Ninth Annual Report

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

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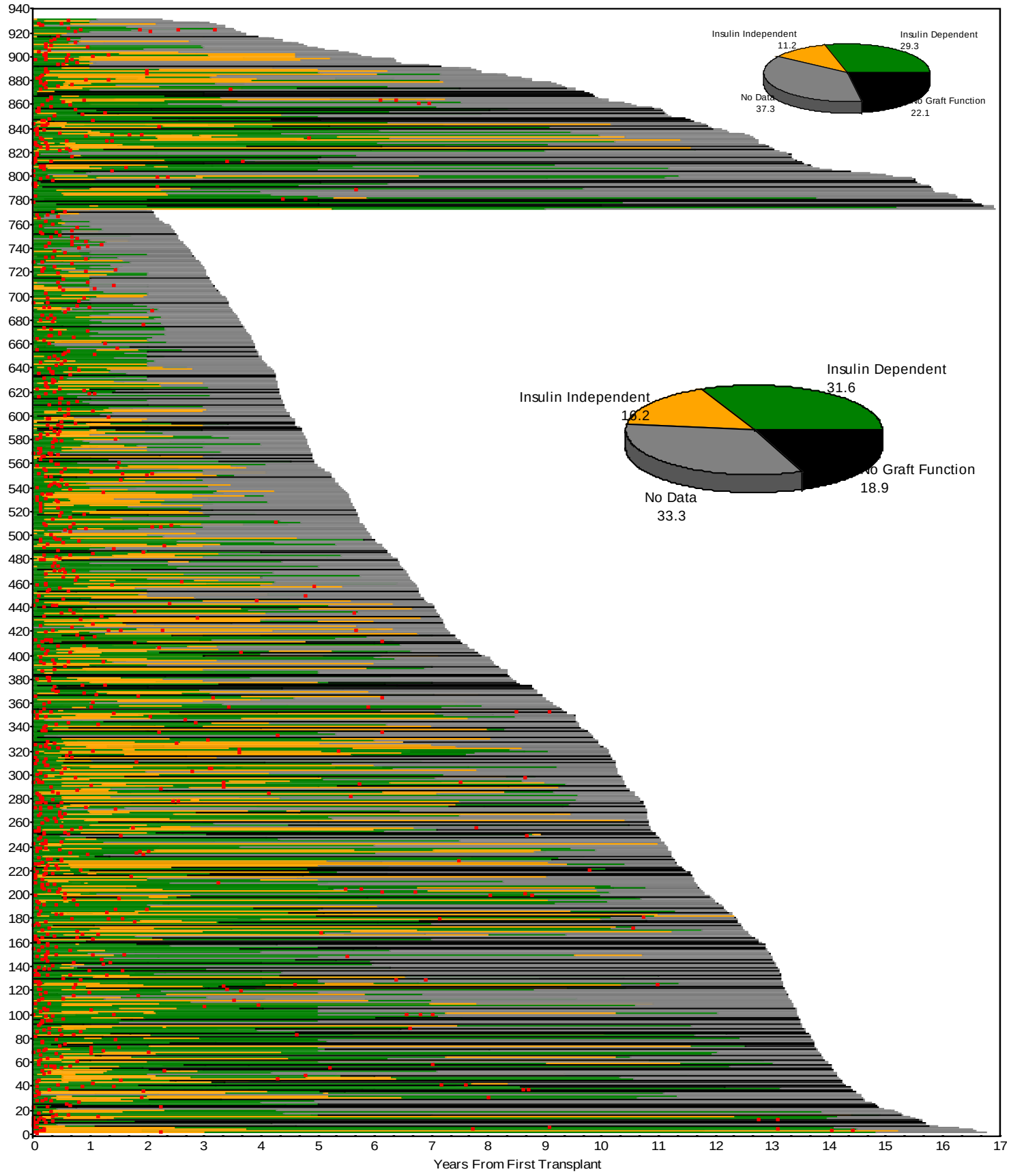
December 8, 2016



Collaborative Islet Transplant Registry 2013

TOP: Islet after kidney or simultaneous islet-kidney (IAK/SIK, N=192)

BOTTOM: Islet transplant alone (ITA, N=819)

Yellow: insulin independent; Green: insulin-using with graft function (50% average reduction in daily insulin use); Black: no islet function (C-peptide<0.3 ng/ml); Gray: missing data; Red: re-infusions.

Pie charts show percent of all follow-up time.

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

December 8, 2016

M E M O R A N D U M

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

FROM: Thomas Eggerman, MD, PhD
Guillermo Arreaza-Rubin, MD
Program Directors, Division of Diabetes, Endocrinology and Metabolic Diseases
National Institute of Diabetes and Digestive and Kidney Diseases

Bernhard Hering, MD
CITR Medical Director and
CITR Scientific Advisory Committee Chair

SUBJECT: CITR Ninth Annual Report (2013)

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) with supplemental funding from the Juvenile Diabetes Research Foundation (JDRF) for 2006-2015, the Collaborative Islet Transplant Registry (CITR) serves the mission to expedite progress and promote safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on human-to-human islet/beta cell transplants performed in North America, and Juvenile Diabetes Research Institute-sponsored European and Australian sites.

We are pleased to present this Ninth Annual Report (2013) including data from the great majority of the islet transplant programs active in 1999-2013. We are privileged to have the ongoing collaboration of the United Network for Organ Sharing for the USA donor data, and the University of Iowa Clinical Trials Statistical Data Management Center for data from the Clinical Islet Transplantation Consortium (CIT; www.isletstudy.org; www.citisletstudy.org). The US Food and Drug Administration and the National Institute of Allergy and Infectious Diseases (NIAID) lend continuing support and advice.

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

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

NOTICE:

The CITR Annual Report details data received as of December 17, 2015 for all islet transplant recipients transplanted by December 31, 2013.

As exhibited in Chapter 8: Data Quality, an unexpectedly high level of data has not been reported to the CITR Registry by the data closure.

The Scientific Summary of the CITR Ninth Annual Report may be downloaded at www.CITRegistry.org > Reports > Annual Reports.

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Detailed Methods and Definitions

Background and Purpose

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases with a supplemental grant from the Juvenile Diabetes Research Foundation International (2006-2015), the Collaborative Islet Transplant Registry (CITR) expedites progress and promotes safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America, and JDRF-sponsored European and Australian centers since 1999. The main vehicle of communicating accumulated results is the CITR Annual Report. This ninth report summarizing Registry progress summarizes information on patients who received one or more islet cell transplants between 1999 and 2013. All CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Status and History

This report focuses on 1,011 islet allograft recipients (819 islet alone and 192 islet after kidney). Islet autografts are also conducted for other indications (principally pancreatitis) and centers may voluntarily report these data also to the Registry. As of December 31, 2013, a total of 660 autologous islet transplant recipients were registered in CITR. Results on the autograft transplants are summarized in a separate report.

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

CITR Annual Report (data through)	Allograft Recipients	Allograft Infusions	Allograft Donors
First (2004)	86	158	173
Second (2005)	138	256	266
Third (2006)	227	429	469
Fourth (2007)	292	579	634
Fifth (2008)	325	649	712
Sixth (2009)	412	828	905
Seventh (2011)	571	1,072	905
Eighth (2012)	864	1,679	2,146
Ninth (2013)	1,011	1,927	2,421

The current report represents a 17% increase in the number of recipients, a 15% increase in the number of infusion procedures, and 13% increase in donors, compared to the 8th Report.

Data Sources

CITR implements web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry and obtain donor, organ procurement, and islet processing data through data

sharing agreements with respective organizations (the United Network for Organ Sharing and the Data Coordinating Center for the Clinical Islet Transplant Consortium). These data characterize and follow trends in safety and efficacy for recipients of islet transplantation, including donor information, islet processing, transplant techniques, and treatment protocols. Data reported to the Registry are abstracted from the medical record routinely collected by the CITR investigators in their care of the transplant recipients, and for scientific evaluations and reports to various agencies required by US Food and Drug Administration (FDA) regulated trials or according to the requirements of the respective nation. In US centers, demographic information is collected in CITR only once, at the time of the islet transplant recipient's registration. For each islet/beta cell infusion, information is collected on the pancreas donor(s), islet processing and testing of all pancreata used for the infusion procedure, and recipient status from screening through the early transplant period.

Follow-up data are abstracted at Days 28, 75, Month 6, Month 12 and annually post each islet infusion for five primary outcomes (insulin use, severe hypoglycemic episodes, hemoglobin A1C, fasting blood glucose and C-peptide). At each new infusion, a new follow-up schedule is established. There is also continuous, event-driven data reporting on vital status, relevant adverse events, non-islet transplant and follow-up, islet graft dysfunction, loss to follow-up, and transfer of the recipient to another islet transplant center. Secondary outcomes include monitoring for specified laboratory surveillance, periodic metabolic testing, concomitant medications and quality of life measures. A copy of the CITR data collection forms may be viewed at the CITR Website (www.citregistry.org).

CITR also collects annual islet transplant activity survey information from all islet allograft transplant centers in North America, regardless of their participation with CITR. All potential islet transplant programs are sent an annual questionnaire requesting the number of islet transplant infusions performed at their islet transplant center as well as the number of recipients.

Study Endpoints

The primary endpoints presented in this report are:

- Insulin independence (no exogeneous insulin ≥ 14 consecutive days)
- HbA_{1C} level <6.5, 6.5 to <7.0 or ≥7.0%
- C-peptide ≥0.5 ng/mL
- Severe hypoglycemia
- Complete islet graft failure (fasting C-peptide<0.3 ng/mL without recovery or subsequent infusion)

Secondary endpoints include:

- Average daily insulin and percent of baseline insulin
- Fasting plasma glucose
- Laboratory indicators of complications of diabetes and major organ function
- Metabolic testing
- Adverse events

These are variously described by prevalence bar charts (frequency distributions) pre-infusion and post first and last infusion, accounting for all participants expected at each time point. For prevalence bar charts, all recipients expected at each follow-up time point based on the dates of their infusions and the report cut-off date are included in the analysis. Bar charts are intended to display prevalence and generally represent 100% of data expected and available at each time point. Event analysis of incidence and persistence of specified endpoints are analyzed by Kaplan-Meier time-to-event or survival estimates and by Cox proportional hazards regression using relevant baseline factors as stratifying or adjusting covariates.

Insulin use, and dose if used, are available from patient-reported daily diaries post each infusion as well as at pre-specified study time points. Prevalence of insulin independence at each follow-up time point is shown in addition to achievement and loss, because this endpoint in particular can "come and go." A change from insulin dependence to independence by definition requires at least 14 consecutive days of no insulin use. A change from insulin independence to insulin dependence by definition requires a minimum of 14 consecutive days of insulin use. Average daily insulin use is recorded for periods of insulin use before and after any re-infusion procedures, changes in islet graft function, and all scheduled CITR follow-up visits.

Despite the possible transitioning back and forth from insulin dependence to independence, the initial achievement of insulin independence and the final loss are clinically meaningful events that can be analyzed as event-based outcomes with Kaplan-Meier and proportional hazards analysis.

Complete islet failure (CIF) or complete graft loss (CGL) is a reportable event. In addition, C-peptide data was used to impute CIF: any recipient with fasting C-peptides less than 0.3 ng/ml or less than local detectable levels for two consecutive scheduled follow-up visits and no simultaneous stress C-peptide >0.3 ng/mL was imputed as a complete islet failure for this report.

Boxplots used in the report display the distribution of specified continuous measures, e.g., laboratory results. The mean is indicated by a symbol, along with the median (50th percentile, center line of the box), the 25th percentile (lower line of box), and the 75th percentile (upper line of box). Whiskers extend to 2.5 X interquartile range, and outliers are plotted with individual symbols.

Statistical significance of univariate analyses not adjusted for repeated testing or other covariates, is shown for a number of the Exhibits. These are considered observed, nominal p-values outside of any pre-planned Type I error structure. In drawing any conclusions, readers should be mindful that the significance levels control for random variance, but not systematic biases in the data nor multiple testing. It may be that nominal statistical significance of the analyses in other CITR Annual Reports are based on a different sample sizes and will vary from this year's report. However, these analyses do provide insight and direction for future questions and analyses.

Statistical Modeling

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

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

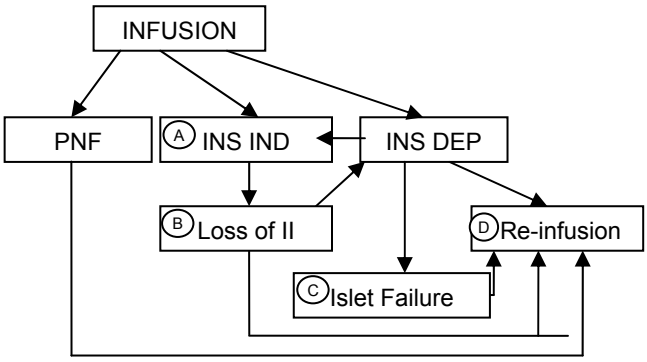


Figure 1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

In Chapter 5, we present analyses of factors affecting transition to insulin independence and loss of the insulin independent state. Because the insulin dependent state is substantially the complement of the independent state, it is not modeled separately. Because of low event numbers, primary non-function is not analyzed. The absorbing state of death has occurred too infrequently to be analyzed separately; further follow-up and/or a larger sample size will be required before its inclusion would be meaningful. Initial analysis of the transition to the islet failure state is provided. This continues to be analyzed in each Annual Report with more extensive follow-up. There are multiple paths leading to reinfusion; factors affecting this decision include site treatment plans which may not depend on the individual's paths or outcome states. Analysis of this outcome state is done by logistic regression, as time to event is clinically meaningless.

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

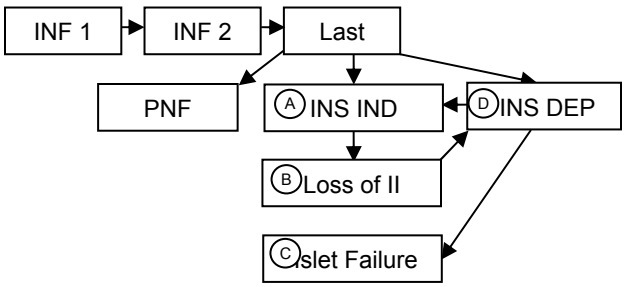


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

We call these analyses "post last infusion," defined as all infusions performed in a recipient with at least 6 months follow-up available post last infusion and excluding primary non-function. Only those recipients meeting this definition are included in this analysis. In this view, the outcomes after each infusion are regarded as intermediary steps with focused consideration of the outcome states post last infusion. Chapter 5 also presents univariate analyses of the primary endpoints as well as multivariate results.

Limitations and Disclaimers

Data contained in this report must be interpreted cautiously. Even with the combined efforts of the participating centers, the total number of islet transplant recipients remains relatively small. As with any registry, a number of potential biases may exist. First, not all active islet transplant centers in North America or the international sites have submitted data to CITR. Second, not all of the islet transplant recipients or all of the infusion procedures have been reported. Third, some information, especially on follow-up after two years of follow-up, may be reported selectively based on the center's protocol or other local decisions.

No center-specific information is presented in this report.

Data Quality Assurance and Closure

CITR adheres to strict quality control and assurance procedures. All data submitted are reviewed through several quality review processes. Islet transplant recipient data for this report reflect data entered by the islet transplant centers on participants receiving their first infusion from **January 1, 1999 through December 31, 2013**. These data were reviewed by the Coordinating Center for quality assurance, errors and data outliers. Any missing follow-up information on these participants were identified and conveyed back to the center for verification and correction. Any questions concerning specific data elements were also sent to the islet transplant centers for review and correction, if necessary. All islet transplant centers were provided ample time for completing any identified data discrepancies. **The database was then updated and closed for analysis on December 17, 2015 based on the recipients that had been registered for CITR at the December 31, 2013 participant registration closure date.**

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

Definitions

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

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

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

Adverse Event: Grade 3-5 as classified by the Clinical Islet Transplantation Consortium (CIT), Terminology Criteria for Adverse Events (TCAE), Version 5.0. Adverse event relationships to the infusion procedure and to the immunosuppression regimen are determined by the local CITR Investigator.

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

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

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

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

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

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

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

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

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

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

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

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

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

Islet after kidney recipient/simultaneous islet-kidney (IAK/SIK): A recipient of an islet cell transplant with prior or simultaneous kidney transplantation.

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

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

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

Islet graft dysfunction:

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

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

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

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

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

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

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

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

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

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

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

Chapter 1
Islet Transplant Activity

Introduction

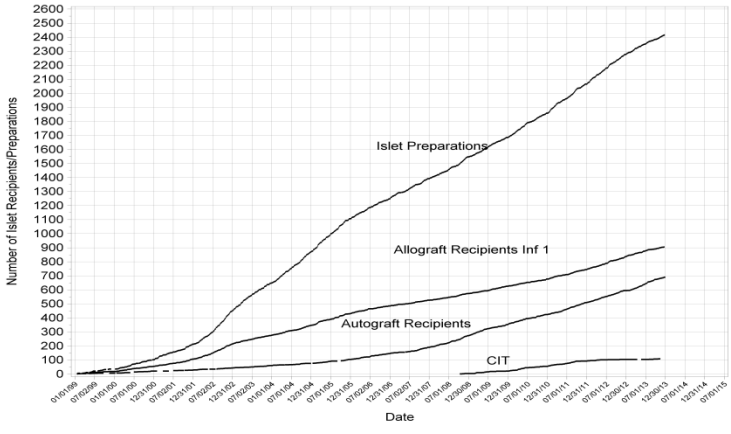
From 1999 through 2013, 28 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored North American and 9 international European and Australian islet transplant centers (37 total) contributed data to the Collaborative Islet Transplant Registry (CITR). These sites registered 819 islet transplant alone (ITA) and 192 islet after kidney or simultaneous islet-kidney (IAK/SIK) allograft recipients consenting to have their data reported to the Registry, for a total of 1,011 allogeneic, human-to-human islet transplant recipients. In 2013, nine North American sites performed allogeneic islet transplantation of which eight participated in CITR. Exhibit 1-1A and 1-1B summarize the total allograft recipients, donors and infusions included in this report.

In 2008, the Consortium for Islet Transplantation (CIT; www.citisletstudy.org/) began enrolling islet transplant patients. CIT enrollment was completed in 2012. All of the CIT sites also participate in CITR. Under collaborative agreements stipulated by the common sponsor, the NIDDK of the US National Institutes of Health (NIH), CITR-required data is transmitted to CITR for CITR-consenting patients. Most CIT sites have offered both CIT and non-CIT islet transplant protocols during 2008-2013.

Exhibit 1 – 1A
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK
Consented, Registered and First Infused in 1999-2013

	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK/SIK)			
	Total	North America	Europe/ Australia/ Asia	Total	North America	Europe/ Australia/ Asia	GRAND TOTALS
Recipients	**819**	488	331	**192**	64	128	**1,011**
Infusions	**1,584**	933	651	**343**	112	231	**1,927**
Donors	**2,032**	1,005	1,027	**389**	123	266	**2,421**

Exhibit 1 – 1B
Cumulative Enrollment in CITR

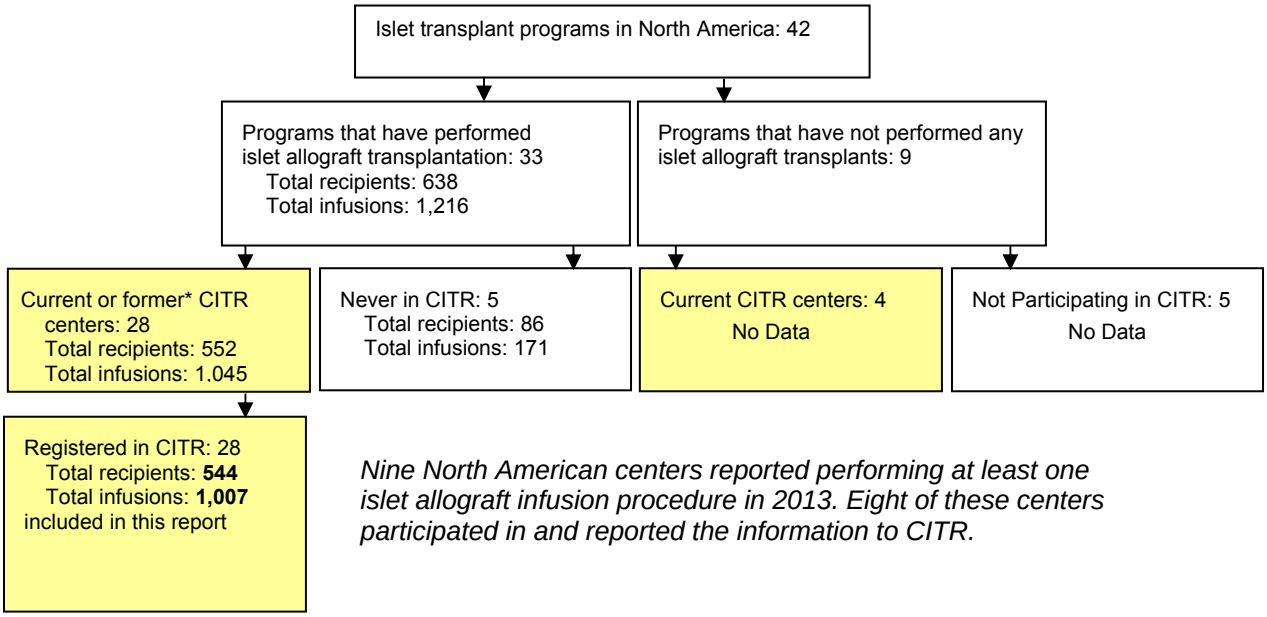


NORTH AMERICAN CENTERS

In addition to the data collection for registered islet transplant recipients, CITR conducts an on-going survey, updated at least annually, to identify active islet transplant centers and ascertain the total number of recipients and islet infusions conducted in North America. The following diagram shows the number of centers, recipients and infusions identified and captured by CITR. Overall, 552 (86.5%) of 638 islet allograft recipients and 1,045 (85.9%) of all islet allograft infusion procedures performed in North America from 1999-2013 are included in this report.

North American Islet Allograft Transplant Centers, Recipients and Infusions

Total Performed and Total Reported to CITR 1999-2013



Nine North American centers reported performing at least one islet allograft infusion procedure in 2013. Eight of these centers participated in and reported the information to CITR.

* Former CITR centers (N=10) are those who reported islet transplant data to CITR then subsequently stopped performing islet transplants and/or discontinued CITR participation.

Exhibit 1-2A maps the geographic locations of all current and former CITR-participating North American centers. A listing of CITR-participating centers and their clinical personnel is found in Appendix A.

Exhibit 1-3 displays the number of North American centers conducting allograft transplants and of those, the number of centers contributing to this report, by year.

Exhibits 1-4 and 1-5A display the number of allograft recipients and allograft infusions performed in all of North America, and the respective numbers contained in this report, by year.

Overall, there was a steady increase in the number of islet transplant programs joining CITR up to 2005, followed by a decline in centers performing islet transplantation in 2006-2007, then a resurgence starting in 2008.

INTERNATIONAL CENTERS

Supplemental funding from the Juvenile Diabetes Research Foundation supported data reporting to CITR from five European (Exhibit 1-2B) and three Australian (Exhibit 1-2C) centers from 2006 through 2015. These centers continue to report data to CITR.

Exhibits 1-4B and 1-5B display the numbers of allograft recipients and allograft infusions performed in the CITR European and Australian sites by year.

Infusions

A summary of the total 1,927 North American and international islet allograft infusions by year of infusion is included in Exhibit 1-5. These infusions derived from 2,421 total donors: 1,676 (86%) were single donor preparations and 266 (14%) were multiple (2-3) donor preparations.

Three hundred sixteen (316) recipients (31.2%) have received a single islet infusion at the time of this report, 492 (48.7%) received a total of two infusions, 177 (17.5%) received three infusions, and 26 recipients (2.6%) received a total of four to six islet infusions (Exhibit 1-7).

Of the 1,011 islet allograft recipients presented in this report, 819 (81.0%) are islet alone recipients, and 192 (19.0%) are islet after kidney recipients of which 9 were islet simultaneous with kidney. Seven islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

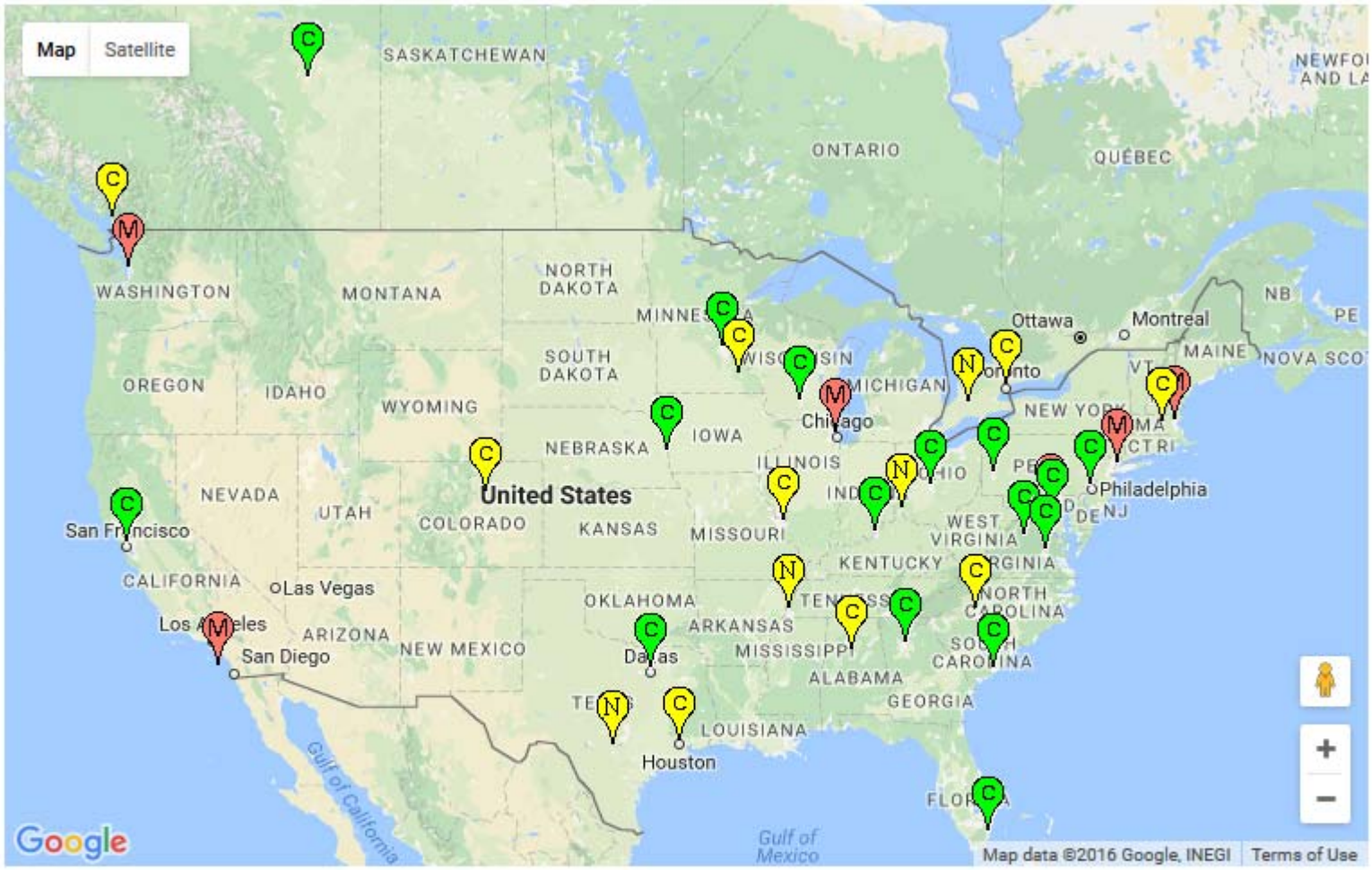
CITR Allografts Overall

There has been a 17% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 15% increase in the total number of islet allograft infusion procedures reported.

Autografts

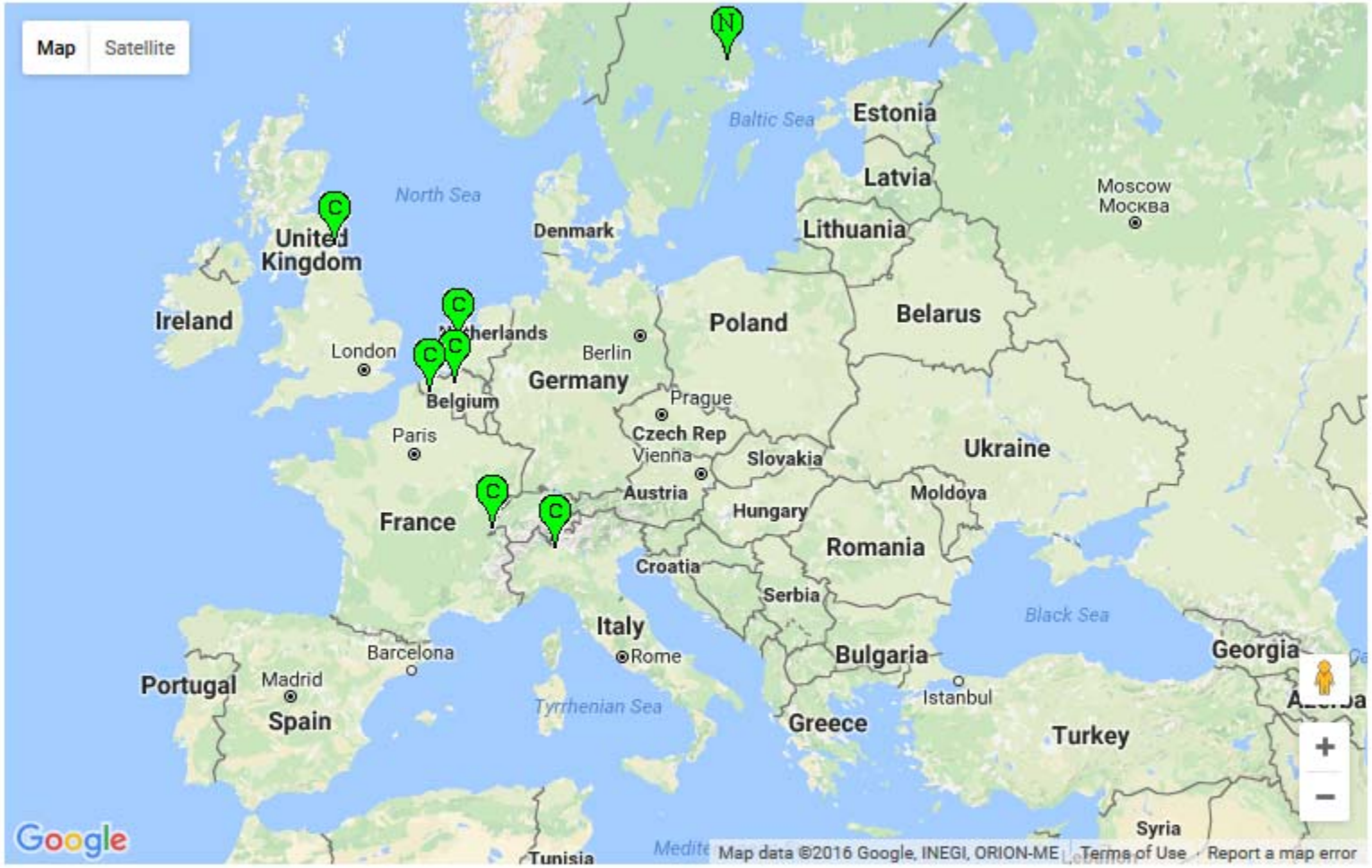
Six hundred ten (610) North American and 50 international autograft consenting recipients have been registered in the Registry. A brief supplemental Annual Report will present analyses for autologous islet transplants through 2013.

Exhibit 1 – 2A
Islet Transplant Centers Reporting Data to CITR
Participating North American Centers 1999-2013



CITR Islet Transplant Centers = C
Non-CITR Islet Transplant Centers = N
Active
InActive
CITR Coordinating Center
Mutiple Centers

Exhibit 1 – 2B
Islet Transplant Centers Reporting Data to CITR
Participating European Centers 1999-2013

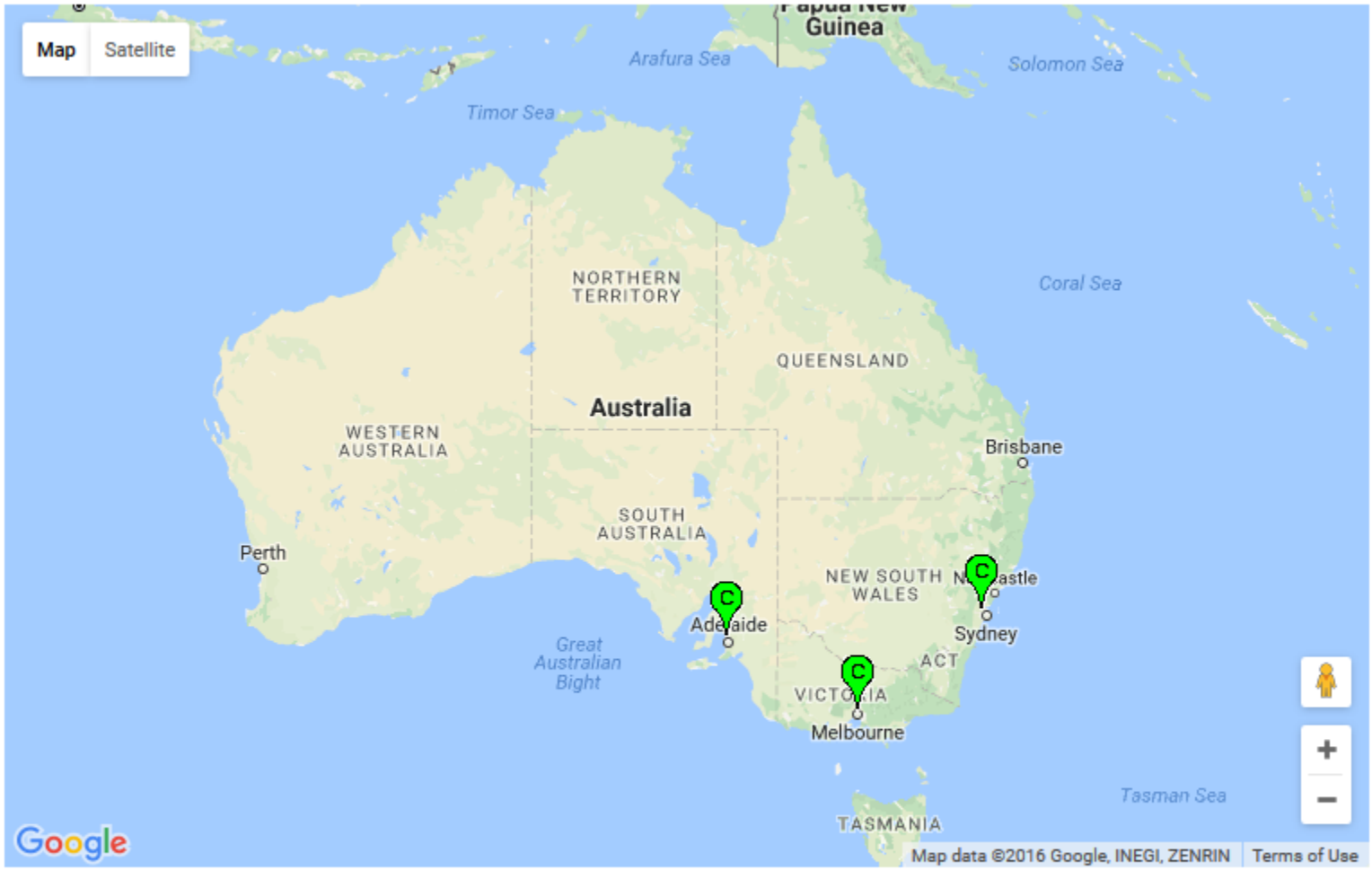


CITR Islet Transplant Centers = C

Non-CITR Islet Transplant Centers = N

Active InActive CITR Coordinating Center Mutiple Centers

Exhibit 1 – 2C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2013

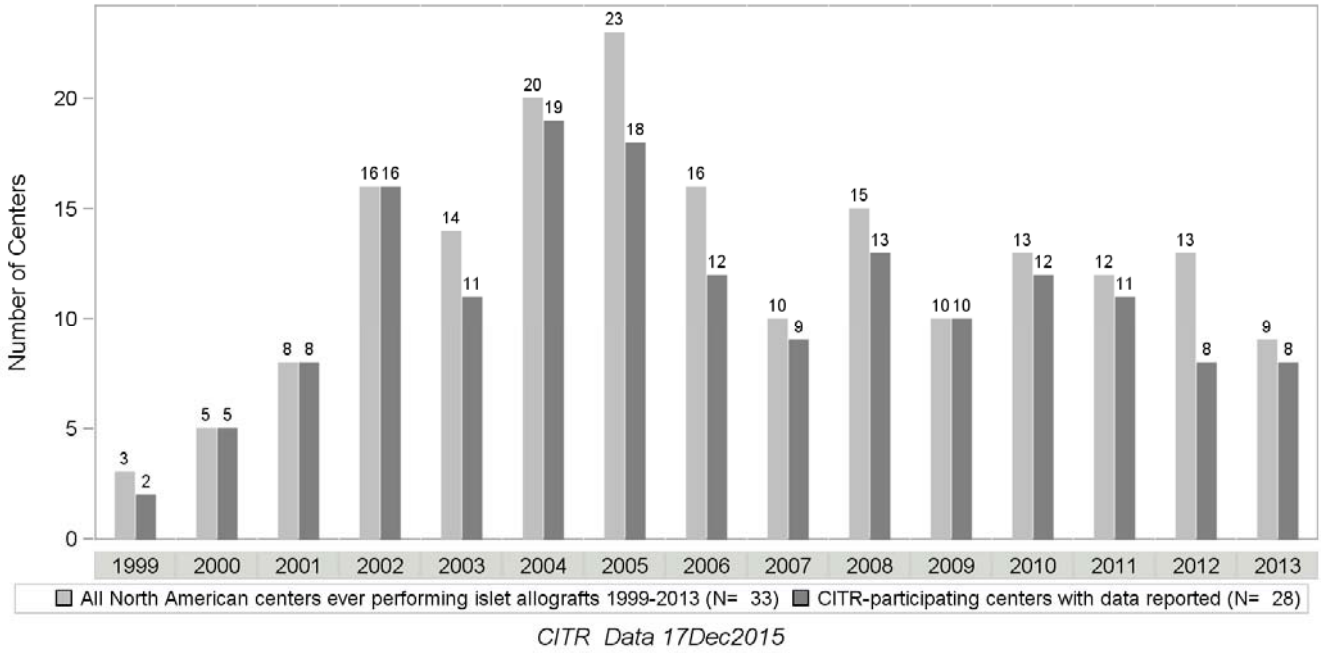


CITR Islet Transplant Centers = C

Non-CITR Islet Transplant Centers = N

Active InActive CITR Coordinating Center Mutiple Centers

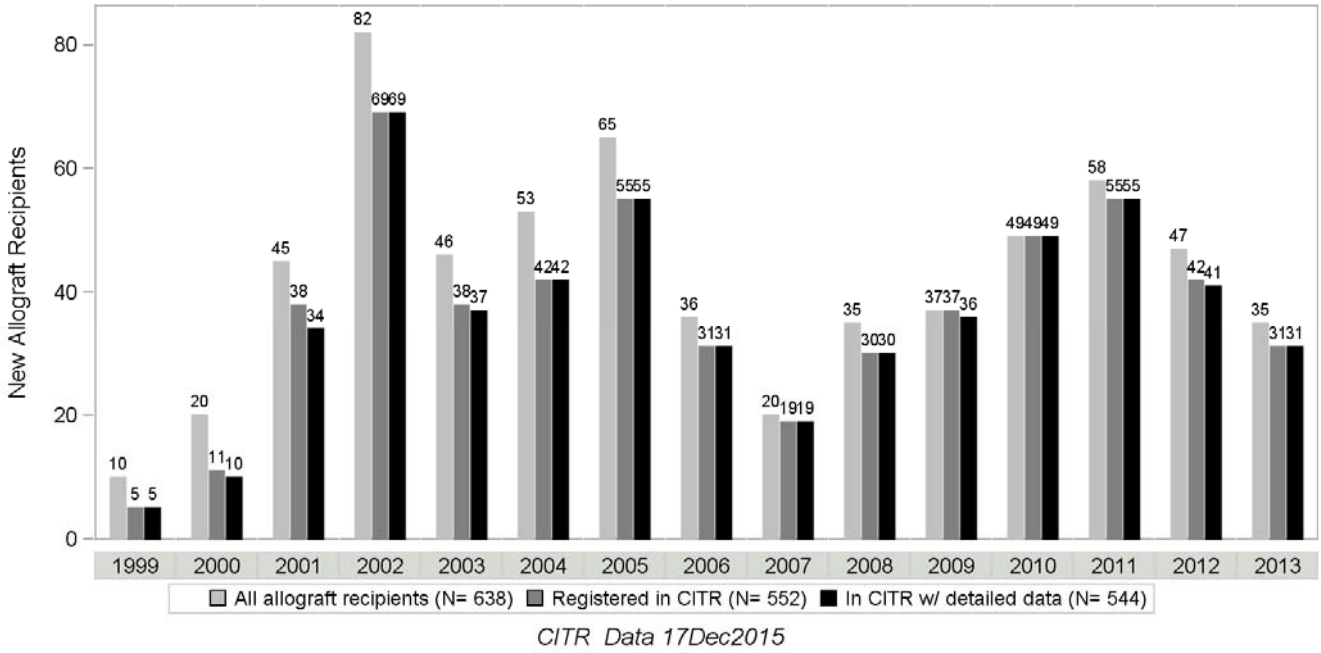
Exhibit 1 – 3
Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
North American Islet Transplant Centers 1999-2013



CITR Data 17Dec2015

"All North American Centers Performing Islet Allografts" includes sites that reported performing at least one islet infusion procedure in the specified year. "CITR-Participating Centers with Data Entered" represents the number of islet transplant programs in the specified year that have contributed data for the analyses included in this Annual Report.

Exhibit 1 – 4A
Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion: Allograft recipients at North American Islet Transplant Centers 1999-2013



From 1999-2013, 638 patients with type 1 diabetes mellitus received at least one islet allograft infusion procedure in North America. Of these, 552 (86.5%) consented to and were registered in CITR. Detailed data was available on 544 of these recipients, representing 85.3% of the overall 638.

Exhibit 1 – 4B
Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion: Allograft recipients at CITR-Participating European and Australian JDRF Centers 1999-2013

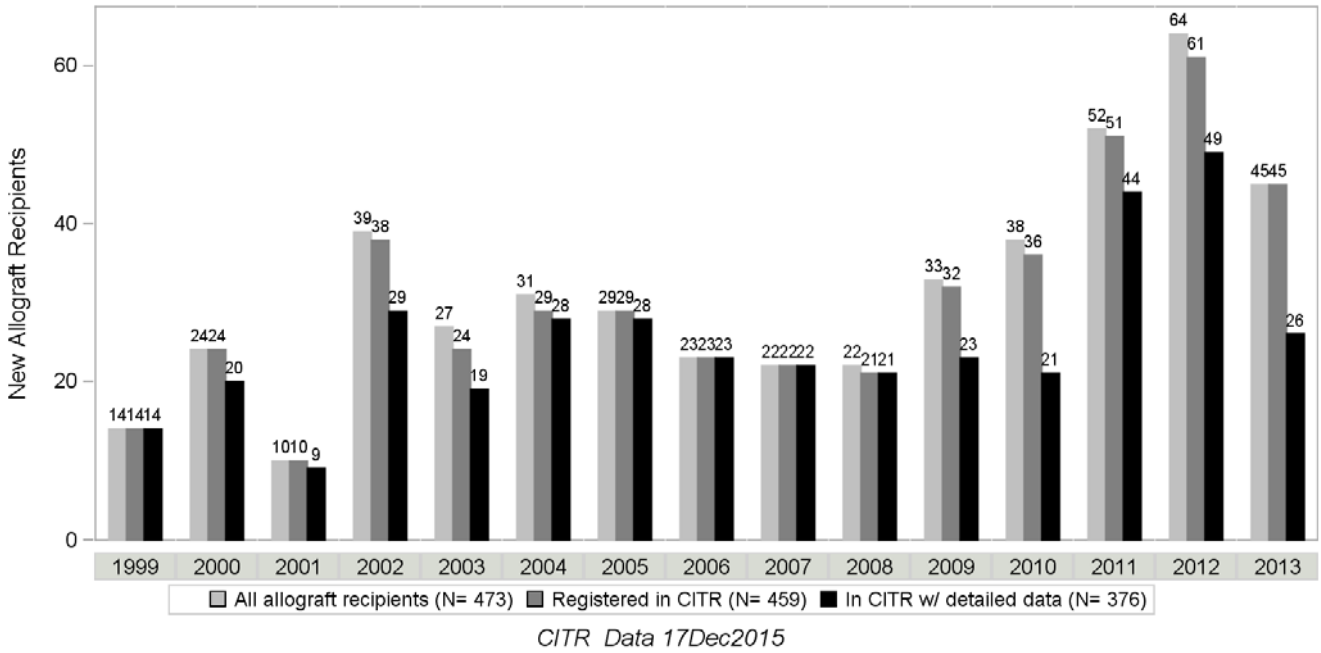
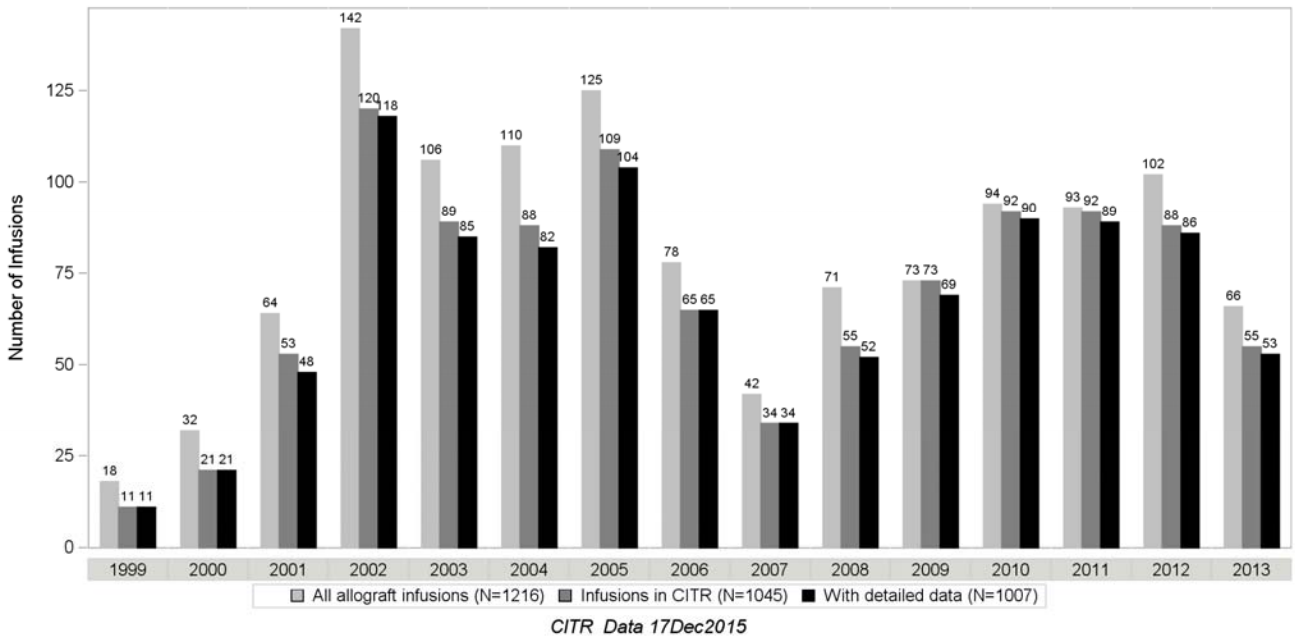


Exhibit 1 – 5A
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR:
CITR-Participating North American Islet Transplant Centers 1999-2013



From 1999-2013, 638 North American islet transplant recipients of allograft islets received a total of 1,216 infusion procedures. CITR-participating centers reported 1,045 (85.9%) of those procedures. The Registry has received detailed data relative to 1,007 of those procedures, representing 82.8% of all 1,216 infusions.

Exhibit 1 – 5B
Total Number of Islet Allograft Infusion Procedures Performed and Number with Data Reported to CITR:
CITR-Participating European and Australian JDRF Centers 1999-2013

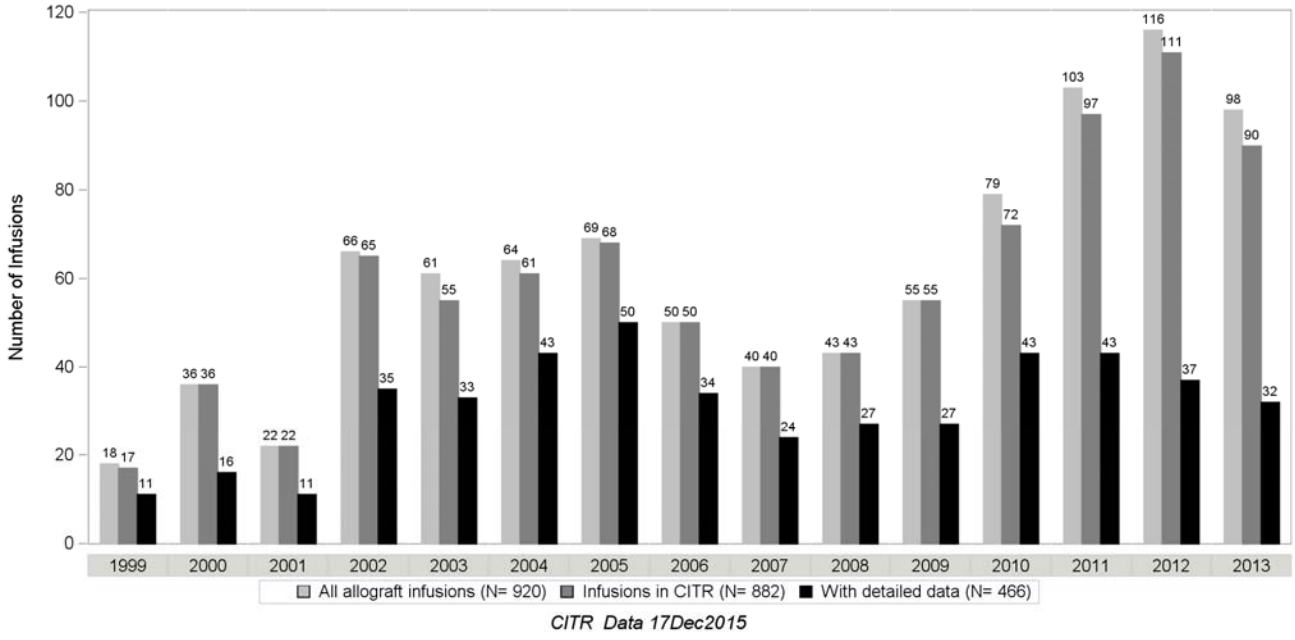


Exhibit 1 – 6A
Islet Allograft Infusions by Infusion Sequence Number and Year
CITR-Participating North American and International Centers, 1999-2013

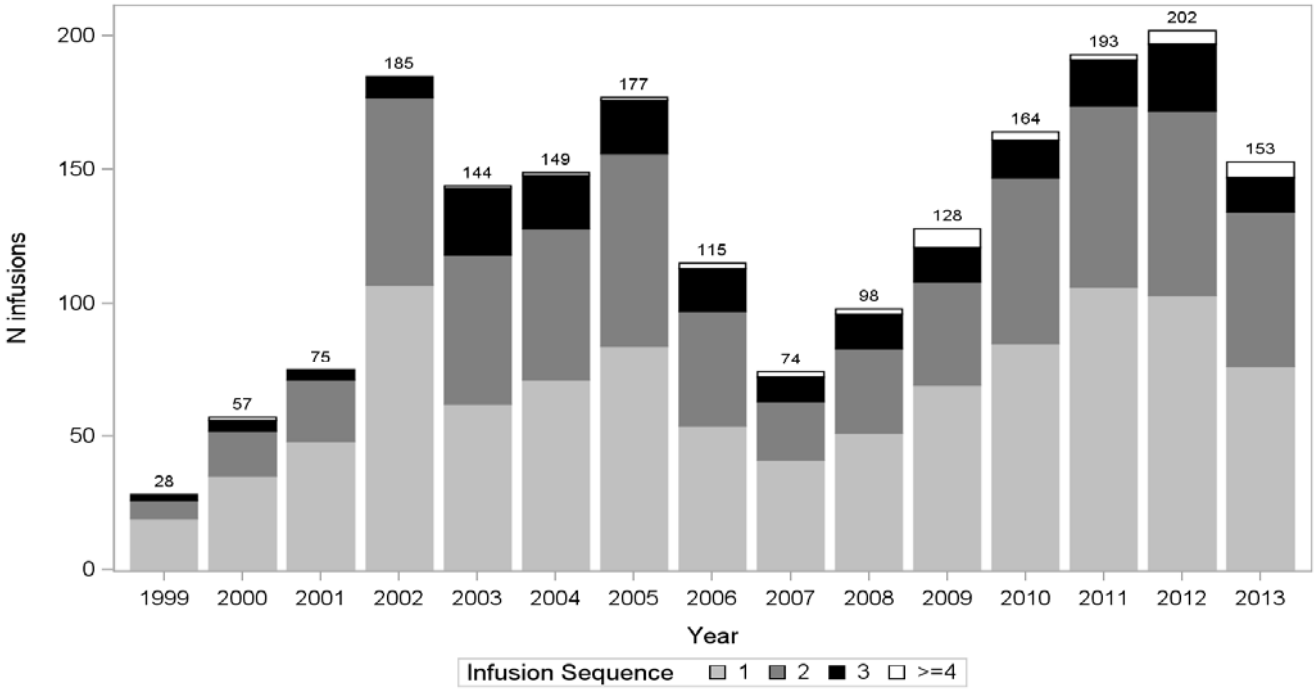


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Exhibit 1 – 6B
Islet Allograft Recipients by Total Infusions to Date and Year
CITR-Participating North American and International Centers, 1999-2013

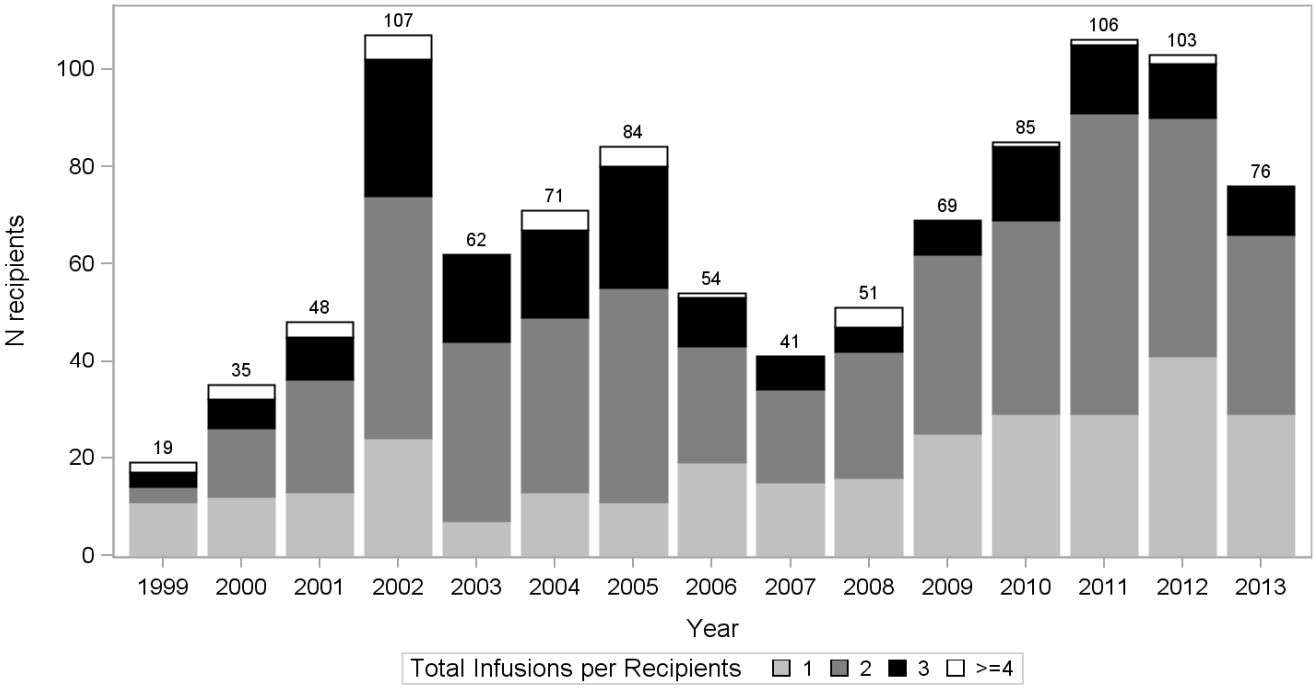

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Exhibit 1 – 7
Total Number of Islet Allograft Infusions Per Recipient:
CITR-Participating North American and International Centers, 1999-2013

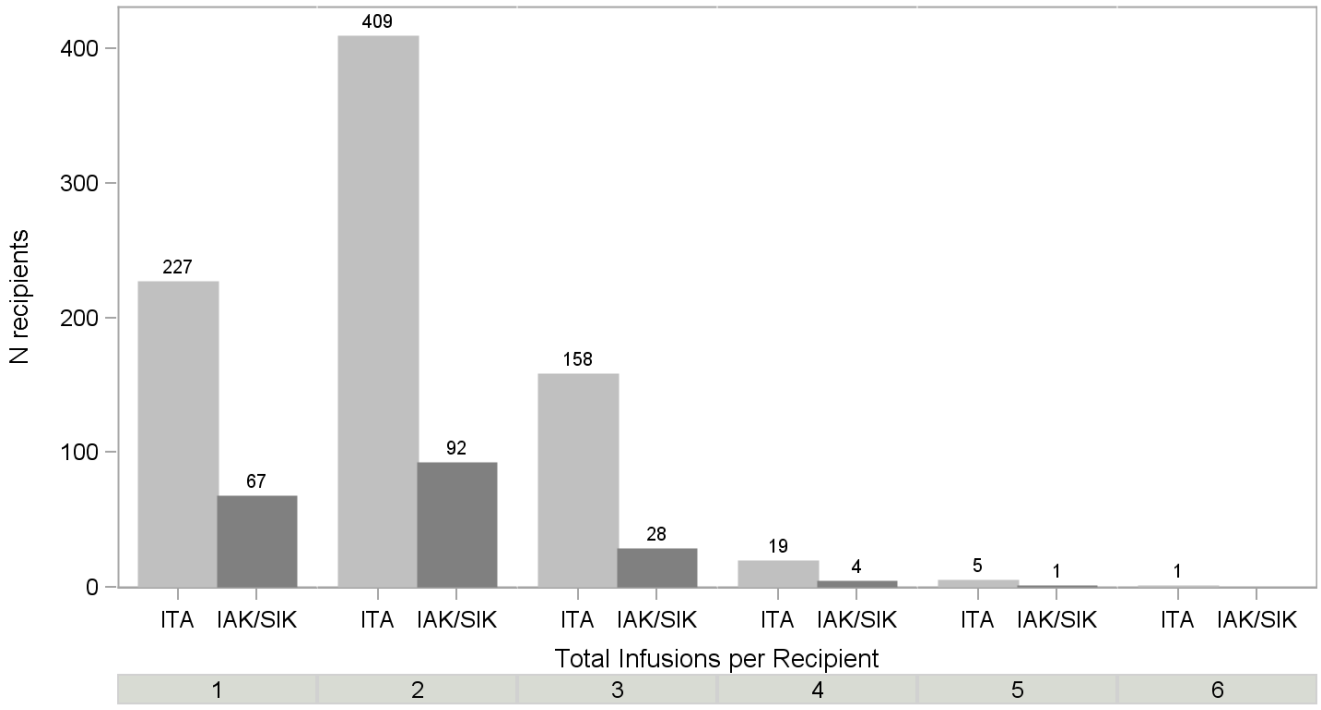

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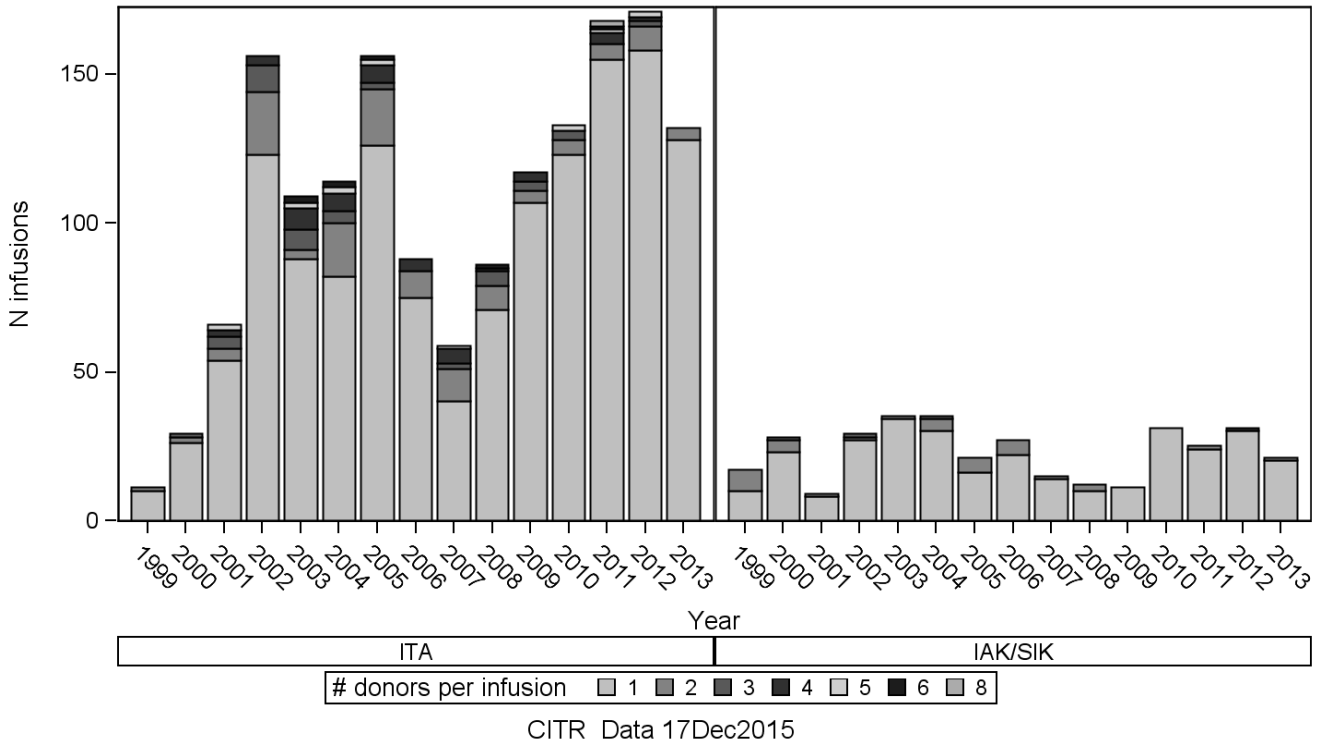
Exhibit 1 – 8
Total Number of Deceased Donors per Islet Allograft Infusion
CITR-Participating North American and International Centers, 1999-2013



CITR Data 17Dec2015

Chapter 2
Recipient and Donor Characteristics

Introduction

All pre-infusion recipient characteristics are displayed in Exhibits 2-1 to 2-9. The distribution of each characteristic (variable) is shown according to transplant type (ITA or IAK/SIK) and era (1999-2002, 2003-2006, 2007-2010, and 2011-2014). In the first paired table per variable, the distribution of available data is shown and tested for differences by transplant type and era. Data availability is shown in the second, dimmed, paired table. Nominal p-values are calculated but are not based on experimental design.

In Exhibits 2-10 to 2-16, multiple donor information has been summarized over one to several donors/pancreata per islet infusion. There were 1,676 single-donor, 155 two-donor, 45 three-donor, 43 four-donor, 14 five-donor, and 9 six-donor or more infusions, for a total of 2,421 donors and 1,942 infusions.

Any remarkable results are noted following each exhibit.

Summary of Results

Over the eras of the Registry, the following trends are observed for recipients of allogeneic islets:

- Recipients have been selected at older age and longer wait time at initial transplant
- Recipients have been selected with lower initial C-peptide, higher HbA1c, increased use of insulin pump and higher prevalence of hypoglycemia unawareness
- Greater proportions had positive GAD65 autoantibody and lower proportions had positive insulin autoantibody
- Recipients had higher levels of HbA1c in recent eras
- Recipients had lower levels of total and LDL cholesterol in recent eras
- Recipients had slightly higher initial levels of estimated GFR in recent eras

There were also notable differences in medical characteristics between ITA and IAK/SIK recipients, most notably, a much lower prevalence of hypoglycemia unawareness, and much lower initial eGFR in the IAK/SIK recipients.

The following trends are observed among donors of allogeneic islets:

- Substantial increase in donor weight and BMI over the eras
- Increased use of transfusion during hospitalization
- Increased use of steroids and insulin during hospitalization
- Donor serum amylase and stimulated blood glucose have declined substantially over the eras

Exhibit 2 – 1
Recipient Demographics

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Gender	**Female**	497	60.8	106	55.5		118	56.5	162	60.0	153	62.4	170	59.6	
	Male	321	39.2	85	44.5		91	43.5	108	40.0	92	37.6	115	40.4	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Gender	Available	818	99.9	191	99.5		209	100.0	270	99.6	245	99.6	285	100.0	
	Missing	1	0.1	1	0.5			0.0	1	0.4	1	0.4		0.0	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Race	**White**	585	98.5	139	97.9		148	99.3	199	99.0	186	96.9	191	98.5	
	Multiple		0.0	1	0.7		1	0.7		0.0		0.0		0.0	
	American Indian	2	0.3		0.0			0.0	1	0.5	1	0.5		0.0	
	Black	5	0.8	2	1.4			0.0	1	0.5	5	2.6	1	0.5	
	Asian	2	0.3		0.0			0.0		0.0		0.0	2	1.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Race	Available	594	72.5	142	74.0		149	71.3	201	74.2	192	78.0	194	68.1	
	Missing	225	27.5	50	26.0		60	28.7	70	25.8	54	22.0	91	31.9	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Ethnicity	**Not Hispanic**	515	98.5	137	95.8		146	98.6	193	96.0	175	98.9	138	98.6	
	Hispanic	8	1.5	6	4.2		2	1.4	8	4.0	2	1.1	2	1.4	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Ethnicity	Available	523	63.9	143	74.5		148	70.8	201	74.2	177	72.0	140	49.1	
	Missing	296	36.1	49	25.5		61	29.2	70	25.8	69	28.0	145	50.9	

* = p <.05; ** = p <.01; *** = p <.001

Race and ethnicity are not collected at the JDRF sites.

Exhibit 2 – 1 *(continued)*
Recipient Demographics

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Employment	**Full time**	273	56.1	27	31.0		86	62.3	112	53.1	53	48.6	49	42.2	
	Not working disease	87	17.9	35	40.2	***	22	15.9	44	20.9	20	18.3	36	31.0	**
	Not working by choice	31	6.4	4	4.6		5	3.6	13	6.2	9	8.3	8	6.9	
	Part time by choice	28	5.7	6	6.9		6	4.3	11	5.2	13	11.9	4	3.4	
	Retired	25	5.1		0.0		3	2.2	13	6.2	5	4.6	4	3.4	
	Part time by disease	22	4.5	3	3.4		11	8.0	9	4.3	3	2.8	2	1.7	
	Not working unknown	7	1.4	6	6.9		1	0.7	4	1.9	4	3.7	4	3.4	
	Part time unknown	7	1.4		0.0		1	0.7	1	0.5		0.0	5	4.3	
	Student	5	1.0	4	4.6		1	0.7	3	1.4	2	1.8	3	2.6	
	Not working no employ	2	0.4		0.0			0.0	1	0.5		0.0	1	0.9	
	Not applicable		0.0	2	2.3		2	1.4		0.0		0.0		0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Employment	**Available**	487	59.5	87	45.3		138	66.0	211	77.9	109	44.3	116	40.7	
	Missing	332	40.5	105	54.7		71	34.0	60	22.1	137	55.7	169	59.3	

* p < 0.05 ** p < 0.01 *** p < 0.001

Exhibit 2 – 2
Indication for Islet Transplantation: Diabetes, Severe Hypoglycemia (SHE), and C-peptide

			ITA										IAK/SIK									
			Total		Era								Total		Era							
					1999-2002		2003-2006		2007-2010		2011-2014				1999-2002		2003-2006		2007-2010		2011-2014	
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL with data			**466**	**100.0**	131	100.0	179	100.0	94	100.0	62	100.0	**127**	**100.0**	47	100.0	52	100.0	19	100.0	9	100.0
Cystic fibrosis	**ASHE**	**<0.3**	1	0.2	-	-	-	-	-	-	1	1.6	-	-	-	-	-	-	-	-	-	-
		>=0.5	1	0.2	-	-	1	0.6	-	-	-	-	1	0.8	-	-	-	-	-	-	1	11.1
Pancreatectomy	**SHE**	**0.3-0.4**	1	0.2	-	-	-	-	1	1.1	-	-	-	-	-	-	-	-	-	-	-	-
Type 1	**ASHE**	**<0.3**	85	18.2	27	20.6	32	17.9	10	10.6	16	25.8	55	43.3	20	42.6	19	36.5	11	57.9	5	55.6
		0.3-0.4	1	0.2	-	-	1	0.6	-	-	-	-	8	6.3	6	12.8	-	-	2	10.5	-	-
		>=0.5	4	0.9	2	1.5	-	-	2	2.1	-	-	12	9.4	6	12.8	6	11.5	-	-	-	-
	SHE	**<0.3**	337	72.3	85	64.9	132	73.7	77	81.9	43	69.4	44	34.6	13	27.7	24	46.2	6	31.6	1	11.1
		0.3-0.4	15	3.2	2	1.5	8	4.5	4	4.3	1	1.6	-	-	-	-	-	-	-	-	-	-
		>=0.5	21	4.5	15	11.5	5	2.8	-	-	1	1.6	5	3.9	2	4.3	3	5.8	-	-	-	-
Type 2	**ASHE**	**0.3-0.4**	-	-	-	-	-	-	-	-	-	-	1	0.8	-	-	-	-	-	-	1	11.1
	SHE	**<0.3**	-	-	-	-	-	-	-	-	-	-	1	0.8	-	-	-	-	-	-	1	11.1

Missing data			ITA										IAK/SIK									
			Total		Era								Total		Era							
					1999-2002		2003-2006		2007-2010		2011-2014				1999-2002		2003-2006		2007-2010		2011-2014	
			N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL with missing data			353	100.0	21	100.0	37	100.0	114	100.0	181	100.0	65	100.0	10	100.0	3	100.0	19	100.0	33	100.0
DiabHx	SHE	C-peptide																				
Missing	Missing	Missing	65	18.4	-	-	-	-	27	23.7	38	21.0	24	36.9	4	40.0	-	-	9	47.4	11	33.3
		Available	29	8.2	-	-	14	37.8	4	3.5	11	6.1	21	32.3	-	-	-	-	4	21.1	17	51.5
	Available	Missing	1	0.3	-	-	-	-	-	-	1	0.6	-	-	-	-	-	-	-	-	-	-
		Available	1	0.3	-	-	-	-	-	-	1	0.6	-	-	-	-	-	-	-	-	-	-
Available	Missing	Missing	41	11.6	10	47.6	3	8.1	9	7.9	19	10.5	7	10.8	-	-	2	66.7	2	10.5	3	9.1
		Available	119	33.7	7	33.3	12	32.4	57	50.0	43	23.8	7	10.8	1	10.0	-	-	4	21.1	2	6.1
	Available	Missing	97	27.5	4	19.0	8	21.6	17	14.9	68	37.6	6	9.2	5	50.0	1	33.3	-	-	-	-

Exhibit 2 – 3
Recipient Characteristics at First Infusion

	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Age at transplant	819	46.2	0.4	192	46.0	0.6		209	42.0	0.6	271	44.6	0.6	246	48.0	0.6	285	49.0	0.6	***
Days listed	510	321.6	16.4	122	382.6	45.9		168	236.7	21.4	230	316.9	22.5	112	482.9	53.0	122	360.2	39.1	***
Duration of Diabetes (yrs)	662	28.9	0.4	141	32.8	0.8	***	198	27.3	0.8	254	29.6	0.6	190	31.1	0.9	161	30.7	0.9	***
Weight (kg)	732	67.5	0.4	164	62.8	0.8	***	196	66.0	0.8	263	65.2	0.6	208	67.1	0.8	229	68.3	0.8	**
Body mass index (kg/m2)	632	23.8	0.1	159	22.7	0.2	***	189	23.4	0.2	262	23.3	0.2	194	23.9	0.2	146	23.9	0.3	
Daily insulin requirement prior to infusion (units)	642	37.5	0.6	137	36.6	1.1		194	39.5	1.1	266	37.2	0.9	161	34.6	1.1	158	37.5	1.3	
Duration of intensive therapy (yrs)	326	20.4	0.8	24	24.3	3.1		110	18.2	1.1	143	23.6	1.2	68	19.6	2.0	29	18.0	2.5	
Avg daily insulin / kg recipient body weight	612	0.6	0.0	134	0.6	0.0	*	191	0.6	0.0	261	0.6	0.0	156	0.5	0.0	138	0.6	0.0	**
Fasting plasma glucose (mg/dL)	601	171.5	3.5	134	173.1	8.1		170	182.2	7.2	250	173.7	5.8	173	153.5	5.6	142	178.4	7.2	
Basal C-Peptide (ng/mL)	615	0.1	0.0	155	0.2	0.1	***	186	0.2	0.0	257	0.1	0.0	182	0.1	0.0	145	0.1	0.0	*
HbA1C (%)	636	7.9	0.1	142	8.1	0.1		195	7.9	0.1	264	7.8	0.1	163	8.0	0.1	156	8.4	0.1	***
Class I PRA (%)	383	3.6	0.6	75	1.1	0.7		133	1.5	0.5	189	4.2	1.1	83	2.5	0.9	53	5.2	2.2	
Class II PRA (%)	263	3.1	0.8	33	0.0	0.0		75	1.6	1.3	105	2.7	1.1	64	3.5	1.5	52	3.6	2.1	

* = p <.05; ** = p <.01; *** = p <.001

Mean recipient age has increased over the eras, as has mean waiting time and duration of diabetes.

Mean HbA1c has increased substantially over the eras.

Significant differences by type and era are displayed in the following box-and-whisker plots.

Exhibit 2 – 3 *(continued)*
Recipient Characteristics at First Infusion

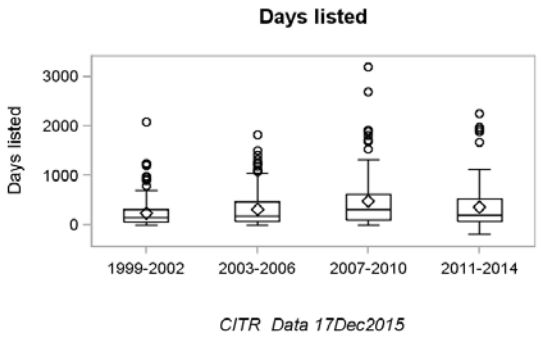
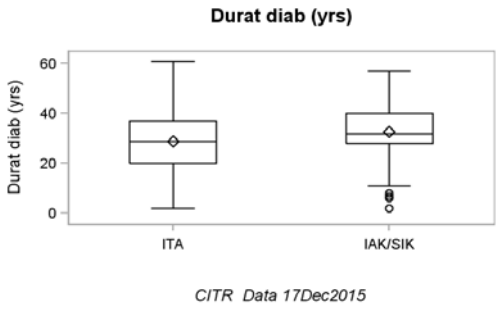
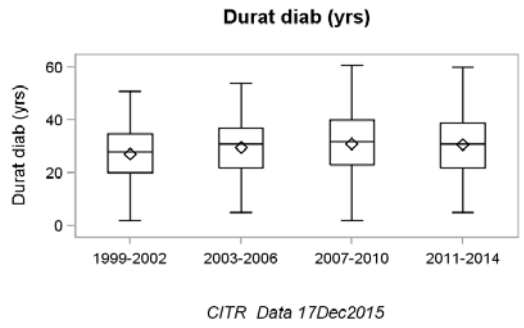
Significant Trends in Patient Characteristics from Table Above	
By ITA or IAK/SIK	**By ERA**
	
	
	

Exhibit 2 – 3 *(continued)*
Recipient Characteristics at First Infusion

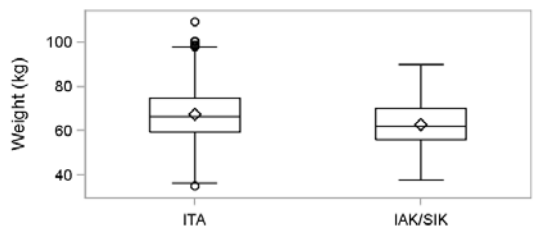
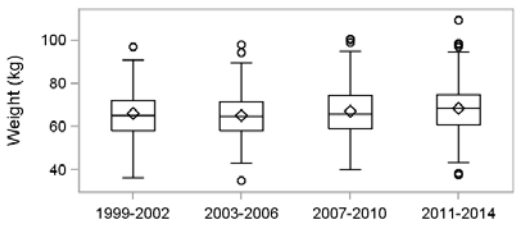
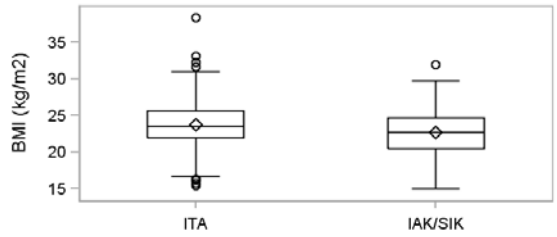
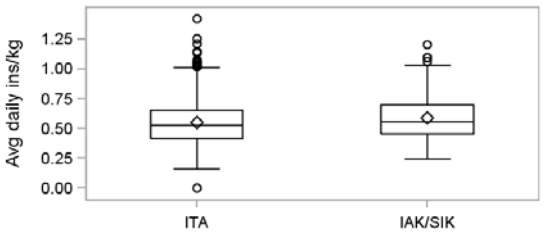
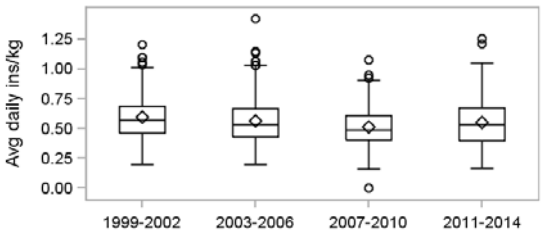
Significant Trends in Patient Characteristics from Table Above	
By ITA or IAK/SIK	**By ERA**
Weight (kg)  *CITR Data 17Dec2015*	**Weight (kg)**  *CITR Data 17Dec2015*
BMI (kg/m2)  *CITR Data 17Dec2015*	
Avg daily ins/kg  *CITR Data 17Dec2015*	**Avg daily ins/kg**  *CITR Data 17Dec2015*

Exhibit 2 – 3 *(continued)*
Recipient Characteristics at First Infusion

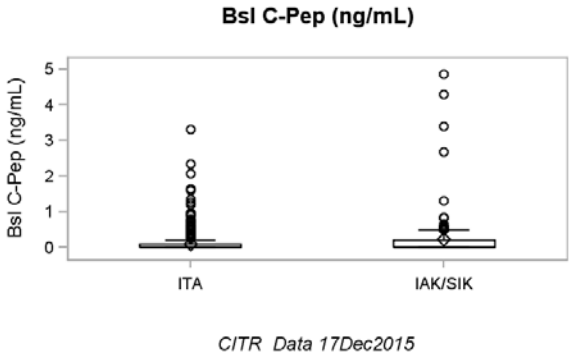
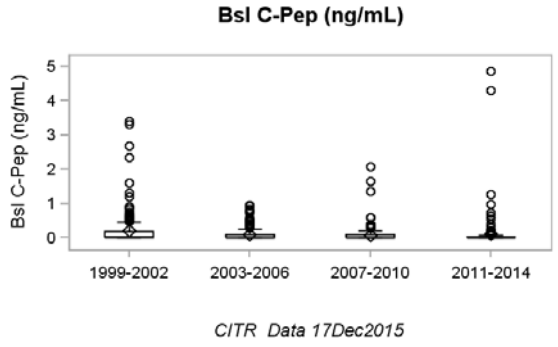
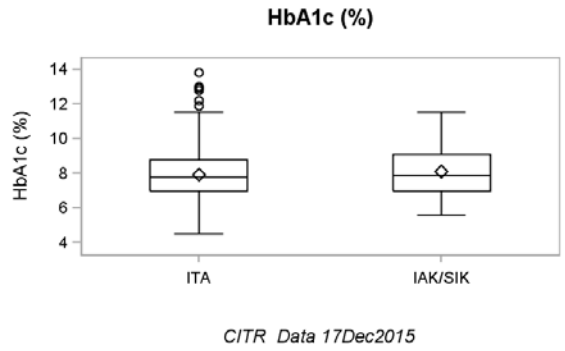
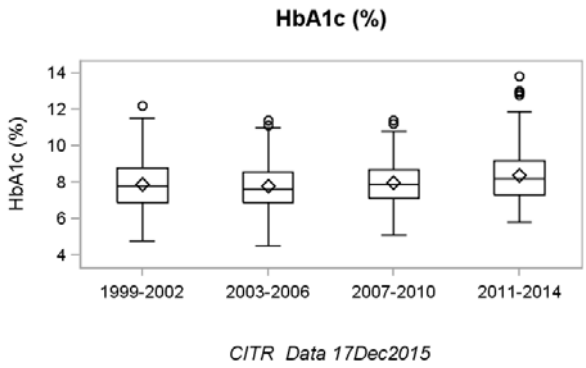
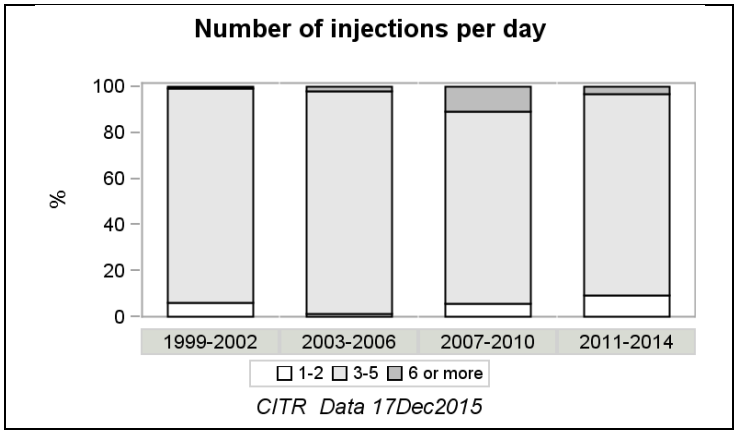
Significant Trends in Patient Characteristics from Table Above	
By ITA or IAK/SIK	**By ERA**
	
	

Exhibit 2 – 4
Recipient Diabetes Characteristics and Medical History

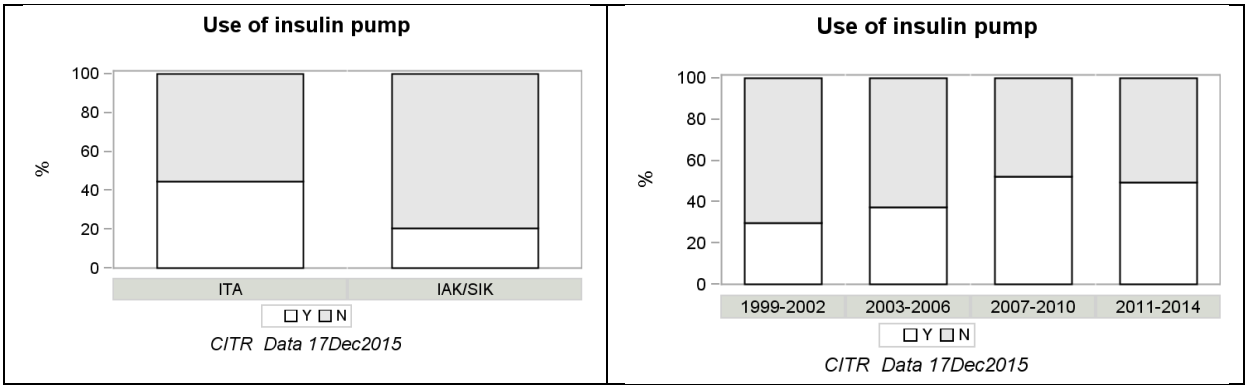
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Number of injections per day	**1-2**	11	4.1	4	4.9		7	6.1	2	1.3	3	5.5	3	9.1	
	3-5	252	93.0	75	91.5		107	93.0	145	96.7	46	83.6	29	87.9	
	6 or more	8	3.0	3	3.7		1	0.9	3	2.0	6	10.9	1	3.0	**

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Number of injections per day	Available	271	33.1	82	42.7	115	55.0	150	55.4	55	22.4	33	11.6
	Missing	548	66.9	110	57.3	94	45.0	121	44.6	191	77.6	252	88.4



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Use of insulin pump	**No**	311	55.4	106	79.7		134	70.2	167	62.8	67	47.9	49	50.5	
	Yes	250	44.6	27	20.3	***	57	29.8	99	37.2	73	52.1	48	49.5	***

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Use of insulin pump	Available	561	68.5	133	69.3	191	91.4	266	98.2	140	56.9	97	34.0
	Missing	258	31.5	59	30.7	18	8.6	5	1.8	106	43.1	188	66.0

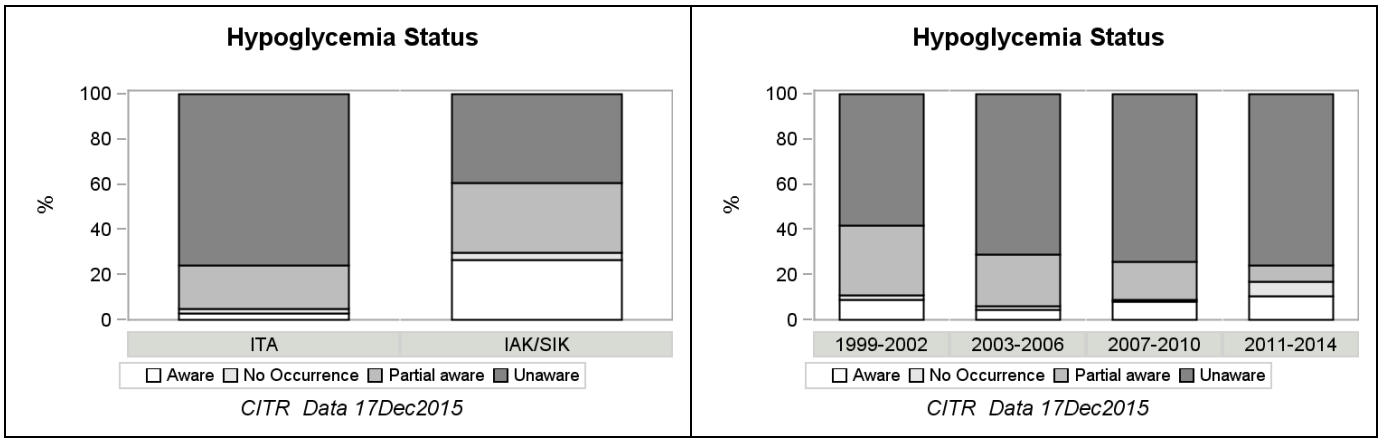


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

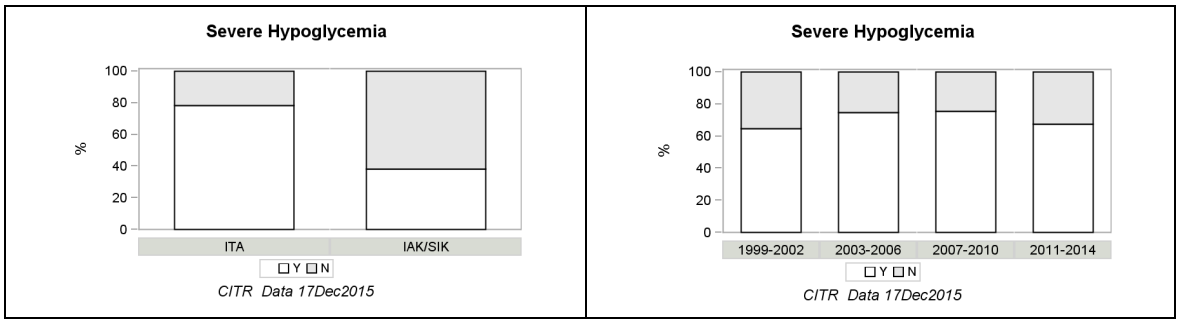
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hypoglycemia status	**Unaware**	403	76.0	49	39.2	***	101	58.4	186	71.0	93	74.4	72	75.8	***
	Partial aware	102	19.2	39	31.2		53	30.6	60	22.9	21	16.8	7	7.4	
	No Occurrence	11	2.1	4	3.2		4	2.3	4	1.5	1	0.8	6	6.3	
	Aware	14	2.6	33	26.4		15	8.7	12	4.6	10	8.0	10	10.5	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Hypoglycemia status	Available	530	64.7	125	65.1		173	82.8	262	96.7	125	50.8	95	33.3	
	Missing	289	35.3	67	34.9		36	17.2	9	3.3	121	49.2	190	66.7	



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Severe hypoglycemia	**No**	123	21.8	82	61.7	***	66	35.3	61	25.4	32	24.6	46	32.6	
	Yes	442	78.2	51	38.3		121	64.7	179	74.6	98	75.4	95	67.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Severe hypoglycemia	Available	565	69.0	133	69.3	187	89.5	240	88.6	130	52.8	141	49.5
	Missing	254	31.0	59	30.7	22	10.5	31	11.4	116	47.2	144	50.5

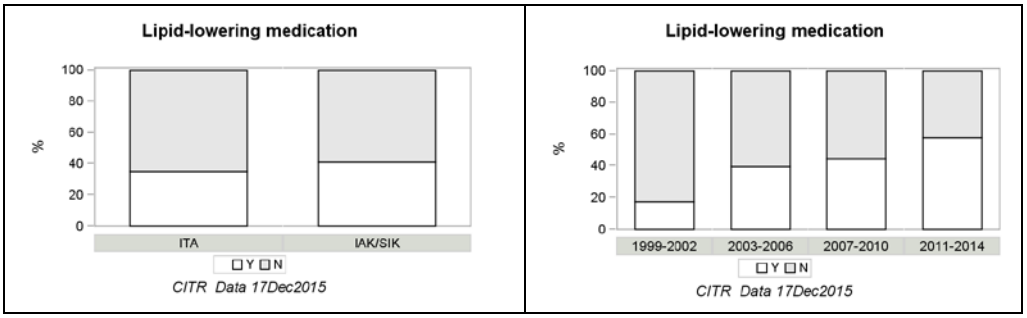


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

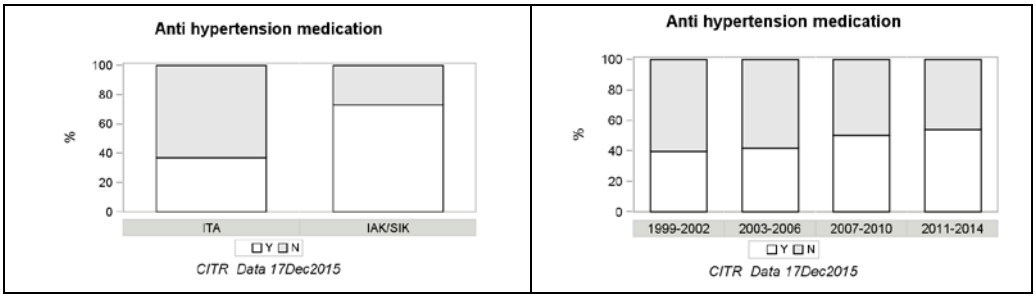
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Lipid lowering medication	**No**	339	64.9	78	59.1	***	153	82.7	160	60.8	72	55.4	32	42.1	*
	Yes	183	35.1	54	40.9		32	17.3	103	39.2	58	44.6	44	57.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Lipid lowering medication	Available	522	63.7	132	68.8	185	88.5	263	97.0	130	52.8	76	26.7
	Missing	297	36.3	60	31.3	24	11.5	8	3.0	116	47.2	209	73.3



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Anti hypertension medication	**No**	331	63.2	36	26.9		114	60.3	153	58.2	66	50.0	34	45.9	
	Yes	193	36.8	98	73.1	***	75	39.7	110	41.8	66	50.0	40	54.1	*

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Anti hypertension medication	Available	524	64.0	134	69.8	189	90.4	263	97.0	132	53.7	74	26.0
	Missing	295	36.0	58	30.2	20	9.6	8	3.0	114	46.3	211	74.0



* = p <.05; ** = p <.01; *** = p <.001

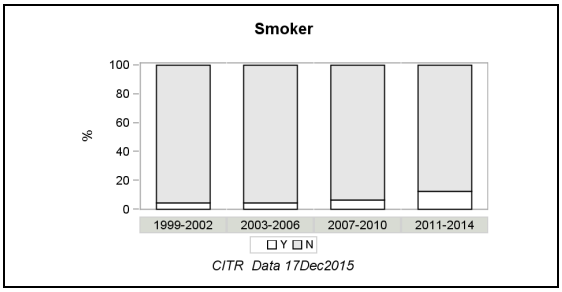
Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Anti-hyperglycemia medication	**No**	197	94.7	53	96.4		39	95.1	81	98.8	74	93.7	56	91.8	
	Yes	11	5.3	2	3.6		2	4.9	1	1.2	5	6.3	5	8.2	*

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Anti-hyperglycemia medication	Available	208	25.4	55	28.6	41	19.6	82	30.3	79	32.1	61	21.4
	Missing	611	74.6	137	71.4	168	80.4	189	69.7	167	67.9	224	78.6

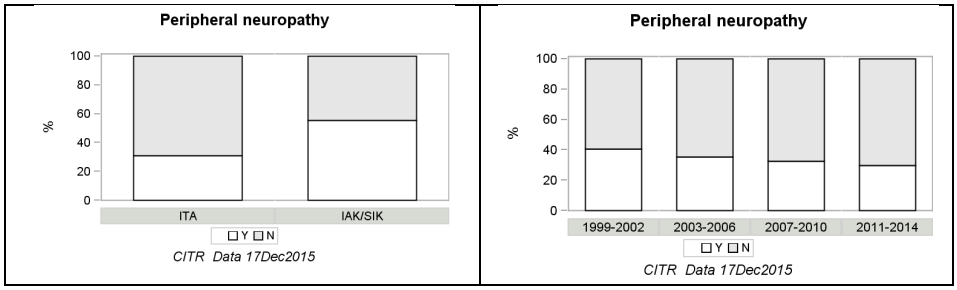
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Smoker	**No**	554	93.0	80	96.4		145	95.4	225	95.7	130	93.5	134	87.6	
	Yes	42	7.0	3	3.6		7	4.6	10	4.3	9	6.5	19	12.4	**

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Smoker	Available	596	72.8	83	43.2	152	72.7	235	86.7	139	56.5	153	53.7
	Missing	223	27.2	109	56.8	57	27.3	36	13.3	107	43.5	132	46.3



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Peripheral neuropathy	**No**	421	69.2	56	44.4		112	59.3	166	64.8	98	67.6	101	70.1	
	Yes	187	30.8	70	55.6	***	77	40.7	90	35.2	47	32.4	43	29.9	**

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Peripheral neuropathy	Available	608	74.2	126	65.6	189	90.4	256	94.5	145	58.9	144	50.5
	Missing	211	25.8	66	34.4	20	9.6	15	5.5	101	41.1	141	49.5

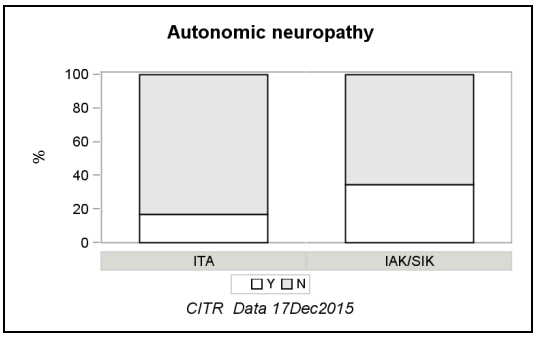


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Autonomic neuropathy	**No**	438	83.0	74	65.5		137	76.1	196	81.0	99	81.8	80	81.6	
	Yes	90	17.0	39	34.5	***	43	23.9	46	19.0	22	18.2	18	18.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Autonomic neuropathy	**Available**	528	64.5	113	58.9	180	86.1	242	89.3	121	49.2	98	34.4
	Missing	291	35.5	79	41.1	29	13.9	29	10.7	125	50.8	187	65.6



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CAD history	**No**	558	92.1	106	80.3		178	93.7	232	88.9	124	86.7	130	90.3	
	Yes	48	7.9	26	19.7	***	12	6.3	29	11.1	19	13.3	14	9.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CAD history	**Available**	606	74.0	132	68.8	190	90.9	261	96.3	143	58.1	144	50.5
	Missing	213	26.0	60	31.3	19	9.1	10	3.7	103	41.9	141	49.5

* = p <.05; ** = p <.01; *** = p <.001

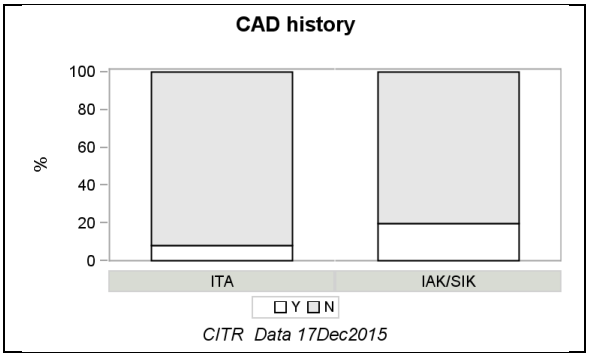
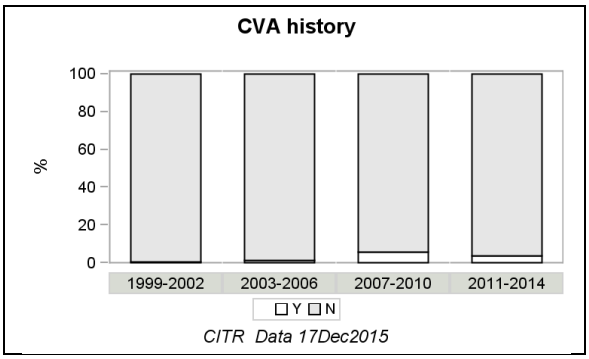


Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CVA history	**No**	587	98.2	119	95.2		185	99.5	250	98.8	133	94.3	138	96.5	
	Yes	11	1.8	6	4.8		1	0.5	3	1.2	8	5.7	5	3.5	*

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CVA history	**Available**	598	73.0	125	65.1	186	89.0	253	93.4	141	57.3	143	50.2
	Missing	221	27.0	67	34.9	23	11.0	18	6.6	105	42.7	142	49.8



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
PVD history	**No**	504	97.5	84	81.6		162	95.3	234	94.7	110	94.0	82	95.3	
	Yes	13	2.5	19	18.4	***	8	4.7	13	5.3	7	6.0	4	4.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
PVD history	**Available**	517	63.1	103	53.6	170	81.3	247	91.1	117	47.6	86	30.2
	Missing	302	36.9	89	46.4	39	18.7	24	8.9	129	52.4	199	69.8

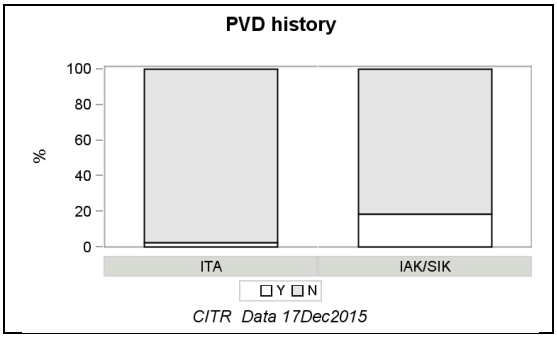
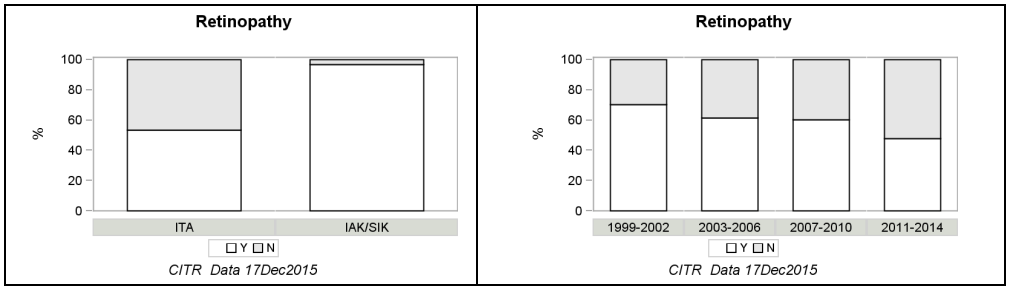


Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Retinopathy	**No**	246	46.8	4	3.1	***	57	29.7	97	38.6	50	39.7	46	52.3	***
	Yes	280	53.2	127	96.9		135	70.3	154	61.4	76	60.3	42	47.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Retinopathy	Available	526	64.2	131	68.2	192	91.9	251	92.6	126	51.2	88	30.9
	Missing	293	35.8	61	31.8	17	8.1	20	7.4	120	48.8	197	69.1

* = p <.05; ** = p <.01; *** = p <.001



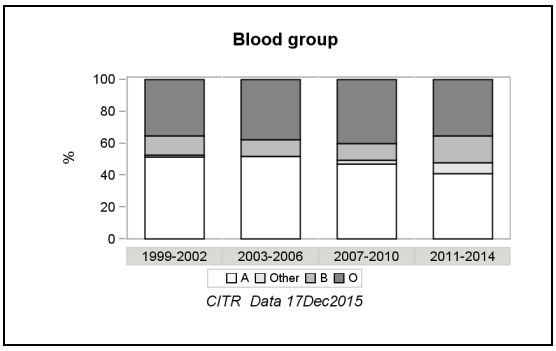
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Macular edema	**No**	453	97.8	73	92.4		138	97.2	209	96.8	96	97.0	83	97.6	
	Yes	10	2.2	6	7.6		4	2.8	7	3.2	3	3.0	2	2.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Macular edema	Available	463	56.5	79	41.1	142	67.9	216	79.7	99	40.2	85	29.8
	Missing	356	43.5	113	58.9	67	32.1	55	20.3	147	59.8	200	70.2

Exhibit 2 – 4 *(continued)*
Recipient Diabetes Characteristics and Medical History

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Blood group	**A**	336	47.2	89	50.9		103	51.5	133	52.0	97	46.9	92	41.1	***
	O	270	37.9	60	34.3		71	35.5	97	37.9	83	40.1	79	35.3	
	B	89	12.5	21	12.0		24	12.0	26	10.2	22	10.6	38	17.0	
	AB	16	2.2	4	2.3		1	0.5		0.0	4	1.9	15	6.7	
	A1		0.0	1	0.6		1	0.5		0.0		0.0		0.0	
	A2	1	0.1		0.0			0.0		0.0	1	0.5		0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Blood group	**Available**	712	86.9	175	91.1		200	95.7	256	94.5	207	84.1	224	78.6	
	Missing	107	13.1	17	8.9		9	4.3	15	5.5	39	15.9	61	21.4	

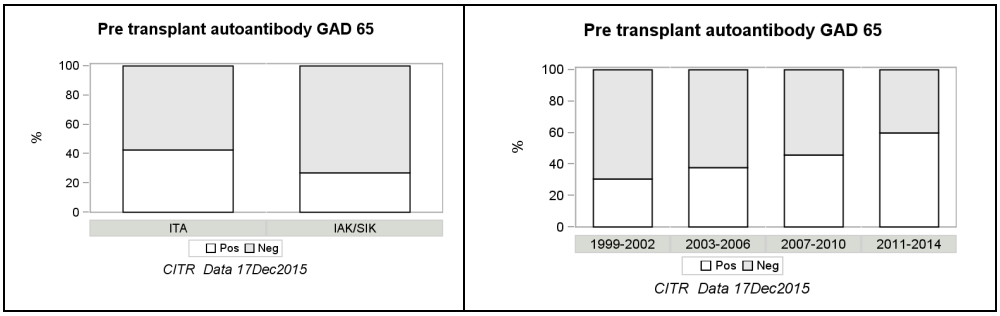


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 5
Recipient Autoantibody and Sensitization at First Infusion

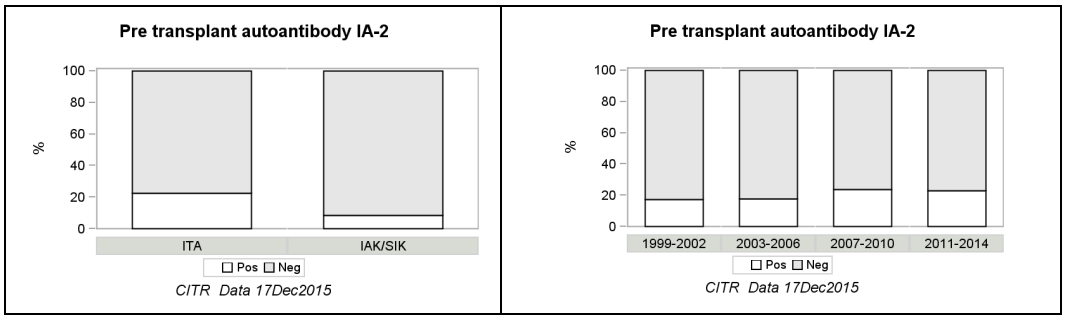
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody GAD 65	**Negative**	228	57.6	70	72.9	*	107	69.5	115	62.2	56	54.4	20	40.0	***
	Positive	168	42.4	26	27.1		47	30.5	70	37.8	47	45.6	30	60.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Pre transplant autoantibody GAD 65	Available	396	48.4	96	50.0		154	73.7	185	68.3	103	41.9	50	17.5	
	Missing	423	51.6	96	50.0		55	26.3	86	31.7	143	58.1	235	82.5	



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody IA-2	**Negative**	456	77.7	127	91.4		166	82.6	221	82.2	122	76.3	74	77.1	
	Positive	131	22.3	12	8.6	**	35	17.4	48	17.8	38	23.8	22	22.9	*

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Pre transplant autoantibody IA-2	Available	587	71.7	139	72.4		201	96.2	269	99.3	160	65.0	96	33.7	
	Missing	232	28.3	53	27.6		8	3.8	2	0.7	86	35.0	189	66.3	

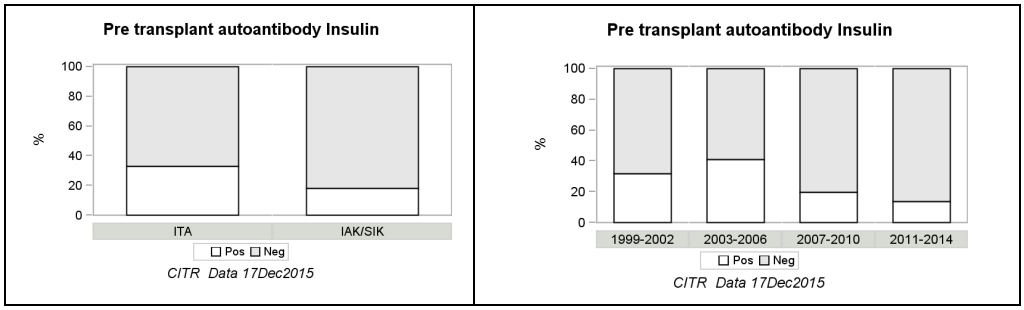


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 5 *(continued)*
Recipient Autoantibody and Sensitization at First Infusion

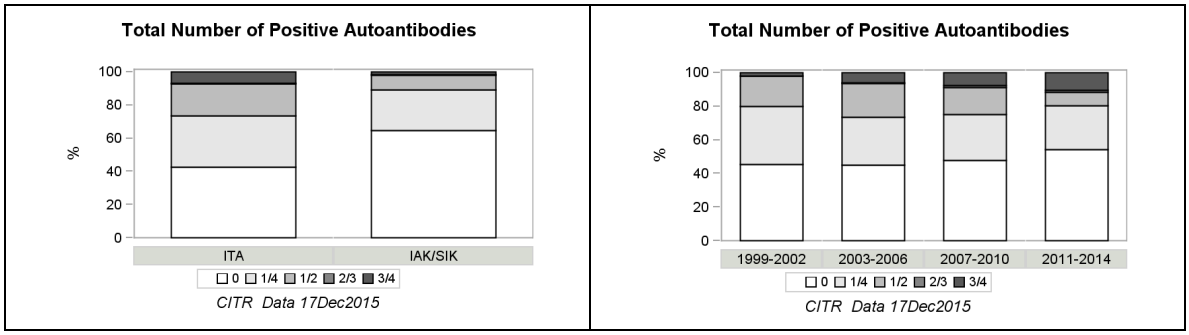
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody Insulin	**Negative**	394	67.0	114	82.0		137	68.2	159	59.1	129	80.1	83	86.5	
	Positive	194	33.0	25	18.0	**	64	31.8	110	40.9	32	19.9	13	13.5	***

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Pre transplant autoantibody Insulin	Available	588	71.8	139	72.4		201	96.2	269	99.3	161	65.4	96	33.7	
	Missing	231	28.2	53	27.6		8	3.8	2	0.7	85	34.6	189	66.3	



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Total Number of Positive Autoantibodies	**0**	251	42.7	90	64.7	***	91	45.3	121	45.0	77	47.8	52	54.2	**
	1/4	182	31.0	34	24.5		70	34.8	77	28.6	44	27.3	25	26.0	
	1/2	112	19.0	12	8.6		36	17.9	54	20.1	26	16.1	8	8.3	
	2/3	3	0.5	1	0.7			0.0	1	0.4	2	1.2	1	1.0	
	3/4	40	6.8	2	1.4		4	2.0	16	5.9	12	7.5	10	10.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Total Number of Positive Autoantibodies	Available	588	71.8	139	72.4	201	96.2	269	99.3	161	65.4	96	33.7
	Missing	231	28.2	53	27.6	8	3.8	2	0.7	85	34.6	189	66.3

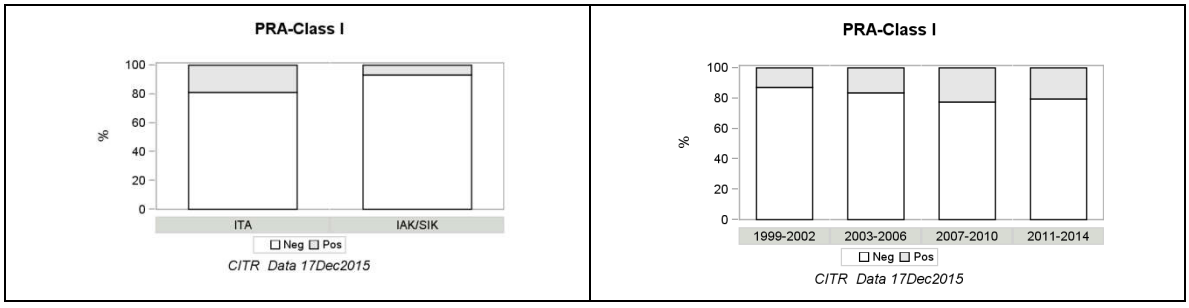


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 5 *(continued)*
Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
PRA-Class I	Neg	313	81.1	70	93.3	*	116	87.2	159	83.7	65	77.4	43	79.6	*
	Pos	73	18.9	5	6.7		17	12.8	31	16.3	19	22.6	11	20.4	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
PRA-Class I	Available	386	47.1	75	39.1		133	63.6	190	70.1	84	34.1	54	18.9	
	Missing	433	52.9	117	60.9		76	36.4	81	29.9	162	65.9	231	81.1	



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
PRA-Class II	Neg	232	87.2	33	97.1	*	72	96.0	94	89.5	56	83.6	43	81.1	
	Pos	32	12.0		0.0		3	4.0	11	10.5	9	13.4	9	17.0	
	Equ	2	0.8	1	2.9			0.0		0.0	2	3.0	1	1.9	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
PRA-Class II	Available	266	32.5	34	17.7		75	35.9	105	38.7	67	27.2	53	18.6	
	Missing	553	67.5	158	82.3		134	64.1	166	61.3	179	72.8	232	81.4	

* = p <.05; ** = p <.01; *** = p <.001

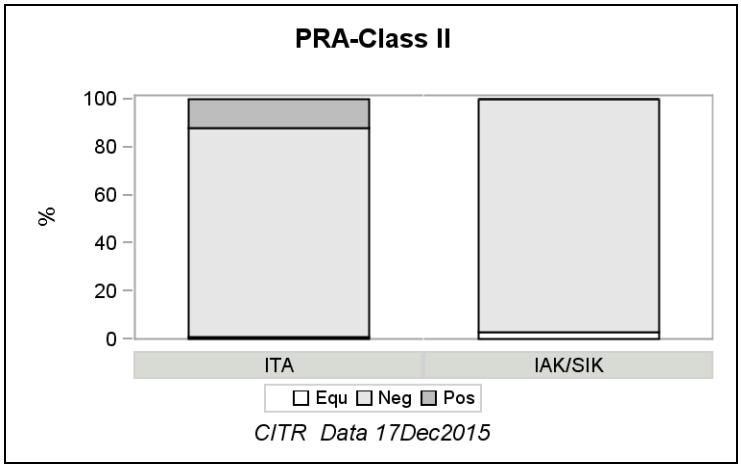


Exhibit 2 – 6
Recipient Infectious Disease Testing at First Infusion

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HIV	NEG	645	100.0	106	99.1		179	100.0	246	100.0	173	99.4	153	100.0	
	POS	-	0.0	1	0.9		-	0.0	-	0.0	1	0.6	-	0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HIV	Available	645	78.8	107	55.7		179	85.6	246	90.8	174	70.7	153	53.7	
	Missing	174	21.2	85	44.3		30	14.4	25	9.2	72	29.3	132	46.3	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CMV-IgG	NEG	363	55.5	44	38.6		94	51.9	134	54.0	99	54.1	80	51.3	
	POS	291	44.5	70	61.4		87	48.1	114	46.0	84	45.9	76	48.7	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
CMV-IgG	Available	654	79.9	114	59.4		181	86.6	248	91.5	183	74.4	156	54.7	
	Missing	165	20.1	78	40.6		28	13.4	23	8.5	63	25.6	129	45.3	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CMV-IgM	NEG	440	91.5	66	85.7		108	94.7	163	96.4	119	92.2	116	79.5	
	POS	41	8.5	11	14.3		6	5.3	6	3.6	10	7.8	30	20.5	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
CMV-IgM	Available	481	58.7	77	40.1		114	54.5	169	62.4	129	52.4	146	51.2	
	Missing	338	41.3	115	59.9		95	45.5	102	37.6	117	47.6	139	48.8	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hepatitis B Core	NEG	497	97.6	73	93.6		128	98.5	204	98.1	142	95.9	96	95.0	
	POS	12	2.4	5	6.4		2	1.5	4	1.9	6	4.1	5	5.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hepatitis B Core	Available	509	62.1	78	40.6		130	62.2	208	76.8	148	60.2	101	35.4	
	Missing	310	37.9	114	59.4		79	37.8	63	23.2	98	39.8	184	64.6	

Exhibit 2 – 6 *(continued)*
Recipient Infectious Disease Testing at First Infusion

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hepatitis B Surface	**NEG**	152	79.2	19	57.6		25	71.4	34	82.9	53	67.1	59	84.3	
	POS	40	20.8	14	42.4	**	10	28.6	7	17.1	26	32.9	11	15.7	*

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hepatitis B Surface	**Available**	192	23.4	33	17.2		35	16.7	41	15.1	79	32.1	70	24.6	
	Missing	627	76.6	159	82.8		174	83.3	230	84.9	167	67.9	215	75.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HCV	**NEG**	623	99.2	112	95.7		171	97.7	247	99.6	171	99.4	146	97.3	
	POS	5	0.8	5	4.3		4	2.3	1	0.4	1	0.6	4	2.7	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HCV	**Available**	628	76.7	117	60.9	745.0	175	83.7	248	91.5	172	69.9	150	52.6	745.0
	Missing	191	23.3	75	39.1	266.0	34	16.3	23	8.5	74	30.1	135	47.4	266.0

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
EBV-IgG	**NEG**	64	10.8	4	3.6		11	6.4	17	7.5	20	12.7	20	13.6	
	POS	530	89.2	107	96.4		162	93.6	211	92.5	137	87.3	127	86.4	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
EBV-IgG	**Available**	594	72.5	111	57.8		173	82.8	228	84.1	157	63.8	147	51.6	
	Missing	225	27.5	81	42.2		36	17.2	43	15.9	89	36.2	138	48.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
EBV-IgM	**NEG**	325	77.2	69	90.8		84	79.2	131	88.5	86	86.0	93	65.0	
	POS	96	22.8	7	9.2	**	22	20.8	17	11.5	14	14.0	50	35.0	**

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
EBV-IgM	**Available**	421	51.4	76	39.6		106	50.7	148	54.6	100	40.7	143	50.2	
	Missing	398	48.6	116	60.4		103	49.3	123	45.4	146	59.3	142	49.8	

Exhibit 2 – 7
Recipient Characteristics at First Infusion According to Total Number of Infusions Received

	ITA									IAK/SIK								
	Total Number of Infusions Received									Total Number of Infusions Received								
	One Infusion			Two Infusions			>= Three Infusions			One Infusion			Two Infusions			>= Three Infusions		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Age (yrs)	227	46.0	0.7	409	47.2	0.5	183	44.1	0.7	67	45.9	1.2	92	46.8	0.9	33	43.8	1.3
Duration of Diabetes (yrs)	173	29.0	0.9	342	29.8	0.6	147	26.7	0.9	48	33.2	1.6	67	32.9	1.1	26	32.1	1.2
Weight (kg)	190	65.4	0.8	372	67.7	0.6	170	69.2	0.8	52	61.1	1.4	81	63.4	1.1	31	64.4	1.8
Body Mass Index (kg/m2)	164	23.2	0.2	310	24.0	0.2	158	24.1	0.2	50	22.4	0.4	78	22.8	0.3	31	22.9	0.6
Daily insulin requirement (units)	145	34.5	1.1	330	37.0	0.8	167	40.9	1.2	42	37.6	2.1	67	37.3	1.4	28	33.2	2.4
Average daily insulin / kg recipient body weight	137	0.5	0.0	314	0.5	0.0	161	0.6	0.0	39	0.6	0.0	67	0.6	0.0	28	0.5	0.0
Duration of intensive insulin therapy (yrs)	64	17.2	2.0	168	21.9	1.1	94	19.7	1.3	12	28.4	4.1	10	23.5	4.6	2	4.0	3.1
Fasting plasma glucose (mg/dL)	152	159.4	6.9	295	173.5	5.1	154	179.7	6.9	38	175.6	14.0	69	169.2	10.3	27	179.4	23.5
Basal C-Peptide (ng/mL)	153	0.1	0.0	305	0.1	0.0	157	0.1	0.0	51	0.3	0.1	74	0.2	0.1	30	0.1	0.0
HbA1C (%)	151	7.9	0.1	319	7.9	0.1	166	7.9	0.1	45	8.1	0.2	69	8.3	0.2	28	7.7	0.2

Exhibit 2 – 8
Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - GAD 65	**Negative**	52	60.5	120	61.5	56	48.7	26	86.7	32	68.1	12	63.2
	Positive	34	39.5	75	38.5	59	51.3	4	13.3	15	31.9	7	36.8

Data completeness		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - GAD 65	**Missing**	141	62.1	214	52.3	68	37.2	37	55.2	45	48.9	14	42.4
	Available	86	37.9	195	47.7	115	62.8	30	44.8	47	51.1	19	57.6

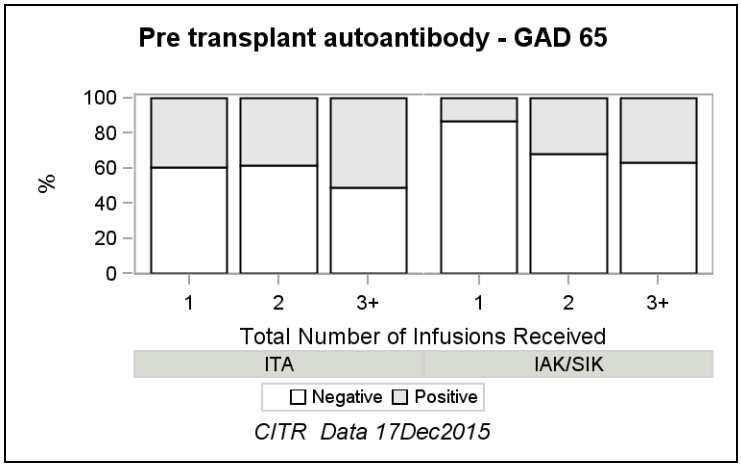


Exhibit 2 – 8 *(continued)*
Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - IA-2	**Negative**	112	84.8	228	79.4	116	69.0	38	86.4	63	95.5	26	89.7
	Positive	20	15.2	59	20.6	52	31.0	6	13.6	3	4.5	3	10.3

Data completeness		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - IA-2	**Missing**	95	41.9	122	29.8	15	8.2	23	34.3	26	28.3	4	12.1
	Available	132	58.1	287	70.2	168	91.8	44	65.7	66	71.7	29	87.9

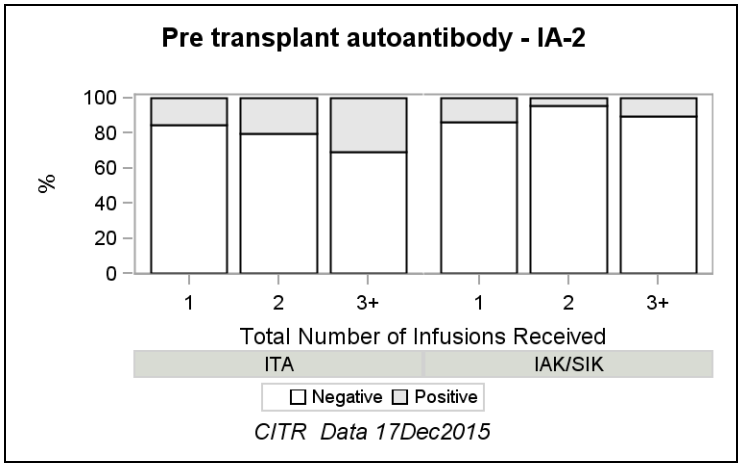


Exhibit 2 – 8 *(continued)*
Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - Insulin	**Negative**	97	73.5	191	66.3	106	63.1	36	81.8	53	80.3	25	86.2
	Positive	35	26.5	97	33.7	62	36.9	8	18.2	13	19.7	4	13.8

Data completeness		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - Insulin	**Missing**	95	41.9	121	29.6	15	8.2	23	34.3	26	28.3	4	12.1
	Available	132	58.1	288	70.4	168	91.8	44	65.7	66	71.7	29	87.9

Pre transplant autoantibody - Insulin

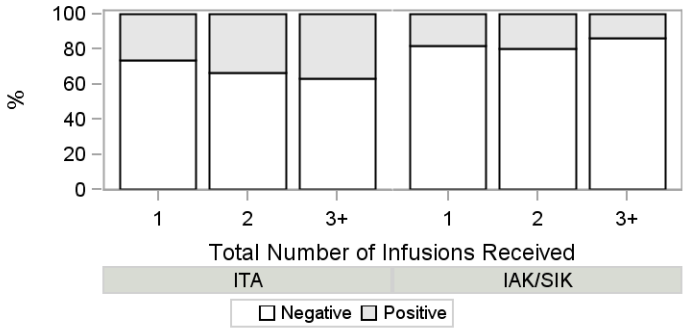


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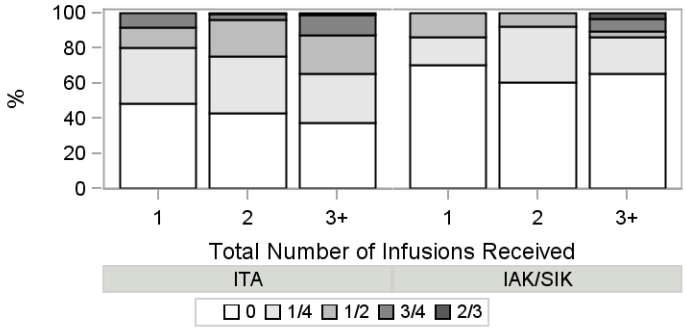
Exhibit 2 – 8 *(continued)*
Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Total Number of Positive Autoantibodies	**0**	64	48.5	124	43.1	63	37.5	31	70.5	40	60.6	19	65.5
	1/4	42	31.8	93	32.3	47	28.0	7	15.9	21	31.8	6	20.7
	1/2	15	11.4	60	20.8	37	22.0	6	13.6	5	7.6	1	3.4
	2/3	-	-	1	0.3	2	1.2	-	-	-	-	1	3.4
	3/4	11	8.3	10	3.5	19	11.3	-	-	-	-	2	6.9

Data completeness		ITA						IAK/SIK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Total Number of Positive Autoantibodies	**Missing**	95	41.9	121	29.6	15	8.2	23	34.3	26	28.3	4	12.1
	Available	132	58.1	288	70.4	168	91.8	44	65.7	66	71.7	29	87.9

Total Number of Positive Autoantibodies



CITR Data 17Dec2015

Exhibit 2 – 9
Recipient Laboratory Values at First Infusion

	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
HbA1C (%)	636	7.9	0.1	142	8.1	0.1		195	7.9	0.1	264	7.8	0.1	163	8.0	0.1	156	8.4	0.1	***
Basal C-Peptide (ng/mL)	615	0.1	0.0	155	0.2	0.1	***	186	0.2	0.0	257	0.1	0.0	182	0.1	0.0	145	0.1	0.0	*
Fasting blood glucose (mg/dL)	601	171.5	3.5	134	173.1	8.1		170	182.2	7.2	250	173.7	5.8	173	153.5	5.6	142	178.4	7.2	
ALT (U/L)	652	23.6	0.5	137	24.3	1.2		151	22.0	1.0	244	24.2	0.7	186	24.5	1.1	208	23.7	1.0	
AST (U/L)	601	26.0	0.7	137	25.6	1.1		157	23.4	0.7	250	26.2	0.7	169	28.2	1.9	162	25.8	1.2	
Alkaline phosphatase (U/L)	529	81.3	1.9	105	126.2	8.5	***	151	92.6	4.7	234	98.9	4.5	147	79.6	3.6	102	73.1	2.9	***
Total bilirubin (mg/dL)	545	0.7	0.0	134	1.2	0.2	***	152	0.6	0.0	223	0.6	0.0	154	0.8	0.1	150	1.1	0.2	***
Total cholesterol (mg/dL)	558	172.2	1.6	120	176.9	3.9		166	181.3	2.8	246	173.8	2.1	149	169.5	3.5	117	164.3	3.9	***
HDL (mg/dL)	536	65.0	0.8	108	63.6	1.8		159	65.3	1.3	237	64.9	1.2	133	65.3	1.7	115	63.2	1.9	
LDL (mg/dL)	523	92.5	1.3	87	92.4	3.4		137	98.5	2.5	233	94.9	1.7	137	88.6	2.7	103	84.0	3.2	***
Triglycerides (mg/dL)	559	53.5	1.5	120	67.7	3.9	***	166	55.8	2.8	246	56.7	2.5	150	51.8	2.2	117	60.3	3.5	
eGFR-CKD (mL/min/1.73m2)	673	90.6	0.8	142	58.6	2.6	***	180	82.1	2.1	254	84.3	1.6	192	87.3	1.9	189	86.5	1.8	0.06

* = p<.05; ** = p<.01; *** = p<.001

Recipients' HbA1C increased over the decade.

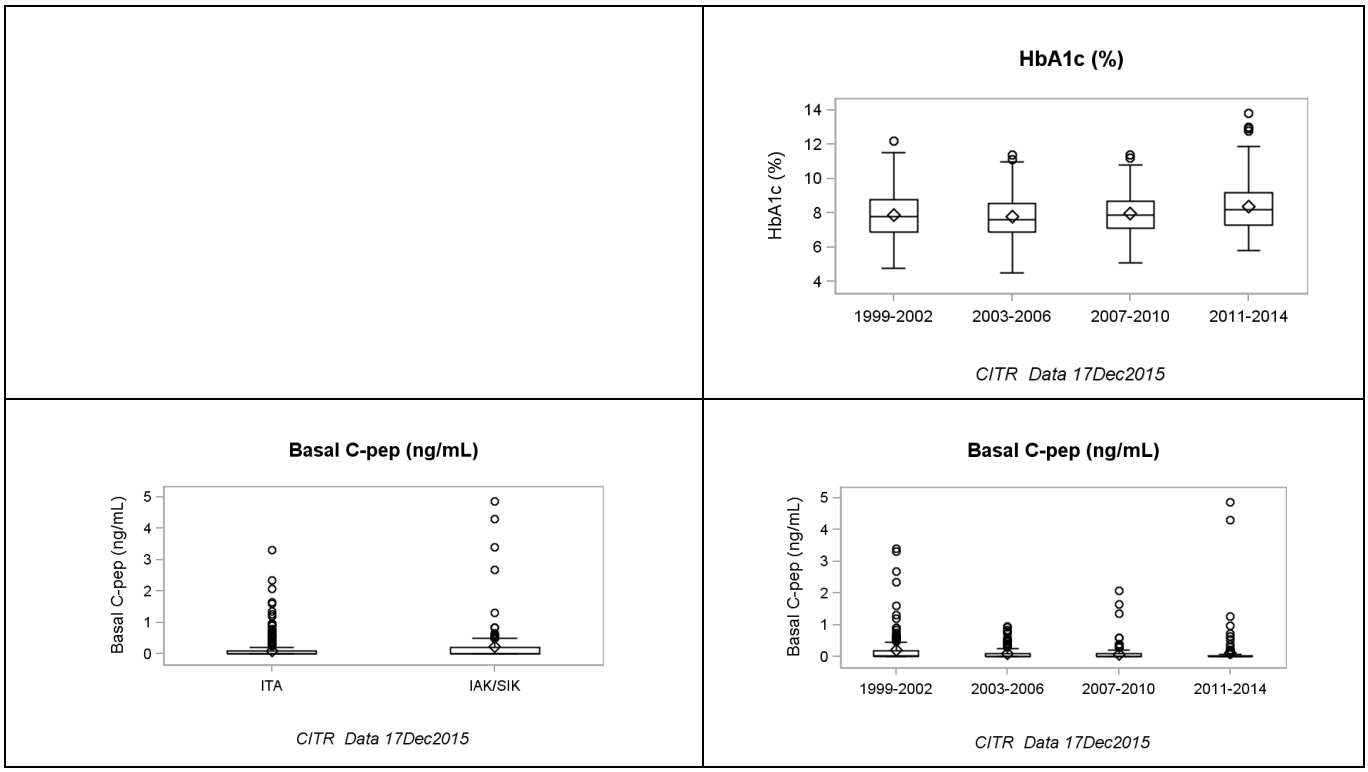
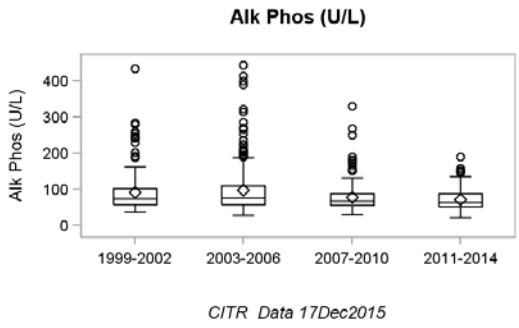
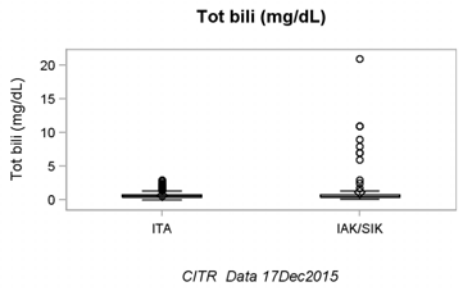
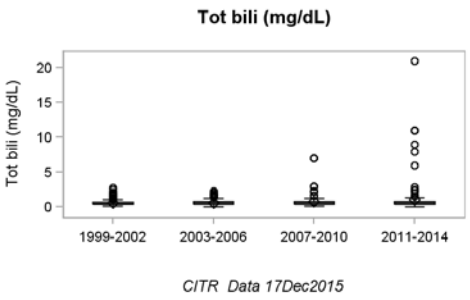
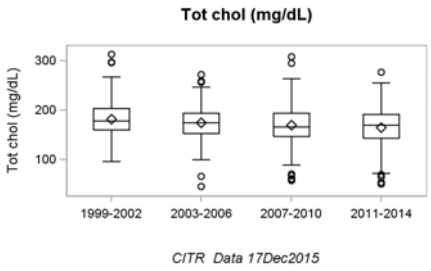


Exhibit 2 – 9 *(continued)*
Recipient Laboratory Values at First Infusion









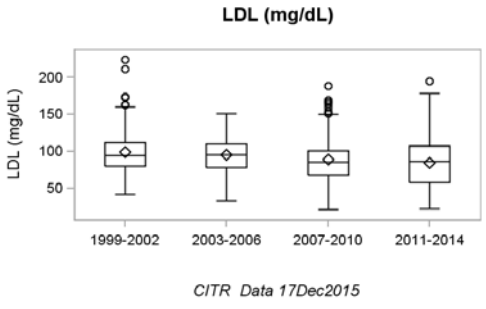
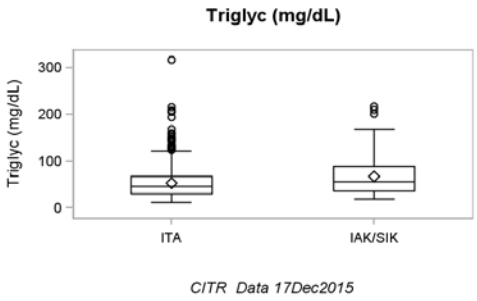


Exhibit 2 – 9 *(continued)*
Recipient Laboratory Values at First Infusion



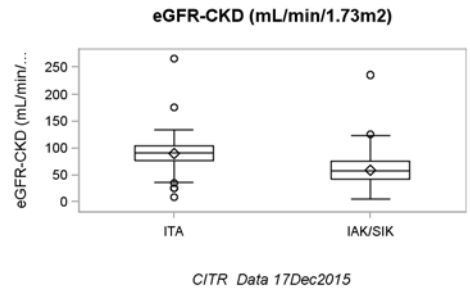


Exhibit 2 – 10
Donor Demographics (per Infusion)

	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014			
	N	Mean	StdErr	N	Mean	StdErr	p	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	p
Age (yrs)	1124	43.8	0.3	232	44.3	0.8		296	43.8	0.7	401	43.5	0.6	360	44.1	0.6	299	44.3	0.6	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Gender	**Female**	477	37.9	99	36.1		136	37.2	189	38.7	144	38.0	107	35.8	
	Mixed	59	4.7	13	4.7		16	4.4	23	4.7	30	7.9	3	1.0	
	Male	723	57.4	162	59.1		214	58.5	277	56.6	205	54.1	189	63.2	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Gender	Available	1259	78.9	274	79.0	366	84.3	489	85.0	379	84.2	299	61.9
	Missing	336	21.1	73	21.0	68	15.7	86	15.0	71	15.8	184	38.1

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Race	**White**	761	88.8	115	87.8		223	92.1	246	86.0	207	88.8	200	88.1	
	Mixed	4	0.5		0.0			0.0	3	1.0	1	0.4		0.0	
	Non-white	92	10.7	16	12.2		19	7.9	37	12.9	25	10.7	27	11.9	

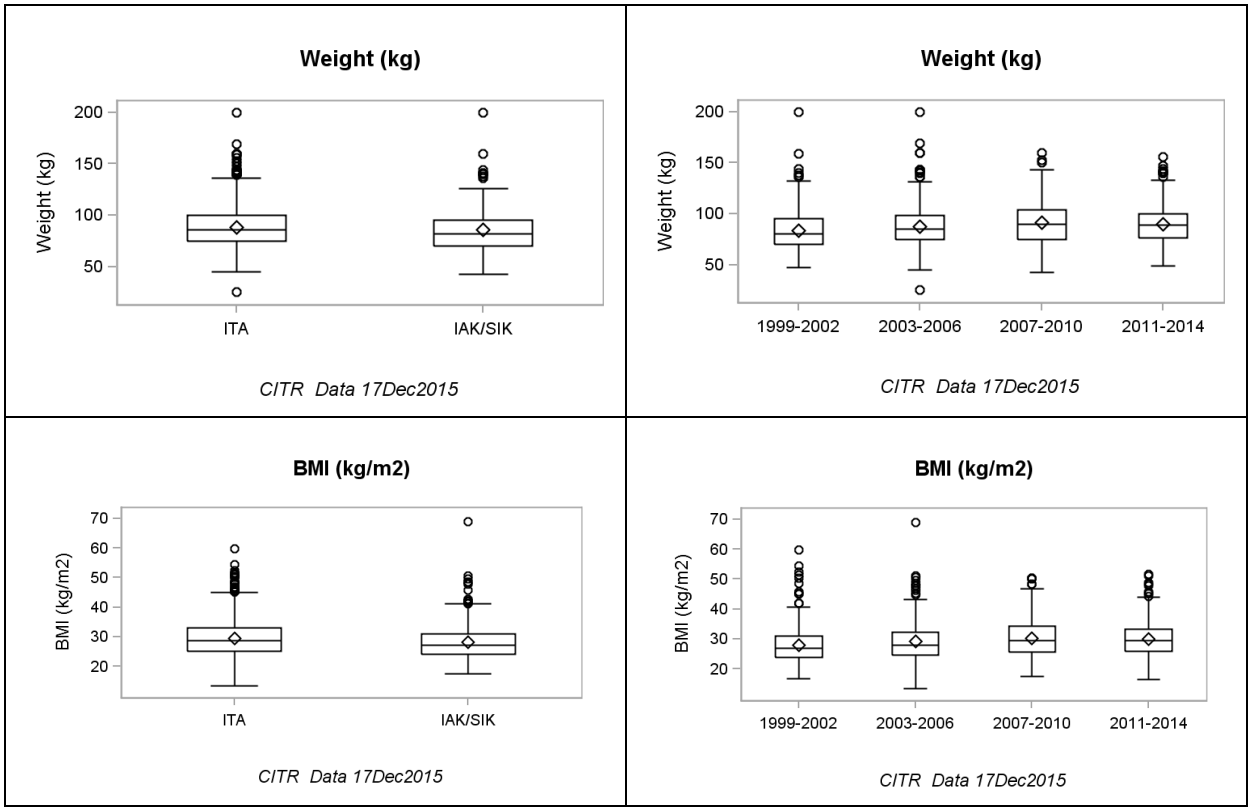
Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Race	Available	857	53.7	131	37.8	242	55.8	286	49.7	233	51.8	227	47.0
	Missing	738	46.3	216	62.2	192	44.2	289	50.3	217	48.2	256	53.0

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Ethnicity	**Non-Hispanic**	204	80.6	36	78.3		82	98.8	53	72.6	66	75.9	39	69.6	
	Hispanic	49	19.4	10	21.7		1	1.2	20	27.4	21	24.1	17	30.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Ethnicity	Missing	1342	84.1	301	86.7	351	80.9	502	87.3	363	80.7	427	88.4
	Available	253	15.9	46	13.3	83	19.1	73	12.7	87	19.3	56	11.6

Exhibit 2 – 11
Donor Characteristics

	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Donor age (yrs)	1124	43.8	0.3	232	44.3	0.8		296	43.8	0.7	401	43.5	0.6	360	44.1	0.6	299	44.3	0.6	
Weight (kg)	1382	88.5	0.5	275	85.7	1.3	*	366	83.6	1.1	497	87.6	0.9	408	90.9	1.0	386	89.7	1.0	***
Height (cm)	1380	173.0	0.3	275	173.9	0.5		364	172.9	0.5	497	173.5	0.4	408	173.1	0.5	386	172.8	0.5	
Body Mass Index(kg/m2)	1380	29.5	0.2	275	28.3	0.4	**	364	27.9	0.3	497	29.1	0.3	408	30.2	0.3	386	30.0	0.3	***



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Donor Blood Type	**O**	730	53.3	152	55.1		183	49.9	270	54.5	223	56.0	206	53.4	
	A	569	41.5	114	41.3		173	47.1	203	41.0	163	41.0	144	37.3	
	Other	71	5.2	10	3.6		11	3.0	22	4.4	12	3.0	36	9.3	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Donor Blood Type	**Available**	1370	85.9	276	79.5	367	84.6	495	86.1	398	88.4	386	79.9
	Missing	225	14.1	71	20.5	67	15.4	80	13.9	52	11.6	97	20.1

Exhibit 2 – 11 *(continued)*
Donor Characteristics

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hx Diabetes	**No**	1293	99.7	220	100.0		327	99.7	461	99.8	376	100.0	349	99.4	
	Yes	4	0.3		0.0		1	0.3	1	0.2		0.0	2	0.6	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Hx Diabetes	**Available**	1297	81.3	220	63.4	328	75.6	462	80.3	376	83.6	351	72.7
	Missing	298	18.7	127	36.6	106	24.4	113	19.7	74	16.4	132	27.3

* = p<.05; ** = p<.01; *** = p<.001

Over the decade, donor weight and BMI have increased notably.

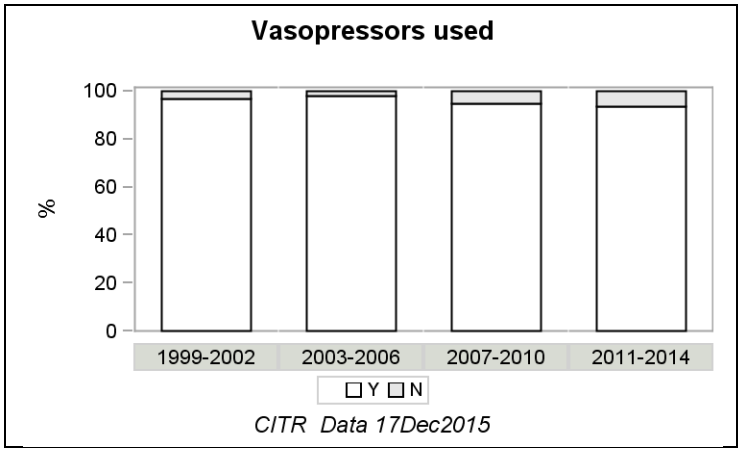
Exhibit 2 – 12
Characteristics of Hospitalization and Organ Procurement

		ITA		IAK/SIK			2003-2006		2007-2010		2011-2014		1999-2002		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Cause of death	**CVA**	777	59.1	155	65.7		285	60.1	238	61.7	209	59.2	200	59.3	
	Trauma	367	27.9	57	24.2		137	28.9	107	27.7	88	24.9	92	27.3	
	Other	170	12.9	24	10.2		52	11.0	41	10.6	56	15.9	45	13.4	

Data completeness		ITA		IAK/SIK			2003-2006		2011-2014		2007-2010		1999-2002		
		N	%	N	%		N	%	N	%	N	%	N	%	
Cause of death	**Available**	1314	82.4	236	68.0		474	82.4	353	73.1	386	85.8	337	77.6	
	Missing	281	17.6	111	32.0		101	17.6	130	26.9	64	14.2	97	22.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Vasopressors used	**No**	52	4.4	4	2.0		10	3.3	10	2.2	17	5.1	19	6.5	*
	Yes	1140	95.6	197	98.0		295	96.7	453	97.8	314	94.9	275	93.5	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Vasopressors used	**Available**	1192	74.7	201	57.9	305	70.3	463	80.5	331	73.6	294	60.9
	Missing	403	25.3	146	42.1	129	29.7	112	19.5	119	26.4	189	39.1



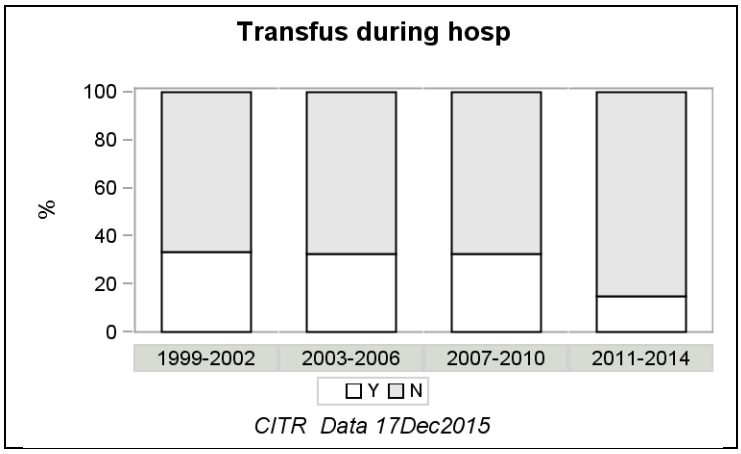
* = p <.05; ** = p <.01; *** = p <.001

Over the eras, time from admission to brain death has increased appreciably.

Exhibit 2 – 12 *(continued)*
Characteristics of Hospitalization and Organ Procurement

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Transfusions during hospitalization	**No**	596	69.5	117	71.3		178	66.7	282	67.5	131	67.5	122	85.3	
	Yes	262	30.5	47	28.7		89	33.3	136	32.5	63	32.5	21	14.7	***

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Transfusions during hospitalization	**Missing**	737	46.2	183	52.7	167	38.5	157	27.3	256	56.9	340	70.4
	Available	858	53.8	164	47.3	267	61.5	418	72.7	194	43.1	143	29.6



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Transfusions intraoperatively	**No**	611	93.9	114	93.4		210	91.7	338	94.7	135	95.7	42	91.3	
	Yes	40	6.1	8	6.6		19	8.3	19	5.3	6	4.3	4	8.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Transfusions intraoperatively	**Missing**	944	59.2	225	64.8	205	47.2	218	37.9	309	68.7	437	90.5
	Available	651	40.8	122	35.2	229	52.8	357	62.1	141	31.3	46	9.5

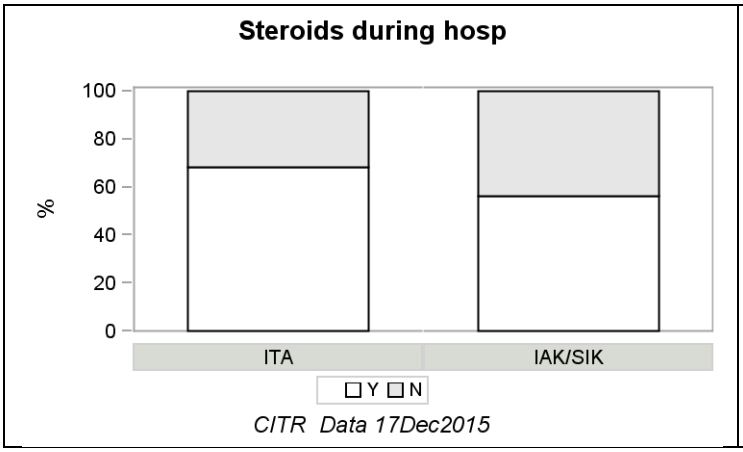
* = p <.05; ** = p <.01; *** = p <.001

Over the eras, use of steroids in the donor has increased appreciably.

Exhibit 2 – 12 *(continued)*
Characteristics of Hospitalization and Organ Procurement

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Steroids given to donor during hospitalization	**No**	252	31.5	60	43.8		52	29.9	135	41.5	78	29.2	47	27.6	
	Yes	547	68.5	77	56.2	**	122	70.1	190	58.5	189	70.8	123	72.4	**

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Steroids given to donor during hospitalization	**Available**	799	50.1	137	39.5	174	40.1	325	56.5	267	59.3	170	35.2
	Missing	796	49.9	210	60.5	260	59.9	250	43.5	183	40.7	313	64.8



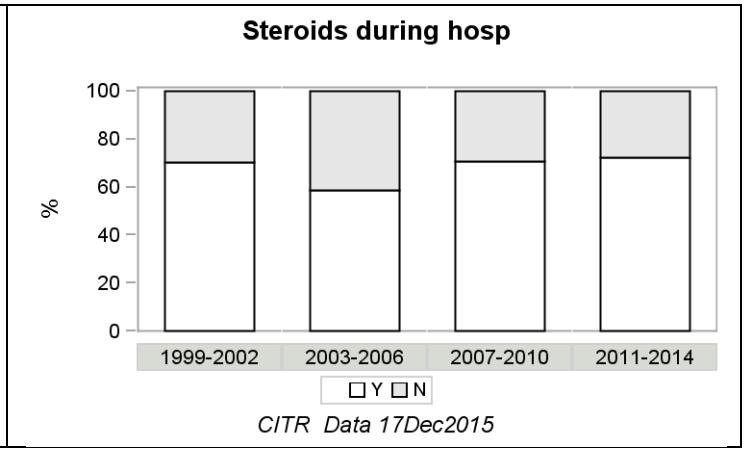
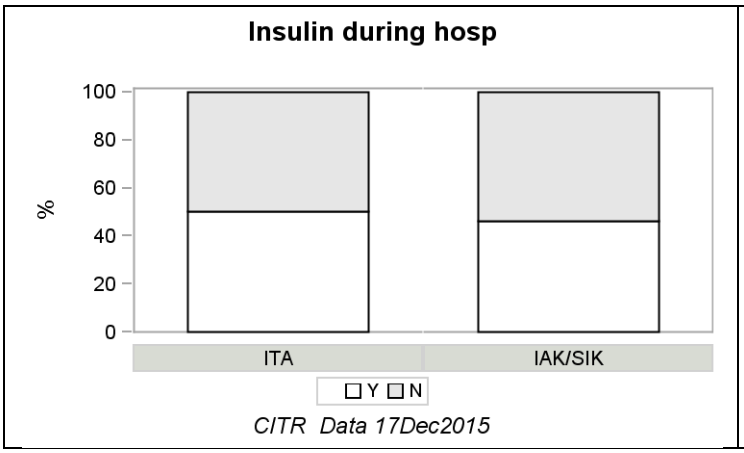
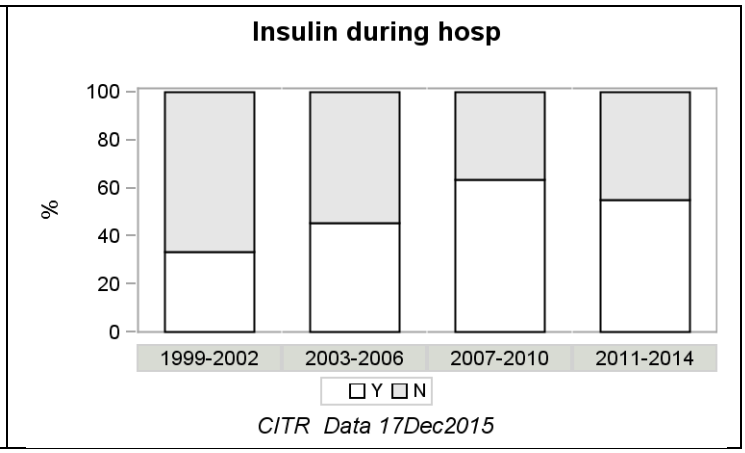


Exhibit 2 – 12 *(continued)*
Characteristics of Hospitalization and Organ Procurement

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Insulin given to donor during hospitalization	**No**	537	49.9	91	53.8		172	66.7	231	54.5	122	36.5	103	45.0	
	Yes	539	50.1	78	46.2	*	86	33.3	193	45.5	212	63.5	126	55.0	***

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Insulin given to donor during hospitalization	**Available**	1076	67.5	169	48.7	258	59.4	424	73.7	334	74.2	229	47.4
	Missing	519	32.5	178	51.3	176	40.6	151	26.3	116	25.8	254	52.6





* = p <.05; ** = p <.01; *** = p <.001

Insulin has increasingly been given to donors over the eras.

Exhibit 2 – 13
Donor Serology

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HIV	NEG	1326	100.0	233	100.0		342	100.0	471	100.0	389	100.0	357	100.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
HIV	Missing	269	16.9	114	32.9		92	21.2	104	18.1	61	13.6	126	26.1	
	Available	1326	83.1	233	67.1		342	78.8	471	81.9	389	86.4	357	73.9	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HTLV	NEG	1019	100.0	179	100.0	1198	290	100.0	421	100.0	295	100.0	192	100.0	1198

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
HTLV	Missing	576	36.1	168	48.4		144	33.2	154	26.8	155	34.4	291	60.2	
	Available	1019	63.9	179	51.6		290	66.8	421	73.2	295	65.6	192	39.8	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
VDRL	NEG	1057	99.9	189	100.0		300	100.0	429	99.8	308	100.0	209	100.0	
	POS	1	0.1	-	0.0		-	0.0	1	0.2	-	0.0	-	0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
VDRL	Missing	537	33.7	158	45.5		134	30.9	145	25.2	142	31.6	274	56.7	
	Available	1058	66.3	189	54.5		300	69.1	430	74.8	308	68.4	209	43.3	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
CMV	NEG	573	44.7	103	44.8		129	39.6	207	45.8	163	43.0	177	50.0	
	POS	708	55.3	127	55.2		197	60.4	245	54.2	216	57.0	177	50.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
CMV	Missing	314	19.7	117	33.7		108	24.9	123	21.4	71	15.8	129	26.7	
	Available	1281	80.3	230	66.3		326	75.1	452	78.6	379	84.2	354	73.3	

Exhibit 2 – 13 *(continued)*
Donor Serology

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%		N	%	N	%	N	%	N	%
HBSag	NEG	1314	99.8	232	100.0		337	100.0	470	99.8	385	100.0	354	99.7
	POS	2	0.2	-	0.0		-	0.0	1	0.2	-	0.0	1	0.3

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%		N	%	N	%	N	%	N	%
HBSag	Missing	279	17.5	115	33.1		97	22.4	104	18.1	65	14.4	128	26.5
	Available	1316	82.5	232	66.9		337	77.6	471	81.9	385	85.6	355	73.5

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%		N	%	N	%	N	%	N	%
HBC	NEG	1249	99.2	219	99.1		306	98.4	464	99.6	362	98.6	336	100.0
	POS	10	0.8	2	0.9		5	1.6	2	0.4	5	1.4	-	0.0

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%		N	%	N	%	N	%	N	%
HBC	Missing	336	21.1	126	36.3		123	28.3	109	19.0	83	18.4	147	30.4
	Available	1259	78.9	221	63.7		311	71.7	466	81.0	367	81.6	336	69.6

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%		N	%	N	%	N	%	N	%
HCV	NEG	1229	99.9	202	99.5		329	99.7	461	100.0	360	99.7	281	100.0
	POS	1	0.1	1	0.5		1	0.3	-	0.0	1	0.3	-	0.0

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%		N	%	N	%	N	%	N	%
HCV	Missing	365	22.9	144	41.5		104	24.0	114	19.8	89	19.8	202	41.8
	Available	1230	77.1	203	58.5		330	76.0	461	80.2	361	80.2	281	58.2

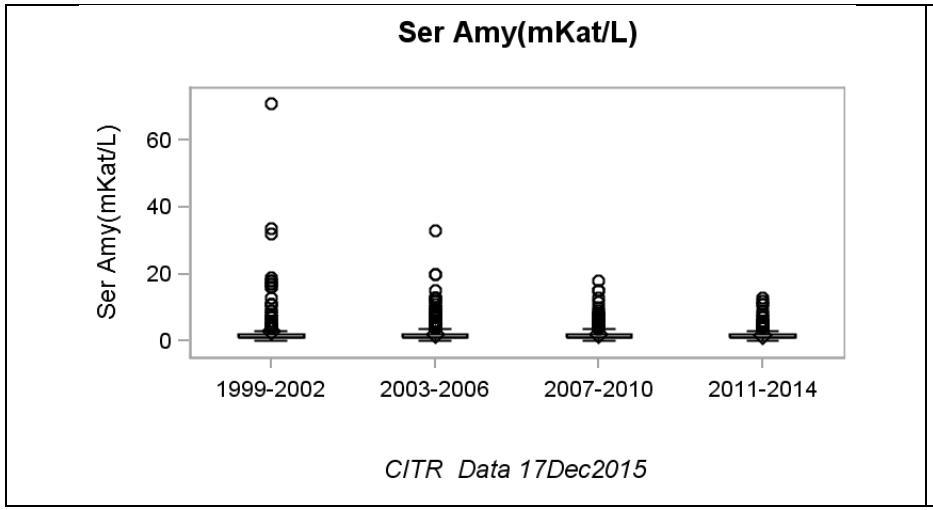
No Testing

Exhibit 2 – 14
Donor Laboratory Data

	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Serum creatinine (mg/dL)	1058	1.1	0.0	228	1.1	0.1		259	1.2	0.1	440	1.2	0.0	330	1.1	0.0	257	1.1	0.1	
BUN (mg/dL)	746	15.5	0.4	221	15.1	0.6		199	15.1	0.6	337	14.9	0.5	238	16.3	0.7	193	15.3	0.7	
Total bilirubin (mg/dL)	940	0.9	0.0	215	0.8	0.0		215	0.9	0.0	367	0.9	0.0	322	0.8	0.0	251	0.8	0.1	
AST (U/L)	994	74.9	5.9	223	77.3	11.5		224	98.2	19.5	376	64.0	5.6	339	82.5	10.4	278	63.4	7.7	
ALT (U/L)	1072	64.6	4.7	224	65.6	9.3		225	79.7	16.6	381	51.3	4.4	363	70.6	8.3	327	63.9	6.0	
Serum lipase (mKat/L)	935	1.1	0.1	178	0.9	0.1		242	0.9	0.1	360	1.1	0.1	286	1.1	0.1	225	1.0	0.1	
Serum amylase (mKat/L)	981	2.2	0.1	218	2.0	0.2		256	2.8	0.4	429	2.2	0.1	300	2.0	0.1	214	1.7	0.1	***
Minimum pre-insulin blood glucose (mg/dL)	831	127.7	1.3	166	127.9	3.1		275	128.8	2.2	395	124.6	1.9	165	125.0	3.0	162	136.5	3.5	
Maximum blood glucose (mg/dL)	920	222.3	2.7	169	234.5	6.6		242	243.9	6.3	420	226.5	3.9	231	217.8	4.5	196	202.4	4.9	***

* = p <.05; ** = p <.01; *** = p <.001

Donors' serum amylase and stimulated blood glucose declined significantly over the decade.



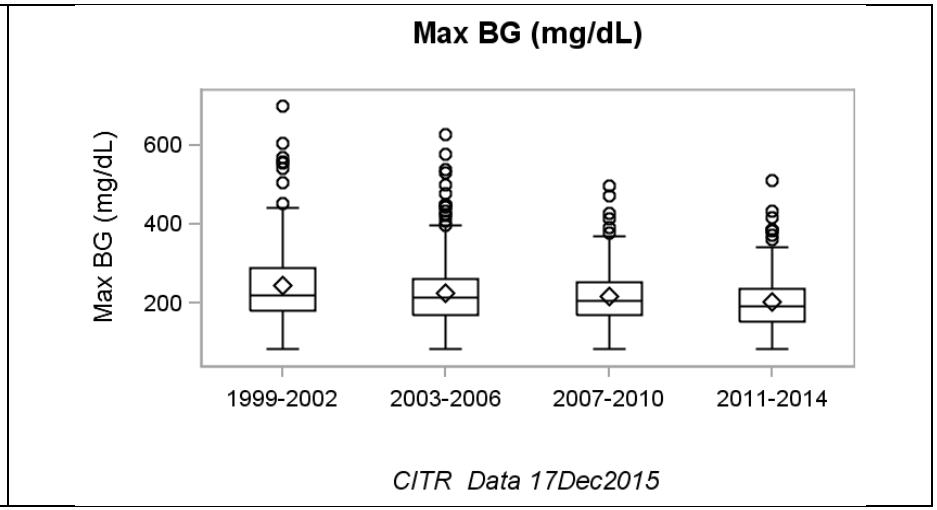


Exhibit 2 – 15
Organ Crossmatch Results

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Positive cross match	**No**	659	97.1	173	97.7		184	99.5	314	96.0	219	96.9	115	97.5	
	Yes	20	2.9	4	2.3		1	0.5	13	4.0	7	3.1	3	2.5	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Positive cross match	**Available**	679	42.6	177	51.0	185	42.6	327	56.9	226	50.2	118	24.4
	Missing	916	57.4	170	49.0	249	57.4	248	43.1	224	49.8	365	75.6

Chapter 3
Pancreas Procurement, Islet Processing, and Infusion Characteristics

Introduction

Chapter 3 describes the pancreas procurement, islet processing, transplant procedure and final islet product information of the islet products used for clinical transplantation in the recipients in this report, namely those described in Chapter 1.

For the roughly 15% of infusions which were derived from more than one donor pancreas, the donor information was collapsed appropriately, either by logical combination (e.g., an infusion product derived from a female donor and a male donor is termed “Mixed”); averaging, (e.g., viability, stimulation index, etc); or summation (e.g., total beta cells, islet particle count, total IEQs infused, etc.). Exhibits 3-1 to 3-4 describe all the variables according to ITA vs. IAK/SIK and by era (1999-2002, 2003-2006, 2007-2010, and 2011-2014).

Exhibits 3-5 to 3-7 relate the final islet product characteristics to donor, procurement and processing factors in a univariate manner. Factors that are categorical in nature, e.g., gender, are summarized in Exhibit 3-6, while those that are continuous are shown as correlations with the islet product characteristics in Exhibit 3-7.

Exhibit 3 – 1A
Islet Processing Summary

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Procurement Team	**Unrelated**	306	28.4	48	19.9		82	29.6	160	32.5	73	23.5	39	16.4	
	Procurement/transplant centers related	718	66.6	177	73.4	*	175	63.2	306	62.1	225	72.3	189	79.4	***
	Mixed	26	2.4	4	1.7		8	2.9	14	2.8	8	2.6		0.0	
	Unknown	28	2.6	12	5.0		12	4.3	13	2.6	5	1.6	10	4.2	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Procurement Team	Available	1078	67.6	241	69.5		277	80.3	493	84.3	311	67.0	238	43.4	
	Missing	517	32.4	106	30.5		68	19.7	92	15.7	153	33.0	310	56.6	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Islet processing center	**Processing/transplant centers related**	922	92.1	237	96.7	*	278	100.0	504	98.2	249	81.9	128	84.8	***
	Unrelated	79	7.9	8	3.3			0.0	9	1.8	55	18.1	23	15.2	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Islet processing center	Available	1001	62.8	245	70.6		278	80.6	513	87.7	304	65.5	151	27.6	
	Missing	594	37.2	102	29.4		67	19.4	72	12.3	160	34.5	397	72.4	

Exhibit 3 – 1A *(continued)*
Islet Processing Summary

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Pancreas preservation	**2L only**	199	12.6	23	6.9		41	12.6	149	25.8	27	5.9	5	0.9	
	Other	716	45.5	183	54.6		103	31.7	129	22.3	268	58.4	*399*	*72.8*	
	UW only	421	26.7	105	31.3	***	*166*	*51.1*	233	40.3	78	17.0	49	8.9	***
	UW+2L	32	2.0	10	3.0		10	3.1	25	4.3	7	1.5		0.0	
	HTK only	184	11.7	1	0.3			0.0	33	5.7	69	15.0	*83*	*15.1*	
	Celsior	23	1.5	13	3.9		5	1.5	9	1.6	10	2.2	12	2.2	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Pancreas preservation	**Available**	1575	98.7	335	96.5		325	94.2	578	98.8	459	98.9	548	100.0	
	Missing	20	1.3	12	3.5		20	5.8	7	1.2	5	1.1		0.0	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Cultured	**Islets cultured >=6 hrs**	643	68.8	109	69.4		83	35.0	263	62.5	197	90.0	209	97.7	***
	None	291	31.2	48	30.6		154	65.0	158	37.5	22	10.0	5	2.3	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Cultured	**Available**	934	58.6	157	45.2		237	68.7	421	72.0	219	47.2	214	39.1	
	Missing	661	41.4	190	54.8		108	31.3	164	28.0	245	52.8	334	60.9	

Exhibit 3 – 1A *(continued)*
Islet Processing Summary

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Gradient type	**Continuous**	891	88.7	174	85.3		181	78.0	390	83.2	267	95.7	227	99.6	
	Discontinuous	33	3.3	21	10.3		24	10.3	28	6.0	1	0.4	1	0.4	
	Both	65	6.5	5	2.5	***	24	10.3	39	8.3	7	2.5		0.0	
	Mixed	14	1.4	4	2.0		3	1.3	11	2.3	4	1.4		0.0	
	None	1	0.1		0.0			0.0	1	0.2		0.0		0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Gradient type	**Available**	1004	62.9	204	58.8		232	67.2	469	80.2	279	60.1	228	41.6	
	Missing	591	37.1	143	41.2		113	32.8	116	19.8	185	39.9	320	58.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Pulmozyme	**No**	476	46.8	130	64.4	***	212	81.5	208	43.2	105	38.5	81	39.3	***
	Yes	542	53.2	72	35.6		48	18.5	273	56.8	168	61.5	125	60.7	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Pulmozyme	**Available**	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Collagenase P	**No**	995	97.7	201	99.5		258	99.2	463	96.3	269	98.5	206	100.0	
	Yes	23	2.3	1	0.5		2	0.8	18	3.7	4	1.5		0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Collagenase P	**Available**	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

Exhibit 3 – 1A *(continued)*
Islet Processing Summary

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Thermolysin	**No**	925	90.9	194	96.0	*	260	100.0	424	88.1	262	96.0	173	84.0	***
	Yes	93	9.1	8	4.0			0.0	57	11.9	11	4.0	33	16.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Thermolysin	**Available**	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Serva	**No**	771	75.7	147	72.8		260	100.0	462	96.0	83	30.4	113	54.9	***
	Yes	247	24.3	55	27.2			0.0	19	4.0	190	69.6	93	45.1	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Serva	**Available**	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Liberase HI	**Yes**	570	56.0	129	63.9	*	257	98.8	380	79.0	22	8.1	40	19.4	***
	No	448	44.0	73	36.1		3	1.2	101	21.0	251	91.9	166	80.6	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Liberase HI	**Available**	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

Exhibit 3 – 1A *(continued)*
Islet Processing Summary

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Sigmablend	No	1009	99.1	202	100.0		260	100.0	481	100.0	264	96.7	206	100.0	*
	Yes	9	0.9		0.0			0.0		0.0	9	3.3		0.0	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Sigmablend	Available	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Collagenase Other	No	866	85.1	184	91.1	*	259	99.6	401	83.4	212	77.7	178	86.4	***
	Yes	152	14.9	18	8.9		1	0.4	80	16.6	61	22.3	28	13.6	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Collagenase Other	Available	1018	63.8	202	58.2		260	75.4	481	82.2	273	58.8	206	37.6	
	Missing	577	36.2	145	41.8		85	24.6	104	17.8	191	41.2	342	62.4	

* = p .05

** = p .01

*** = p .001

- The proportion of islet processing centers that were unrelated to the islet transplant center rose appreciably (from 0% to 15%) over the duration of the Registry (p. 3-4). The detailed patterns regarding transplant type, continent and other factors will be described in a separate report.
- Pancreas preservation methods have evolved substantially over the duration of the Registry, from the majority (51%) using UW only to 15% using HTK and 73% using other preservation methods. These will be the focus of a detailed analysis.
- Islet preparations were cultured more frequently in the recent eras (98% in 2011-2014 vs. 35% in 1999-2002).
- Pulmozyme use increased substantially in the recent eras (61% in 2011-2014 vs. 19% in 1999-2002).

Exhibit 3 – 1B
Pancreas Digestion Combinations Involving Thermolysin/Pulmozyme

		Thermolysin		Pulmozyme	
		No	Yes	No	Yes
		N	N	N	N
Collagenase P	**No**	1096	100	591	605
	Yes	23	1	15	9
Serva	**No**	818	100	451	467
	Yes	301	1	155	147
Liberase HI	**No**	427	94	220	301
	Yes	692	7	386	313
Sigmablend	**No**	1110	101	599	612
	Yes	9	-	7	2
Collagenase Other	**No**	1021	29	548	502
	Yes	98	72	58	112

In several instances, more than one primary enzyme was used in conjunction with thermolysin or pulmozyme; hence, the totals are higher than in the previous table.

Exhibit 3 – 1C
Final Islet Preparation Microbiology

		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Gram stain	**Negative**	912	99.8	155	100.0	209	100.0	398	100.0	233	100.0	227	99.1
	Positive	2	0.2	-	0.0	-	0.0	-	0.0	-	0.0	2	0.9

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Gram stain	**Available**	914	57.3	155	44.7	209	60.6	398	68.0	233	50.2	229	41.8
	Missing	681	42.7	192	55.3	136	39.4	187	32.0	231	49.8	319	58.2

		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Aerobic culture	**Negative**	997	98.5	187	98.4	227	97.0	452	99.3	278	97.9	227	99.1
	Positive	15	1.5	3	1.6	7	3.0	3	0.7	6	2.1	2	0.9

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Aerobic culture	**Available**	1012	63.4	190	54.8	234	67.8	455	77.8	284	61.2	229	41.8
	Missing	583	36.6	157	45.2	111	32.2	130	22.2	180	38.8	319	58.2

		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Anaerobic culture	**Negative**	882	99.2	166	100.0	176	97.8	367	99.7	278	100.0	227	99.1
	Positive	7	0.8	-	0.0	4	2.2	1	0.3	-	0.0	2	0.9

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Anaerobic culture	**Available**	889	55.7	166	47.8	180	52.2	368	62.9	278	59.9	229	41.8
	Missing	706	44.3	181	52.2	165	47.8	217	37.1	186	40.1	319	58.2

		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Fungal Culture	**Negative**	966	98.8	188	98.4	227	100.0	457	99.1	263	99.6	207	95.4
	Positive	12	1.2	3	1.6	-	0.0	4	0.9	1	0.4	10	4.6

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Fungal Culture	**Available**	978	61.3	191	55.0	227	65.8	461	78.8	264	56.9	217	39.6
	Missing	617	38.7	156	45.0	118	34.2	124	21.2	200	43.1	331	60.4

Exhibit 3 – 1C *(continued)*
Final Islet Preparation Microbiology

		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Mycoplasma	**Negative**	610	99.8	49	100.0	170	99.4	250	100.0	123	100.0	116	100.0
	Positive	1	0.2	-	0.0	1	0.6	-	0.0	-	0.0	-	0.0

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Mycoplasma	**Available**	611	38.3	49	14.1	171	49.6	250	42.7	123	26.5	116	21.2
	Missing	984	61.7	298	85.9	174	50.4	335	57.3	341	73.5	432	78.8

Exhibit 3 – 1D
Pancreas Preservation Method by Era

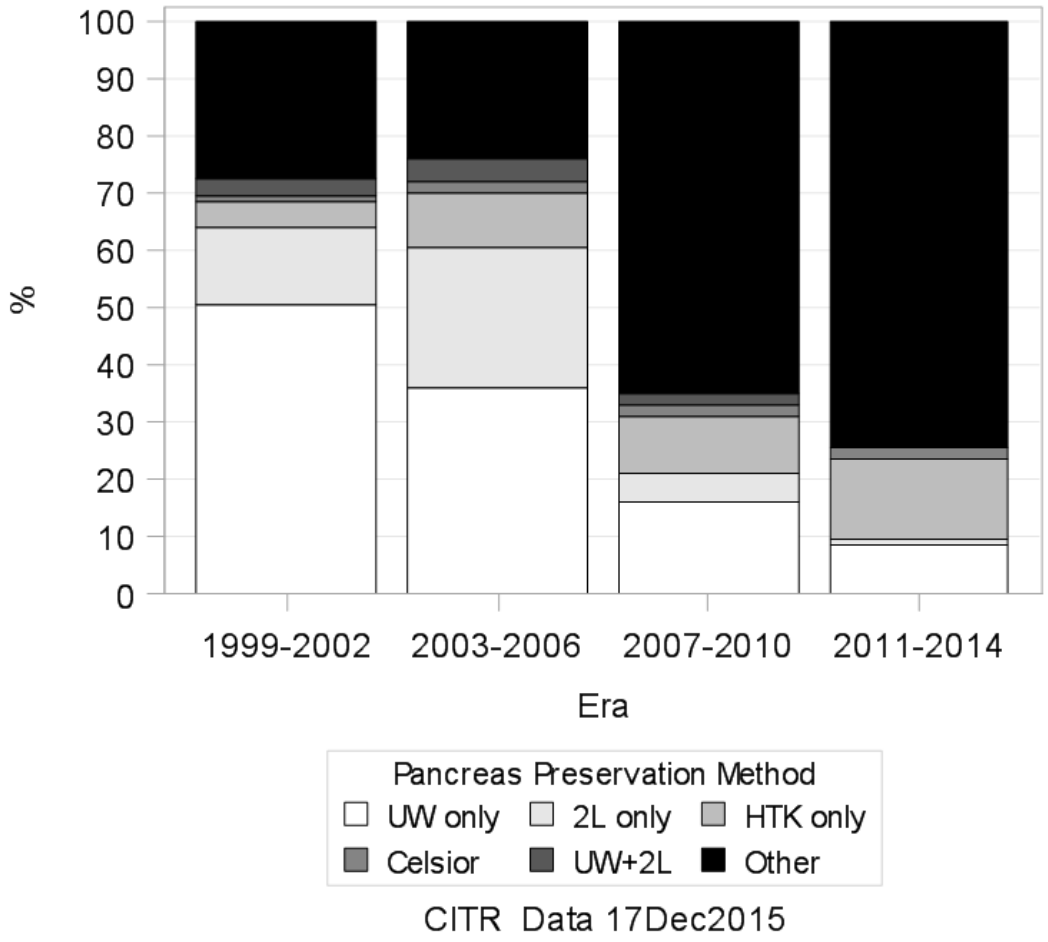


Exhibit 3 – 2
Cold Ischemia Information

	Transplant type						p	Era											p
	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014		
	N	Mean	SD	N	Mean	SD		N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	
Time from cross clamp to pancreas recovery (hrs)	667	0.9	1.2	180	0.9	0.4		147	0.6	0.4	364	0.9	1.3	185	0.9	1.1	151	1.1	0.9	**
Duration of cold ischemia (hrs)	851	7.6	4.6	182	7.7	8.6		238	7.2	3.4	432	7.2	3.2	246	8.4	8.6	117	8.2	6.9	***
Time from brain death to pancreas recovery (hrs)	611	19.9	8.6	168	16.9	8.5	***	138	16.6	7.0	327	18.9	8.8	169	21.1	9.5	145	20.2	8.1	***
Culture time (hrs)	934	19.4	17.6	157	19.1	17.8		237	10.9	17.4	421	17.6	17.8	219	26.9	17.5	214	24.4	11.6	***

* = p <.05; ** = p <.01; *** = p <.001

Mean time from brain death to pancreas recovery was about 3 hours longer for ITA than IAK, and has increased over the decade by 4 hours.

Mean culture time has increased over the eras by 15 hours, including an increasing proportion of preparations being cultured at all.

Exhibit 3 – 3
Islet Product Characteristics (Cumulative through all infusions per recipient)

Infusions	Transplant type						p	Era											p
	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014		
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	497	7.4	0.2	95	7.4	0.5		143	8.4	0.4	206	8.2	0.3	128	6.9	0.4	115	5.0	0.3	
Total islet particles (final preparation)	437	792.2	19.6	98	824.9	42.2		134	887.0	42.0	188	856.3	27.6	102	711.7	37.8	111	672.2	32.7	
Embedded islets (%)	381	16.5	0.7	52	14.7	1.6		93	14.4	1.5	144	16.4	1.2	86	15.7	1.6	110	18.0	1.2	
Islet equivalents (1000s)	535	834.9	17.4	93	764.7	36.3		143	868.8	36.8	193	874.6	28.7	123	828.0	36.0	169	727.4	25.4	
Islet equivalents(1000s)/kg recipient	557	13.0	0.3	137	12.2	0.4		163	13.7	0.5	224	13.7	0.4	172	12.0	0.4	135	11.4	0.4	
Beta cells (x10^6)	207	409.9	21.9	13	568.3	110.3		61	453.6	41.4	81	436.9	37.4	26	469.8	66.5	52	326.2	38.0	
Beta cells/kg recipient weight	163	6.3	0.4	12	9.5	2.1		58	6.8	0.6	75	6.8	0.7	16	5.5	0.9	26	5.8	0.8	
Insulin content (1000s micrograms)	150	6.2	0.3	17	5.2	0.7		66	6.4	0.5	91	6.0	0.4	7	5.1	1.1	3	5.7	2.1	
Total Endotoxin units	392	37.4	4.8	82	32.4	7.2		120	46.0	7.3	194	51.1	8.6	101	15.1	3.7	59	5.6	2.2	
Endotoxin units/kg recipient weight	362	0.6	0.1	77	0.5	0.1		114	0.8	0.1	186	0.8	0.1	91	0.3	0.1	48	0.1	0.0	
Islet potency: Stimulation index	446	3.1	0.1	83	2.7	0.3		134	3.5	0.3	190	3.2	0.2	97	2.7	0.2	108	2.6	0.2	
Islet viability	508	89.7	0.3	91	91.6	0.5		124	90.7	0.5	204	91.1	0.4	114	89.8	0.5	157	88.0	0.4	
Purity	435	61.9	0.7	102	58.7	1.8		140	58.7	1.4	210	61.9	1.0	102	64.0	1.5	85	61.1	1.6	
Total DNA	233	19.7	1.1	17	16.9	3.5		65	17.0	1.8	97	20.7	1.9	32	20.3	3.1	56	20.2	2.3	

Exhibit 3 – 4A
Islet Product Characteristics

Infusions	Transplant type						p	Era											p
	ITA			IAK/SIK				1999-2002			2003-2006			2007-2010			2011-2014		
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	974	3.7	0.1	179	3.9	0.2		236	4.0	0.1	436	3.9	0.1	256	3.8	0.2	225	3.1	0.1	***
Total islet particles (final preparation)	859	391.6	5.5	193	409.6	13.6		216	409.4	12.1	394	415.2	8.7	225	363.2	10.0	217	376.5	10.8	**
Embedded islets (%)	720	16.5	0.7	89	15.2	1.5		139	13.9	1.5	284	16.6	1.2	189	16.9	1.3	197	17.2	1.0	
Islet equivalents (1000s)	1027	421.8	4.6	179	385.9	12.5	**	231	412.8	10.1	402	412.7	7.9	255	423.4	8.9	318	418.2	8.4	
Islet equivalents(1000s)/kg recipient	1102	6.5	0.1	250	6.5	0.2		264	6.5	0.1	481	6.5	0.1	338	6.5	0.1	269	6.4	0.1	
Beta cells (x10^6)	348	232.3	10.6	23	321.2	39.8	*	93	190.5	18.0	140	240.0	16.1	60	293.7	28.2	78	247.4	23.9	*
Beta cells/kg recipient weight	280	3.5	0.2	21	5.5	0.7	**	87	2.9	0.3	128	3.8	0.3	46	3.9	0.4	40	4.3	0.5	*
Insulin content (1000s micrograms)	269	3.5	0.1	30	3.0	0.4		106	3.4	0.2	170	3.6	0.2	17	2.2	0.3	6	2.8	0.7	
Total Endotoxin units	737	19.8	1.9	146	18.2	3.1		163	27.5	4.6	399	26.9	3.0	214	7.4	1.6	107	4.3	1.4	***
Endotoxin units/kg recipient weight	689	0.3	0.0	138	0.3	0.1		155	0.5	0.1	381	0.4	0.0	196	0.1	0.0	95	0.1	0.0	***
Islet potency: Stimulation index	849	3.1	0.1	150	2.7	0.2		216	3.7	0.3	386	3.1	0.2	205	2.5	0.1	192	2.8	0.2	***
Islet viability	953	89.6	0.2	181	91.5	0.4	***	170	91.0	0.5	446	91.3	0.3	243	89.2	0.4	275	87.7	0.4	***
Purity	809	62.2	0.6	196	59.0	1.4	*	191	58.8	1.4	460	61.8	0.9	210	63.3	1.1	144	61.8	1.4	
Total DNA	419	10.2	0.5	32	9.0	1.7		99	6.1	0.7	184	10.1	0.9	80	12.0	1.1	88	12.8	1.2	***

* = p <.05; ** = p <.01; *** = p <.001

Total cell volume infused has declined appreciably over the eras, while total IEQs and IEQ/Kg recipients have remained remarkably stable.

Total Beta cells and β-cells/kg have increased substantially over the eras, and were higher for IAK/SIK .

Endotoxin (both total and /kg) has declined sharply over the eras.

Stimulation index was higher for ITA than IAK/SIK, and has declined over the eras.

Exhibit 3 – 4B
Islet Product Characteristic by Infusion Sequence

Transplant type ITA										
	Infusion Number									p
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	*468*	3.9	0.1	354	3.6	0.1	152	3.3	0.1	***
Total islet particles (final preparation)	*415*	398.6	8.4	314	391.2	9.0	130	370.4	12.5	*
Embedded islets (%)	348	16.4	0.9	260	16.7	1.2	112	16.3	1.7	
Islet equivalents (1000s)	510	427.4	6.7	376	418.5	7.7	141	410.2	11.7	
Islet equivalents(1000s)/kg recipient	*555*	6.7	0.1	396	6.3	0.1	151	6.1	0.2	**
Beta cells (x10^6)	171	234.8	16.1	127	216.4	15.4	50	264.3	29.3	*
Beta cells/kg recipient weight	131	3.6	0.3	105	3.2	0.2	44	3.8	0.5	**
Insulin content (1000s micrograms)	137	3.6	0.2	104	3.2	0.2	28	4.0	0.4	
Total Endotoxin units	357	17.7	2.1	264	22.5	3.8	116	20.3	5.8	***
Endotoxin units/kg recipient weight	332	0.3	0.0	248	0.4	0.1	109	0.3	0.1	***
Islet potency: Stimulation index	420	3.1	0.1	305	3.3	0.2	124	2.6	0.2	**
Islet viability	470	89.8	0.3	343	89.8	0.4	140	88.5	0.7	***
Purity	395	62.1	0.9	293	62.2	1.0	121	62.6	1.6	
Total DNA	201	10.8	0.9	155	9.0	0.7	63	11.0	1.3	***

* = p <.05; ** = p <.01; *** = p <.001

Total cell volume and IEQs/kg recipient have decreased notably with subsequent infusions.

The remaining statistically significant results may not indicate any clinical important trends.

Exhibit 3 – 4B *(continued)*
Islet Product Characteristic by Infusion Sequence

Transplant type IAK/SIK										
	Infusion Number									p
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	86	4.0	0.3	71	3.5	0.3	22	4.4	0.4	**
Total islet particles (final preparation)	92	434.0	22.5	72	388.3	18.8	29	384.8	30.4	
Embedded islets (%)	42	13.8	1.8	35	12.7	1.9	12	27.2	6.0	
Islet equivalents (1000s)	85	404.1	22.0	66	369.7	15.7	28	368.9	23.1	
Islet equivalents(1000s)/kg recipient	132	7.1	0.2	91	6.1	0.2	27	5.3	0.4	***
Beta cells (x10^6)	9	348.2	74.4	10	312.0	47.9	4	283.5	123.5	
Beta cells/kg recipient weight	8	5.3	1.2	9	6.0	0.9	4	4.5	2.0	*
Insulin content (1000s micrograms)	11	3.1	0.5	13	3.2	0.7	6	2.2	0.5	
Total Endotoxin units	72	16.1	3.7	54	20.5	6.0	20	19.3	9.7	**
Endotoxin units/kg recipient weight	67	0.3	0.1	52	0.3	0.1	19	0.3	0.2	**
Islet potency: Stimulation index	73	2.9	0.3	56	2.3	0.3	21	2.6	0.5	*
Islet viability	85	91.8	0.6	69	91.6	0.7	27	90.3	1.2	
Purity	97	58.9	2.0	73	61.0	2.2	26	53.5	4.7	**
Total DNA	13	7.8	2.6	14	10.9	3.0	5	6.9	2.6	

* = p <.05; ** = p <.01; *** = p <.001

For IAK/SIK, total IEQs/recipient has declined notably with subsequent infusion sequence.

Other statistically significant differences may not indicate clinical importance.

Exhibit 3 – 5
Islet Characteristics by Pancreas Preservation Method

	Pancreas Preservation Method																					p
	Missing/Unknown			UW only			2L only			HTK only			Celsior			UW+2L			Other			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	25	4.8	0.6	*444*	3.9	0.1	*211*	3.7	0.1	*160*	3.3	0.1	*28*	3.3	0.3	*36*	4.2	0.3	*249*	3.5	0.1	*
Total islet particles (final preparation)	25	469.3	46.9	*430*	404.7	7.9	*179*	366.1	12.1	*163*	418.8	10.3	*36*	351.7	25.9	*38*	447.4	32.5	*181*	366.0	14.0	
Embedded islets (%)	10	26.4	10.0	318	16.1	1.0	123	18.2	1.9	167	16.0	1.3	33	12.5	2.3	23	18.1	3.3	135	15.5	1.2	
Islet equivalents (1000s)	31	400.8	33.9	451	422.0	7.3	174	415.1	12.2	179	444.7	9.6	36	352.5	17.5	33	477.0	31.5	302	394.7	8.4	*
Islet equivalents(1000s)/kg recipient	28	6.9	0.7	470	6.6	0.1	210	6.4	0.2	139	6.3	0.2	28	5.6	0.3	37	7.4	0.4	440	6.4	0.1	
Beta cells (x10^6)	0	-	-	165	202.8	15.2	75	257.7	22.1	108	275.5	19.9	0	-	-	7	241.1	58.6	16	249.9	41.2	*
Beta cells/kg recipient weight	0	-	-	144	3.2	0.3	69	4.1	0.4	71	3.9	0.3	0	-	-	7	3.7	1.0	10	4.6	0.9	*
Insulin content (1000s micrograms)	0	-	-	180	3.3	0.2	83	3.5	0.3	3	5.7	1.2	0	-	-	9	5.1	0.9	24	2.8	0.3	
Total Endotoxin units	16	5.0	3.2	384	23.6	2.9	181	29.5	3.9	98	4.6	2.1	21	0.5	0.0	32	45.4	16.6	151	5.7	1.6	***
Endotoxin units/kg recipient weight	13	0.1	0.0	372	0.4	0.0	174	0.5	0.1	88	0.1	0.0	19	0.0	0.0	29	0.6	0.2	132	0.1	0.0	***
Islet potency: Stimulation index	11	4.4	1.2	444	3.3	0.2	189	3.1	0.2	169	2.8	0.2	21	1.5	0.2	31	3.0	0.6	134	2.5	0.2	***
Islet viability	19	91.5	1.1	431	90.5	0.3	212	92.4	0.4	180	85.0	0.6	26	89.3	0.9	37	91.2	0.9	229	90.2	0.4	
Purity	28	49.2	3.8	408	63.1	0.9	213	61.6	1.2	120	62.9	1.4	33	55.7	3.4	39	64.1	2.9	164	59.4	1.3	*
Total DNA	0	-	-	210	7.9	0.7	86	11.8	1.4	113	13.3	0.9	1	12.3	-	13	7.5	1.6	28	9.7	1.9	*

* = p <.05; ** = p <.01; *** = p <.001

UW + 2L yielded the highest total islet particles, and the highest IEQs/kg recipient.

UW, 2L and their combination yielded the highest stimulation index and purity.

HTK yielded the lowest endotoxin and the highest total beta cells and total DNA.

Exhibit 3 – 6
Relationship between (Categorical) Donor and Processing Predictors and Final Islet Product Characteristics

p<0.05	Islet characteristics													
	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg donor	Total beta cells	Beta cells/kg donor	Insulin content	Total endotoxin	Endotoxin /kg donor	Stimulation index	Viability	Purity	DNA content
Islet predictors														
ITA vs IAK/SIK				0.04		0.02	0.002					0.002	0.02	
Year	<0.0001	0.02		0.002					<0.0001	<0.0001	<0.0001	<0.0001	0.02	<0.0001
Donor gender		0.0003		<0.0001	0.0003									
Donor blood type A	0.0006		0.003											
Donor CMV									0.01	0.03				
Donor Hx HPT			0.007		0.02				0.005	0.008				
Donor Hx ETOH	0.002			0.02	0.02							0.04		
Donor hospital transfusion									0.02			0.02		0.04
Donor intra-op transfusion												0.04		
Donor given steroid				<0.0001	0.001	0.003	0.01	0.02	<0.0001	<0.0001			<0.0001	
Donor given insulin				0.0003	0.0005	0.0005	0.004							0.03
Procurement team related													0.02	
Pancreas preservation	0.03					0.02	0.03		0.006	0.003	0.003	0.004	0.02	0.03
Pulmozyme	0.006				0.03						0.003	<0.0001	0.04	
Thermolysin												<0.0001		
Gradient type	0.006			0.003	0.01	0.002	0.0002							<0.0001

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

The CORR Procedure

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

	pckclvol	TOTPARTICLES	TOTTRAP	totieq	ieqinfkg	totalbeta	totbetakg	totalinsulin	totalendo	TOTENDOKG	isstimin_mean
donage_mean Mean donor age (yrs)	-0.10619 0.0014 903	0.05293 0.1325 809	-0.16341 <.0001 628	-0.06266 0.0541 945	-0.09525 0.0017 1080	-0.03818 0.5384 262	-0.07335 0.2587 239	0.05344 0.3791 273	0.00237 0.9468 793	-0.01006 0.7830 752	-0.14035 <.0001 819
caweight_mean Donor Weight (kg)	0.05028 0.0927 *1119*	0.07235 0.0191 1049	0.00272 0.9385 806	0.32889 <.0001 1202	0.30675 <.0001 1321	0.05662 0.2780 369	0.02717 0.6398 299	0.01386 0.8120 297	0.06872 0.0415 880	0.05982 0.0862 824	0.03744 0.2383 994
caheight_mean Donor height	0.02502 0.4034 1117	0.12726 <.0001 1047	-0.00979 0.7816 804	0.15337 <.0001 1200	0.15072 <.0001 1319	-0.07165 0.1702 368	-0.08997 0.1212 298	0.11872 0.0412 296	-0.02874 0.3945 880	-0.02896 0.4065 824	0.01473 0.6430 993
donbmi_mean Donor Body Mass Index (kg/m2)	0.02998 0.3167 *1117*	0.00277 0.9287 1047	0.00259 0.9416 804	0.27677 <.0001 1200	0.25885 <.0001 1319	0.08411 0.1072 368	0.06810 0.2412 298	-0.03218 0.5813 296	0.09157 0.0066 880	0.08433 0.0155 824	0.04025 0.2050 993
preinsbg_mean Pre-ins donor glucose	-0.05881 0.0954 805	0.00378 0.9165 770	0.07294 0.0795 579	-0.03680 0.3015 790	-0.05029 0.1318 899	-0.07195 0.2361 273	-0.04961 0.4511 233	0.04572 0.4621 261	0.00486 0.8987 689	0.00682 0.8620 652	0.02108 0.5562 782
maxinsbg_mean Max donor glucose	0.02191 0.5188 869	-0.02271 0.5103 843	-0.00854 0.8300 635	0.06746 0.0473 865	0.08725 0.0068 960	0.08487 0.1480 292	0.12051 0.0634 238	-0.04501 0.5047 222	0.13662 0.0002 739	0.13649 0.0003 693	0.04409 0.2039 832
sercreat_mean Donor creatinine	0.08866 0.0062 951	0.01727 0.6053 898	-0.01219 0.7491 691	0.16195 <.0001 952	0.13565 <.0001 1091	-0.07425 0.2074 290	-0.07332 0.2734 225	0.02964 0.6731 205	0.01989 0.5731 805	0.01297 0.7226 751	0.08330 0.0136 878
bun_mean Donor BUN	0.11071 0.0035 694	0.02993 0.4490 642	-0.03510 0.4668 432	0.12285 0.0014 676	0.10232 0.0030 842	-0.04689 0.5662 152	-0.07719 0.4250 109	0.04954 0.5554 144	-0.02698 0.4913 653	-0.03196 0.4335 603	0.11053 0.0041 674
totbili_mean Donor bilirubin	0.07078 0.0410 834	0.07243 0.0434 778	-0.08191 0.0492 577	0.12841 0.0002 824	0.10772 0.0008 968	0.04456 0.5080 223	0.12316 0.1162 164	0.10287 0.2198 144	0.04664 0.2119 718	0.04446 0.2519 666	0.05878 0.1007 781
ast_mean Donor AST	0.03952 0.2497 850	0.00698 0.8437 800	0.03019 0.4654 587	0.00599 0.8602 868	-0.00335 0.9162 989	-0.05862 0.3815 225	-0.04652 0.5505 167	0.08061 0.3171 156	-0.01041 0.7772 741	0.00003 0.9995 689	0.00676 0.8480 807
alt_mean Donor ALT	0.07840 0.0214 861	0.03221 0.3596 811	0.04475 0.2742 599	0.09921 0.0026 920	0.09178 0.0035 1008	-0.02237 0.7352 231	-0.02443 0.7504 172	0.05020 0.5271 161	-0.00668 0.8546 756	-0.00269 0.9432 703	0.04550 0.1934 819

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

The CORR Procedure											
Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations											
	pckclvol	**TOTPARTICLES**	**TOTTRAP**	**totieq**	**ieqinfkg**	**totalbeta**	**totbetakg**	**totalinsulin**	**totalendo**	**TOTENDOKG**	**isstimin_mean**
serlip_mean Donor lipase	0.04121 0.2435 803	-0.00017 0.9964 746	0.00921 0.8248 580	0.06601 0.0630 794	0.08265 0.0111 943	-0.05048 0.4123 266	-0.02519 0.7147 213	-0.02031 0.7725 205	0.01625 0.6633 720	0.00878 0.8201 674	0.04481 0.2086 789
seramy_mean Donor serum amylase	0.06692 0.0472 880	0.03798 0.2744 830	0.00875 0.8262 632	-0.00087 0.9795 875	-0.01747 0.5770 1022	-0.10769 0.0796 266	-0.14167 0.0417 207	0.09500 0.1754 205	-0.05255 0.1519 745	-0.05204 0.1693 699	0.05342 0.1271 817
clptorec_mean Time from cross clamp to pancreas recovery (hrs)	-0.05640 0.1295 724	-0.01179 0.7542 708	-0.03007 0.4913 526	-0.12322 0.0008 741	-0.09432 0.0106 734	-0.07467 0.2563 233	-0.00544 0.9416 184	-0.02554 0.7176 203	-0.25101 <.0001 640	-0.26402 <.0001 593	-0.01300 0.7357 677
dthtorec_mean Time from brain death to pancreas recovery (hrs)	0.02432 0.5326 661	-0.04019 0.3081 645	0.04566 0.3207 475	0.14851 0.0001 678	0.07727 0.0453 672	0.11790 0.0824 218	0.07220 0.3438 174	0.00341 0.9625 193	0.09196 0.0232 609	0.08741 0.0380 564	0.15051 0.0001 641
coldstor_mean Cold ischemic time (hrs)	-0.08788 0.0090 882	0.08617 0.0121 847	-0.09449 0.0182 624	0.04643 0.1718 868	0.01341 0.6887 895	-0.01471 0.8051 284	-0.02474 0.6937 256	0.03072 0.6004 293	-0.00214 0.9515 808	-0.01123 0.7577 757	-0.04474 0.1973 832
cultime_mean Culture time (hrs)	-0.16367 <.0001 960	0.01707 0.6029 931	0.03425 0.3528 738	0.06534 0.0406 983	-0.00539 0.8680 953	0.23402 <.0001 363	0.24969 <.0001 293	-0.01078 0.8544 292	0.02950 0.4071 792	0.04107 0.2654 737	-0.02503 0.4530 901

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

	ITA									IAK/SIK								
	1			2			>=3			1			2			>=3		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Islet equivalents infused (1000s)	606	444.3	6.3	429	423.8	7.5	161	410.7	11.0	148	444.3	13.6	100	393.6	14.7	29	354.1	28.4
Islet equivalents infused(1000s)/donor kg	555	6.7	0.1	396	6.3	0.1	151	6.1	0.2	132	7.1	0.2	91	6.1	0.2	27	5.3	0.4
Embedded islets (%)	348	16.4	0.9	260	16.7	1.2	112	16.3	1.7	42	13.8	1.8	35	12.7	1.9	12	27.2	6.0
Cell volume (mL)	468	3.9	0.1	354	3.6	0.1	152	3.3	0.1	86	4.0	0.3	71	3.5	0.3	22	4.4	0.4
Time since first infusion (weeks)	592	29.6	1.9	572	27.5	1.6	202	15.9	1.4	125	28.4	4.5	120	28.3	4.6	34	31.8	12.1
Time since second infusion (weeks)	183	85.5	9.1	181	86.3	9.2	202	83.5	8.2	33	47.1	11.7	32	48.4	12.0	34	58.0	13.7
Time since third infusion (weeks)	25	136.9	40.1	25	136.9	40.1	53	156.1	30.5	5	15.0	5.7	5	15.0	5.7	8	10.0	2.3

Chapter 4
Immunosuppression and Other Medications

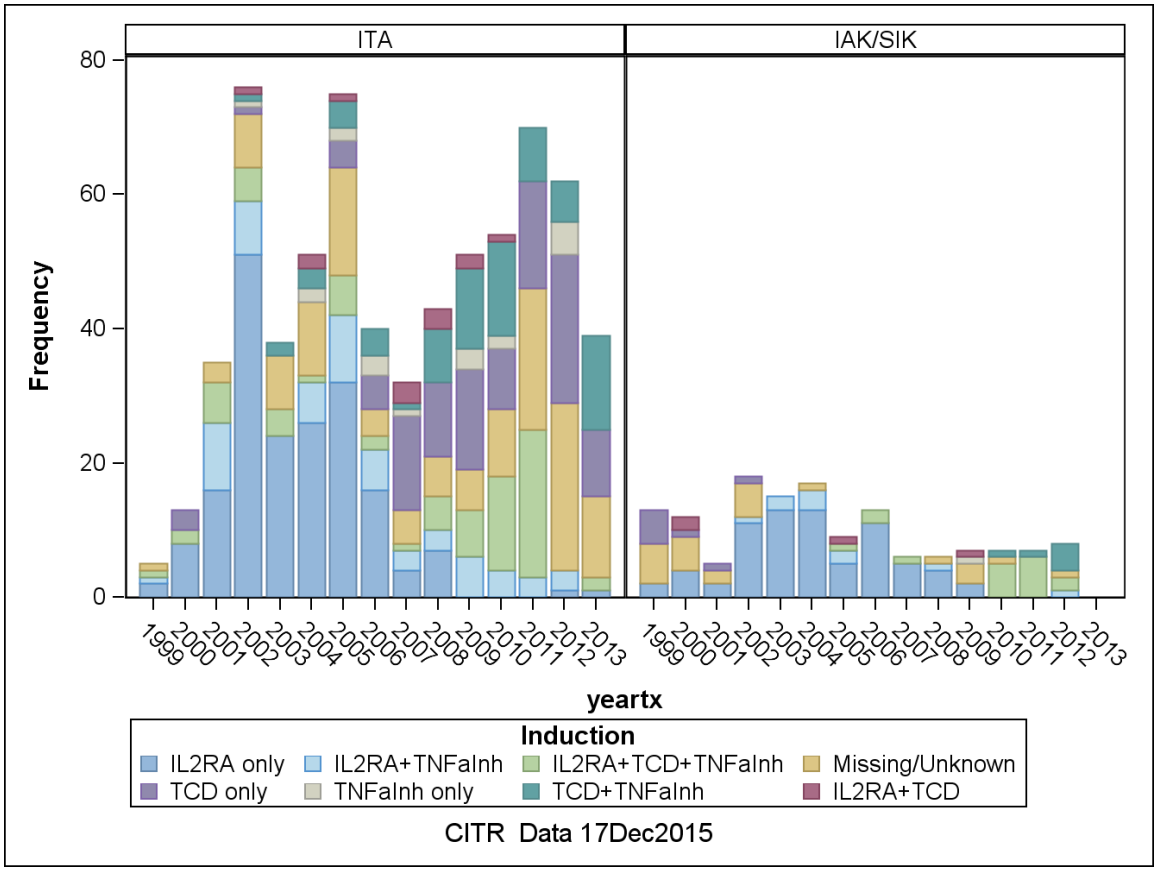
Introduction

The following table classifies the induction and maintenance therapies used in CITR allograft recipients.

Super Category	Category	Agent
T-cell depleting agent	Monoclonal TCD	Alemtuzumab (Campath)
	Monoclonal antiCD3	Teplizumab (hOKT3y-1-ala-ala)
	Polyclonal TCD	Antithymocyte
		Antilymphocyte globulin
T-cell Activation inhibition	IL2R antagonist	Daclizumab
		Basiliximab
Replication inhibition	DNA analogue	Azathioprine
	IMPDH inhibitor	Mycophenolate Mofetil/ Mycophenolic acid
	mTor inhibitor	Sirolimus
		Everolimus
Lymphocyte tracking inhibitor	LFA1 inhibitor	Efalizumab (Raptiva)
Desensitization	Immunoglobulin	IVIG
Co-Stimulation Inhibition	Monoclonal antiCD28	Belatacept/Abatacept
Calcineurin inhibitor	Calcineurin inhibitor	Cyclosporine
		Neoral
		Tacrolimus
B-cell Depleting	Bcell Depleting	Rituximab
Anti-inflammatory	Corticosteroids	Steroid
	IL1 Receptor antagonist (IL1RA)	IL1R
		Deoxyspergualin
	TNF antagonist (TNF-a inhibitor)	Infliximab
		Etanercept

Multiple induction and maintenance agents may have been administered peri- and post- several infusions in the same recipient. In displays of results post last infusion, the cumulated induction agents are classified into the appropriate class combination (e.g., TCD+IL2RA – these could have been given at the same or different infusions in the recipient). For analysis of outcomes post last infusion, the induction and maintenance agents are cumulated over multiple infusions and the resulting combination is carried forward through the patient's follow-up post last infusion. These cumulative categories are shown in this Chapter by type of transplant and year of first infusion (era).

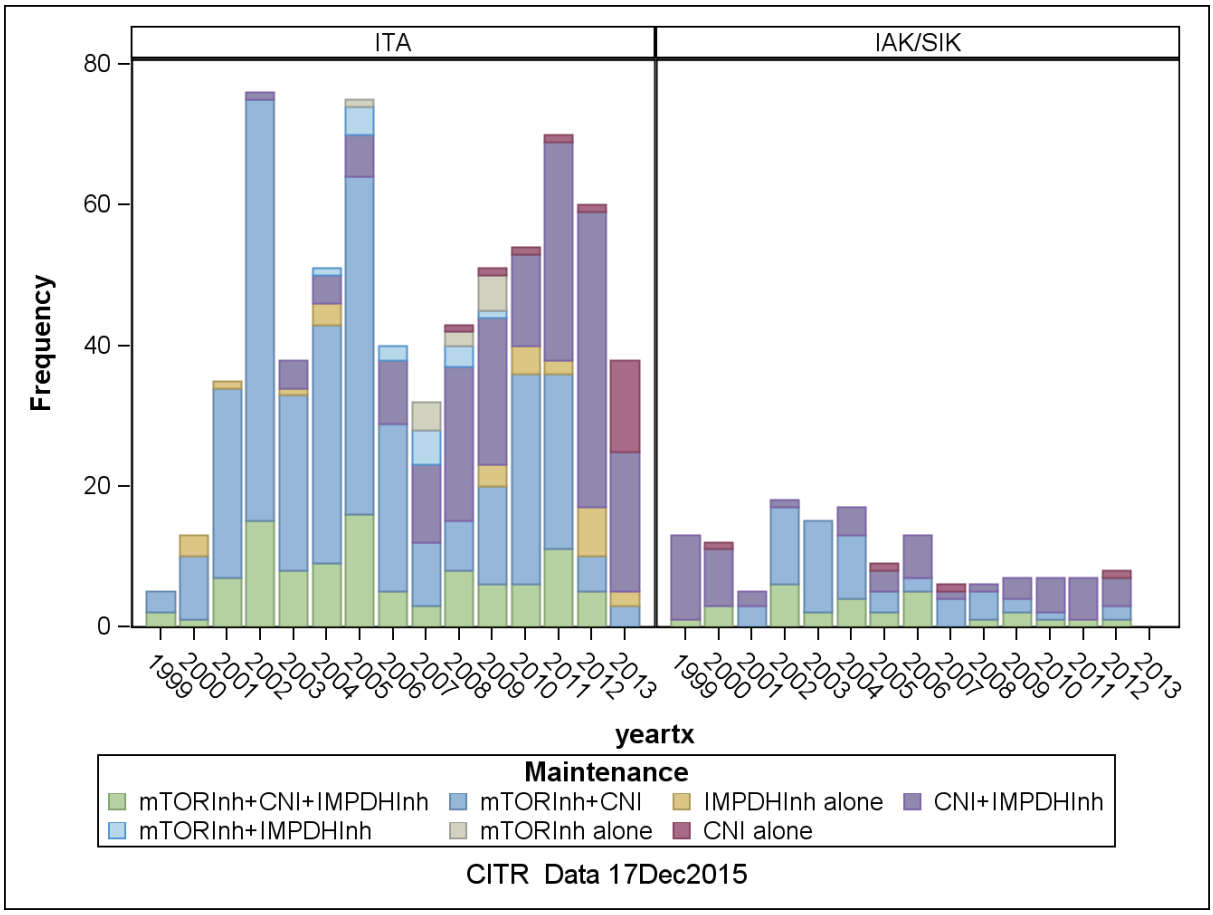
Exhibit 4 – 1
Induction Immunosuppression by Transplant Type and Era



	Type of transplant				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Induction												
IL2RA only	188	27.5	72	50.3	96	54.2	140	54.3	22	10.7	2	1.1
TCD only	110	16.1	8	5.6	12	6.8	9	3.5	49	23.8	48	25.8
TNFaInh only	19	2.8	1	0.7	1	0.6	7	2.7	7	3.4	5	2.7
TCD+TNFaInh	77	11.3	6	4.2	1	0.6	13	5.0	36	17.5	33	17.7
IL2RA+TCD	13	1.9	4	2.8	3	1.7	4	1.6	10	4.9	.	.
IL2RA+TNFaInh	63	9.2	10	7.0	20	11.3	29	11.2	17	8.3	7	3.8
IL2RA+TCD+TNFaInh	78	11.4	17	11.9	14	7.9	16	6.2	33	16.0	32	17.2
Missing/Unknown	136	19.9	25	17.5	30	16.9	40	15.5	32	15.5	59	31.7
TOTAL	684	100.0	143	100.0	177	100.0	258	100.0	206	100.0	186	100.0

In both ITA and IAK/SIK, induction with IL2RA only, the regimen of choice in the early eras (1999-2006), has increasingly been replaced in recent eras with combinations including T-cell depletion and TNF-a inhibition, with or without IL2RA.

Exhibit 4 – 2
Maintenance Immunosuppression by Transplant Type and Era



	Type of transplant				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Maintenance												
mTORInh+CNI+IMPDHInh	102	15.0	29	20.3	35	19.8	51	19.8	27	13.1	18	9.8
mTORInh+CNI	323	47.4	54	37.8	113	63.8	158	61.2	71	34.5	35	19.1
mTORInh+IMPDHInh	16	2.3	.	.	.	.	7	2.7	9	4.4	.	.
CNI+IMPDHInh	184	27.0	56	39.2	24	13.6	36	14.0	77	37.4	103	56.3
mTORInh alone	12	1.8	.	.	.	.	1	0.4	11	5.3	.	.
CNI alone	18	2.6	4	2.8	1	0.6	1	0.4	4	1.9	16	8.7
IMPDHInh alone	26	3.8	.	.	4	2.3	4	1.6	7	3.4	11	6.0
TOTAL	681	100.0	143	100.0	177	100.0	258	100.0	206	100.0	183	100.0

A Calcineurin inhibitor+mTOR inhibitor regimen (“Edmonton protocol”) comprised the abundant majority of maintenance immunosuppression in the early eras 1999-2006. Increasingly it has been replaced with a CNI-IMPDH inhibitor combination in the recent eras in both ITA and IAK/SIK.

Chapter 5
Graft Function

Introduction

Summary

Taken from the combined evidence in the analyses presented in this chapter, the field of allogeneic islet transplantation as represented in the CITR data to date yields reliable, robust results in support of best practices to optimize clinical outcomes of islet transplantation for T1 diabetes. Despite the statistical challenges of multiple primary endpoints, many covariates, and various analytical approaches, the factors contributing to both statistically significant and clinically important improvements in outcomes are becoming clear and robust with accruing data.

The analytical process evolved as follows, and was conducted for the ITA and IAK transplant groups separately. First, every variable available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome (insulin independence, HBa1c, etc.). Those variables significant at $p<0.10$ were then stepped into multivariate models to eliminate duplicative effects and narrow down the final effects. While some predictive variables (factors) consistently exerted a clear beneficial effect across outcomes, each outcome within ITA and IAK yielded a slightly different set of significant favorable factors. To facilitate interpretation for translation into clinical practice, the set of favorable factors that were common to all the outcomes within ITA and IAK respectively were selected, and subgroups comprising all those with the favorable common factors is compared to the remainder (who may have none, one or more, but not all the favorable factors). These final results of the common favorable factors on the primary outcomes are exhibited together (Exhibit 5-8.) Targeting the common favorable factors somewhat dilutes the largest differences seen univariately for each outcome; however, this method identifies the factors that are clinically most relevant to the recipients. These then comprise best practices in terms of patient selection and medical management for allogeneic islet transplantation. That said, some leeway in applying these guidelines should always prevail in the management of specific patients who may benefit from islet transplantation.

Remarkably, only a handful of common favorable factors emerge, and their combined effects appear to be additive, as exhibited by the final multivariate models of the various primary endpoints (Exhibit 5-8). These salutary factors include:

For islet alone:

- Selection of patients aged 35 years or older. The remarkable consistency of this result runs across most of the primary outcomes including achievement and long-term retention of insulin independence or reduction in daily insulin requirement, higher levels of basal C-peptide, lowered HbA1c levels and/or drop by 2%, and near elimination of severe hypoglycemia. As islet transplantation is not life-saving, this selection factor helps optimize use of scarce donor pancreas resources. Obviously, clinical judgment should drive the process: all other favorable factors being in place, someone younger than 35 may still be a good candidate for an islet transplant.
- Use of IL2RA, T-cell depletion, TNF-a inhibition, MTOR inhibition and calcineurin inhibitors continue to be associated with improved clinical outcomes with accruing data in CITR. A major limitation from the CITR data is that these strategies were not assigned at random and independently of each other; hampering the ability to isolate the effects of each factor separately. Nonetheless, from analyses of each factor alone (yes/no) and as combinations of induction and maintenance immunosuppression, the benefit of these agents continues to be well supported by the data.

- Islet product characteristics have remained consistently high over the eras of the Registry (Chapter 3). Because of the consistently high levels and narrow ranges of all islet product criteria used for clinical transplantation, it is difficult to statistically evaluate the effect of low-grade vs. high-grade products. The only factor that consistently yields improved outcomes is higher total IEQs infused, whether in a single infusion or over 2-3 infusions.

For islet-after-kidney:

- As with ITA, total IEQs ≥325,000 over one to several infusions is a primary predictor of the greatest clinical benefit of islet transplantation..
- Donor management with insulin therapy during retrieval is associated with improvements in most of the primary outcomes and now emerges as a favorable common factor for IAK.

Simultaneous islet-kidney (SIK):

- There were 9 cases of SIK reported to the registry as of the data lock for this report. While their data are reported in earlier chapters (IAK/SIK), they were excluded from analyses of primary endpoints to keep the transplant groups clean (SIK is more similar to ITA than IAK in terms of immunosuppression, but also similar to IAK in terms of kidney transplant).

Some possible additional benefits may be associated with certain islet processing factors such as use of UW solution vs. HTK solution. Serva/NB1 and thermolysin also persist in associating with improved outcomes. Again because of the lack of balance and randomization, these effects are being analyzed in a separate focus analysis.

The hallmark effect of islet transplantation as exhibited in these data is the remarkably effective and durable resolution of severe hypoglycemic events (Exhibits 5-7 and 5-8). While many IAK recipients never had SHE before transplantation, and fewer ITA recipients without SHE pre-infusion were transplanted in later eras, this remarkable and important benefit of islet transplantation in T1D could serve as a stand-alone indication for ITx in well-selected recipients.

While the CITR definition of insulin independence is simplistic (≥2 weeks), it is based on patient diaries, is verified at scheduled visits, and does represent the most completely available outcome data in the Registry, with fasting C-peptide also having reasonably complete reporting.

Salient results are presented in Chapter 5 Exhibits. Detailed results are available in supplements online at www.citregistry.org / Reports / CITR 9th Annual Report / Supplemental Exhibits. The following table relates the Chapter 5 exhibits to the supplemental exhibits.

Chapter 5 Exhibits

	Chapter 5 Exhibit	Supplemental Exhibit a=ITA ǀ b=IAK
Achievement of insulin independence post first infusion (Kaplan-Meier)	5-1	A-1
Insulin independence post last infusion (Prevalence / Bar charts)	5-2	A-2a ǀ A-2b
Retention of C-peptide ≥0.3 ng/mL post last infusion (Kaplan-Meier and Cox models on complete graft loss (CGL))	5-3	A-3a ǀ A-3b
Fasting C-peptide ≥0.3 ng/mL post last infusion (Prevalence / Bar charts)	5-4	A-4a ǀ A-4b
Fasting blood glucose 60-140 mg/mL post last infusion (Prevalence / Bar charts)	5-5	A-5a ǀ A-5b

	Chapter 5 Exhibit	**Supplemental Exhibit a=ITA ǀ b=IAK**
HbA1c <6.5% or drop by 2% (Prevalence / Bar charts)	5-6	A-6a ǀ A-6b
Absence of severe hypoglycemia (Prevalence / Bar charts)	5-7	A-7a ǀ A-7b
Combined Effect of Common Favorable Factors on Primary Outcomes Post Last Infusion, ITA and IAK separately (Prevalence / Bar charts)	5-8	—
Insulin dose post last infusion (Box plots and generalized estimating equations)	5-9	A-9a ǀ A-9b
Fasting C-peptide levels post last infusion (Box plots and generalized estimating equations)	5-10	A-10a ǀ A-10b
HbA1c levels post last infusion (Box plots and generalized estimating equations)	5-11	A-11a ǀ A-11b
Fasting blood glucose levels post last infusion (Box plots and generalized estimating equations)	5-12	A-12a ǀ A-12b
Association of C-peptide ≥0.3 ng/mL on other primary outcomes (Prevalence / Bar charts)	5-13	—
Reinfusion (Bar charts and Kaplan-Meier)	5-14	—

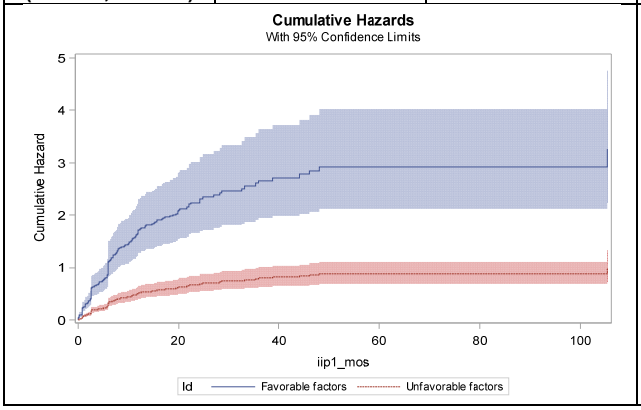
Insulin Independence

First achievement of insulin independence is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft function or loss, islet resource availability for re-infusion, individual tolerance of immunosuppression, patient/doctor decisions, and myriad other factors, some of which are characterized in the CITR data and others not. Notably, the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope.

Using all the information in the Registry over the eras, factors predictive of first achievement of insulin independence in ITA and IAK were identified. In ITA patients predictive factors were induction immunosuppression with IL2RA inhibitor (P<0.0001), ≥500K IEQs infused overall (p=0.0081), and donor serum creatinine ≥1.3 (p=0.0087). In IAK patients predictive factors were maintenance immunosuppression with mTOR inhibitor and CNI (p=0.0331) and insulin autoantibody negative at baseline. From both Cox modeling and by subgroup analysis, ITA recipients with these favorable factors Exhibit 3-fold higher likelihood of achieving insulin independence following allo-islet transplantation IAK with their respective common factors exhibit a 2-fold higher likelihood of achieving insulin independence relative to the comparator with all unfavorable factors (Figure 5-1 left panel). The individual effects of the predictive factors are shown in Exhibit 5-1, B1-B3 for ITA and C1-C2 for IAK.

Exhibit 5 – 1
First Achievement of Insulin Independence Post First Infusion, ITA and IAK Recipients Separately
(Through all infusions, censored at final graft loss or end of follow-up)

Final Multivariate Cox Models					
A1. ITA			**A2. IAK**		
Factors	**p-value**	**Hazard Ratio**	**Factors**	**p-value**	**Hazard Ratio**
IL2RA Inhibitor (1=Given, 0=Not Given)	<0.0001	1.673	**Maintenance Immunosuppression (1=mTOR Inhibitor and CNI , 0=Other)**	0.0331	1.766
IEQ's Infused (1=≥500,000, 0=<500,000	0.0081	1.408			
Donor Serum Creatinine (1= <1.3, 0= ≥1.3)	0.0087	1.411	**Baseline Insulin Autoantibody (1=Pos, 0=Neg)**	0.0399	0.503



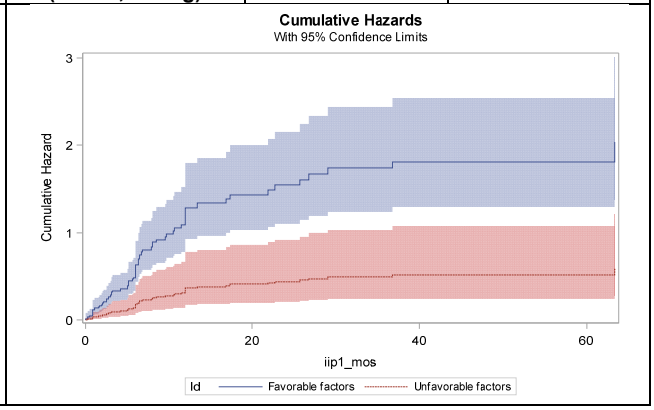
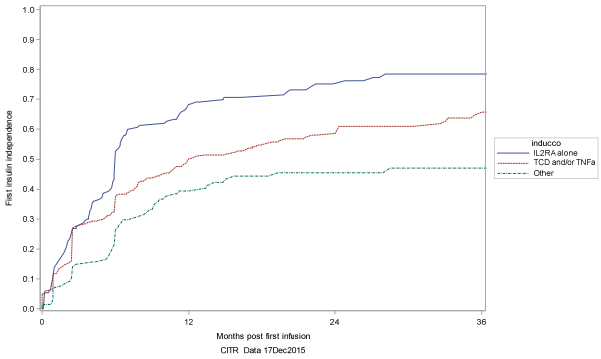
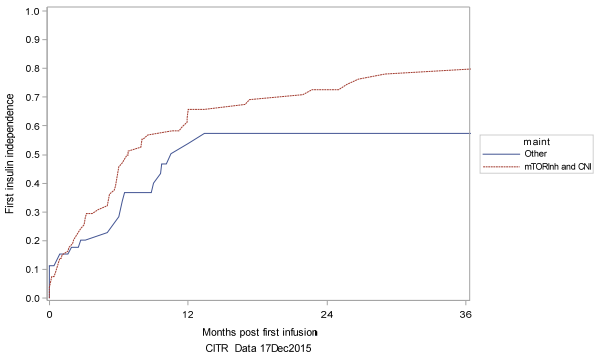
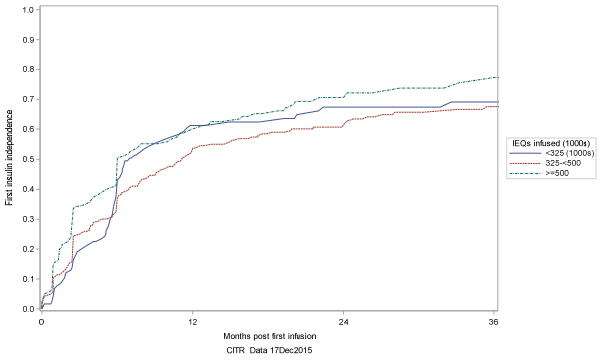
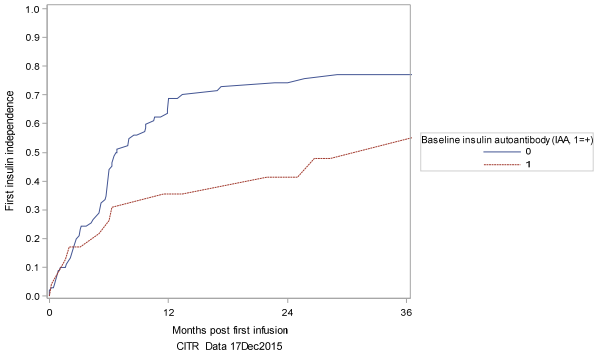
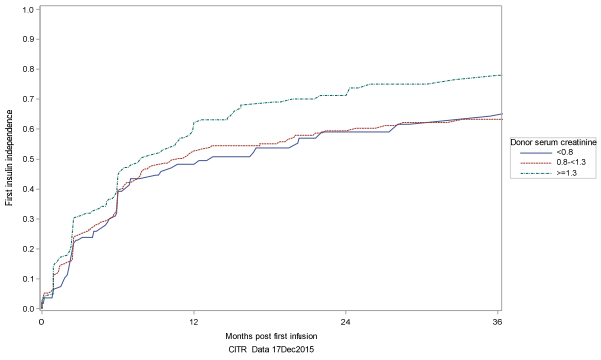


Exhibit 5 – 1 *(continued)*
First Achievement of Insulin Independence Post First Infusion, ITA and IAK Recipients Separately
(Through all infusions, censored at final graft loss or end of follow-up)

ITA	IAK
B1. Induction Immunosuppression with IL2RA Inhibitor favorable	**C1. Maintenance Immunosuppression with mTOR Inhibitor and CNI favorable**
	
B2. IEQ's Infused ≥500,000 favorable	**C2. Baseline Insulin Autoantibody Negative favorable**
	
B3. Donor Serum Creatinine ≥ 1.3 favorable	
	

Prevalence of insulin independence post last infusion (Exhibit 5-2) is the optimal way to characterize the probability of being insulin independent in follow-up time post islet transplantation, because insulin independence can be lost and re-gained, often over periods spanning months or years. Prevalence also reconciles disparities in factors that may be predictive of retention but not of achievement, or vice versa. However, multivariate analysis of prevalence is much more complex because of non-linearity over the multiple time points and the high order of interactions that are required to test for changes in the response across 2-3 levels each of numerous predictors (e.g., recipient baseline characteristics, islet processing and product criteria, and immunosuppression) over time.

The raw, unadjusted prevalence of insulin independence stratified by transplant type is shown in Exhibit 5-2A. For both ITA and IAK patients, prevalence of insulin independence is about 50% at 1 year post last infusion and declines over 5-years of follow-up time, more sharply in the IAK group. Individual factors that were significantly ($p<0.05$) associated with maintaining insulin independence at higher levels through 5 years are presented in Exhibit 5-2B for ITA and Exhibit 5-2C for IAK.

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-8, stratified for ITA and IAK separately.

Exhibit 5 – 2A
Unadjusted Prevalence of Insulin Independence Post Last Infusion

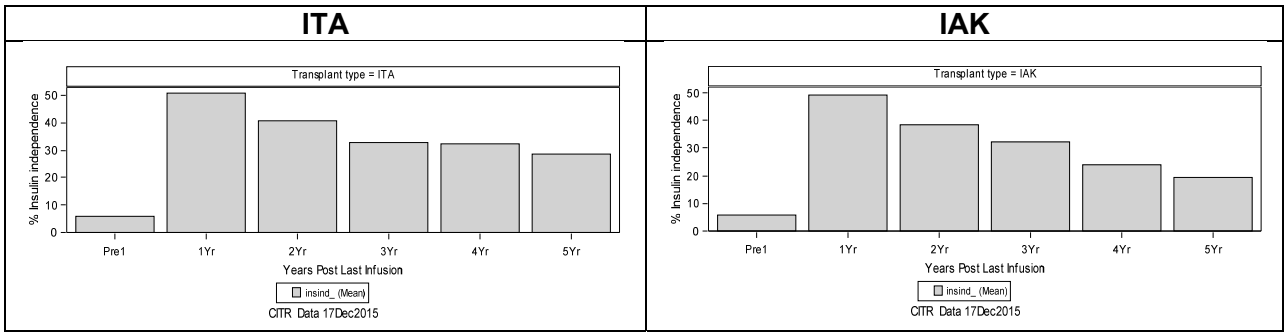
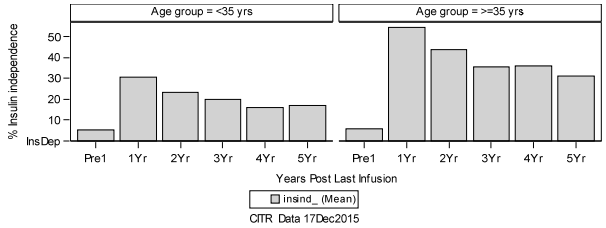
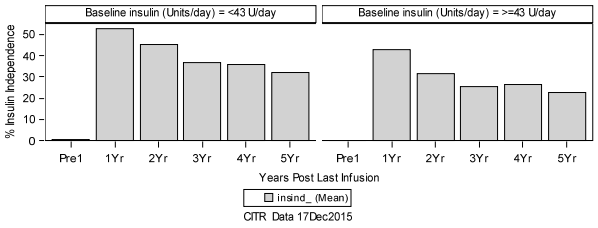


Exhibit 5 – 2B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

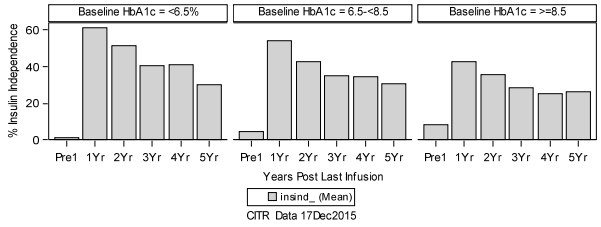
A. Recipient Age ≥ 35 years favorable (p<0.0001)



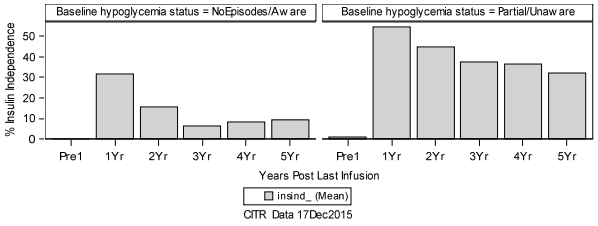
B. Baseline Insulin <43 units/day favorable (p=0.0056)



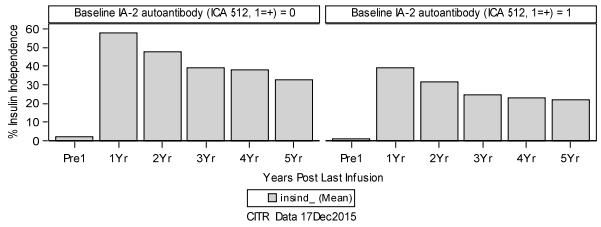
C. Baseline HbA1c <8.5 favorable (p=0.0055)



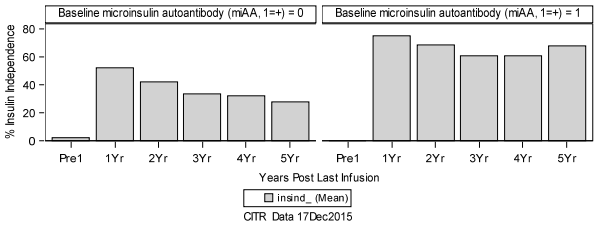
D. Baseline Hypoglycemia Awareness: partial/unaware favorable (p=0.0178)



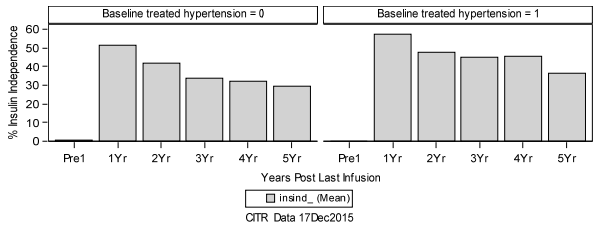
E. IA-2 (ICA 512) negative at baseline favorable (p=0.0006)



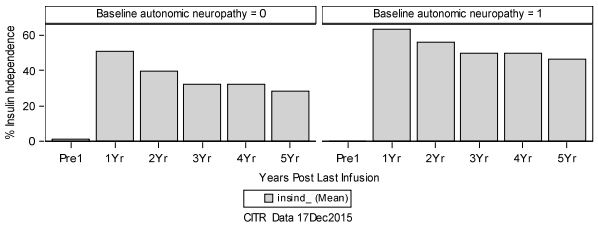
F. Microinsulin (mIAA) positive at baseline favorable (p=0.0009)



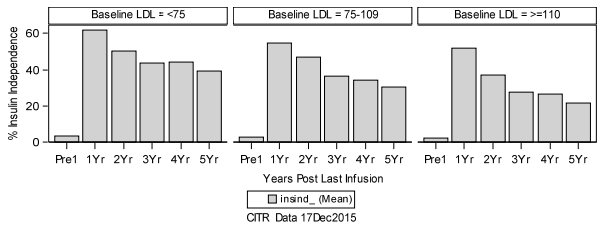
G. Antihypertensives at baseline favorable (p=0.0410, R^2 with age=0.04)



H. Autonomic neuropathy at baseline favorable (p=0.0037, R^2 with age=0.002)



I. Baseline LDL < 75 favorable (p=0.0288)



J. Baseline triglycerides < 30 favorable (p=0.0058)

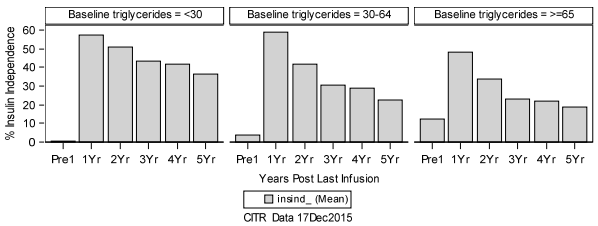
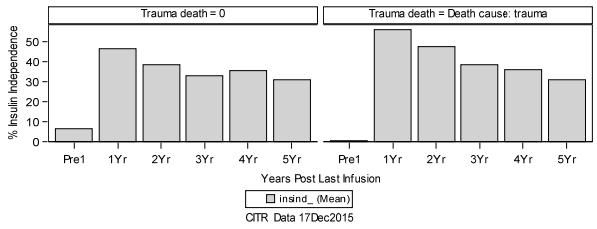
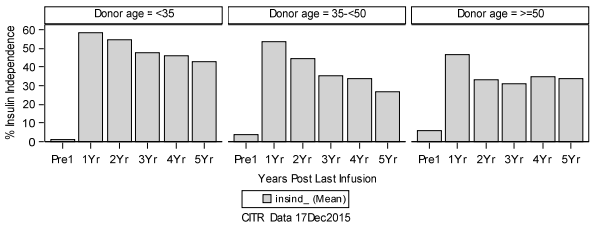


Exhibit 5 – 2B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

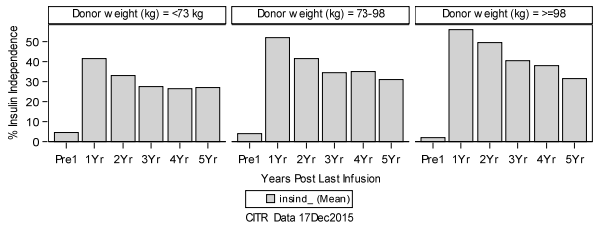
K. Donor Cause of Death: Trauma favorable (p=0.0292)



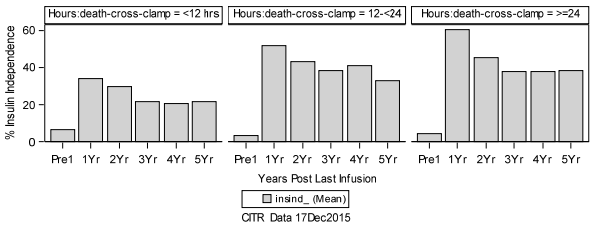
L. Donor Age <35 favorable (p=0.0096)



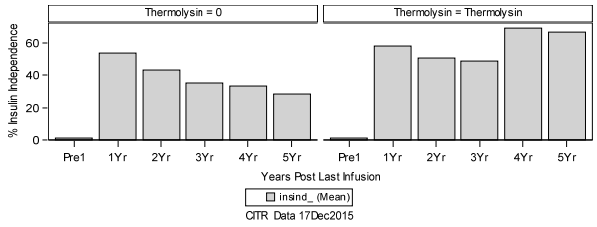
M. Donor Weight ≥ 98 kg favorable (p=0.0089)



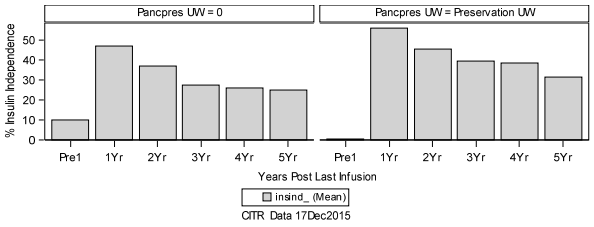
N. Hours from Death to Cross-Clamp ≥ 12 favorable (p=0.0013)



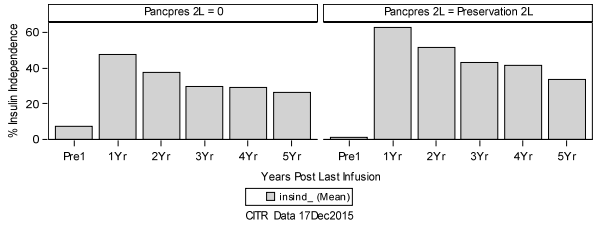
O. Thermolysin favorable (p=0.0323)



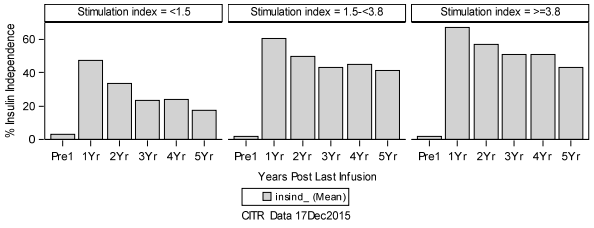
P. Preservation UW favorable (p=0.0062)



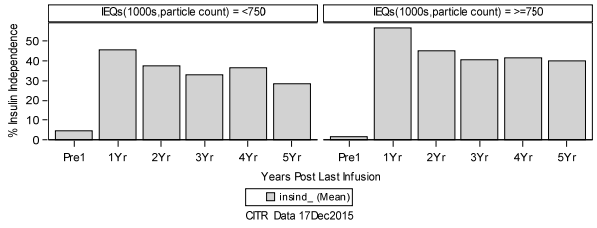
Q. Preservation 2L favorable (p=0.0011)



R. Stimulation Index ≥ 1.5 favorable (p=0.0005)



S. IEQs(1000s,particle count) ≥750 (p=0.0386)



T. Total IEQs infused ≥ 500 (p<0.0001)

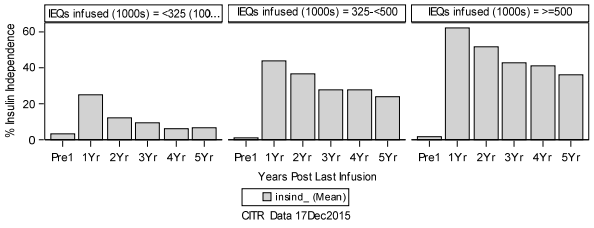
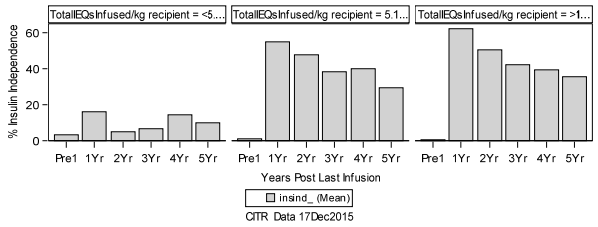
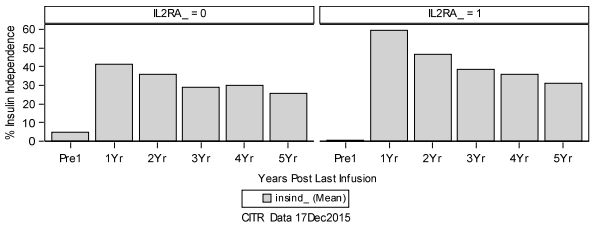


Exhibit 5 – 2B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

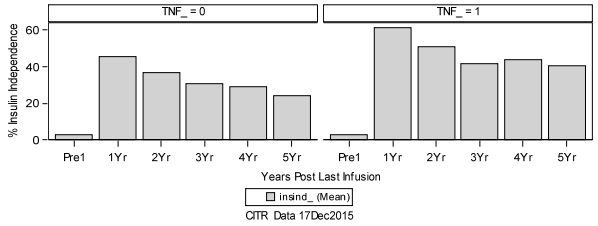
U. Total IEQs infused/kg recipient weight >5.15 (p=0.0002)



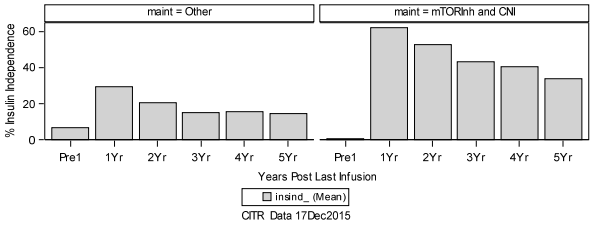
V. Induction Immunosuppression with IL2R antagonist favorable (p=0.0004)



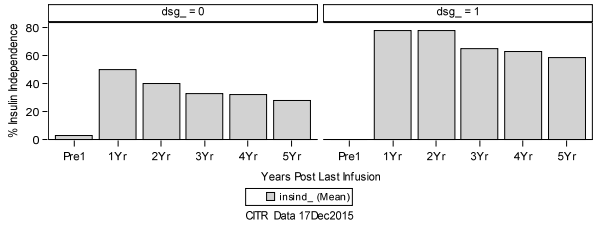
W. Induction Immunosuppression with TNF-a-blockade favorable (p=0.0001)



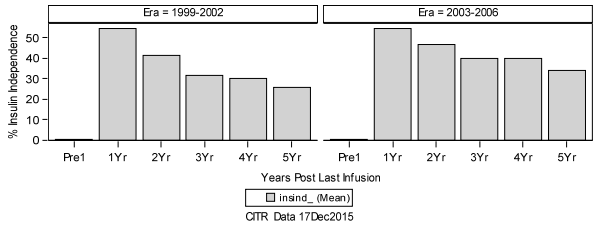
X. Maintenance Immunosuppression with mTOR Inhibitor and Calcineurin Inhibitor (p<0.0001)



Y. DSG favorable (p=0.0008)



Z. Era (p=0.0115)



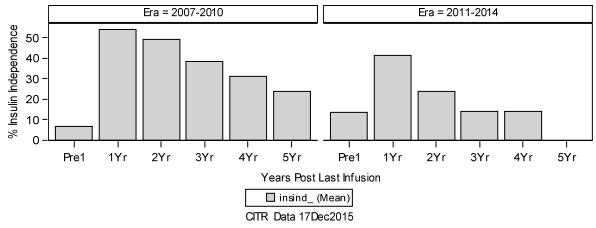
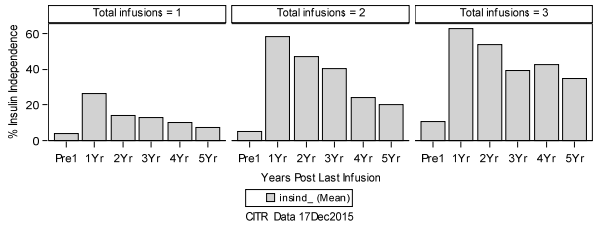
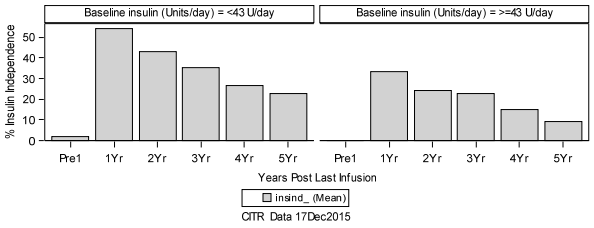


Exhibit 5 – 2C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

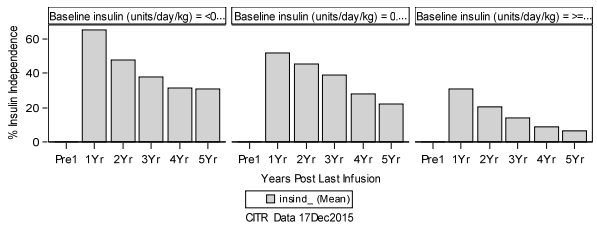
A. Total infusions ≥ 2 favorable (p=0.0003)



B. Baseline insulin <43 units/day favorable (p=0.0344)

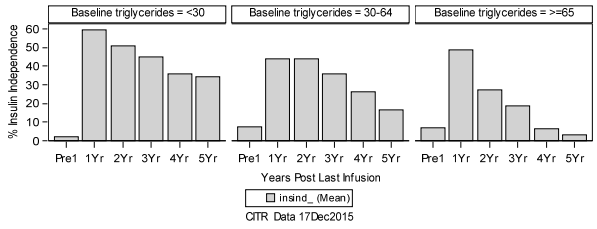


C. Baseline insulin <0.66 units/day/kg recipient weight favorable (p=0.0041)

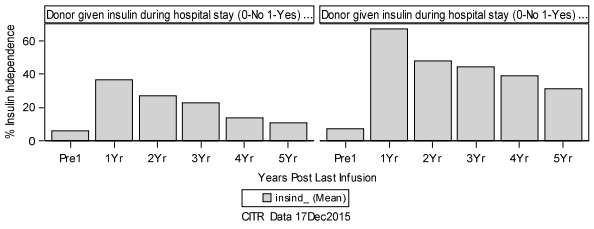


D. Baseline insulin autoantibody negative favorable (p=0.0054)

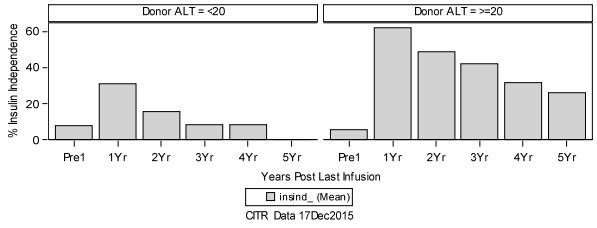
E. Baseline triglycerides < 30 favorable (p=0.0305)



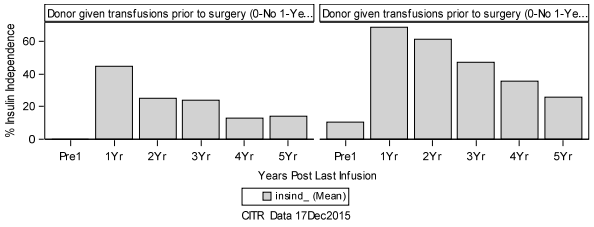
F. Donor given insulin during hospital stay favorable (p=0.0107)



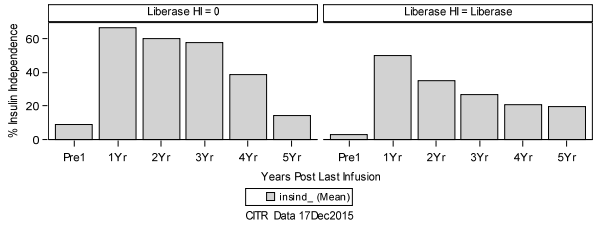
G. Donor ALT ≥ 20 favorable (p=0.0228)



H. Donor given transfusions prior to surgery favorable (p=0.0043)



I. Liberase unfavorable (p=0.0241)



J. Serva/NB1 favorable (p=0.0063)

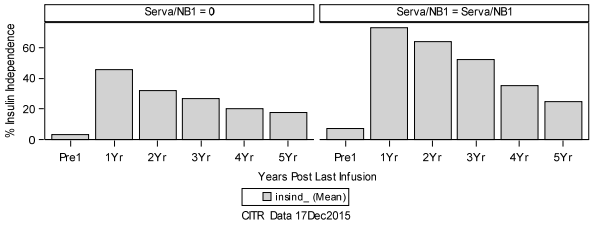
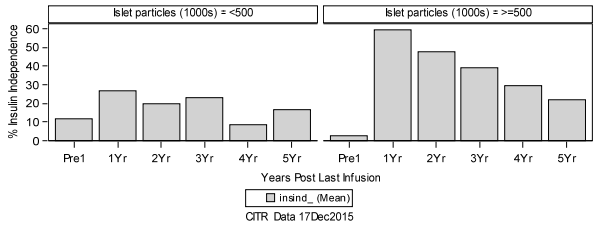
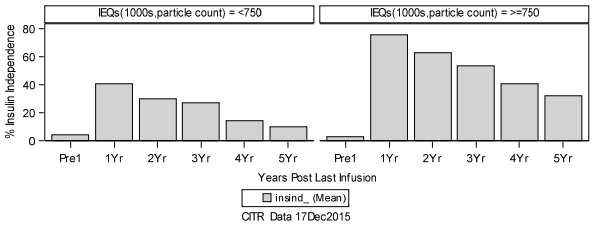


Exhibit 5 – 2C *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

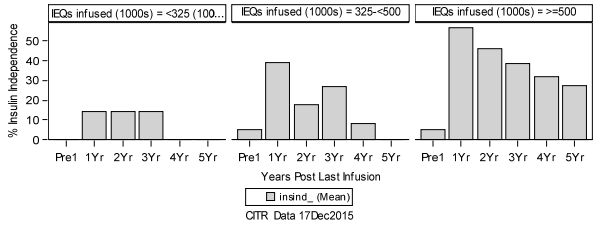
K. Islet particles ≥ 500 (1000s) favorable (p=0.0279)



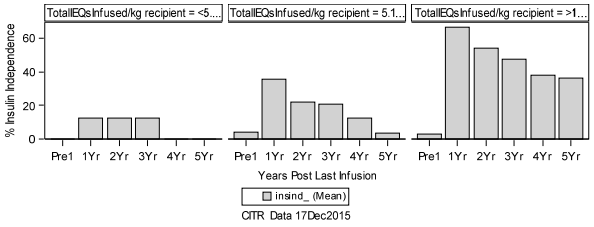
L. IEQ particle count ≥ 750 (1000s) favorable (p=0.0028)



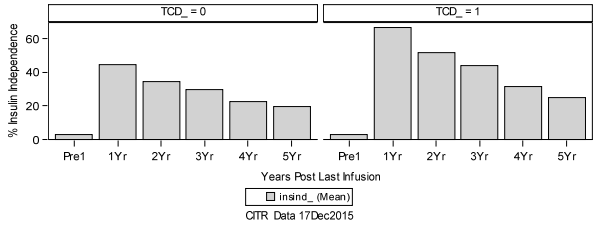
M. IEQs infused ≥500 (1000s) favorable (p=0.0183)



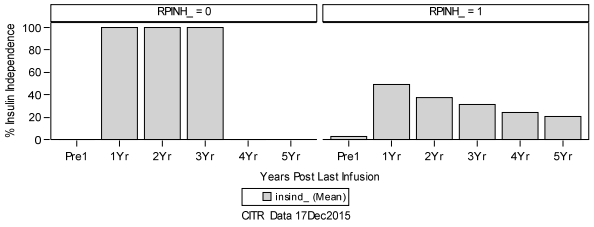
N. IEQs infused per kg recipient weight > 10.45 favorable (p=0.0001)



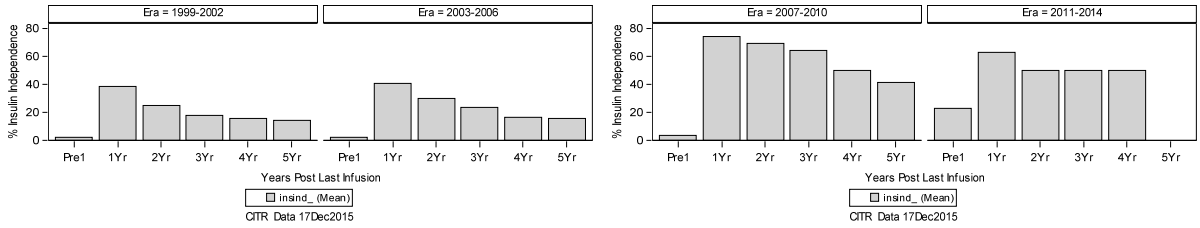
O. Induction Immunosuppression with T-cell depletion favorable (p=0.0389)



P. Maintenance Immunosuppression with RPINH favorable (p=0.0387)



Q. Era (p=0.0010)



C-peptide≥0.3 ng/mL

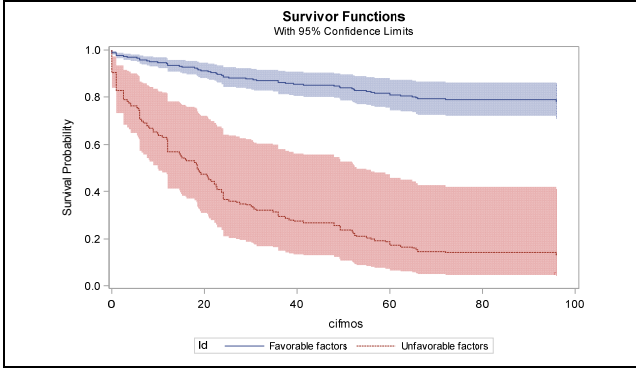
Of all 1,942 allogeneic islet infusions with C-peptide data, 62 (3.2%) resulted in primary non-function (C-peptide never ≥ 0.3 ng/mL up to reinfusion: 3.2% in 1999-2002, 3.1% in 2003-2006, 2.2% in 2007-2010, and 4.1% in 2011-2013.

Retention of graft function (C-peptide ≥0.3 ng/mL; Exhibit 5-3) post last infusion – modeled as time to complete graft loss (CGL) -- is maximized in ITA patients by recipient age ≥ 35 (p=<0.0001), induction immunosuppression with TNF-α (p=0.0036), and total IEQs infused ≥500K (p=0.0391) and in IAK patients by maintenance immunosuppression with mTOR inhibitor (p= 0.0249) and total IEQs infused ≥500K (p=0.0012). With these their respective favorable factors combined, graft retention rate remained at 80% through 8 years in both ITA and IAK groups.

Exhibit 5 – 3
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion

Combined effects of most favorable factors

A1. ITA			A2. IAK		
Factors	**p-value**	**Hazard Ratio**	**Factors**	**p-value**	**Hazard Ratio**
Age (1= ≥35, 0= <35)	<0.0001	0.397	**mTOR Inhibitor (1=Given, 0=Not Given)**	0.0249	0.425
TNF alpha (1=Given, 0=Not Given)	0.0036	0.555			
IEQ's Infused	0.0391	0.743	**IEQ's Infused**	0.0012	0.416



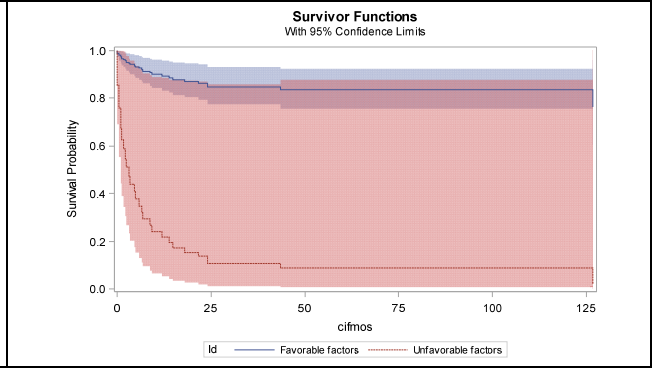
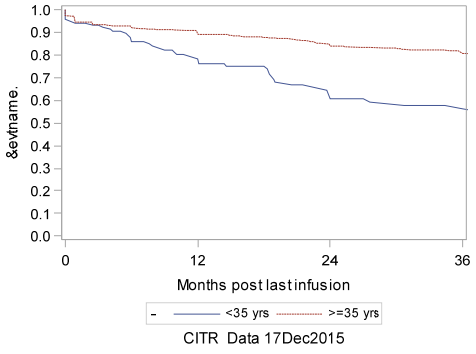
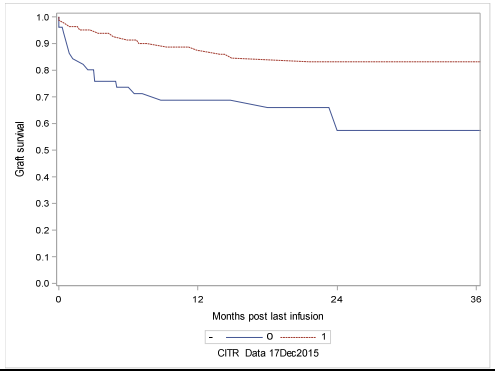
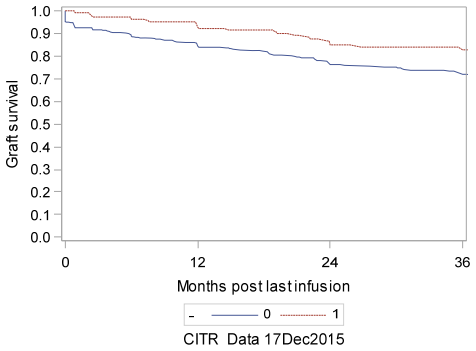
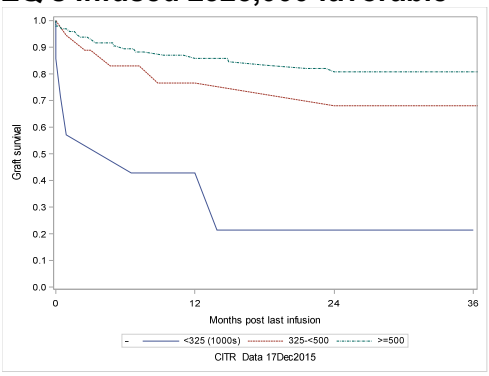
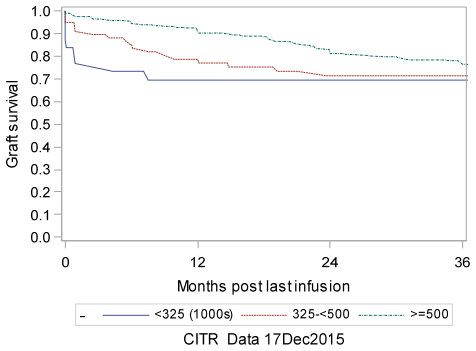


Exhibit 5 – 3 *(continued)*
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion

Effects of individual factors

ITA	IAK
B1. Recipient Age ≥ 35 years favorable	**B2. Maintenance Immunosupression with mTOR Inhibitor favorable**
	
C1. Induction Immunnosuppression with TNF alpha favorable	**C2. IEQ's Infused ≥325,000 favorable**
	
D1. IEQ's Infused ≥500,000 favorable	
	

The raw, unadjusted prevalence of C-peptide ≥0.3 ng/mL stratified by transplant type is shown in Exhibit 5-4A. For ITA patients, prevalence of C-peptide ≥0.3 ng/mL was 80% at one year post last transplant and gradually declined to 45% at 5 year post last infusion. IAK patients had a slightly lower prevalence of 75% at 1 year, but experienced less decline, with 50% of IAK patients still having C-peptide ≥0.3 ng/mL after 5 years of follow-up time. Individual factors that were significantly ($p<0.05$) associated with maintaining C-peptide ≥0.3 ng/mL at higher levels through 5 years are presented in Exhibit 5-4B for ITA and Exhibit 5-4C for IAK. The factors which were significant differed substantially between the transplant type groups.

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-8, stratified for ITA and IAK separately.

Exhibit 5-4A
Unadjusted Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion

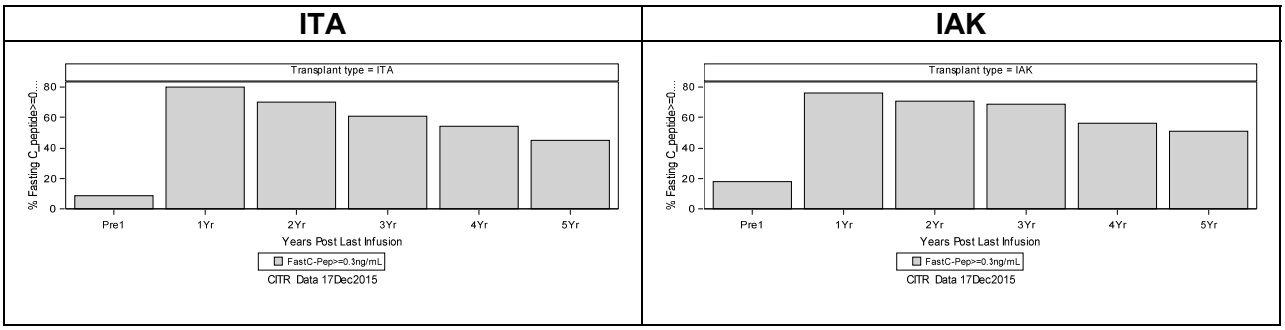
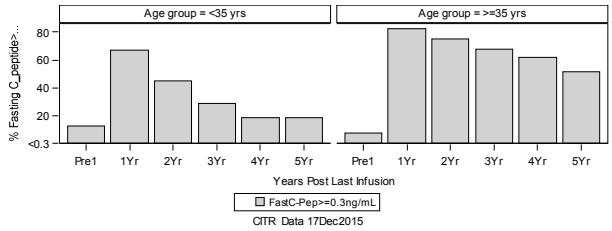
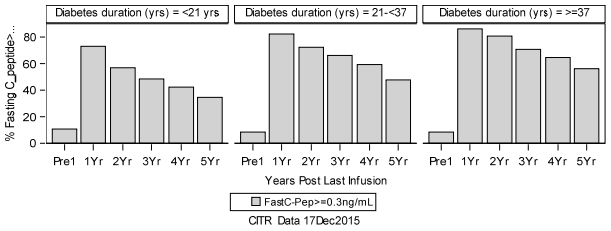


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

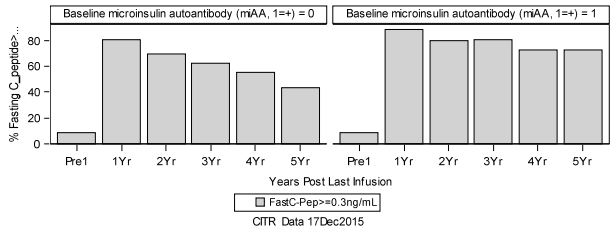
A. Recipient Age ≥ 35 years favorable (p<0.0001)



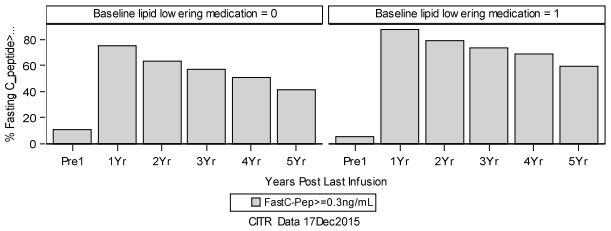
B. Duration of Diabetes (p=0.0002)



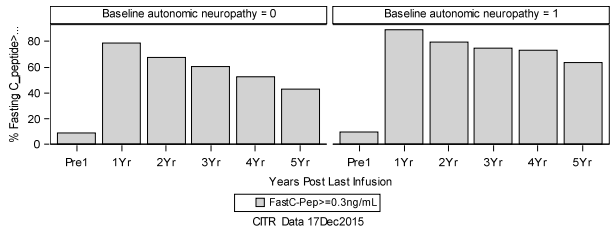
C. Microinsulin (mIAA) positive at baseline favorable (p=0.0099)



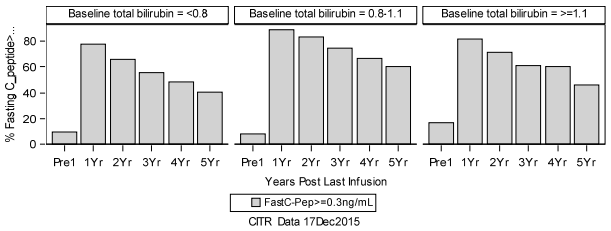
D. Baseline lipid lowering medication favorable (p=0.0022)



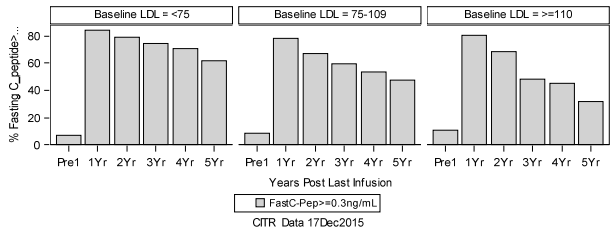
E. Baseline autonomic neuropathy favorable (p=0.0162)



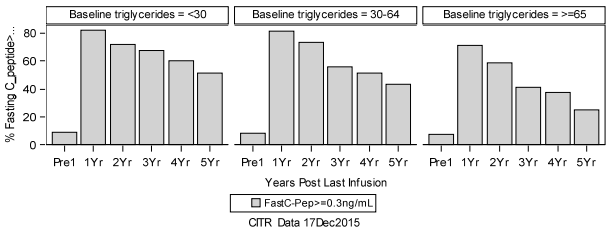
F. Baseline total bilirubin 0.8-1.1 favorable (p=0.0254)



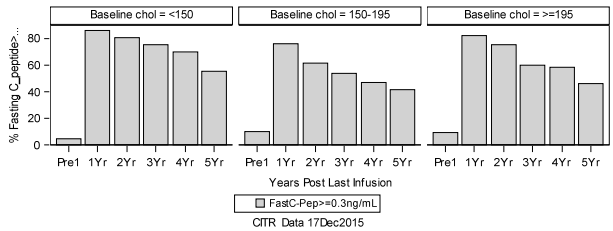
G. Baseline LDL <110 favorable (p=0.0016)



H. Baseline triglycerides < 65 (p=0.0028)



I. Baseline cholesterol <150 favorable (p=0.0227)



J. Donor ethnicity Hispanic favorable (p=0.0118)

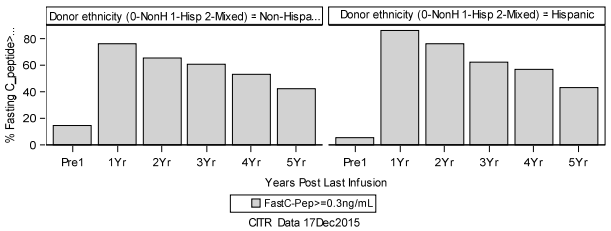
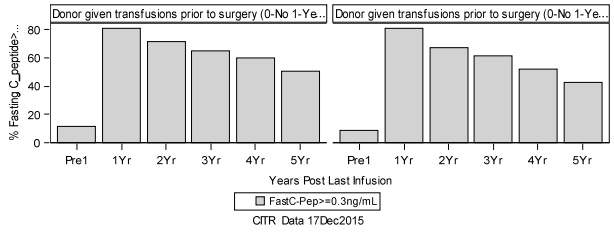
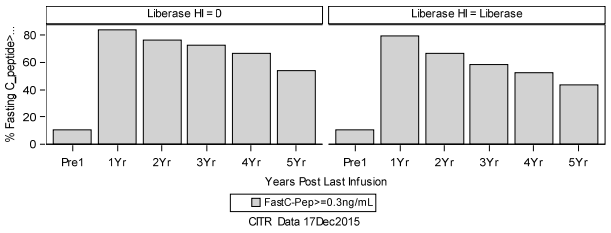


Exhibit 5-4B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

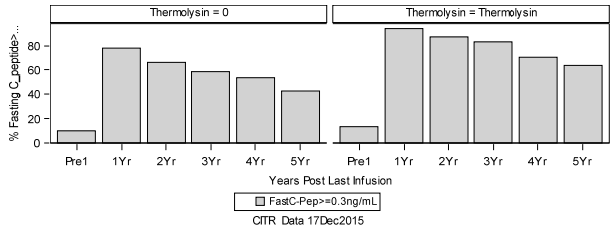
K. Donor not given transfusions prior to surgery favorable (p=0.0315)



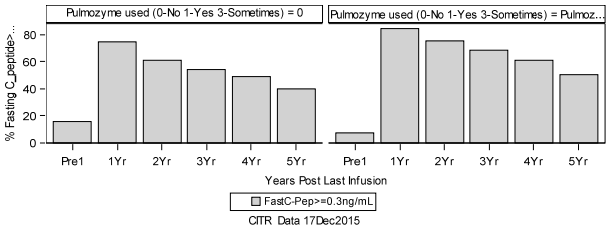
L. Liberase unfavorable (p=0.0003)



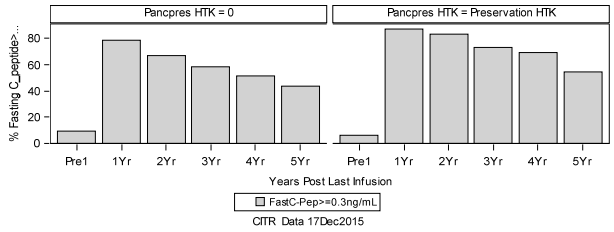
M. Thermolysin favorable (p=0.0003)



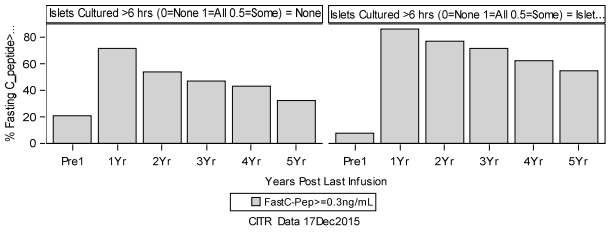
N. Pulmozyme favorable (p=0.0007)



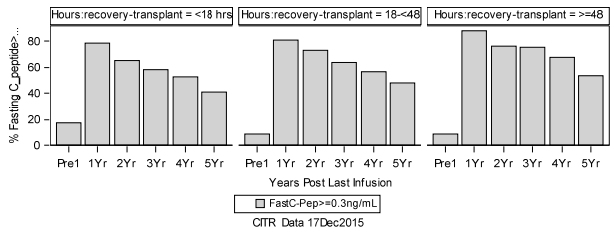
O. Pancreas Preservation with HTK favorable (p=0.0003)



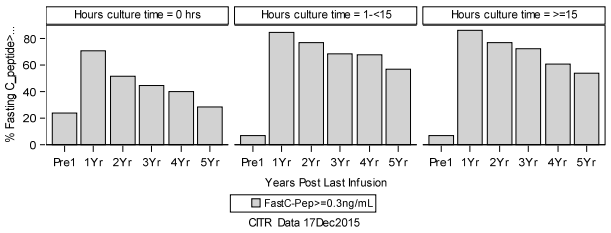
P. Islets Cultured > 6 hours favorable (p<0.0001)



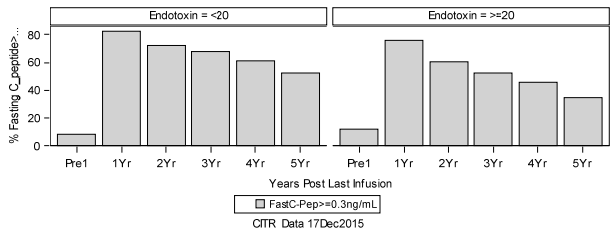
Q. Hours from recover to transplant ≥ 48 hours favorable (p=0.0260)



R. Hours culture time > 0 favorable (p<0.0001)



S. Endotoxin < 20 favorable (p=0.0149)



T. IEQs infused ≥325 (1000s) favorable (p=0.0084)

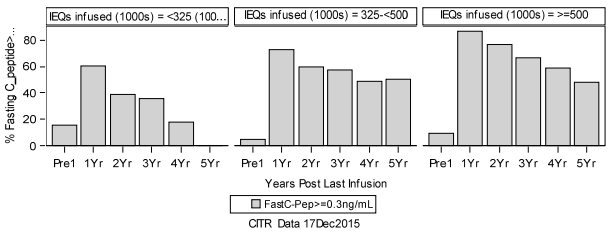
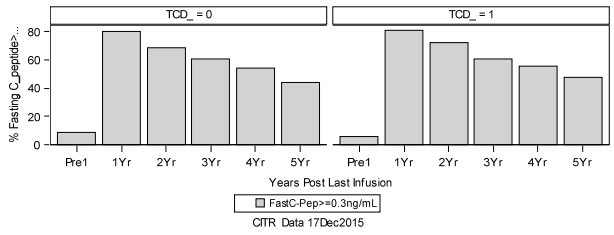
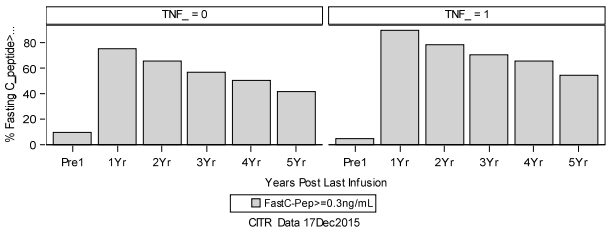


Exhibit 5-4B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

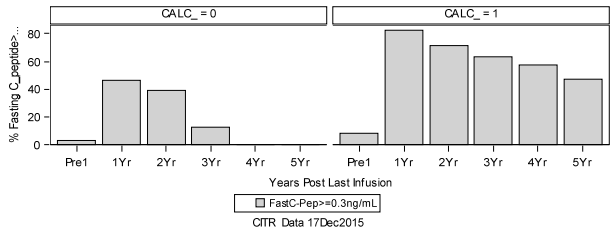
U. Induction Immunosuppression with T-cell depletion favorable (p=0.0416)



V. Induction Immunosuppression with TNF-a-blockade favorable (p=0.0001)



W. Maintenance Immunosuppression with Calcineurin Inhibitor (p=0.0002)



X. Era (p=0.0126)

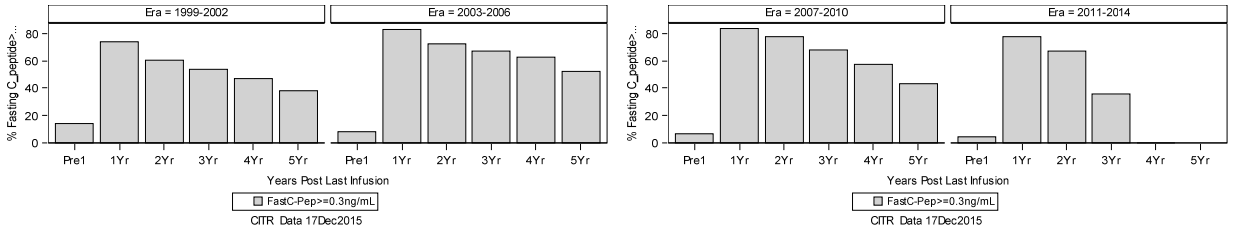
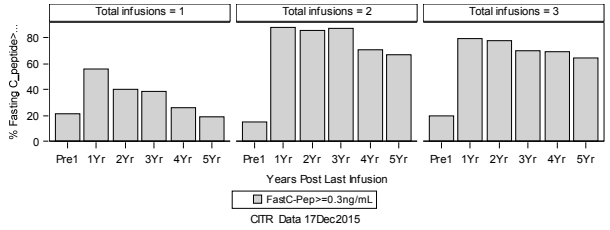
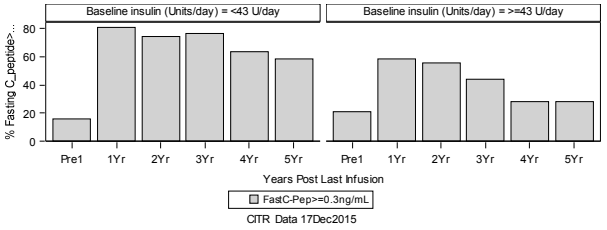


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

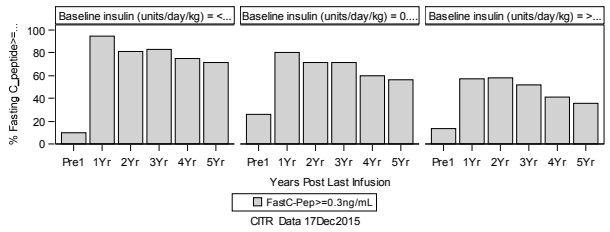
A. Total infusions ≥ 2 favorable (p=0.0044)



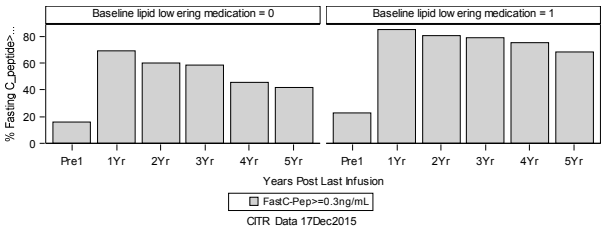
B. Baseline insulin <43 units/day favorable (p=0.0034)



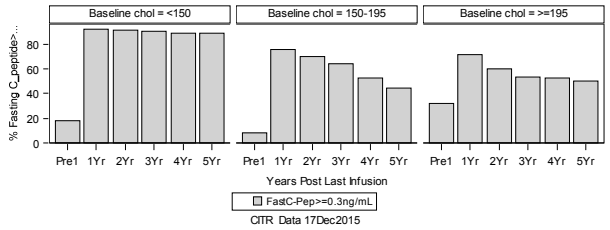
C. Baseline insulin <0.66 units/day/kg recipient weight favorable (p=0.0103)



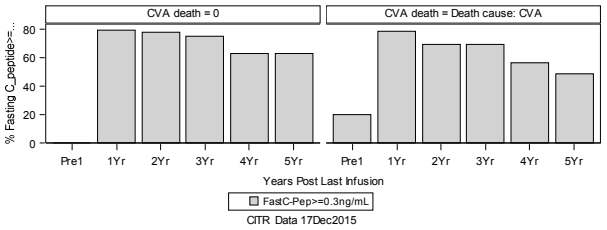
D. Baseline lipid lowering medication favorable (p=0.0140)



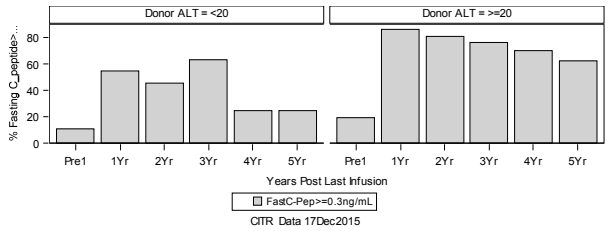
E. Baseline cholesterol <150 favorable (p=0.0049)



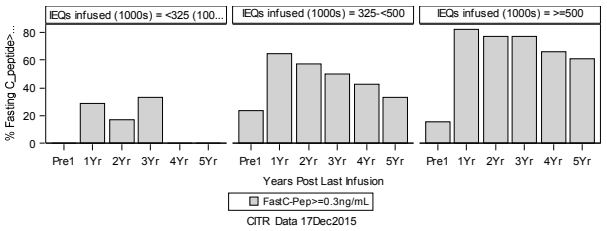
F. Donor Cause of Death CVA (p=0.0323)



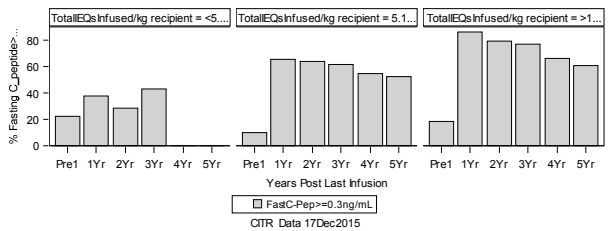
G. Donor ALT ≥ 20 favorable (p=0.0146)



H. IEQs infused ≥325 (1000s) favorable (p=0.0017)



I. IEQs infused per kg recipient weight ≥ 5.15 (1000s) favorable (p=0.0083)



J. Maintenance Immunosuppression with mTOR Inhibitor and Calcineurin Inhibitor (p=0.0042)

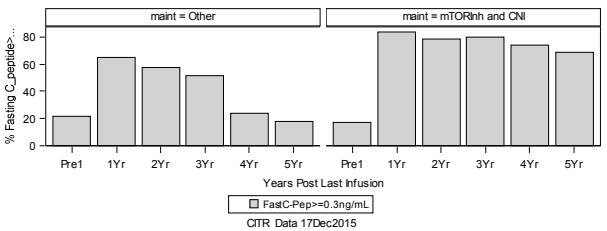
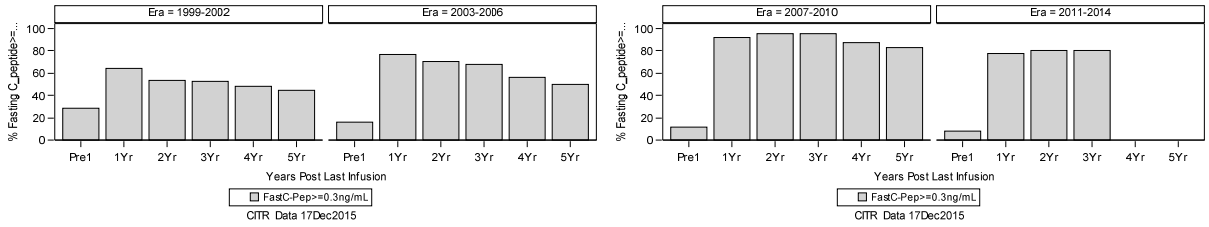


Exhibit 5-4C *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

K. Era (p=0.0121)



Persistence of Primary Outcomes

The raw, unadjusted prevalence of fasting blood glucose 60-140 mg/mL stratified by transplant type is shown in Exhibit 5-5A. Fasting blood glucose 60-140 mg/mL was maintained in over 70% of ITA patients over 5 years of follow-up time. IAK patients have similar prevalence at 1 year post last infusion, but glycemic control gradually declines in this group with only ~60% of patients in the target range at 5 years. Individual factors that were significantly ($p<0.05$) associated with fasting blood glucose 60-140 mg/mL through 5 years are presented in Exhibit 5-5B for ITA and Exhibit 5-5C for IAK. Factors which were significant differed substantially between the transplant type groups.

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-8, stratified for ITA and IAK separately.

Exhibit 5 – 5A
Unadjusted Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion

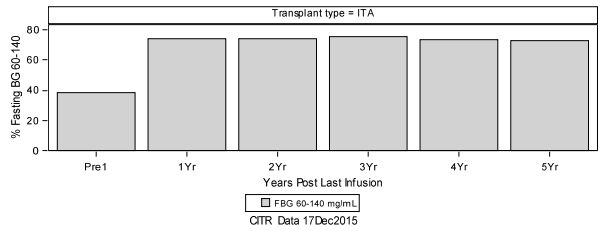
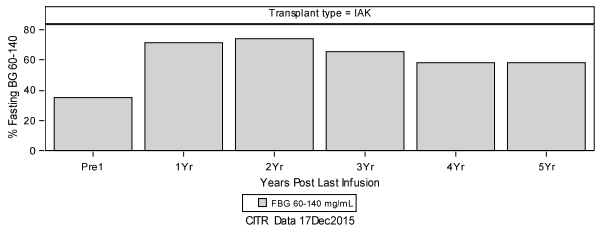
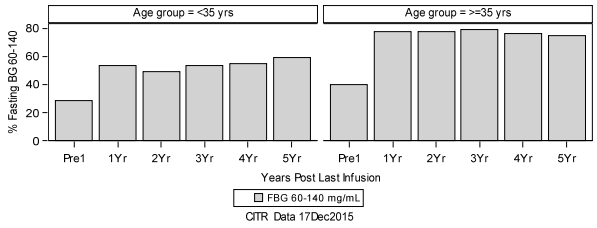
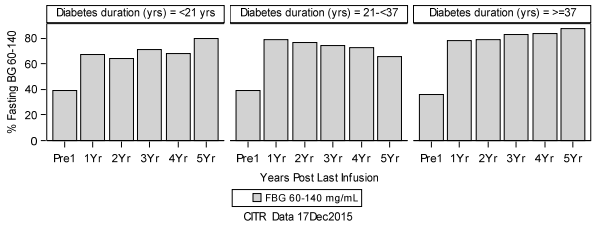
ITA	IAK
	

Exhibit 5 – 5B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

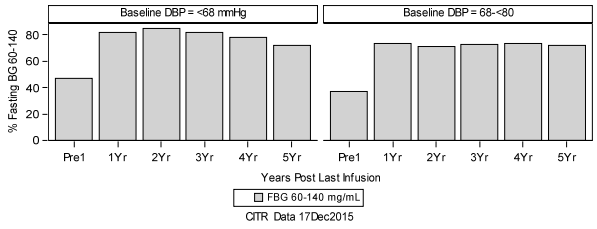
A. Recipient Age ≥35 years favorable (p<0.0001)



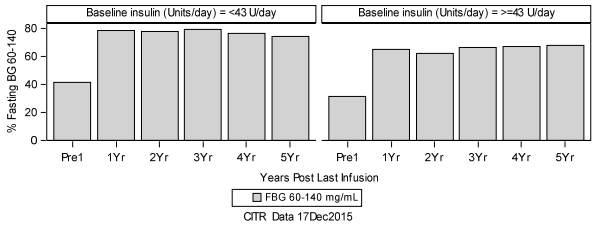
B. Duration of diabetes ≥ 37 years favorable (p=0.0127)



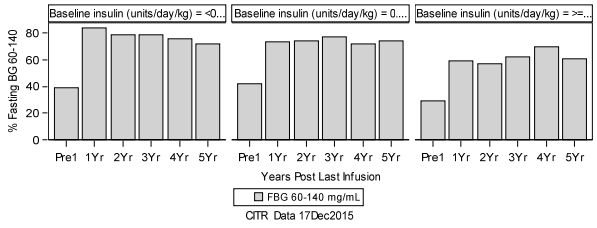
C. Baseline DBP <68 mmHg favorable (p=0.0325)



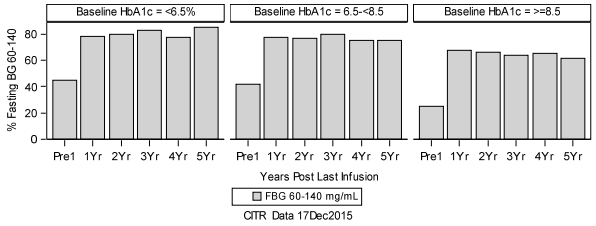
D. Baseline Insulin <43 units/day favorable (p=0.0010)



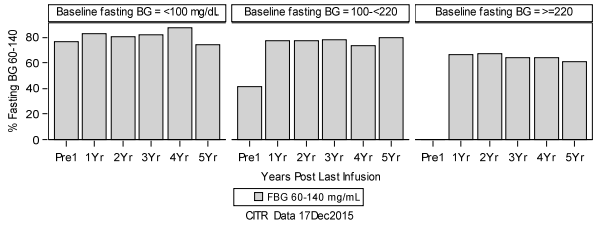
E. Baseline Insulin <0.66 units/day per kg recipient weight favorable (p=0.0010)



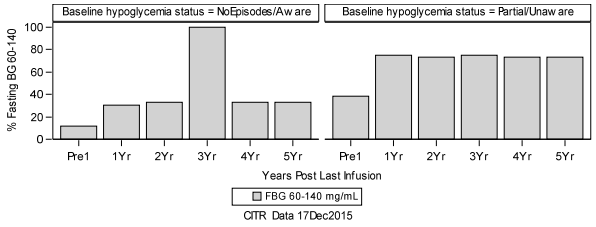
F. Baseline HbA1c < 8.5% favorable (p=0.0013)



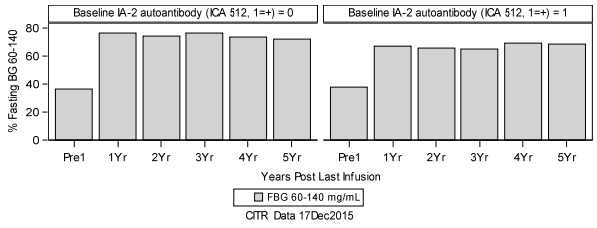
G. Baseline Fasting Blood Glucose < 220 favorable (p=0.0030)



H. Baseline hypoglycemia status: Partial/Unaware favorable (p=0.0069)



I. Baseline IA-2 autoantibody negative favorable (p=0.0329)



J. Baseline insulin autoantibody negative favorable (p=0.0010)

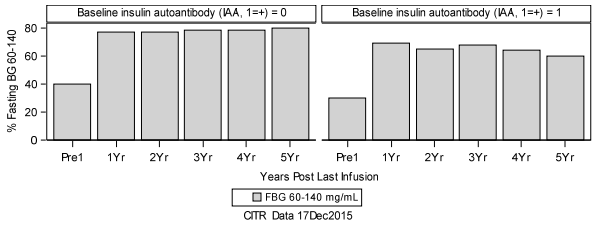
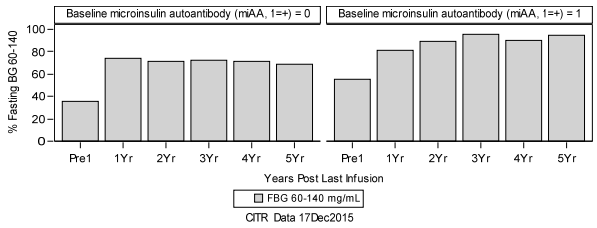
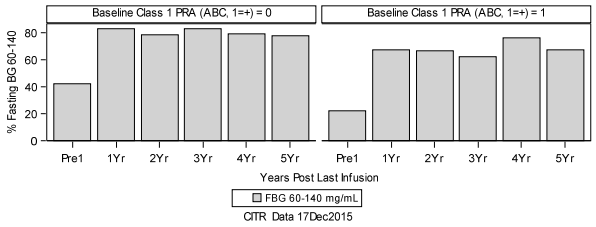


Exhibit 5 – 5B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

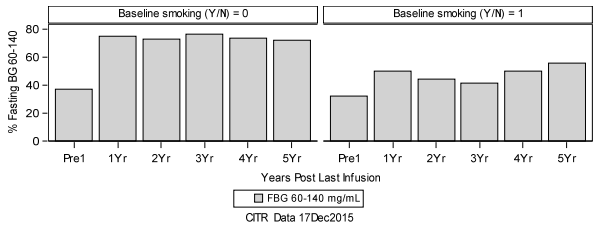
K. Baseline microinsulin autoantibody positive favorable (p=0.0067)



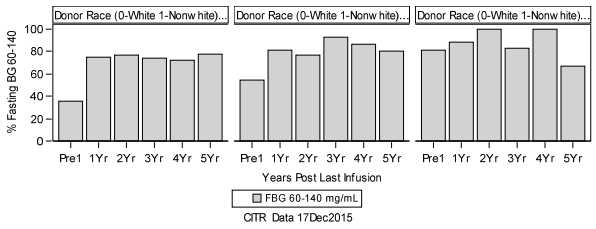
L. Baseline Class 1 PRA negative favorable (p=0.0021)



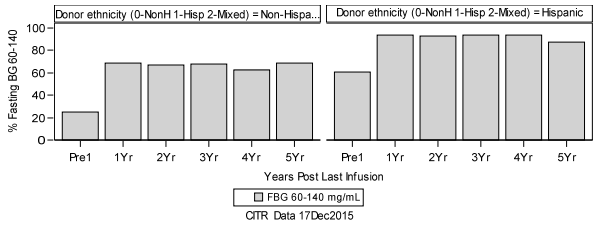
M. Baseline nonsmoker favorable (p=0.0029)



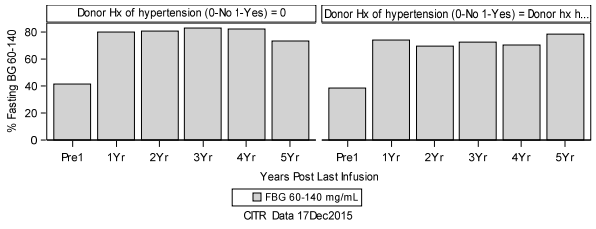
N. Donor Race: Nonwhite favorable (p=0.0379)



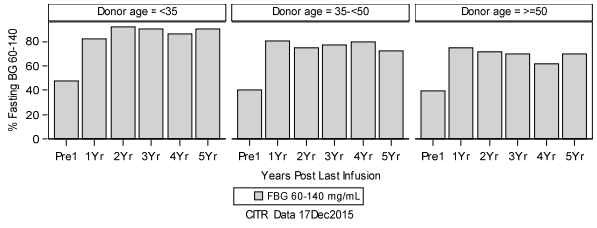
O. Donor Ethnicity: Hispanic favorable (p=0.0002)



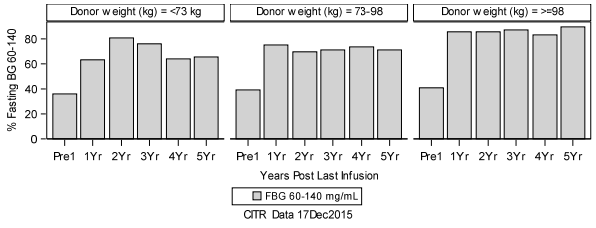
P. Donor with no history of hypertension favorable (p=0.0316)



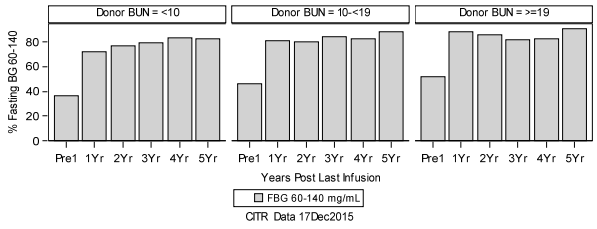
Q. Donor age < 35 favorable (p=0.0017)



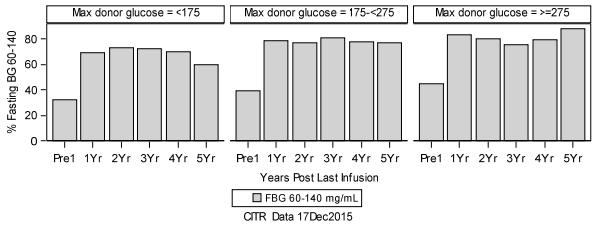
R. Donor weight ≥98 kg favorable (p<0.0001)



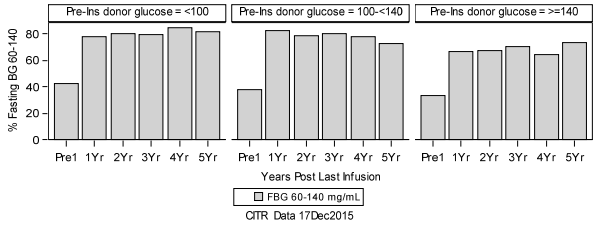
S. Donor BUN ≥19 favorable (p=0.0417)



T. Max donor glucose ≥ 275 favorable (p=0.0273)



U. Pre-Insulin donor glucose <100 favorable (p=0.0175)



V. Hours from Death to Cross-Clamp ≥ 24 favorable (p=0.0119)

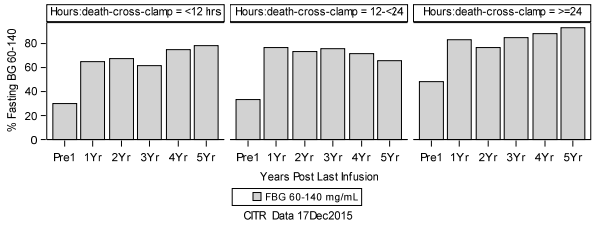
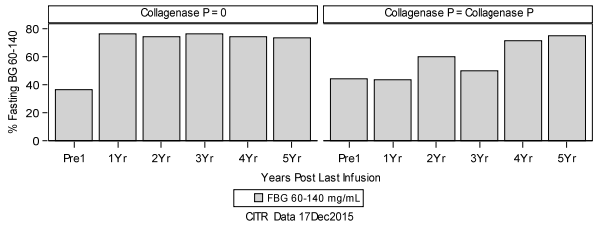
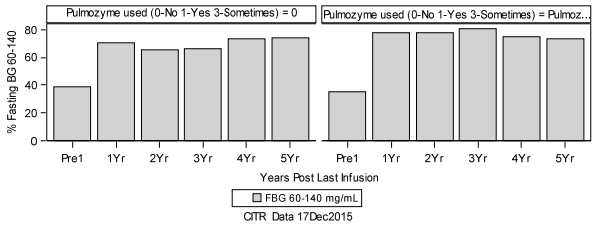


Exhibit 5 – 5B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

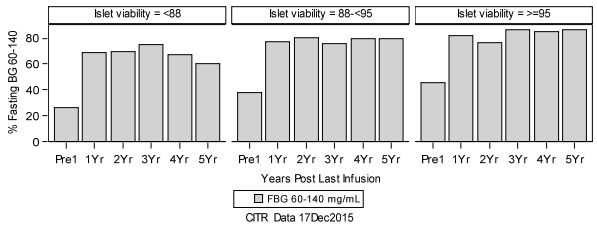
W. Collagenase Unfavorable (p=0.0145)



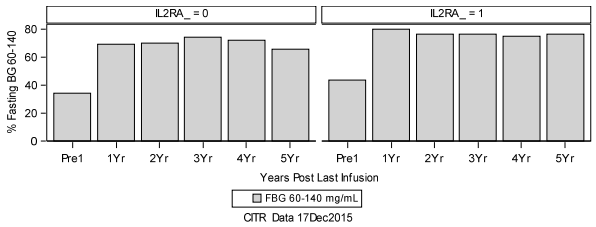
X. Pulmozyme favorable (p=0.0492)



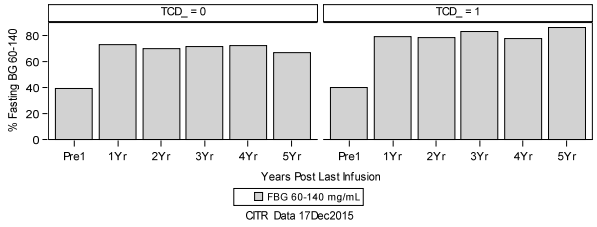
Y. Islet viability ≥ 95 favorable (p=0.0066)



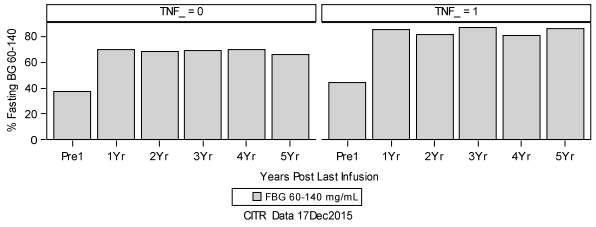
Z. Induction Immunosuppression with IL2RA favorable (p=0.0170)



AA. Induction Immunosuppression with T-cell depletion (p=0.0095)



BB. Induction Immunosuppression with TNF-a favorable (p<0.0001)



CC. Maintenance Immunosuppression with mTOR inhibitor and Calcineurin inhibitor (p<0.0001)

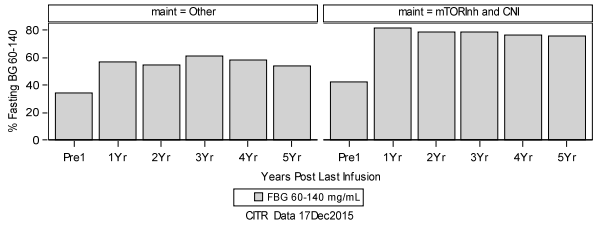
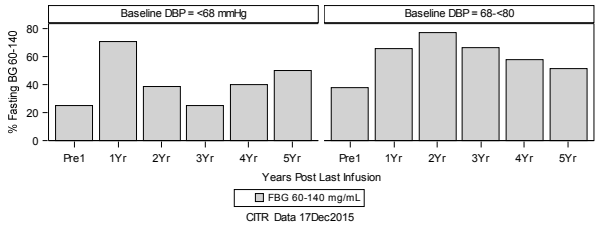
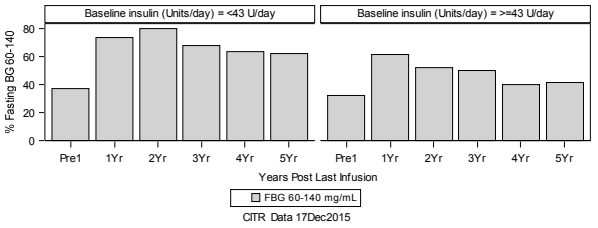


Exhibit 5 – 5C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

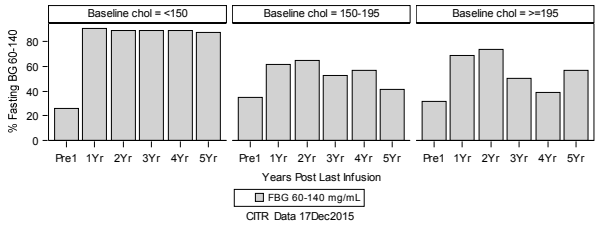
A. Baseline DBP 68-<80 mm Hg favorable (p=0.0418)



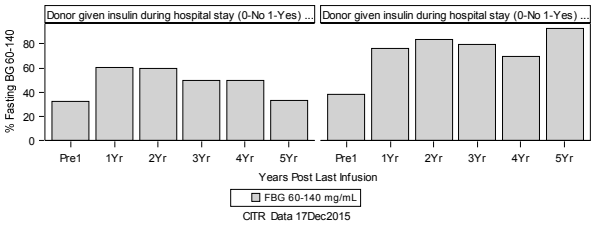
B. Baseline insulin <43 units/day favorable (p=0.0069)



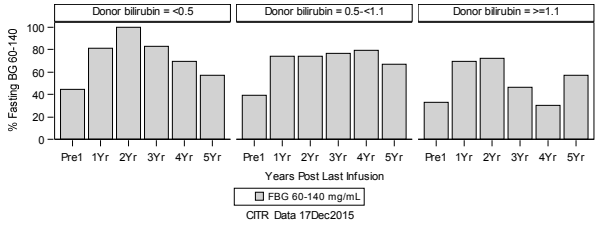
C. Baseline cholesterol < 150 favorable (p=0.0063)



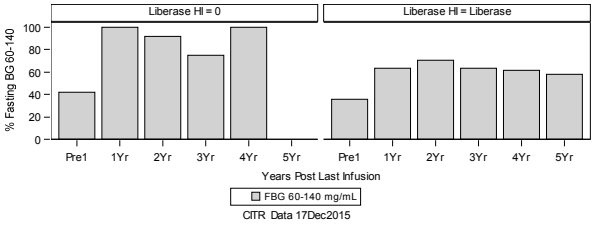
D. Donor given insulin during hospital stay favorable (p=0.0017)



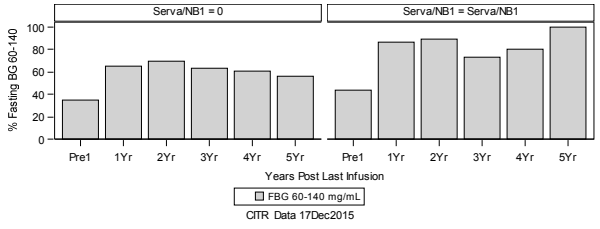
E. Donor bilirubin <1.1 favorable (p=0.0245)



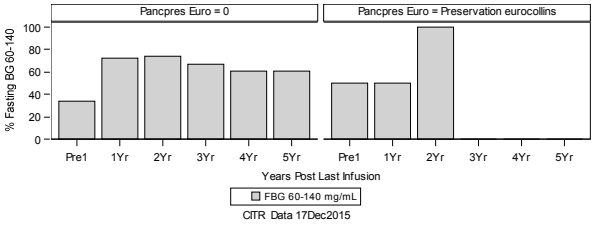
F. Liberase unfavorable (p=0.0107)



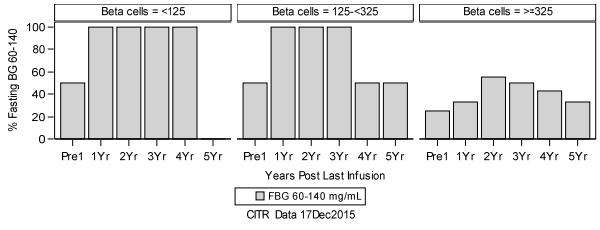
G. Serva/NB1 favorable (p=0.0404)



H. Pancpres Euro unfavorable (p=0.0003)



I. Beta cells < 325 favorable (p=0.0013)



J. Beta cells per kg recipient weight < 3.9 favorable (p=0.0001)

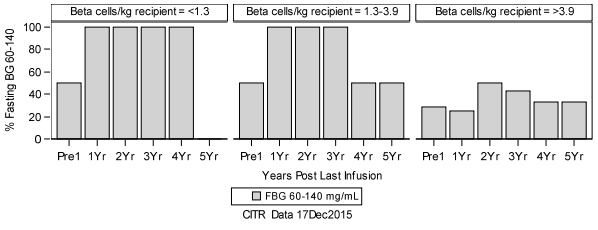
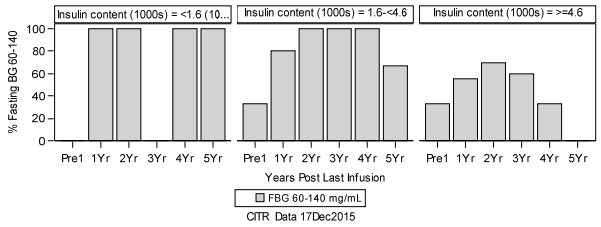
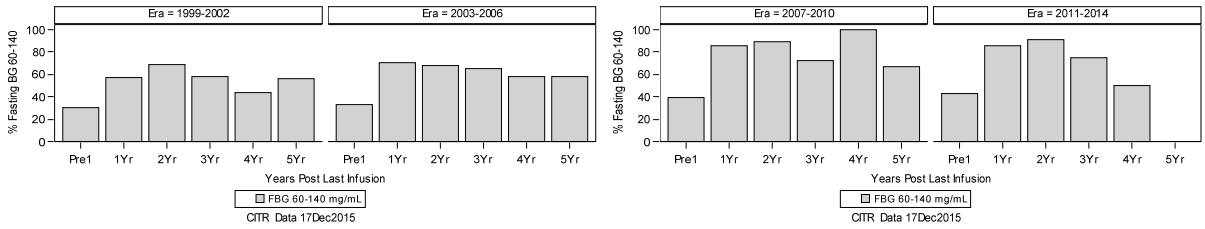


Exhibit 5 – 5C *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

K. Insulin content <4.6 (1000s) favorable (p=0.0205)



L. Era (p=0.0027)



The raw, unadjusted prevalence of HbA1c<6.5% or drop by 2% stratified by transplant type is shown in Exhibit 5-6A. For both ITA and IAK patients, prevalence of HbA1c<6.5% or drop by 2% was maintained in just under 50% of patients over 5 years of follow-up time. Individual factors that were significantly ($p<0.05$) associated with maintaining HbA1c<6.5% or drop by 2% at significantly higher levels through 5 years are presented in Exhibit 5-6B for ITA and Exhibit 5-6C for IAK. The factors which were significant differed substantially between the transplant type groups.

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-8, stratified for ITA and IAK separately.

Exhibit 5-6A
Unadjusted Prevalence of HbA1c<6.5% or Drop by 2% Post Last Infusion

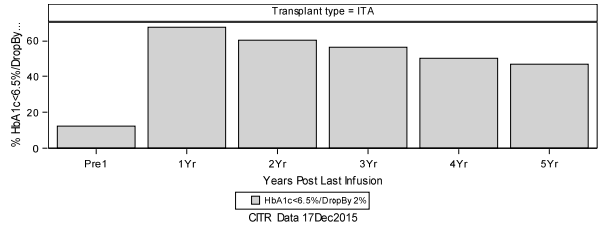
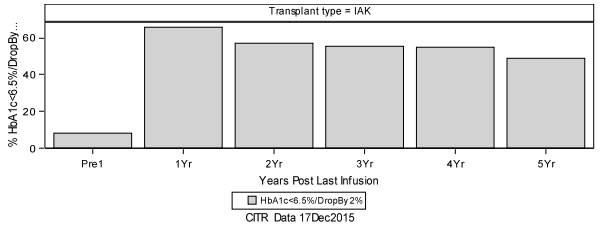
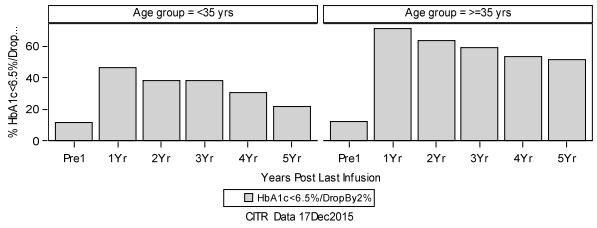
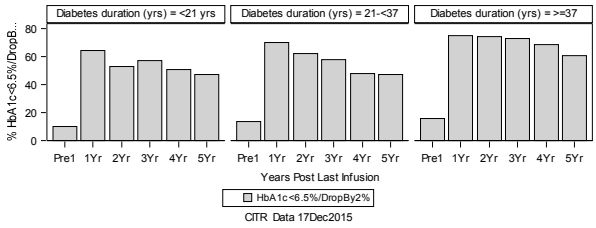
ITA	IAK
	

Exhibit 5 – 6B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<6.5% or Drop by 2% Post Last Infusion among ITA Recipients

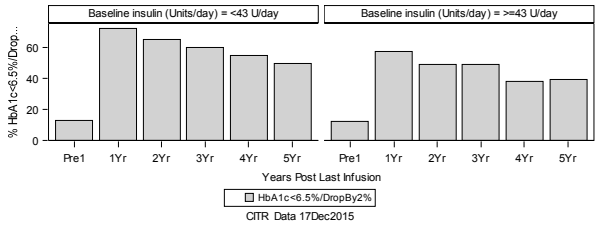
A. Recipient Age ≥ 35 years (p<0.0001)



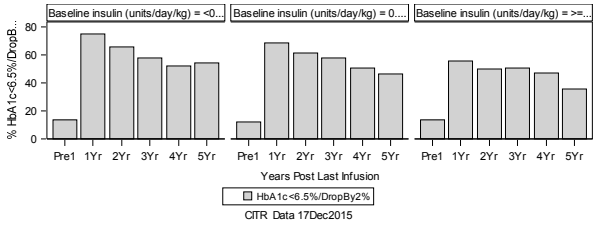
B. Duration of diabetes ≥ 37 (p=0.0007)



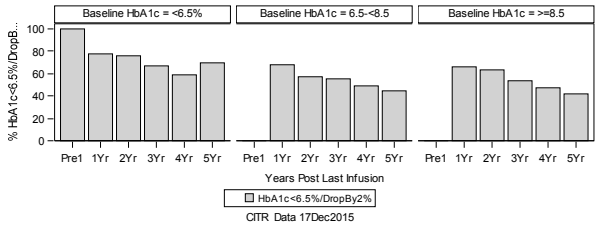
C. Baseline insulin <43 units/day (p=0.0003)



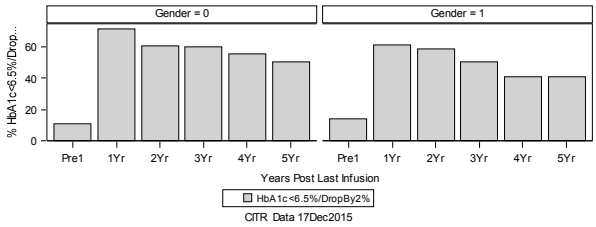
D. Baseline insulin <0.66 units/day per kg recipient weight (p=0.0017)



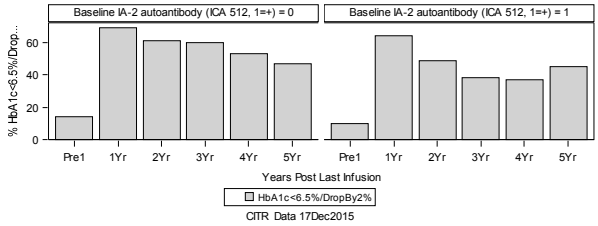
E. Baseline HbA1c (p=0.0333)



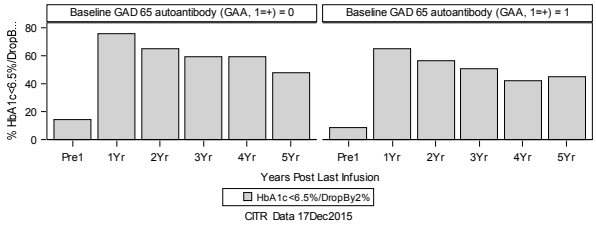
F. Recipient gender: female favorable (p=0.0437)



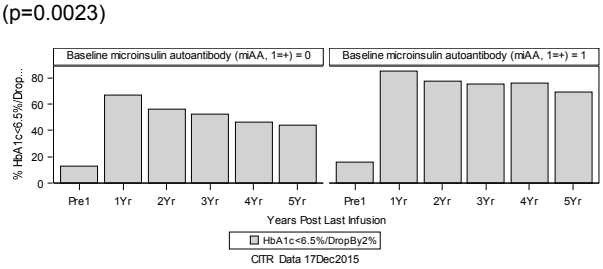
G. Baseline IA-2 autoantibody negative favorable (p=0.0182)



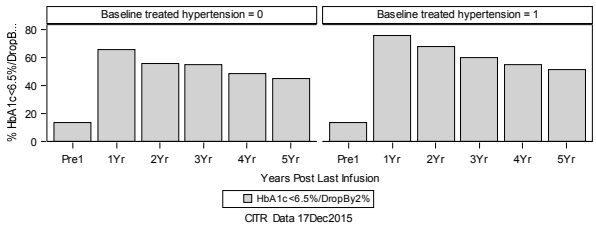
H. Baseline GAD 65 autoantibody negative favorable (p=0.0491)



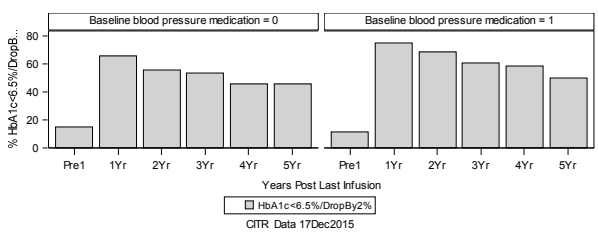
I. Baseline microinsulin autoantibody positive favorable (p=0.0023)



J. Baseline treated hypertension favorable (p=0.0099)



K. Baseline blood pressure medication favorable (p=0.0034)



L. Baseline autonomic neuropathy favorable (p=0.0265)

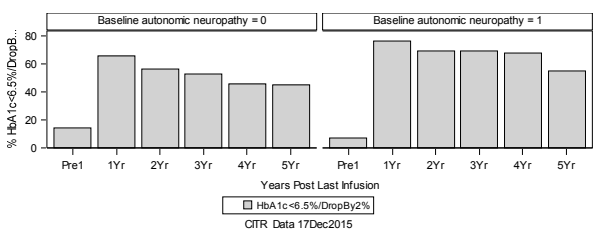
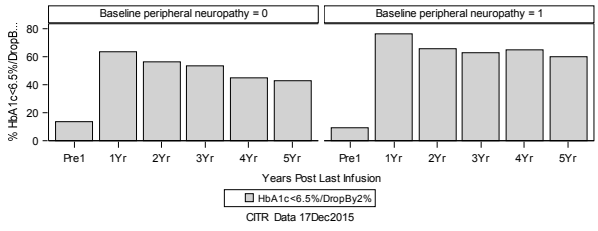
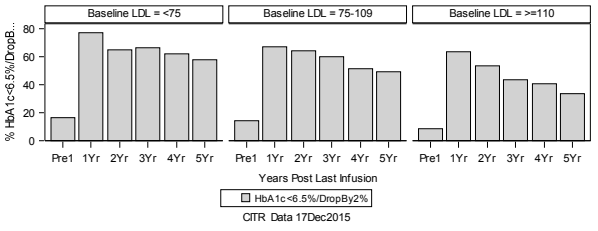


Exhibit 5 – 6B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<6.5% or Drop by 2% Post Last Infusion among ITA Recipients

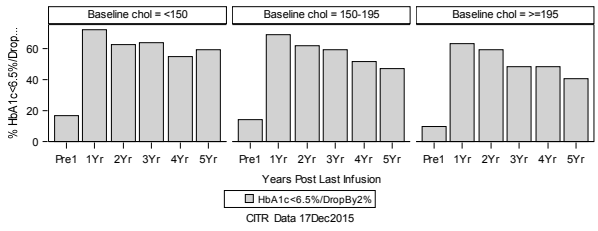
M. Baseline peripheral neuropathy favorable (p=0.0020)



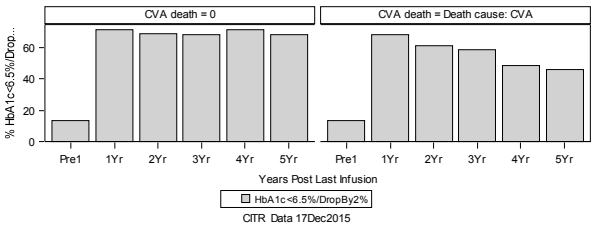
N. Baseline LDL < 75 favorable (p=0.0051)



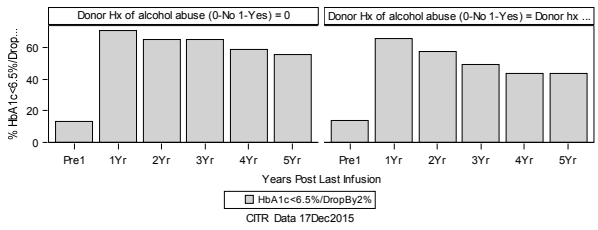
O. Baseline cholesterol < 150 favorable (p=0.0477)



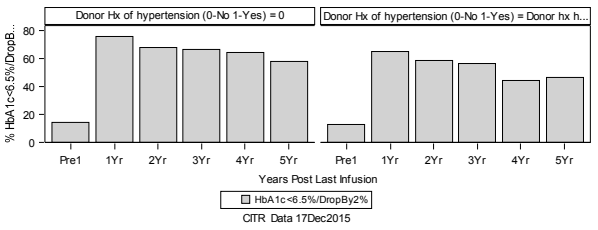
P. CVA death of donor unfavorable (p=0.0478)



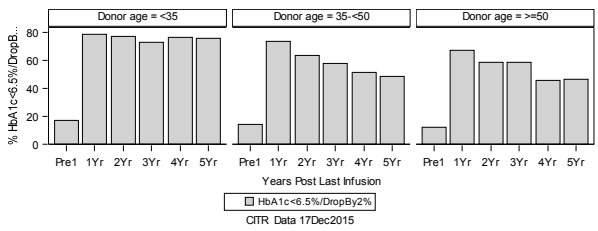
Q. No donor history of alcohol abuse favorable (p=0.0471)



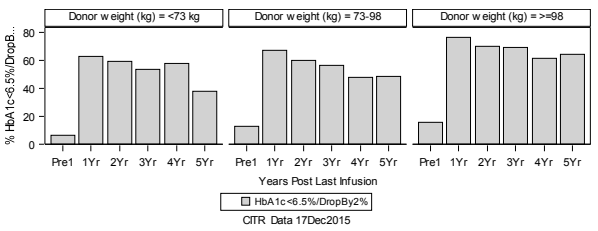
R. No donor history of hypertension favorable (p=0.0065)



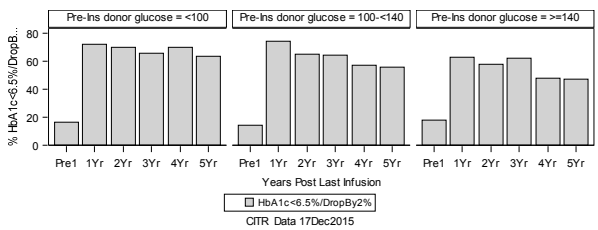
S. Donor age < 35 favorable (p=0.0089)



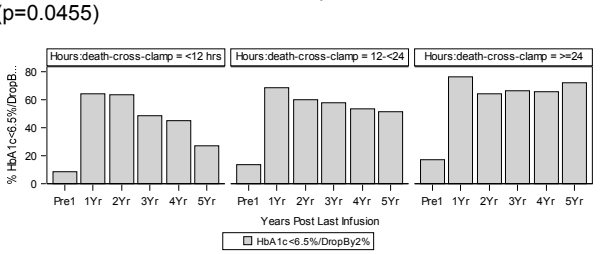
T. Donor weight ≥ 98 kg favorable (p=0.0079)



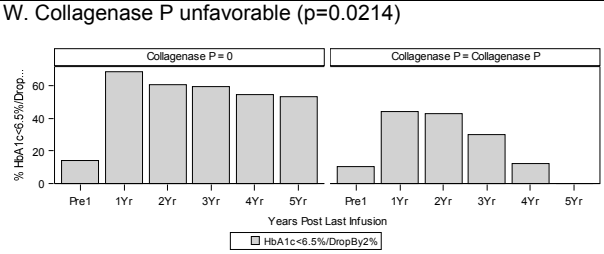
U. Pre-Insulin donor glucose <100 favorable (p=0.0397)



V. Hours from death to cross-clamp ≥ 24 hours favorable (p=0.0455)



W. Collagenase P unfavorable (p=0.0214)



X. Processing Center/ Inf Center related favorable (p=0.0322)

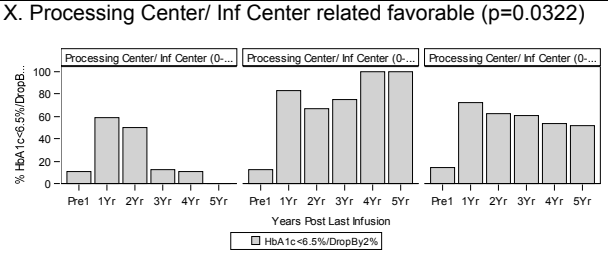
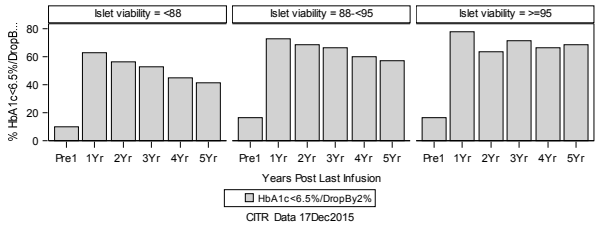
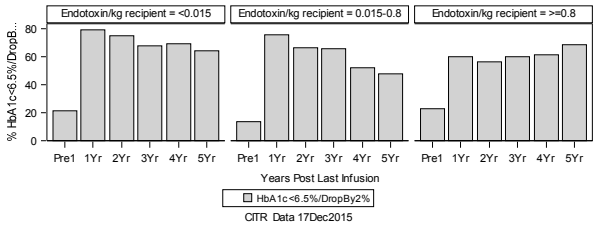


Exhibit 5 – 6B *(continued)*
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<6.5% or Drop by 2% Post Last Infusion among ITA Recipients

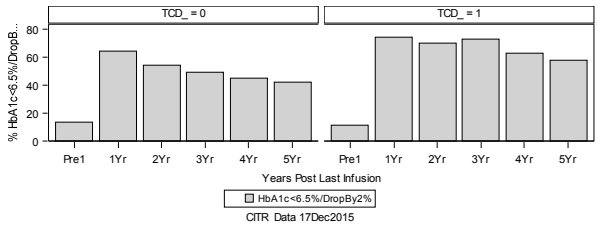
W. Islet viability ≥ 95 (p=0.0037)



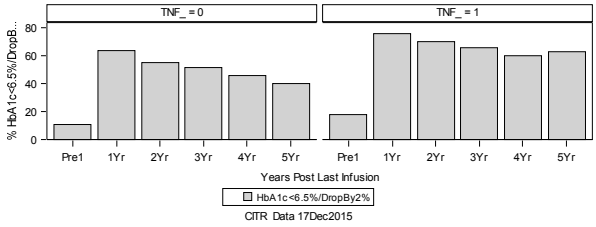
X. Endotoxin / kg recipient weight <0.015 favorable (p=0.0243)



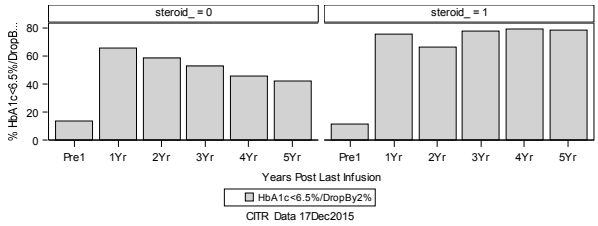
Y. Induction Immunosuppression with T-cell depletion (p<0.0001)



Z. Induction Immunosuppression with TNF-a (p=0.0001)



AA. Steroid favorable (p=0.0043)



BB. Maintanence Immunosuppression with mTOR inhibitor and Calcineurin inhibitor (p<0.0001)

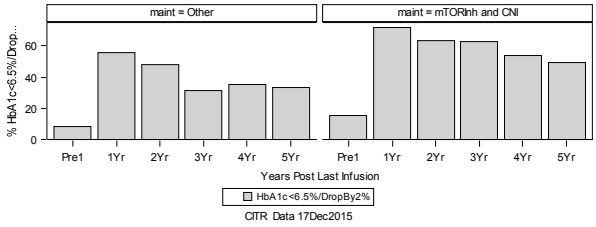
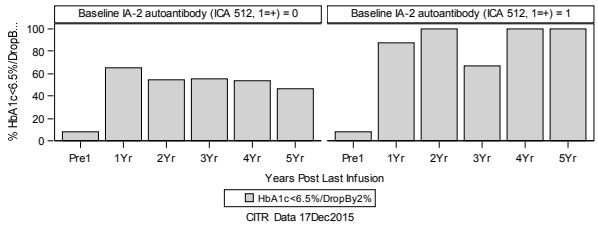
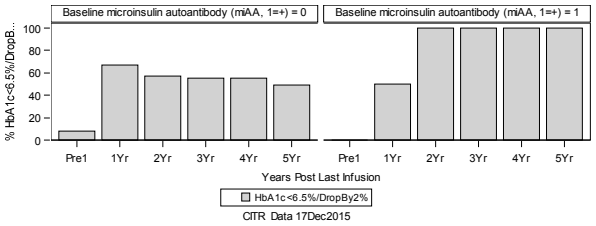


Exhibit 5 – 6C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<6.5% or Drop by 2% Post Last Infusion among IAK Recipients

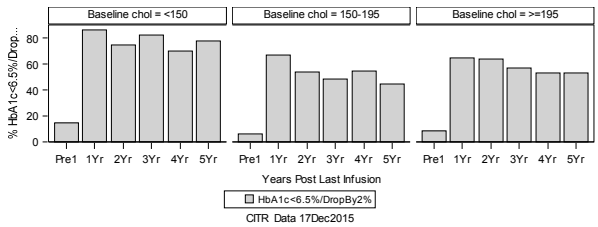
A. Baseline IA-2 autoantibody positive favorable (p=0.0118)



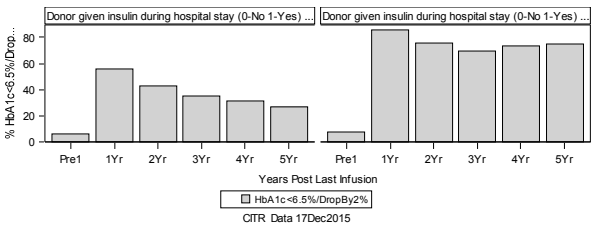
B. Baseline microinsulin autoantibody positive favorable (p<0.0001)



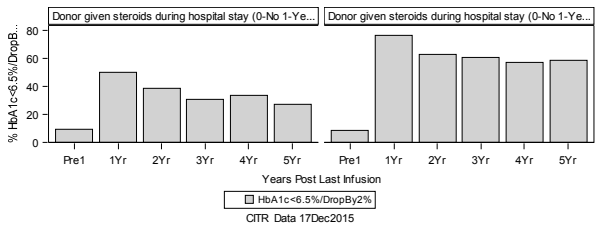
C. Baseline cholesterol <150 favorable (p=0.0336)



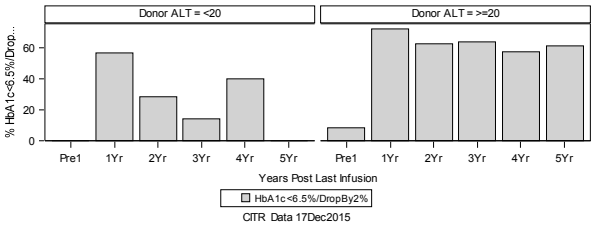
D. Donor given insulin during hospital stay favorable (p=0.0007)



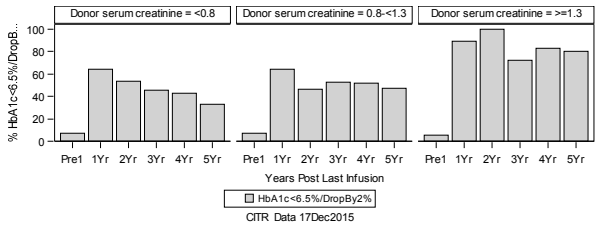
E. Donor given steroids during hospital stay favorable (p=0.0126)



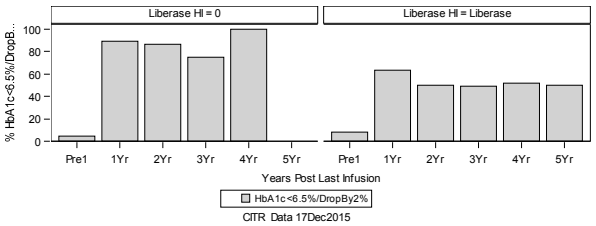
F. Donor ALT ≥ 20 favorable (p=0.0156)



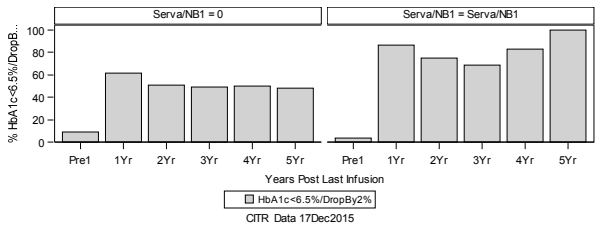
G. Donor serum creatinine ≥1.3 favorable (p=0.0249)



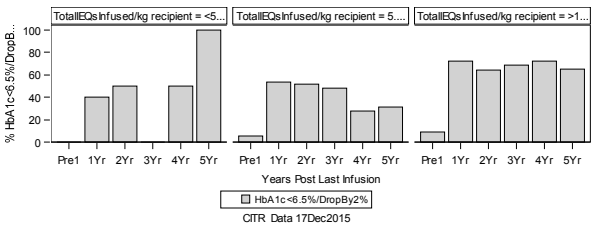
H. Liberase unfavorable (p=0.0118)



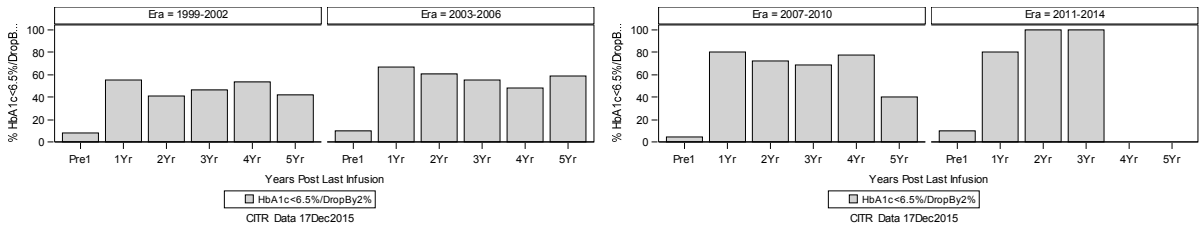
I. Serva/NB1 favorable (p=0.0137)



J. IEQs infused /kg recipient weight >10.45 favorable (p=0.0164)



K. Era post-2006 favorable (p=0.0066)



The raw, unadjusted prevalence of Absence of Severe Hypoglycemic Events (ASHE) stratified by transplant type is shown in Exhibit 5-7A. For both ITA and IAK patients, prevalence of ASHE was maintained in around 90% of patients over 5 years of follow-up time. Factors that were significantly ($p<0.05$) associated with maintaining ASHE at higher levels through 5 years are presented in Exhibit 5-7B for ITA and Exhibit 5-7C for IAK The factors which were significant differed substantially between the transplant type groups.

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-8, stratified for ITA and IAK separately.

Exhibit 5 – 7A
Unadjusted Prevalence of Absence of Severe Hypoglycemia Events Post Last Infusion

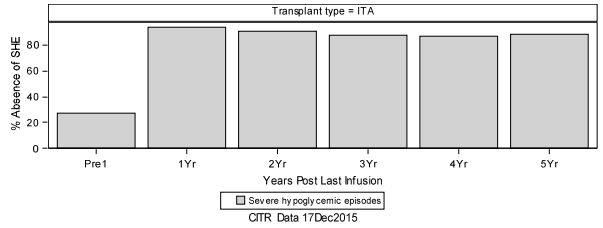
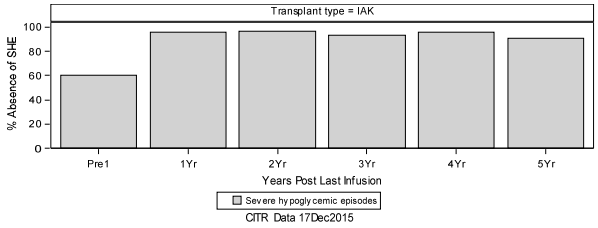
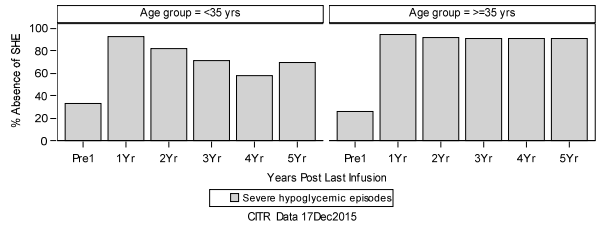
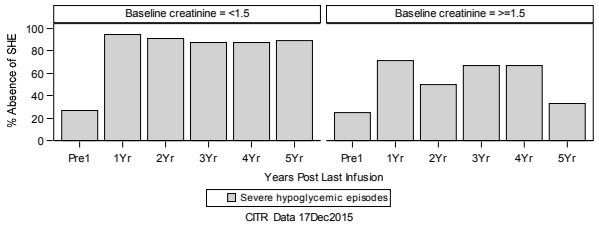
ITA	IAK
	

Exhibit 5 – 7B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipient

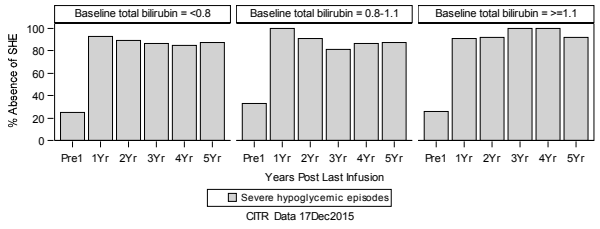
A. Recipient age ≥ 35 (p=0.0027)



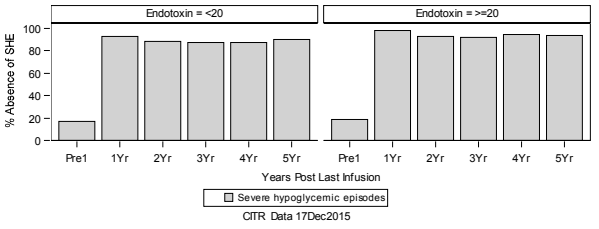
B. Baseline creatinine <1.5 favorable (p=0.0052)



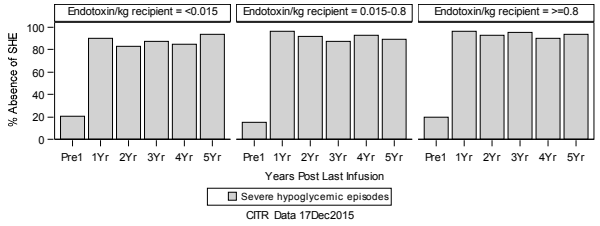
C. Baseline Total Bilirubin ≥ 1.1 favorable (p=0.0304)



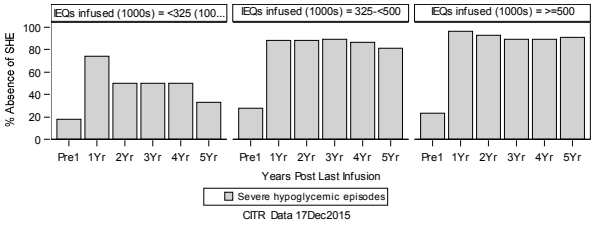
D. Endotoxin ≥ 20 EU favorable (p=0.0473)



E. Endotoxin/kg recipient weight ≥0.80 favorable (p=0.0388)



F. IEQs infused ≥ 325 (1000s) favorable (p=<0.0001)



G. IEQs infused per kg recipient weight ≥ 5.15 (1000s) favorable (p=0.0005)

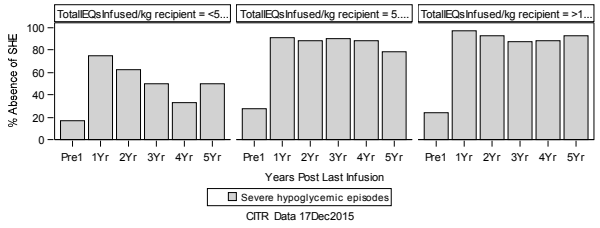
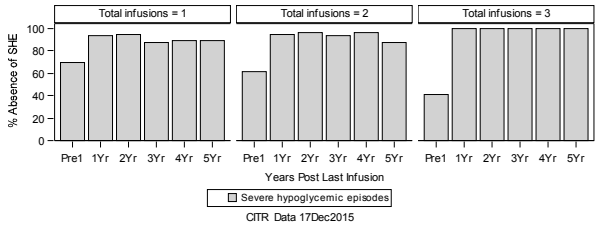
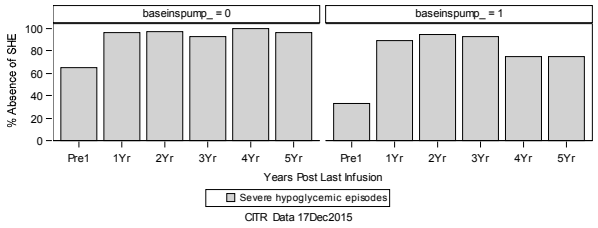


Exhibit 5 – 7C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

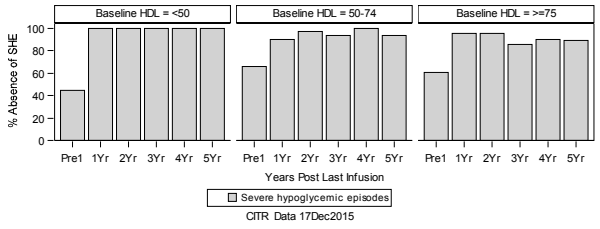
A. Total infusions ≥ 3 favorable (p=0.0177)



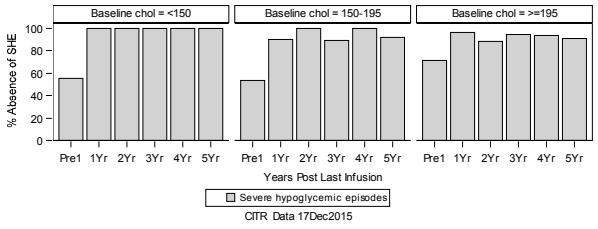
B. No insulin pump use at baseline favorable (p=0.0219)



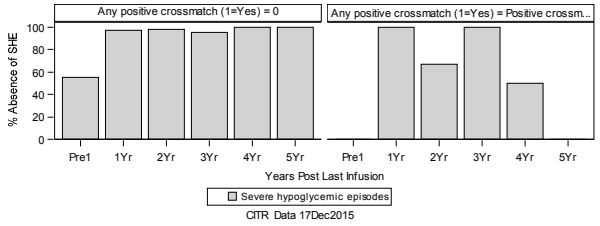
C. Baseline HDL <50 favorable (p=0.0397)



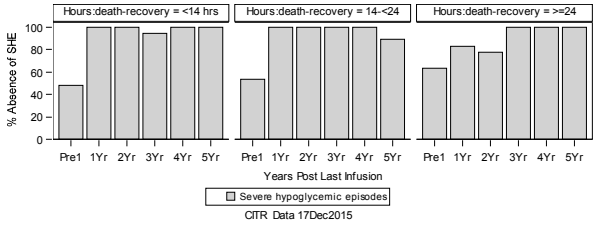
D. Baseline Cholesterol < 150 favorable (p=0.0478)



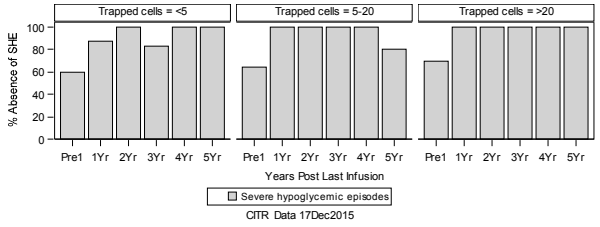
E. No positive crossmatch favorable (p=0.0008)



F. Hours from death to recovery <24 favorable (p=0.0495)



G. Trapped cells > 20 (p=0.0209)



H. Endotoxin (EU)/kg recipient weight <0.015 favorable (p=0.0096)

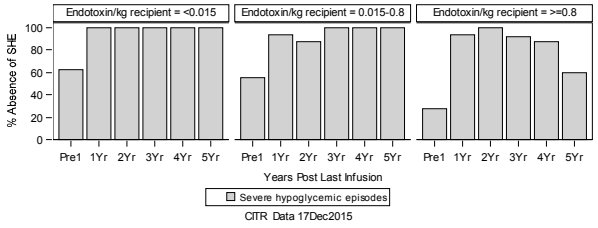
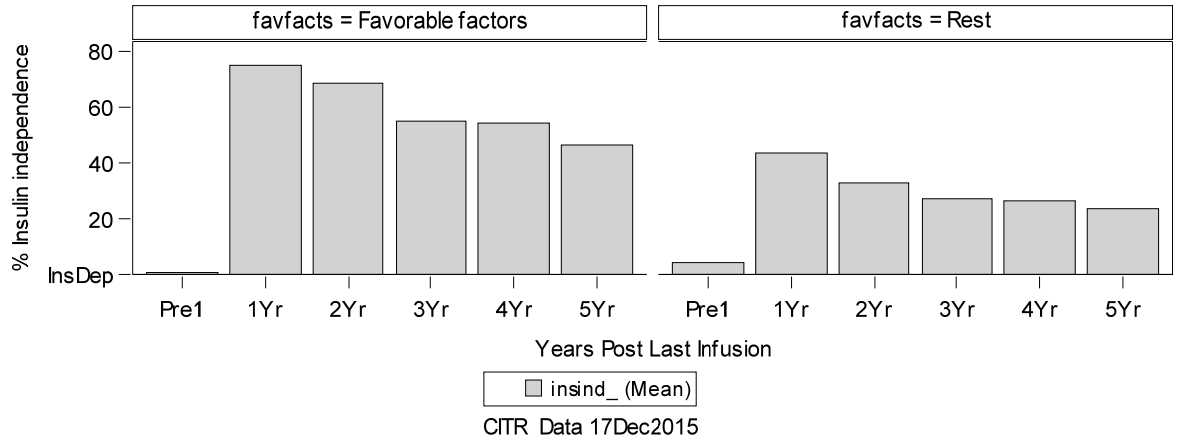


Exhibit 5 – 8A
Combined Effect of Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

Favorable Factors:

- Induction Immunosuppression with T-cell depletion **and/or** TNF-alpha inhibitor
- Maintenance Immunosuppression with mTOR inhibitor **and** calcineurin inhibitor
- IEQ's ≥ 325,000
- Recipient Age ≥ 35 years

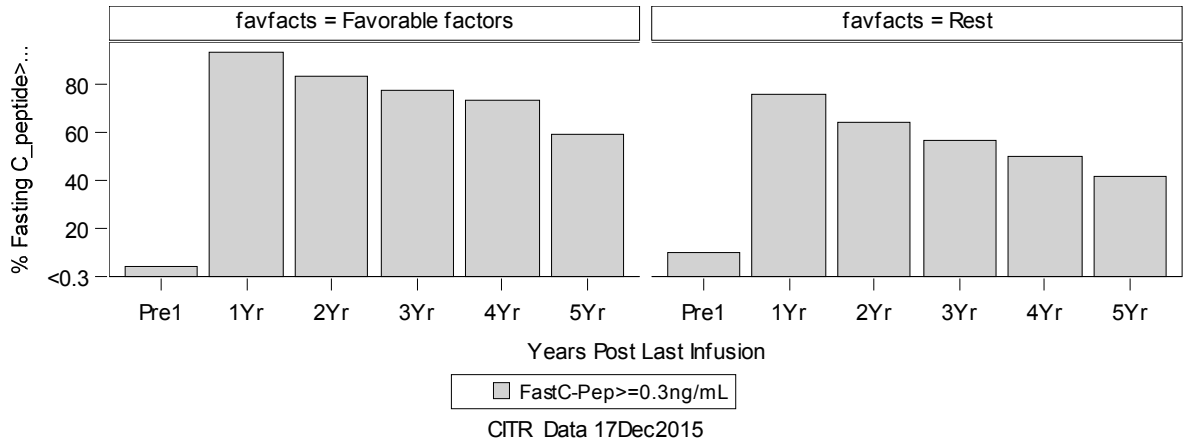
Insulin Independence (Prevalence, p<0.0001)



	Favorable factors *Years Post Last Infusion*												*Rest* *Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Insulin Dependent	165	99.4	39	25.2	47	31.8	61	44.9	54	45.4	53	53.5	494	95.6	271	56.6	307	67.5	288	72.7	238	73.7	212	76.3
Insulin Independent	1	0.6	116	74.8	101	68.2	75	55.1	65	54.6	46	46.5	23	4.4	208	43.4	148	32.5	108	27.3	85	26.3	66	23.7
Total	166	100.0	155	100.0	148	100.0	136	100.0	119	100.0	99	100.0	517	100.0	479	100.0	455	100.0	396	100.0	323	100.0	278	100.0

Exhibit 5 – 8A *(continued)*
Combined Effect of Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

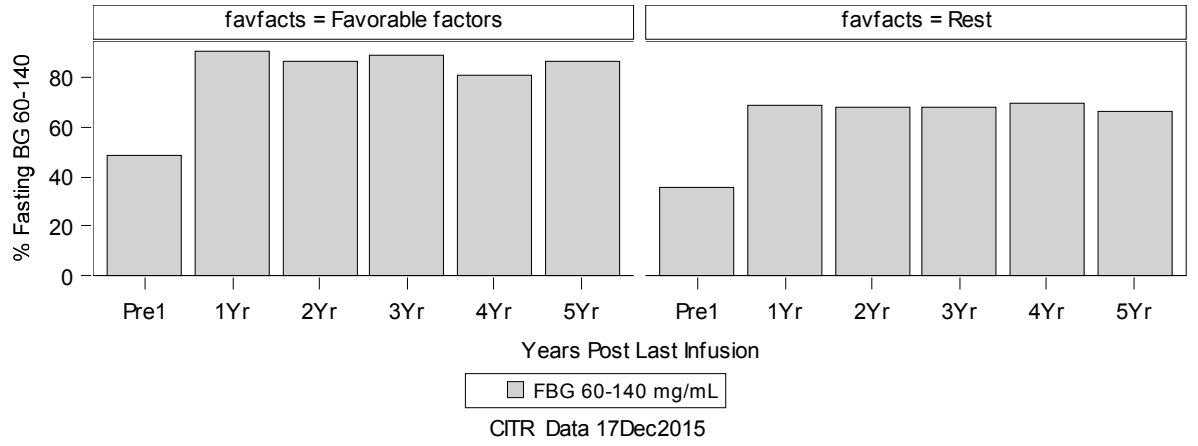
C-peptide ≥0.3 ng/mL (Prevalence, p<0.0001)



	favfacts																							
	Favorable factors												*Rest*											
	Years Post Last Infusion												*Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
<0.3 ng/mL	152	95.6	9	6.3	21	16.2	18	22.0	19	26.4	26	40.6	353	90.3	91	24.1	114	35.3	120	43.3	120	50.0	127	58.3
>=0.3 ng/mL	7	4.4	135	93.8	109	83.8	64	78.0	53	73.6	38	59.4	38	9.7	287	75.9	209	64.7	157	56.7	120	50.0	91	41.7
Total	159	100.0	144	100.0	130	100.0	82	100.0	72	100.0	64	100.0	391	100.0	378	100.0	323	100.0	277	100.0	240	100.0	218	100.0

Exhibit 5 – 8A *(continued)*
Combined Effect of Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

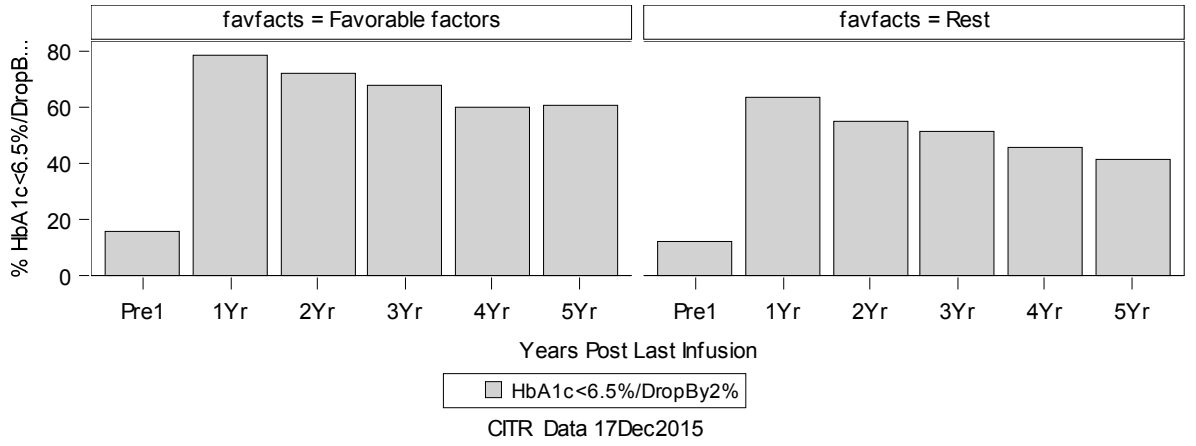
Fasting Blood Glucose 60-140 mg/mL (Prevalence, p<0.0001)



	Favorable factors Years Post Last Infusion												*Rest Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Fasting BG < 60 or > 140 mg/mL	74	51.4	13	9.4	17	13.4	11	10.8	17	19.1	8	13.3	248	64.4	108	31.2	82	32.2	62	32.0	47	30.5	44	33.6
Fasting BG 60-140 mg/mL	70	48.6	126	90.6	110	86.6	91	89.2	72	80.9	52	86.7	137	35.6	238	68.8	173	67.8	132	68.0	107	69.5	87	66.4
Total	144	100.0	139	100.0	127	100.0	102	100.0	89	100.0	60	100.0	385	100.0	346	100.0	255	100.0	194	100.0	154	100.0	131	100.0

Exhibit 5 – 8A *(continued)*
Combined Effect of Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

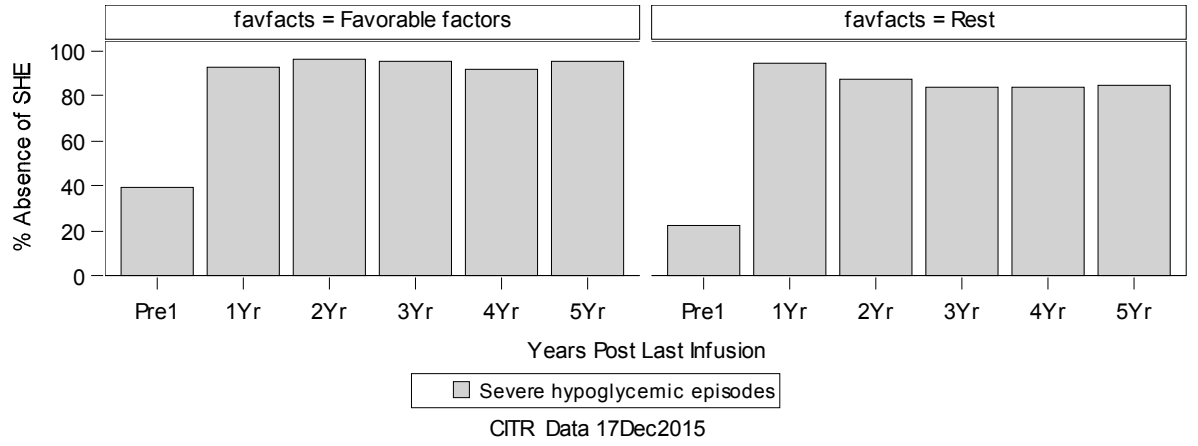
HbA1c<6.5% or Drop by 2% (Prevalence, p<0.0001)



	Favorable factors Years Post Last Infusion												*Rest Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
HbA1c>6.5%/DropBy<2%	124	84.4	28	21.4	33	28.2	29	31.9	31	39.7	21	39.6	404	87.8	132	36.8	128	45.2	108	48.9	97	54.2	88	58.3
HbA1c<6.5%/DropBy2%	23	15.6	103	78.6	84	71.8	62	68.1	47	60.3	32	60.4	56	12.2	227	63.2	155	54.8	113	51.1	82	45.8	63	41.7
Total	147	100.0	131	100.0	117	100.0	91	100.0	78	100.0	53	100.0	460	100.0	359	100.0	283	100.0	221	100.0	179	100.0	151	100.0

Exhibit 5 – 8A *(continued)*
Combined Effect of Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

Absence of Severe Hypoglycemic Events (Prevalence, p=0.0118)



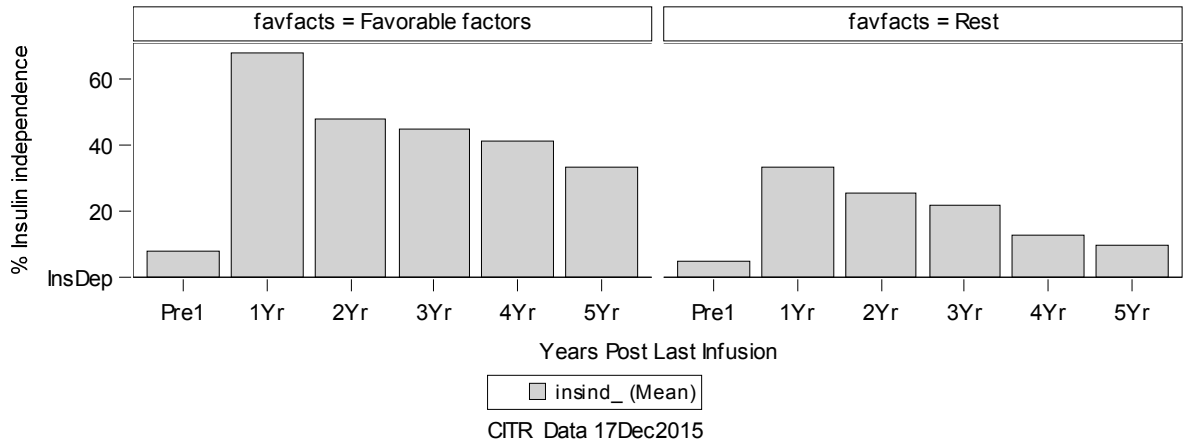
	Favorable factors *Years Post Last Infusion*												*Rest* *Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
SHE	90	60.8	9	7.1	4	3.4	4	4.8	6	8.3	2	4.5	323	77.5	15	5.3	28	12.9	28	15.8	20	15.9	13	15.3
Absence of SHE	58	39.2	118	92.9	113	96.6	80	95.2	66	91.7	42	95.5	94	22.5	266	94.7	189	87.1	149	84.2	106	84.1	72	84.7
Total	148	100.0	127	100.0	117	100.0	84	100.0	72	100.0	44	100.0	417	100.0	281	100.0	217	100.0	177	100.0	126	100.0	85	100.0

Exhibit 5 – 8B
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for IAK Recipients

Favorable Factors:

- Donor Given Insulin
- IEQ's ≥ 325,000

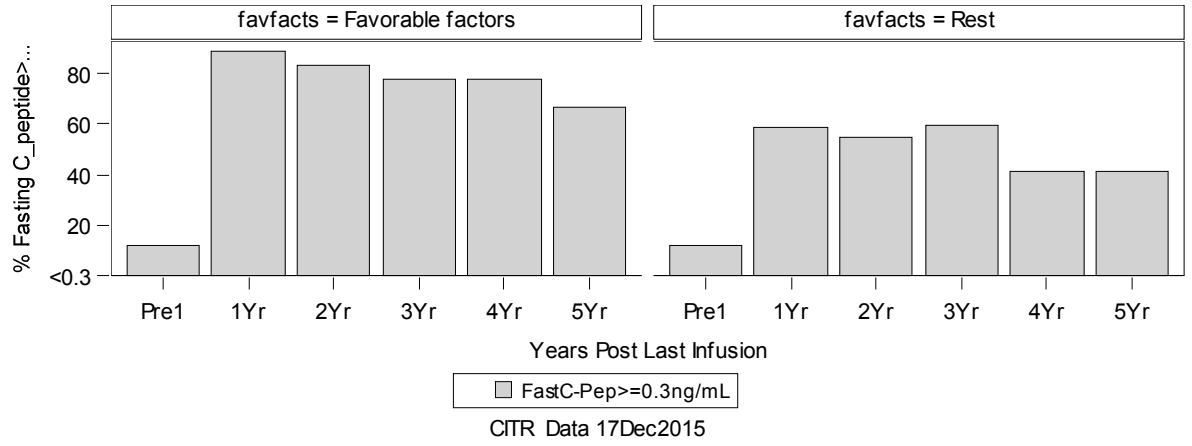
Insulin Independence (Prevalence, p=0.0045)



	Favorable factors Years Post Last Infusion												*Rest Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Insulin Dependent	47	92.2	15	31.9	24	52.2	22	55.0	20	58.8	18	66.7	38	95.0	26	66.7	29	74.4	29	78.4	28	87.5	27	90.0
Insulin Independent	4	7.8	32	68.1	22	47.8	18	45.0	14	41.2	9	33.3	2	5.0	13	33.3	10	25.6	8	21.6	4	12.5	3	10.0
Total	51	100.0	47	100.0	46	100.0	40	100.0	34	100.0	27	100.0	40	100.0	39	100.0	39	100.0	37	100.0	32	100.0	30	100.0

Exhibit 5 – 8B *(continued)*
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for IAK Recipients

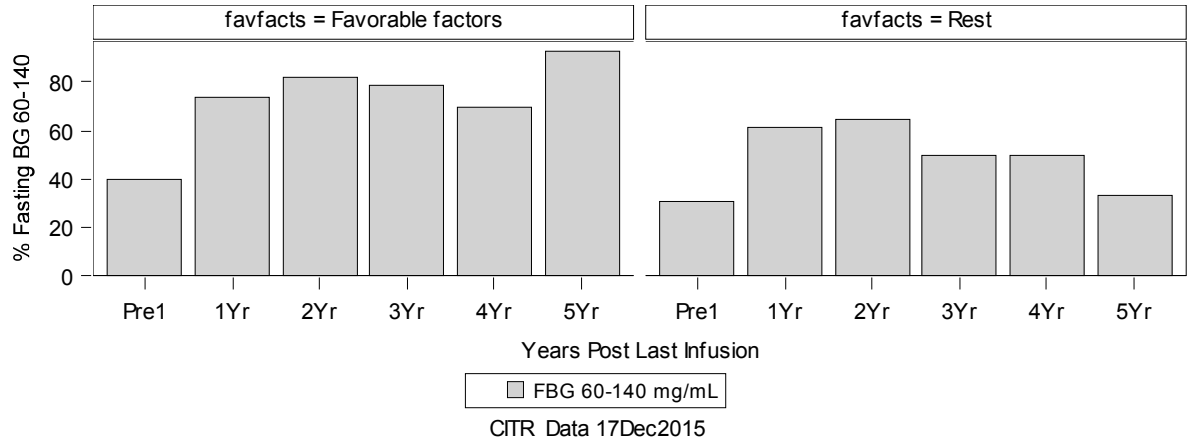
C-peptide ≥0.3 ng/mL (Prevalence, p=0.0286)



	favfacts																							
	Favorable factors												*Rest*											
	Years Post Last Infusion												*Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
<0.3 ng/mL	43	87.8	5	11.1	7	17.1	7	21.9	4	22.2	5	33.3	30	88.2	14	41.2	14	45.2	13	40.6	13	59.1	13	59.1
>=0.3 ng/mL	6	12.2	40	88.9	34	82.9	25	78.1	14	77.8	10	66.7	4	11.8	20	58.8	17	54.8	19	59.4	9	40.9	9	40.9
Total	49	100.0	45	100.0	41	100.0	32	100.0	18	100.0	15	100.0	34	100.0	34	100.0	31	100.0	32	100.0	22	100.0	22	100.0

Exhibit 5 – 8B *(continued)*
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for IAK Recipients

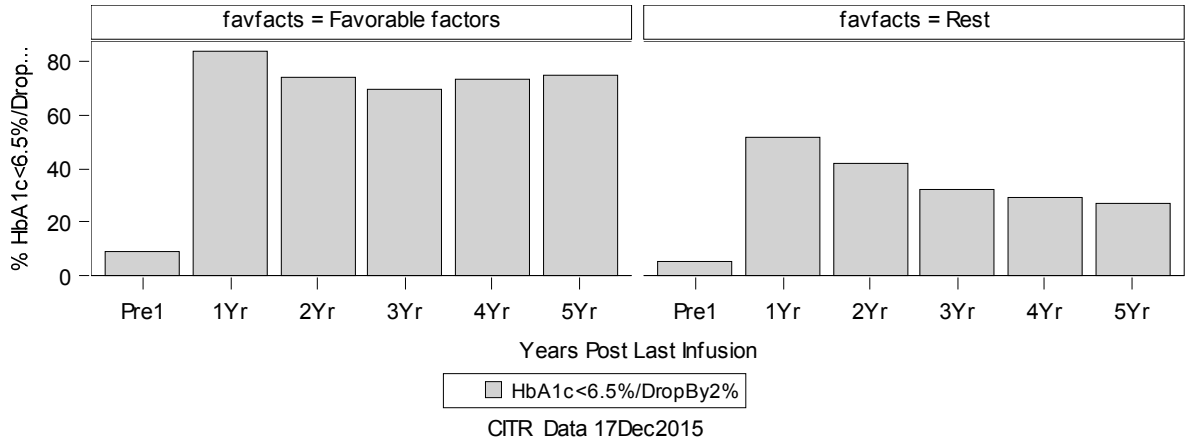
Fasting Blood Glucose 60-140 mg/mL (Prevalence, p=0.0056)



	Favorable factors Years Post Last Infusion												*Rest Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Fasting BG < 60 or > 140 mg/mL	29	60.4	11	26.2	7	17.9	7	21.2	6	30.0	1	7.1	25	69.4	12	38.7	10	35.7	13	50.0	9	50.0	10	66.7
Fasting BG 60-140 mg/mL	19	39.6	31	73.8	32	82.1	26	78.8	14	70.0	13	92.9	11	30.6	19	61.3	18	64.3	13	50.0	9	50.0	5	33.3
Total	48	100.0	42	100.0	39	100.0	33	100.0	20	100.0	14	100.0	36	100.0	31	100.0	28	100.0	26	100.0	18	100.0	15	100.0

Exhibit 5 – 8B *(continued)*
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for IAK Recipients

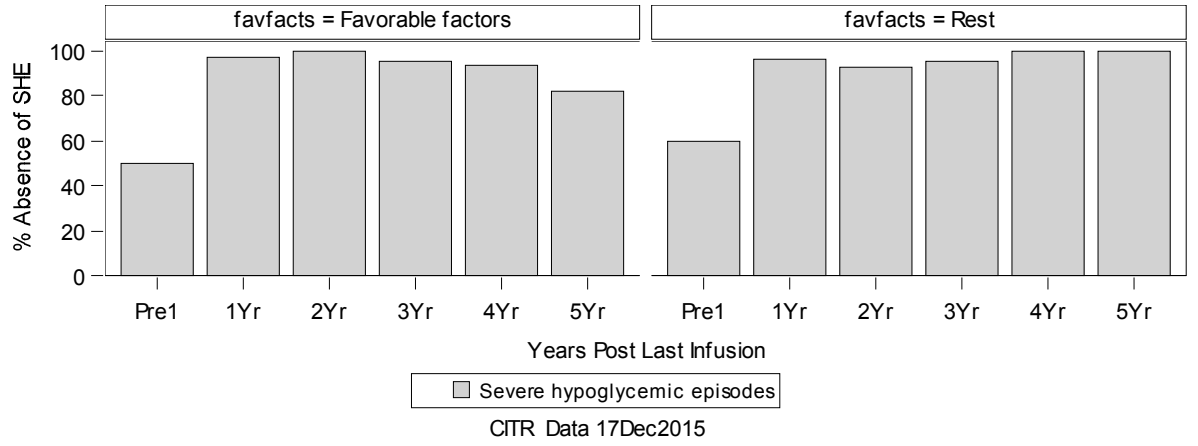
HbA1c<6.5% or Drop by 2% (Prevalence, p=0.0006)



	Favorable factors Years Post Last Infusion												*Rest Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
HbA1c>6.5%/DropBy<2%	31	91.2	5	16.1	7	25.9	7	30.4	4	26.7	3	25.0	34	94.4	15	48.4	14	58.3	15	68.2	12	70.6	11	73.3
HbA1c<6.5%/DropBy2%	3	8.8	26	83.9	20	74.1	16	69.6	11	73.3	9	75.0	2	5.6	16	51.6	10	41.7	7	31.8	5	29.4	4	26.7
Total	34	100.0	31	100.0	27	100.0	23	100.0	15	100.0	12	100.0	36	100.0	31	100.0	24	100.0	22	100.0	17	100.0	15	100.0

Exhibit 5 – 8B *(continued)*
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for IAK Recipients

Absence of Severe Hypoglycemic Events (Prevalence, p=0.8)



	Favorable factors Years Post Last Infusion												*Rest Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
SHE																								
	16	50.0	1	3.1	.	.	1	4.5	1	6.7	2	18.2	14	40.0	1	3.2	2	7.4	1	4.5	.	.	.	.
Absence of SHE	16	50.0	31	96.9	27	100.0	21	95.5	14	93.3	9	81.8	21	60.0	30	96.8	25	92.6	21	95.5	15	100.0	7	100.0
Total	32	100.0	32	100.0	27	100.0	22	100.0	15	100.0	11	100.0	35	100.0	31	100.0	27	100.0	22	100.0	15	100.0	7	100.0

Levels of daily insulin requirement (U/day) declined dramatically in follow-up through 5-years after islet transplantation, with some return upwards over 5 years of follow-up for both ITA and IAK patients (Exhibit 5-9). Factors associated with improved results for each group are shown in Exhibit 5-9. Among ITA's favorable factors included age ≥35 ($p<0.0001$); total IEQs infused ≥ 325,000 ($p=0.03$); and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p<0.0001$). Among IAK's favorable factors included maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p=0.0258$).

Exhibit 5 – 9
Insulin Dose (U/day) Post Last Infusion

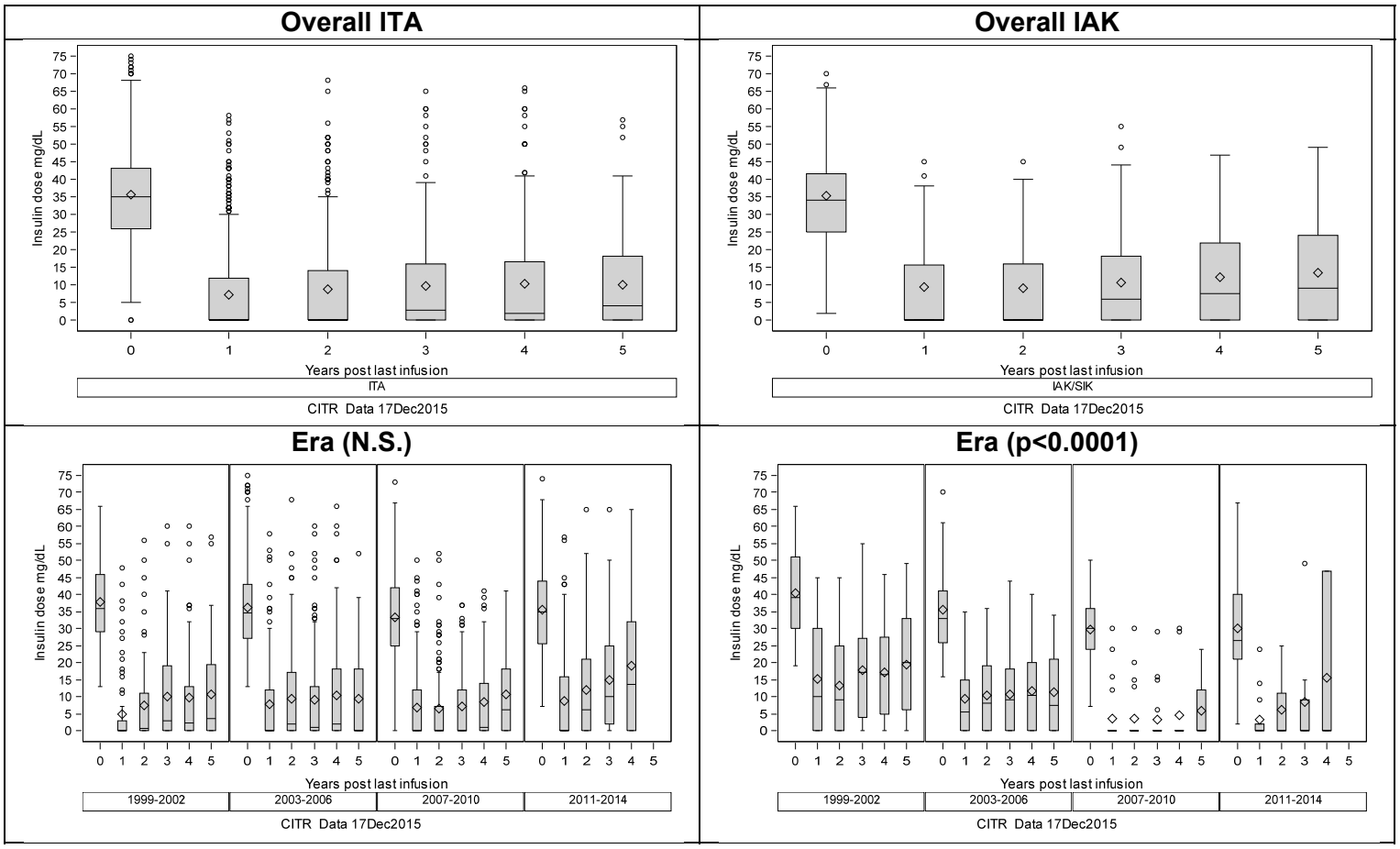
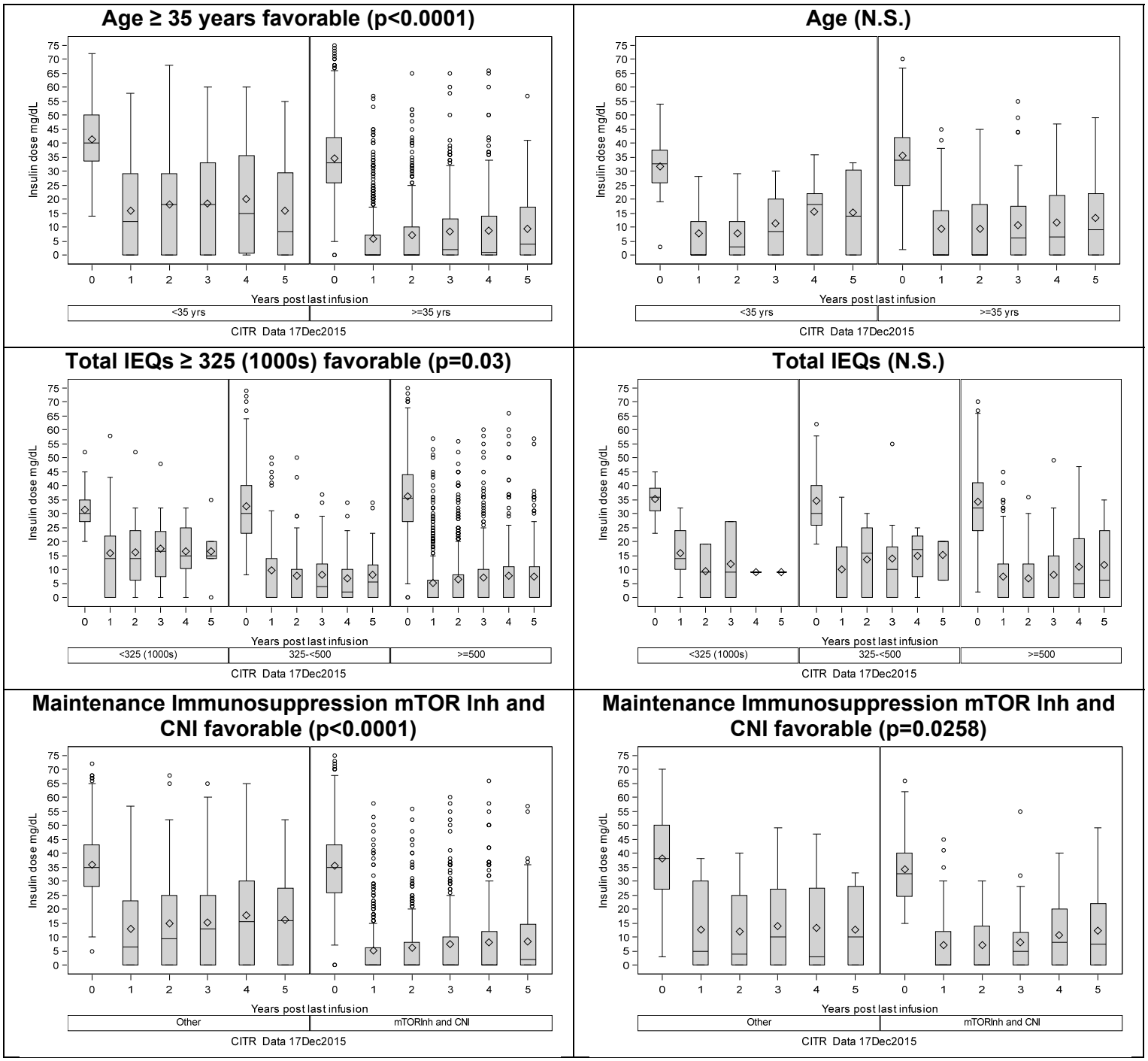


Exhibit 5 – 9 *(continued)*
Insulin Dose (U/day) Post Last Infusion



Fasting C-peptide rises dramatically after islet transplantation with decline over 5 years although more than 50% retain C-peptide >0.3 ng/mL at 5 years post last infusion in both ITA and IAK groups (Exhibit 5-10). Factors associated with improved results for each group are shown in Exhibit 5-10. Among ITA's favorable factors included age ≥35 (p<0.0001); total IEQs infused ≥ 325,000 (p<0.0001); Islets Cultured ≥ 6 hours (p=0.0014) and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors (p=0.0081). Among IAK's favorable factors included total IEQs ≥ 500,000 favorable (p=0.0431) and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors (p=0.0218).

Exhibit 5 – 10
Fasting C-peptide (ng/ml) Post Last Infusion

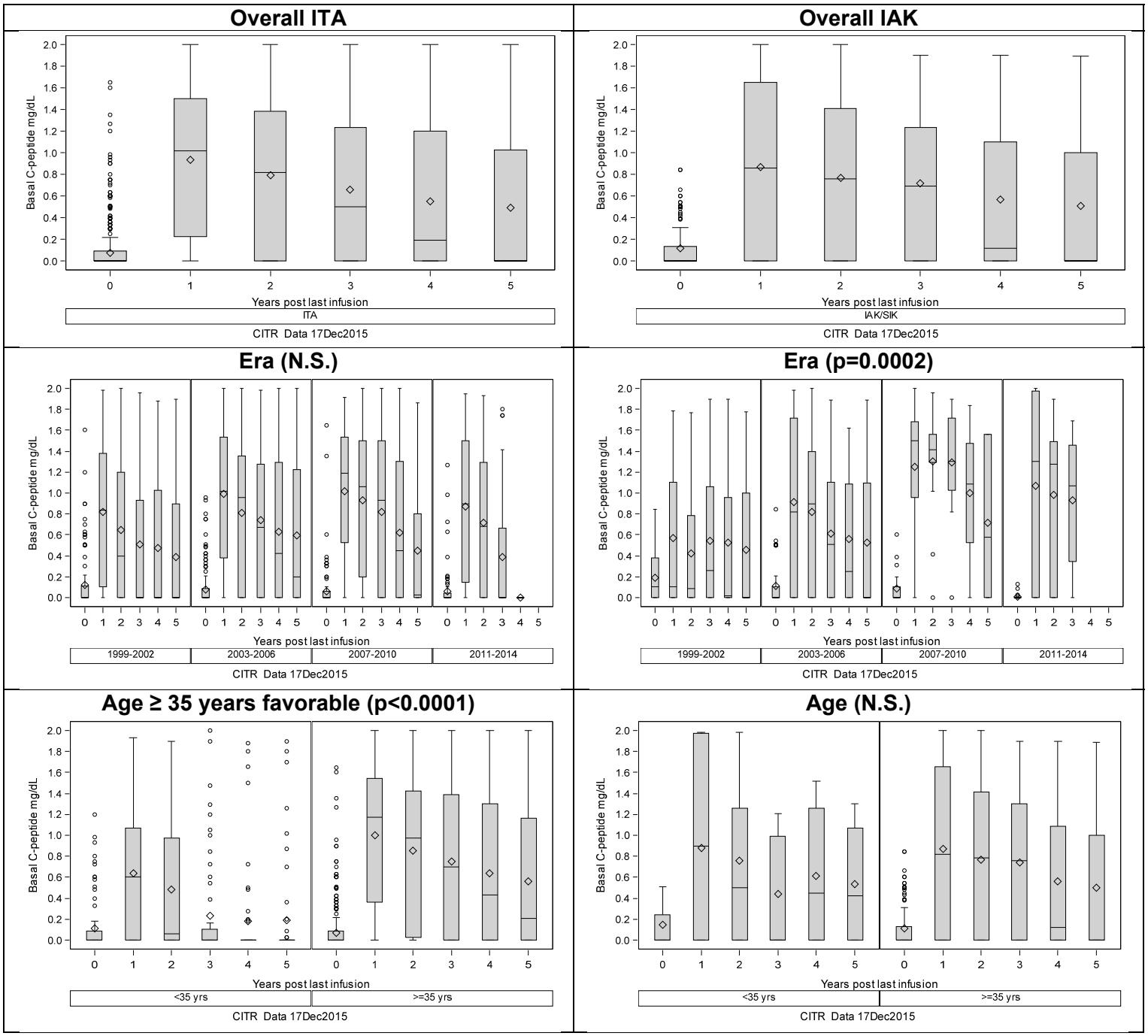
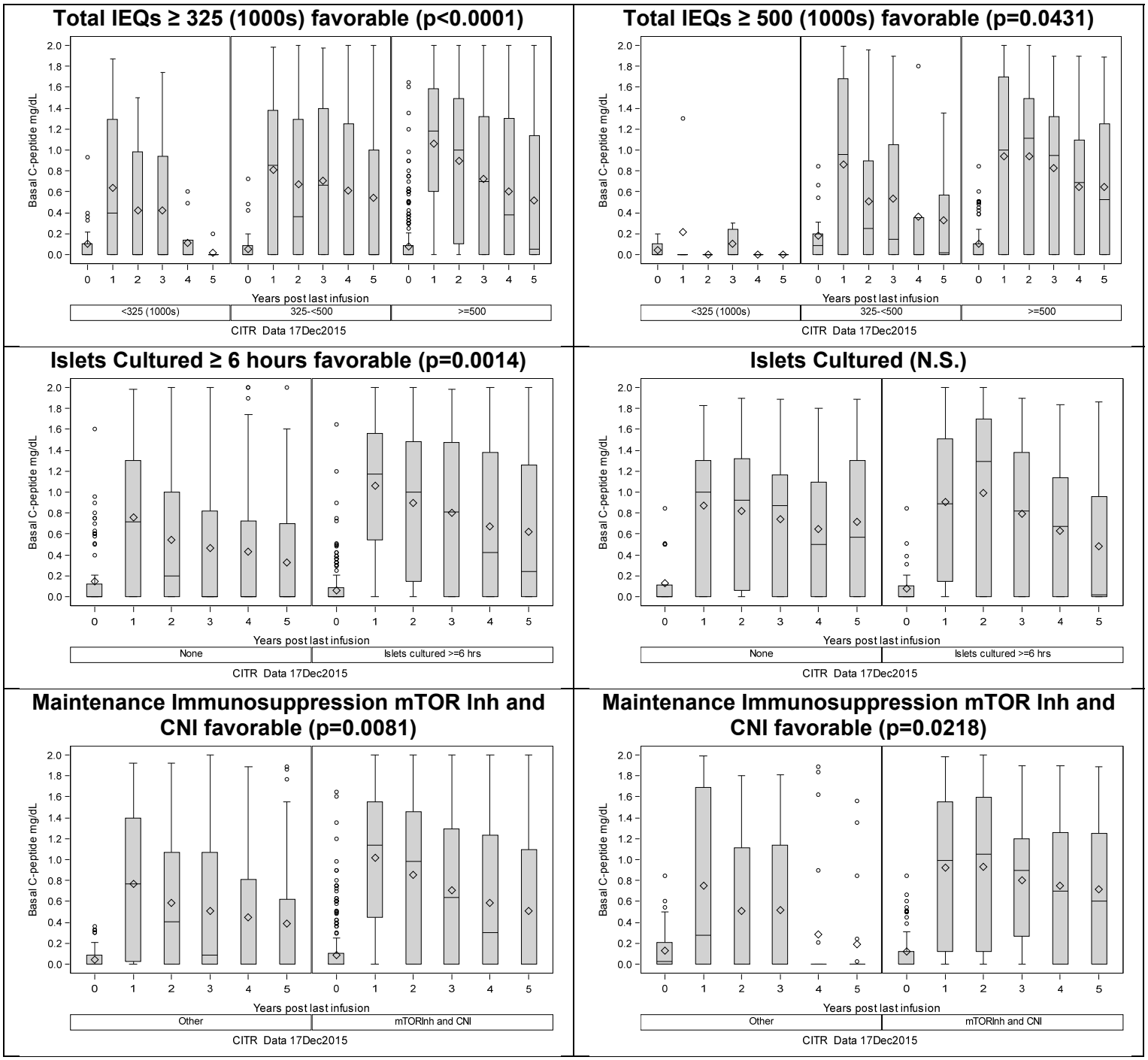


Exhibit 5 – 10 *(continued)*
Fasting C-peptide (ng/ml) Post Last Infusion



HbA1c in both ITA and IAK groups declines sharply after islet transplantation, and does not return to pre-transplant levels (Exhibit 5-11). Factors associated with improved results in each group are shown in Exhibit 5-11. Among ITA's favorable factors included age ≥35 (p<0.0001); and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors (p<0.0001). Among IAK's favorable factors included total IEQs ≥ 500,000 favorable (p=0.0122).

Exhibit 5 – 11
HbA1c (%) Post Last Infusion

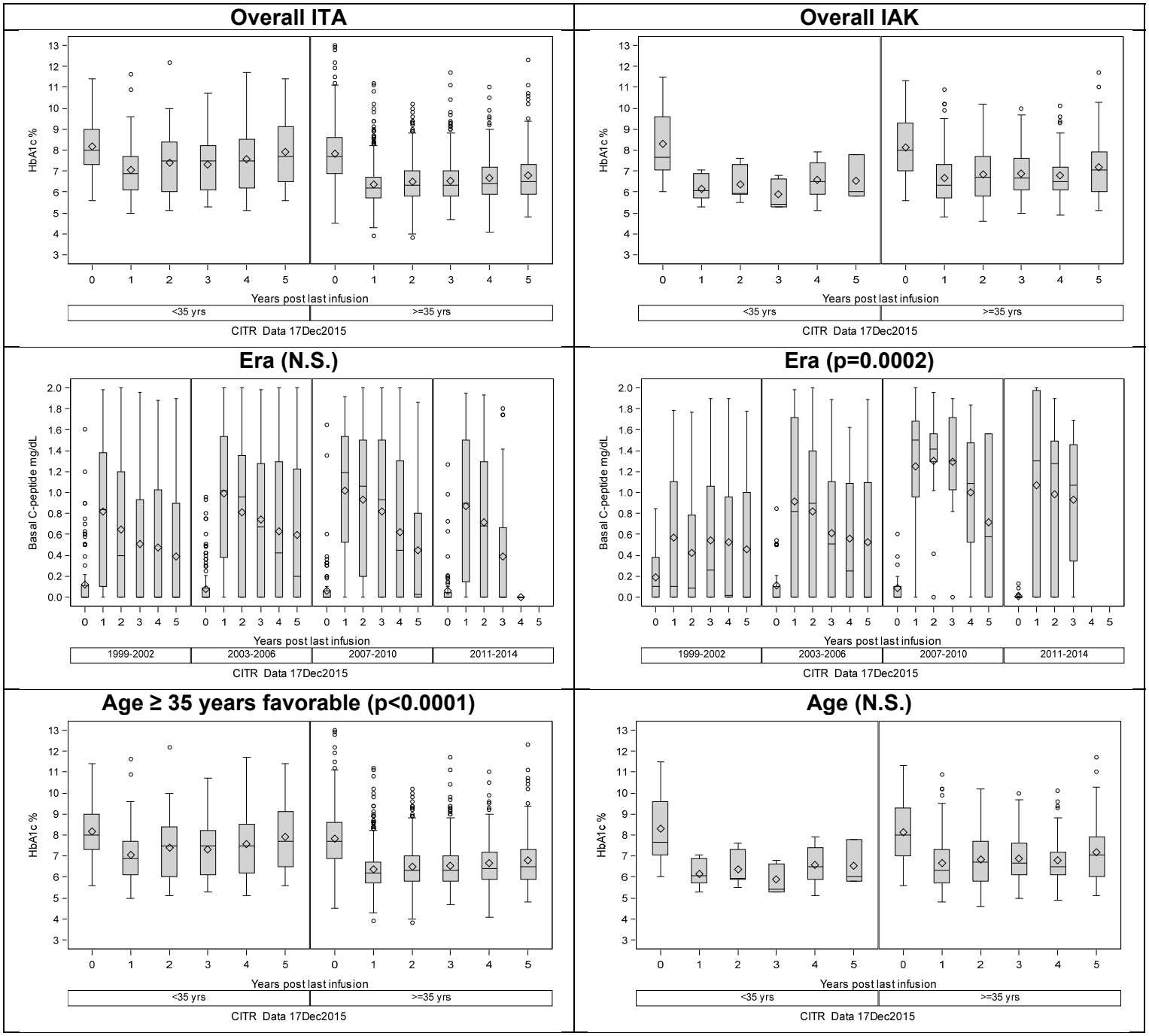
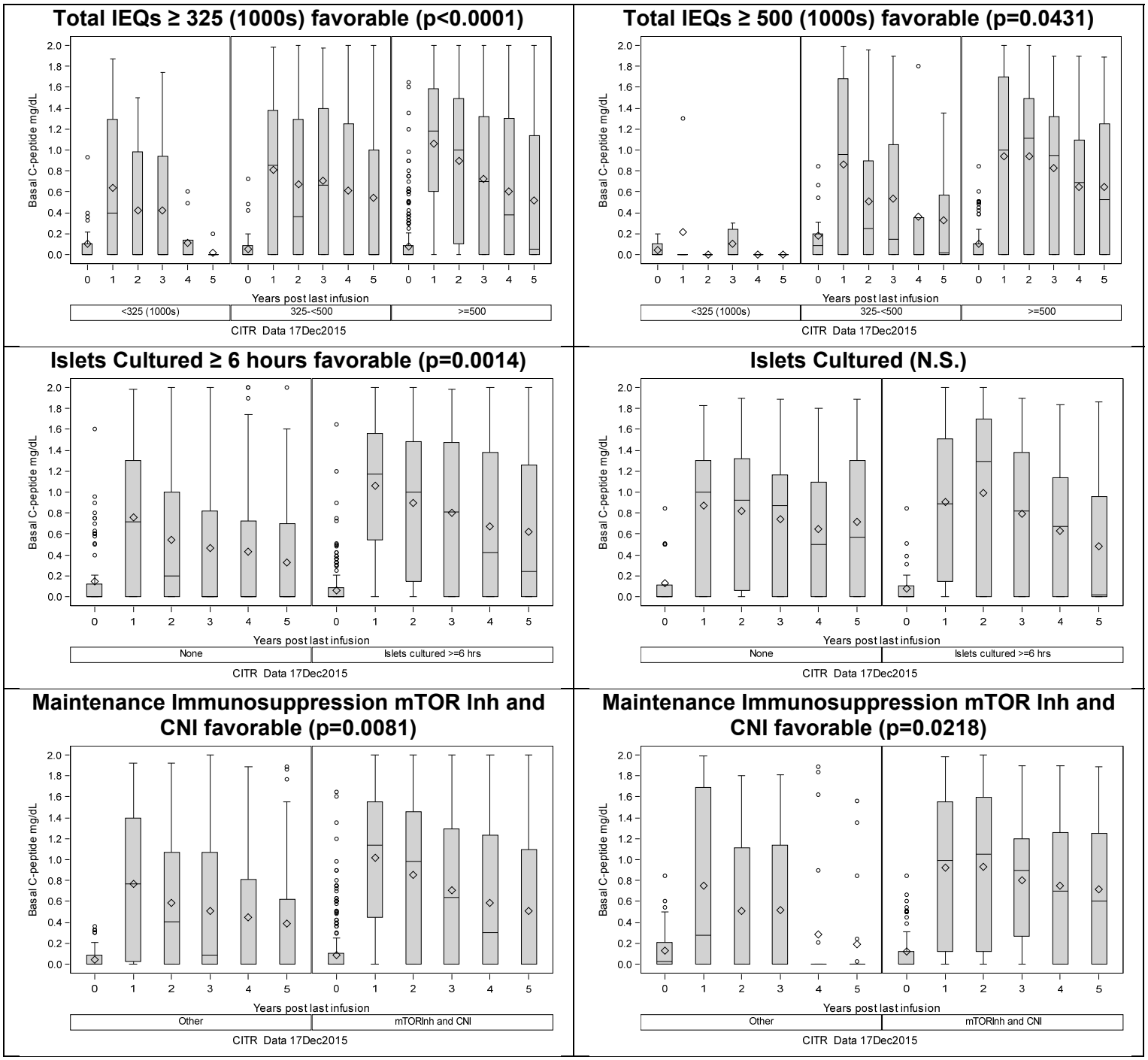


Exhibit 5 – 11 *(continued)*
HbA1c (%) Post Last Infusion



Fasting blood glucose also declines dramatically after islet transplantation and in over 70% of ITA patients and almost 60% of IAK patient remains at levels of 60-140 mg/dL (Exhibits 5-12 and 5-5). Factors associated with improved results in each group are shown in Exhibit 5-12. Among ITA's favorable factors included age ≥ 35 ($p<0.0001$); induction immunosuppression with TCD and/or TNF alpha ($p=0.049$); and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p<0.0001$).

Exhibit 5 – 12
Fasting Blood Glucose (mg/dl) Post Last Infusion

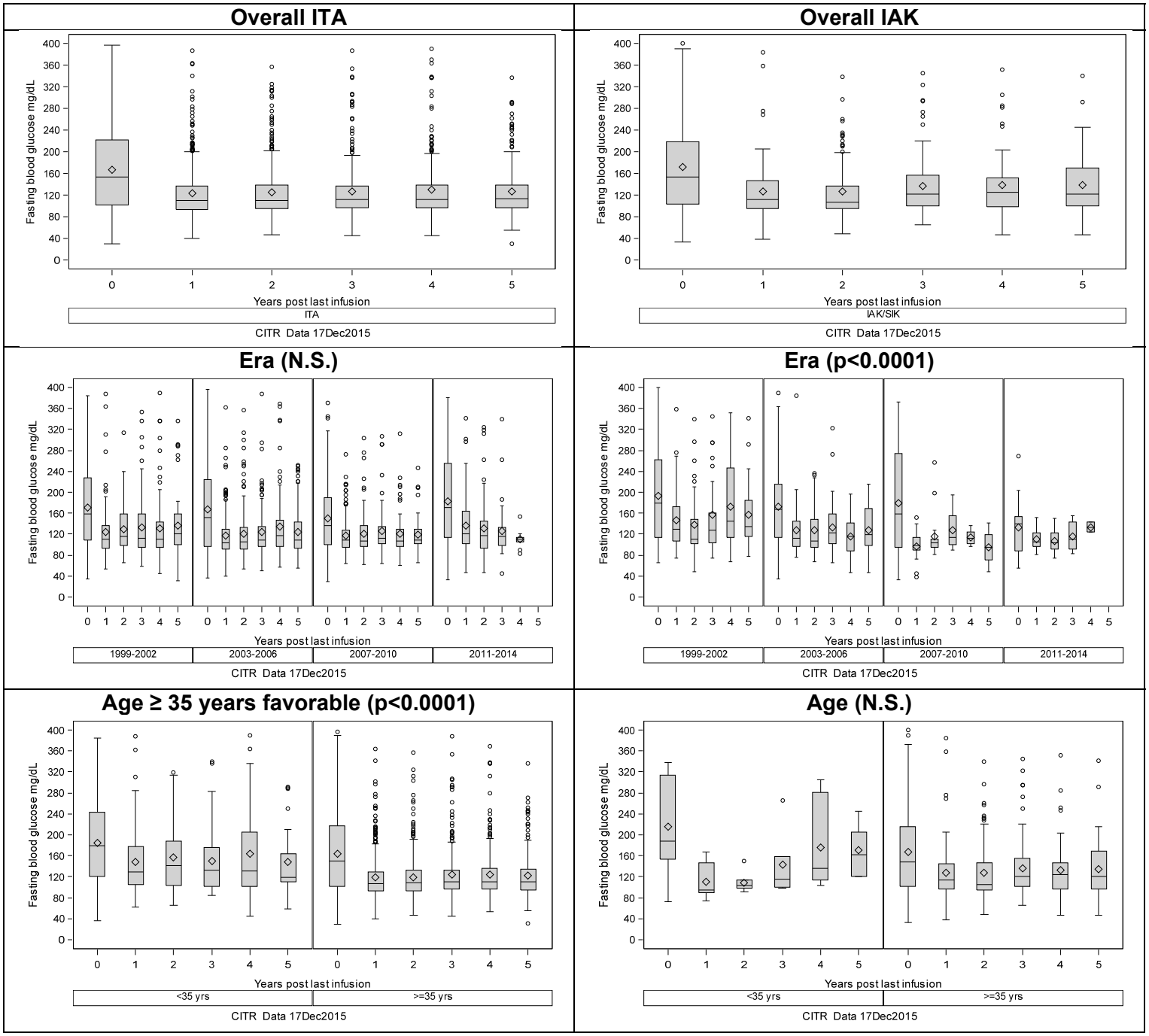
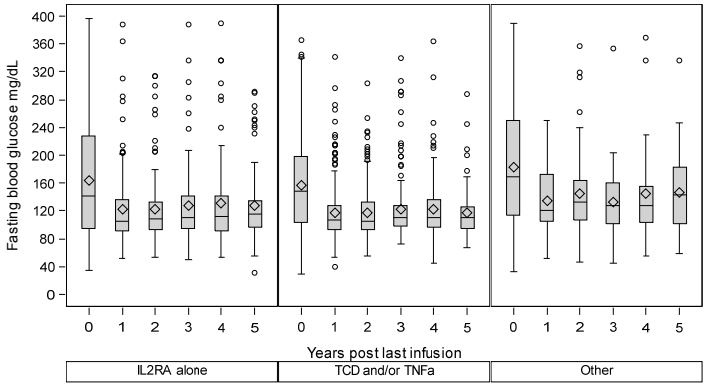
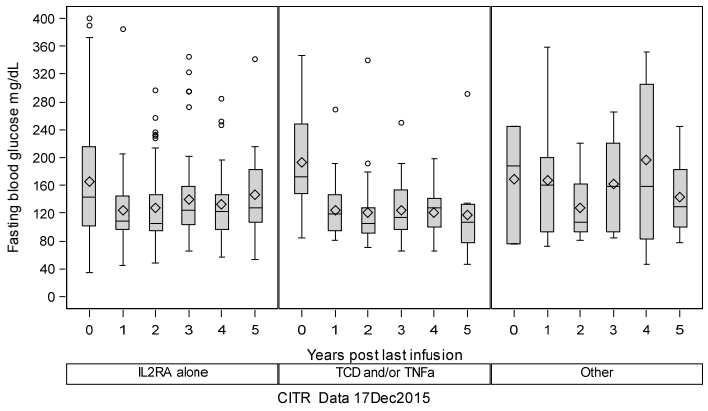


Exhibit 5 – 12 *(continued)*
Fasting Blood Glucose (mg/dl) Post Last Infusion

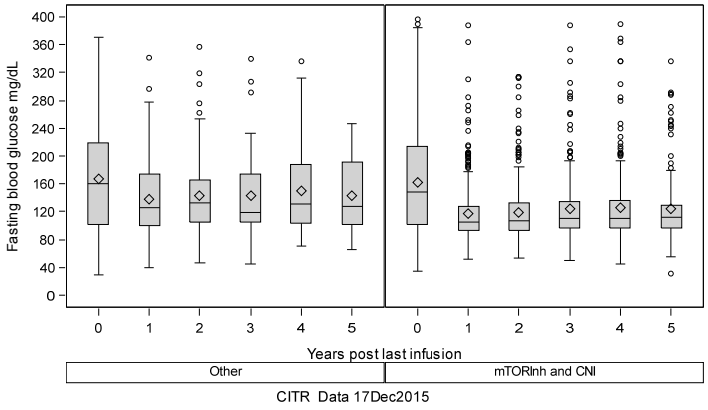
Induction Immunosuppression TCD and/or TNF alpha favorable (p=0.049)



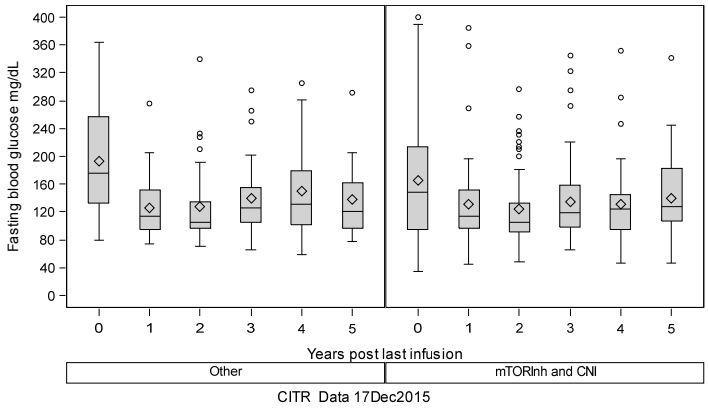
Induction Immunosuppression (N.S.)



Maintenance Immunosuppression mTOR Inh and CNI favorable (p<0.0001)



Maintenance Immunosuppression (N.S.)



The higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c <6.5% or drop by 2%, fasting blood glucose of 60-140 mg/dL, and the lower the likelihood of severe hypoglycemia (Exhibit 5-13). This holds true for both ITA and IAK patients. Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced over all follow-up even with C-peptide <0.3 ng/mL. While these strong associations among the co-primary outcomes are highly significant, any causal relationships cannot be deduced just from the associations; a temporal analysis is a separate focus topic.

Exhibit 5 – 13
Association of C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion

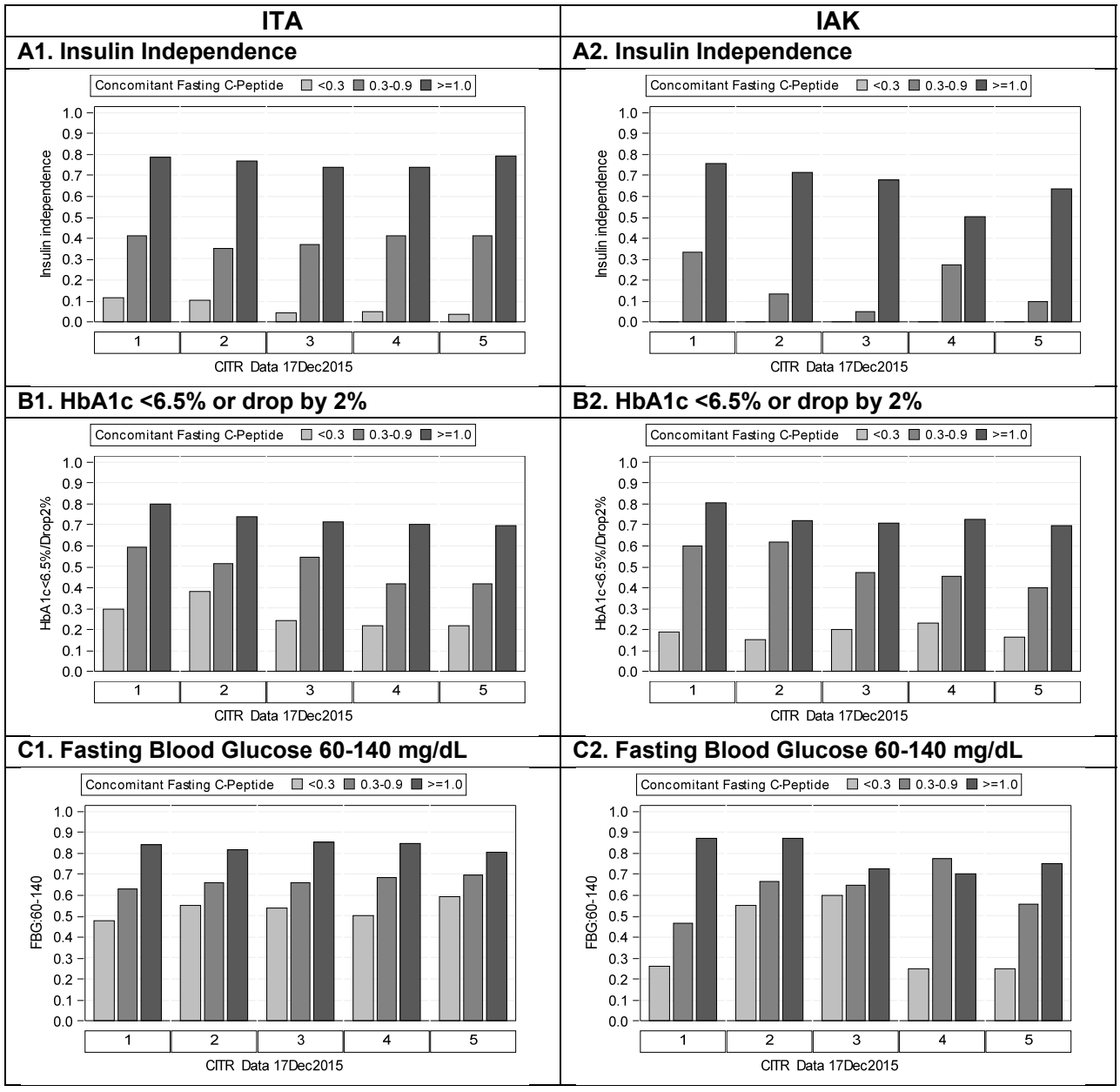
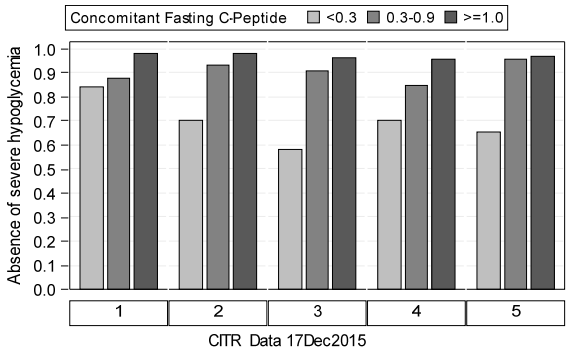
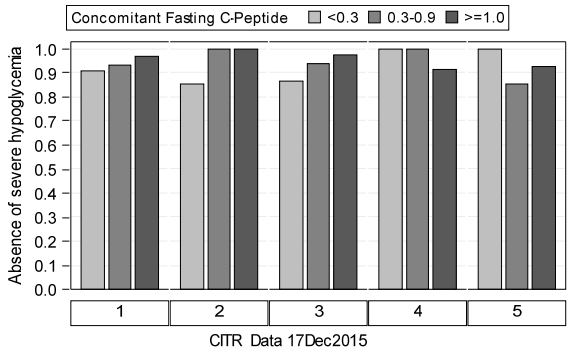


Exhibit 5 – 13 *(continued)*
Association of C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion

D1. Absence of Severe Hypoglycemic Events



D2. Absence of Severe Hypoglycemic Events

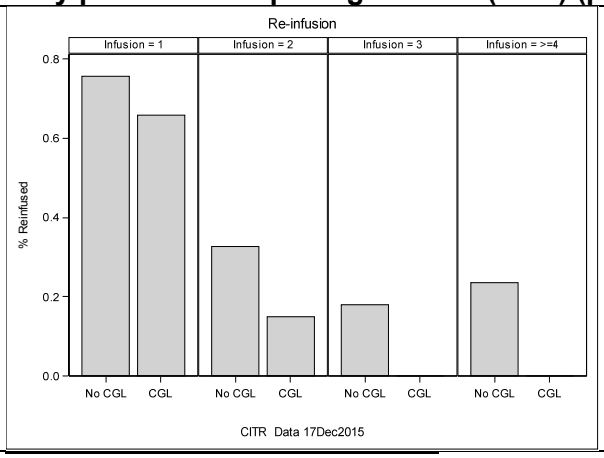


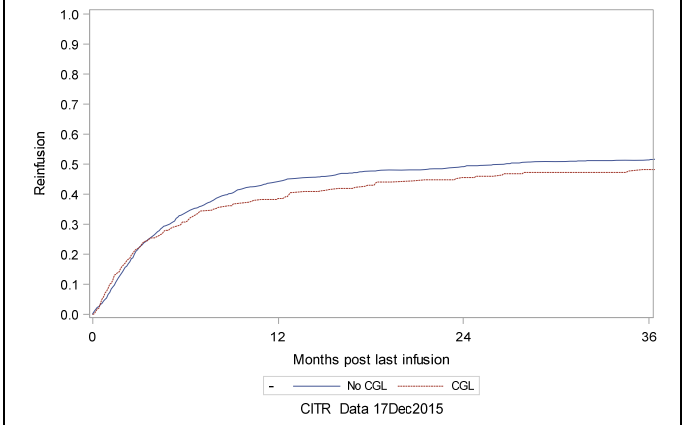
Re-infusion

Re-infusion may have been conducted without (749/1475=50.8%) or after (173/378=45.8%) complete graft failure (fasting C-peptide<0.3 ng/mL without recovery, Exhibit 5-4A). Viewed as time-to-event, reinfusion was no more likely with a functioning graft than with a lost graft (p=0.12). A number of re-infusions were conducted while the patient was not only C-peptide positive but also insulin independent (Exhibit 5-4B, 38/256=14.8%, for all infusions): re-infusion was much more likely when the patient had not yet achieved insulin independence (p<0.001, Exhibit 5-14B). Second infusion rates have been remarkably constant over the whole history of the CITR (p=0.04, Exhibit 5-14C).

Exhibit 5 – 14
Re-Infusion
(After each infusion sequence)

A. By previous complete graft loss (CGL) (p=0.33)

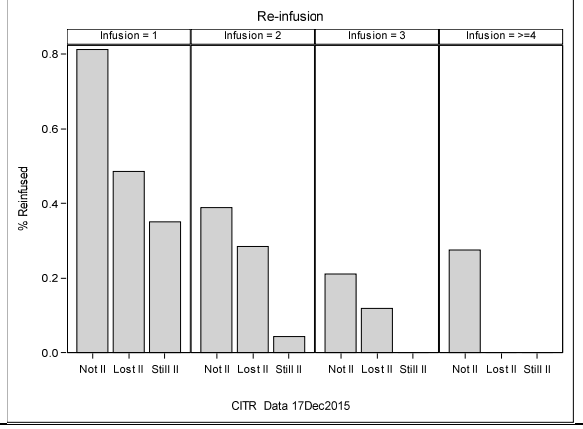


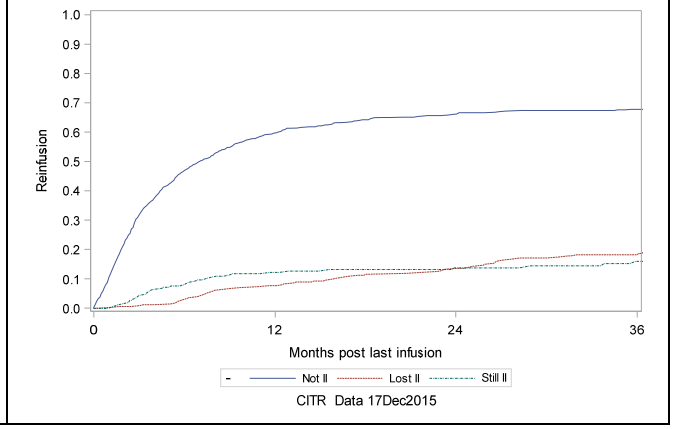


	Reinfusion		
	No	*Yes*	*Total*
	N	*N*	*N*
Infusion 1	252	679	931
Infusion 2	474	205	679
Infusion 3	175	30	205
Infusion>=4	30	8	38
All	931	922	1853

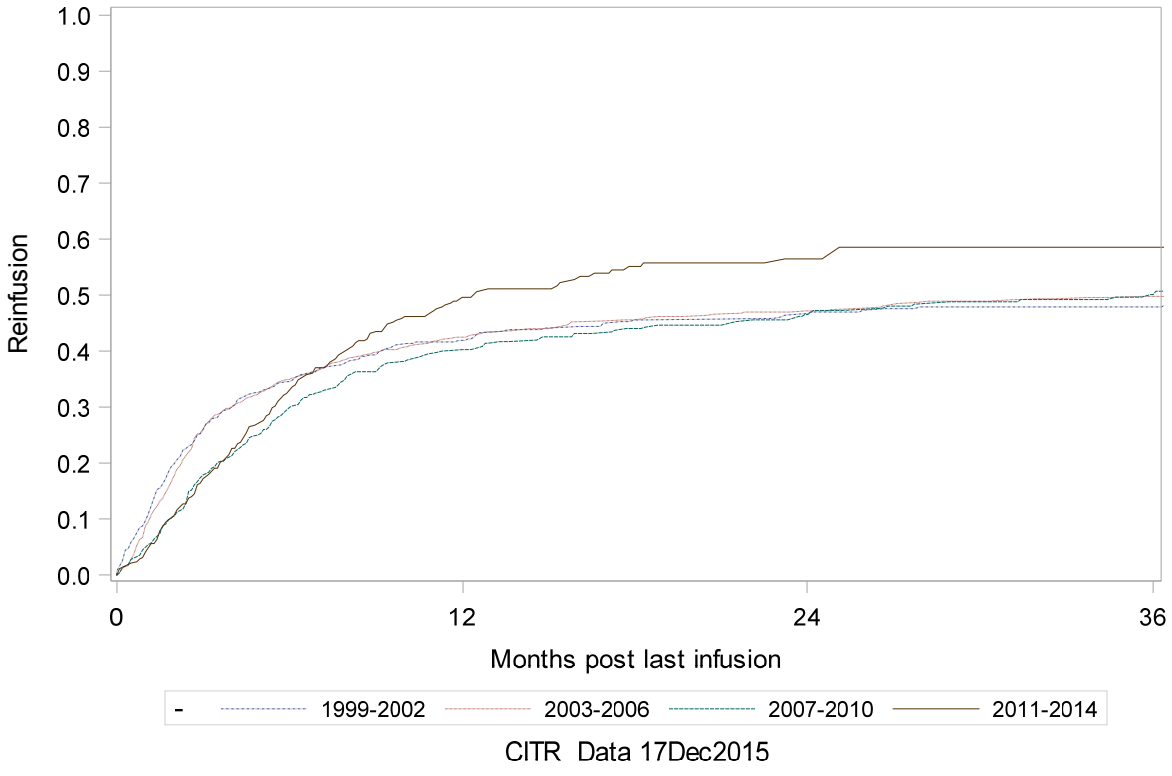
Exhibit 5 – 14 *(continued)*
Re-Infusion
(After each infusion sequence)

B. By concurrent insulin independence (p=<0.0001)





C. By Era (p=0.36)



Chapter 6
Liver, Kidney Lipid, and PRA Effects

Introduction

Exhibits 6-1 to 6-10 display various laboratory results at major time points following islet transplantation, according to annual follow-up post last transplant, era, and type of transplant. Additionally, important factors previously identified to impact primary clinical outcomes of islet transplantation, along with any effects of induction and maintenance immunosuppression strategies, are shown if they were significant. A preliminary interpretation of the findings is included with each exhibit.

Exhibit 6 – 1A
ALT (IU/L)

ALT typically rises after islet transplantation and then levels off. In recent eras, the maximum rise has been significantly lower. Induction with TCD or other non-IL2RA agent is associated with lower increase in ALT after islet transplantation.

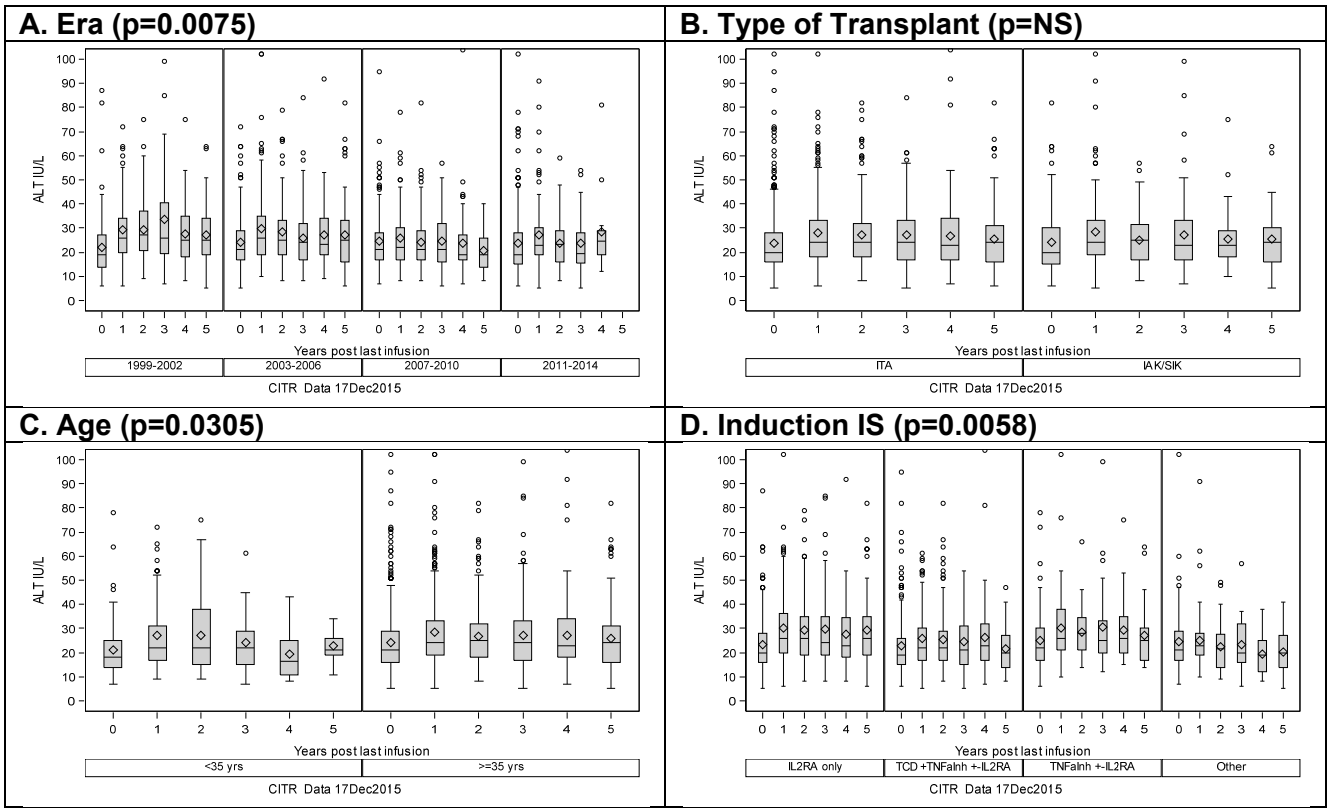


Exhibit 6 – 1B
AST (IU/L)

AST also rises after islet transplantation; however, no significant difference over the eras is observed. Long-term recovery appears to be better in recipients aged <35 years. The same difference with respect to induction agents are seen with change in AST as in ALT.

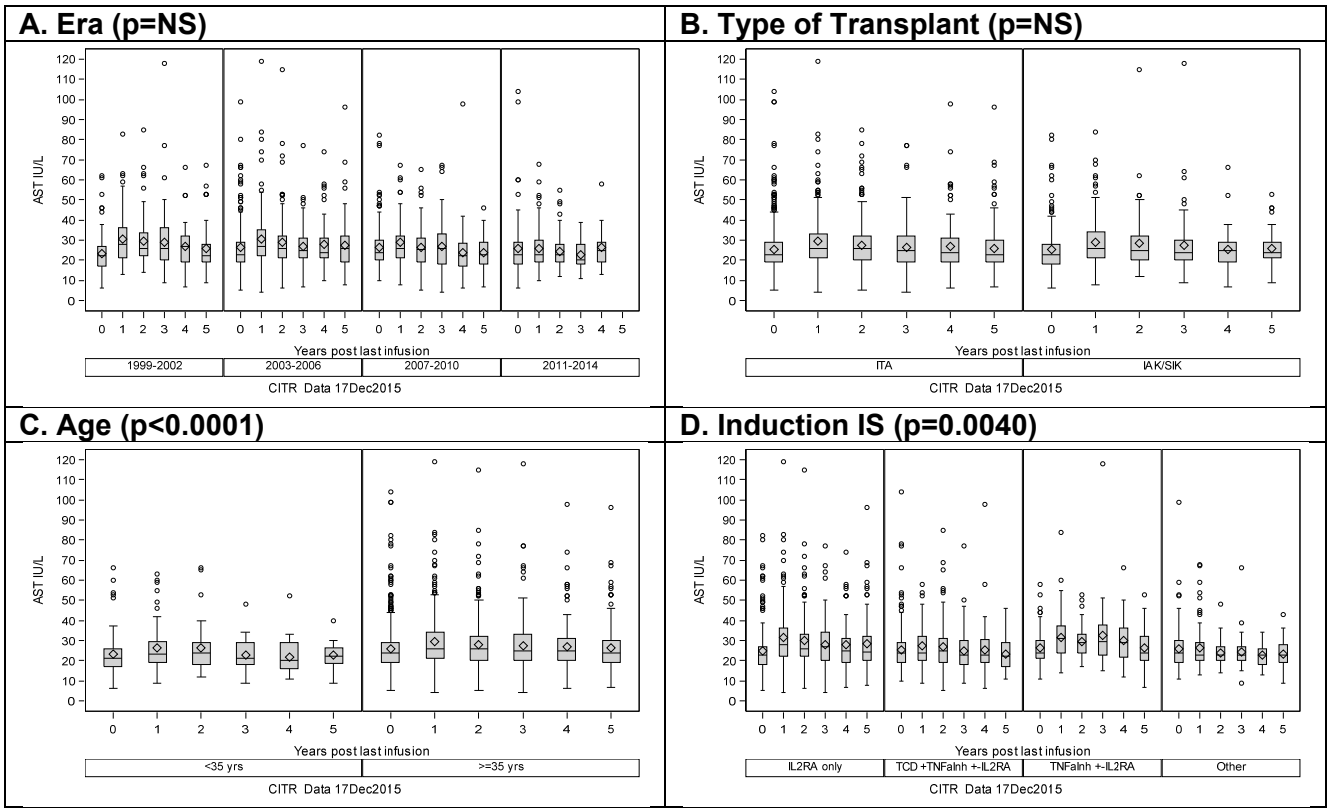


Exhibit 6 – 2
Alkaline Phosphatase (IU/L)

There is very little change in alkaline phosphatase in follow-up after islet transplantation. Initial levels are higher in IAK/SIK compared to ITA, and these levels persist relatively unchanged over follow-up. Recipients given induction with TCD and TNFa inhibitor had lower initial levels which then persisted relatively unchanged over long-term follow-up, except for induction regimens that did not include IL2RA inhibitors, TCD, or TNF-a inhibitors, in which case substantially higher elevations were seen. Maintenance immunosuppression with combinations involving mTOR inhibitors and calcineurin inhibitors were associated with the lower initial levels of alkaline phosphatase.

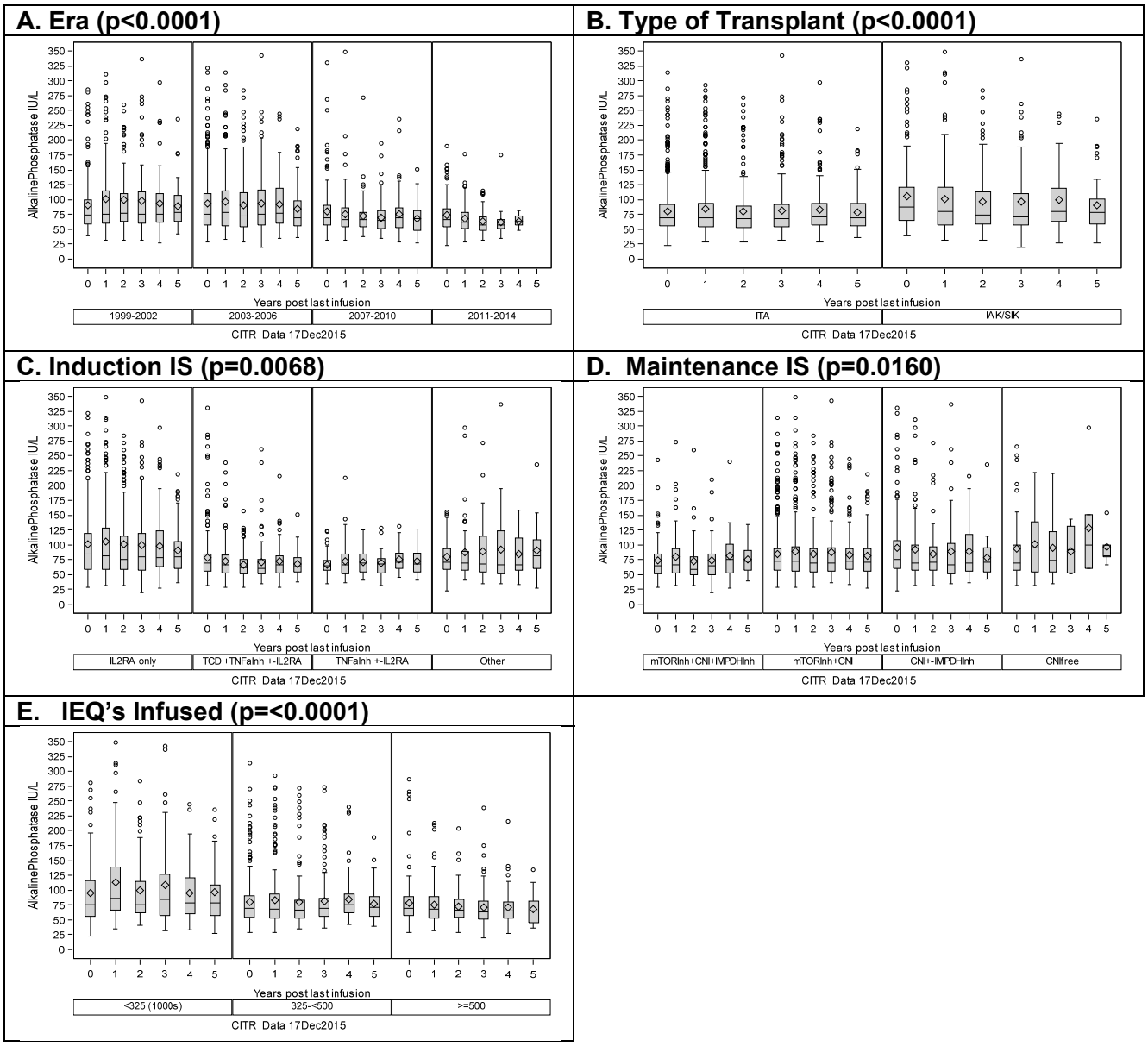


Exhibit 6 – 3
Total Bilirubin

Total bilirubin varied at statistically significant levels over years of follow-up after islet transplantation, but in no consistent upward or downward trend. Era was significantly associated with total bilirubin with higher levels in more recent eras. No other factors, particularly immunosuppression, were associated with changes in total bilirubin.

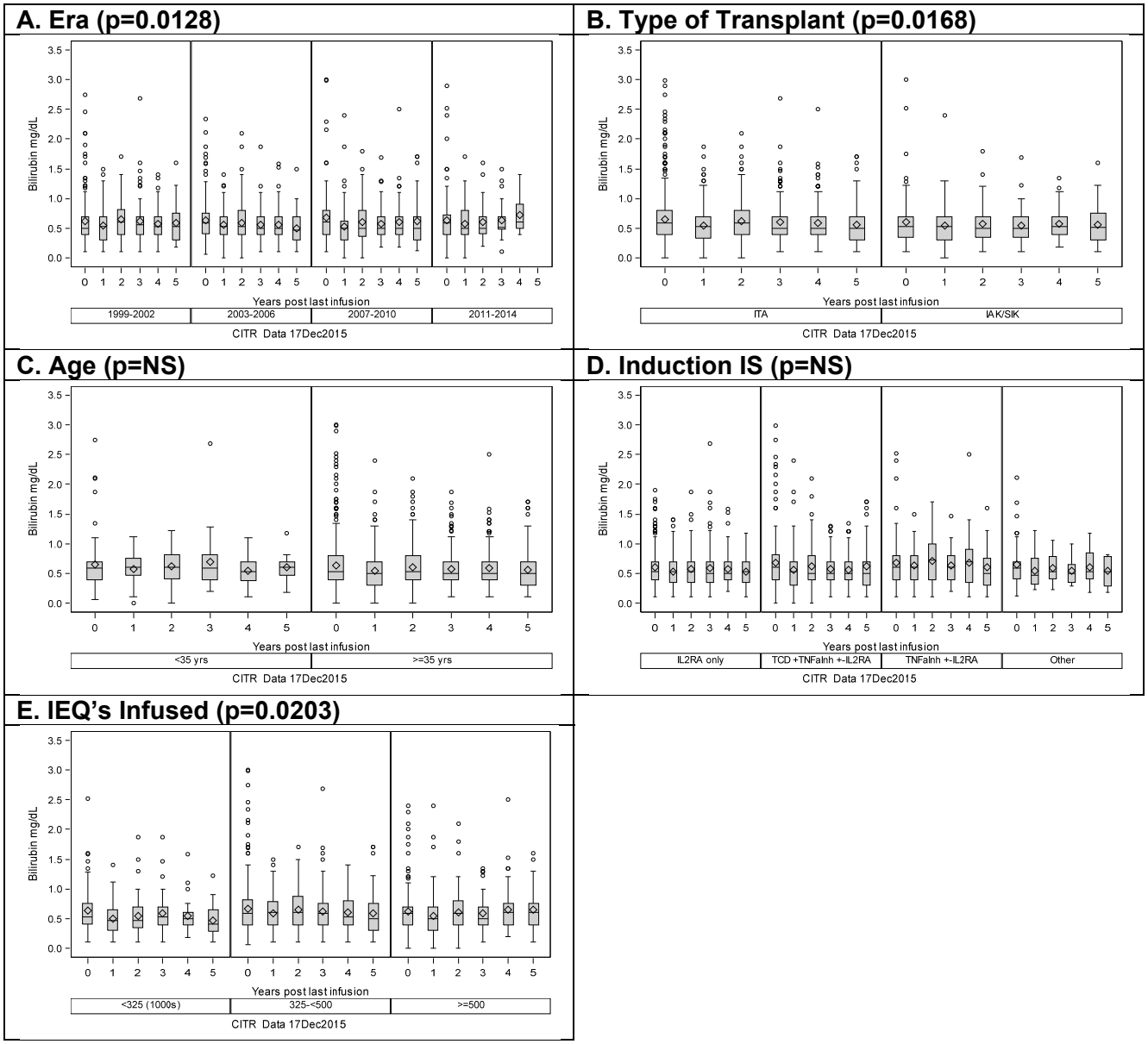


Exhibit 6 – 4
HDL Cholesterol (mg/dL)

There is a statistically significant decline in HDL cholesterol following islet transplantation in both ITA and IAK/SIK, which was consistent across the eras, though the decline over follow-up time was more pronounced in IAK/SIK and for those under 35. There were no differences by immunosuppression regimen.

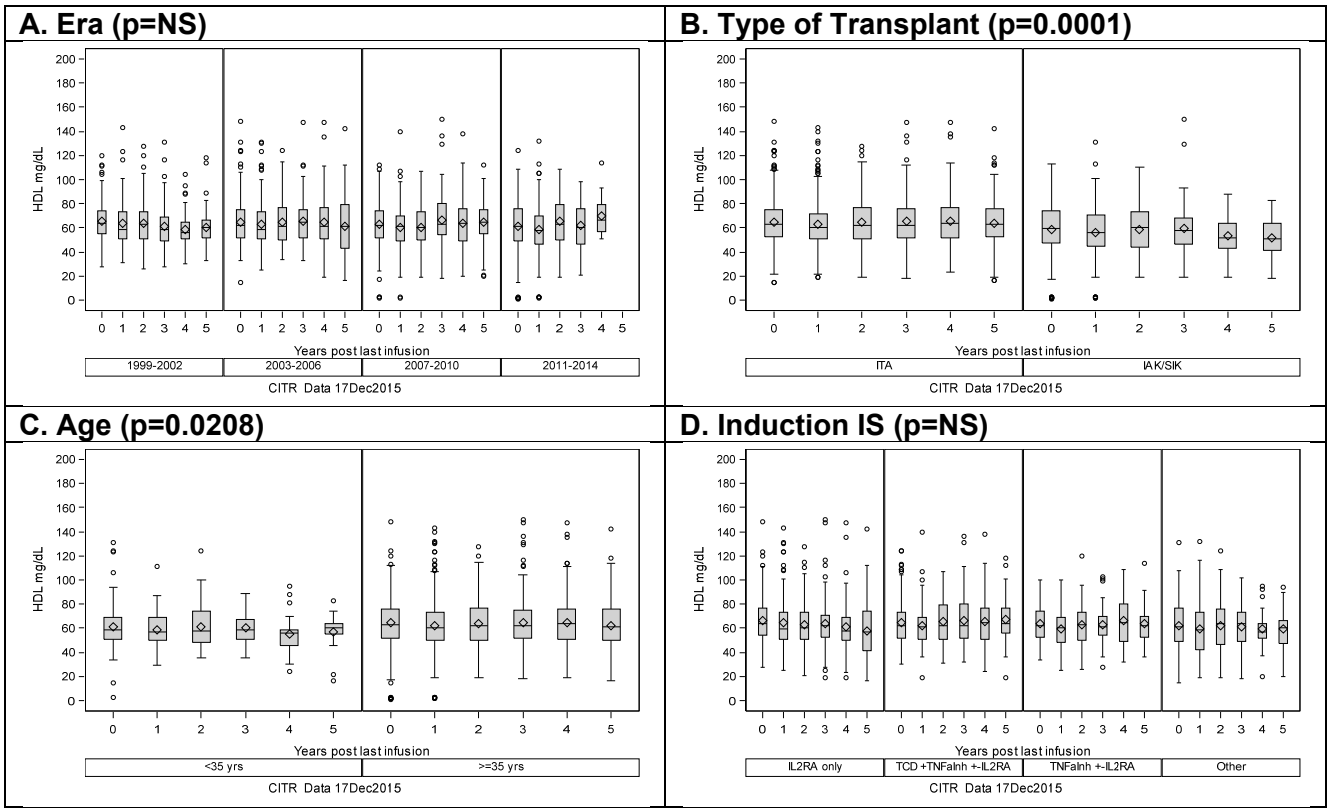


Exhibit 6 – 5
LDL Cholesterol (mg/dL)

In the early eras a significant decline in LDL cholesterol was noted, which did not differ by type of transplant. Initial LDL levels were higher in recipients aged<35 years, though the subsequent rate of decline was comparable. The decline was not nearly as pronounced in those receiving TCD+TNFa inhibition induction.

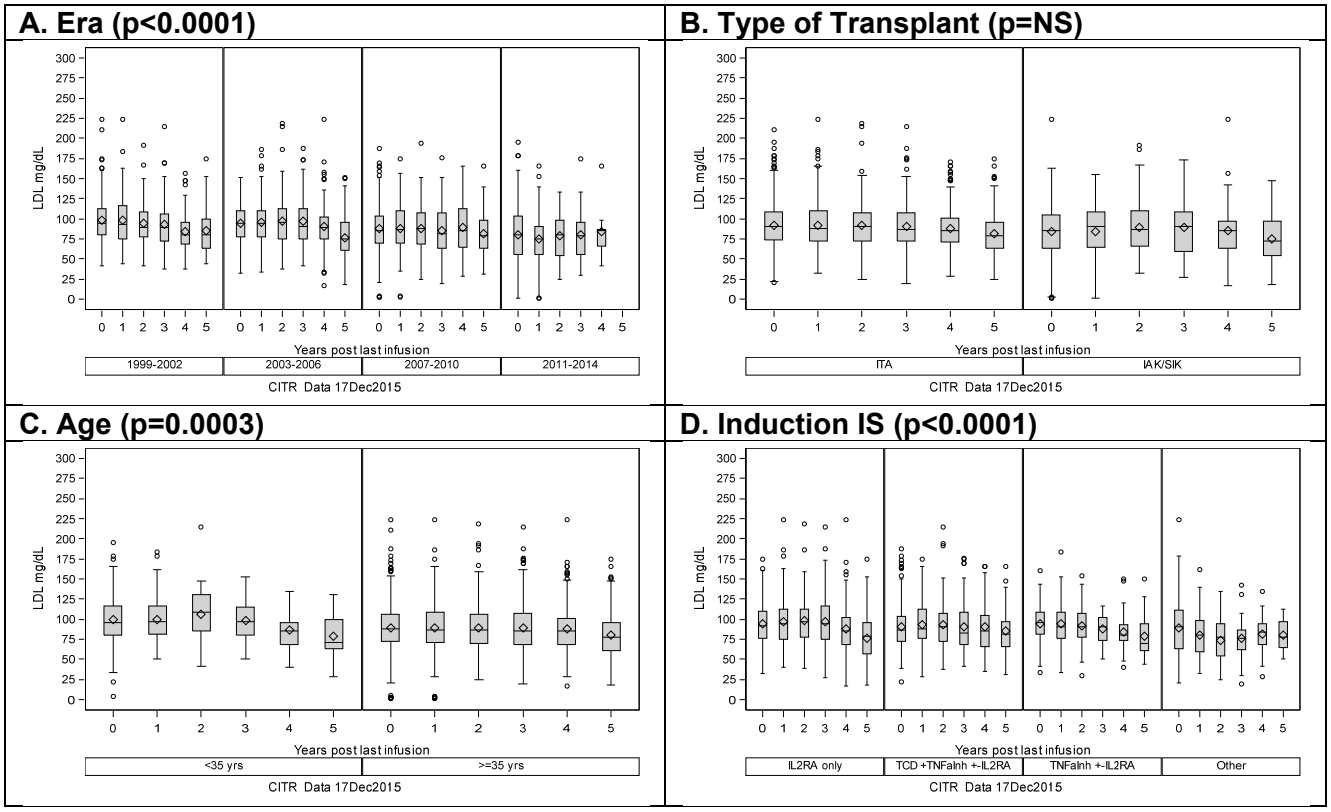


Exhibit 6 – 6
Triglycerides (mg/dL)

Triglycerides rose somewhat following islet transplantation. There were no net effects of transplant type, age, or maintenance immunosuppression.

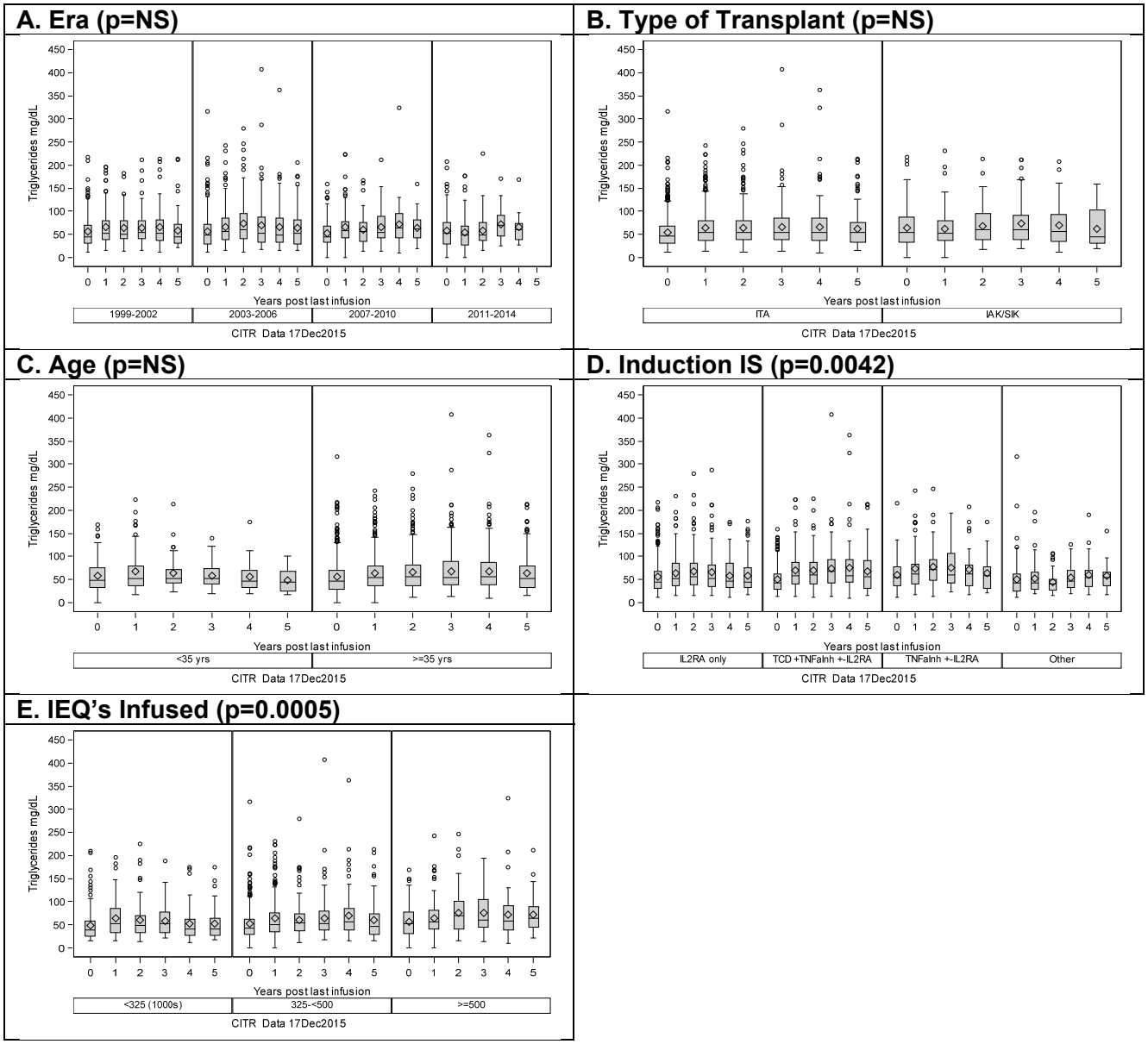


Exhibit 6 – 7
Total Cholesterol (mg/dL)

Total cholesterol generally declined in follow-up after islet transplantation, though with lower initial levels in the recent eras, total cholesterol over follow-up remained level. There was a notable difference between ITA and IAK/SIK with IAK/SIK dropping to slightly lower levels, and differences by age with those under 35 experiencing a greater decline. Induction with non-IL2RA alone inhibition is associated with significantly greater decline over follow-up. There were no notable effects of maintenance immunosuppression on changes in total cholesterol.

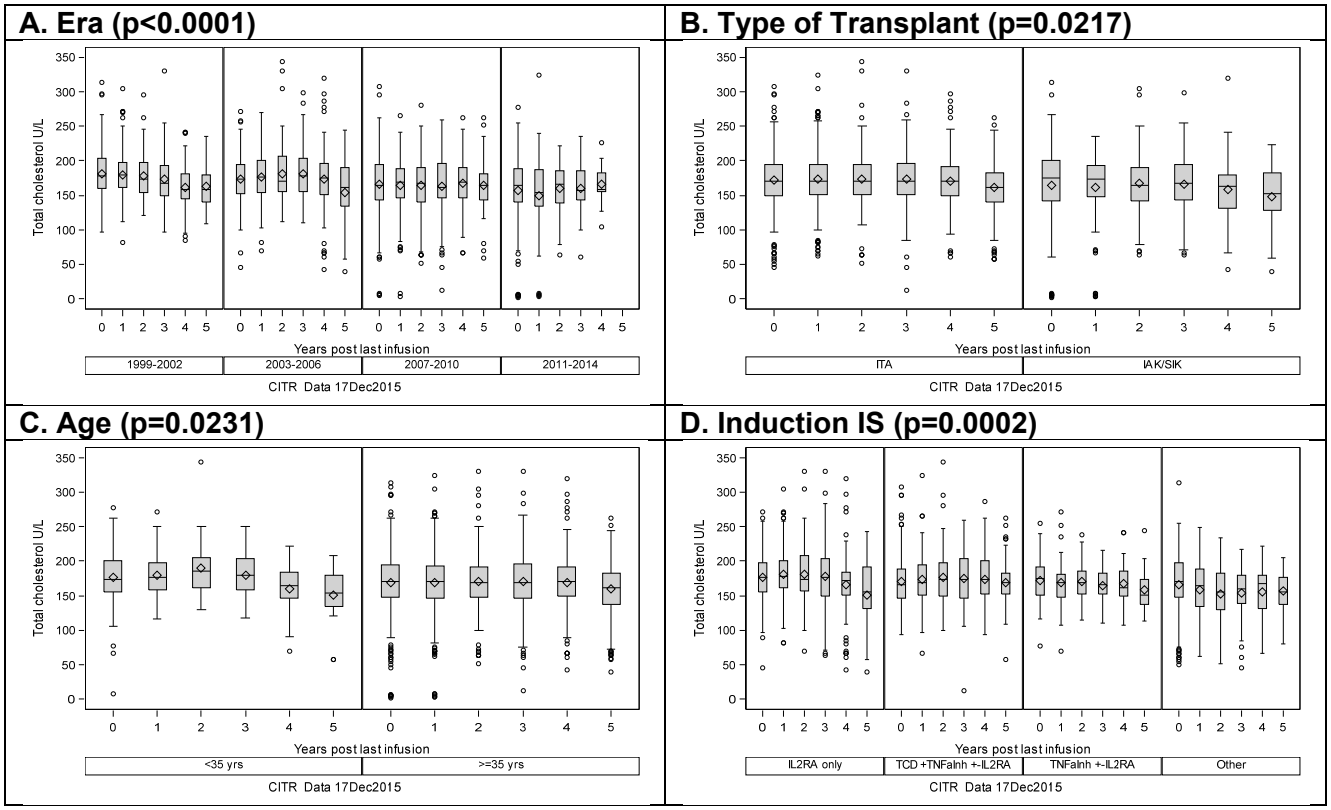


Exhibit 6 – 8
Serum Creatinine (mg/dL)

Serum creatinine rose over years of follow-up after initial islet transplant, in both ITA and IAK/SIK, with the IAKs starting at higher levels. Differences between eras are largely explained by lower initial levels of serum creatinine in selected recipients in recent years. IAK/SIK recipients had significantly higher levels of serum creatinine prior to transplant. Whether the increase over years of follow-up is significantly different from ITA is the subject of a focus analysis. There were no significant differences by immunosuppression regimen, or age, but levels rose significantly less in patients with ≥325,000 IEQ's infused.

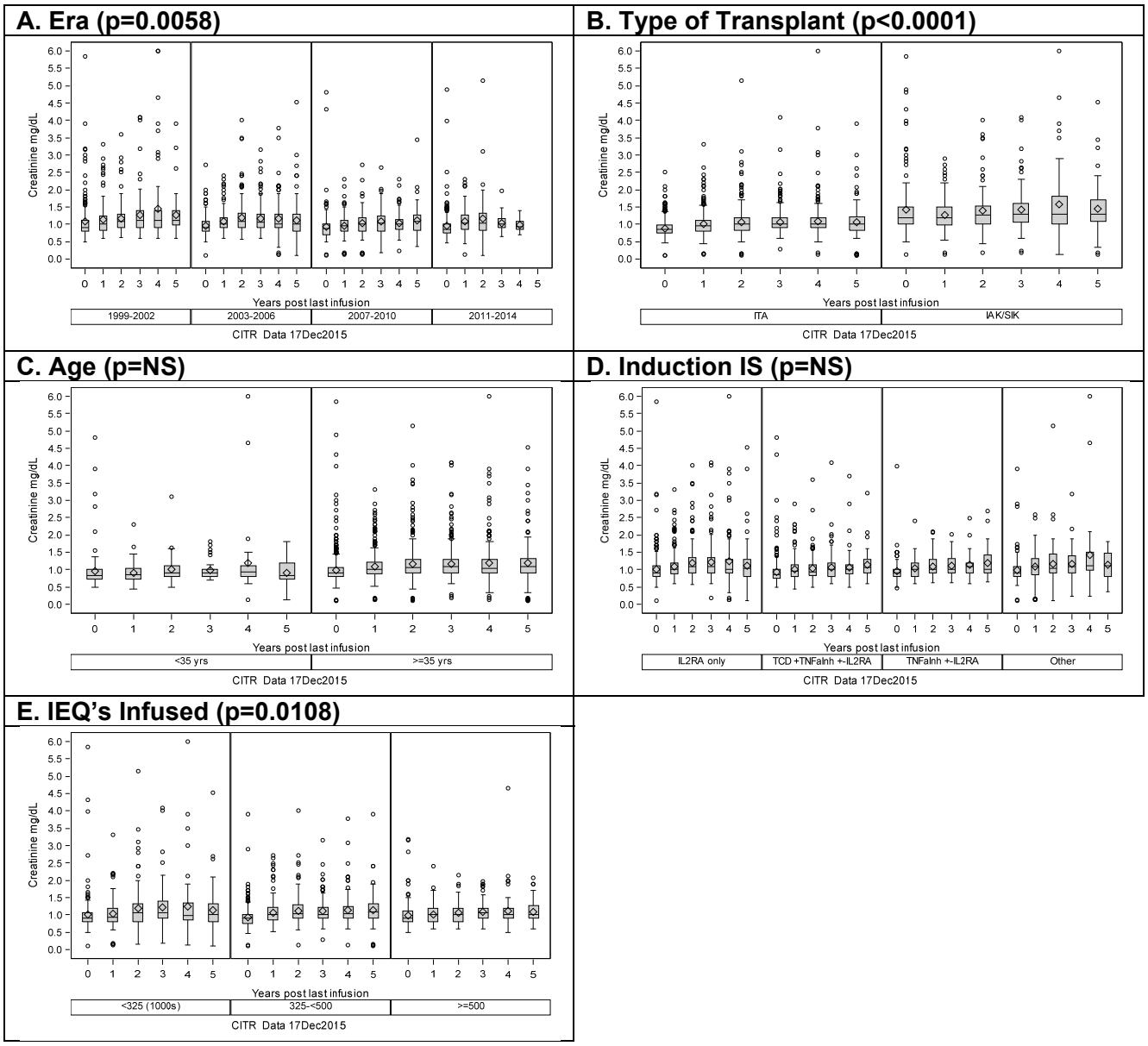


Exhibit 6 – 9
CKD-EPI eGFR

The decline in eGFR after islet transplantation is both statistically significant and clinically important. IAK/SIK had much lower pre-transplant levels than ITA, which then declined at a slower rate. Importantly, there were no differences in initial levels or subsequent decline over follow-up by immunosuppression regimens.

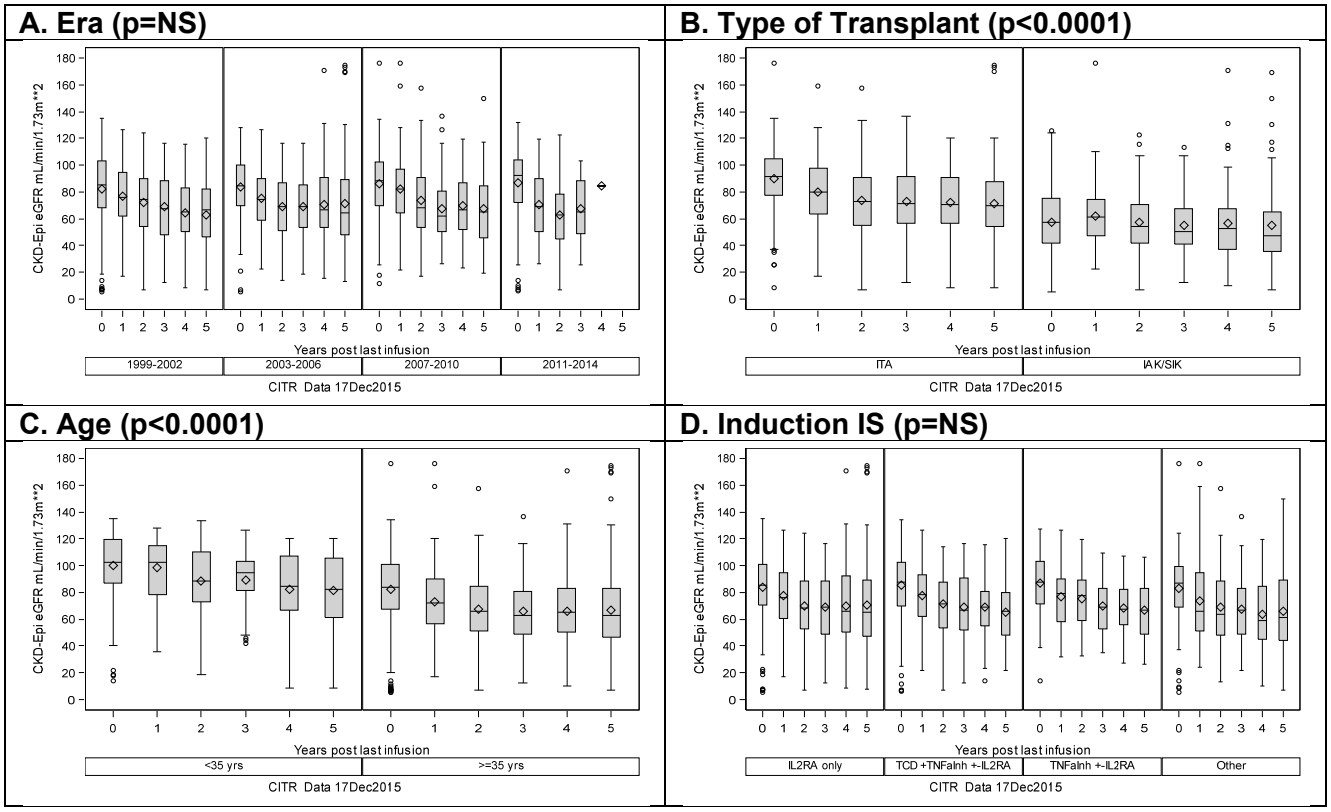
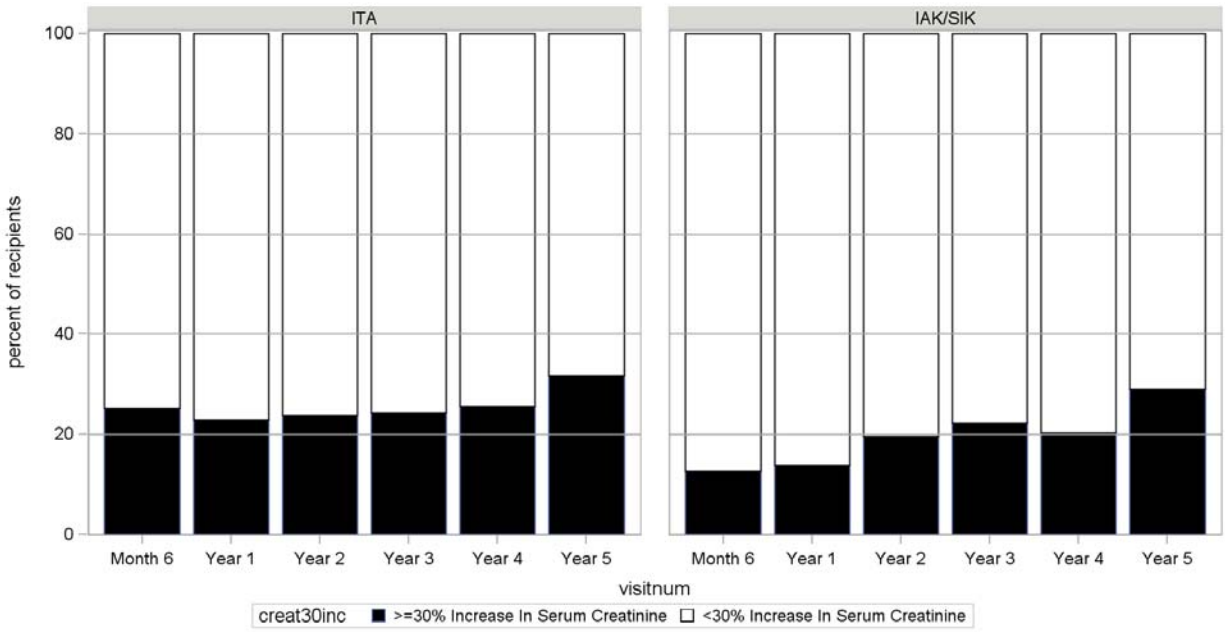
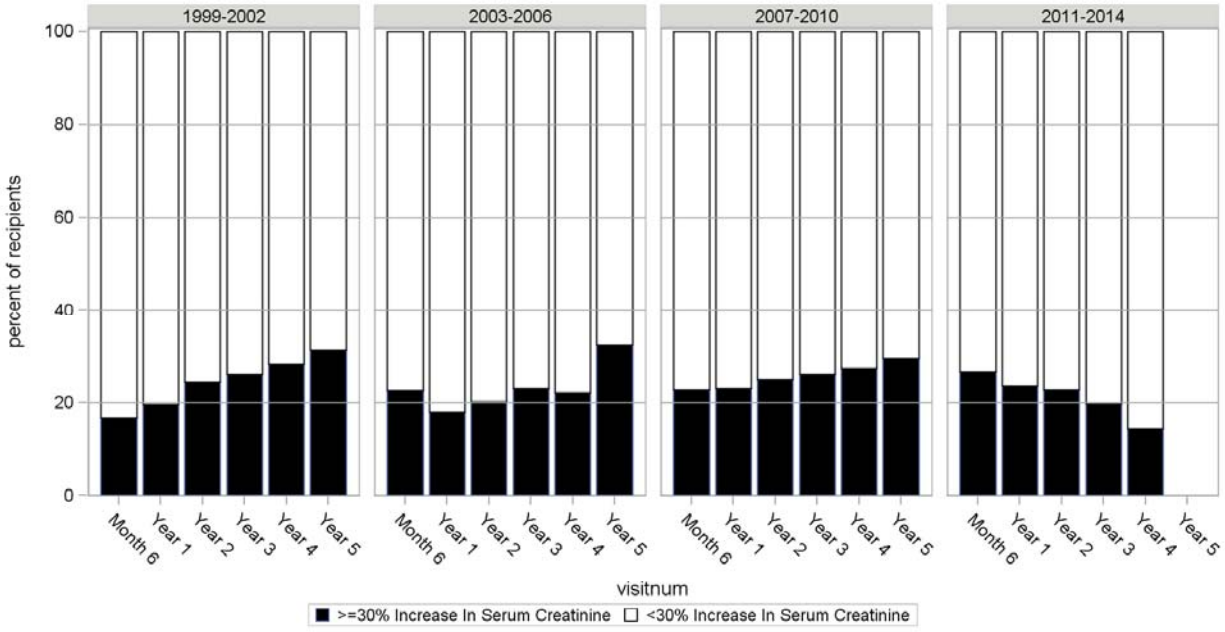


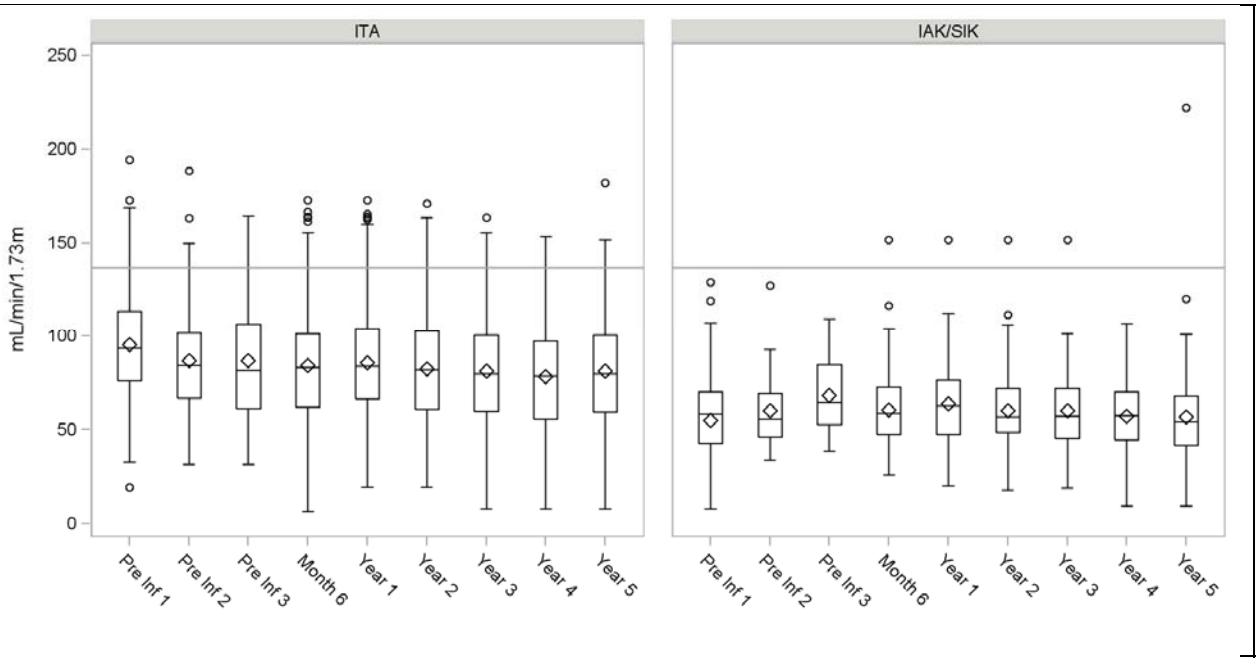
Exhibit 6 – 10
Percent of Recipients with a 30% increase in Serum Creatinine at each Follow-up Time Point by Infusion Type and Era

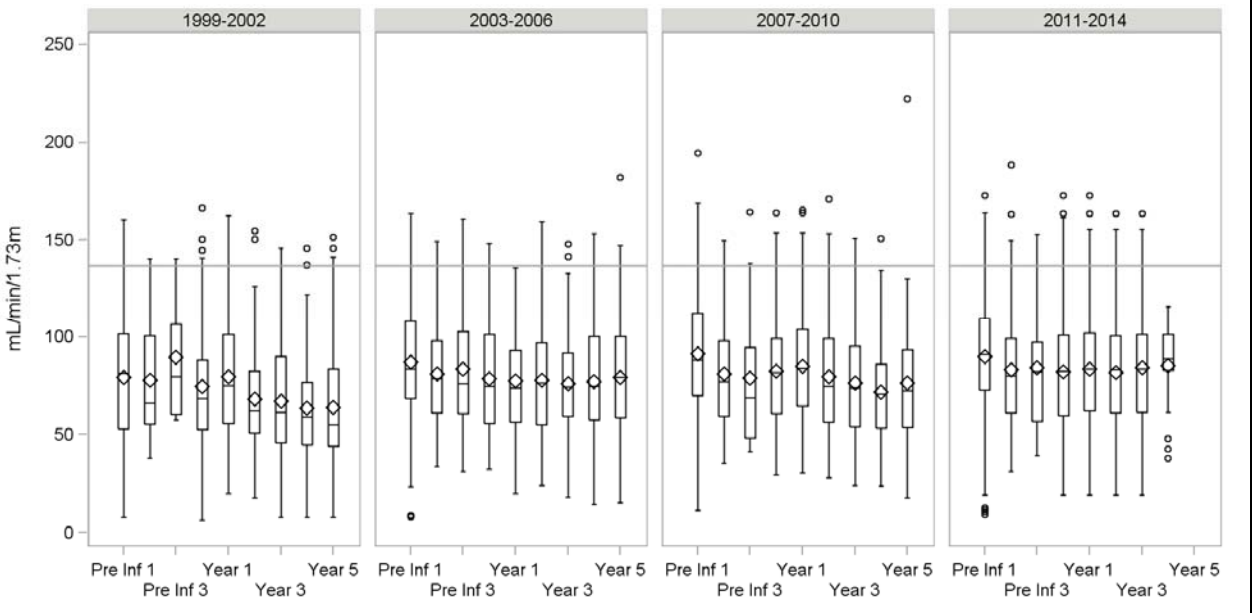




	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	591	618	580	513	405	345
IAK/SIK	119	124	123	113	99	90
1999-2002	113	133	115	119	106	109
2003-2006	177	184	189	182	163	173
2007-2010	198	200	196	188	179	153
2011-2014	222	225	203	137	56	.

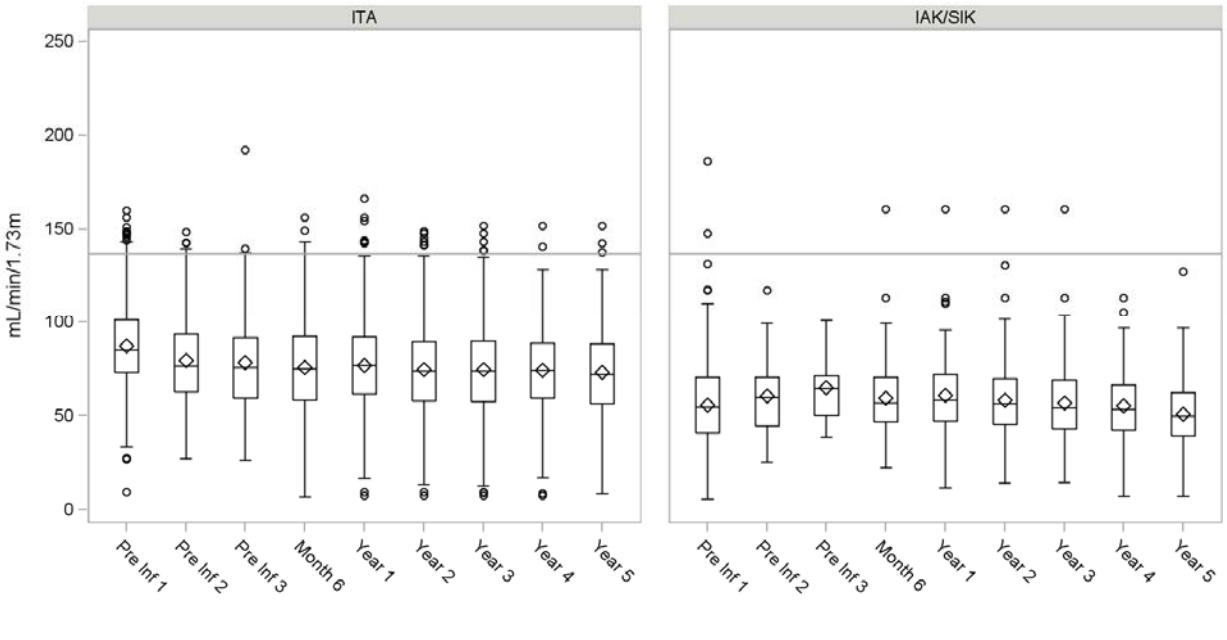
Exhibit 6 – 11
Cockgroft-Gault Calculated Clearance (mL/min/1.73m^2) by Infusion Type and Era

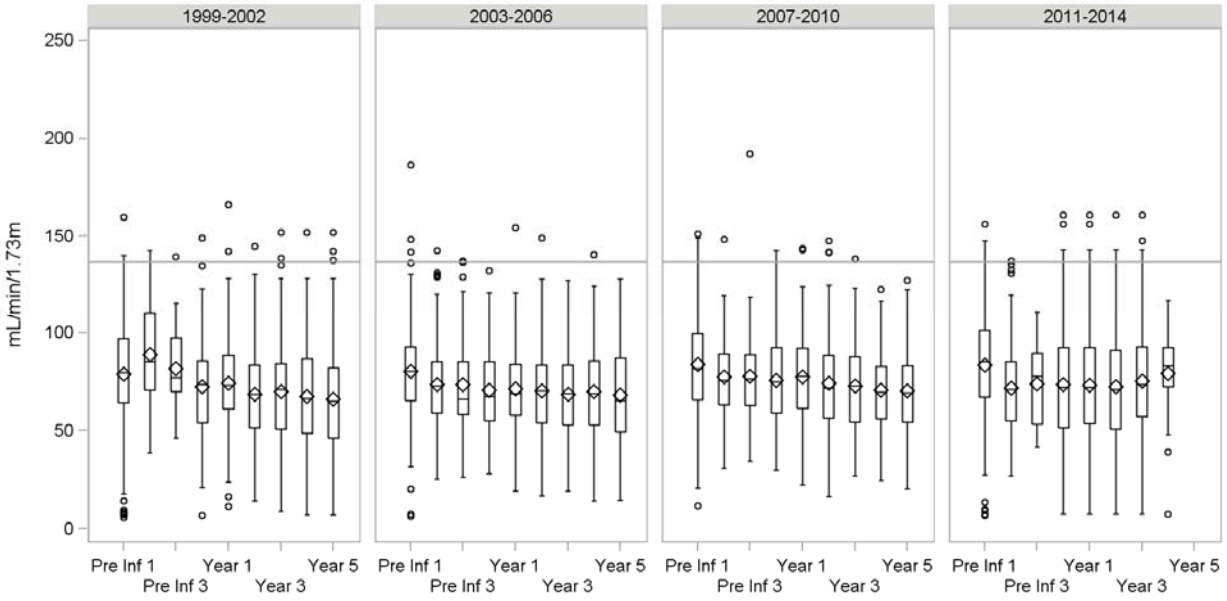




	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	443	151	58	321	346	298	251	177	141
IAK/SIK	104	37	15	62	67	73	71	64	61
1999-2002	104	12	11	61	67	60	60	57	55
2003-2006	143	50	28	80	90	85	83	67	70
2007-2010	132	59	21	116	132	115	105	94	77
2011-2014	168	67	13	126	124	111	74	23	.

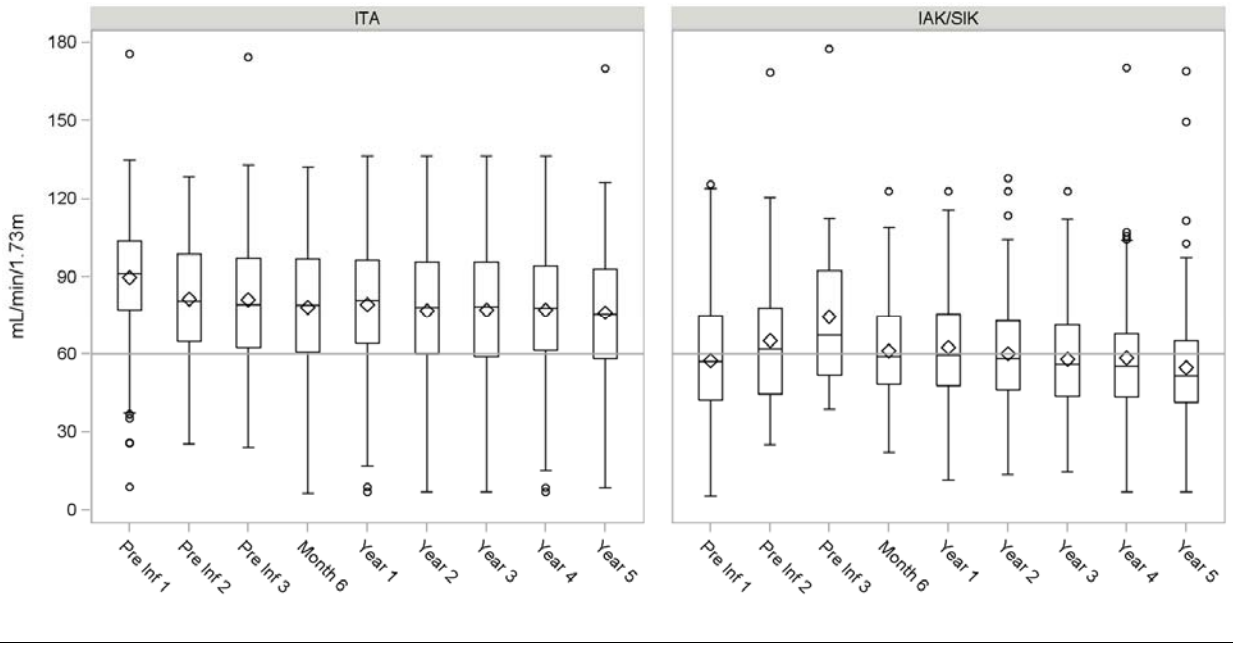
Exhibit 6 – 12
MDRD Estimated Cockgroft-Gault (mL/min/1.73m^2) by Infusion Type and Era

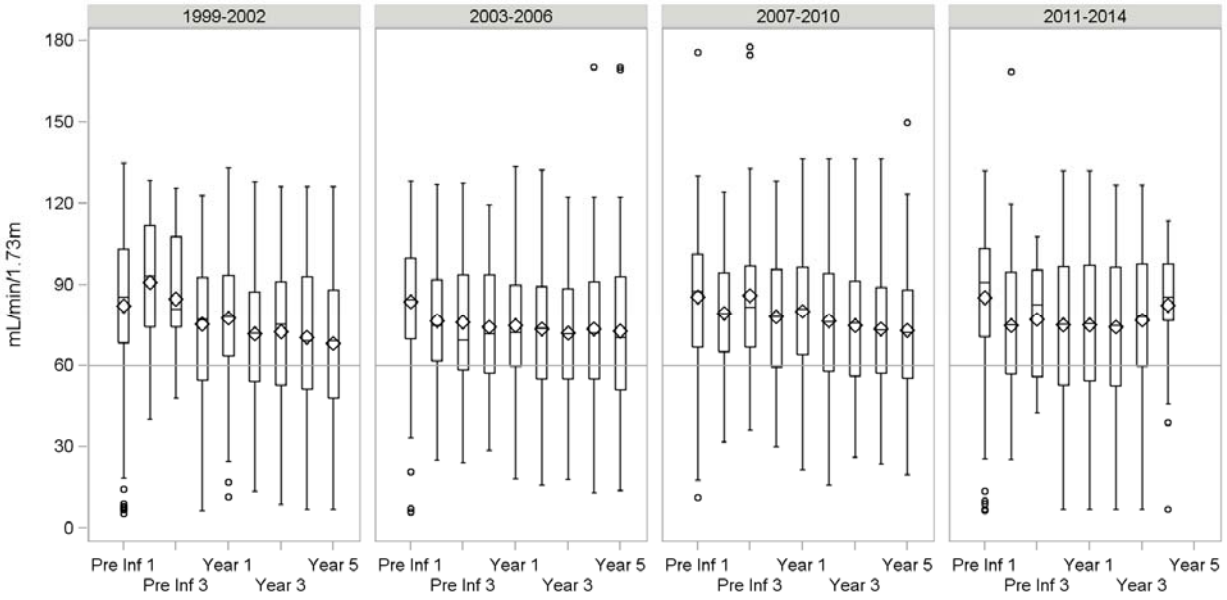




	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	654	251	98	509	554	496	430	327	291
IAK/SIK	142	55	20	93	95	101	96	85	83
1999-2002	180	38	21	104	117	102	111	101	107
2003-2006	254	104	50	159	166	173	163	144	154
2007-2010	176	76	28	162	184	158	151	138	113
2011-2014	186	88	19	177	182	164	101	29	.

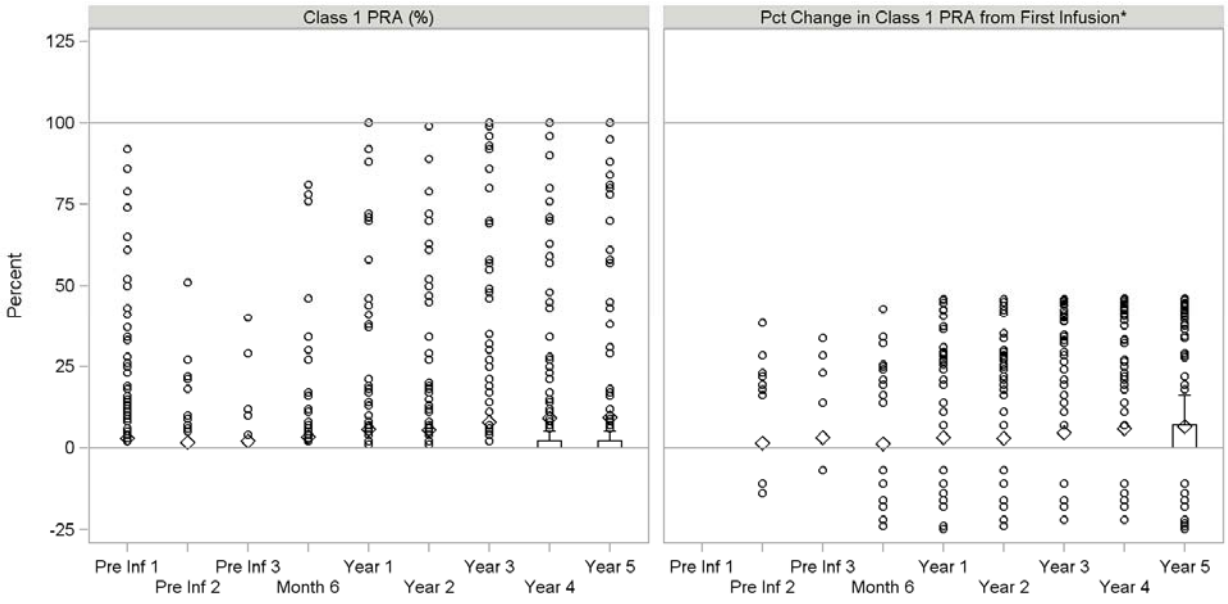
Exhibit 6 – 13
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m^2) by Infusion Type and Era





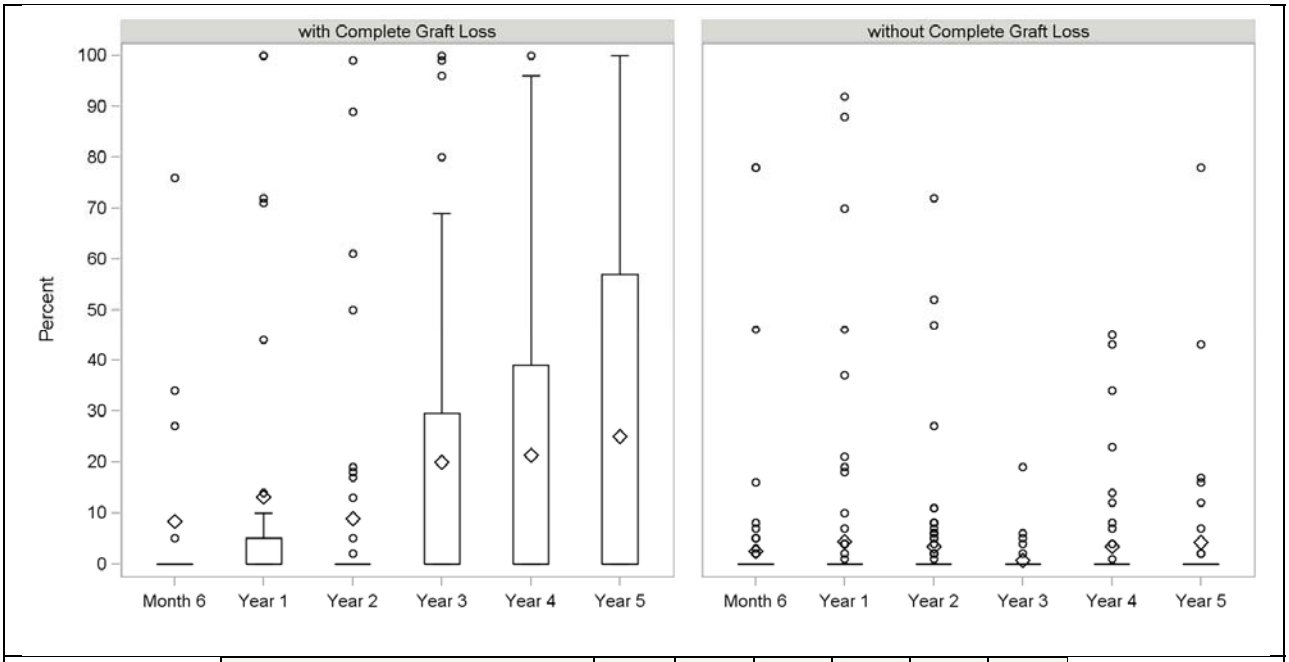
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	654	251	98	509	554	496	430	327	291
IAK/SIK	142	55	20	93	95	101	96	85	83
1999-2002	180	38	21	104	117	102	111	101	107
2003-2006	254	104	50	159	166	173	163	144	154
2007-2010	176	76	28	162	184	158	151	138	113
2011-2014	186	88	19	177	182	164	101	29	.

Exhibit 6 – 14
Class 1 PRA and its Percent Change from First Infusion



	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Class 1 PRA (%)	454	103	45	175	204	211	186	157	147
Pct Change in Class 1 PRA from First Infusion*	.	92	41	167	194	197	167	141	127

Exhibit 6 – 15
Class 1 PRA Post Last Infusion by Graft Loss for Islet Alone Recipients



	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
with Complete Graft Loss	17	32	42	40	32	33
without Complete Graft Loss	102	99	84	57	56	42

Chapter 7
Adverse Events

Introduction

Adverse Events

Data collection on adverse events and other effects of islet transplantation continues for all islet transplant recipients. The data are confirmed via regularly scheduled site visits that include 100% data audit for adverse events. The reported data are coded for system/organ class and preferred term for tabulation and summary reporting, using the Medical Dictionary for Regulatory Activities, a part of the overall data quality and assurance process integral to The Emmes Corporation's AdvantageEDC system. The coding is conducted by trained Emmes medical coders. Over the years of the Registry, both the MedDRA lexicon and coding processes, as well as the data structures for reporting adverse events have evolved. Therefore, it was decided during the production of the 9th Annual Report to have the entire history of adverse events re-coded to the current MedDRA lexicon, using a uniform process and the most complete descriptions of all the reported adverse events. This process is expected to be complete by the end of 2016. To avoid holding up the 9th Annual Report, the results on adverse events (Chapter 7) are being deferred until the re-coding process is complete. They will be published in the report available online, as well as in print version as an addendum.

Chapter 8
Registry Data Quality Review

Introduction

Total number of patients expected at each follow-up visit post last infusion

Ns	Overall Post LastTx						EurAusAsia Post LastTx						NorthAm Post LastTx					
	0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
1999 - 2002	209	204	204	199	195	194	86	81	81	80	78	78	123	123	123	119	117	116
2003 - 2006	271	269	264	262	252	248	105	104	104	104	101	100	166	165	160	158	151	148
2007 - 2010	246	247	239	236	226	196	111	112	110	110	108	90	135	135	129	126	118	106
2011 - 2014	285	284	256	171	69	.	157	156	142	86	34	.	128	128	114	85	35	.

The bar charts in this Chapter show the percent of expected data that is available at each major time point post last infusion. The highest levels of reporting are on insulin use, which is based on patient diaries, and fasting C-peptide levels. For insulin use, prior complete graft loss is used to impute that the recipient has returned to insulin use, further increasing the available information. Similarly, for fasting C-peptide, a report of complete graft loss with no subsequent re-infusion is used to impute fasting C-peptide of 0 ng/mL, further increasing the availability of C-peptide data. Missing data increases with longer follow-up and in the most recent cohort.

Exhibit 8 – 1
Missing Data for Insulin Independence by Era and Continent

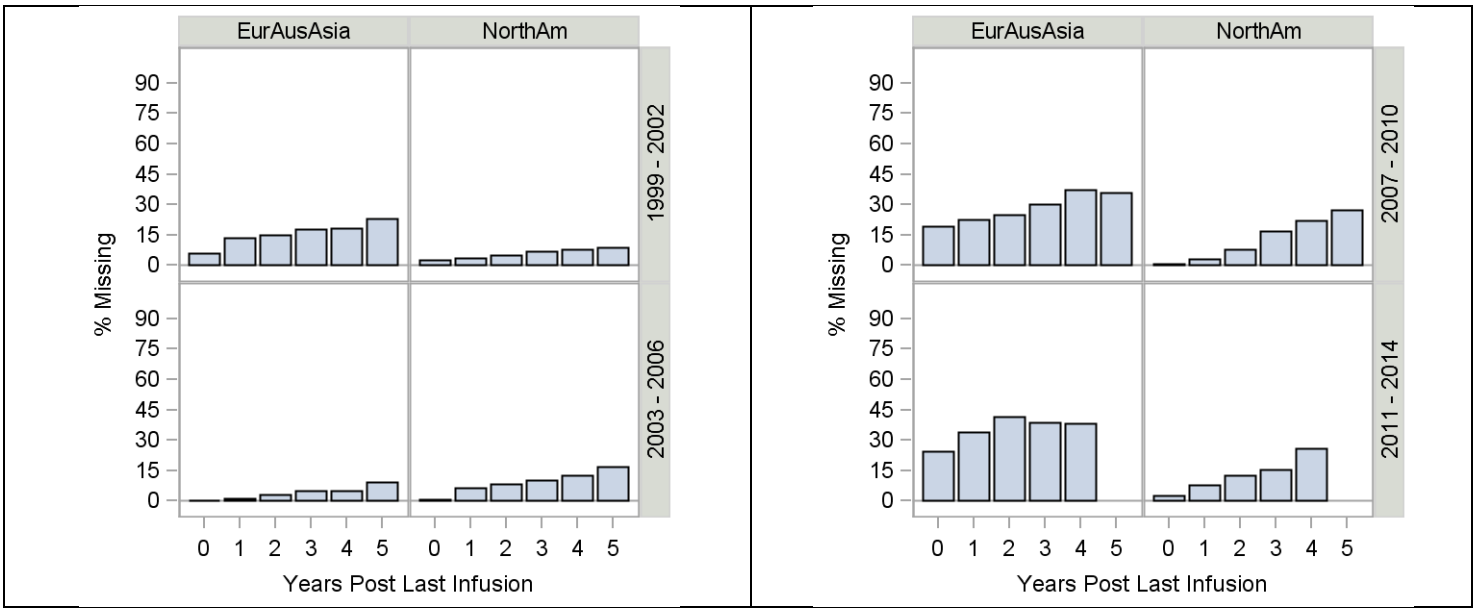


Exhibit 8 – 2
Missing Data for Fasting C-Peptide by Era and Continent

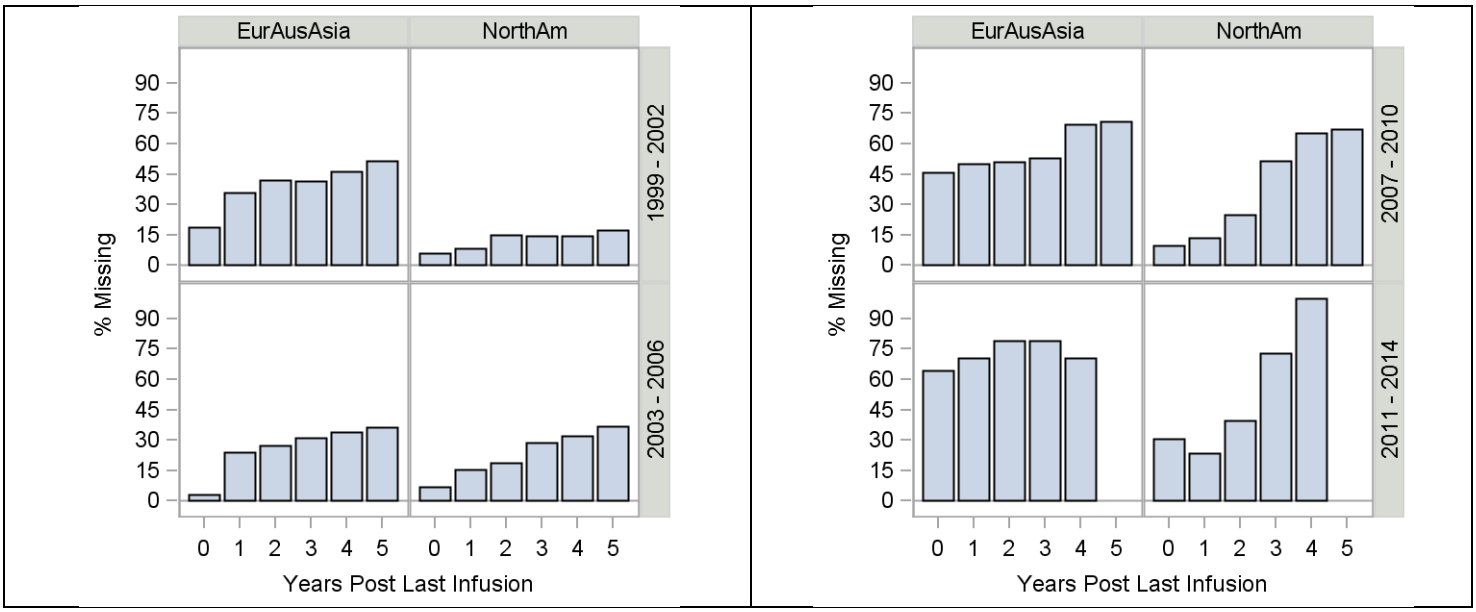


Exhibit 8 – 3
Missing Data for Hemoglobin A1c by Era and Continent

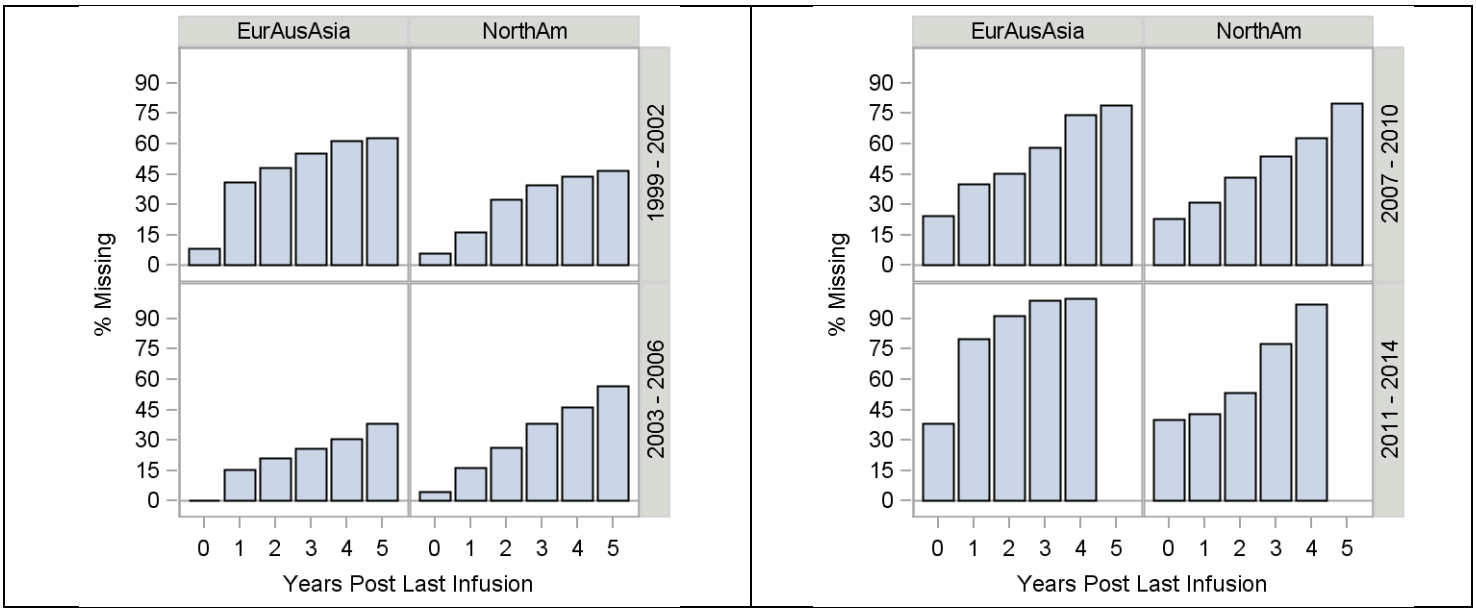


Exhibit 8 – 4
Missing Data for Fasting Blood Glucose by Era and Continent

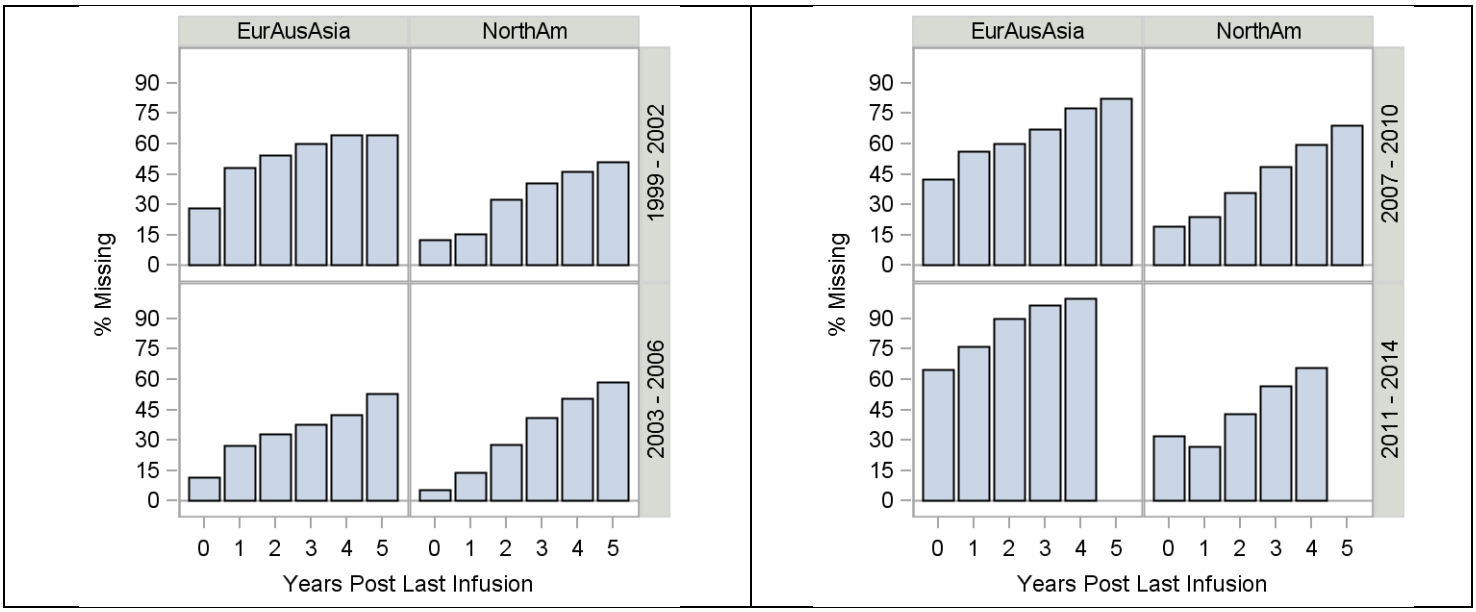


Exhibit 8 – 5
Missing Data for Severe HypoGlycemia by Era and Continent

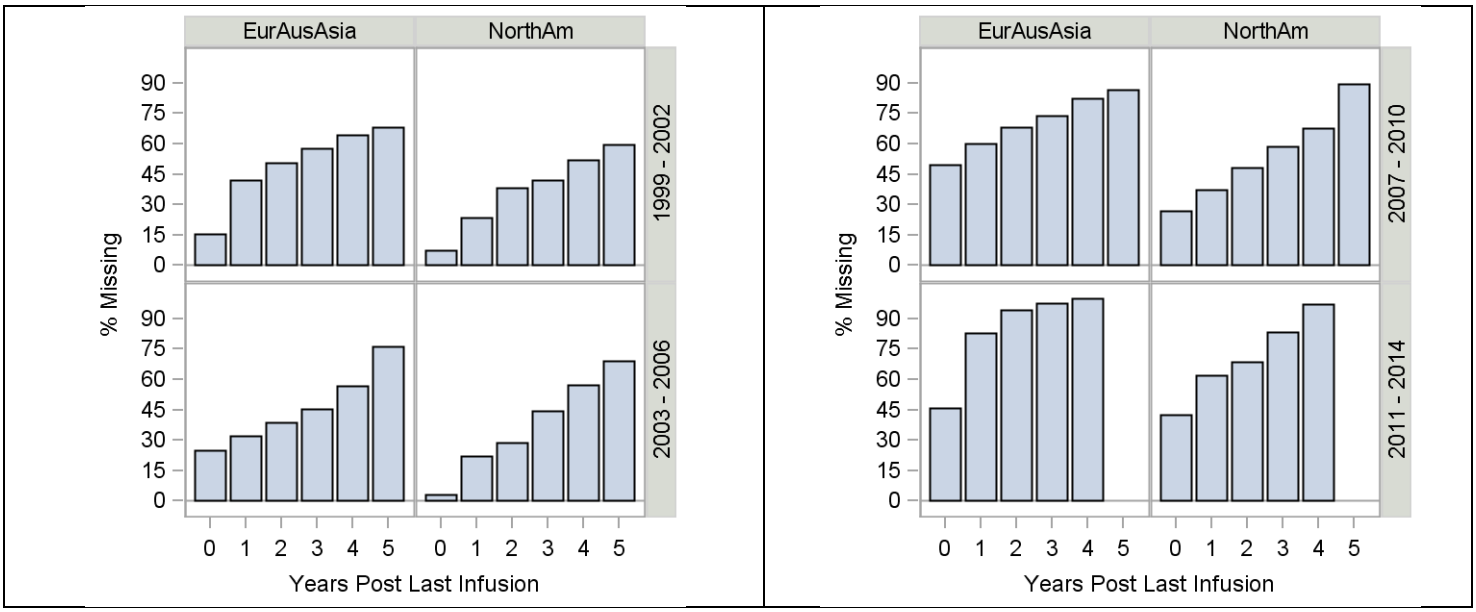


Exhibit 8 – 6
Missing Data for BMI by Era and Continent

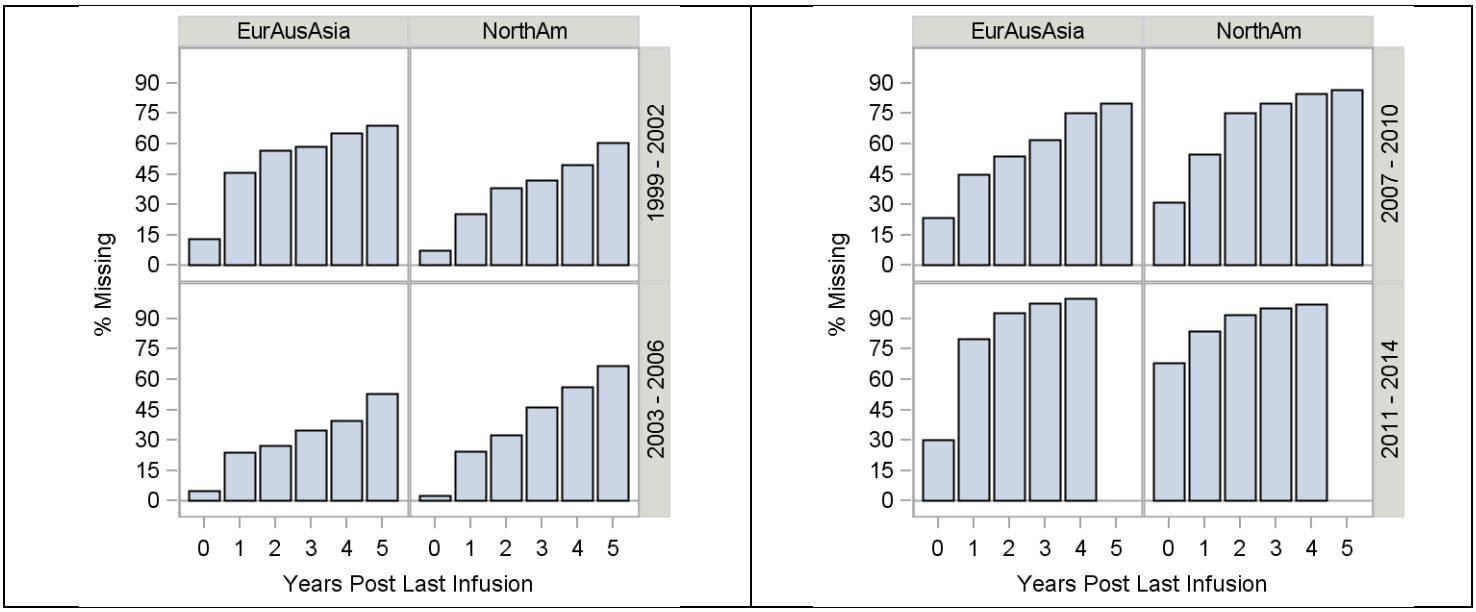


Exhibit 8 – 7
Missing Data for Clarke Score by Era and Continent

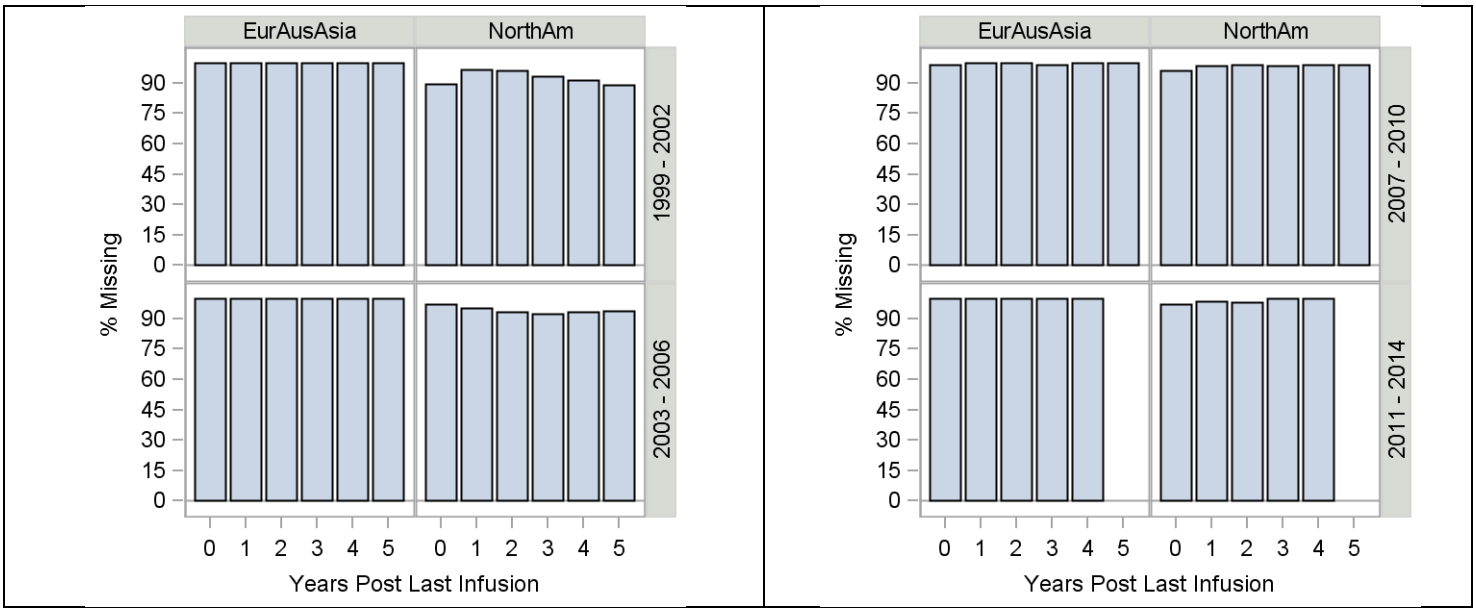


Exhibit 8 – 8
Missing Data for Ryan Hypo by Era and Continent

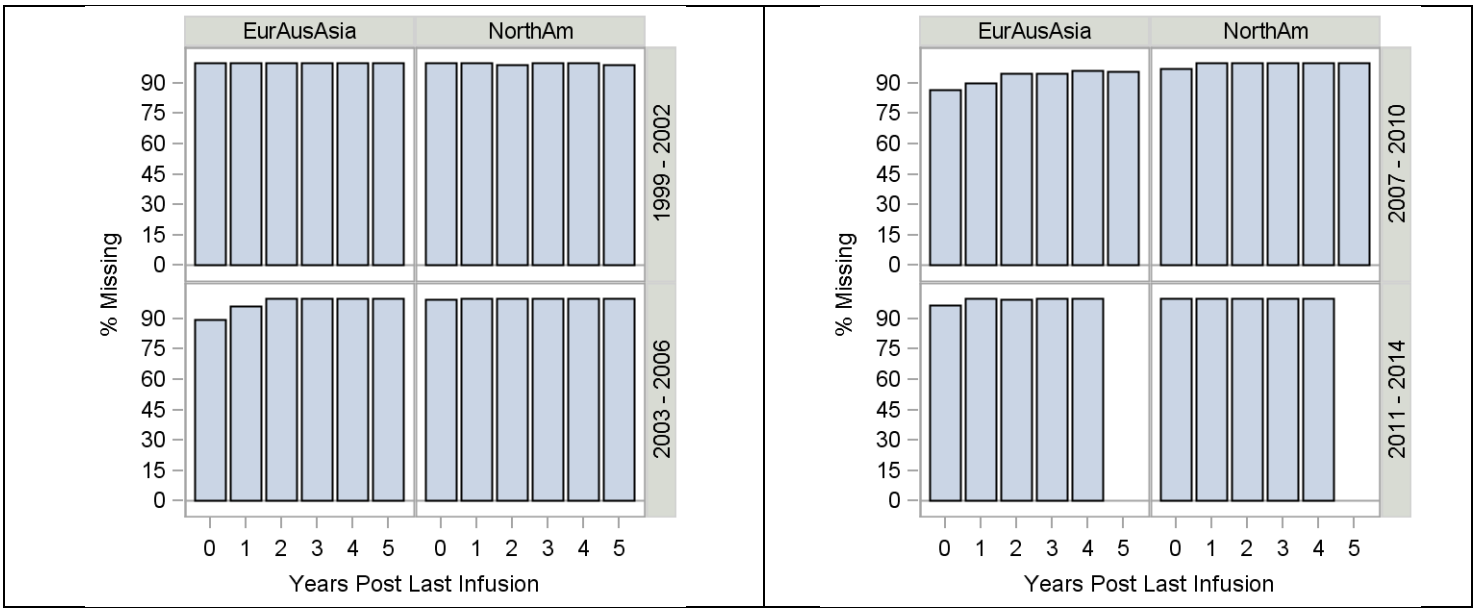


Exhibit 8 – 9
Missing Data for C-Peptide AUC by Era and Continent

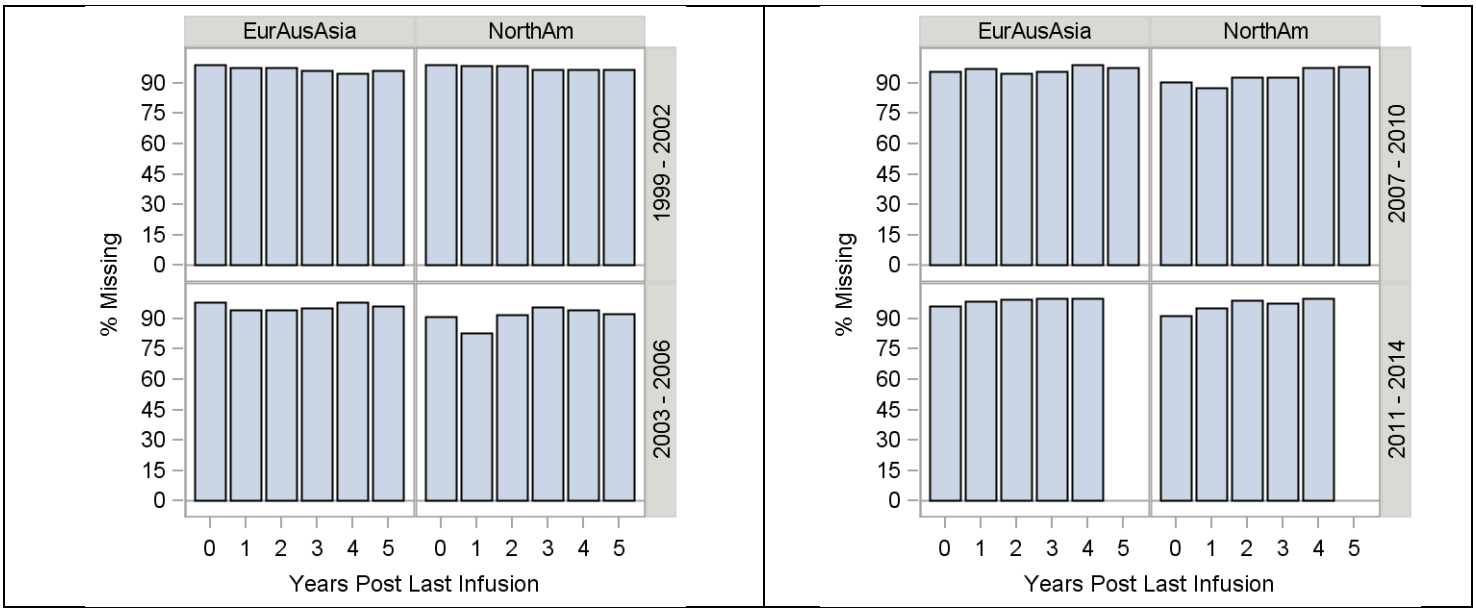


Exhibit 8 – 10
Missing Data for Cockcroft-Gaullt by Era and Continent

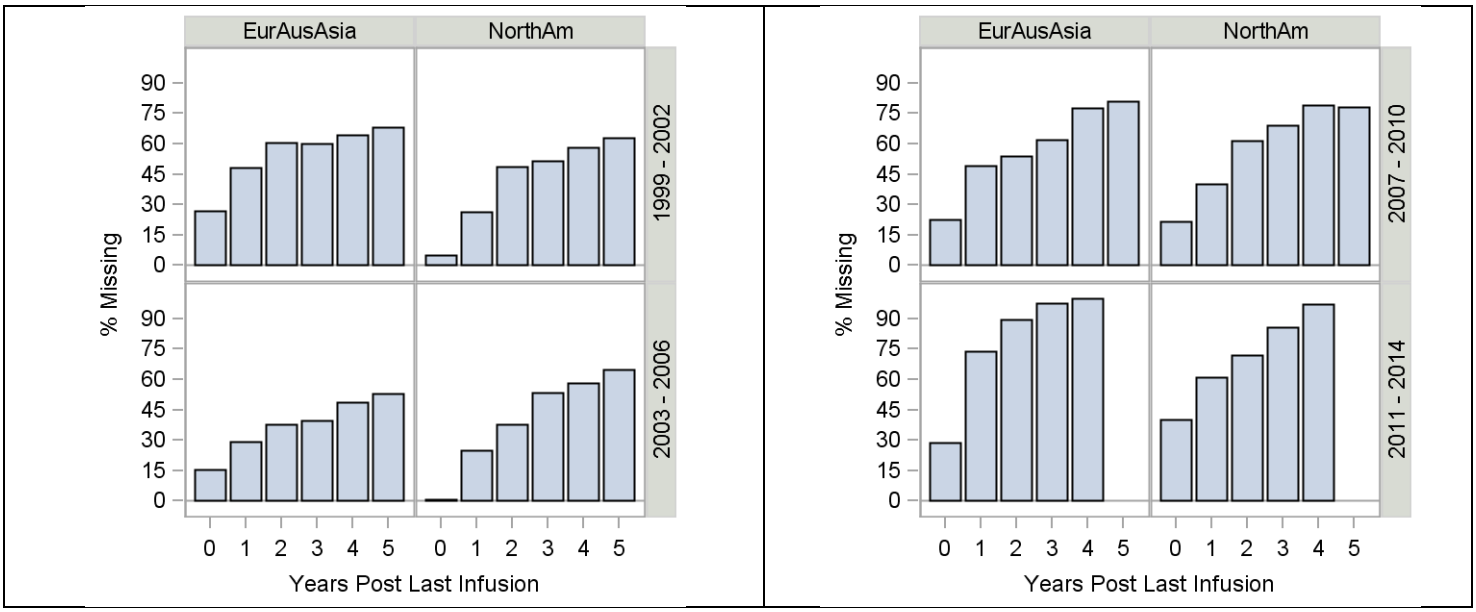


Exhibit 8 – 11
Missing Data for Creatinine by Era and Continent

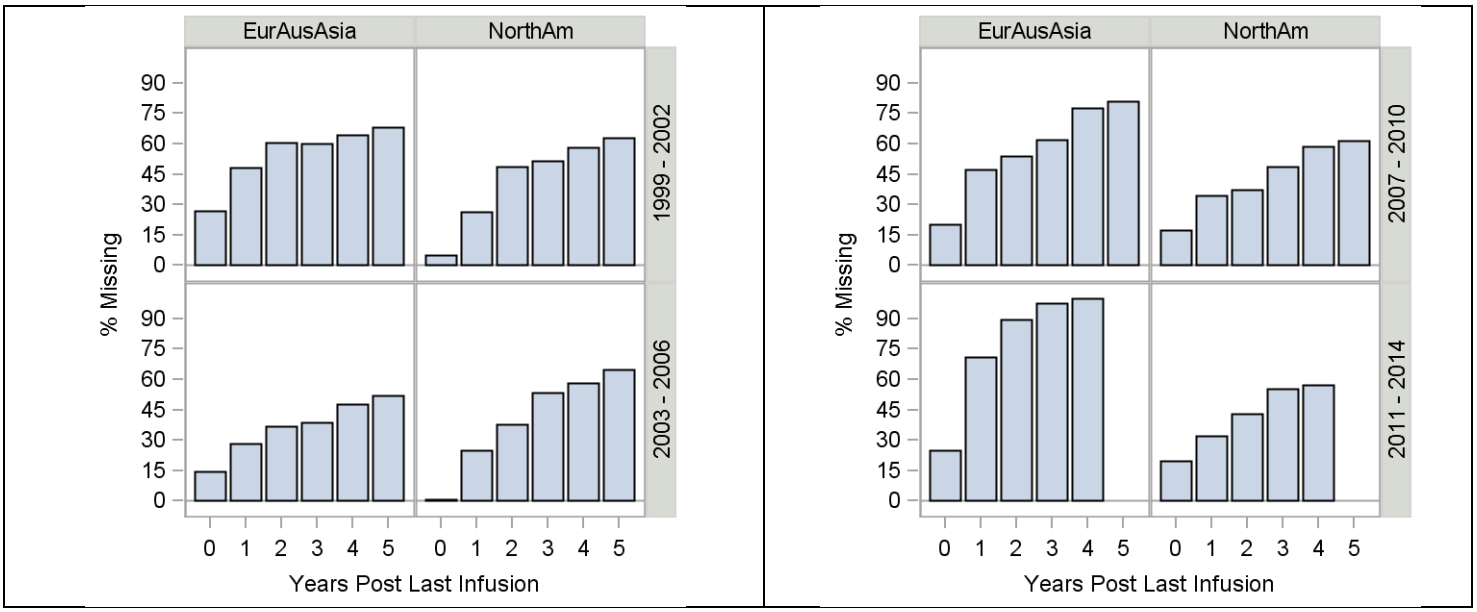


Exhibit 8 – 12
Missing Data for Cholesterol by Era and Continent

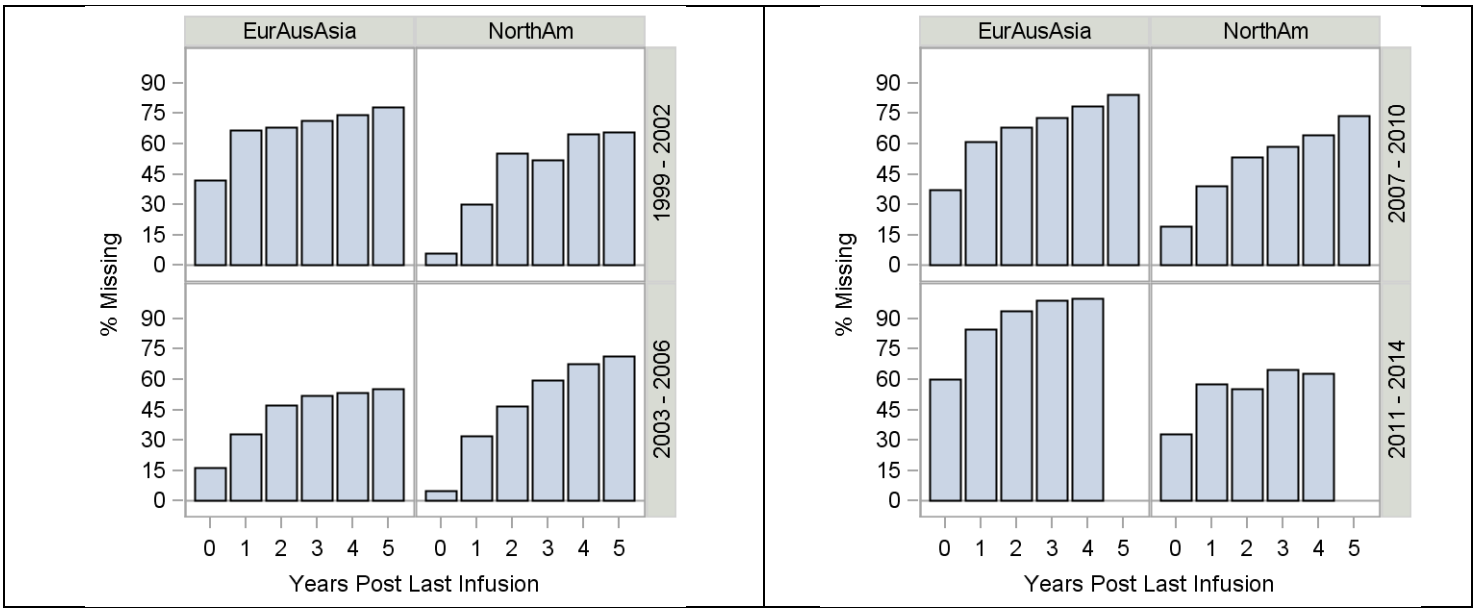


Exhibit 8 – 13
Missing Data for HDL by Era and Continent

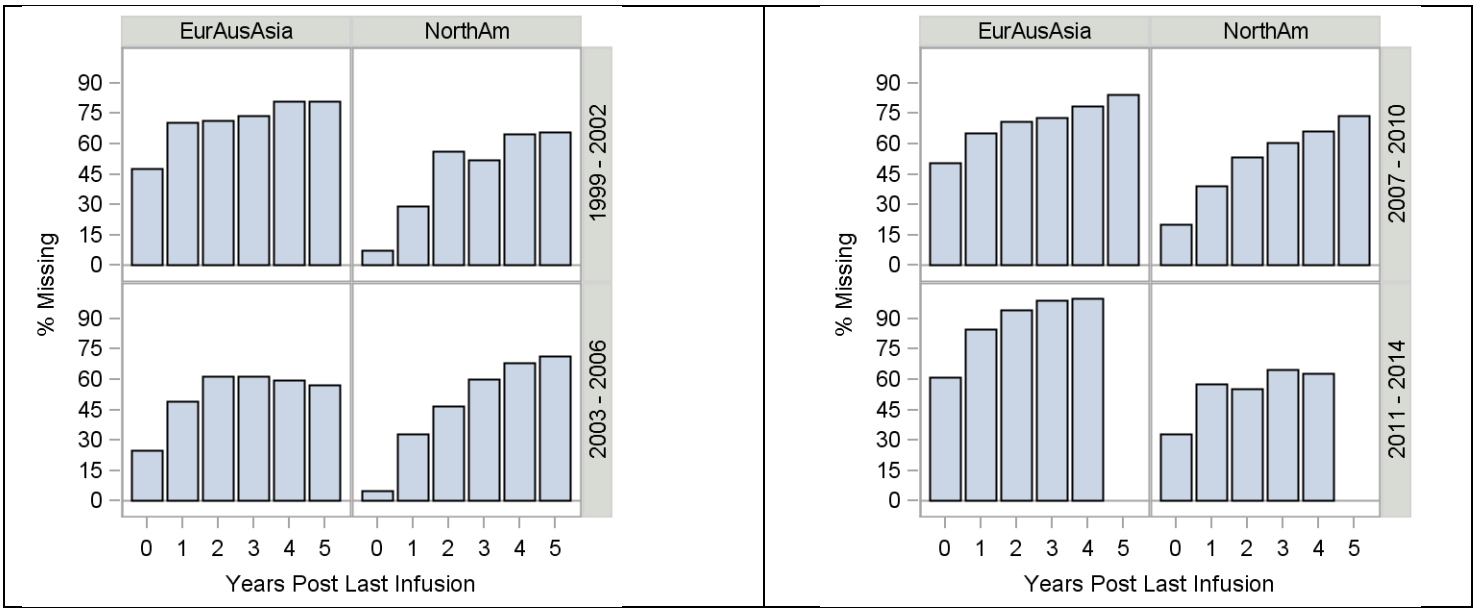


Exhibit 8 – 14
Missing Data for LDL by Era and Continent

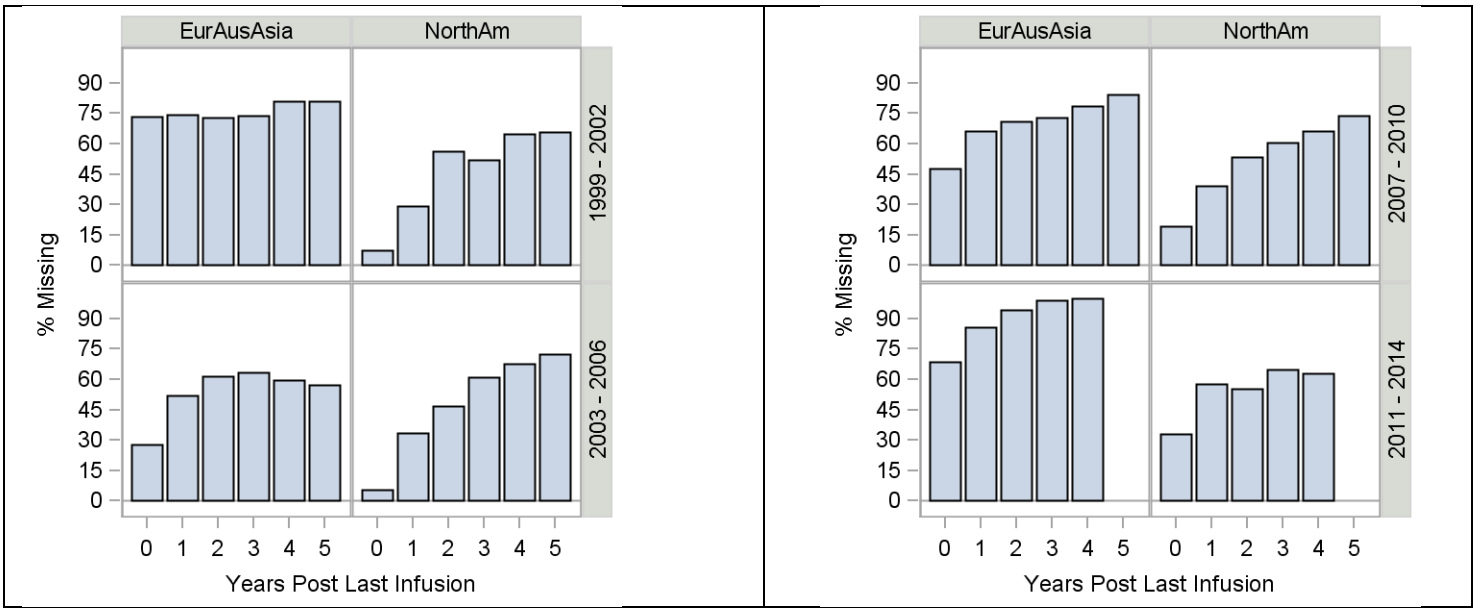


Exhibit 8 – 15
Missing Data for Triglicerides by Era and Continent -

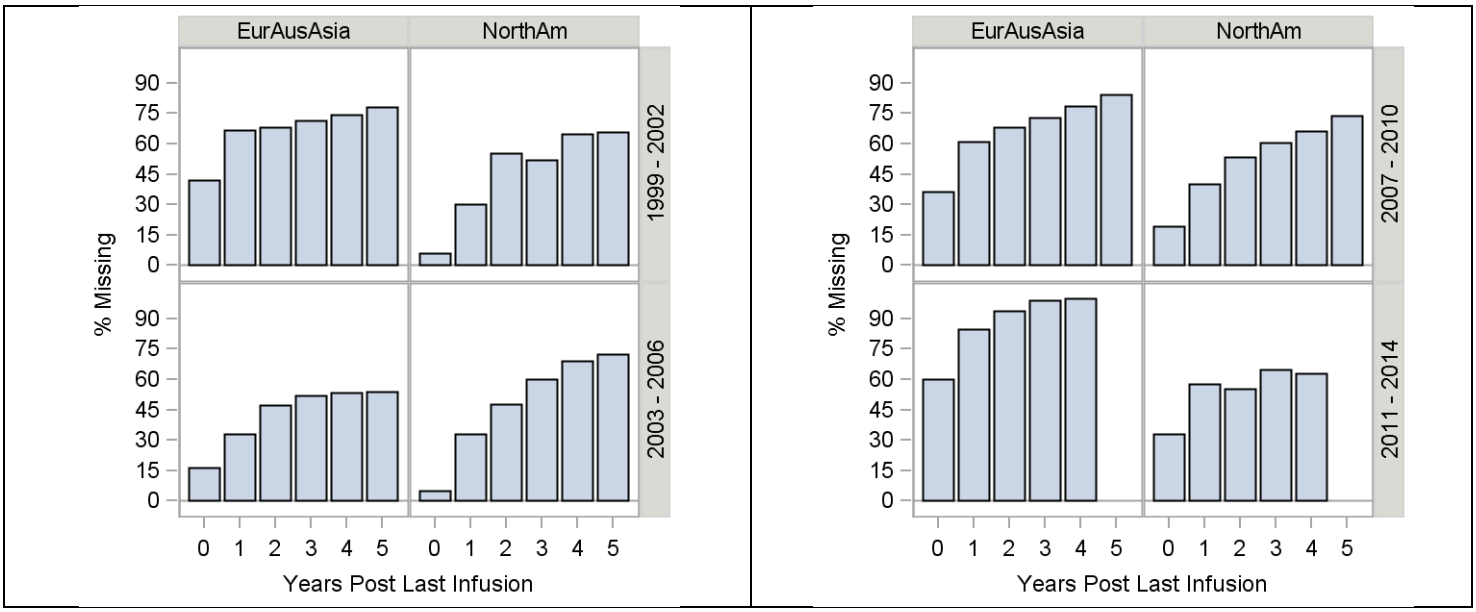


Exhibit 8 – 16
Missing Data for Bilirubin by Era and Continent

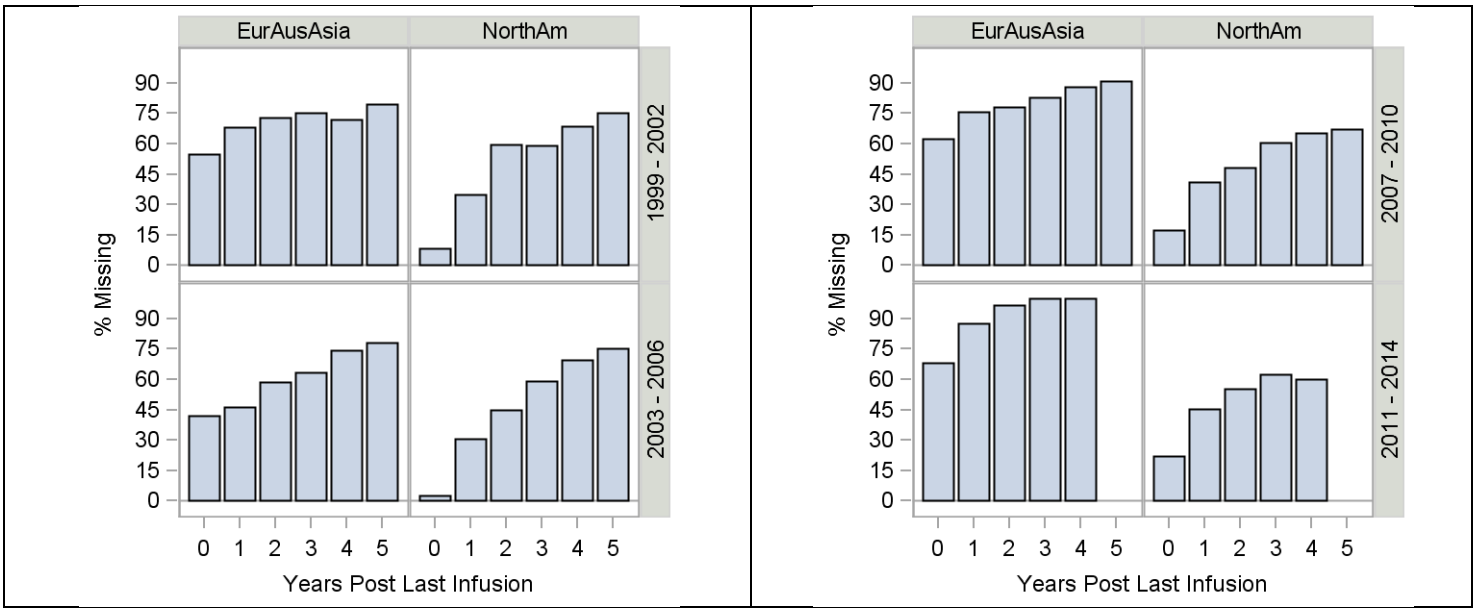


Exhibit 8 – 17
Missing Data for ALT by Era and Continent

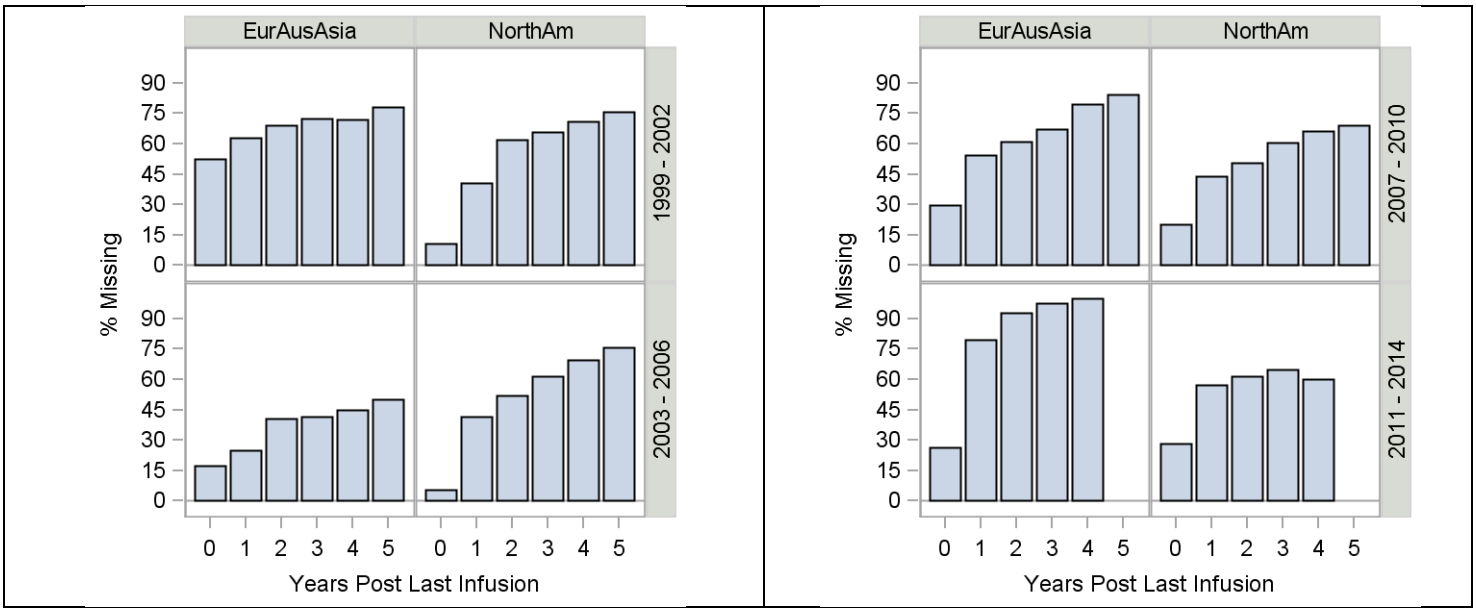


Exhibit 8 – 18
Missing Data for AST by Era and Continent

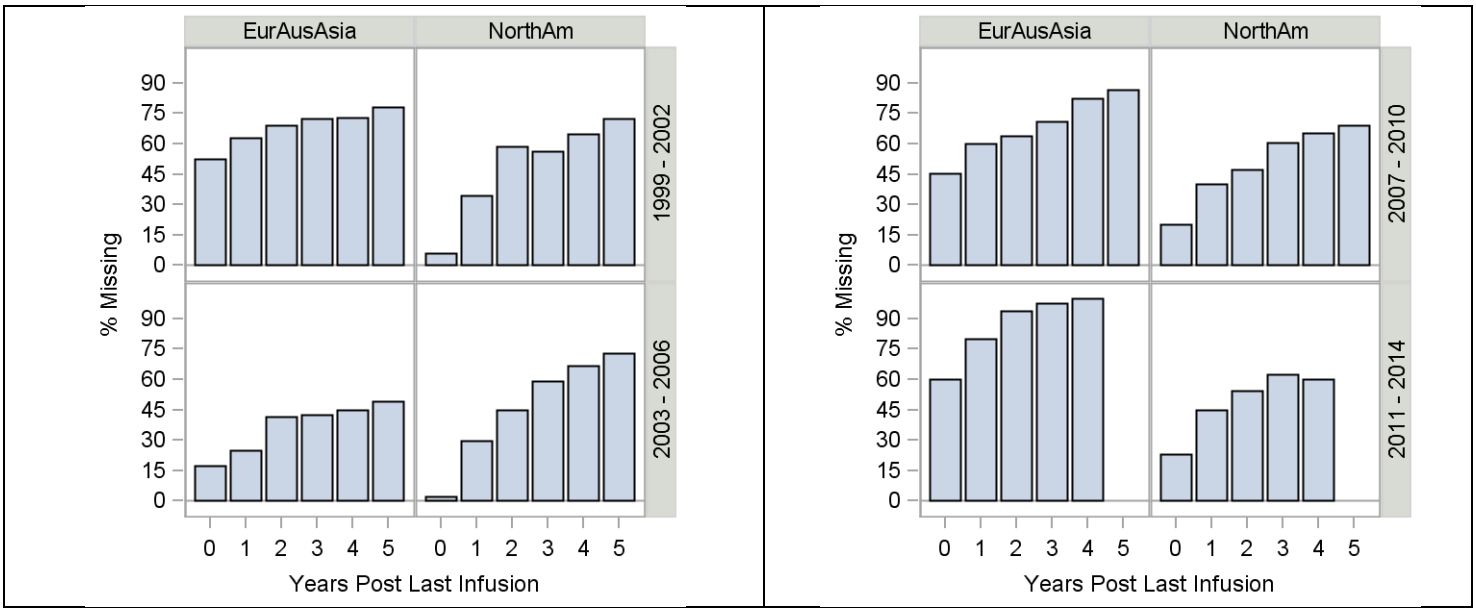
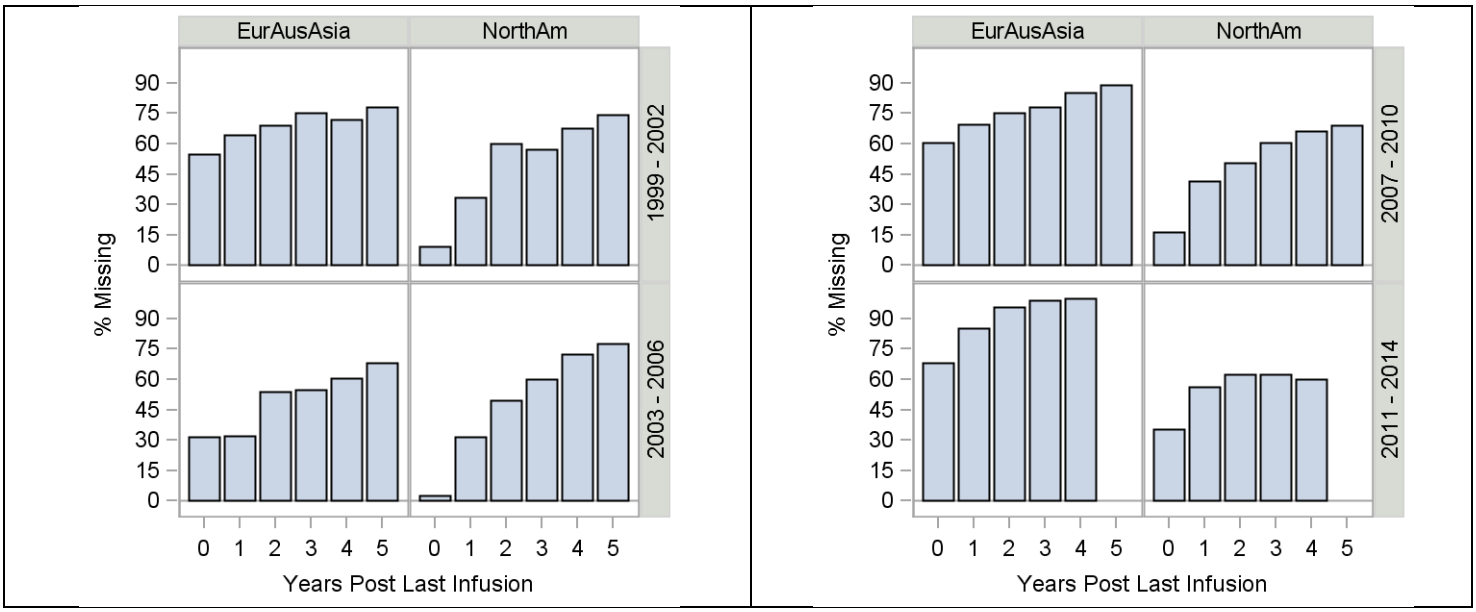


Exhibit 8 – 19
Missing Data for Alkaline Phosphate by Era and Continent



Appendix A: Islet Transplant Center Contributors

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