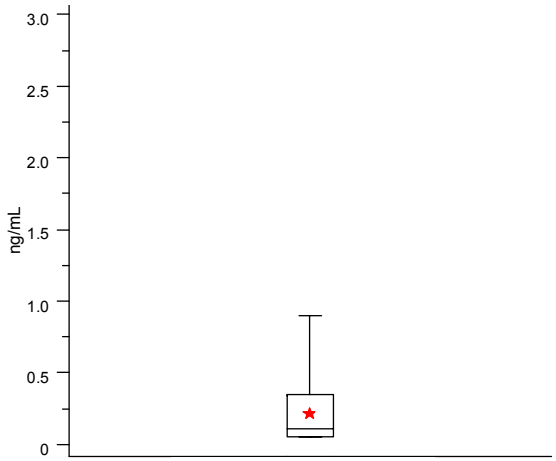


Exhibit 72
Basal C-peptide (ng/mL) by Infusion Sequence for Recipients of Two Infusions

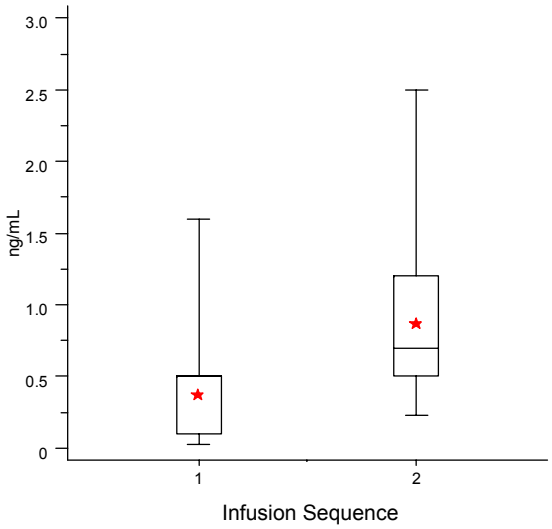


Exhibit 73
Basal C-peptide (ng/mL) by Infusion Sequence for Recipients of Three Infusions

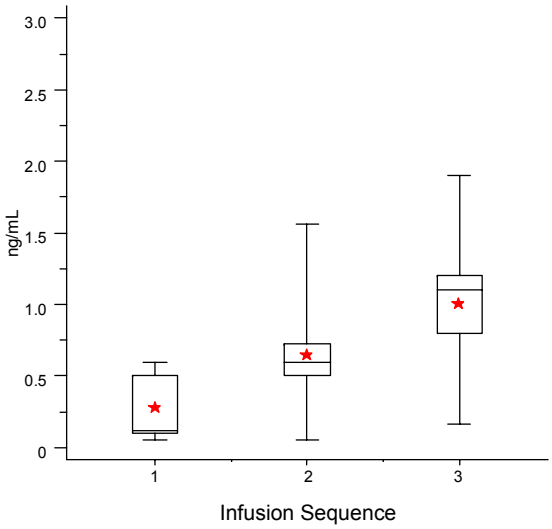


Exhibit 74
Change in Basal C-peptide (ng/mL) from Pre Infusion 1 to Pre Infusion 2 for Recipients of Two Infusions

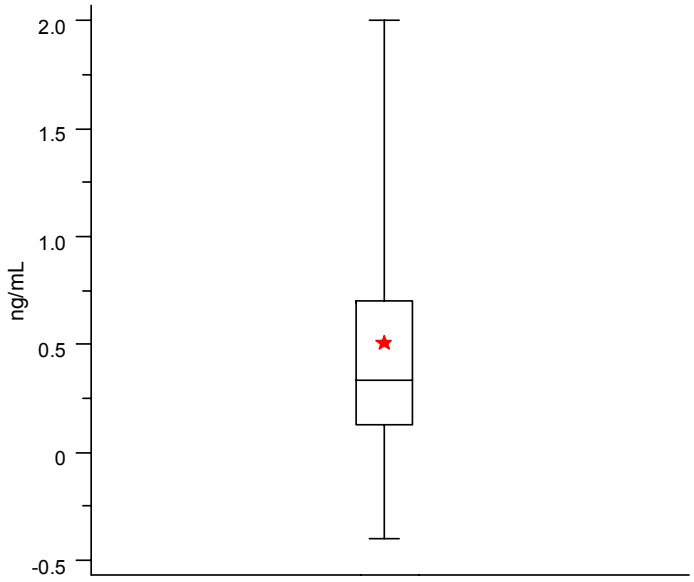


Exhibit 75
Change in Basal C-peptide (ng/mL) from Pre Infusion 1 to Pre Infusion 2 and to Pre Infusion 3 for Recipients of Three Infusions

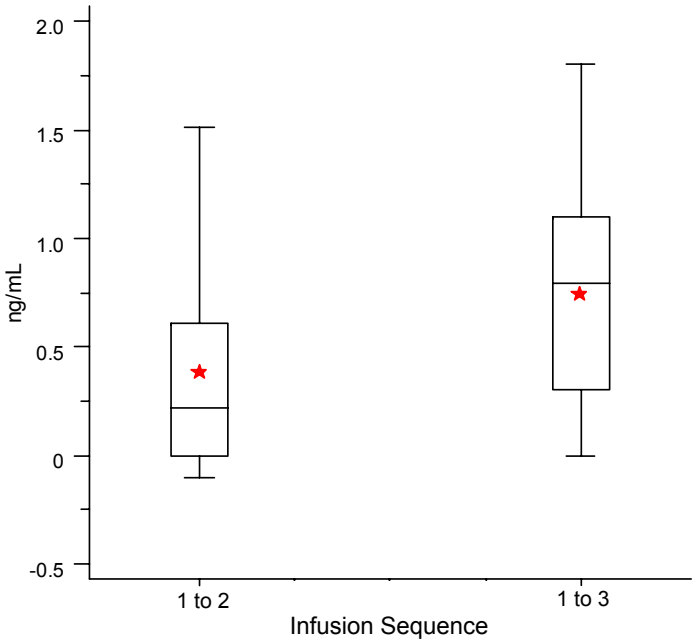


Exhibit 76
Graft Function Summary During the First 30 Days Following Infusion by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Insulin Use (total units/day)						
Day 7						
Insulin Use	77	15.1 (9.2)	28	12.5 (10.0)	12	13.8 (8.8)
No Insulin Use	8	---	28	---	2	---
Day 30						
Insulin Use	65	14.6 (10.3)	20	12.3 (8.9)	11	12.1 (10.0)
No Insulin Use	17	---	36	---	3	---
Fasting C-Peptide (ng/mL)						
Day 7	70	1.3 (0.7)	38	1.5 (0.7)	10	2.0 (1.0)
Day 30	74	1.2 (0.7)	51	2.2 (3.2)	13	1.3 (0.9)
Fasting Plasma Glucose (mg/dL)						
Day 7	80	133.8 (39.3)	47	121.8 (28.8)	14	134.0 (20.2)
Day 30	77	127.5 (42.9)	49	112.2 (34.5)	12	106.0 (19.1)

Exhibit 77
Insulin Use Over Time Post Last Infusion

	Month 6				Month 12			
	N	%	N	Mean (SD)	N	%	N	Mean (SD)
	54	100.0	54	11.5 (9.7)	38	100.0	38	19.0 (15.6)
Days of Insulin Use								
0	12	22.2	---	---	21	55.3	---	---
<14	4	7.4	4	5.0 (2.4)	1	2.6	1	4.0 (---)
14 – 30	2	3.7	2	6.1 (0.7)	0	0.0	0	--- (---)
31 – 60	8	14.8	8	7.8 (2.3)	1	2.6	1	7.0 (---)
61 – 90	5	9.3	5	8.6 (5.1)	0	0.0	0	--- (---)
91 – 120	2	3.7	2	9.1 (0.1)	0	0.0	0	--- (---)
> 120	20	37.0	20	15.8 (12.2)	13	34.2	13	21.1 (15.7)
On Insulin, Use Missing	0	0.0			1	2.6		
Insulin Follow-up Information Missing	1	1.9	1	1.9	1	2.6	2	5.3

Exhibit 78
Metabolic Summary Post Last Infusion

	Month 6				Month 12			
	N	Mean	SD	Median	N	Mean	SD	Median
Fasting Plasma Glucose (mg/dL)	52	114.9	35.9	106.5	34	109.9	45.7	98.0
HbA_{1c} (%)	51	6.1	0.6	6.0	34	6.2	1.2	6.0
Basal Plasma C-peptide (ng/mL)	48	1.2	0.7	1.2	28	1.0	0.6	1.0

Exhibit 79
Insulin Independence Status at Recipient's Last Follow-up
(Post Last Infusion)

	N	%
Total	55	100.0
Insulin Independent	28	50.9
Insulin Dependent	25	45.5
Missing	2	3.6

Exhibit 80
Insulin Independence Status at 6 Months and 12 Months
(Post Last Infusion)

	6 Months		12 Months	
	N	%	N	%
Total	54	100.0	38	100.0
Insulin Independent	33	61.1	22	57.9
Insulin Dependent	19	35.2	14	36.8
Missing	2	3.7	2	5.3

Section 5
Recipient's Laboratory Data Over Time

Recipient's Laboratory Data Over Time
Data Summary

In this section is a summary of the islet transplant recipient's laboratory data by CITR visit month from the last infusion procedure. Screening visits identified in the Exhibits represent data collected prior to the recipient's first infusion procedure. For each of the laboratory tests, boxplots are displayed for the screening visit, six months post last infusion procedure and 12 months post last infusion procedure. In addition, the change in the value from screening to the six month visit, as well as the change from screening to the 12 month visit is also displayed with a boxplot. 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 represents the median (50th percentile).

Fasting plasma glucose (mg/dL), ALT (IU/L), AST (IU/L), total bilirubin (mg/dL), total cholesterol (mg/dL), HDL (mg/dL), LDL (mg/dL), triglycerides (mg/dL), and serum creatinine (mg/dL) are plotted. There was a decrease in the recipient's fasting plasma glucose from pre infusion to visit month 6 post their last infusion procedure (Exhibit 81). There were increases in both ALT and AST from pre infusion to 6 months post last infusion procedure (Exhibit 83 and Exhibit 85). Total bilirubin remained virtually the same from pre infusion to visit month 6 post their last infusion procedure (Exhibit 87). There were increases in total cholesterol and LDL from screening to post last infusion six and twelve months (Exhibit 89 and Exhibit 93), but little change in HDL and triglycerides from screening to post last infusion at 6 and 12 months (Exhibit 91 and Exhibit 95). Serum creatinine also remained unchanged (Exhibit 97).

Exhibit 81
Fasting Plasma Glucose (mg/dL) by Visit Month Post Last Infusion

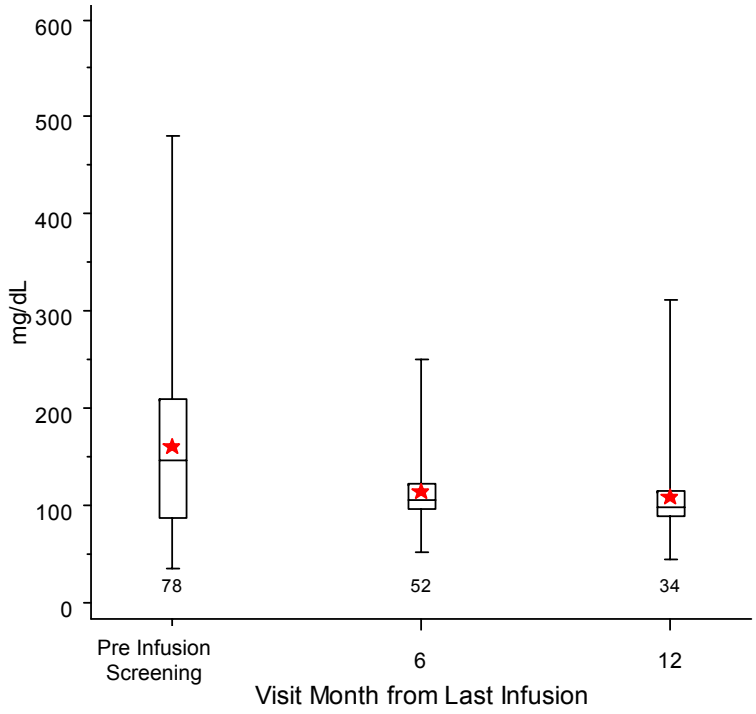


Exhibit 82
Change in Fasting Plasma Glucose (mg/dL) from Screening to Post Last Infusion

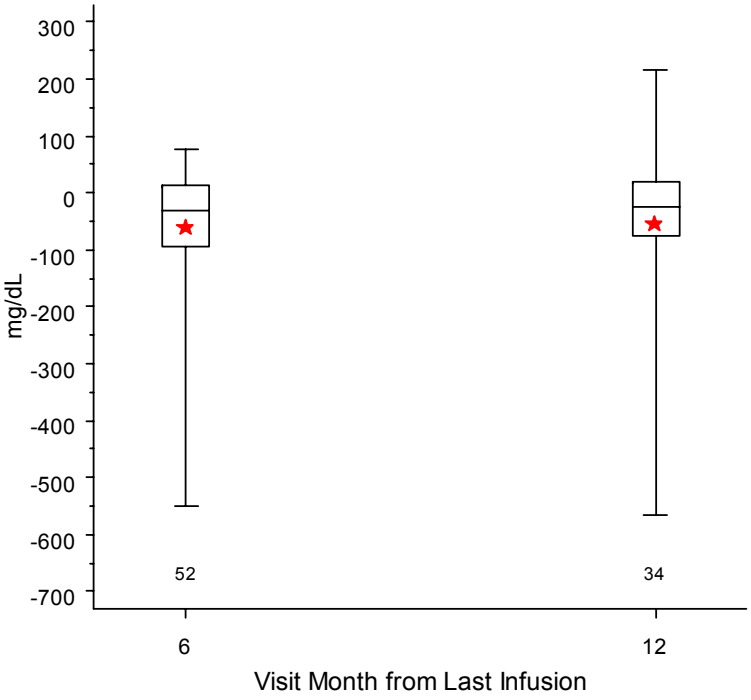


Exhibit 83
ALT (IU/L) by Visit Month

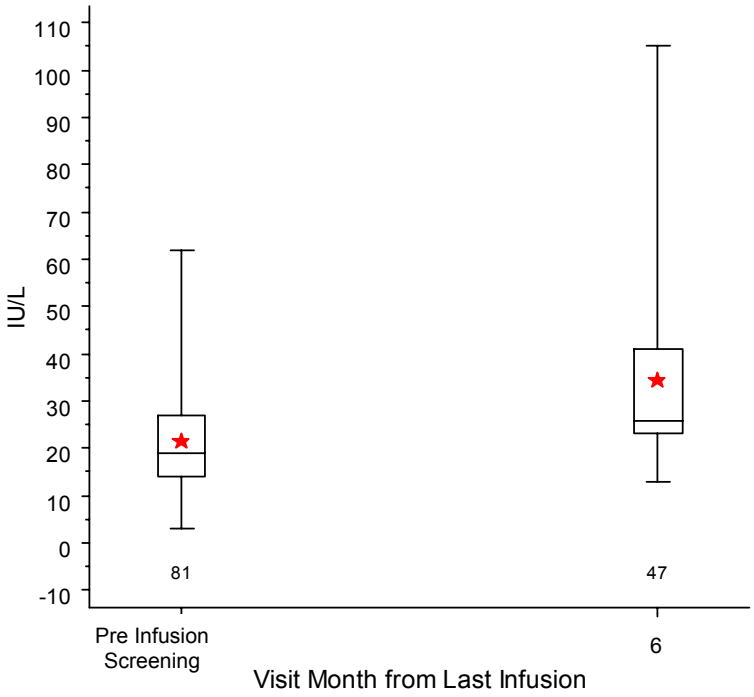


Exhibit 84
Change in ALT (IU/L) from Screening

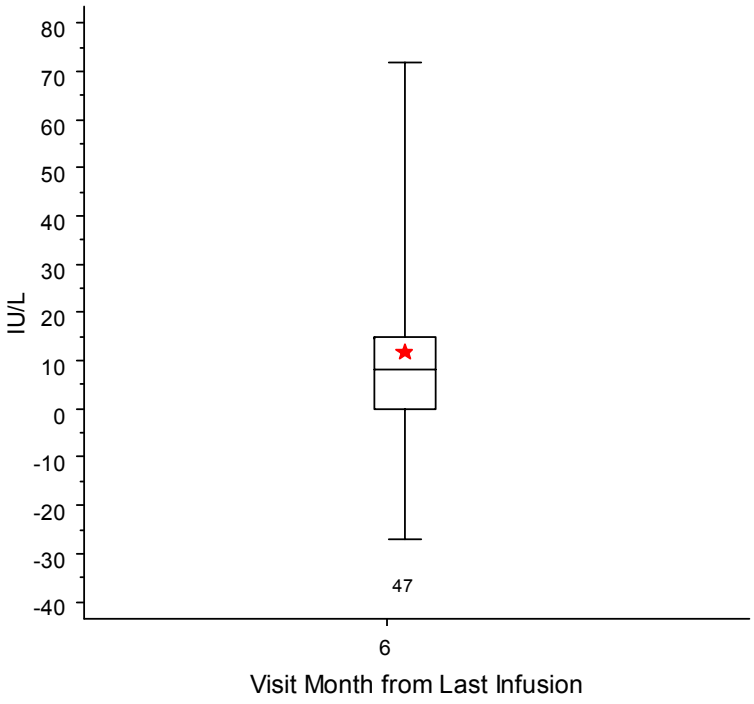


Exhibit 85
AST (IU/L) by Visit Month

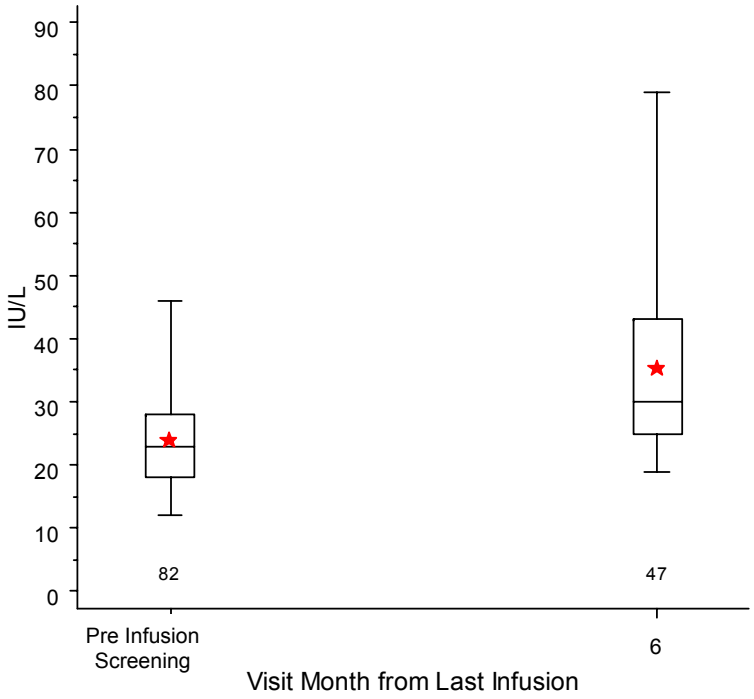


Exhibit 86
Change in AST (IU/L) from Screening

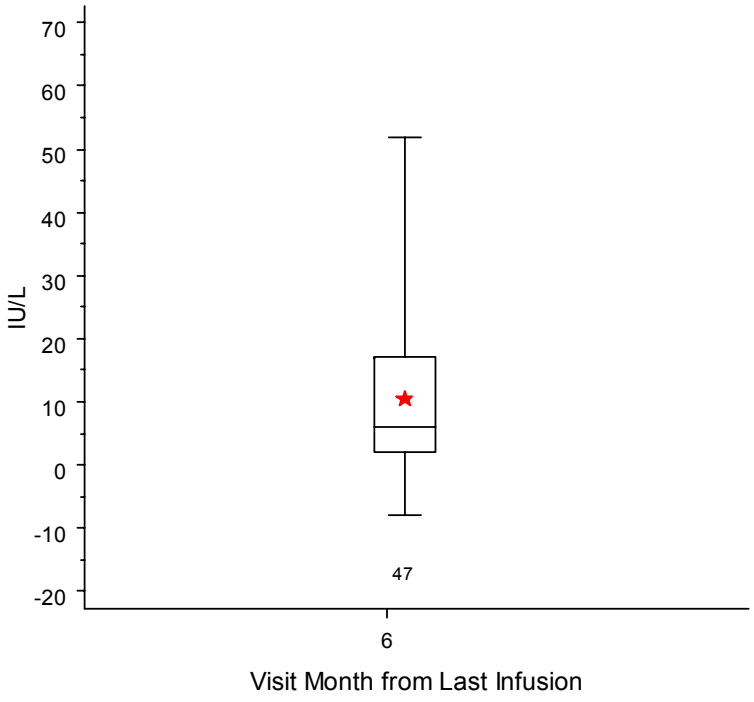


Exhibit 87
Total Bilirubin (mg/dL) by Visit Month

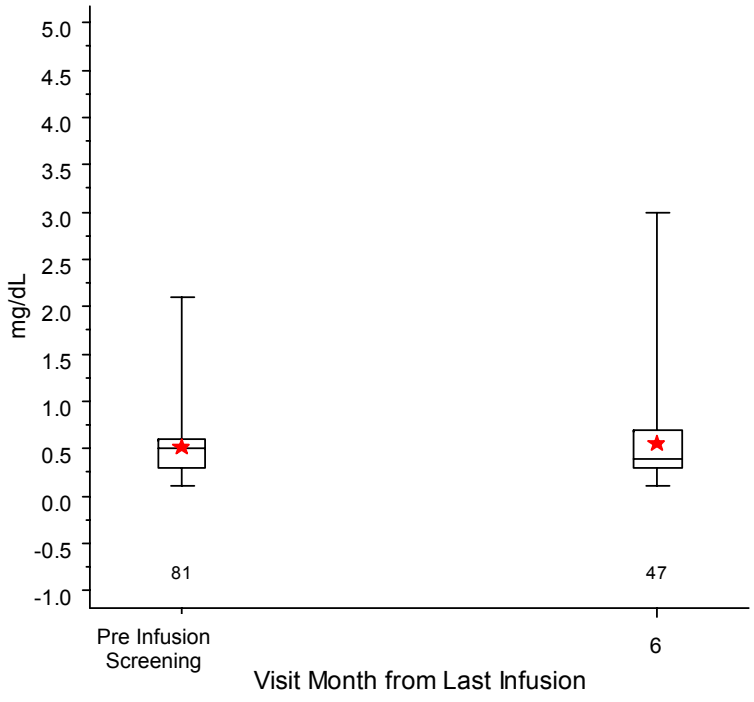


Exhibit 88
Change in Total Bilirubin (mg/dL) from Screening

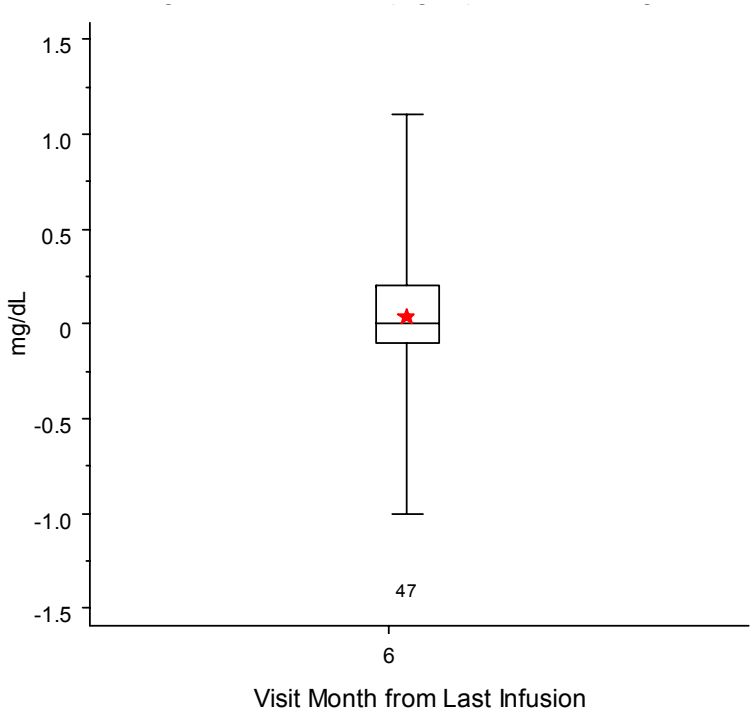


Exhibit 89
Total Cholesterol (mg/dL) by Visit Month

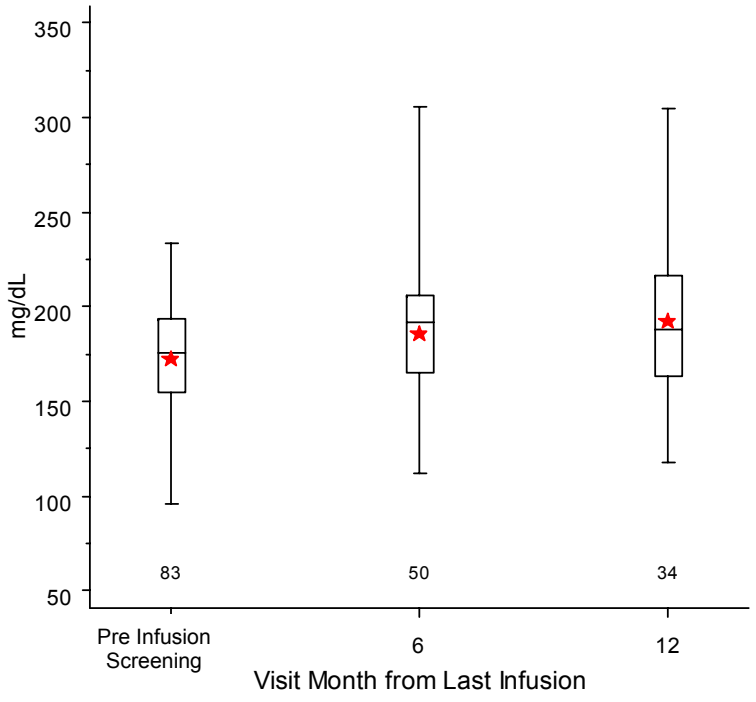


Exhibit 90
Change in Total Cholesterol (mg/dL) from Screening

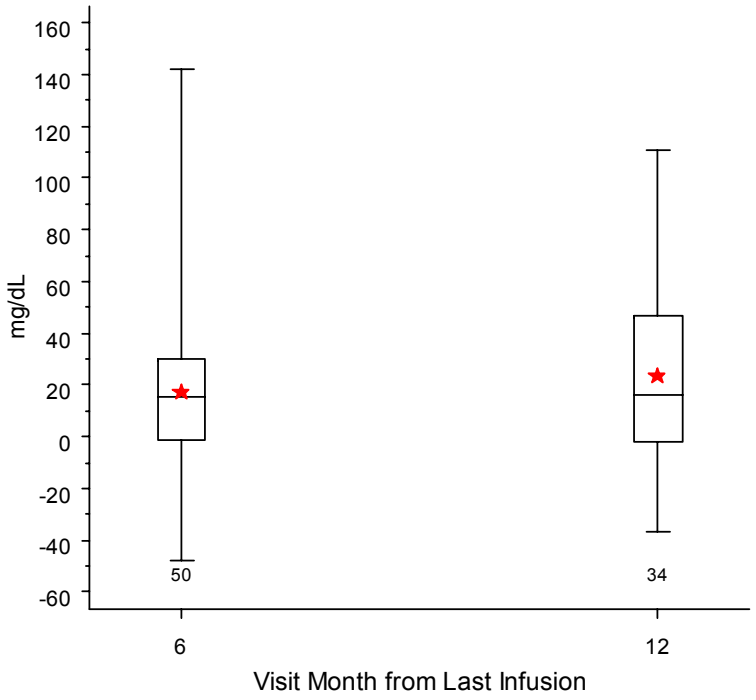


Exhibit 91
HDL (mg/dL) by Visit Month

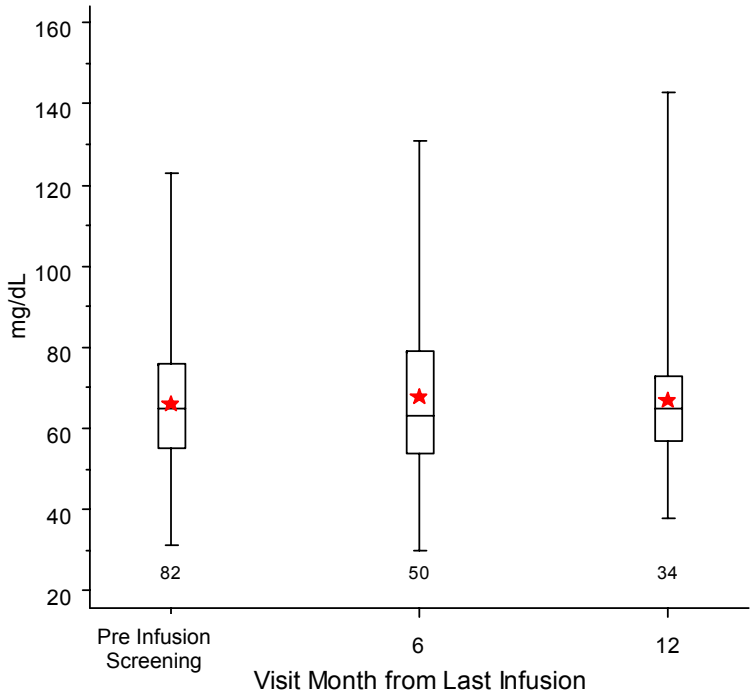


Exhibit 92
Change in HDL (mg/dL) from Screening

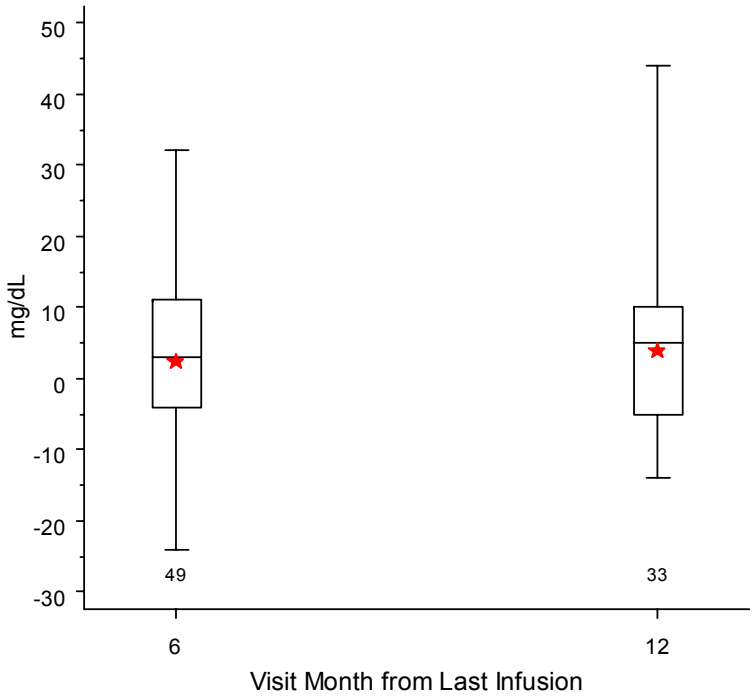


Exhibit 93
LDL (mg/dL) by Visit Month

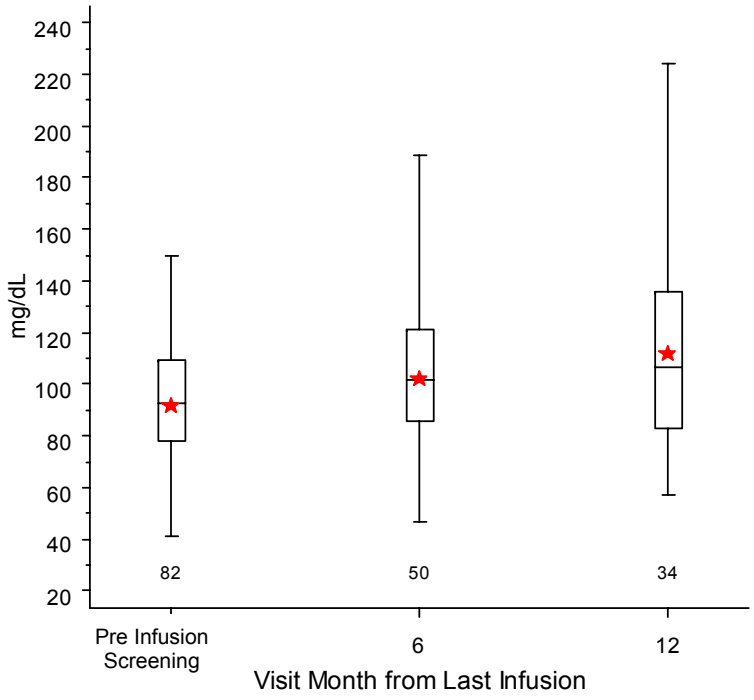


Exhibit 94
Change in LDL (mg/dL) from Screening

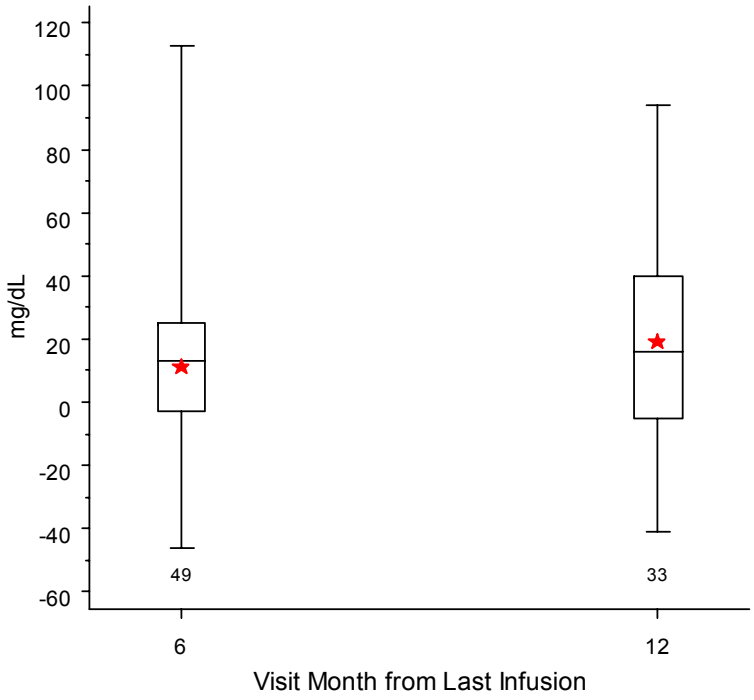


Exhibit 95
Triglycerides (mg/dL) by Visit Month

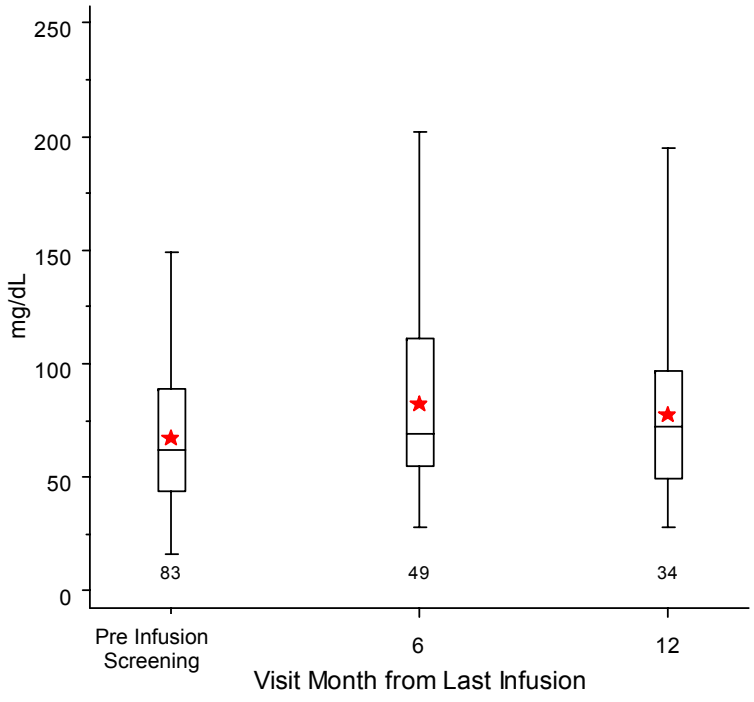


Exhibit 96
Change in Triglycerides (mg/dL) from Screening

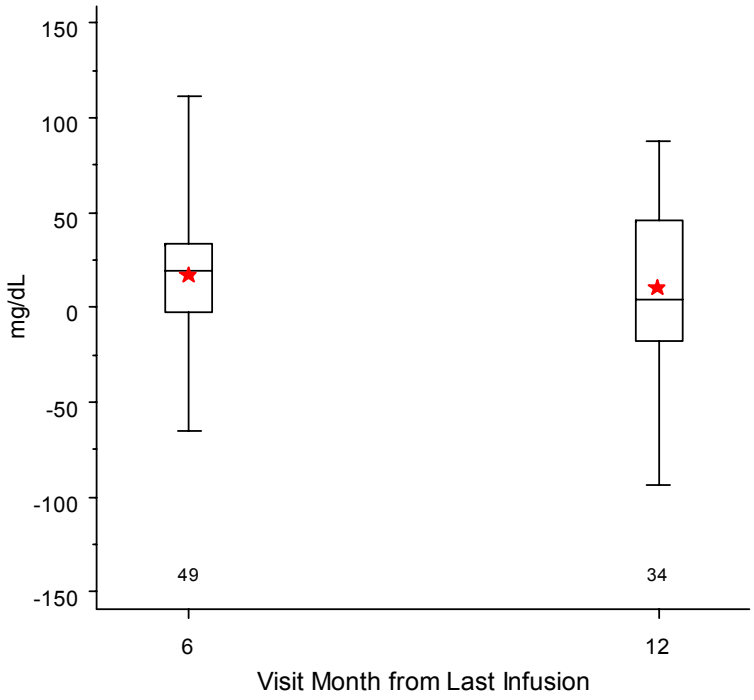


Exhibit 97
Serum Creatinine (mg/dL) by Visit Month

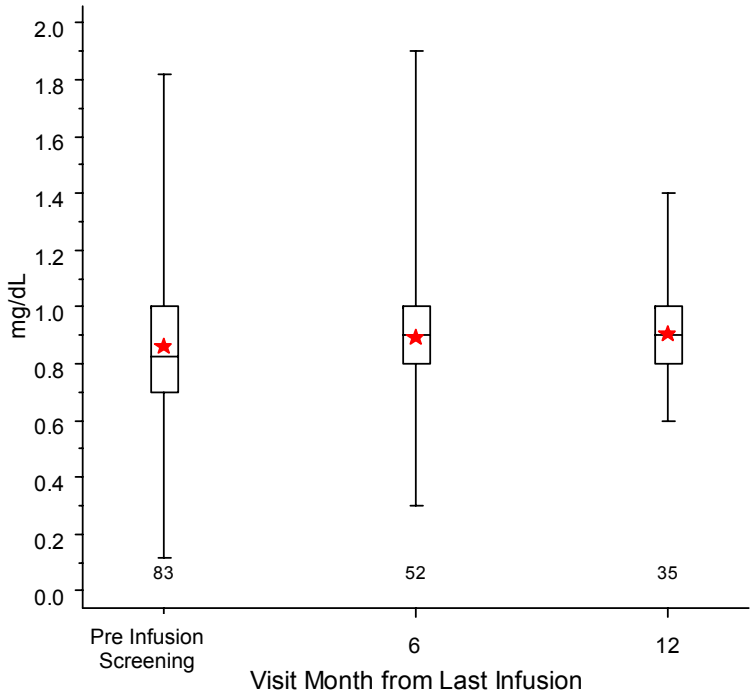
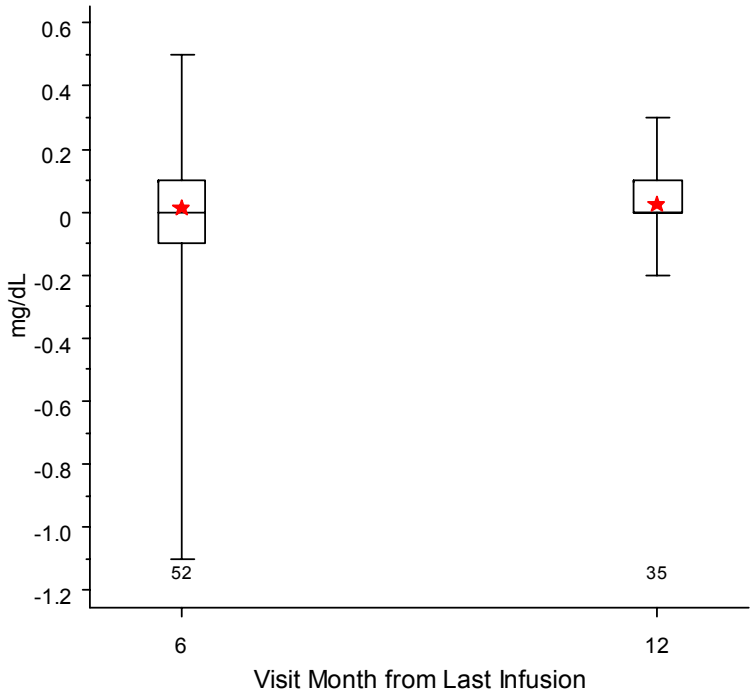


Exhibit 98
Change in Serum Creatinine (mg/dL) from Screening



Section 6
Adverse Events

Adverse Events
Data 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. Adverse events are summarized in this section in the first month following infusion by infusion sequence (1, 2, and 3) and by time periods following the recipient's first infusion procedure (0-1 month, 1-6 months, and 6-12 months). In the first month following infusion, almost 33% of the recipients reported at least one adverse event following their first infusion procedure, almost 28% reported at least one adverse event following their second infusion procedure, and almost 29% reported at least one adverse event following their third infusion procedure (Exhibit 99). Only 3.5% of recipients reported a serious adverse event in the first month following their first infusion, which increased to 13.8% for one month post the second infusion and 21.4% for one month post the third infusion (Exhibit 99).

A summary of all serious adverse events reported to the Registry is listed in Exhibit 101. As of this report there were a total of 45 serious adverse events reported for the 86 recipients. These events are further classified as to their definition for seriousness (death, life threatening, inpatient hospitalization, prolongation of existing hospitalization and persistent or significant disability/incapacity). The serious adverse event could be classified in more than one of these categories (i.e., they are not mutually exclusive). There were no deaths reported to the Registry. Almost 58% of the serious adverse events were classified as inpatient hospitalizations with 27% classified as life threatening. All serious adverse events are listed in Exhibit 102 with their reason for seriousness classification, event relationship to the islet infusion, relationship to immunosuppressive medications and the outcome of the serious adverse event. Classification of the event's relationship to the islet infusion and to the immunosuppressive medications is made by each Center's Principal Investigator.

There were 10 serious adverse events related to the islet transplant and 10 events related to the immunosuppression therapy. Events related to the transplant included elevated ALT, elevated AST, hemoperitoneum, intra-abdominal bleed, low hemoglobin, peripherally inserted catheter (pic) line infection/cellulitis, right hemothorax and a subcapsular hematoma of the liver. The 10 serious adverse events related to immunosuppressive medications included anemia, aseptic meningitis, febrile neutropenia, neutropenia, pic line infection/cellulitis and neurotoxicity. All Centers are encouraged to report events as they are notified at the Center so that a complete and accurate report of all events may be maintained by CITR.

In addition to grade 3, 4, and 5 adverse events, additional complications post infusion have been reported to the Registry. Boxplots are used in this section to describe some of data. The "star" in the boxplot represents the mean value. The whiskers of the plot 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).

First, all infusions were performed as inpatient procedures. On average, recipients were hospitalized for 2.5 days (SD 2.4 days) for Infusion 1, for 2.3 days (SD 2.4 days) for Infusion 2 and for 1.8 days (SD 1.3 days) for Infusion 3 (Exhibit 103). There were 14 recipients who were hospitalized between day 30 and six months from the first infusion (25.5%) and seven (14.0%)

were hospitalized between month six and month twelve visits following the first infusion (Exhibit 105).

In the first month following the first infusion, only two recipients (2.3%) experienced a hypoglycemic event requiring the assistance of another person and no recipient experienced a hypoglycemic event resulting in the loss of consciousness. There were no reports of hypoglycemic events at the six or twelve month visit post the recipient's last infusion.

There were no procedural complications reported to the Registry and no deaths.

Portal pressures (pre infusion, peak infusion and closure) of the recipients are summarized in Exhibits 107-114. The change in portal pressures from pre infusion to peak infusion increased by the infusion sequence. The mean change pre infusion portal pressure to peak infusion portal pressure at Infusion 1 is 2.96 mmHg (SD 2.84). At Infusion 2 it is 3.47 mmHg (SD 2.37) and at Infusion 3 it is 3.79 mmHg (SD 2.36).

In subsequent reports, as the length of follow-up increases in the Registry, changes from baseline in secondary complications and ocular complications will be summarized.

Exhibit 99
Number of Recipients Experiencing Adverse Events in the First Month Following Infusion by Infusion Sequence

	Infusion 1		Infusion 2		Infusion 3	
	N	%	N	%	N	%
Total	86	100.0	58	100.0	14	100.0
Recipients with No Adverse Events Reported (Grade 3, 4, or 5)	58	67.4	42	72.4	10	71.4
Total Adverse Events Reported for Recipient (Grade 3, 4, or 5)						
1	16	18.6	11	19.0	2	14.3
2	8	9.3	3	5.2	1	7.1
3	2	2.3	2	3.4	1	7.1
4	1	1.2	0	0.0	0	0.0
>4	1	1.2	0	0.0	0	0.0
Recipients with No Serious Adverse Events Reported	83	96.5	50	86.2	11	78.6
Total Serious Adverse Events Reported for Recipient						
1	1	1.2	6	10.5	2	14.3
2	2	2.3	2	3.5	1	7.1
Recipients with a Reported Serious Adverse Event Related to Islet Infusion	1	1.2	4	7.0	2	14.3
Recipients with a Reported Serious Adverse Event Related to Immunosuppressive Medications	1	1.2	1	1.8	0	0.0

Exhibit 100
Number of Recipients with Reported Adverse Events Following First Infusion by Visit Month

	0-1 Month		1-6 Months		6-12 Months		Ever Experienced	
	N	%	N	%	N	%	N	%
Total	86	100.0	86	100.0	79	100.0	86	100.0
Recipients with No Adverse Events Reported (Grade 3, 4, or 5)	58	67.4	53	61.6	64	81.0	38	44.2
Total Adverse Events Reported for Recipient (Grade 3, 4, or 5)								
1	15	17.4	17	19.8	9	11.4	12	14.0
2	8	9.3	9	10.5	1	1.3	16	18.6
3	3	3.5	3	3.5	1	1.3	5	5.8
4	1	1.2	4	4.7	0	0.0	4	4.7
>4	1	1.2	0	0.0	4	5.1	11	12.8
Recipients with No Serious Adverse Events Reported	82	95.3	69	80.2	73	92.4	60	69.8
Total Serious Adverse Events Reported for Recipient								
1	1	1.2	10	11.6	5	6.3	12	14.0
2	3	3.5	7	8.1	0	0.0	9	10.5
3	0	0.0	0	0.0	1	1.3	4	4.7
4	0	0.0	0	0.0	0	0.0	1	1.2
Recipients with a Reported Serious Adverse Event Related to Islet Infusion	2	2.3	5	5.8	1	1.3	7	8.1
Recipients with a Reported Serious Adverse Event Related to Immunosuppressive Medications	1	1.2	6	7.0	1	1.3	8	9.3

Exhibit 101
Summary of Serious Adverse Events

	N	%
Total Number of Serious Adverse Events	45	100.0
Death	0	0.0
Life Threatening	12	26.7
Inpatient Hospitalization	26	57.8
Prolongation of Existing Hospitalization	8	17.8
Persistent or Significant Disability/Incapacity	2	4.4
Serious Adverse Event Relation		
Related to Islet Transplant	10	22.2
Related to Immunosuppression Therapy	10	22.2
Serious Adverse Event Outcome		
Resolved with No Residual Effects	44	97.8
Resolved with Sequelae	1	2.2

Exhibit 102
All Serious Adverse Events Reported by Alphabetical Order

Type Of Serious Adverse Event	Reason For Serious Adverse Event Classification	Serious Adverse Event Related To Islet Infusion*	Serious Adverse Event Related To Immunosuppressive Medications*	Serious Adverse Event Outcome
Abdominal Pain	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Abdominal Pain	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Abdominal Pain	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Abdominal Pain	Life Threatening + Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Acalculous Cholecystitis	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Atypical Chest Pain	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Pancreatitis	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Anemia	Life Threatening	No	No	Resolved With No Residual Effects
Anemia	Inpatient Hospitalization	No	Yes	Resolved With No Residual Effects
Aseptic Meningitis	Inpatient Hospitalization	No	Yes	Resolved With No Residual Effects
Aspiration Pneumonia	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
C-Spine Surgery	Inpatient Hospitalization	No	No	Resolved With Sequelae

Type Of Serious Adverse Event	Reason For Serious Adverse Event Classification	Serious Adverse Event Related To Islet Infusion*	Serious Adverse Event Related To Immunosuppressive Medications*	Serious Adverse Event Outcome
Cholecystitis	Life Threatening + Prolongation Of Existing Hospitalization	No	No	Resolved With No Residual Effects
Confusion	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Dehydration	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Elevated ALT	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Elevated AST	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Elevated Liver Enzymes	Inpatient Hospitalization	Yes	No	Resolved With No Residual Effects
Febrile Neutropenia	Inpatient Hospitalization	No	Yes	Resolved With No Residual Effects
Finger Inflammation	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Hemoperitoneum	Inpatient Hospitalization	Yes	No	Resolved With No Residual Effects
Hypoglycemia	Life Threatening	No	No	Resolved With No Residual Effects
Hypoglycemia	Life Threatening	No	No	Resolved With No Residual Effects
Hypoglycemia	Life Threatening	No	No	Resolved With No Residual Effects
Hypoglycemia	Life Threatening	No	No	Resolved With No Residual Effects

Type Of Serious Adverse Event	Reason For Serious Adverse Event Classification	Serious Adverse Event Related To Islet Infusion*	Serious Adverse Event Related To Immunosuppressive Medications*	Serious Adverse Event Outcome
Intra-Abdominal Bleed	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Intra-Abdominal Bleed	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Left Eye Retinal Detachment	Persistent Or Significant Disability/Incapacity	No	No	Resolved With No Residual Effects
Low Hemoglobin	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Neutropenia	Life Threatening	No	Yes	Resolved With No Residual Effects
Neutropenia	Life Threatening	No	Yes	Resolved With No Residual Effects
Neutropenia	Life Threatening	No	Yes	Resolved With No Residual Effects
Neutropenia	Life Threatening	No	Yes	Resolved With No Residual Effects
Neutropenia	Inpatient Hospitalization	No	Yes	Resolved With No Residual Effects
Neutropenia/Leukopenia	Life Threatening + Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Pic Line Infection/Cellulitis	Inpatient Hospitalization	Yes	Yes	Resolved With No Residual Effects
Right Hemothorax	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Severe Somnolence	Inpatient Hospitalization	No	No	Resolved With No Residual Effects

Type Of Serious Adverse Event	Reason For Serious Adverse Event Classification	Serious Adverse Event Related To Islet Infusion*	Serious Adverse Event Related To Immunosuppressive Medications*	Serious Adverse Event Outcome
Subcapsular Hematoma Of Liver	Prolongation Of Existing Hospitalization	Yes	No	Resolved With No Residual Effects
Neurotoxicity	Persistent Or Significant Disability/Incapacity	No	Yes	Resolved With No Residual Effects
Thrombocytopenia	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Thrombosed Hemorrhoid	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Urinary Tract Infection	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Viral Gastroenteritis	Inpatient Hospitalization	No	No	Resolved With No Residual Effects
Vomiting	Inpatient Hospitalization	No	No	Resolved With No Residual Effects

*Classified by the Principal Investigator at the Center

Exhibit 103
Length of Hospitalization Days at Infusion by Infusion Sequence

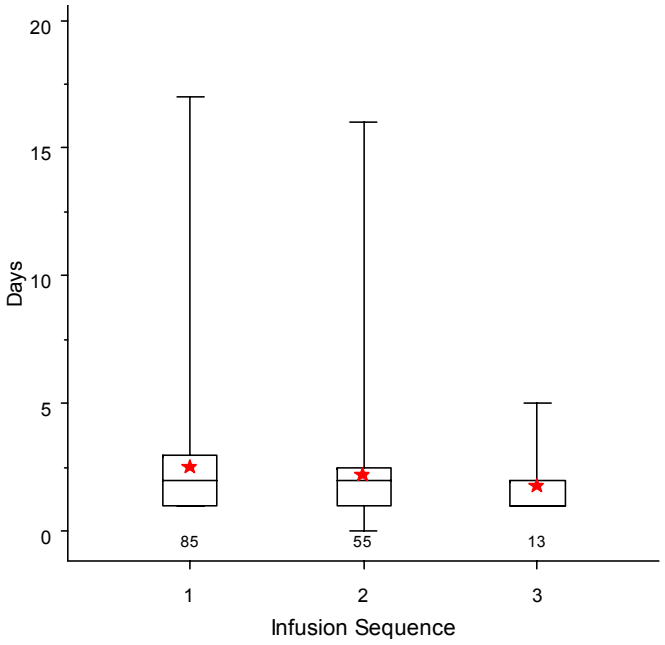


Exhibit 104
Total Days Hospitalized at Infusion Through 30 Days Following Infusion by Infusion Sequence

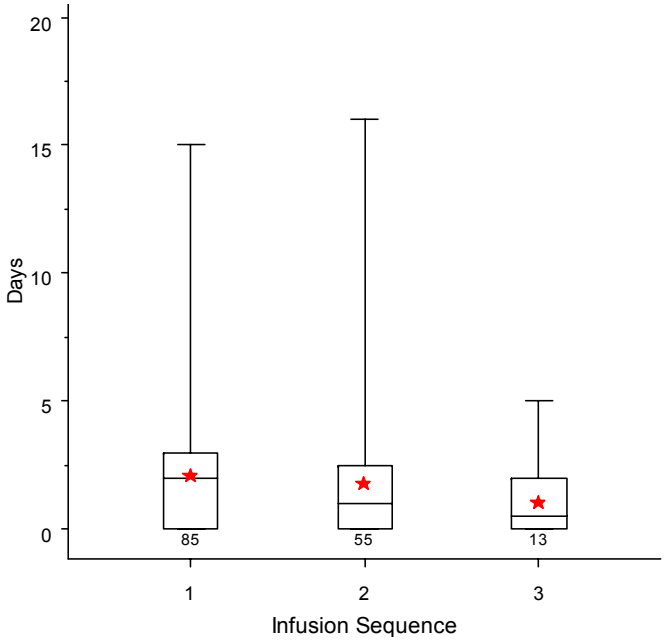


Exhibit 105
Hospitalizations Experienced Following First Infusion

	Follow-up			
	1 - 6 months		6 - 12 months	
	N	%	N	%
Total	55	100.0	50	100.0
Recipients requiring at least one hospitalization post first infusion	14	25.5	7	14.0
Total number of hospitalizations				
0	41	74.5	43	86.0
1	10	18.2	6	12.0
2	2	3.6	1	2.0
≥3	2	3.6	0	0.0

Exhibit 106
Days Hospitalized Following First Infusion

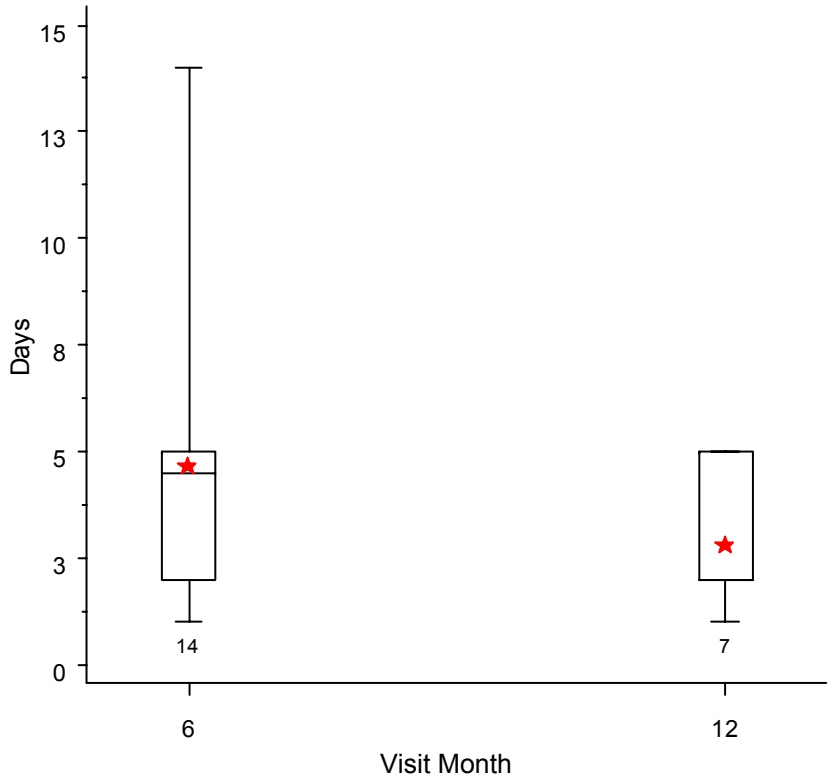


Exhibit 107
Infusion Summary by Infusion Sequence

	Infusion 1 (N=86)	Infusion 2 (N=58)	Infusion 3 (N=14)
	Mean (SD)	Mean (SD)	Mean (SD)
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure, mmHg	2.96 (2.84)	3.47 (2.37)	3.79 (2.36)
Change in Portal Pressure from Pre to Post Infusion, mmHg	1.14 (1.42)	1.26 (1.63)	0.86 (1.29)
Islet Equivalents Infused	473,705 (159,592)	436,805 (137,883)	482,225 (166,894)
Islet Packed Cell Volume, mL	4.13 (2.34)	3.52 (1.59)	2.99 (1.37)

Exhibit 108
Infusion Summary by Year of Infusion

	1999-2001 (N=42)	2002 (N=69)	2003 (N=47)
	Mean (SD)	Mean (SD)	Mean (SD)
Change in Portal Pressure from Pre Infusion to Peak Portal Pressure, mmHg	2.97 (2.46)	2.84 (2.33)	4.02 (3.04)
Change in Portal Pressure from Pre to Post Infusion, mmHg	1.43 (1.44)	0.84 (1.15)	1.39 (1.85)
Islet Equivalents Infused	482,382 (165,331)	454,291 (151,078)	451,772 (145,008)
Islet Packed Cell Volume, mL	4.35 (1.90)	3.70 (1.88)	3.50 (2.34)

Exhibit 109
Pre Infusion Portal Pressures

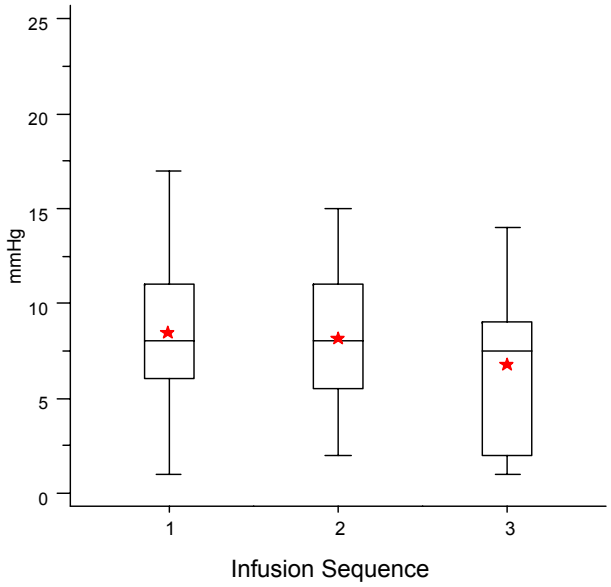


Exhibit 110
Peak Infusion Portal Pressures

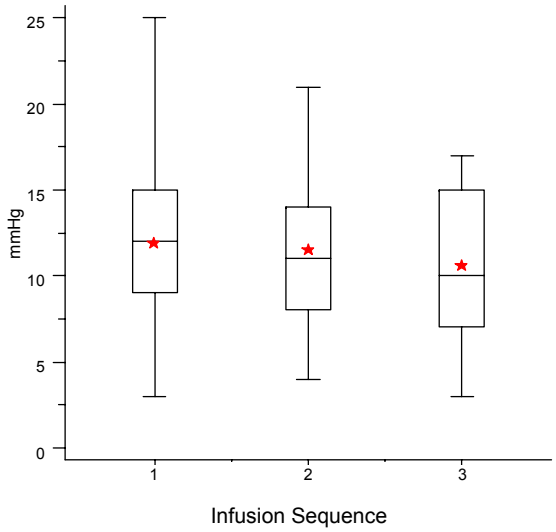


Exhibit 111
Closure Portal Pressures

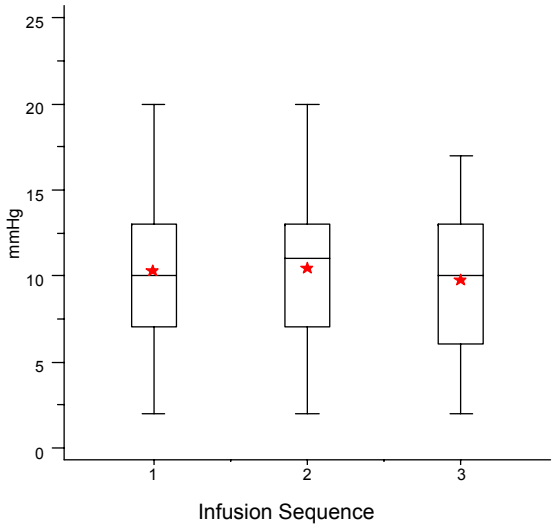


Exhibit 112
Change from Pre Infusion to Closure Portal Pressures for All Recipients

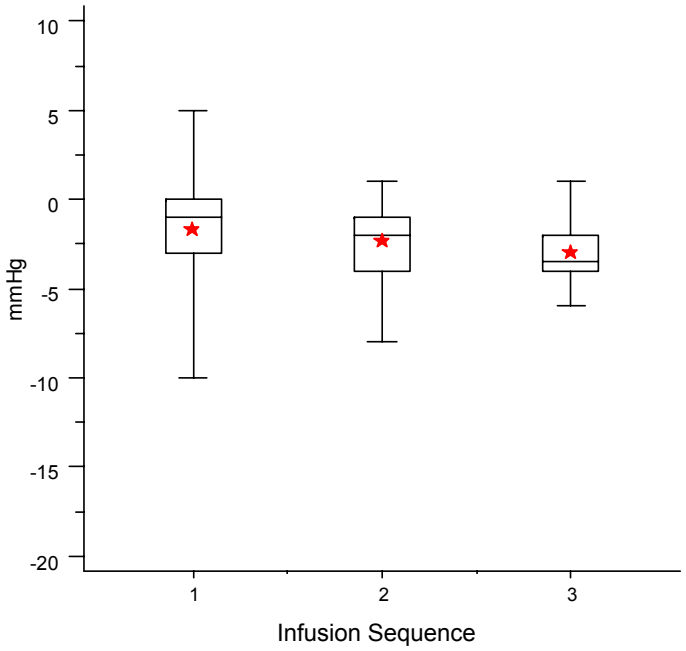


Exhibit 113
Change from Pre Infusion to Peak Portal Pressures for All Recipients

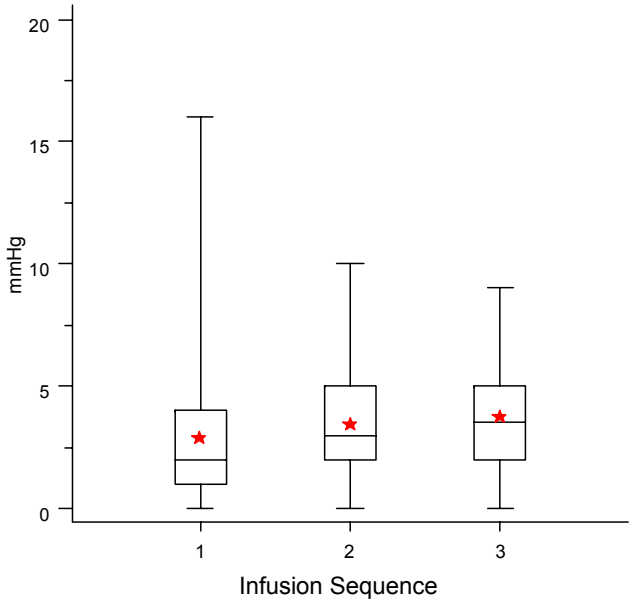
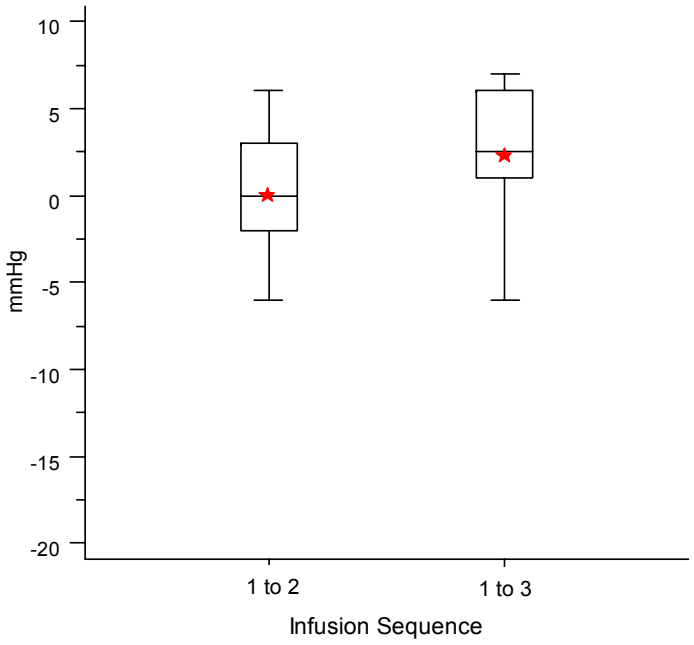


Exhibit 114
Change in Portal Pressures from Pre Infusion 1 to Pre Infusion 2 and from Pre Infusion 1 to Pre Infusion 3



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