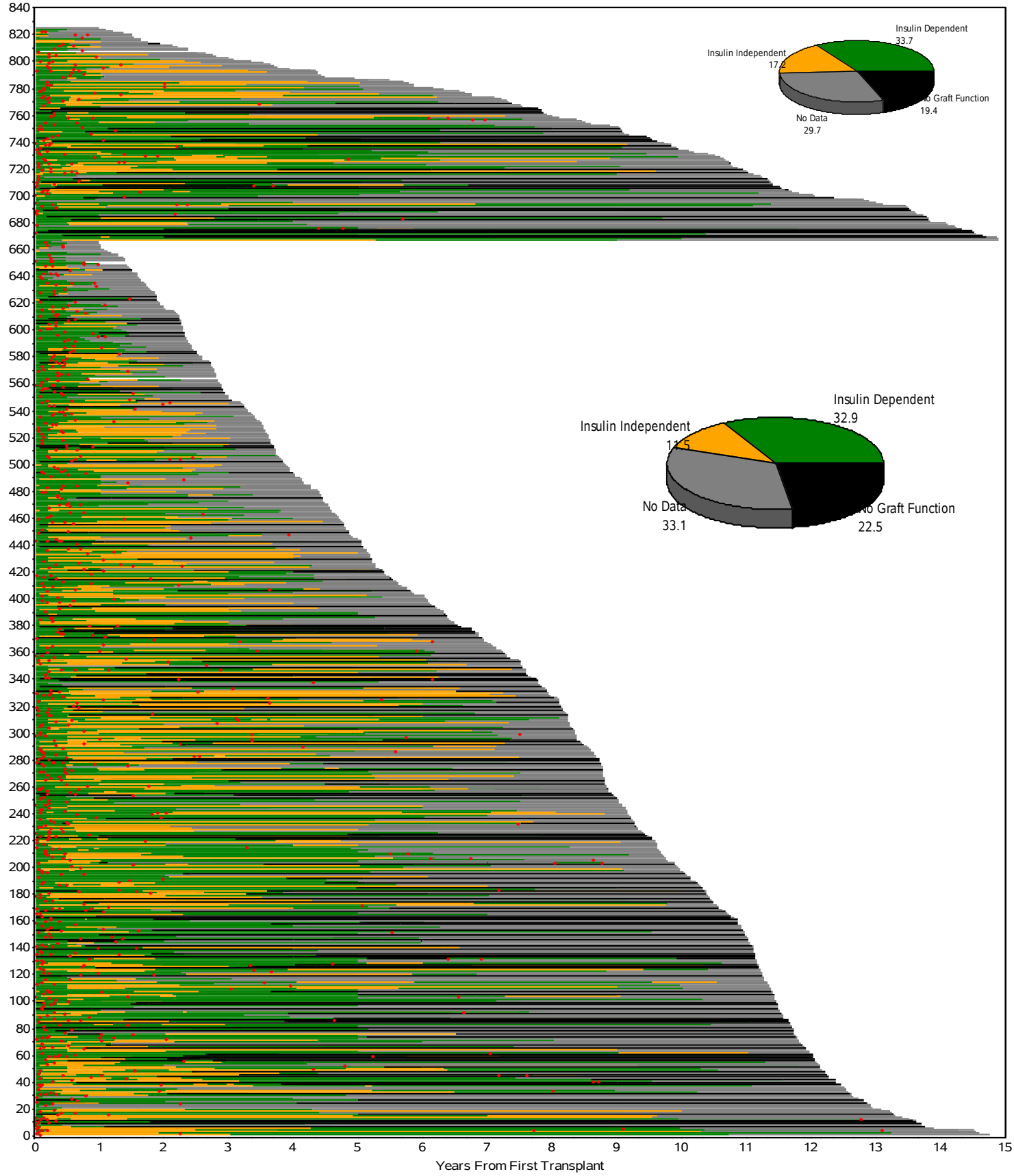
Eighth Annual Report

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

Sponsored by:
National Institute of Diabetes & Digestive & Kidney Diseases
National Institutes of Health
US Department of Health and Human Services
Bethesda, MD

Additional support from:
The Juvenile Diabetes Research Foundation International
New York, NY

December 31, 2014



Collaborative Islet Transplant Registry 2012
TOP: Islet after kidney or simultaneous islet-kidney (IAK/SIK, N=178)
BOTTOM: Islet transplant alone (ITA, N=686)
Yellow: insulin independent; Green: insulin-using with graft function(70% 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 31, 2014

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
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Program Directors, Division of Diabetes, Endocrinology & Metabolic Diseases
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Bernhard Hering, MD
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SUBJECT: CITR Eighth Annual Report (2012)

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

We are pleased to present this Eighth Annual Report (2012) including data from the great majority of the islet transplant programs active in 1999-2012. We are privileged to have the ongoing collaboration of the United Network for Organ Sharing for the USA donor data, and the past collaboration with United Network for Organ Sharing and the Islet Cell Resource Center Consortium (coordinated by the Administrative and Bioinformatics Coordinating Center, City of Hope, CA), for transplanted islet data for 1999-2007. The US Food and Drug Administration and the National Institute of Allergy and Infectious Disease (NIAID) lend continuing support and advice.

The report has been prepared by staff of The EMMES Corporation under the leadership of the CITR Publications and Presentations Committee chaired by Dr. 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, 2013 for all islet transplant recipients transplanted by December 31, 2012.

As exhibited in Chapter 8 Data Quality, an unexpectedly high level of data has not been reported to the CITR Registry for the planned data closure of December 17, 2013.

The Scientific Summary of the CITR Eighth Annual Report is available as a separate document downloadable at www.CITRegistry.org/Annual Report.

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Detailed Methods and Definitions

Background and Purpose

Funded by the National Institute of Diabetes & Digestive & Kidney Diseases with a supplemental grant from the Juvenile Diabetes Research Foundation International, the Collaborative Islet Transplant Registry (CITR) expedites progress and promotes safety in islet/beta cell transplantation through the collection, analysis, and communication of comprehensive and current data on all islet/beta cell transplants performed in North America, and JDRF-sponsored European and Australian centers since 1999. The main vehicle of communicating accumulated results is the CITR Annual Report. This eighth report summarizing Registry progress through 2012 summarizes information on patients who received one or more islet cell transplants between 1999 and 2012. 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 864 islet allograft recipients (686 islet alone and 178 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, 2012, a total of 525 autologous islet transplant recipients were registered in CITR. Efforts are underway to collect complete autograft information in the Registry.

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

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

The current report represents a 109% increase in the number of recipients, a 137% increase in the number of infusion procedures, and 103% increase in donors, compared to the 7th Report.

Data Sources

CITR implements web-based forms to capture pertinent information necessary to achieve the primary objectives of the Registry and obtain donor, organ procurement, and islet processing data through data sharing agreements with respective organizations (the United Network for Organ Sharing and the Islet Cell Resource Centers). These data characterize and follow trends in safety and efficacy for recipients of islet transplantation, including donor information, islet processing, transplant techniques, and treatment protocols. Data reported to the Registry 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 Day 30, 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
- 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

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 at each time point. Event analysis of incidence and persistence of specified endpoints (e.g., achievement and retention of insulin independence) 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 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.

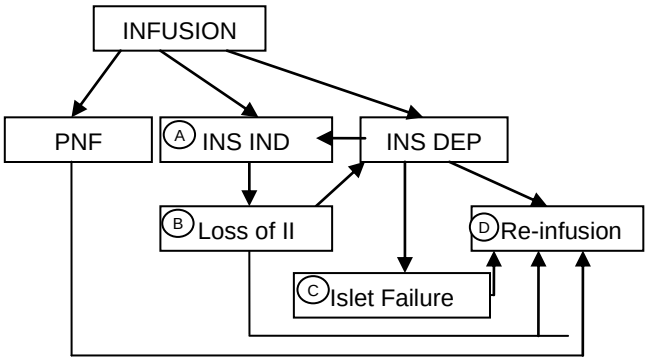


Figure1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

In Chapter 5, we present proportional hazard regression 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.

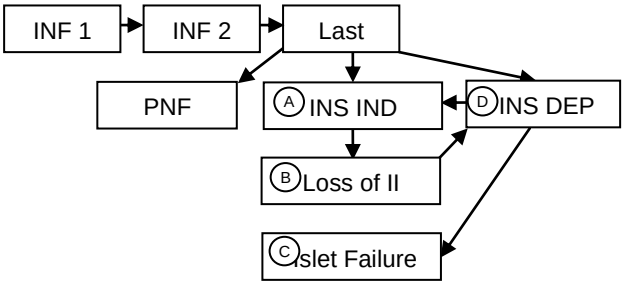


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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 insulin independence, loss of insulin independence and islet failure states post last infusion, 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 small. As with any registry, a number of potential biases may exist. First, not all active islet transplant centers in North America or the JDRF 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 from **January 1, 1999 through December 31, 2012**. 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, 2013 based on the recipients that had been registered for CITR at the December 31, 2012 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

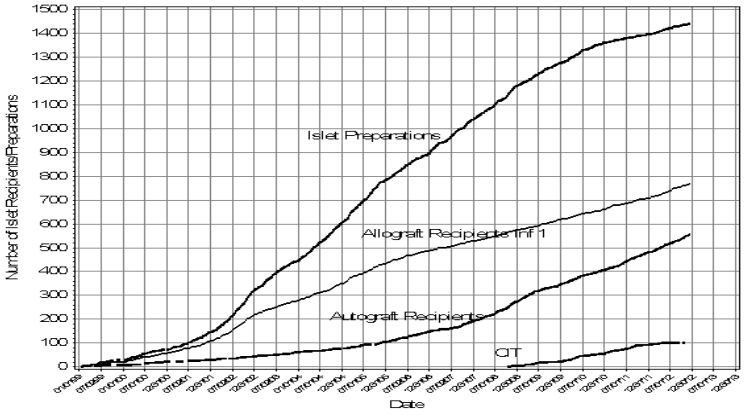
From 1999 through 2012, 28 National Institute of Diabetes, Digestive and Kidney Diseases (NIDDK) sponsored North American and 9 Juvenile Diabetes Research Foundation (JDRF) sponsored European and Australian islet transplant centers (37 total) contributed data to the Collaborative Islet Transplant Registry (CITR). These sites registered 686 islet transplant alone (ITA) and 178 islet after kidney or simultaneous islet-kidney (IAK/SIK) allograft recipients consenting to have their data reported to the Registry, for a total of 864 allogeneic, human-to-human islet transplant recipients. Five North American sites transplanted 86 allogeneic islet recipients. In 2012, twelve 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; http://www.citisletstudy.org/) began enrolling islet transplant patients. CIT enrollment was completed in 2012. All of the CIT sites 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 2008-2012.

Exhibit 1 – 1A
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK
Consented, Registered and First Infused in 1999-2012

	Islet Transplant Alone (ITA)			Islet After Kidney or Simultaneous Islet-Kidney (IAK/SIK)			
	Total	North America	Europe/ Australia	Total	North America	Europe/ Australia	GRAND TOTALS
Recipients	**686**	461	225	**178**	55	123	**864**
Infusions	**1,356**	879	477	**323**	102	221	**1,679**
Donors	**1,785**	944	845	**361**	110	251	**2,146**

Exhibit 1 – 1B
Cumulative Enrollment in CITR



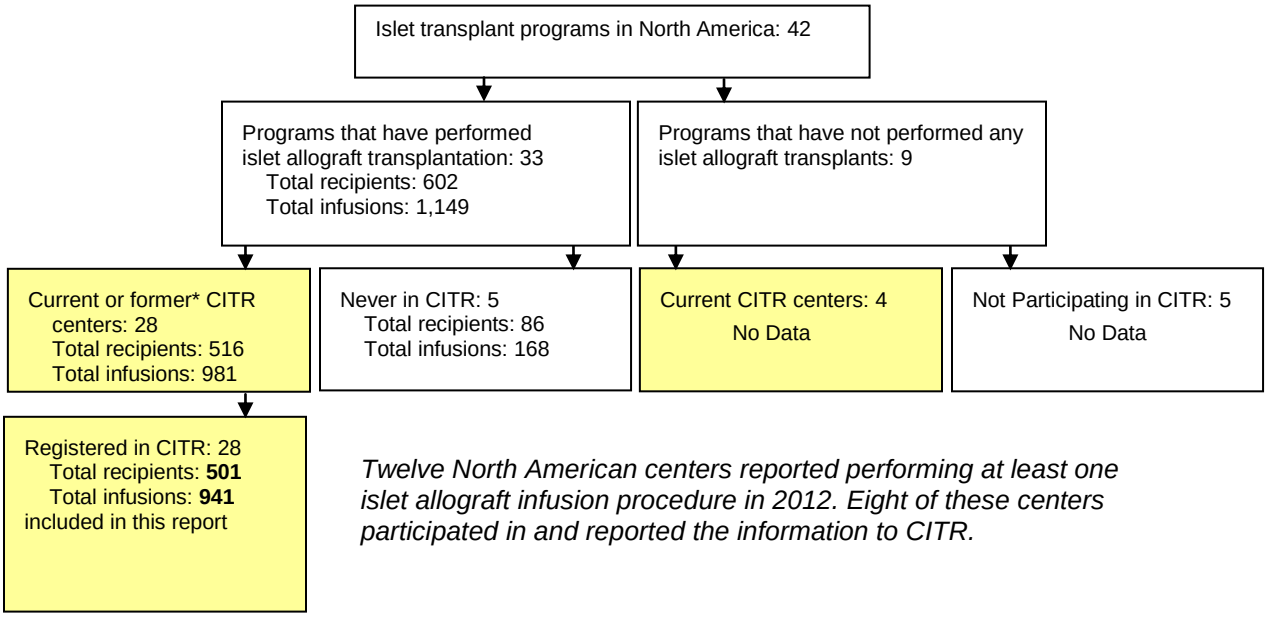
*Partial data for two additional infusions was available and included in subsequent chapters of this report.

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, 516 (85.7%) of 602 islet allograft recipients and 981 (85.4%) of all islet allograft infusion procedures performed in North America from 1999-2012 are included in this report.

North American Islet Allograft Transplant Centers, Recipients and Infusions

Total Performed and Total *Reported* to CITR 1999-2012



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

JDRF CENTERS

Five European (Exhibit 1-2B) and three Australian (Exhibit 1-2C) JDRF centers have contributed detailed data to the Registry. Overall, 348 of 362 (96%) allograft recipients and 698 of 718 (97%) allograft infusions performed between 1999 and 2012 at these eight centers are included in this year's Annual Report.

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

Infusions

A summary of the total 1,679 North American and JDRF islet allograft infusions by year of infusion is included in Exhibit 1-5. These infusions derived from 2,146 total donors: 1,419 were single donor preparations, 260 were multiple donor preparations, and the remainder pending.

Two hundred forty-six (246) recipients (28%) have received a single islet infusion at the time of this report, 424 (49%) received a total of two infusions, 170 (20%) received three infusions, and 24 recipients (3%) received a total of four to six islet infusions (Exhibit 1-7).

Of the 864 islet allograft recipients presented in this report, 686 (79%) are islet alone recipients, and 178 (21%) are islet after kidney recipients. Seven islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

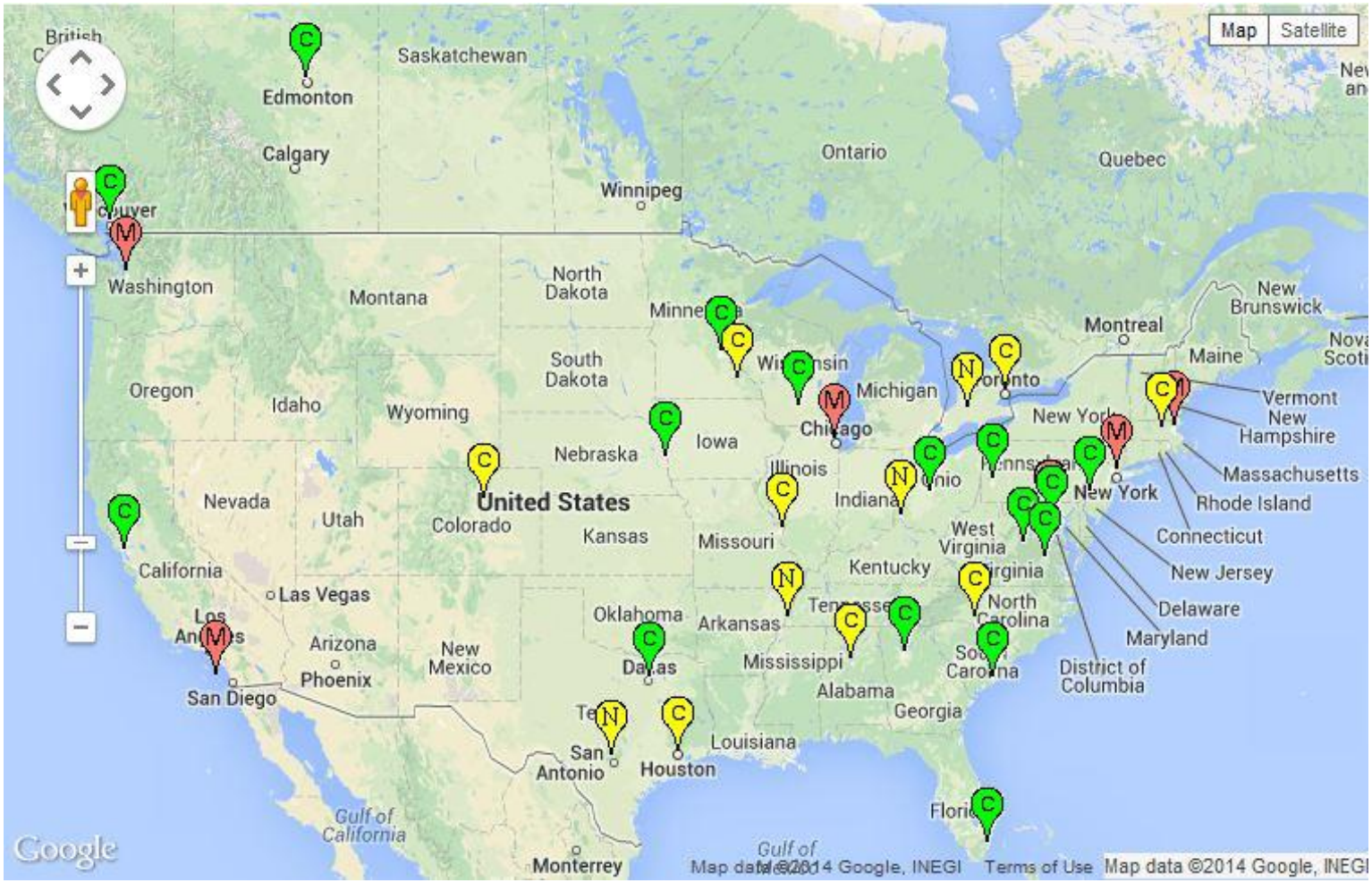
CITR Allografts Overall

There has been a 51% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 57% increase in the total number of islet allograft infusion procedures reported.

Autografts

Four hundred eighty (480) North American and 45 JDRF autograft consenting recipients have been registered in the Registry. Detailed data for these recipients is becoming available. A brief supplemental Annual Report will present analyses for autologous islet transplants for 2013.

Exhibit 1 – 2A
Islet Transplant Centers Reporting Data to CITR
Participating North American Centers 1999-2012



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 1999-2012

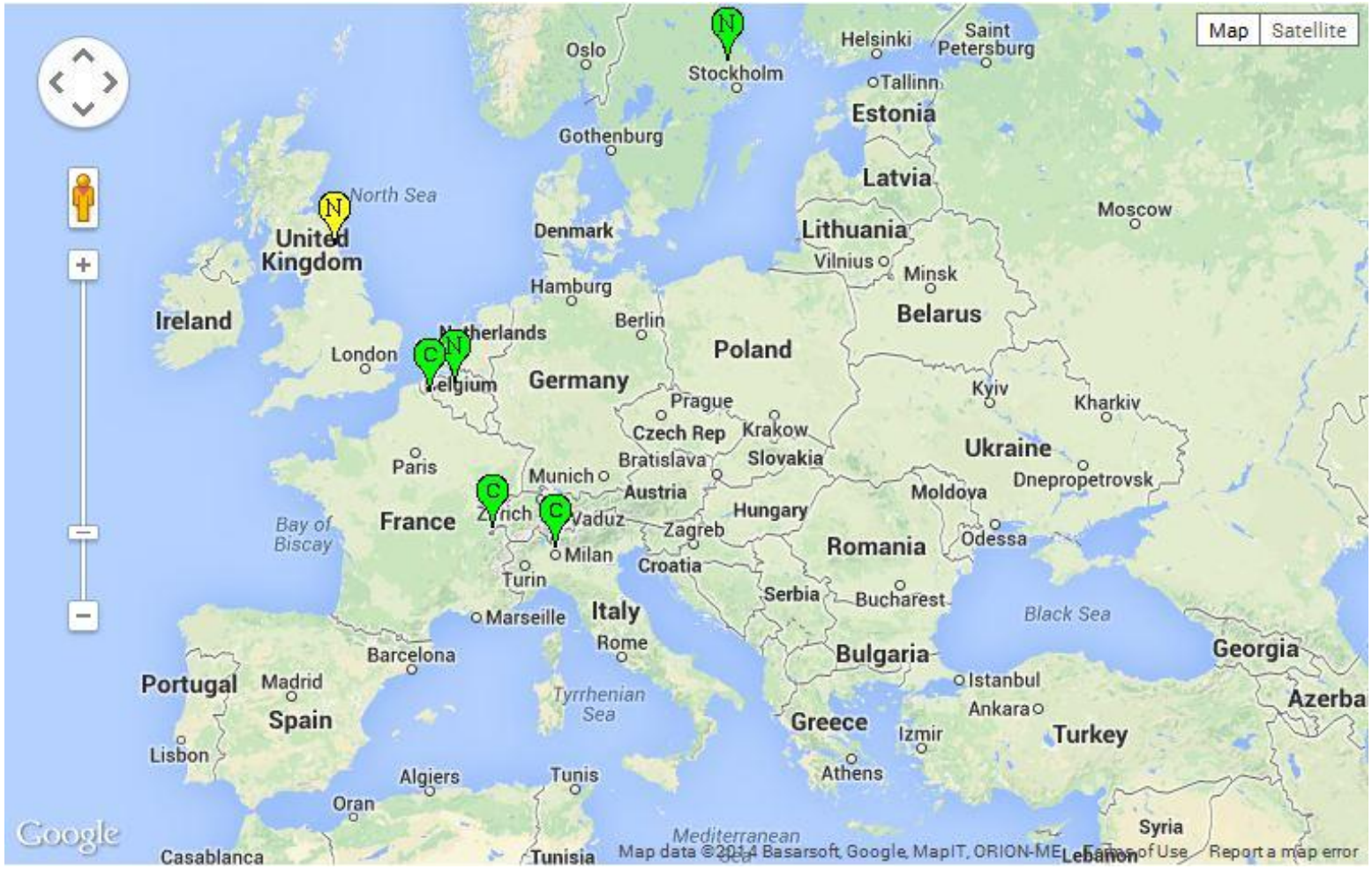


Exhibit 1 – 2C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2012

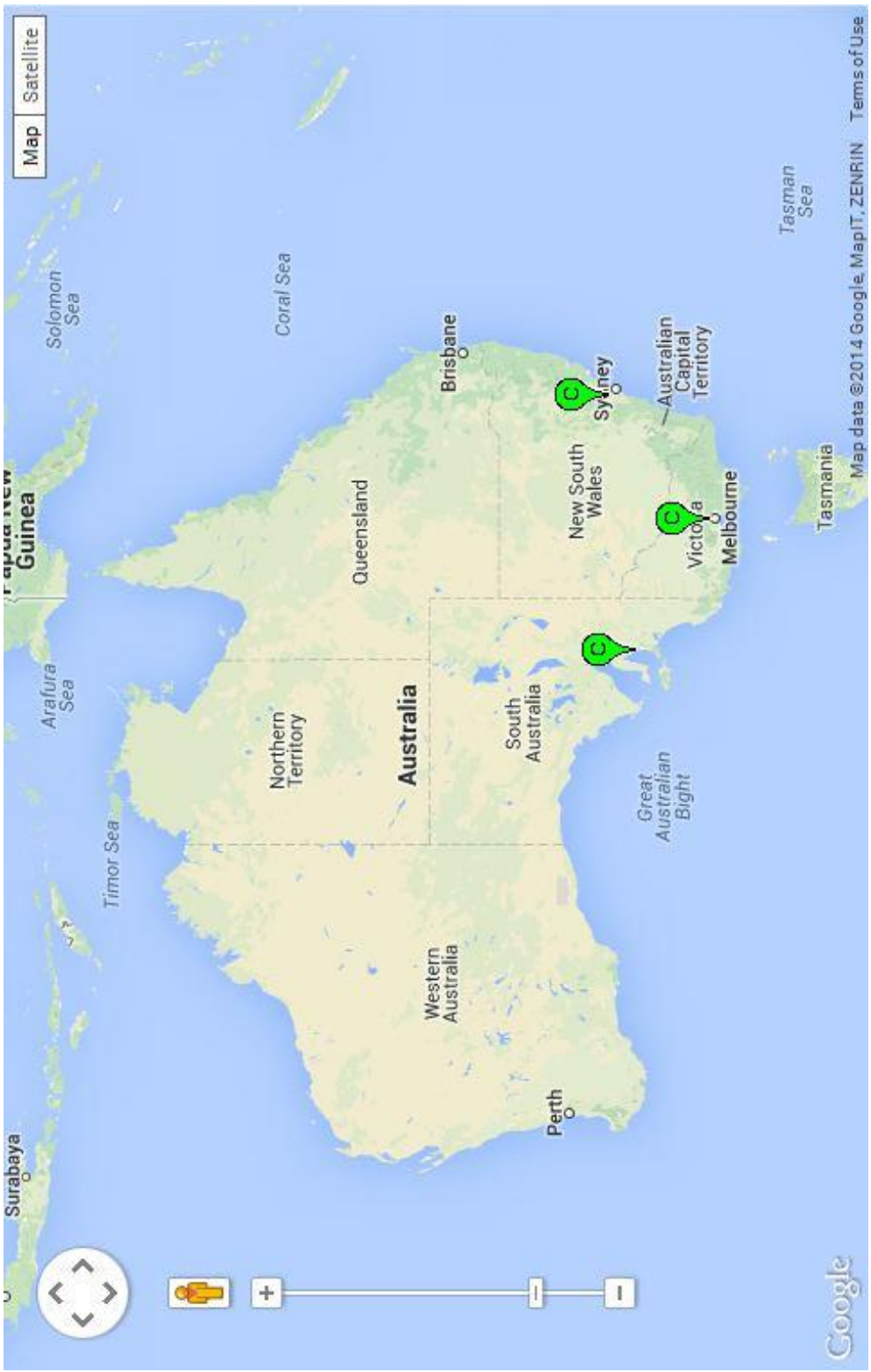
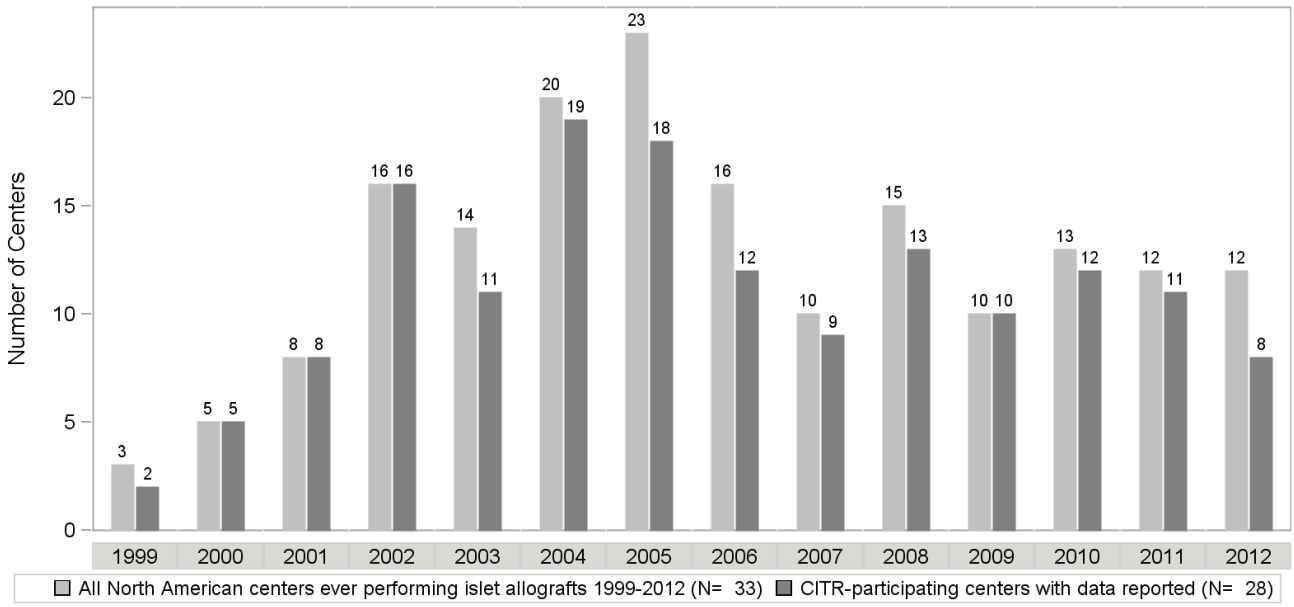


Exhibit 1 – 3
Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
North American Islet Transplant Centers 1999-2012

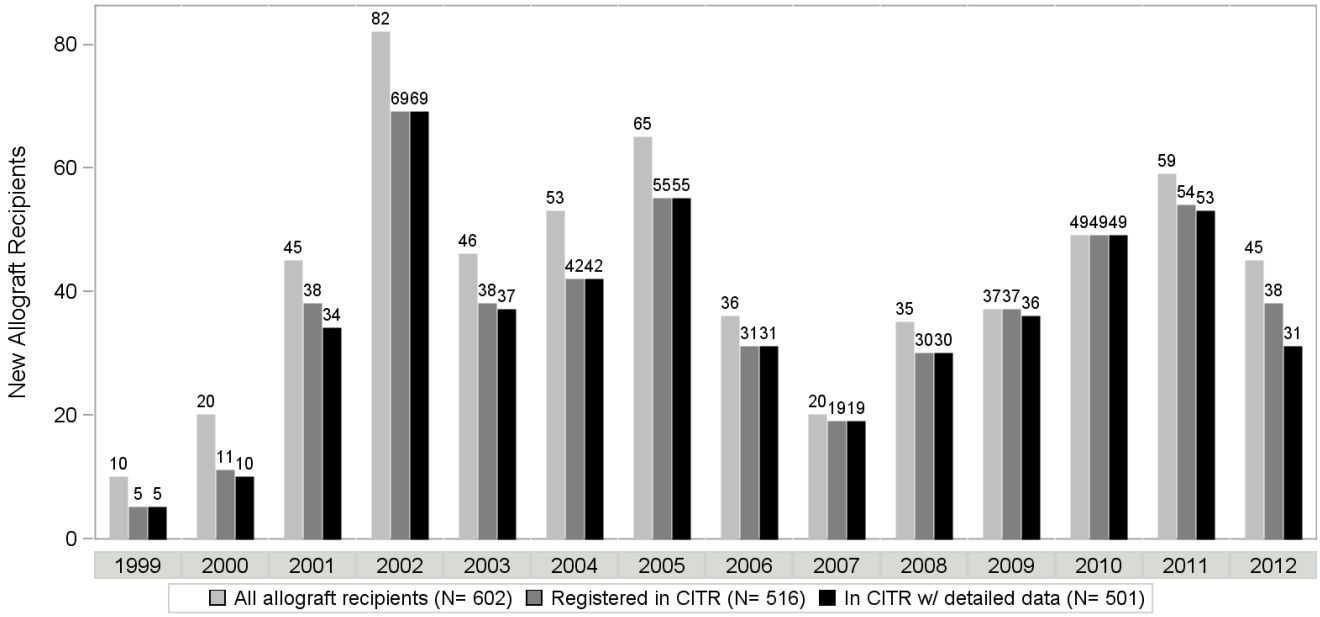


CITR Data 17Dec2013

"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.

Since the last report, there has been one new North American center conducting allogeneic islet transplantation.

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 1999-2012



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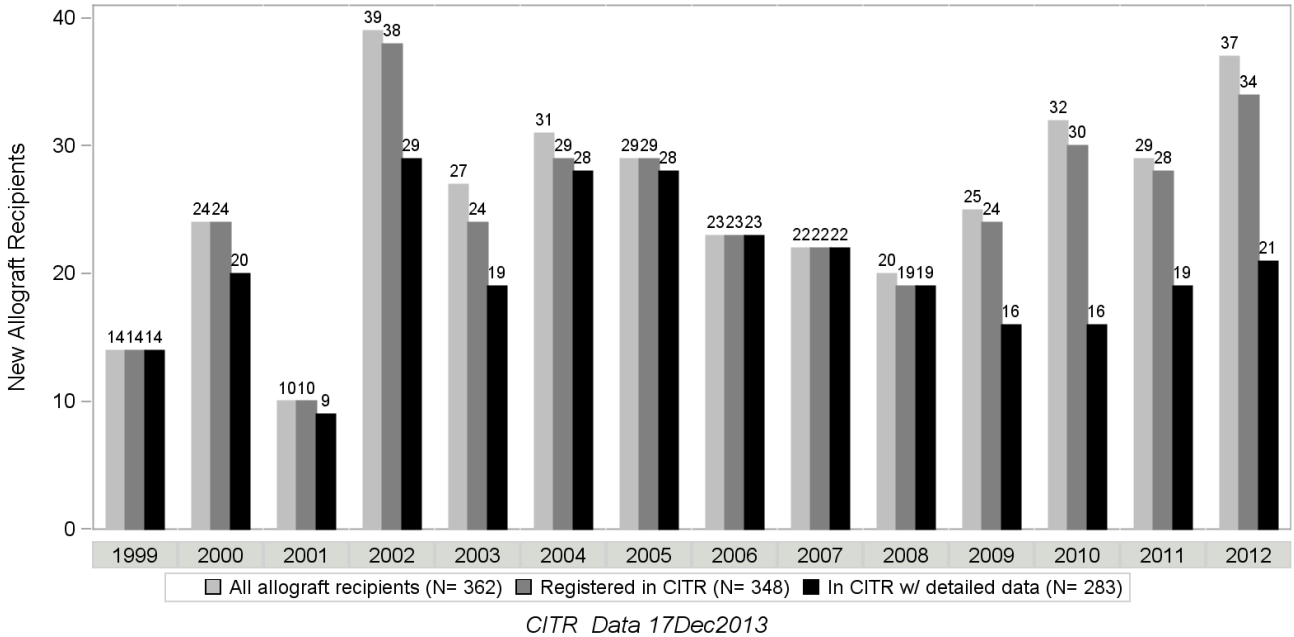
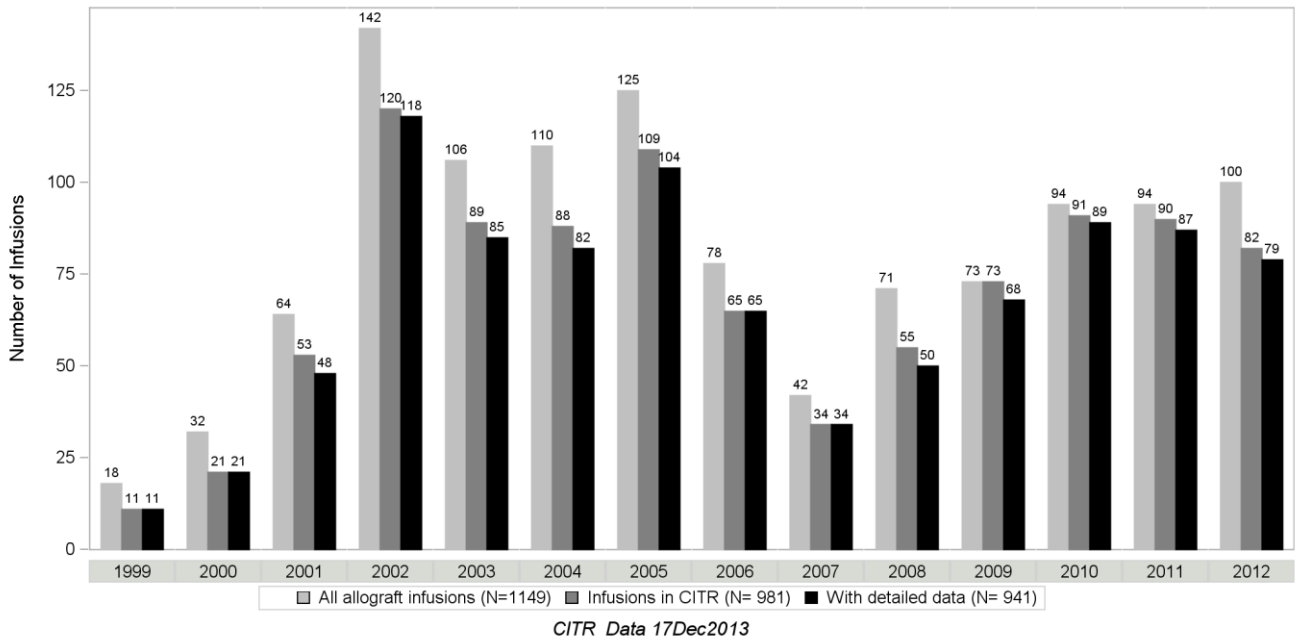
From 1999-2012, 602 patients with type 1 diabetes mellitus received at least one islet allograft infusion procedure in North America. Of these, 516 (85.7%)) consented to and were registered in CITR. Detailed data was available on 501 of these recipients, representing 83.2% of the overall 602.

Exhibit 1 – 4B
Total Number of Islet Allograft <u>Recipients</u>, 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 <u>European and Australian JDRF Centers</u> 1999-2012



CITR Data 17Dec2013

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 1999-2012



From 1999-2012, 601 North American islet transplant recipients of allograft islets received a total of 1,149 infusion procedures. CITR-participating centers reported 981 (85.4%) of those procedures. The Registry has received detailed data relative to 941 of those procedures, representing 81.9% of all 1,149 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 1999-2012

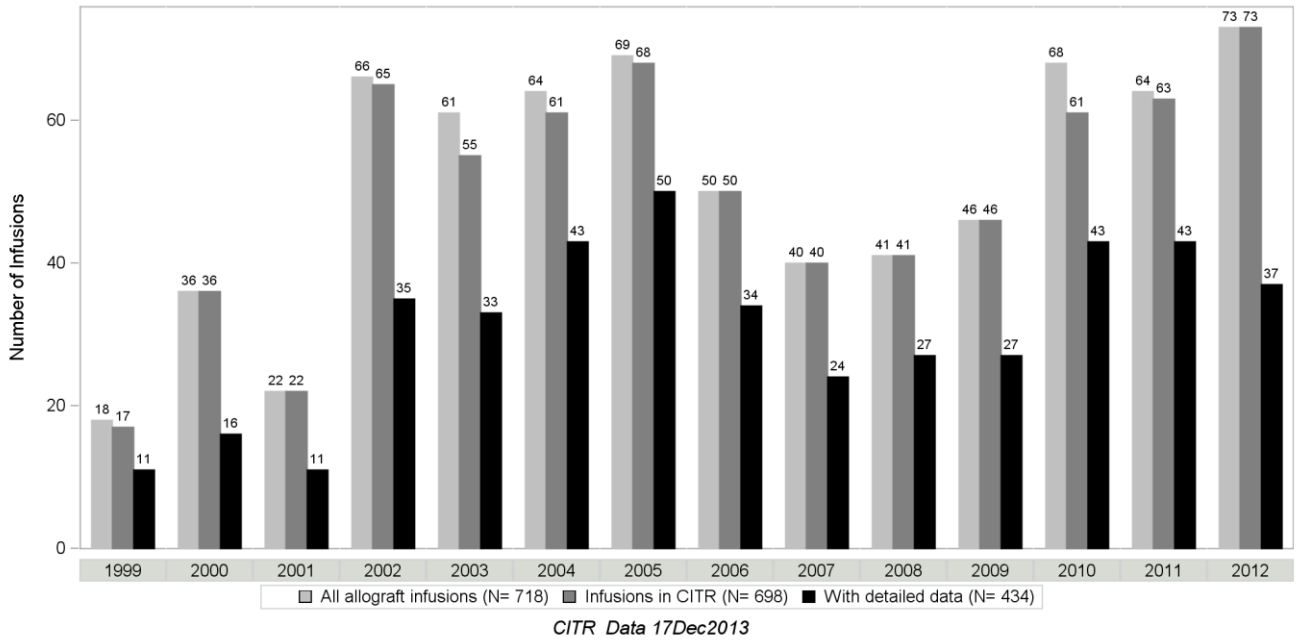


Exhibit 1 – 6A
Islet Allograft Infusions by Infusion Sequence Number and Year
CITR-Participating North American and JDRF Centers, 1999-2012

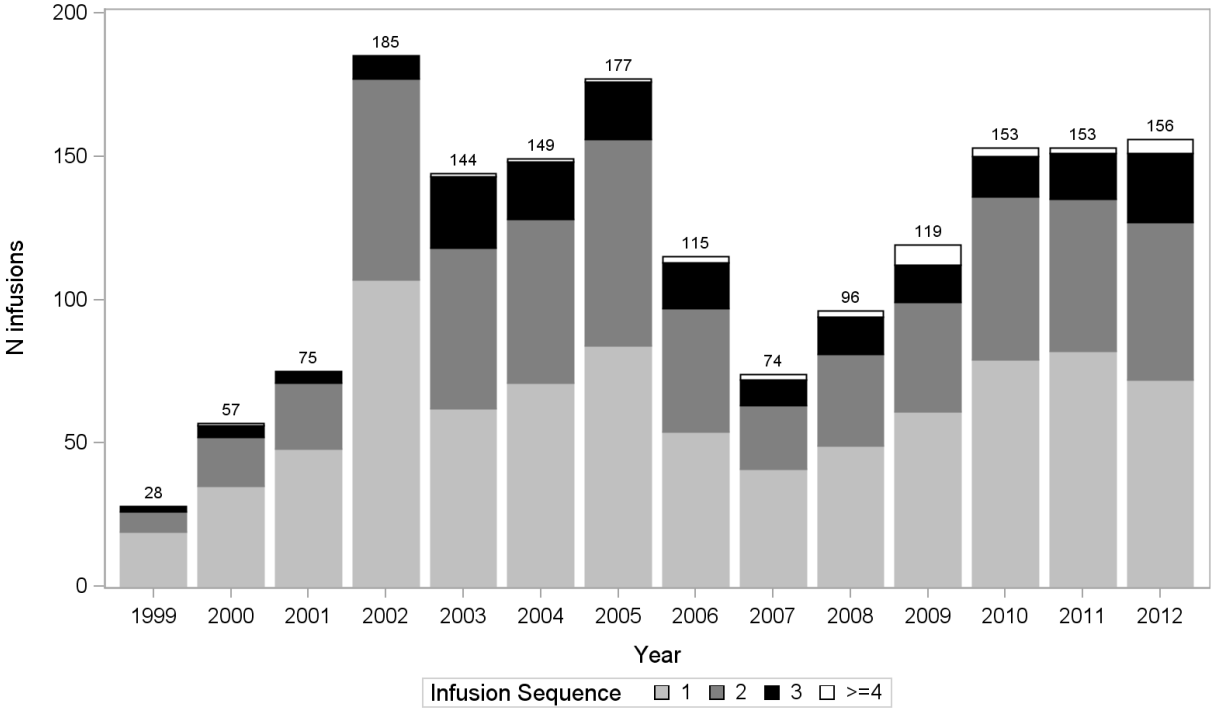


Exhibit 1 – 6B
Islet Allograft Recipients by Total Infusions to Date and Year
CITR-Participating North American and JDRF Centers, 1999-2012

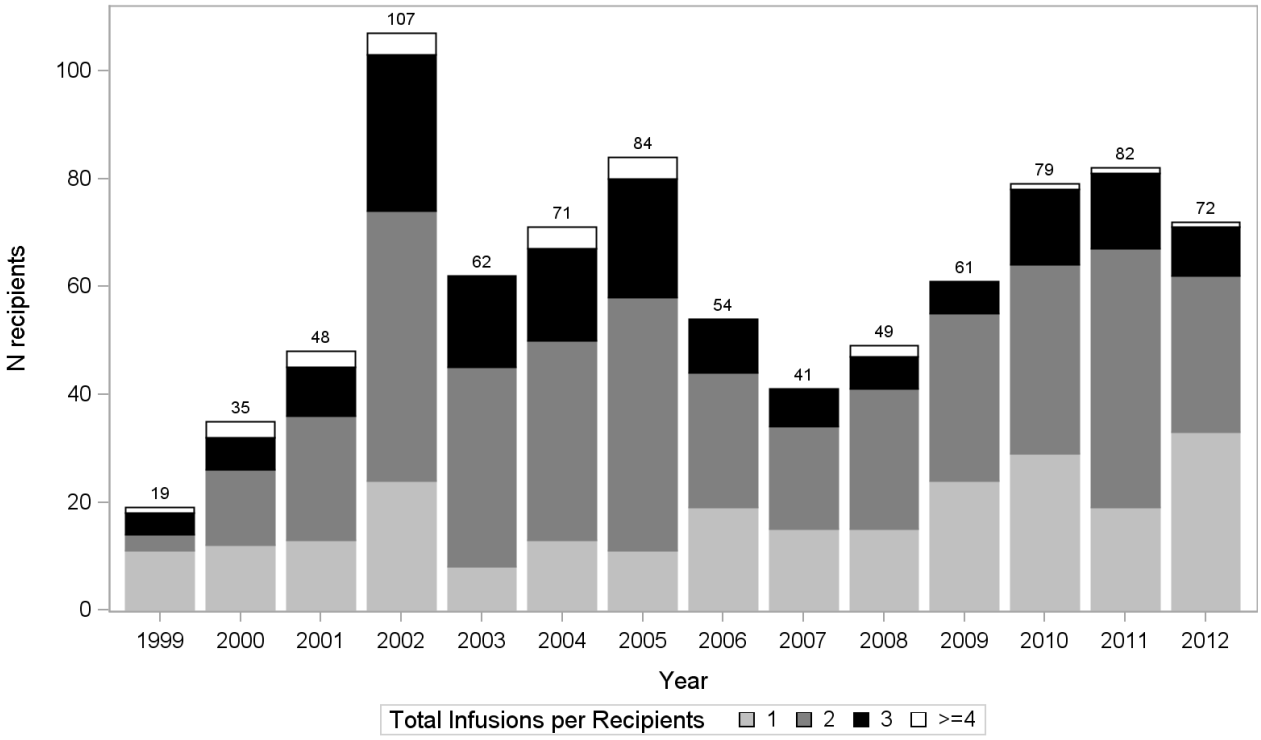


Exhibit 1 – 7
Total Number of Islet Allograft Infusions Per Recipient:
CITR-Participating North American and JDRF Centers, 1999-2012

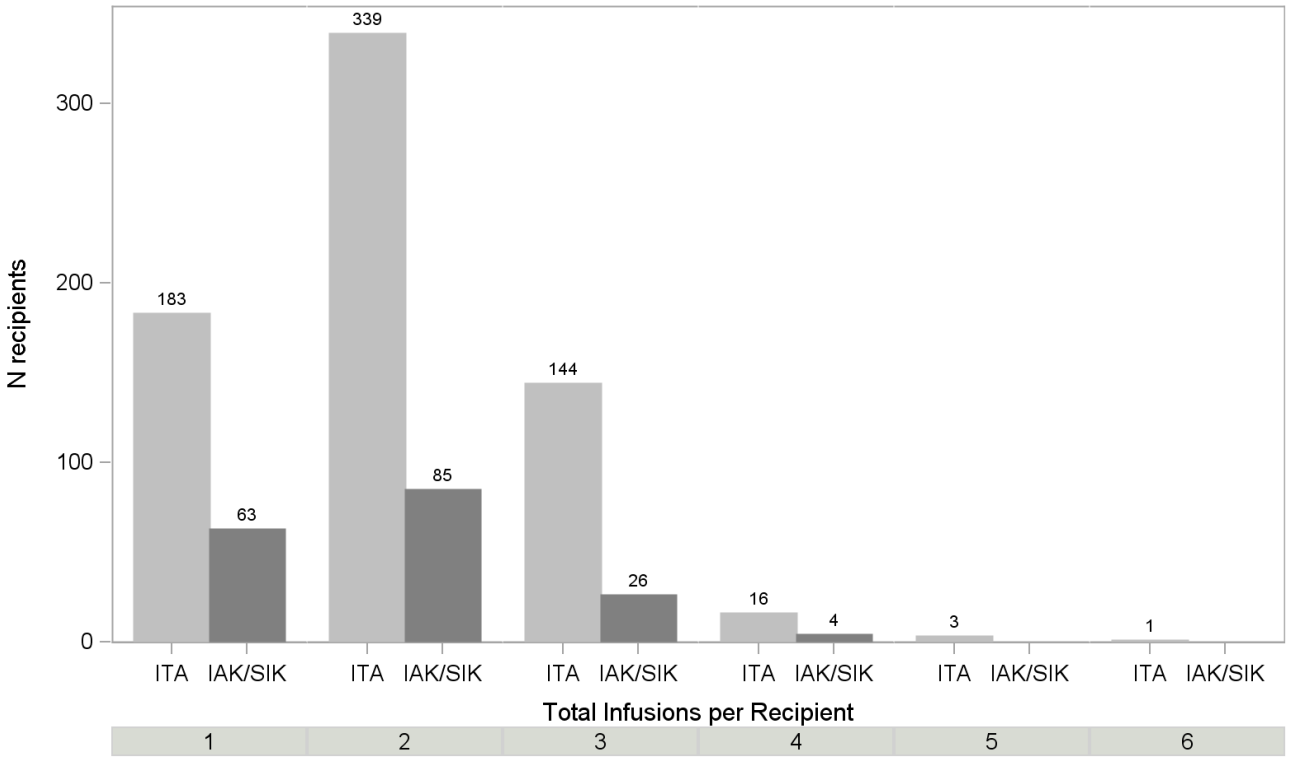
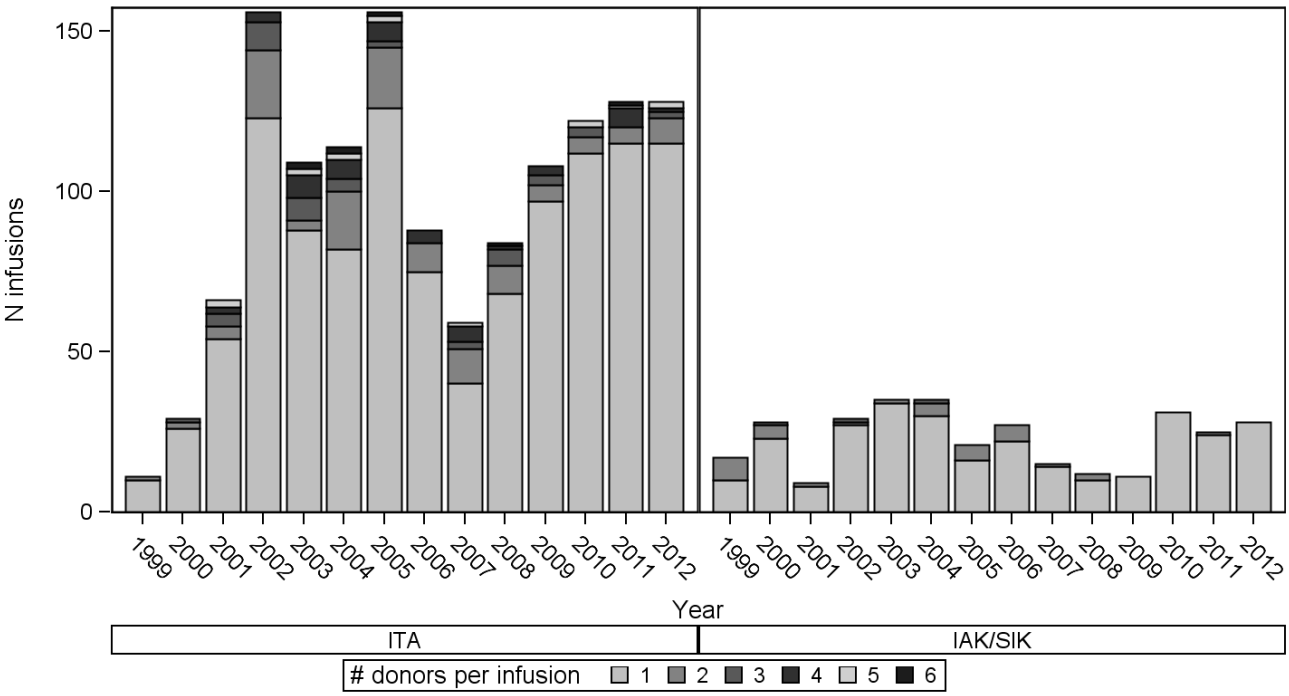


Exhibit 1 – 8
Total Number of Deceased Donors per Islet Allograft Infusion
CITR-Participating North American and JDRF Centers, 1999-2012



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 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 1,419 single-donor, 152 two-donor, 45 three-donor, 44 four-donor, 14 five-donor, and 7 six-donor infusions, for a total of 2,146 donors and 1,681 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 lower levels of total and LDL cholesterol in recent eras
- Recipients had somewhat 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 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 of steroids and insulin during hospitalization
- Donor serum creatinine 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	412	60.1	98	55.4		118	56.5	162	60.0	141	61.6	89	57.8	
	Male	273	39.9	79	44.6		91	43.5	108	40.0	88	38.4	65	42.2	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Gender	Available	685	99.9	177	99.4	209	100.0	270	99.6	229	99.6	154	100.0
	Missing	1	0.1	1	0.6		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	479	98.8	129	98.5		148	99.3	199	99.0	171	97.2	90	100.0	
	Multiple		0.0	1	0.8		1	0.7		0.0		0.0		0.0	
	American Indian	2	0.4		0.0			0.0	1	0.5	1	0.6		0.0	
	Black	4	0.8	1	0.8			0.0	1	0.5	4	2.3		0.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Race	Available	485	70.7	131	73.6	149	71.3	201	74.2	176	76.5	90	58.4
	Missing	201	29.3	47	26.4	60	28.7	70	25.8	54	23.5	64	41.6

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Ethnicity	Not Hispanic	477	98.4	126	95.5		146	98.6	193	96.0	175	98.9	89	97.8	
	Hispanic	8	1.6	6	4.5		2	1.4	8	4.0	2	1.1	2	2.2	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Ethnicity	Available	485	70.7	132	74.2	148	70.8	201	74.2	177	77.0	91	59.1
	Missing	201	29.3	46	25.8	61	29.2	70	25.8	53	23.0	63	40.9

* = 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**	244	58.1	26	31.0		86	62.3	112	53.1	50	49.0	22	41.5	
	Not working disease	63	15.0	34	40.5		22	15.9	44	20.9	17	16.7	14	26.4	
	Not working by choice	26	6.2	4	4.8		5	3.6	13	6.2	8	7.8	4	7.5	
	Part time by choice	25	6.0	5	6.0		6	4.3	11	5.2	13	12.7		0.0	
	Retired	25	6.0		0.0		3	2.2	13	6.2	5	4.9	4	7.5	
	Part time by disease	20	4.8	3	3.6	***	11	8.0	9	4.3	3	2.9		0.0	***
	Not working unknown	6	1.4	6	7.1		1	0.7	4	1.9	4	3.9	3	5.7	
	Part time unknown	7	1.7		0.0		1	0.7	1	0.5		0.0	5	9.4	
	Student	3	0.7	4	4.8		1	0.7	3	1.4	2	2.0	1	1.9	
	Not working no employ	1	0.2		0.0			0.0	1	0.5		0.0		0.0	
	Not applicable		0.0	2	2.4		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**	420	61.2	84	47.2	138	66.0	211	77.9	102	44.3	53	34.4
	Missing	266	38.8	94	52.8	71	34.0	60	22.1	128	55.7	101	65.6

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

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Exhibit 2 – 3
Recipient Characteristics at First Infusion

		ITA		IAK/SIK		p	1999-2002		2003-2006		2007-2010		2011-2014		p
		N	%	N	%		N	%	N	%	N	%	N	%	
Indication for ITx	**Cystic fibrosis**	5	0.8	1	0.7		-	-	1	0.4	2	1.1	3	2.8	
	Pancreatomy	1	0.2	-	-		-	-	-	-	1	0.5	-	-	
	Type 1	606	99.0	140	97.9		205	100.0	256	99.6	183	98.4	102	95.3	
	Type 2	-	-	2	1.4		-	-	-	-	-	-	2	1.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx	Missing	74	10.8	35	19.7	4	1.9	14	5.2	44	19.1	47	30.5
	Available	612	89.2	143	80.3	205	98.1	257	94.8	186	80.9	107	69.5

	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	686	45.4	0.4	178	45.3	0.6		209	42.0	0.6	271	44.6	0.6	230	47.9	0.6	154	47.7	0.9	***
Days listed	426	313.3	17.6	120	381.9	46.6		168	236.7	21.4	230	316.9	22.5	99	490.9	58.3	49	367.6	68.6	***
Duration of Diabetes (yrs)	572	28.5	0.5	138	32.7	0.8	***	198	27.3	0.8	254	29.6	0.6	177	31.4	0.9	81	29.0	1.4	*
Weight (kg)	618	67.2	0.4	150	62.4	0.8	***	196	66.0	0.8	263	65.2	0.6	195	67.3	0.8	114	67.6	1.1	
Body mass index (kg/m2)	592	23.8	0.1	146	22.7	0.2	***	189	23.4	0.2	262	23.3	0.2	193	23.9	0.2	94	23.9	0.4	
Daily insulin requirement prior to infusion (units)	552	37.6	0.6	134	36.7	1.1		194	39.5	1.1	266	37.2	0.9	151	34.7	1.1	75	38.5	2.0	
Duration of intensive therapy (yrs)	319	20.3	0.8	24	24.3	3.1		109	18.1	1.1	143	23.6	1.2	66	19.9	2.0	25	16.4	2.6	
Avg daily insulin / kg recipient body weight	525	0.6	0.0	131	0.6	0.0	*	191	0.6	0.0	261	0.6	0.0	146	0.5	0.0	58	0.6	0.0	*
Fasting plasma glucose (mg/dL)	570	170.4	3.6	125	175.7	8.5		170	182.2	7.2	250	174.6	5.8	173	153.9	5.6	102	174.8	8.0	
Basal C-Peptide (ng/mL)†	579	0.1	0.0	145	0.2	0.1	***	186	0.2	0.0	257	0.1	0.0	180	0.1	0.0	101	0.2	0.1	*
HbA1C (%)	544	7.9	0.1	138	8.1	0.1	*	195	7.9	0.1	264	7.8	0.1	152	7.9	0.1	71	8.4	0.1	*
Class I PRA (%)	366	3.3	0.6	73	1.2	0.7		133	1.5	0.5	188	4.2	1.1	83	2.5	0.9	35	2.5	1.3	
Class II PRA (%)	246	2.9	0.7	31	0.0	0.0		75	1.6	1.3	104	2.8	1.1	64	3.5	1.5	34	2.3	1.6	

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

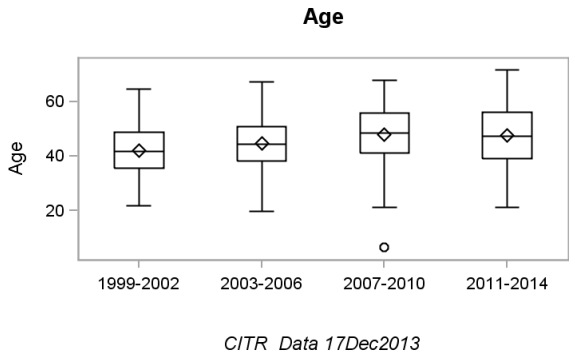
Mean recipient age has increased over the eras, as has mean waiting time and duration of diabetes.

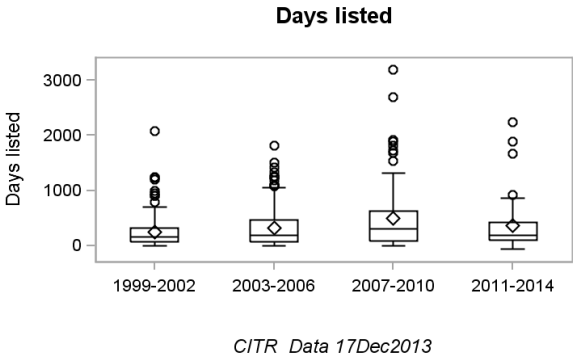
†In 1999-2006, 41/251 (16%) ITAs and 23/107 (21%) of IAK/SIKs had basal C-peptide > 0.3 ng/mL pre-first infusion. In 2007-2014, 16/296 (5%) of ITAs and 6/50 (12%) of IAK/SIKs had basal C-peptide < 0.3 ng/mL pre-transplant.

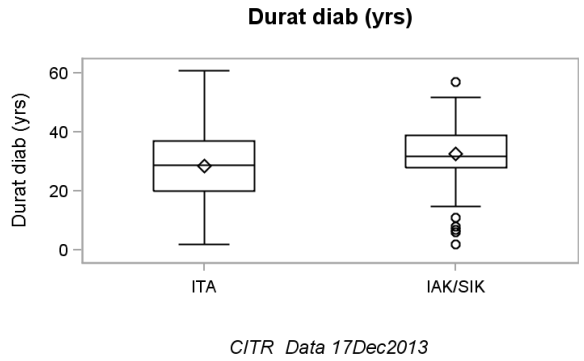
Mean HbA1c has increased substantially over the eras.

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

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







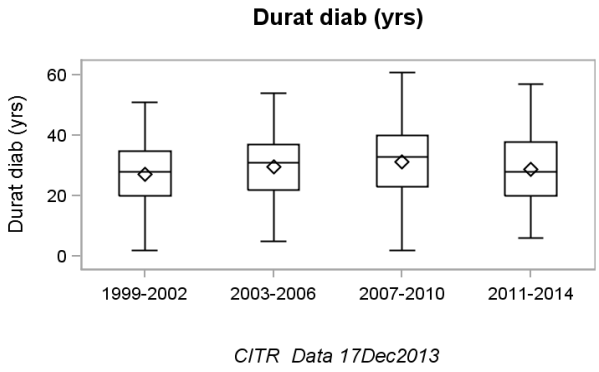
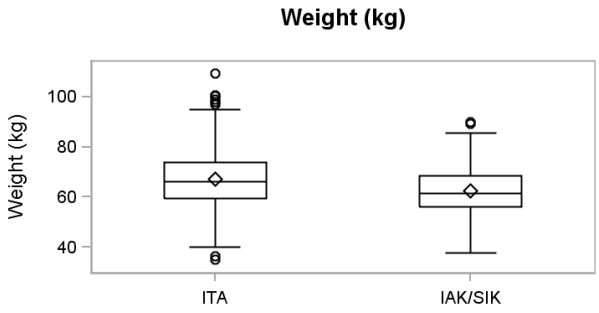


Exhibit 2 – 3 *(continued)*
Recipient Characteristics at First Infusion



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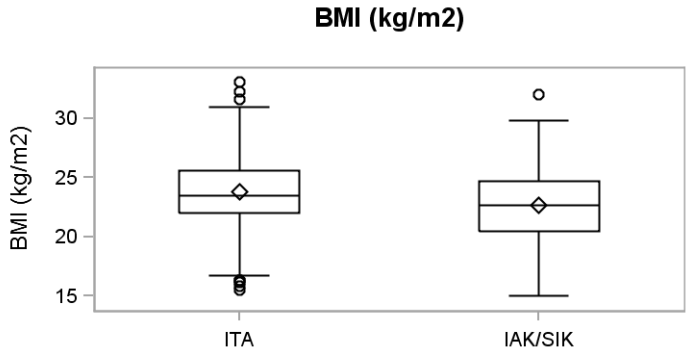
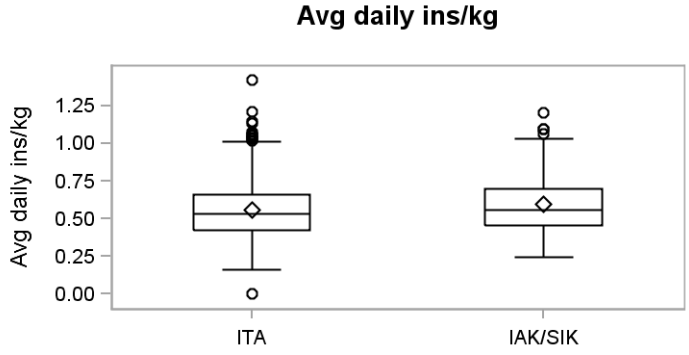
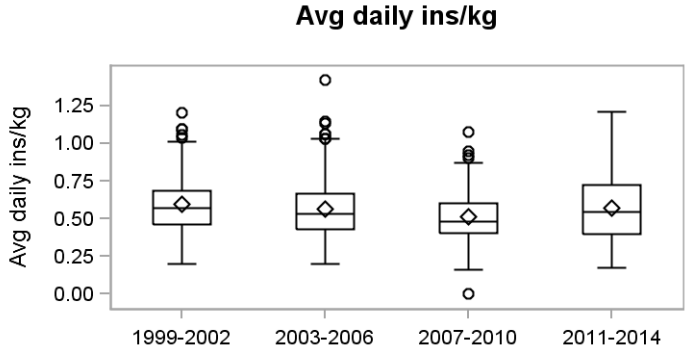


CITR Data 17Dec2013

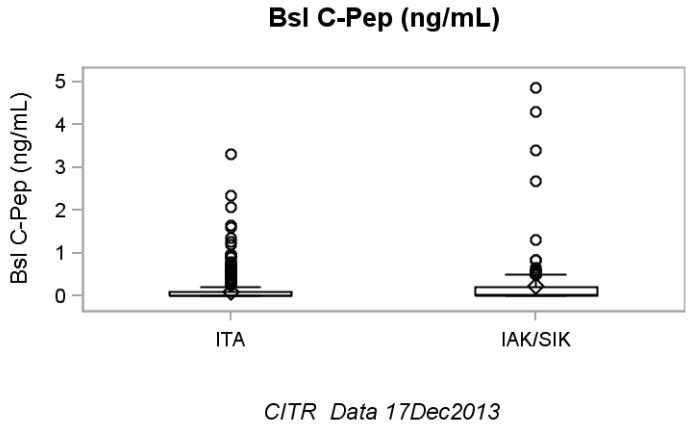


CITR Data 17Dec2013



CITR Data 17Dec2013

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



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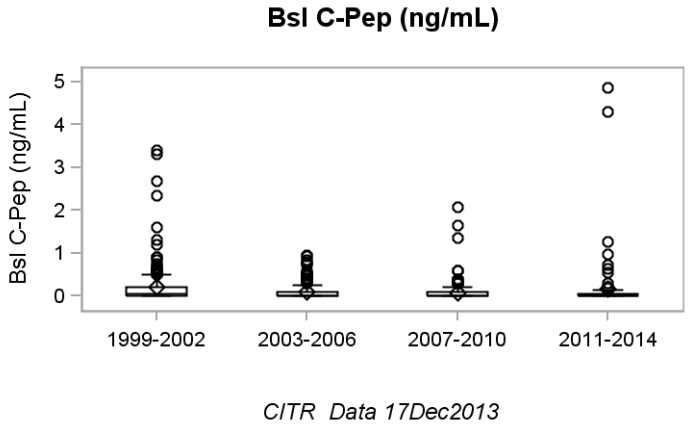
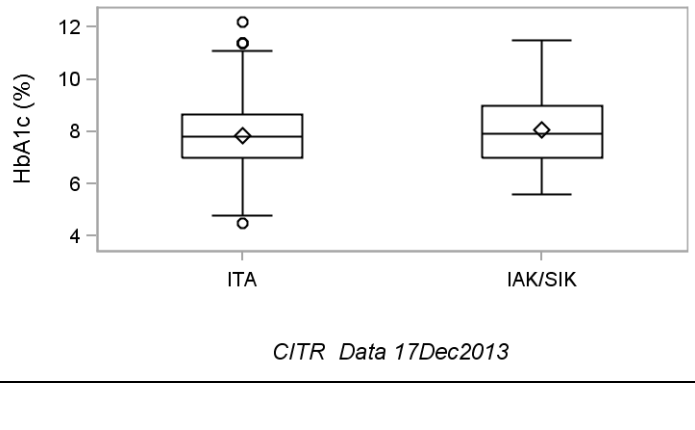


CITR Data 17Dec2013



CITR Data 17Dec2013

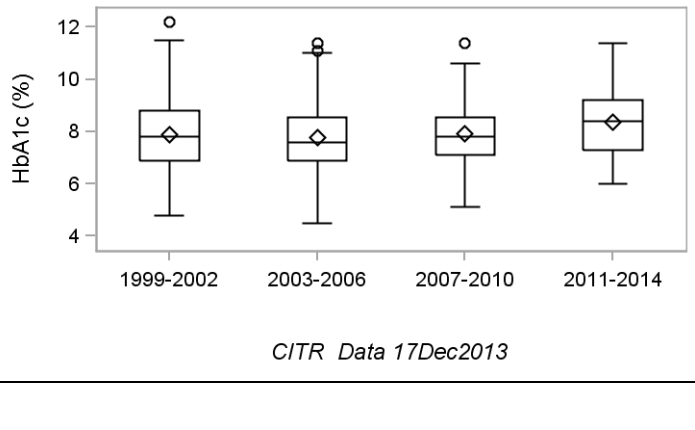


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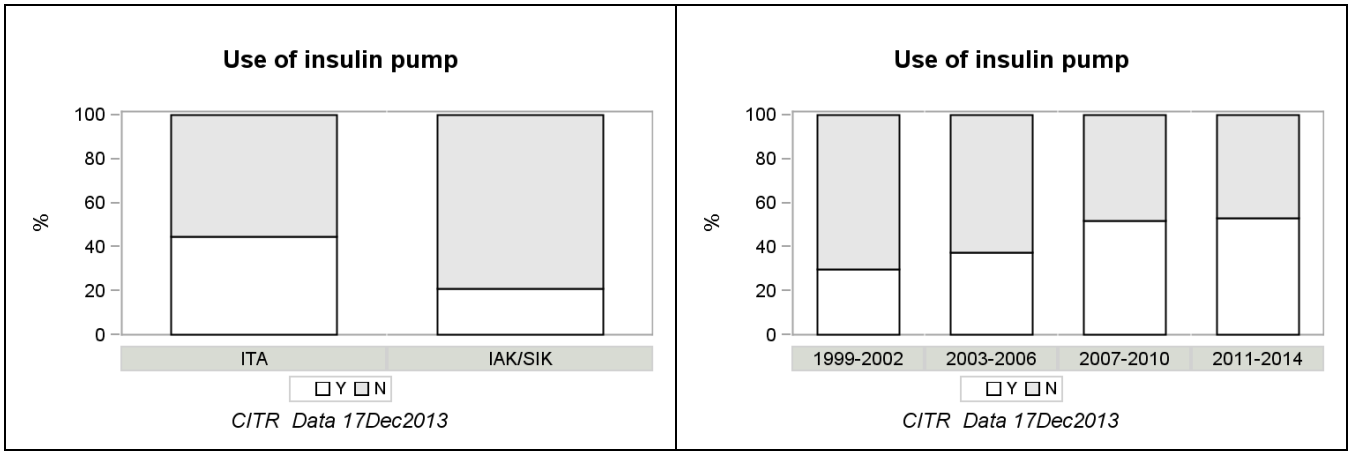
Exhibit 2 – 4
Recipient Diabetes Characteristics and Medical History

		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	5.0		7	6.1	2	1.3	3	5.5	3	11.5	
	3-5	247	92.9	73	91.3		107	93.0	145	96.7	46	83.6	22	84.6	
	6 or more	8	3.0	3	3.8		1	0.9	3	2.0	6	10.9	1	3.8	

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	266	38.8	80	44.9	115	55.0	150	55.4	55	23.9	26	16.9
	Missing	420	61.2	98	55.1	94	45.0	121	44.6	175	76.1	128	83.1

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Use of insulin pump	**No**	298	55.6	103	79.2	***	134	70.2	167	62.8	67	48.2	33	47.1	***
	Yes	238	44.4	27	20.8		57	29.8	99	37.2	72	51.8	37	52.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Use of insulin pump	Available	536	78.1	130	73.0	191	91.4	266	98.2	139	60.4	70	45.5
	Missing	150	21.9	48	27.0	18	8.6	5	1.8	91	39.6	84	54.5



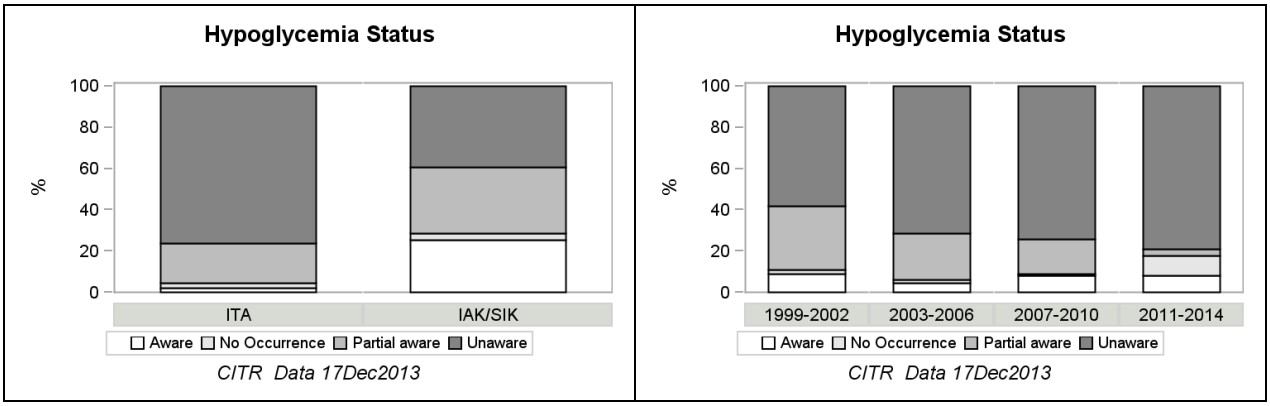
* = p <.05; ** = p <.01; *** = p <.001

Increased use of insulin pump is noted in the most recent era.

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

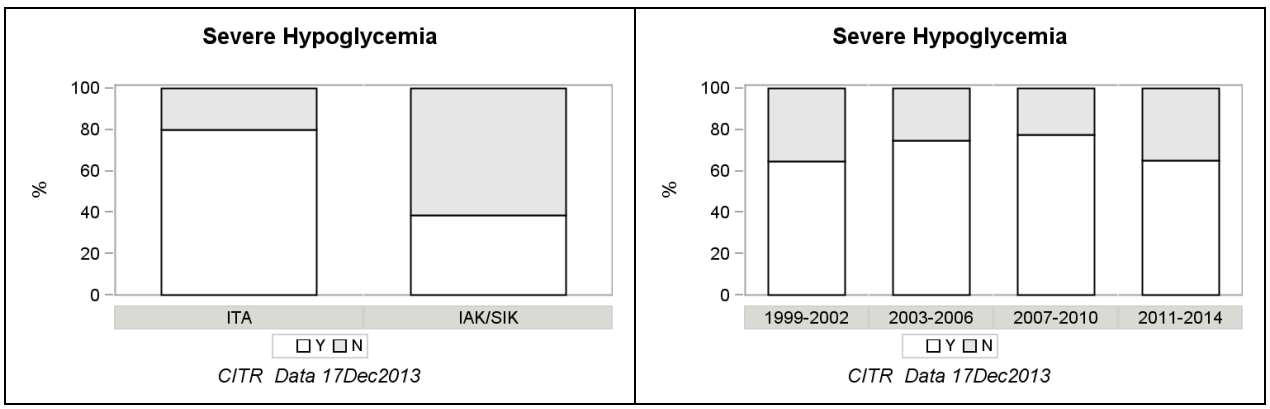
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hypoglycemia status	**Unaware**	381	76.4	48	39.3		101	58.4	187	71.4	92	74.2	49	79.0	
	Partial aware	96	19.2	39	32.0	***	53	30.6	59	22.5	21	16.9	2	3.2	***
	No Occurrence	11	2.2	4	3.3		4	2.3	4	1.5	1	0.8	6	9.7	
	Aware	11	2.2	31	25.4		15	8.7	12	4.6	10	8.1	5	8.1	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Hypoglycemia status	Available	499	72.7	122	68.5	173	82.8	262	96.7	124	53.9	62	40.3
	Missing	187	27.3	56	31.5	36	17.2	9	3.3	106	46.1	92	59.7



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Severe hypoglycemia	**No**	96	20.0	80	61.5	***	66	35.3	61	25.4	27	22.7	22	34.9	*
	Yes	383	80.0	50	38.5		121	64.7	179	74.6	92	77.3	41	65.1	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Severe hypoglycemia	Available	479	69.8	130	73.0	187	89.5	240	88.6	119	51.7	63	40.9
	Missing	207	30.2	48	27.0	22	10.5	31	11.4	111	48.3	91	59.1

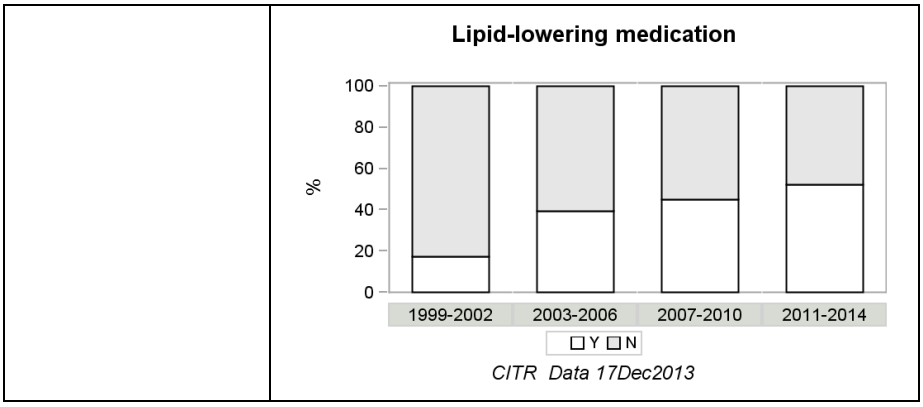


* = p <.05; ** = p <.01; *** = p <.001

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

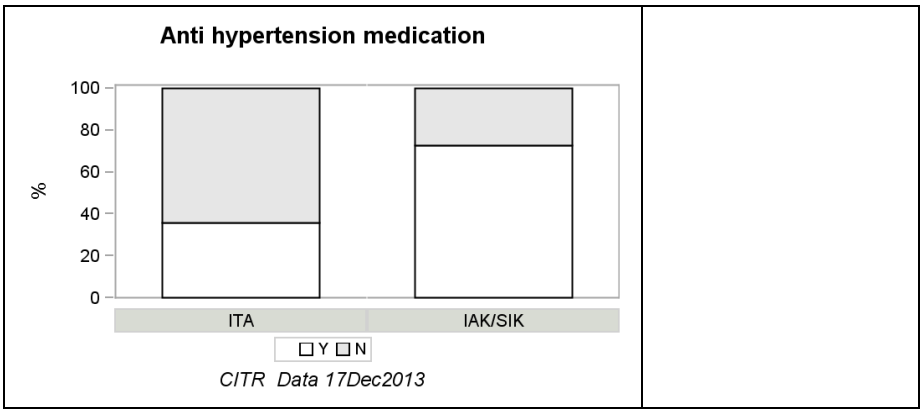
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Lipid-lowering medication	**No**	329	66.6	77	59.7		153	82.7	160	60.8	71	55.0	22	47.8	***
	Yes	165	33.4	52	40.3		32	17.3	103	39.2	58	45.0	24	52.2	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Lipid-lowering medication	Available	494	72.0	129	72.5	185	88.5	263	97.0	129	56.1	46	29.9
	Missing	192	28.0	49	27.5	24	11.5	8	3.0	101	43.9	108	70.1



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Anti-hypertension medication	**No**	321	64.2	36	27.5	***	114	60.3	153	58.2	65	49.6	25	52.1	
	Yes	179	35.8	95	72.5		75	39.7	110	41.8	66	50.4	23	47.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Anti-hypertension medication	Available	500	72.9	131	73.6	189	90.4	263	97.0	131	57.0	48	31.2
	Missing	186	27.1	47	26.4	20	9.6	8	3.0	99	43.0	106	68.8



* = 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**	179	94.7	49	98.0		37	94.9	80	98.8	72	93.5	39	92.9	
	Yes	10	5.3	1	2.0		2	5.1	1	1.2	5	6.5	3	7.1	

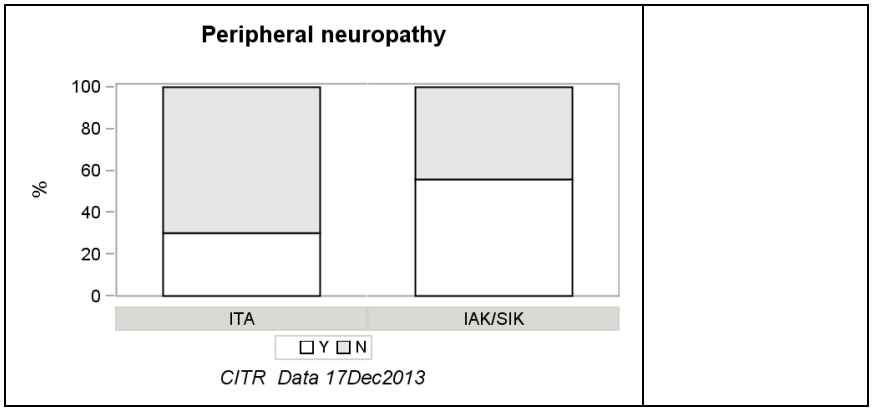
Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Anti-hyperglycemia medication	Available	189	27.6	50	28.1	39	18.7	81	29.9	77	33.5	42	27.3
	Missing	497	72.4	128	71.9	170	81.3	190	70.1	153	66.5	112	72.7

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Smoker	**No**	471	93.8	78	97.5		145	95.4	225	95.7	118	94.4	61	87.1	
	Yes	31	6.2	2	2.5		7	4.6	10	4.3	7	5.6	9	12.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Smoker	Available	502	73.2	80	44.9	152	72.7	235	86.7	125	54.3	70	45.5
	Missing	184	26.8	98	55.1	57	27.3	36	13.3	105	45.7	84	54.5

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Peripheral neuropathy	**No**	363	69.8	55	44.4	***	112	59.3	166	64.8	90	68.7	50	73.5	
	Yes	157	30.2	69	55.6		77	40.7	90	35.2	41	31.3	18	26.5	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Peripheral neuropathy	Available	520	75.8	124	69.7	189	90.4	256	94.5	131	57.0	68	44.2
	Missing	166	24.2	54	30.3	20	9.6	15	5.5	99	43.0	86	55.8

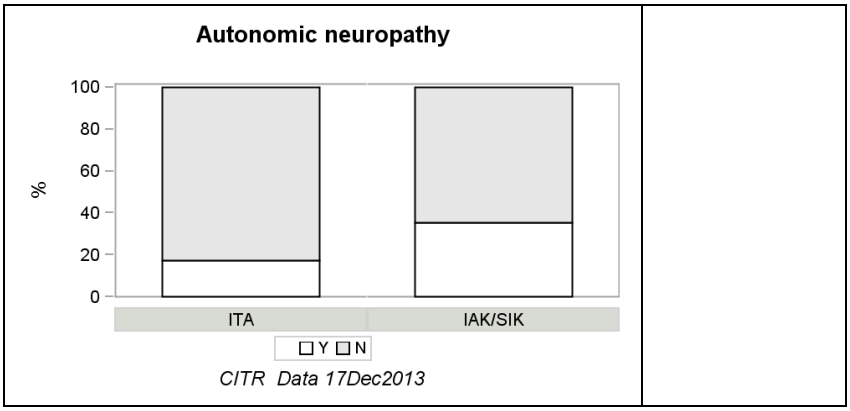


* = p <.05; ** = p <.01; *** = p <.001

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**	413	82.8	71	64.5	***	137	76.1	196	81.0	98	81.7	53	79.1	
	Yes	86	17.2	39	35.5		43	23.9	46	19.0	22	18.3	14	20.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Autonomic neuropathy	Available	499	72.7	110	61.8	180	86.1	242	89.3	120	52.2	67	43.5
	Missing	187	27.3	68	38.2	29	13.9	29	10.7	110	47.8	87	56.5



		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CAD history	**No**	474	91.7	105	80.8	***	178	93.7	232	88.9	110	85.3	59	88.1	
	Yes	43	8.3	25	19.2		12	6.3	29	11.1	19	14.7	8	11.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CAD history	Available	517	75.4	130	73.0	190	90.9	261	96.3	129	56.1	67	43.5
	Missing	169	24.6	48	27.0	19	9.1	10	3.7	101	43.9	87	56.5

* = 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**	502	98.4	118	95.9		185	99.5	250	98.8	120	94.5	65	97.0	
	Yes	8	1.6	5	4.1		1	0.5	3	1.2	7	5.5	2	3.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CVA history	**Available**	510	74.3	123	69.1	186	89.0	253	93.4	127	55.2	67	43.5
	Missing	176	25.7	55	30.9	23	11.0	18	6.6	103	44.8	87	56.5

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
PVD history	**No**	485	97.4	83	82.2	**	162	95.3	234	94.7	109	94.0	63	95.5	
	Yes	13	2.6	18	17.8		8	4.7	13	5.3	7	6.0	3	4.5	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
PVD history	**Available**	498	72.6	101	56.7	170	81.3	247	91.1	116	50.4	66	42.9
	Missing	188	27.4	77	43.3	39	18.7	24	8.9	114	49.6	88	57.1

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Retinopathy	**No**	234	47.1	4	3.1	***	57	29.7	96	38.4	49	39.2	36	62.1	**
	Yes	263	52.9	124	96.9		135	70.3	154	61.6	76	60.8	22	37.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Retinopathy	**Available**	497	72.4	128	71.9	192	91.9	250	92.3	125	54.3	58	37.7
	Missing	189	27.6	50	28.1	17	8.1	21	7.7	105	45.7	96	62.3

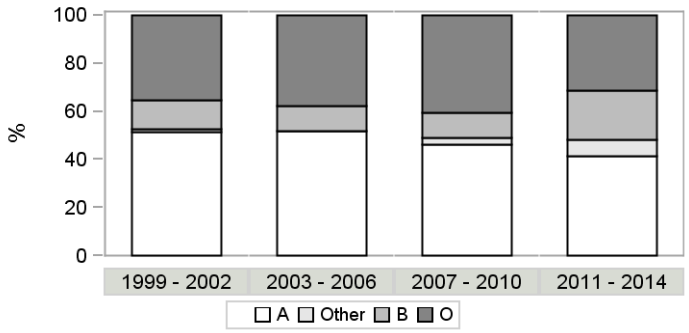
* = p <.05; ** = p <.01; *** = p <.001

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
Blood group	**A**	295	48.6	77	49.7		103	51.5	133	52.0	87	46.3	49	41.5	
	O	226	37.2	55	35.5		71	35.5	97	37.9	76	40.4	37	31.4	
	B	75	12.4	19	12.3		24	12.0	26	10.2	20	10.6	24	20.3	***
	AB	10	1.6	3	1.9		1	0.5		0.0	4	2.1	8	6.8	
	A1		0.0	1	0.6		1	0.5		0.0		0.0		0.0	
	A2	1	0.2		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**	607	88.5	155	87.1	200	95.7	256	94.5	188	81.7	118	76.6
	Missing	79	11.5	23	12.9	9	4.3	15	5.5	42	18.3	36	23.4

Blood group

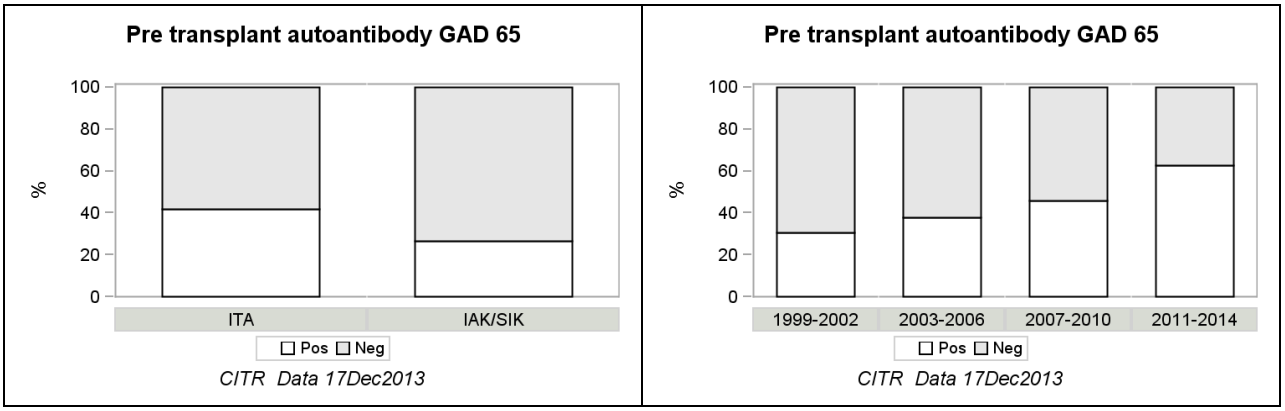


* = p <.05; ** = p <.01; *** = p <.001

Exhibit 2 – 5
Recipient Autoantibody and Sensitization at First Infusion

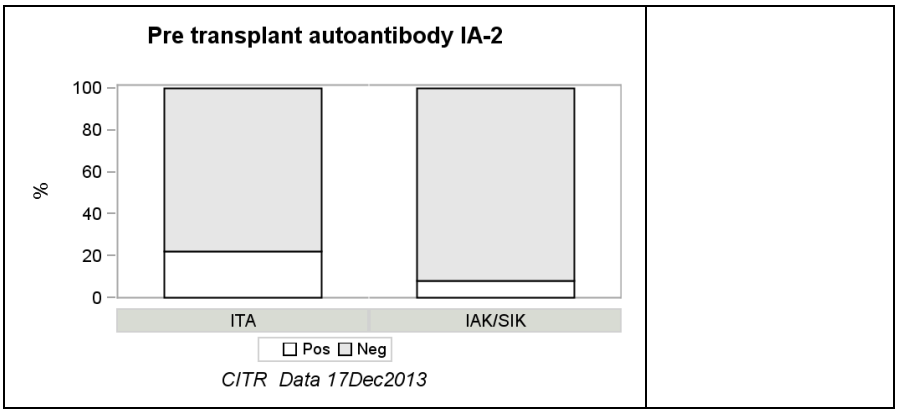
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody GAD 65	**Negative**	218	58.1	69	73.4	**	107	69.5	115	62.2	53	54.1	12	37.5	**
	Positive	157	41.9	25	26.6		47	30.5	70	37.8	45	45.9	20	62.5	

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	375	54.7	94	52.8	154	73.7	185	68.3	98	42.6	32	20.8
	Missing	311	45.3	84	47.2	55	26.3	86	31.7	132	57.4	122	79.2



		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**	440	77.7	125	91.9	***	166	82.6	221	82.2	124	77.0	54	76.1	
	Positive	126	22.3	11	8.1		35	17.4	48	17.8	37	23.0	17	23.9	

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	566	82.5	136	76.4	201	96.2	269	99.3	161	70.0	71	46.1
	Missing	120	17.5	42	23.6	8	3.8	2	0.7	69	30.0	83	53.9

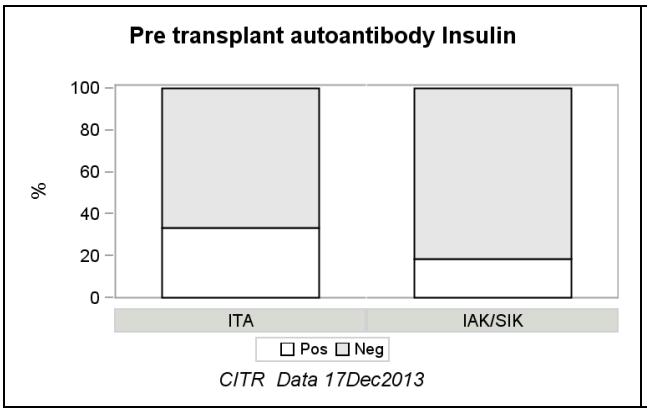


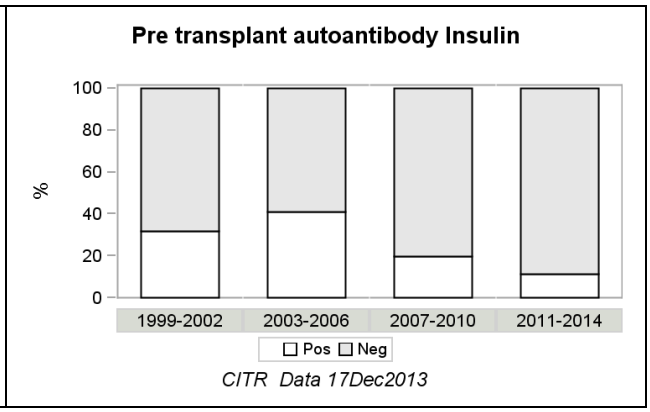
* = p <.05; ** = p <.01; *** = p <.001

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**	377	66.6	111	81.6	***	137	68.2	159	59.1	129	80.1	63	88.7	***
	Positive	189	33.4	25	18.4		64	31.8	110	40.9	32	19.9	8	11.3	

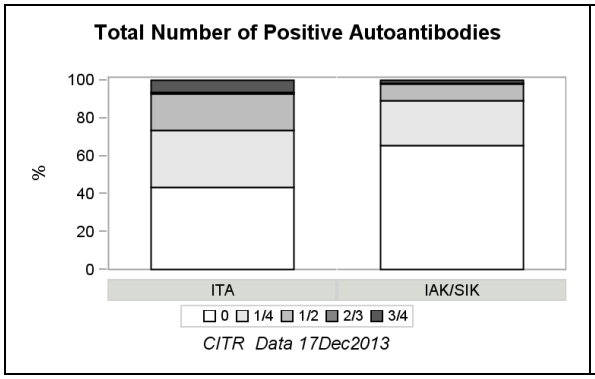
Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody Insulin	Available	566	82.5	136	76.4	201	96.2	269	99.3	161	70.0	71	46.1
	Missing	120	17.5	42	23.6	8	3.8	2	0.7	69	30.0	83	53.9

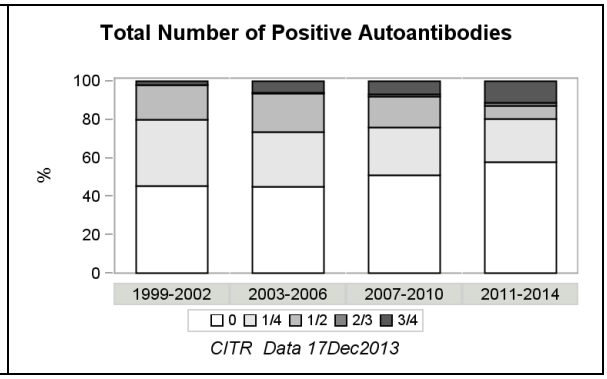




		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Total Number of Positive Autoantibodies	**0**	246	43.5	89	65.4		91	45.3	121	45.0	82	50.9	41	57.7	
	1/4	171	30.2	32	23.5		70	34.8	77	28.6	40	24.8	16	22.5	
	1/2	109	19.3	12	8.8	***	36	17.9	54	20.1	26	16.1	5	7.0	***
	2/3	3	0.5	1	0.7			0.0	1	0.4	2	1.2	1	1.4	
	3/4	37	6.5	2	1.5		4	2.0	16	5.9	11	6.8	8	11.3	

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	566	82.5	136	76.4	201	96.2	269	99.3	161	70.0	71	46.1
	Missing	120	17.5	42	23.6	8	3.8	2	0.7	69	30.0	83	53.9





* = 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	301	81.8	68	93.2		116	87.2	158	83.6	65	77.4	30	85.7	
	Pos	67	18.2	5	6.8		17	12.8	31	16.4	19	22.6	5	14.3	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
PRA-Class I	Available	368	53.6	73	41.0	133	63.6	189	69.7	84	36.5	35	22.7
	Missing	318	46.4	105	59.0	76	36.4	82	30.3	146	63.5	119	77.3

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
PRA-Class II	Neg	220	88.4	31	96.9		72	96.0	93	89.4	56	83.6	30	85.7	
	Pos	27	10.8		0.0		3	4.0	11	10.6	9	13.4	4	11.4	
	Equ	2	0.8	1	3.1			0.0		0.0	2	3.0	1	2.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
PRA-Class II	Available	249	36.3	32	18.0	75	35.9	104	38.4	67	29.1	35	22.7
	Missing	437	63.7	146	82.0	134	64.1	167	61.6	163	70.9	119	77.3

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

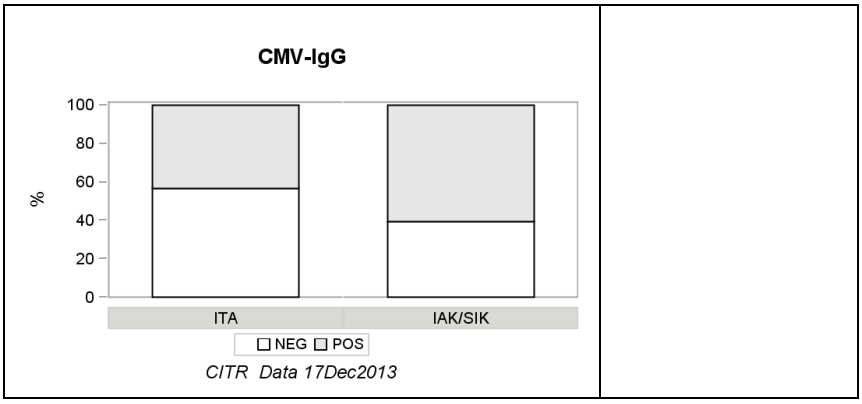
Exhibit 2 – 6
Recipient Infectious Disease Testing at First Infusion

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HIV	NEG	552	100.0	104	99.0		179	100.0	246	100.0	161	99.4	70	100.0	
	POS	-	0.0	1	1.0		-	0.0	-	0.0	1	0.6	-	0.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
HIV	Available	552	80.5	105	59.0	179	85.6	246	90.8	162	70.4	70	45.5
	Missing	134	19.5	73	41.0	30	14.4	25	9.2	68	29.6	84	54.5

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CMV-IgG	NEG	317	56.8	44	39.3	*	94	51.9	133	53.8	95	55.9	39	54.2	
	POS	241	43.2	68	60.7		87	48.1	114	46.2	75	44.1	33	45.8	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgG	Available	558	81.3	112	62.9	181	86.6	247	91.1	170	73.9	72	46.8
	Missing	128	18.7	66	37.1	28	13.4	24	8.9	60	26.1	82	53.2



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

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
CMV-IgM	NEG	383	99.5	64	85.3		108	94.7	163	96.4	112	99.1	64	100.0	
	POS	2	0.5	11	14.7		6	5.3	6	3.6	1	0.9	-	0.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgM	Available	385	56.1	75	42.1	114	54.5	169	62.4	113	49.1	64	41.6
	Missing	301	43.9	103	57.9	95	45.5	102	37.6	117	50.9	90	58.4

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hepatitis B Core	NEG	468	97.5	70	93.3		128	98.5	204	98.1	140	95.9	66	93.0	
	POS	12	2.5	5	6.7		2	1.5	4	1.9	6	4.1	5	7.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Core	Available	480	70.0	75	42.1	130	62.2	208	76.8	146	63.5	71	46.1
	Missing	206	30.0	103	57.9	79	37.8	63	23.2	84	36.5	83	53.9

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Hepatitis B Surface	NEG	124	76.1	17	56.7		23	69.7	33	82.5	52	66.7	33	78.6	
	POS	39	23.9	13	43.3		10	30.3	7	17.5	26	33.3	9	21.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Surface	Available	163	23.8	30	16.9	33	15.8	40	14.8	78	33.9	42	27.3
	Missing	523	76.2	148	83.1	176	84.2	231	85.2	152	66.1	112	72.7

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HCV	NEG	537	99.6	109	95.6		171	97.7	247	99.6	158	99.4	70	98.6	
	POS	2	0.4	5	4.4		4	2.3	1	0.4	1	0.6	1	1.4	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
HCV	Available	539	78.6	114	64.0	175	83.7	248	91.5	159	69.1	71	46.1
	Missing	147	21.4	64	36.0	34	16.3	23	8.5	71	30.9	83	53.9

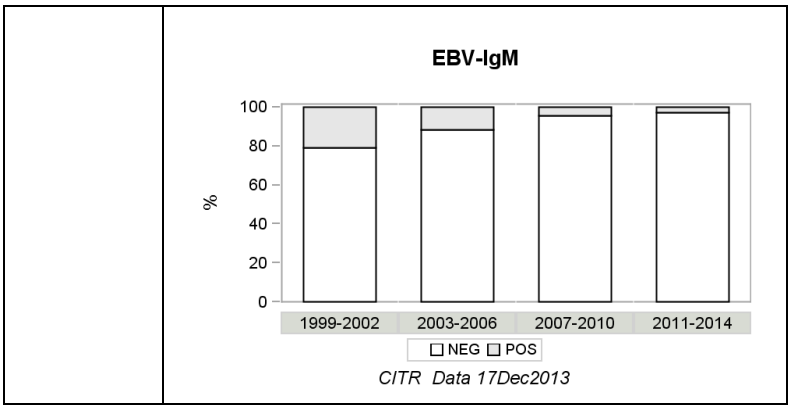
Exhibit 2 – 6 *(continued)*
Recipient Infectious Disease Testing at First Infusion

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
EBV-IgG	NEG	53	10.5	4	3.7		11	6.4	17	7.5	18	12.4	11	15.7	
	POS	454	89.5	105	96.3		162	93.6	211	92.5	127	87.6	59	84.3	

Data completeness		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
EBV-IgG	Available	507	73.9	109	61.2		173	82.8	228	84.1	145	63.0	70	45.5	
	Missing	179	26.1	69	38.8		36	17.2	43	15.9	85	37.0	84	54.5	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
EBV-IgM	NEG	297	88.7	67	90.5		84	79.2	131	88.5	83	95.4	66	97.1	*
	POS	38	11.3	7	9.5		22	20.8	17	11.5	4	4.6	2	2.9	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgM	Available	335	48.8	74	41.6	106	50.7	148	54.6	87	37.8	68	44.2
	Missing	351	51.2	104	58.4	103	49.3	123	45.4	143	62.2	86	55.8



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

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)	183	45.0	0.8	339	46.7	0.6	164	43.2	0.8	63	45.3	1.2	85	45.9	0.9	30	43.5	1.3
Duration of Diabetes (yrs)	147	28.5	1.0	291	29.6	0.7	134	26.2	0.9	47	32.9	1.6	66	32.6	1.1	25	32.6	1.1
Weight (kg)	155	64.9	0.8	309	67.5	0.6	154	69.0	0.9	48	60.0	1.5	74	63.1	1.2	28	64.9	1.5
Body Mass Index (kg/m2)	150	23.2	0.2	295	23.9	0.2	147	24.1	0.2	46	22.3	0.5	72	22.8	0.3	28	23.0	0.6
Daily insulin requirement (units)	119	33.4	1.1	281	37.5	0.9	152	41.1	1.3	41	38.0	2.1	67	37.3	1.4	26	33.4	2.6
Average daily insulin / kg recipient body weight	112	0.5	0.0	267	0.5	0.0	146	0.6	0.0	38	0.6	0.0	67	0.6	0.0	26	0.5	0.0
Duration of intensive insulin therapy (yrs)	62	16.5	2.0	170	22.3	1.1	87	19.2	1.3	12	28.4	4.1	10	23.5	4.6	2	4.0	3.1
Fasting plasma glucose (mg/dL)	147	158.6	6.8	281	171.2	5.1	142	181.1	7.1	36	174.6	14.5	65	173.5	10.8	24	183.2	25.7
Basal C-Peptide (ng/mL)	147	0.1	0.0	287	0.1	0.0	145	0.1	0.0	48	0.4	0.1	70	0.2	0.1	27	0.1	0.0
HbA1C (%)	122	7.8	0.1	271	7.8	0.1	151	8.0	0.1	45	8.0	0.2	67	8.3	0.2	26	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**	45	57.7	120	62.8	53	50.0	26	86.7	33	70.2	10	58.8
	Positive	33	42.3	71	37.2	53	50.0	4	13.3	14	29.8	7	41.2

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	105	57.4	148	43.7	58	35.4	33	52.4	38	44.7	13	43.3
	Available	78	42.6	191	56.3	106	64.6	30	47.6	47	55.3	17	56.7

Pre transplant autoantibody - GAD 65

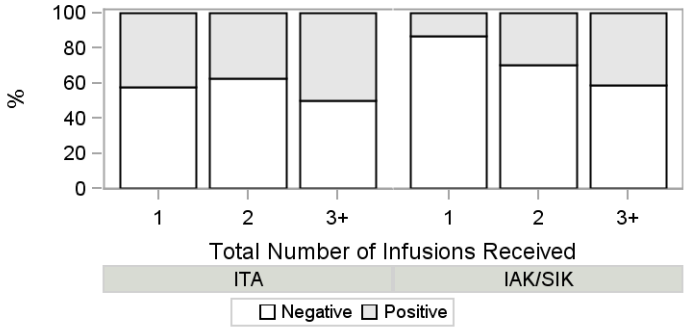


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Exhibit 2 – 8 *(continued)*
Recipient Baseline Autoantibodies by Total Infusions Received

		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	%
Pre transplant autoantibody - IA-2	**Negative**	105	84.0	230	80.1	105	68.2	37	86.0	64	97.0	24	88.9
	Positive	20	16.0	57	19.9	49	31.8	6	14.0	2	3.0	3	11.1

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	58	31.7	52	15.3	10	6.1	20	31.7	19	22.4	3	10.0
	Available	125	68.3	287	84.7	154	93.9	43	68.3	66	77.6	27	90.0

Pre transplant autoantibody - IA-2

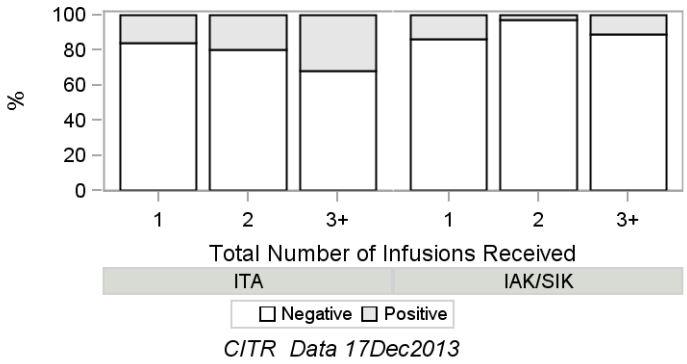

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Exhibit 2 – 8 *(continued)*
Recipient Baseline Autoantibodies by Total Infusions Received

		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	%
Pre transplant autoantibody - Insulin	**Negative**	91	72.8	189	65.9	97	63.0	35	81.4	53	80.3	23	85.2
	Positive	34	27.2	98	34.1	57	37.0	8	18.6	13	19.7	4	14.8

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	58	31.7	52	15.3	10	6.1	20	31.7	19	22.4	3	10.0
	Available	125	68.3	287	84.7	154	93.9	43	68.3	66	77.6	27	90.0

Pre transplant autoantibody - Insulin

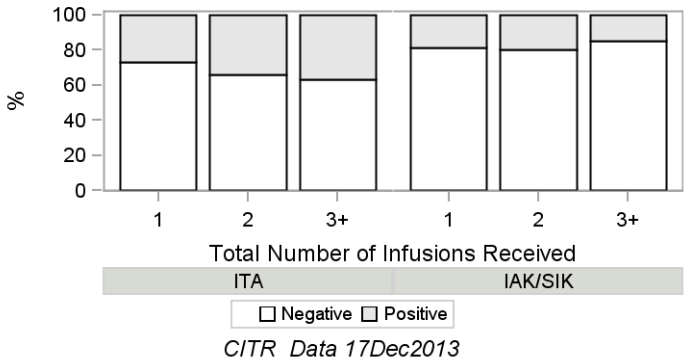

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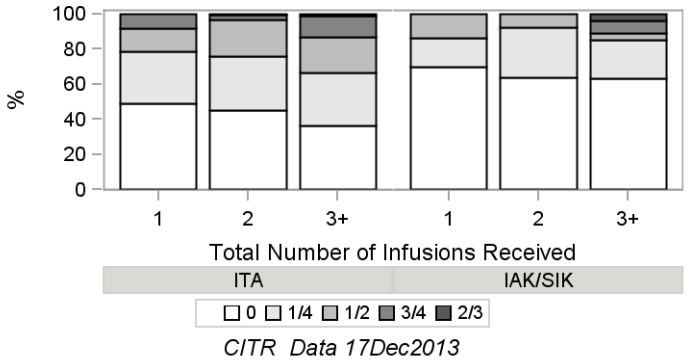
Exhibit 2 – 8 *(continued)*
Recipient Baseline Autoantibodies by Total Infusions Received

		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**	61	48.8	129	44.9	56	36.4	30	69.8	42	63.6	17	63.0
	1/4	37	29.6	88	30.7	46	29.9	7	16.3	19	28.8	6	22.2
	1/2	17	13.6	60	20.9	32	20.8	6	14.0	5	7.6	1	3.7
	2/3	-	-	1	0.3	2	1.3	-	-	-	-	1	3.7
	3/4	10	8.0	9	3.1	18	11.7	-	-	-	-	2	7.4

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	58	31.7	52	15.3	10	6.1	20	31.7	19	22.4	3	10.0
	Available	125	68.3	287	84.7	154	93.9	43	68.3	66	77.6	27	90.0

Total Number of Positive Autoantibodies



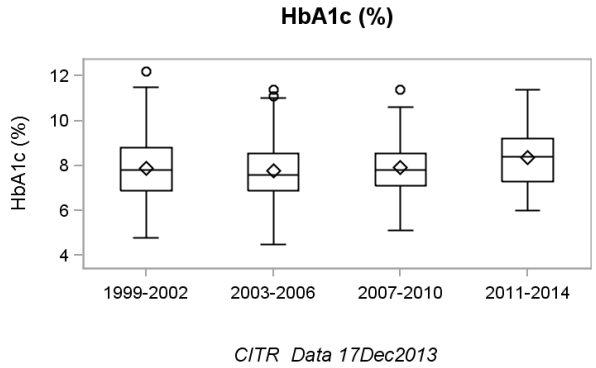
CITR Data 17Dec2013

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 (%)	544	7.9	0.1	138	8.1	0.1		195	7.9	0.1	264	7.8	0.1	152	7.9	0.1	71	8.4	0.1	*
Basal C-Peptide (ng/mL)	579	0.1	0.0	145	0.2	0.1	***	186	0.2	0.0	257	0.1	0.0	180	0.1	0.0	101	0.2	0.1	
Fasting blood glucose (mg/dL)	570	170.4	3.6	125	175.7	8.5		170	182.2	7.2	250	174.6	5.8	173	153.9	5.6	102	174.8	8.0	
ALT (U/L)	547	23.5	0.6	117	24.8	1.3		151	22.0	1.0	244	24.2	0.7	170	24.2	1.1	99	24.5	1.6	
AST (U/L)	560	26.2	0.7	117	25.9	1.3		157	23.4	0.7	250	26.2	0.7	166	28.3	1.9	104	27.0	1.7	*
Alkaline phosphatase (U/L)	491	81.8	2.1	101	127.8	8.8	***	151	92.6	4.7	234	98.9	4.5	147	79.6	3.6	60	71.4	3.9	**
Total bilirubin (mg/dL)	506	0.6	0.0	115	0.6	0.0		152	0.6	0.0	223	0.6	0.0	151	0.7	0.0	95	0.6	0.0	
Total cholesterol (mg/dL)	517	172.7	1.6	116	177.5	4.0		166	181.3	2.8	246	173.8	2.1	149	169.5	3.5	72	163.7	5.6	***
HDL (mg/dL)	495	64.8	0.8	104	64.1	1.9		159	65.3	1.3	237	64.9	1.2	133	65.3	1.7	70	61.6	2.4	
LDL (mg/dL)	485	93.5	1.3	83	92.5	3.6		137	98.5	2.5	233	94.9	1.7	137	88.6	2.7	61	86.4	4.7	***
Triglycerides (mg/dL)	518	52.6	1.4	116	67.5	3.9	***	166	55.8	2.8	246	56.7	2.5	150	51.8	2.2	72	57.0	3.5	
eGFR-CKD (mL/min/1.73m2)	562	91.9	0.9	138	57.8	2.6	***	180	82.1	2.1	254	84.3	1.6	177	88.3	1.9	89	87.7	2.9	*

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

Recipients' fasting blood glucose declined over the decade.



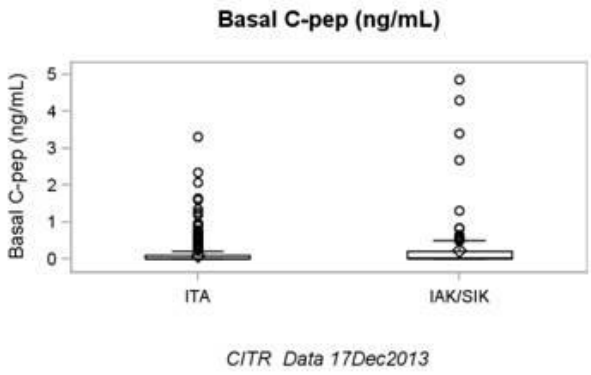
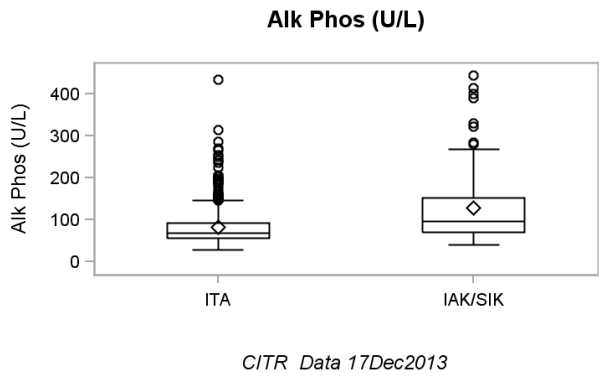


Exhibit 2 – 9 *(continued)*
Recipient Laboratory Values at First Infusion



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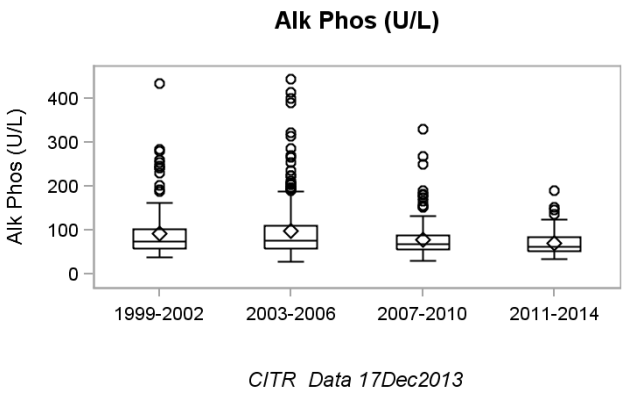

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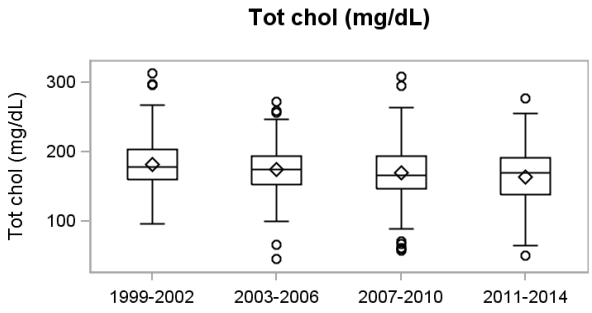

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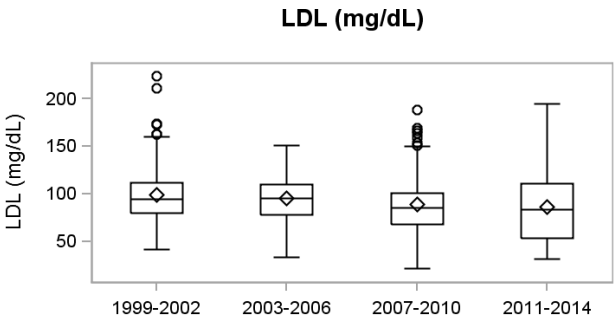
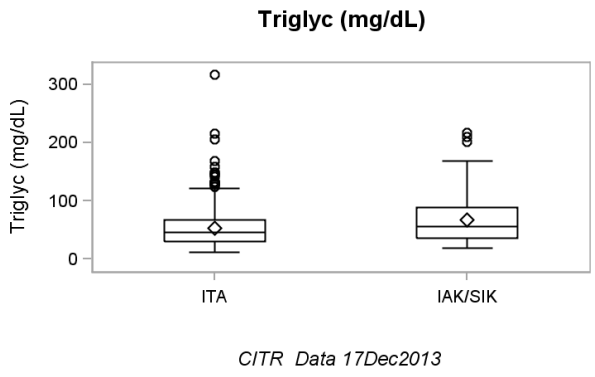
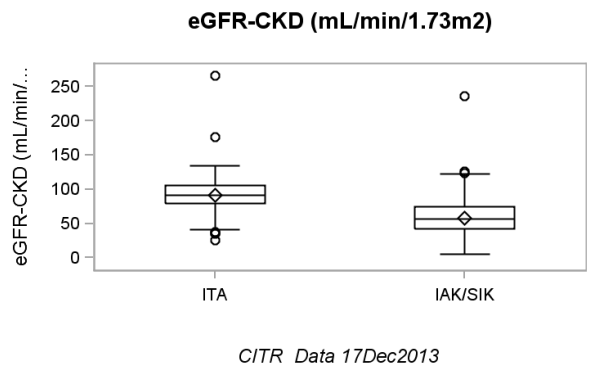


CITR Data 17Dec2013

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





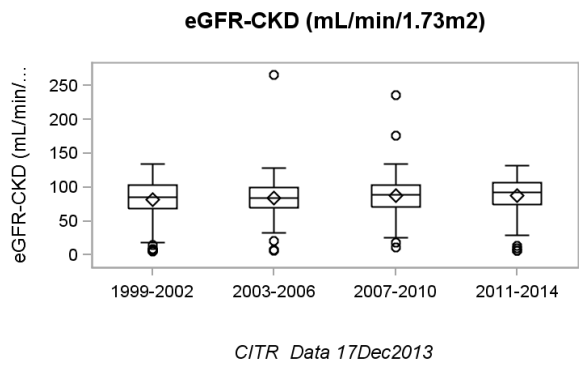


Exhibit 2 – 10
Donor Demographics

	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)	939	43.5	0.4	205	44.0	0.9		292	43.5	0.7	399	43.3	0.6	314	44.5	0.7	139	42.4	1.0	

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Gender	**Female**	432	37.3	102	38.3		135	37.4	189	38.9	138	37.2	72	34.8	
	Mixed	58	5.0	12	4.5		16	4.4	23	4.7	30	8.1	1	0.5	
	Male	669	57.7	152	57.1		210	58.2	274	56.4	203	54.7	134	64.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Gender	Available	1159	85.3	266	82.4	361	84.1	486	85.0	371	89.2	207	78.4
	Missing	199	14.7	57	17.6	68	15.9	86	15.0	45	10.8	57	21.6

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Race	**White**	601	88.5	112	89.6		230	93.1	258	86.9	160	87.9	65	83.3	
	Mixed	6	0.9		0.0		2	0.8	3	1.0	1	0.5		0.0	
	Non-white	72	10.6	13	10.4		15	6.1	36	12.1	21	11.5	13	16.7	

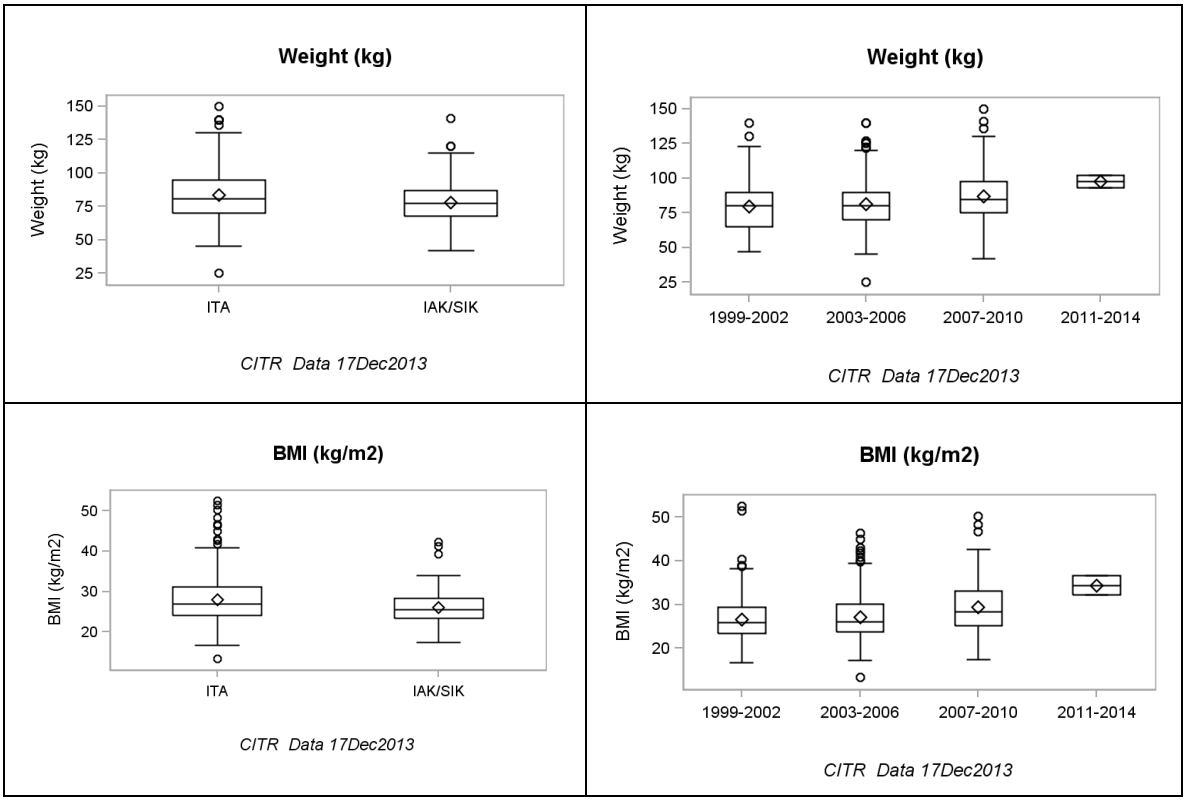
Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Race	Available	679	50.0	125	38.7	247	57.6	297	51.9	182	43.8	78	29.5
	Missing	679	50.0	198	61.3	182	42.4	275	48.1	234	56.3	186	70.5

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Ethnicity	**Non-Hispanic**	583	89.8	117	90.0		213	93.4	243	87.4	169	90.9	75	86.2	
	Mixed	9	1.4	3	2.3		5	2.2	7	2.5		0.0		0.0	
	Hispanic	57	8.8	10	7.7		10	4.4	28	10.1	17	9.1	12	13.8	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Ethnicity	Available	649	47.8	130	40.2	228	53.1	278	48.6	186	44.7	87	33.0
	Missing	709	52.2	193	59.8	201	46.9	294	51.4	230	55.3	177	67.0

Exhibit 2 – 11
Donor Characteristics

	ITA			IAK/SIK			p	1999-2002			2003-2006			2007-2010			2011-2014			p
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Donor age (yrs)	939	43.5	0.4	205	44.0	0.9		292	43.5	0.7	399	43.3	0.6	314	44.5	0.7	139	42.4	1.0	
Weight (kg)	466	83.3	0.8	128	78.2	1.4	***	201	79.8	1.2	247	81.4	1.1	144	86.9	1.5	2	97.6	4.4	***
Height (cm)	1120	173.1	0.3	249	173.3	0.6		353	172.8	0.5	493	173.4	0.4	347	173.3	0.6	176	172.4	1.0	
Body Mass Index(kg/m2)	464	28.0	0.3	128	26.0	0.4	***	199	26.7	0.4	247	27.2	0.3	144	29.5	0.5	2	34.4	2.2	***



		ITA		IAK/SIK		p	1999-2002		2003-2006		2007-2010		2011-2014		p
		N	%	N	%		N	%	N	%	N	%	N	%	
Donor Blood Type	**O**	621	53.1	145	54.1		178	49.2	269	54.6	213	57.3	106	50.5	
	A	505	43.2	117	43.7		178	49.2	213	43.2	149	40.1	82	39.0	
	Other	43	3.7	6	2.2		6	1.7	11	2.2	10	2.7	22	10.5	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Donor Blood Type	Available	1169	86.1	268	83.0	362	84.4	493	86.2	372	89.4	210	79.5
	Missing	189	13.9	55	17.0	67	15.6	79	13.8	44	10.6	54	20.5

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**	1046	99.8	188	100.0		322	100.0	452	99.8	311	100.0	149	99.3	
	Yes	2	0.2		0.0			0.0	1	0.2		0.0	1	0.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Hx Diabetes	Available	1048	77.2	188	58.2	322	75.1	453	79.2	311	74.8	150	56.8
	Missing	310	22.8	135	41.8	107	24.9	119	20.8	105	25.2	114	43.2

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

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

Exhibit 2 – 12
Donor Hospitalization

	ITA			IAK/SIK				2003-2006			1999-2002			2007-2010			2011-2014			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Time from admission to brain death (hrs)	596	53.9	2.7	137	50.0	4.3		311	51.8	3.6	212	48.1	4.1	168	57.1	4.1	42	73.3	15.0	*
Time from cross clamp to pancreas recovery (hrs)	637	0.8	0.0	175	0.9	0.0		366	0.9	0.1	189	0.7	0.0	167	0.9	0.0	90	1.0	0.1	**
Cold ischemia time (hrs)	820	7.5	0.2	174	7.7	0.7		418	7.3	0.2	307	7.3	0.2	206	8.3	0.6	63	7.9	1.2	

		ITA		IAK/SIK		.	2003-2006		1999-2002		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Cause of death	**CVA**	615	57.1	140	68.6	755.0	282	60.1	200	60.2	196	60.3	77	49.7	755.0
	Trauma	327	30.4	47	23.0	374.0	137	29.2	90	27.1	95	29.2	52	33.5	374.0
	Other	135	12.5	17	8.3	152.0	50	10.7	42	12.7	34	10.5	26	16.8	152.0

Data completeness		ITA		IAK/SIK		2003-2006		1999-2002		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Cause of death	Available	1077	79.3	204	63.2	469	82.0	332	77.4	325	78.1	155	58.7
	Missing	281	20.7	119	36.8	103	18.0	97	22.6	91	21.9	109	41.3

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Vasopressors used	**No**	33	3.5	4	2.2		10	3.3	11	2.4	13	5.2	3	2.9	
	Yes	897	96.5	177	97.8		291	96.7	448	97.6	236	94.8	99	97.1	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Vasopressors used	Available	930	68.5	181	56.0	301	70.2	459	80.2	249	59.9	102	38.6
	Missing	428	31.5	142	44.0	128	29.8	113	19.8	167	40.1	162	61.4

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Transfusions during hospitalization	**No**	551	68.5	115	71.4		175	66.5	280	67.3	131	67.2	80	87.9	***
	Yes	253	31.5	46	28.6		88	33.5	136	32.7	64	32.8	11	12.1	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Transfusions during hospitalization	Missing	554	40.8	162	50.2	166	38.7	156	27.3	221	53.1	173	65.5
	Available	804	59.2	161	49.8	263	61.3	416	72.7	195	46.9	91	34.5

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

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

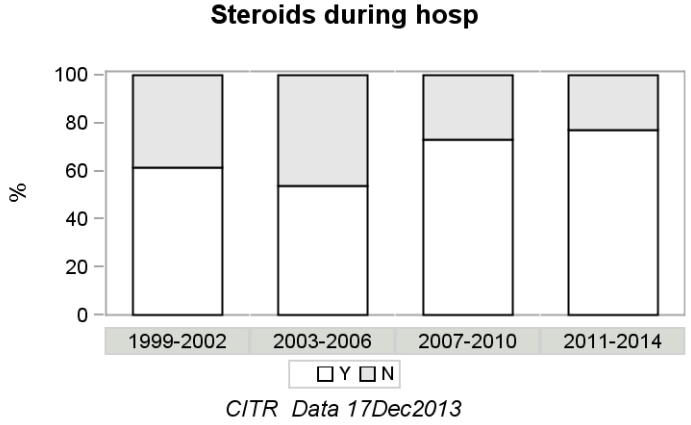
Exhibit 2 – 12 *(continued)*
Donor Hospitalization

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Transfusions intraoperatively	**No**	589	94.1	117	93.6		209	91.7	336	94.6	137	95.8	24	96.0	
	Yes	37	5.9	8	6.4		19	8.3	19	5.4	6	4.2	1	4.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Transfusions intraoperatively	Missing	732	53.9	198	61.3	201	46.9	217	37.9	273	65.6	239	90.5
	Available	626	46.1	125	38.7	228	53.1	355	62.1	143	34.4	25	9.5

		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**	200	37.5	49	47.1		61	38.4	144	46.2	39	27.1	5	22.7	***
	Yes	333	62.5	55	52.9		98	61.6	168	53.8	105	72.9	17	77.3	

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	533	39.2	104	32.2	159	37.1	312	54.5	144	34.6	22	8.3
	Missing	825	60.8	219	67.8	270	62.9	260	45.5	272	65.4	242	91.7



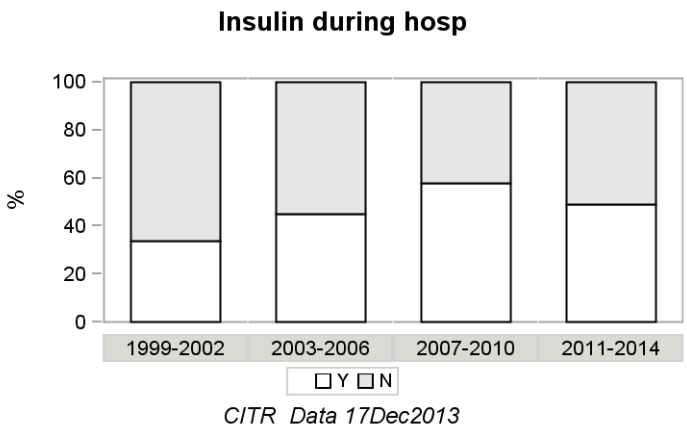
* = p <.05; ** = p <.01; *** = p <.001

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

Exhibit 2 – 12 *(continued)*
Donor Hospitalization

		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**	485	52.5	87	63.5	*	167	66.3	225	55.0	116	42.2	64	51.2	***
	Yes	439	47.5	50	36.5		85	33.7	184	45.0	159	57.8	61	48.8	

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	924	68.0	137	42.4	252	58.7	409	71.5	275	66.1	125	47.3
	Missing	434	32.0	186	57.6	177	41.3	163	28.5	141	33.9	139	52.7



* = 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	1058	100.0	203	100.0		330	100.0	465	100.0	320	100.0	146	100.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
HIV	Missing	300	22.1	120	37.2	99	23.1	107	18.7	96	23.1	118	44.7
	Available	1058	77.9	203	62.8	330	76.9	465	81.3	320	76.9	146	55.3

		ITA		IAK/SIK		.	1999-2002		2003-2006		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HTLV	NEG	902	99.9	173	100.0		277	100.0	417	100.0	270	99.6	111	100.0	
	POS	1	0.1	-	0.0		-	0.0	-	0.0	1	0.4	-	0.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
HTLV	Missing	455	33.5	150	46.4	152	35.4	155	27.1	145	34.9	153	58.0
	Available	903	66.5	173	53.6	277	64.6	417	72.9	271	65.1	111	42.0

		ITA		IAK/SIK		.	1999-2002		2003-2006		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
VDRL	NEG	915	99.9	165	100.0		288	100.0	421	99.8	267	100.0	104	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	442	32.5	158	48.9	141	32.9	150	26.2	149	35.8	160	60.6
	Available	916	67.5	165	51.1	288	67.1	422	73.8	267	64.2	104	39.4

		ITA		IAK/SIK		.	1999-2002		2003-2006		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
CMV	NEG	436	43.3	91	45.7		124	39.5	204	46.2	138	44.5	61	43.3	
	POS	572	56.7	108	54.3		190	60.5	238	53.8	172	55.5	80	56.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
CMV	Missing	350	25.8	124	38.4	115	26.8	130	22.7	106	25.5	123	46.6
	Available	1008	74.2	199	61.6	314	73.2	442	77.3	310	74.5	141	53.4

Exhibit 2 – 13 *(continued)*
Donor Serology

		ITA		IAK/SIK		.	1999-2002		2003-2006		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HBSag	NEG	1042	99.9	197	100.0		325	100.0	464	100.0	310	100.0	140	99.3	
	POS	1	0.1	-	0.0		-	0.0	-	0.0	-	0.0	1	0.7	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
HBSag	Missing	315	23.2	126	39.0	104	24.2	108	18.9	106	25.5	123	46.6
	Available	1043	76.8	197	61.0	325	75.8	464	81.1	310	74.5	141	53.4

		ITA		IAK/SIK		.	1999-2002		2003-2006		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HBC	NEG	992	99.1	182	98.9		298	98.7	458	99.6	289	98.3	129	100.0	
	POS	9	0.9	2	1.1		4	1.3	2	0.4	5	1.7	-	0.0	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
HBC	Missing	357	26.3	139	43.0	127	29.6	112	19.6	122	29.3	135	51.1
	Available	1001	73.7	184	57.0	302	70.4	460	80.4	294	70.7	129	48.9

		ITA		IAK/SIK		.	1999-2002		2003-2006		2007-2010		2011-2014		.
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
HCV	NEG	991	100.0	171	99.4		319	100.0	454	100.0	288	99.7	101	100.0	
	POS	-	0.0	1	0.6		-	0.0	-	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	367	27.0	151	46.7	110	25.6	118	20.6	127	30.5	163	61.7
	Available	991	73.0	172	53.3	319	74.4	454	79.4	289	69.5	101	38.3

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)	910	1.1	0.0	191	1.0	0.0	*	247	1.1	0.0	434	1.1	0.0	286	1.0	0.0	134	1.0	0.1	**
BUN (mg/dL)	633	15.3	0.4	185	14.9	0.6		191	15.0	0.6	333	15.1	0.5	194	16.0	0.7	100	14.5	1.1	
Total bilirubin (mg/dL)	791	0.9	0.0	178	0.8	0.0		203	0.9	0.0	362	0.9	0.0	277	0.8	0.0	127	0.8	0.1	
AST (U/L)	803	81.2	7.2	186	79.5	13.7		212	101.9	20.6	370	65.0	5.7	283	88.9	12.4	124	73.8	15.7	
ALT (U/L)	824	66.6	5.8	187	64.2	10.7		213	82.7	17.5	375	52.3	4.5	294	71.9	9.3	129	66.2	11.7	
Serum lipase (mKat/L)	709	1.1	0.1	143	1.1	0.2		231	0.9	0.1	355	1.2	0.1	180	1.1	0.1	86	1.1	0.2	
Serum amylase (mKat/L)	766	3.2	0.3	182	2.4	0.4		247	2.8	0.4	424	2.7	0.3	192	3.4	0.7	85	4.5	1.3	
Minimum pre-insulin blood glucose (mg/dL)	757	126.0	1.3	161	127.3	3.0		270	128.7	2.3	394	124.9	1.9	163	123.9	3.0	91	129.4	3.7	
Maximum blood glucose (mg/dL)	842	224.1	2.8	166	235.1	6.6		237	244.4	6.4	418	226.9	3.9	230	217.7	4.5	123	202.4	6.4	***

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

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

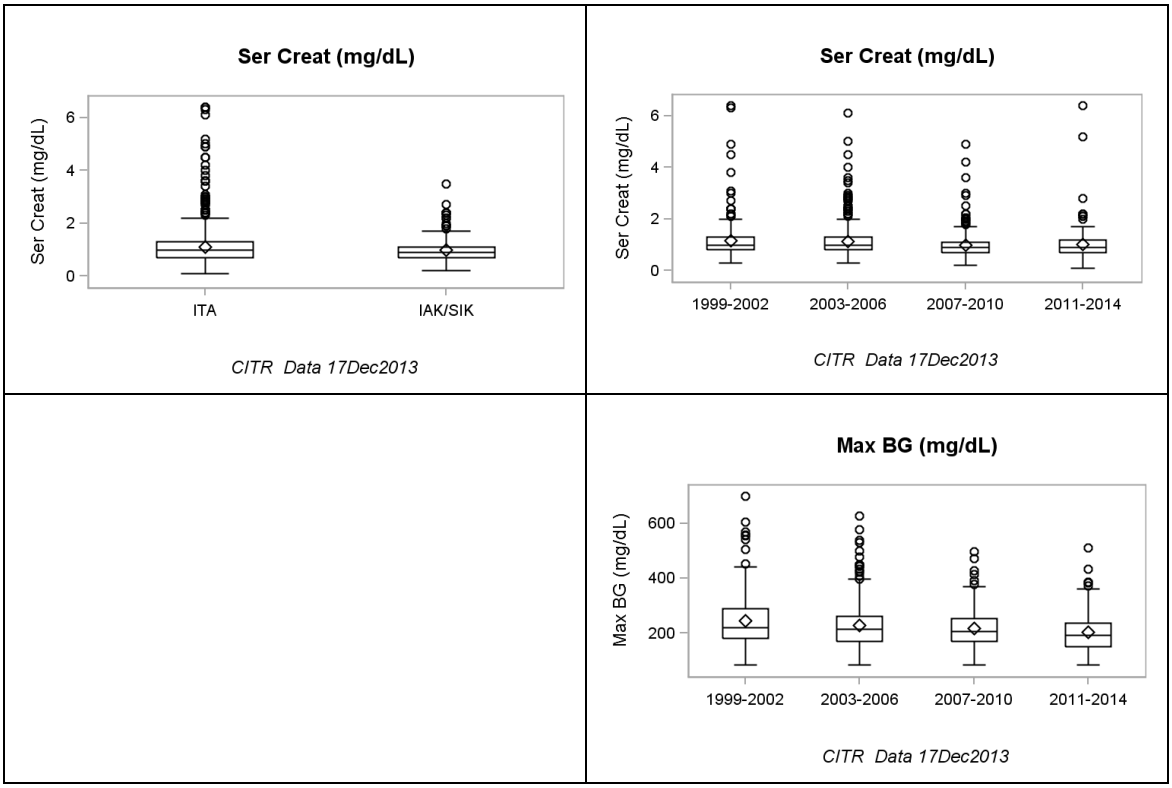


Exhibit 2 – 15
Organ Crossmatch Results

		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%	p	N	%	N	%	N	%	N	%	p
Positive cross match	**No**	621	97.0	176	97.8		184	99.5	313	96.0	226	97.0	74	97.4	
	Yes	19	3.0	4	2.2		1	0.5	13	4.0	7	3.0	2	2.6	

Data completeness		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Positive cross match	**Available**	640	47.1	180	55.7	185	43.1	326	57.0	233	56.0	76	28.8
	Missing	718	52.9	143	44.3	244	56.9	246	43.0	183	44.0	188	71.2

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, on the islet products used for clinical transplantation in the recipients in this report, namely those described in Chapter 1.

For the roughly 10% 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

Per Infusion		Transplant type				p	Era								p
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Procurement team	Missing/Unknown	466	34.3	98	30.3		80	23.2	105	17.9	155	35.1	224	72.5	
	Unrelated	276	20.3	48	14.9		82	23.8	160	27.4	69	15.6	13	4.2	
	Mixed	26	1.9	4	1.2	**	8	2.3	14	2.4	8	1.8	-	0.0	**
	Procurement/transplant centers related	590	43.4	173	53.6		175	50.7	306	52.3	210	47.5	72	23.3	
Islet processing center	Missing/Unknown	411	30.3	83	25.7		67	19.4	72	12.3	135	30.5	220	71.2	
	Unrelated	73	5.4	7	2.2	**	-	0.0	9	1.5	55	12.4	16	5.2	***
	Processing/transplant centers related	874	64.4	233	72.1		278	80.6	504	86.2	252	57.0	73	23.6	
Pancreas preservation	Missing/Unknown	20	1.5	12	3.7		20	5.8	7	1.2	5	1.1	-	0.0	
	UW only	408	30.0	107	33.1		166	48.1	233	39.8	83	18.8	33	10.7	
	2L only	198	14.6	24	7.4		41	11.9	149	25.5	28	6.3	4	1.3	
	HTK only	155	11.4	1	0.3	***	-	0.0	33	5.6	69	15.6	54	17.5	***
	Celsior	20	1.5	12	3.7		5	1.4	9	1.5	10	2.3	8	2.6	
	UW+2L	32	2.4	10	3.1		10	2.9	25	4.3	7	1.6	-	0.0	
	Other	525	38.7	157	48.6		103	29.9	129	22.1	240	54.3	210	68.0	
Cultured	Missing/Unknown	502	37.0	171	52.9		108	31.3	164	28.0	219	49.5	182	58.9	
	None	288	21.2	51	15.8		154	44.6	158	27.0	25	5.7	2	0.6	***
	Islets cultured >=6 hrs	568	41.8	101	31.3		83	24.1	263	45.0	198	44.8	125	40.5	
Gradient type	Missing/Unknown	427	31.4	124	38.4		113	32.8	116	19.8	160	36.2	162	52.4	
	None	1	0.1	-	0.0		-	0.0	1	0.2	-	0.0	-	0.0	
	Mixed	14	1.0	4	1.2		3	0.9	11	1.9	4	0.9	-	0.0	
	Discontinuous	33	2.4	21	6.5		24	7.0	28	4.8	1	0.2	1	0.3	
	Continuous	818	60.2	169	52.3		181	52.5	390	66.7	270	61.1	146	47.2	
	Both	65	4.8	5	1.5		24	7.0	39	6.7	7	1.6	-	0.0	
Pulmozyme	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	445	32.8	122	37.8	***	212	61.4	208	35.6	105	23.8	42	13.6	***
	Yes	511	37.6	75	23.2		48	13.9	273	46.7	171	38.7	94	30.4	

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

Per Infusion		Transplant type				p	Era								p
		ITA		IAK/SIK			1999-2002		2003-2006		2007-2010		2011-2014		
		N	%	N	%		N	%	N	%	N	%	N	%	
Collagenase P	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	933	68.7	196	60.7		258	74.8	463	79.1	272	61.5	136	44.0	**
	Yes	23	1.7	1	0.3		2	0.6	18	3.1	4	0.9	-	0.0	
Thermolysin	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	873	64.3	189	58.5	*	260	75.4	424	72.5	265	60.0	113	36.6	***
	Yes	83	6.1	8	2.5		-	0.0	57	9.7	11	2.5	23	7.4	
Serva	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	732	53.9	148	45.8		260	75.4	462	79.0	83	18.8	75	24.3	
	Yes	224	16.5	49	15.2		-	0.0	19	3.2	193	43.7	61	19.7	
Liberase HI	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	392	28.9	69	21.4		3	0.9	101	17.3	254	57.5	103	33.3	***
	Yes	564	41.5	128	39.6		257	74.5	380	65.0	22	5.0	33	10.7	
Sigmablend	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	947	69.7	197	61.0		260	75.4	481	82.2	267	60.4	136	44.0	***
	Yes	9	0.7	-	0.0		-	0.0	-	0.0	9	2.0	-	0.0	
Collagenase Other	Missing/Unknown	402	29.6	126	39.0		85	24.6	104	17.8	166	37.6	173	56.0	
	No	821	60.5	180	55.7	*	259	75.1	401	68.5	216	48.9	125	40.5	***
	Yes	135	9.9	17	5.3		1	0.3	80	13.7	60	13.6	11	3.6	

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

UW and 2-layer solutions use have declined appreciably over the eras.

Islet preparations were cultured more frequently in the recent eras.

Pulmozyme use increased substantially in the recent eras.

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

	Thermolysin	Pulmozyme
Collagenase P	1	9
Serva	-	149
Liberase HI	7	309
Sigmablend	-	2
Other	68	100

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

Final islet preparations for infusion		Transplant type				Era							
		ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Gram stain	**Missing/Unknown**	516	38.0	173	53.6	136	39.4	187	32.0	207	46.8	159	51.5
	Negative	839	61.8	150	46.4	209	60.6	398	68.0	235	53.2	147	47.6
	Positive	3	0.2	-	0.0	-	0.0	-	0.0	-	0.0	3	1.0
Aerobic culture	**Missing/Unknown**	419	30.9	135	41.8	111	32.2	130	22.2	153	34.6	160	51.8
	Negative	925	68.1	185	57.3	227	65.8	452	77.3	283	64.0	148	47.9
	Positive	14	1.0	3	0.9	7	2.0	3	0.5	6	1.4	1	0.3
Anaerobic culture	**Missing/Unknown**	543	40.0	162	50.2	165	47.8	217	37.1	163	36.9	160	51.8
	Negative	808	59.5	161	49.8	176	51.0	367	62.7	279	63.1	147	47.6
	Positive	7	0.5	-	0.0	4	1.2	1	0.2	-	0.0	2	0.6
Fungal Culture	**Missing/Unknown**	445	32.8	134	41.5	118	34.2	124	21.2	173	39.1	164	53.1
	Negative	905	66.6	187	57.9	227	65.8	457	78.1	268	60.6	140	45.3
	Positive	8	0.6	2	0.6	-	0.0	4	0.7	1	0.2	5	1.6
Mycoplasma	**Missing/Unknown**	778	57.3	274	84.8	174	50.4	335	57.3	319	72.2	224	72.5
	Negative	579	42.6	49	15.2	170	49.3	250	42.7	123	27.8	85	27.5
	Positive	1	0.1	-	0.0	1	0.3	-	0.0	-	0.0	-	0.0

Exhibit 3 – 1D
Pancreas Preservation Method by Era

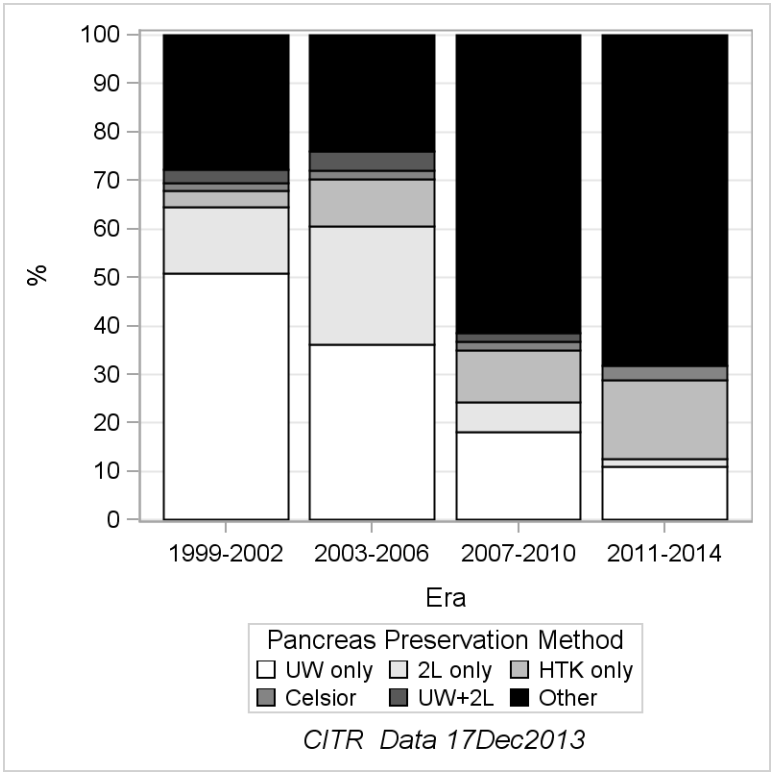


Exhibit 3 – 2
Cold Ischemia Information

	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)	637	0.8	1.2	175	0.9	0.4		147	0.6	0.4	363	0.9	1.3	189	0.9	0.6	113	1.0	1.0	*
Duration of cold ischemia (hrs)	820	7.5	4.6	174	7.7	8.8		238	7.2	3.4	432	7.2	3.2	246	8.4	8.6	78	7.7	8.5	**
Time from brain death to pancreas recovery (hrs)	581	19.9	8.7	163	16.6	8.4	**	138	16.6	7.0	327	18.9	8.8	172	21.0	9.5	107	20.6	8.6	***
Culture time (hrs)	856	19.0	17.9	152	18.8	18.2		237	10.9	17.4	421	17.6	17.8	223	26.5	17.6	127	25.3	10.7	***

* = 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 more than 15 hours, including an increasing proportion of preparations being cultured at all.

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	904	3.8	0.1	173	3.9	0.2		236	4.0	0.1	436	3.9	0.1	255	3.8	0.2	150	3.2	0.1	***
Total islet particles (final preparation)	783	393.9	5.9	188	411.8	13.9		216	409.4	12.1	394	415.2	8.7	226	363.6	10.0	135	382.8	14.1	**
Embedded islets (%)	651	16.6	0.7	82	15.3	1.6		139	13.9	1.5	284	16.6	1.2	188	16.6	1.2	122	19.0	1.4	
Islet equivalents (1000s)	870	422.1	5.0	182	380.0	12.3	**	230	412.4	10.2	402	412.7	7.9	251	422.7	9.1	169	411.4	11.4	
Islet equivalents(1000s)/kg recipient	1022	6.5	0.1	236	6.5	0.2		264	6.5	0.1	481	6.5	0.1	334	6.5	0.1	179	6.5	0.2	
Beta cells (x10^6)	326	225.5	10.5	23	321.2	39.8	*	93	190.5	18.0	140	240.0	16.1	60	293.7	28.2	56	213.4	22.2	
Beta cells/kg recipient weight	261	3.4	0.2	21	5.5	0.7	**	87	2.9	0.3	128	3.8	0.3	46	3.9	0.4	21	3.9	0.5	*
Insulin content (1000s micrograms)	268	3.5	0.1	30	3.0	0.4		106	3.4	0.2	170	3.6	0.2	17	2.2	0.3	5	2.9	0.9	
Total Endotoxin units	700	20.9	2.0	144	18.4	3.2		163	27.2	4.6	399	26.9	3.0	212	7.4	1.6	70	7.3	2.7	***
Endotoxin units/kg recipient weight	657	0.3	0.0	135	0.3	0.1		155	0.4	0.1	381	0.4	0.0	194	0.1	0.0	62	0.1	0.0	***
Islet potency: Stimulation index	782	3.1	0.1	146	2.6	0.2		216	3.7	0.3	386	3.1	0.2	202	2.5	0.1	124	2.7	0.2	***
Islet viability	821	89.7	0.2	181	91.4	0.4	**	170	91.0	0.5	446	91.3	0.3	244	89.2	0.4	142	86.3	0.6	***
Purity	744	62.4	0.6	193	59.1	1.5	*	191	58.8	1.4	460	61.8	0.9	215	63.4	1.1	71	63.2	2.1	*
Total DNA	395	9.9	0.5	32	9.0	1.7		99	6.1	0.7	184	10.1	0.9	80	12.0	1.1	64	12.2	1.3	***

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

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

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	437	4.0	0.1	330	3.7	0.1	137	3.3	0.1	***
Total islet particles (final preparation)	376	402.1	8.8	292	394.4	9.4	115	366.3	13.4	*
Embedded islets (%)	313	16.2	1.0	241	17.0	1.2	97	17.1	1.9	
Islet equivalents (1000s)	429	431.6	7.4	319	414.0	8.3	122	410.3	12.0	
Islet equivalents(1000s)/kg recipient	517	6.8	0.1	371	6.3	0.1	134	6.1	0.2	**
Beta cells (x10^6)	159	228.2	16.4	121	219.2	16.0	46	232.3	23.2	
Beta cells/kg recipient weight	120	3.5	0.3	101	3.3	0.3	40	3.3	0.4	**
Insulin content (1000s micrograms)	137	3.6	0.2	103	3.2	0.2	28	3.9	0.4	
Total Endotoxin units	341	18.6	2.2	252	23.5	4.0	107	21.7	6.2	**
Endotoxin units/kg recipient weight	320	0.3	0.0	237	0.4	0.1	100	0.3	0.1	**
Islet potency: Stimulation index	389	3.2	0.1	283	3.3	0.2	110	2.6	0.3	**
Islet viability	404	89.9	0.3	294	89.9	0.4	123	88.5	0.8	***
Purity	364	62.5	0.9	272	61.8	1.1	108	63.4	1.7	
Total DNA	188	10.5	0.9	148	9.1	0.7	59	10.3	1.3	**

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

Total cell volume 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	84	4.1	0.3	67	3.6	0.3	22	4.4	0.4	**
Total islet particles (final preparation)	90	438.8	22.7	69	391.0	19.0	29	377.6	31.2	
Embedded islets (%)	40	13.7	1.9	31	13.0	2.1	11	27.8	6.5	
Islet equivalents (1000s)	85	404.9	22.2	66	360.3	14.7	31	353.8	22.7	
Islet equivalents(1000s)/kg recipient	122	7.0	0.3	87	6.0	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	71	16.3	3.7	53	20.9	6.1	20	19.3	9.7	**
Endotoxin units/kg recipient weight	66	0.3	0.1	50	0.3	0.1	19	0.3	0.2	**
Islet potency: Stimulation index	71	2.8	0.3	54	2.4	0.3	21	2.6	0.5	**
Islet viability	84	91.6	0.6	69	91.5	0.7	28	90.6	1.2	
Purity	95	58.9	2.1	72	60.8	2.2	26	55.0	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	432	4.0	0.1	211	3.7	0.1	133	3.5	0.1	26	3.3	0.3	36	4.2	0.3	214	3.6	0.1	*
Total islet particles (final preparation)	25	469.3	46.9	415	404.3	8.0	179	365.8	12.1	136	416.7	11.6	32	350.1	28.8	38	447.4	32.5	146	383.6	16.1	
Embedded islets (%)	10	26.4	10.0	302	16.2	1.0	122	18.1	1.9	144	16.9	1.5	29	13.2	2.5	23	18.1	3.3	103	14.5	1.3	
Islet equivalents (1000s)	31	400.8	33.9	437	420.6	7.5	173	414.4	12.3	150	438.9	9.9	32	350.2	19.4	33	477.0	31.5	196	386.2	10.3	*
Islet equivalents(1000s)/kg recipient	28	6.9	0.7	460	6.6	0.1	210	6.4	0.2	113	6.3	0.2	27	5.6	0.3	37	7.4	0.4	383	6.4	0.1	
Beta cells (x10^6)	0	-	-	158	195.0	14.5	75	257.7	22.1	93	269.5	20.9	0	-	-	7	241.1	58.6	16	249.9	41.2	*
Beta cells/kg recipient weight	0	-	-	137	3.1	0.3	69	4.1	0.4	59	3.8	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	23	2.8	0.4	
Total Endotoxin units	16	5.0	3.2	381	23.8	2.9	181	29.3	3.9	97	4.4	2.1	17	0.4	0.1	32	45.4	16.6	120	7.8	2.2	**
Endotoxin units/kg recipient weight	13	0.1	0.0	369	0.4	0.0	174	0.5	0.1	87	0.1	0.0	14	0.0	0.0	29	0.6	0.2	106	0.1	0.0	**
Islet potency: Stimulation index	11	4.4	1.2	431	3.3	0.2	188	3.1	0.2	144	2.7	0.2	16	1.6	0.2	31	3.0	0.6	107	2.5	0.3	**
Islet viability	19	91.5	1.1	419	90.6	0.3	212	92.3	0.4	153	85.2	0.6	23	89.3	0.9	37	91.2	0.9	139	89.6	0.5	**
Purity	28	49.2	3.8	400	63.4	0.9	213	61.7	1.2	99	62.7	1.5	29	55.3	3.7	39	64.1	2.9	129	59.0	1.6	*
Total DNA	0	-	-	203	7.6	0.7	86	11.8	1.4	97	13.1	0.9	1	12.3	-	13	7.5	1.6	27	9.9	2.0	*

* = 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 highest total beta cells and total DNA.

Exhibit 3 – 6
Relationship between (Categorical) Islet 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

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)	-0.09549 0.0057 838	0.04524 0.2159 750	-0.15316 0.0002 574	-0.09913 0.0047 813	-0.10877 0.0005 1011	-0.06205 0.3236 255	-0.10563 0.1078 233	0.05372 0.3811 268	-0.01778 0.6278 746	-0.02608 0.4877 710	-0.13636 0.0002 766
caweight_mean Donor Weight (kg)	-0.00715 0.8732 500	-0.00922 0.8335 522	-0.00789 0.8748 401	0.21801 <.0001 532	0.15668 0.0003 542	0.04069 0.5383 231	-0.03557 0.6152 202	0.06312 0.3639 209	0.06229 0.2365 363	0.04560 0.4076 332	0.01359 0.7828 414
caheight_mean Donor height	0.04755 0.1293 1019	0.11160 0.0006 947	0.00696 0.8532 710	0.14993 <.0001 1019	0.15414 <.0001 1176	-0.08705 0.1091 340	-0.10486 0.0837 273	0.11275 0.0555 289	-0.04405 0.2090 815	-0.04050 0.2635 764	0.02500 0.4543 898
donbmi_mean Donor Body Mass Index (kg/m2)	-0.06276 0.1620 498	-0.07714 0.0788 520	-0.04689 0.3502 399	0.16347 0.0002 530	0.11138 0.0096 540	0.07950 0.2298 230	0.00129 0.9856 201	-0.00063 0.9928 208	0.07198 0.1712 363	0.05403 0.3263 332	0.01713 0.7285 413
preinsbg_mean Pre-ins donor glucose	-0.03681 0.3160 744	0.01481 0.6969 694	0.09176 0.0387 508	-0.04372 0.2447 710	-0.04499 0.1937 836	-0.11412 0.0700 253	-0.08753 0.2000 216	0.04478 0.4721 260	0.00794 0.8396 652	0.00607 0.8803 619	0.02735 0.4641 719
maxinsbg_mean Max donor glucose	0.01616 0.6471 805	-0.01742 0.6304 765	-0.01988 0.6381 562	0.07046 0.0487 783	0.09595 0.0041 895	0.06712 0.2709 271	0.09772 0.1486 220	-0.04659 0.4908 221	0.13669 0.0003 705	0.13359 0.0006 663	0.03922 0.2780 767
sercreat_mean Donor creatinine	0.08573 0.0125 848	0.00622 0.8606 800	-0.00550 0.8933 598	0.19062 <.0001 840	0.13740 <.0001 937	-0.03182 0.6082 262	-0.04075 0.5667 200	0.00231 0.9742 198	0.02587 0.4819 741	0.01205 0.7519 691	0.07076 0.0476 784
bun_mean Donor BUN	0.09828 0.0142 622	0.03037 0.4661 578	-0.04132 0.4287 369	0.13193 0.0012 600	0.12656 0.0007 718	-0.04260 0.6096 146	-0.07551 0.4484 103	0.01906 0.8250 137	-0.02388 0.5633 588	-0.03260 0.4488 542	0.09066 0.0248 613
totbili_mean Donor bilirubin	0.06132 0.0978 730	0.00915 0.8121 678	-0.04668 0.3059 483	0.11315 0.0025 711	0.10852 0.0019 813	0.07955 0.2690 195	0.15551 0.0675 139	0.09389 0.2751 137	0.02933 0.4543 653	0.02500 0.5395 605	0.07436 0.0514 687
ast_mean Donor AST	0.05047 0.1691 744	-0.02556 0.4998 699	0.05949 0.1882 491	0.02843 0.4430 730	-0.00456 0.8956 832	-0.06293 0.3797 197	-0.08481 0.3156 142	0.09476 0.2503 149	-0.00847 0.8264 674	-0.00491 0.9024 626	0.00845 0.8221 710

The only significant association between donor characteristics and islet product criteria was that higher donor weight or BMI predicts higher IEQ yield.

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

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations	pckclvol	TOTPARTICLES	TOTTRAP	totieq	ieqinfkg	totalbeta	totbetakg	totalinsulin	totalendo	TOTENDOKG	isstimin_mean
alt_mean Donor ALT	0.09305 0.0105 755	0.02688 0.4745 710	0.04272 0.3390 503	0.12645 0.0005 745	0.11597 0.0007 852	-0.05771 0.4134 203	-0.08637 0.2983 147	0.05222 0.5201 154	0.00742 0.8458 689	0.00886 0.8231 640	0.06248 0.0934 722
serlip_mean Donor lipase	0.03549 0.3460 707	0.01679 0.6684 653	-0.01666 0.7125 492	0.06478 0.0895 688	0.06380 0.0887 713	-0.10317 0.1087 243	-0.08315 0.2490 194	0.02804 0.6942 199	-0.05422 0.1664 653	-0.05444 0.1786 612	0.03413 0.3668 701
seramy_mean Donor serum amylase	0.04918 0.1681 787	0.01786 0.6268 744	0.02037 0.6334 551	0.00188 0.9583 776	-0.00456 0.8976 800	-0.07855 0.2215 244	-0.11804 0.1076 187	0.08187 0.2503 199	-0.04101 0.2841 684	-0.04266 0.2816 639	0.05708 0.1228 732
clptorec_mean Time from cross clamp to pancreas recovery (hrs)	-0.02242 0.5554 694	0.02066 0.5939 668	-0.05193 0.2527 487	-0.11262 0.0028 702	-0.07929 0.0352 706	-0.07467 0.2563 233	-0.00544 0.9416 184	-0.01863 0.7925 202	-0.24648 <.0001 611	-0.26091 <.0001 566	0.00695 0.8598 648
dthtorec_mean Time from brain death to pancreas recovery (hrs)	0.00681 0.8642 633	-0.02084 0.6080 608	0.03428 0.4747 437	0.16251 <.0001 641	0.09569 0.0151 644	0.11790 0.0824 218	0.07220 0.3438 174	0.00341 0.9625 193	0.10307 0.0129 582	0.09794 0.0230 539	0.14194 0.0004 613
coldstor_mean Cold ischemic time (hrs)	-0.08612 0.0119 852	0.09447 0.0072 808	-0.10044 0.0152 584	0.04180 0.2290 830	0.00978 0.7739 865	-0.01471 0.8051 284	-0.02474 0.6937 256	0.04269 0.4667 293	0.00668 0.8522 779	0.00137 0.9704 732	-0.03258 0.3569 802
cultime_mean Culture time (hrs)	-0.15747 <.0001 894	-0.00355 0.9176 851	0.05911 0.1278 665	0.04514 0.1765 898	-0.01267 0.7063 887	0.21821 <.0001 341	0.23805 <.0001 274	-0.01050 0.8585 291	0.02423 0.5056 757	0.03472 0.3566 707	-0.02719 0.4334 832

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)	567	446.0	6.5	402	423.6	7.8	144	412.1	11.9	138	438.2	13.7	95	389.4	14.9	29	354.1	28.4
Islet equivalents infused(1000s)/donor kg	517	6.8	0.1	371	6.3	0.1	134	6.1	0.2	122	7.0	0.3	87	6.0	0.2	27	5.3	0.4
Embedded islets (%)	313	16.2	1.0	241	17.0	1.2	97	17.1	1.9	40	13.7	1.9	31	13.0	2.1	11	27.8	6.5
Cell volume (mL)	437	4.0	0.1	330	3.7	0.1	137	3.3	0.1	84	4.1	0.3	67	3.6	0.3	22	4.4	0.4
Time since first infusion (weeks)	501	27.5	1.8	489	27.0	1.8	181	15.3	1.3	115	29.0	4.8	111	28.8	5.0	34	31.8	12.1
Time since second infusion (weeks)	164	74.7	8.3	162	75.5	8.4	181	83.4	8.6	30	47.5	12.8	30	47.5	12.8	34	58.0	13.7
Time since third infusion (weeks)	20	94.9	36.9	20	94.9	36.9	43	80.7	20.8	4	10.0	3.5	4	10.0	3.5	8	10.0	2.3

Chapter 4
Immunosuppression and Other Medications

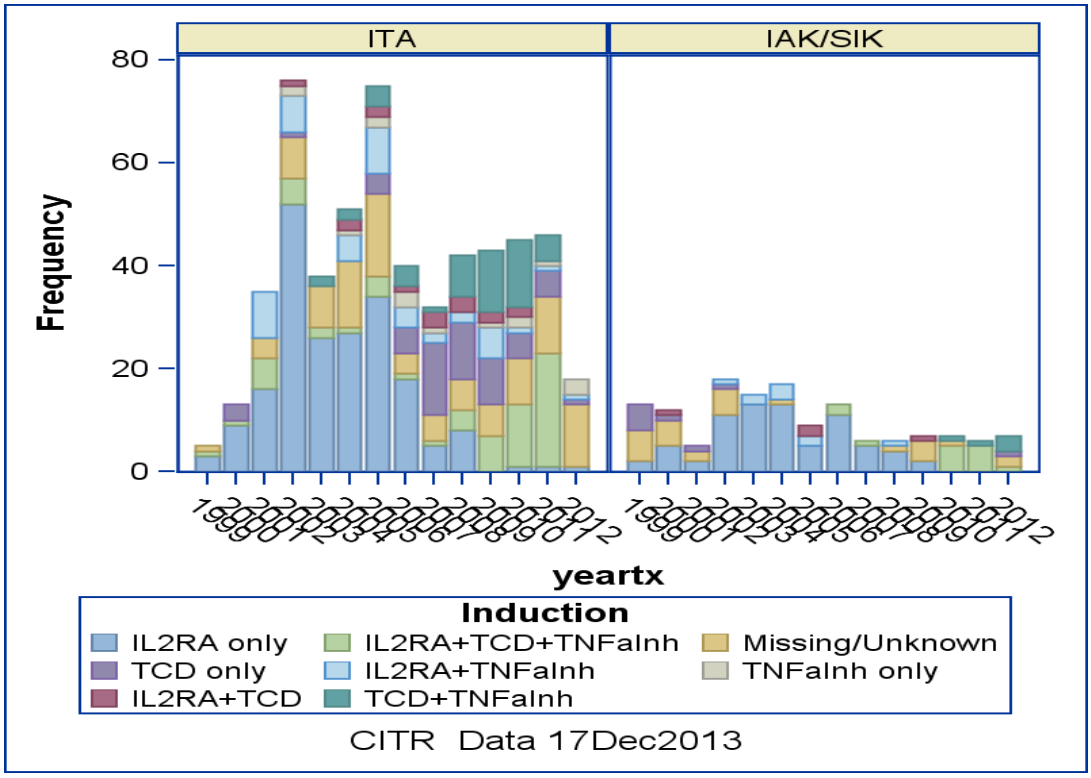
Introduction

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

Super category	Category	Agent
Tcell depleting agent	Monoclonal TCD	Alemtuzumab (Campath)
	Monoclonal antiCD3	Teplizumab (hOKT3y-1-ala-ala)
	Polyclonal TCD	Antithymocyte
		Antilymphocyte globulin
Tcell 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
Bcell 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 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).

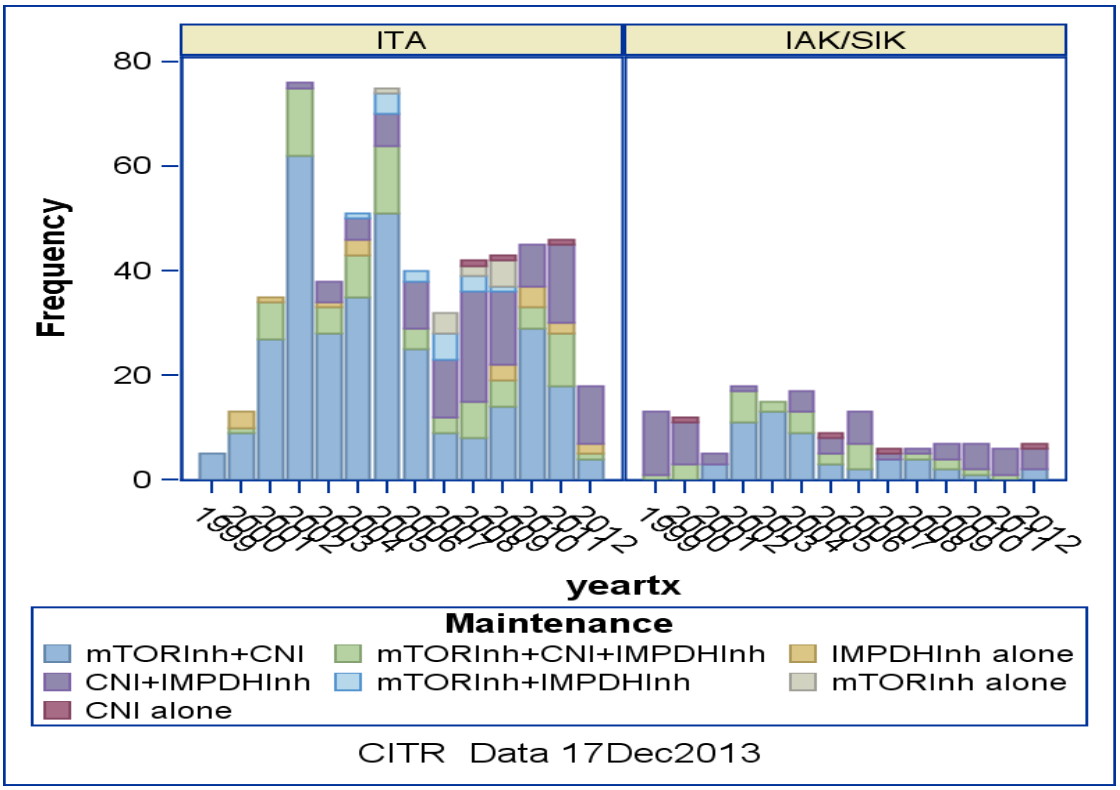
Exhibit 4 – 1
Induction Immunosuppression by Transplant Type and Era



	Type of transplant				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Induction												
IL2RA only	201	36.0	73	51.8	100	56.5	147	57.0	25	13.3	2	2.6
TCD only	58	10.4	9	6.4	12	6.8	9	3.5	39	20.7	7	9.1
TNFaInh only	16	2.9	.	.	2	1.1	6	2.3	4	2.1	4	5.2
TCD+TNFaInh	51	9.1	5	3.5	.	.	12	4.7	35	18.6	9	11.7
IL2RA+TCD	16	2.9	4	2.8	2	1.1	7	2.7	11	5.9	.	.
IL2RA+TNFaInh	47	8.4	9	6.4	17	9.6	25	9.7	12	6.4	2	2.6
IL2RA+TCD+TNFaInh	67	12.0	14	9.9	13	7.3	10	3.9	30	16.0	28	36.4
Missing/Unknown	103	18.4	27	19.1	31	17.5	42	16.3	32	17.0	25	32.5
TOTAL	559	100.0	141	100.0	177	100.0	258	100.0	188	100.0	77	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 regimen												
mTORInh+CNI+IMPDHInh	81	14.5	28	19.9	31	17.5	43	16.7	23	12.2	12	15.6
mTORInh+CNI	324	58.0	54	38.3	117	66.1	166	64.3	71	37.8	24	31.2
mTORInh+IMPDHInh	16	2.9	.	.	.	.	7	2.7	9	4.8	.	.
CNI+IMPDHInh	104	18.6	55	39.0	24	13.6	36	14.0	64	34.0	35	45.5
mTORInh alone	12	2.1	.	.	.	.	1	0.4	11	5.9	.	.
CNI alone	3	0.5	4	2.8	1	0.6	1	0.4	3	1.6	2	2.6
IMPDHInh alone	19	3.4	.	.	4	2.3	4	1.6	7	3.7	4	5.2
TOTAL	559	100.0	141	100.0	177	100.0	258	100.0	188	100.0	77	100.0

A Calcineurin inhibitor+mTOR inhibitor regimen (“Edmonton protocol”) comprised the abundant majority (~70%) of maintenance immunosuppression in the early eras 1999-2006. Increasingly it has been replaced with a switch from the mTOR inhibitor to an IMPDH inhibitor 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 for T1 diabetes. Despite the statistical challenges of multiple primary endpoints and analytical approaches, the factors contributing to both statistically significant and clinically important improvements in outcomes are clear. Remarkably, the combined effects of a handful of favorable factors appear to be additive, as exhibited by the final multivariate models of various primary endpoints (Exhibits 5-1 to 5-4) and subgroup analyses (Exhibits 5-4Z and 5-5A). These salutary factors include:

- Selection of patients aged 35 years or older. The remarkable consistency of this result runs across numerous 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 option for T1 diabetes allows optimal use of scarce donor pancreas resources.
- Recipients with lower LDL cholesterol and/or lower triglycerides exhibit the highest rates of insulin independence. The reason is not clearly apparent.
- Use of IL2RA, T-cell depletion, TNF-a inhibition, MTOR inhibition and calcineurin inhibitors continue to be associated with improved clinical outcomes. A major limitation from the CITR data is that the combinations 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.
- Donor management with vasopressors, transfusion and insulin are associated with improvements in at least some of the primary outcomes.
- Culturing islets >6h is associated with improved outcomes. This necessitates longer intervals from procurement to transplant, which also appears associated with improved outcomes. While it is difficult to completely separate the two factors across all outcomes and methods of analyses, it seems likely that culturing islets is the important contributing factor.
- Islet product characteristics have remained consistently high over the eras of the Registry (Chapter 3). Because of the high levels and narrow ranges of all islet product criteria used for clinical transplantation, it is impossible to statistically test 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.

Some possible benefits may be associated with certain islet processing factors such as use of UW solution, HTK solution. Serva/NB1 and thermolysin persist in associating with improved outcomes.

The hallmark effect of islet transplantation as exhibited in these data is the remarkably effective and durable resolution of severe hypoglycemic events. While many IAK/SIK recipients never had SHE before transplantation and fewer ITA recipients without SHE pre-infusion were included 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 /Annual Report /2012/Supplements. The following table relates the Chapter Exhibits to the Supplements.

Chapter 5 Exhibits

	Chapter 5 Exhibit	Supplemental Exhibit
Achievement of insulin independence, loss of insulin independence and complete graft failure post last infusion: Time to event analysis for all predictors univariately	-	A-1
Achievement of insulin independence post first infusion (Kaplan-Meiers)	5-1	-
Achievement of insulin independence post last infusion (Kaplan-Meiers)	5-2	A-2
Retention of insulin independence post last infusion (K-Ms)	5-3	A-3
Insulin independence prevalence (bar charts)	5-4	A-4
Retention of C-peptide>=0.3 ng/mL post last infusion (K-Ms)	5-5	A-5
Fasting C-peptide>=0.3 ng/mL prevalence post last infusion (Bar charts)	-	A-6
Reinfusion (Bar charts and K-Ms)	5-6	-
Fasting blood glucose 60-140 mg/mL prevalence post last infusion (Bar charts)	5-7	A-7
HbA1c<6.5% or drop by 2% (bar charts)	5-8	A-8
Absence of severe hypoglycemia (bar charts)	5-9	A-9
Insulin dose post last infusion (Box plots)	5-10	A-10
Fasting C-peptide levels post last infusion (Box plots)	5-11	A-10
HbA1c levels post last infusion (Box plots)	5-12	A-10
Fasting blood glucose levels post last infusion (Box plots)	5-13	A-10
Association of C-peptide≥0.3 ng/dL on other primary outcomes	5-14	-

Insulin Independence

First achievement of insulin independence after initial islet infusion, with or without subsequent re-infusion, occurs in 75-80% of cases who are selected and managed with the most favorable factors (Exhibit 5-1A). This result was identified by multivariate Cox proportional hazards modeling based on recipient factors at baseline (first infusion), islet product characteristics averaged over all infusions, and immunosuppression throughout all follow-up. 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 immunossuppression, 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 all eras, factors predictive of first achievement of insulin independence (Exhibit 5-1A) include: negative IA-2 autoantibody at baseline (p=0.03), shorter average

cold storage time (p=0.07), ≥500K IEQs infused overall (p=0.01), and immunosuppression with IL2RA (p=0.03) and mTOR-inhibitor (p=0.02). From both modeling with Cox proportional hazards and by subgroup analysis, recipients with these favorable factors exhibit a 4.5-fold higher likelihood of achieving insulin independence following allo-islet transplantation. The individual effects of these factors are shown in Exhibits 5-1 B-F. Notably, achievement of insulin independence did not vary by type of transplant (ITA vs. IAK/SIK, p=0.34). It is noted that an apparent univariate effect by era was eliminated in the multivariate model by the remaining significant factors.

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

A. Final Multivariate Model

Factors	p	Hazard Ratio
Baseline IA-2 autoantibody (ICA 512, 0=Neg 1=Pos)	0.0333	0.665
Hours cold storage	0.0713	0.856
IEQs infused (1000s)	0.0095	1.246
IL2RA inhibitor (1=Given 0=Not given)	0.0348	1.345
mTOR inhibitor (1=Given 0=Not given)	0.0247	1.517

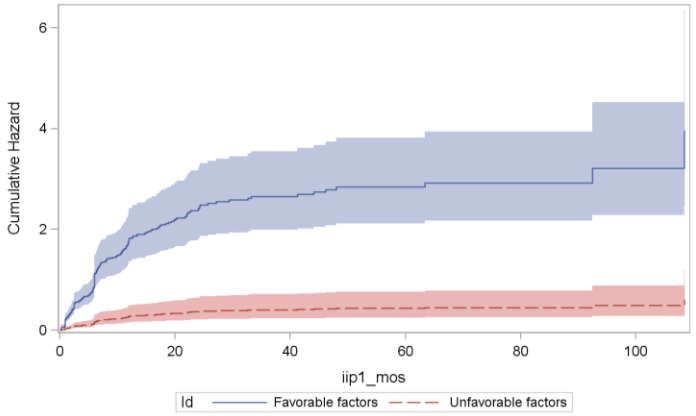
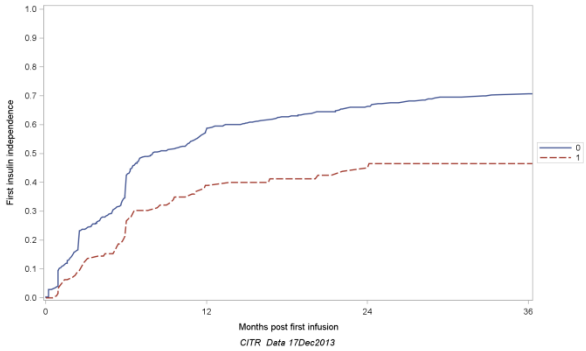
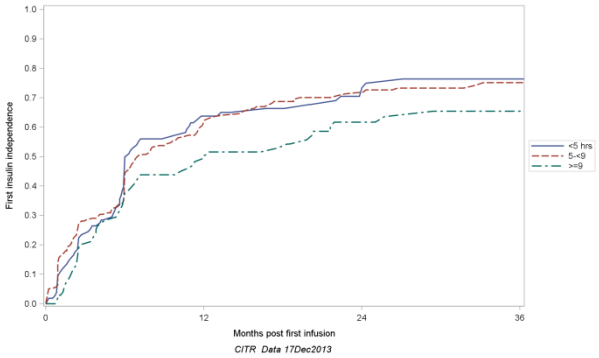


Exhibit 5 – 1 *(continued)*
First Achievement of Insulin Independence Post First Infusion
(Through all infusions, censored at final graft loss or end of follow-up)

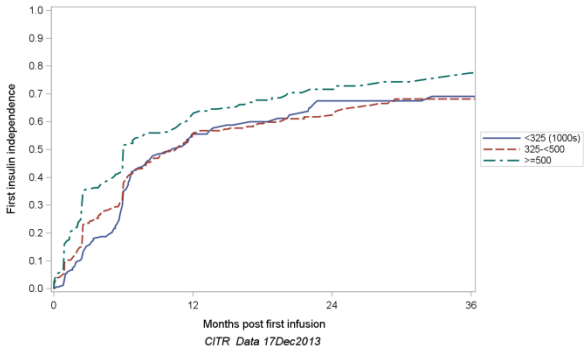
B. IA2 autoantibody (negative is favorable)



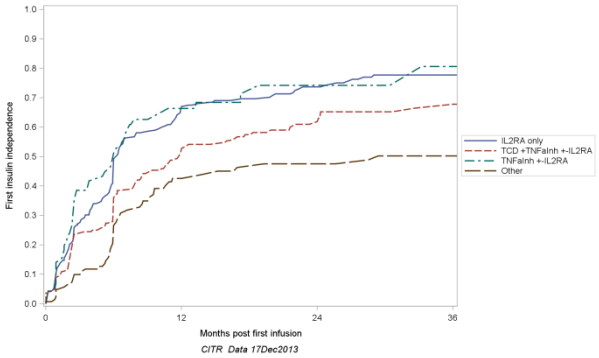
C. Cold storage time (shorter is favorable)



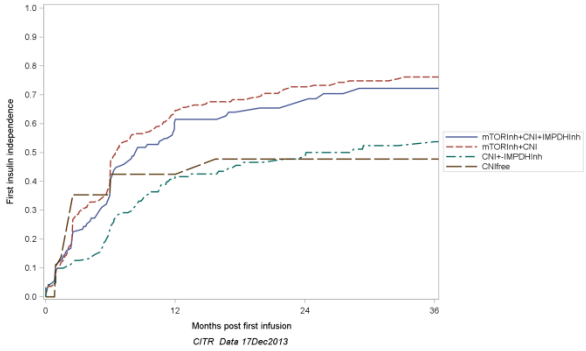
D. IEQs infused (≥500K favorable)



E. Induction IS (IL2RA is favorable)



F. Maintenance IS (mTOR is favorable)



Insulin independence (≥2 weeks) can be lost and re-achieved over long follow-up, making it difficult to analyze by any single method. While achievement and retention post last infusion ignore previous periods of insulin independence (as well as periods of dependence), they facilitate investigation of predictive factors. The cumulative event rates of achieving or re-achieving insulin independence post last infusion (Exhibit 5-2A) rise quickly in contrast to post first infusion (Exhibit 5-1), due mostly to the fact that previously achieving insulin independence is a significant predictor or re-achieving it after re-infusion (p=0.02). Complete graft loss at an earlier infusion also predicts lower likelihood of achieving insulin independence on subsequent infusion (p=0.05). Final factors from a multivariate model (Exhibit 5-2A) favorable for achieving insulin independence post last infusion include: recipient age≥35 (p=0.046); baseline insulin requirement <43 U/day (p=0.009); at least one female donor at any infusion (p=0.005); ≥500K IEQs, typically over one to three infusions (p<0.001), and use of calcineurin inhibitors (trending at p=0.09). The combination of the most favorable factors contrasted to the least favorable factors predicts a greater than 10-fold likelihood of achieving insulin independence (Exhibit 5-2A). While

there is indication from this model that various induction and maintenance combinations impact this outcome, the effects of induction and maintenance immunosuppression agents prove difficult to isolate because they are given in combination, are changed across infusions and over follow-up time within the same patient, and the sample sizes with any single "protocol" other than the Edmonton protocol, are still relatively small (see Chapter 4). Furthermore, the emerging results when accounting for all possible factors can be unstable. With these constraints, additional or alternative approaches to assessing the effect of immunosuppression strategies are indicated, especially prevalence of insulin independence, which combines achievement and retention into an overall rate (see Exhibit 5-4).

Exhibit 5 – 2
Achievement of Insulin Independence Post Last Infusion
(Censored at final graft loss or end of follow-up)

A. Final Multivariate Model

Factors	p	Hazard Ratio
Age group	0.0462	1.543
Baseline insulin (Units/day)	0.0086	0.765
Donor Gender (0=F 1=M 0.5=Mixed)	0.0052	0.584
Islet viability >90%	0.0293	1.211
≥500K IEQs infused	<.0001	2.717
CNI	0.0976	2.311

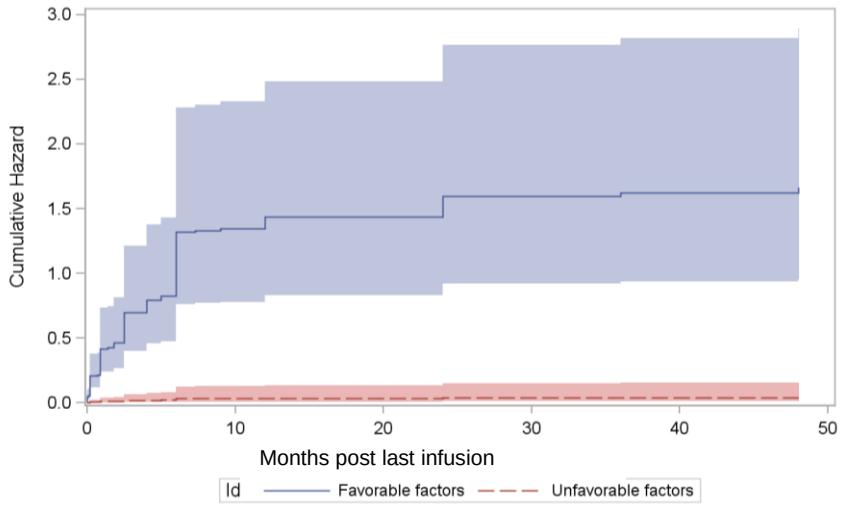
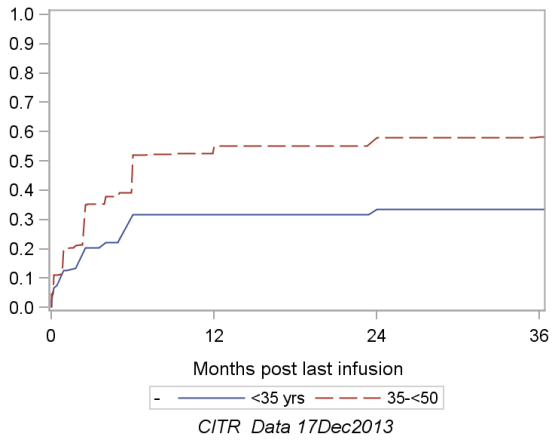


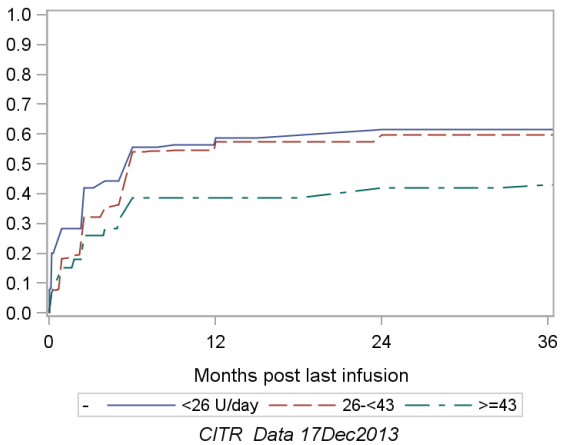
Exhibit 5 – 2 *(continued)*
Achievement of Insulin Independence Post Last Infusion
(Censored at final graft loss or end of follow-up)

B. Recipient age >35 is favorable



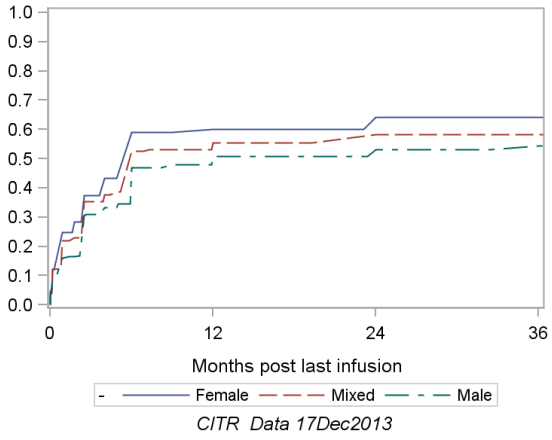
CITR Data 17Dec2013

C. <43U daily insulin is favorable



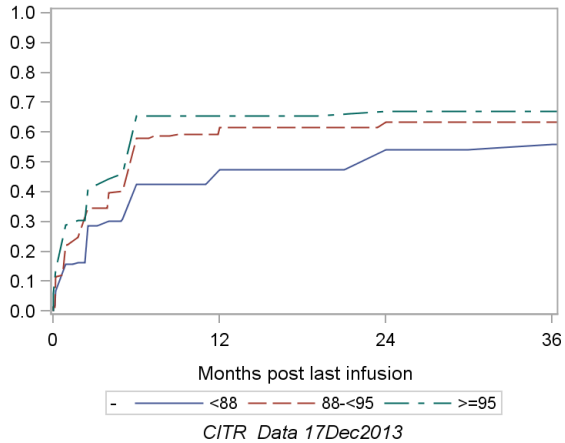
CITR Data 17Dec2013

D. At least 1 female donor is favorable



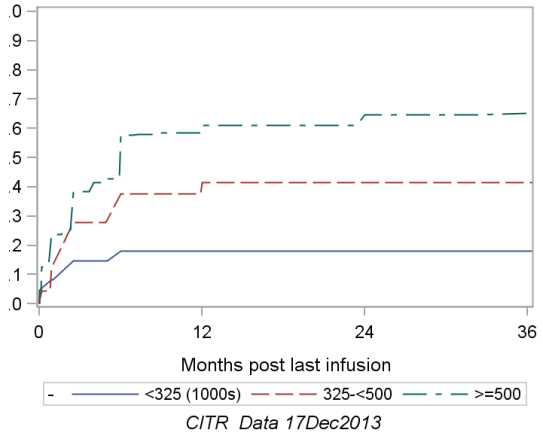
CITR Data 17Dec2013

E. Islet viability >88% is favorable



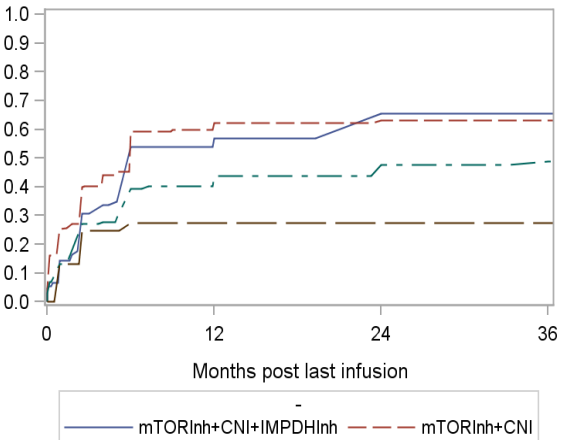
CITR Data 17Dec2013

F. ≥500K IEQs infused is favorable



CITR Data 17Dec2013

G. Calcineurin inhibitor is favorable



CITR Data 17Dec2013

Many factors influence retention of insulin independence post last infusion (Exhibit 5-3). The factors that remain in a multivariable Cox proportional hazards model (Exhibit 5-3A) include: transfusing the donor (p=0.003), use of Serva/NB1 (p=0.005), use of thermolysin (p=0.039), induction with T-cell depleting agents (p=0.001), and high islet count (p=0.024). Note that the event being modeled is loss of insulin independence, with hazard<1.0 being favorable, though the retention (survival) of insulin independence is plotted. Recipients receiving all the favorable factors retain insulin independence at a 90% rate over 7 years of follow-up, after initially achieving insulin independence.

Exhibit 5 – 3
Retention of Insulin Independence Post Last Infusion
(Censored at final graft loss or end of follow-up)

A. Final Multivariate Model

Factors	p	Hazard Ratio
Donor given transfusions prior to surgery (0-No 1-Yes)	0.003	0.574
Serva/NB1	0.005	0.447
Thermolysin	0.039	0.505
TCD	0.001	0.307
Islet particles ≥500K	0.024	0.613

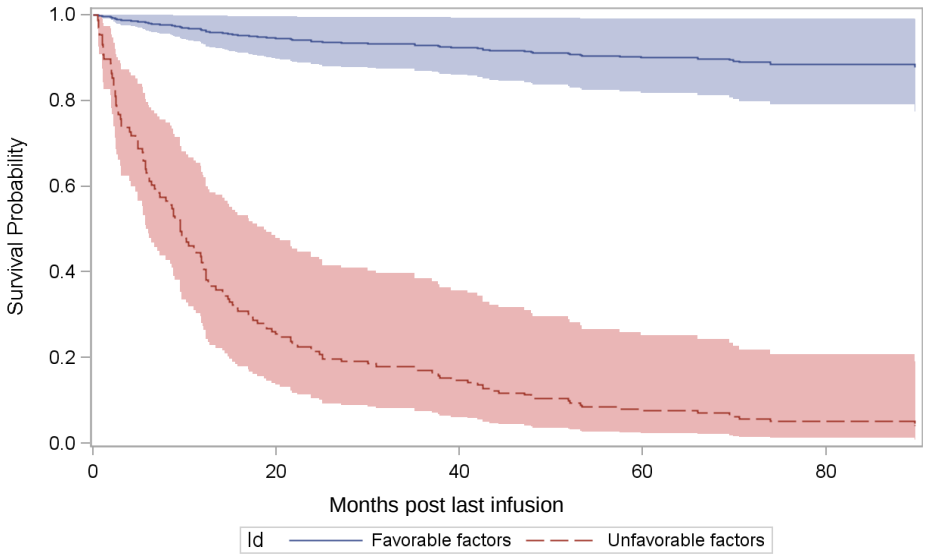
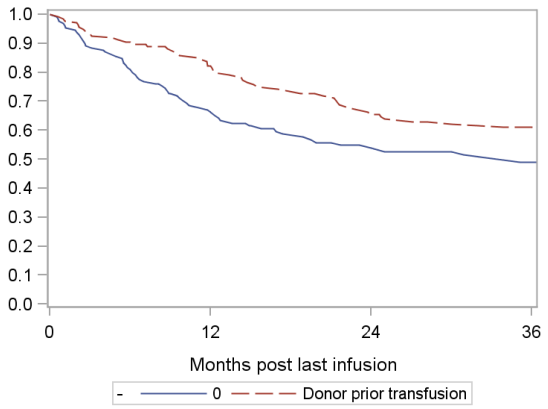


Exhibit 5 – 3 *(continued)*
Retention of Insulin Independence Post Last Infusion
(Censored at final graft loss or end of follow-up)

B. Donor transfused is favorable



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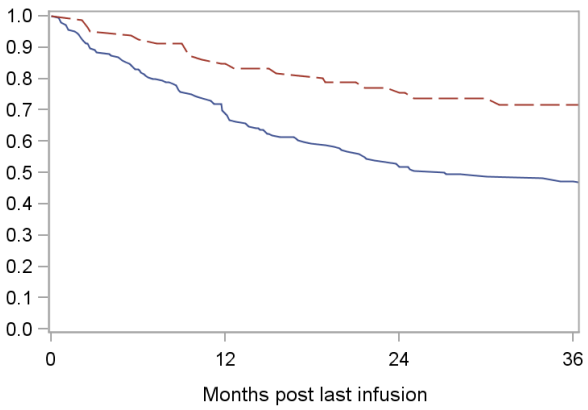
C. Serva/NB1 use is favorable



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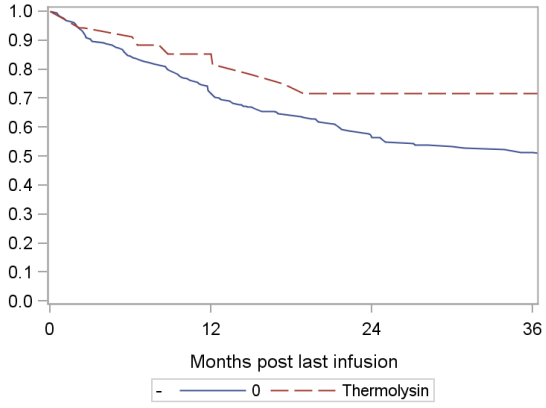
D. Thermolysin use is favorable



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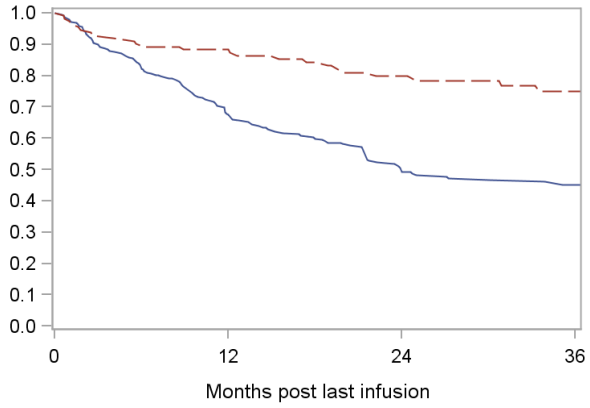
E. TCD use is favorable



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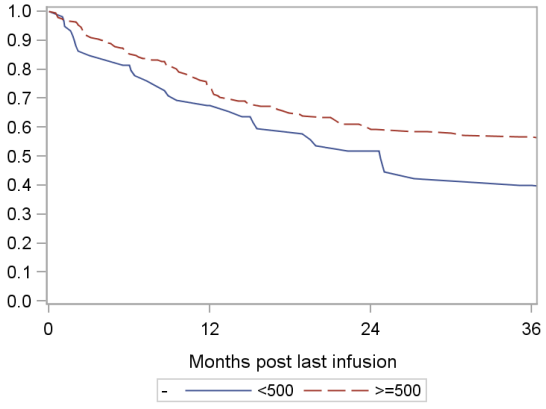
F. Total islet particles ≥500K is favorable

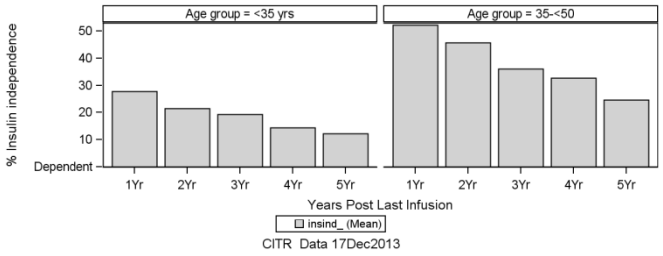


CITR Data 17Dec2013

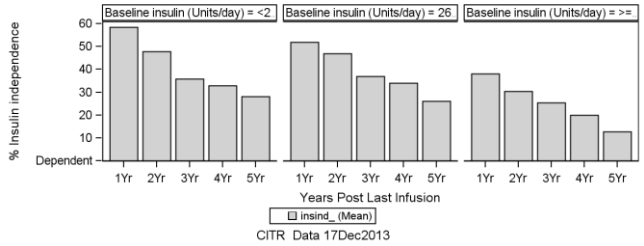
Prevalence of insulin independence post last infusion (Exhibit 5-4) is the optimal way to characterize the probability of being insulin independent in follow-up time post islet transplantation, because insulin independence can be lost and re-gained, often over periods spanning months or years. Prevalence also reconciles disparities in factors that may be predictive of retention but not of achievement, or vice versa (Exhibits 5-1, 5-2 and 5-3). 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 by the model 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. Nonetheless, prevalence rates of insulin independence post last infusion, shown for factors univariately predictive of the outcome (Exhibit 5-4), are: ITA vs. IAK/SIK (not shown, p=0.01), and which is explained by other variables and is the topic of a separate focus analysis); recipient age ≥35 years (p<0.001); baseline insulin <43 U/day (p=0.001); baseline HbA1c<8.5% (p=0.005); negative IA-2 autoantibodies (p=0.001); positive microinsulin autoantibody (p=0.01); baseline LDL<75 (p<0.001); baseline triglycerides <30 mg/dL (p<0.001); baseline cholesterol <150 (p=0.004); ABO type A (p=0.03); donor transfused (p=0.04); thermolysin (p=0.001); UW (p=0.01), 2-layer (p=0.03), and/or HTK preservation (p=0.001); islets cultured>6 hrs (p=0.05); donor BMI<25 or >32 (p=0.05); death-to-recovery>24 hrs (p=0.02); islet stimulation index≥1.5 (p=0.03); IEQ/islet particle ratio>0.83 (p=0.04); DNA content>4 (p=0.04); total IEQs over all infusions≥500K (p<0.001); induction that includes TCD (p=0.001) and/or TNFa-inhibition (p=0.02), CNI (p=0.001), mTOR inhibitor (p<0.001) and/or deoxyspergualin (p=0.004). The subgroup comprised of only four of these favorable factors, namely recipient age≥35, baseline insulin <43 U/kg and induction with TCD and TNFa-inhibition, exhibits insulin independence rates sustained at 55% through 5-years (Panel Z, p=0.001).

Exhibit 5 – 4
Prevalence of Insulin Independence Post Last Infusion

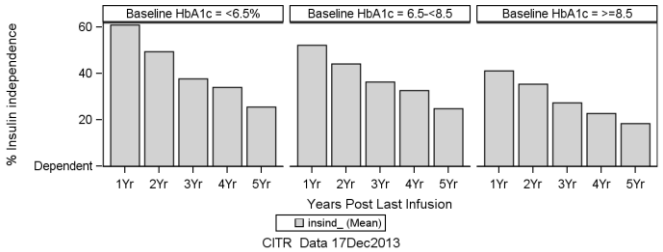
A. Recipient age≥35 favorable (p<0.001)



B. Baseline insulin<43U/day favorable (p<0.001)



C. Baseline HbA1c<8.5% favorable (p=0.005)



D. Negative IA-2 AB favorable (p=0.001)

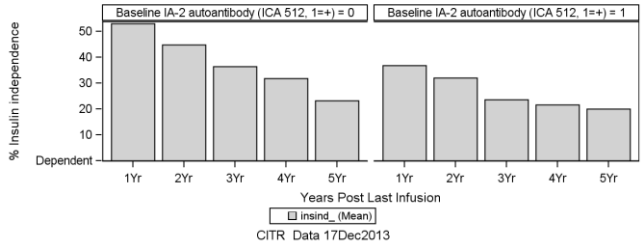
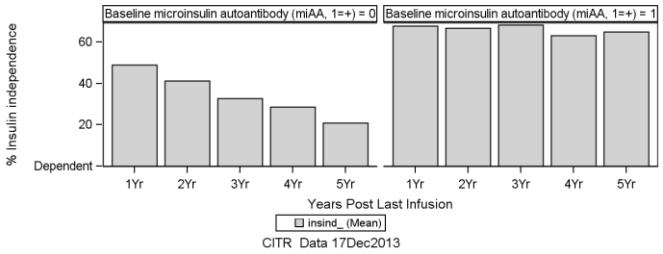
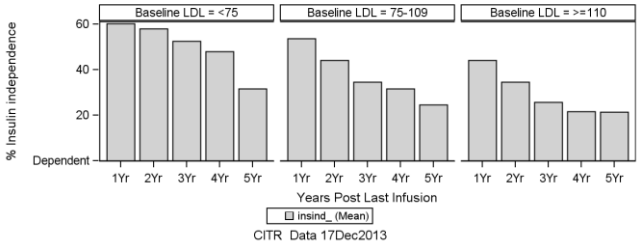


Exhibit 5 – 4 *(continued)*
Prevalence of Insulin Independence Post Last Infusion

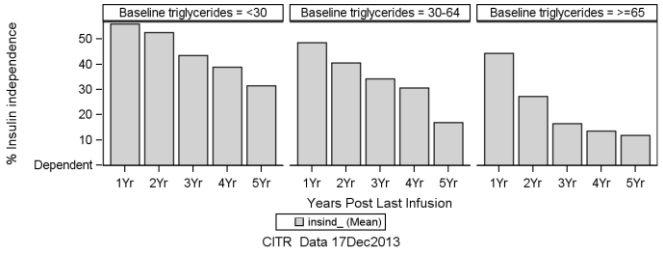
E. Positive microinsulin AB favorable (p=0.01)



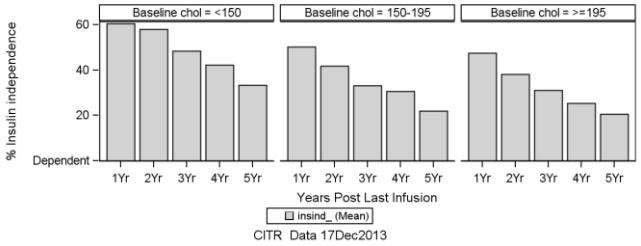
F. Baseline LDL<75 favorable (p<0.001)



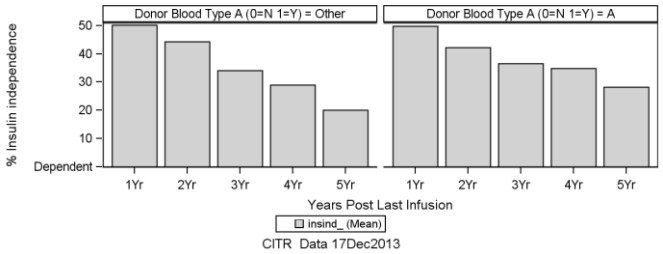
G. Baseline triglycerides <30 favorable (p<0.001)



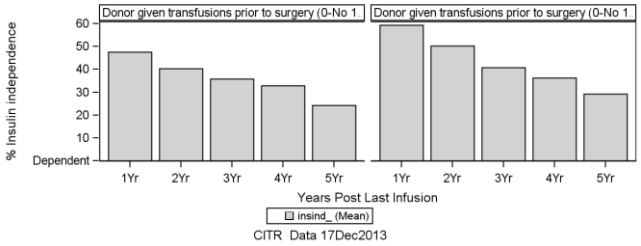
H. Baseline Cholesterol <150 favorable (p=0.004)



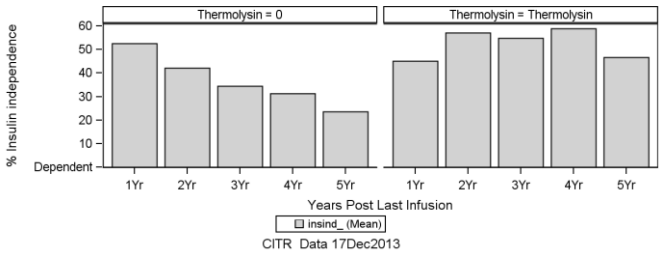
I. Blood type A favorable (p=0.03)



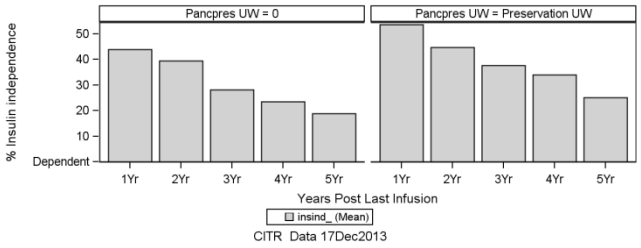
J. Donor transfused favorable (p=0.03)



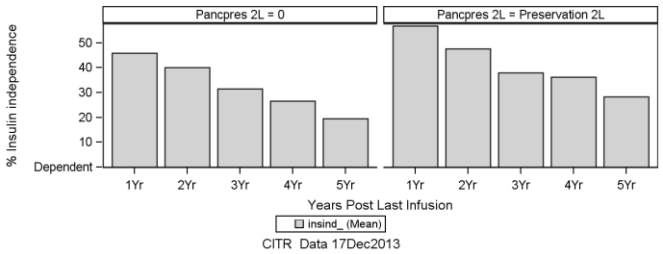
K. Thermolysin favorable (p=0.001)



L. UW preservation favorable (p=0.01)



M. 2-layer preservation favorable (p=0.03)



N. HTK preservation favorable (p<0.001)

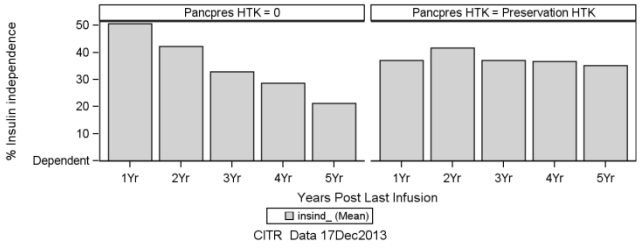
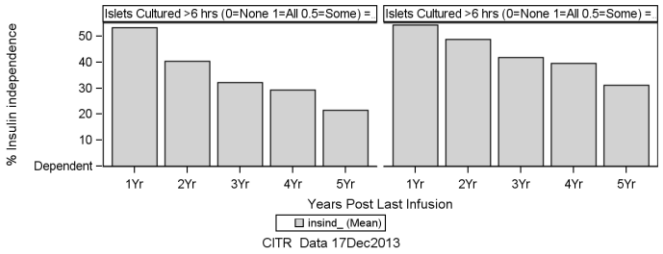
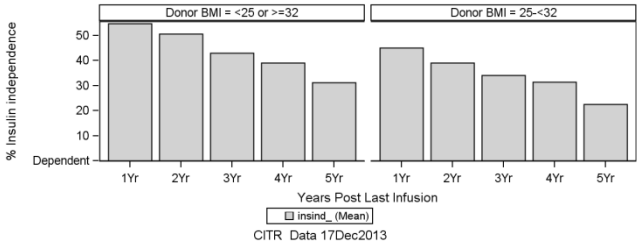


Exhibit 5 – 4 *(continued)*
Prevalence of Insulin Independence Post Last Infusion

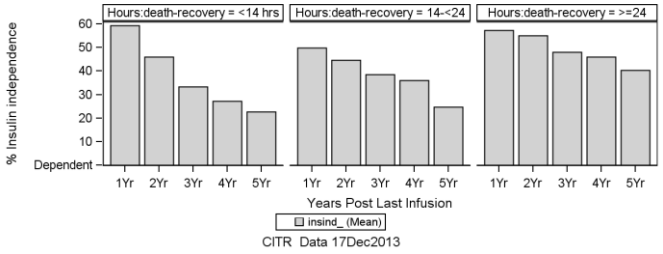
O. Islets cultured>6h favorable (p=0.05)



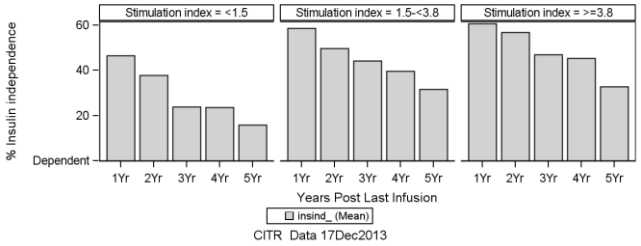
P. Donor BMI<25 or >32 favorable (p=0.05)



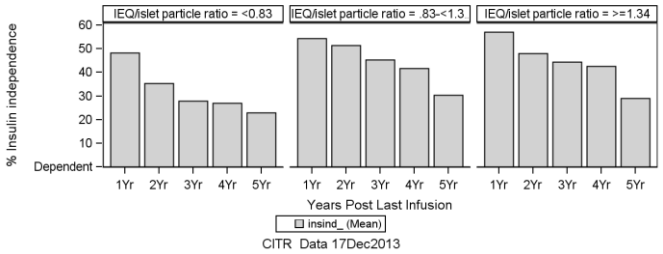
Q. Death-recovery>24hfavorable (p=0.02)



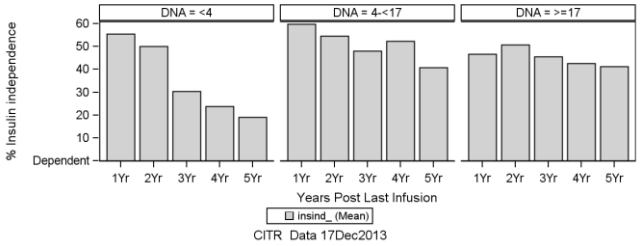
R. Stimulation index ≥1.5 favorable (p=0.03)



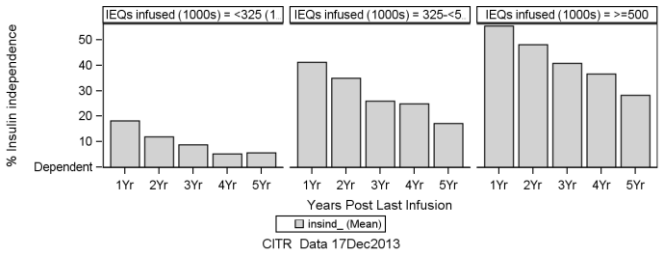
S. IEQ/particle ratio >0.83 favorable (p=0.04)



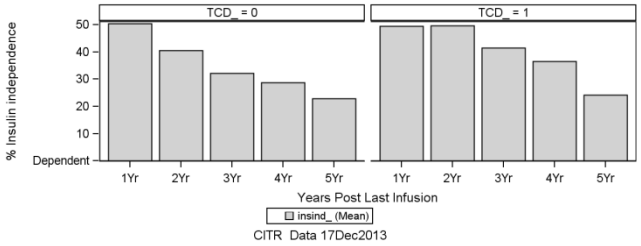
T. DNA content>4 favorable (p=0.04)



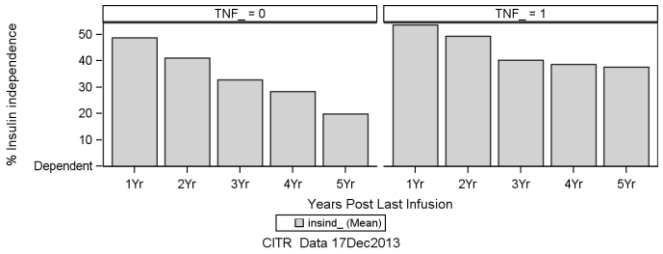
U. Total IEQs infused >500K favorable (p<0.001)



V. TCD favorable (p=0.001)



W. TNFa-Inh favorable (p=0.02)



X. Calcineurin inhibitor favorable (p=0.001)

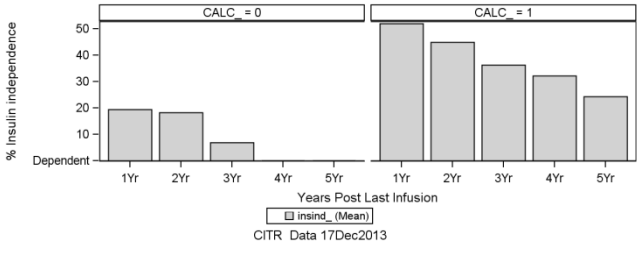
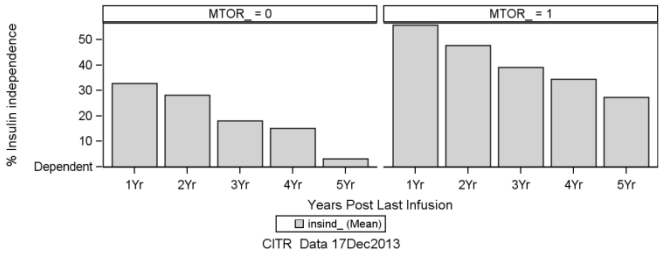
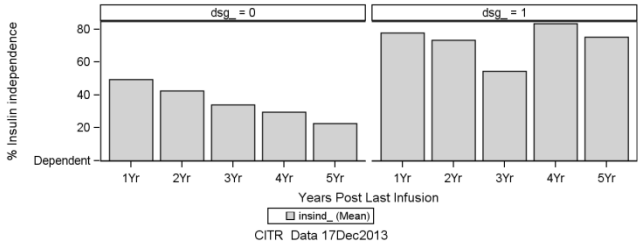


Exhibit 5 – 4 *(continued)*
Prevalence of Insulin Independence Post Last Infusion

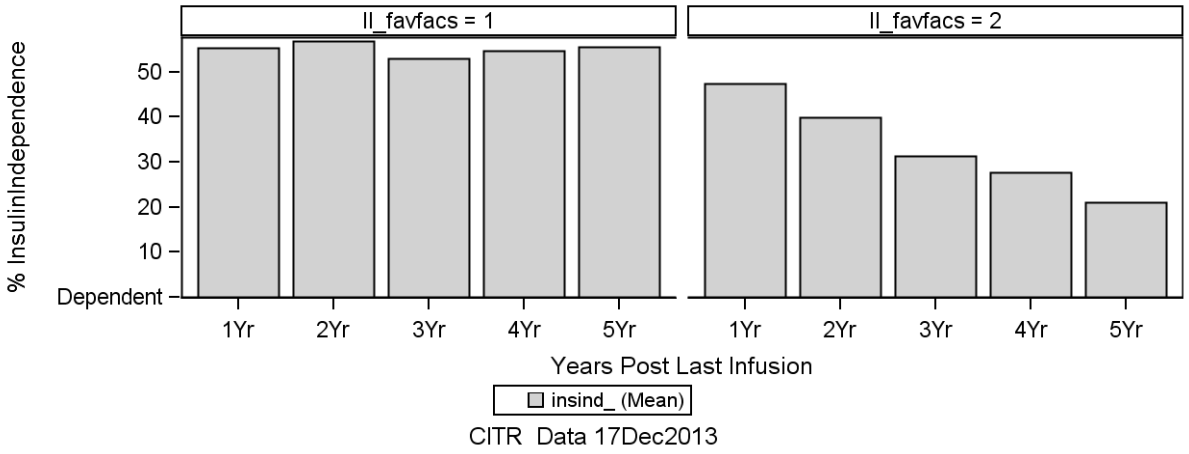
Y. mTOR inhibitor favorable (p<0.001)



Z. Deoxyspegualin favorable (p=0.004)



AA. Subgroup (n=96) with four favorable factors: age≥35, <0.43U/kg/day insulin and managed with T-cell depletion and TNF-a inhibition (p=0.001)



C-peptide≥0.3 ng/mL

Of all 1,681 allogeneic islet infusions with C-peptide data, 46 (2.7%) resulted in primary non-function (C-peptide never ≥0.3 ng/mL up to reinfusion): 3.3% in 1999-2002, 3.2% in 2003-2006, and 1.7% in 2007-2010, and 2.7% in 2011-2012.

Retention of graft function (C-peptide≥0.3 ng/mL) post last infusion is maximized by recipient age≥35 years (exhibit 5-5A, p<0.001), baseline LDL<75 (p=0.008), ≥500K IEQs infused (p=0.01), Serva/NB1 (p=0.002), and calcineurin inhibitors (p<0.001). With these factors combined, graft retention rates remain at 80% for 7-8 years.

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

Parameter	p	Hazard Ratio
Age group	<0.0001	0.456
Baseline LDL<75	0.0079	1.443
Total IEQs infused ≥500K	0.0104	0.664
Serva/NB1	0.0019	0.383
Calcineurin inhibitor	<0.0001	0.155

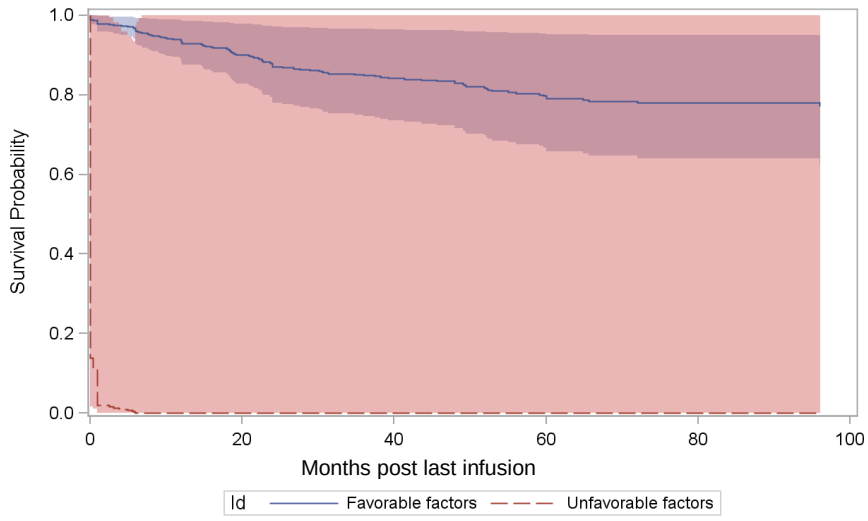
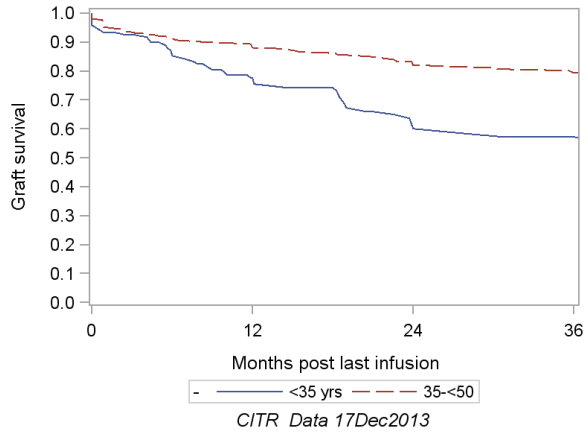
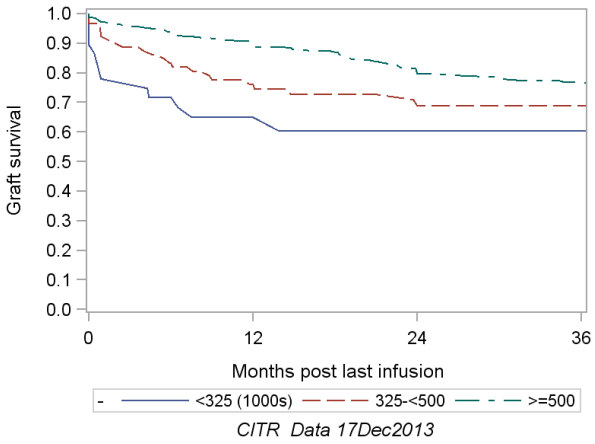


Exhibit 5 – 5 *(continued)*
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion

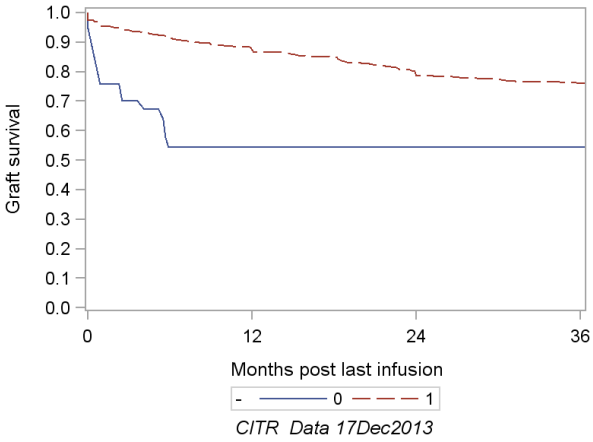
Recipient age >=35 (p<0.001)



≥500K IEQs infused (p=0.03)



Calcineurin inhibitors (p<0.001)

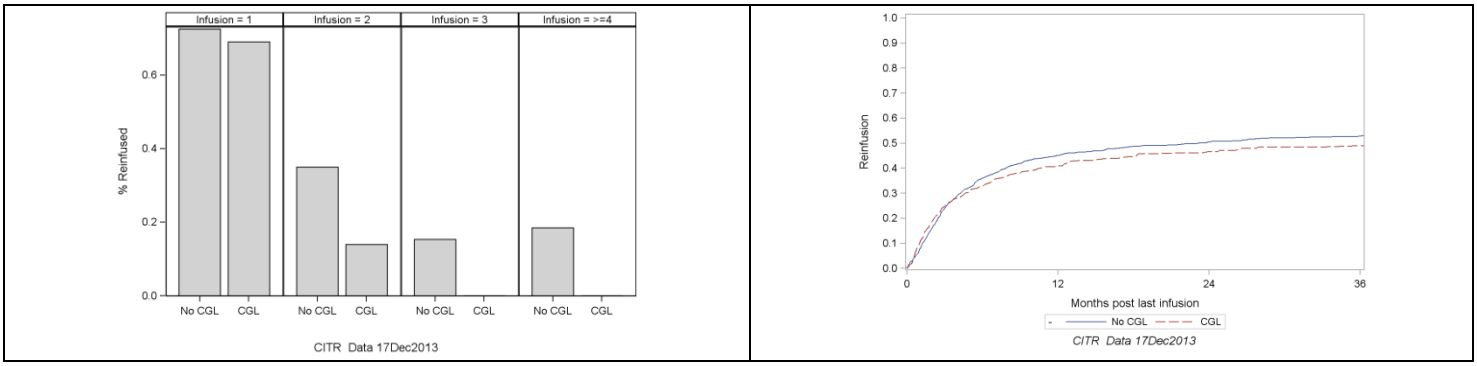


Re-infusion

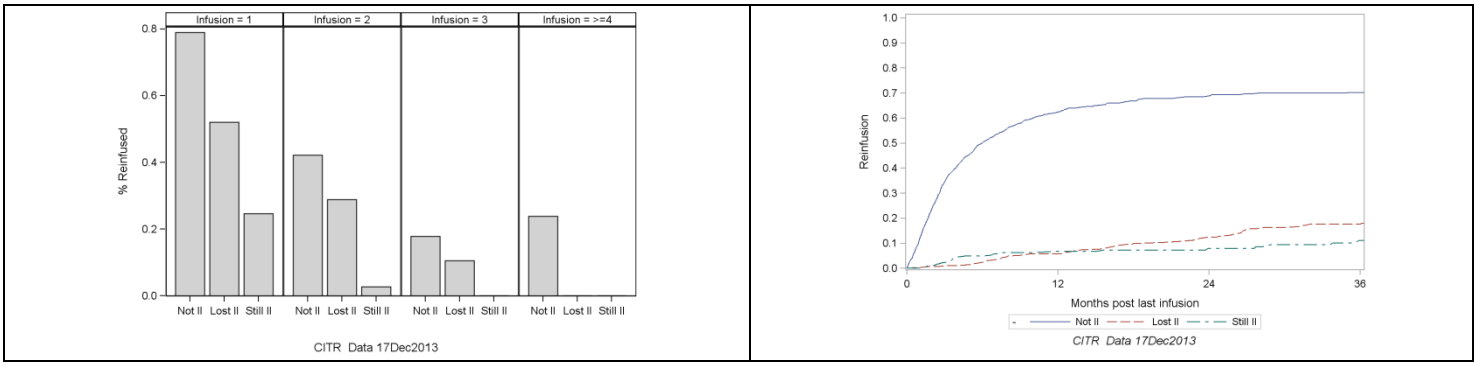
Re-infusion may have been conducted without (665/1324=50.2%) or after (160/344=46.5%) complete graft failure (fasting C-peptide<0.3 ng/mL without recovery, Exhibit 5-6A). Viewed as time-to-event, reinfusion was no more likely with a functioning graft than with a lost graft (p=0.14). A number of re-infusions were conducted while the patient was not only C-peptide positive but also insulin independent (Exhibit 5-6B, 22/209=9.5%, for all infusions): re-infusion was much more likely when the patient had not yet achieved insulin independence (p<0.001).

Exhibit 5 – 6
Re-Infusion
(All infusions)

A. By complete graft failure (CGL)



B. By insulin independence

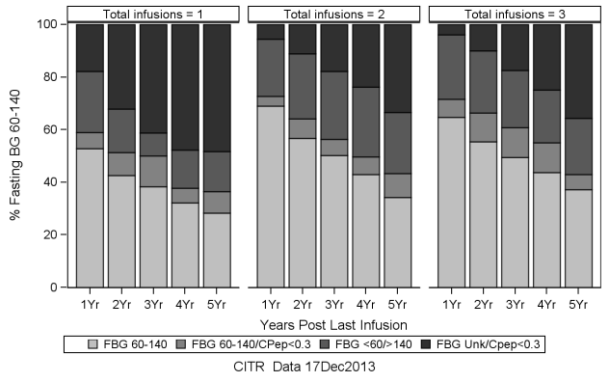


Persistence of primary outcomes

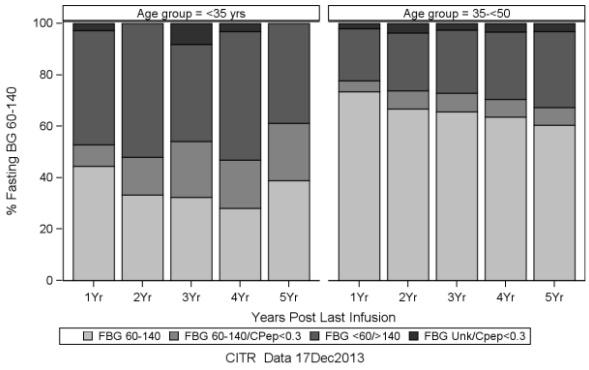
The factors associated with higher levels of controlled blood glucose are shown in Exhibit 5-7. Many of these were also favorable factors for insulin independence (exhibit 5-4).

Exhibit 5 – 7
Fasting blood glucose 60-140 mg/mL post last infusion

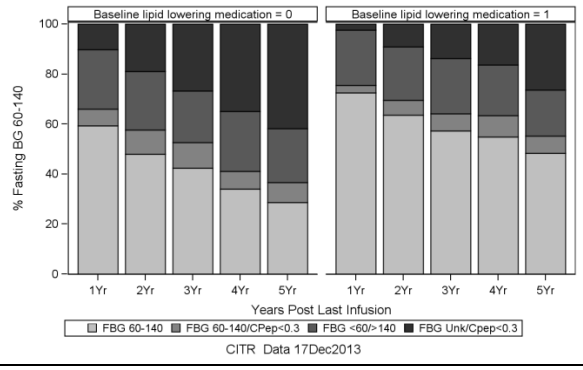
Total infusions p<0.001



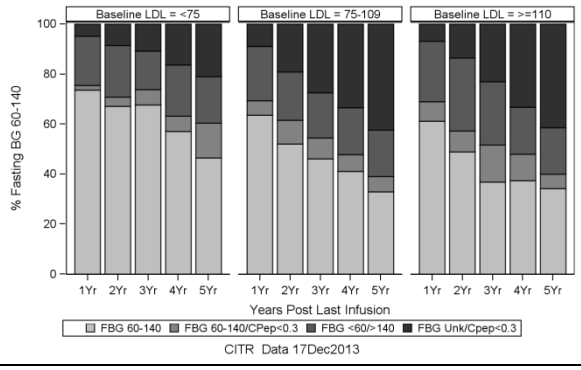
Age >=35 p<0.001



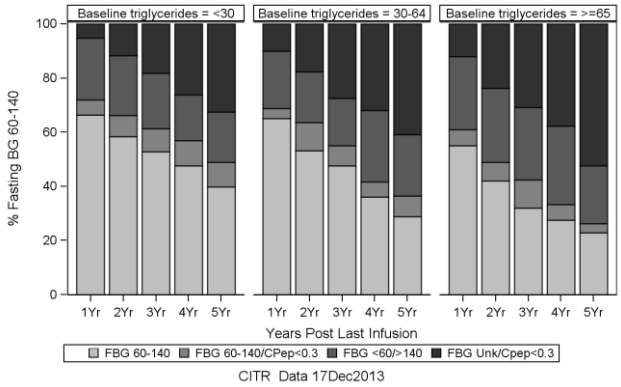
Lipid-lowering medication p=0.008



Baseline LDL<75 (p0.04)



Baseline triglycerides<30 (p=0.01)



Pulmozyme p=0.02

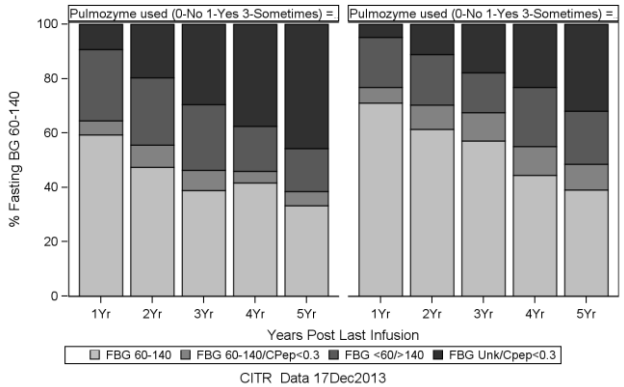
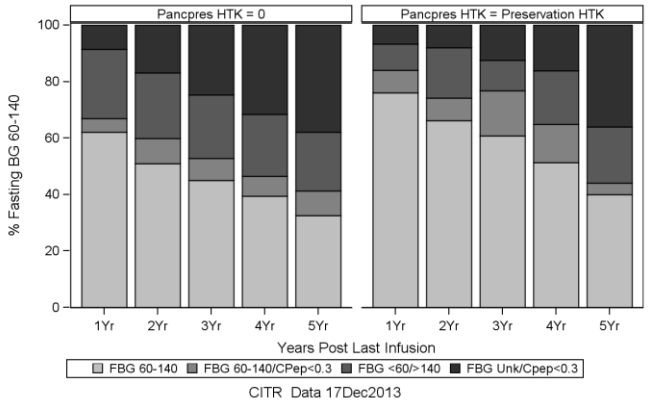
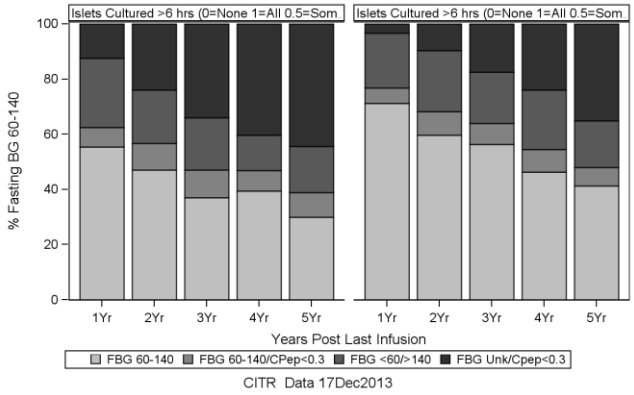


Exhibit 5 – 7 *(continued)*
Fasting blood glucose 60-140 mg/mL post last infusion

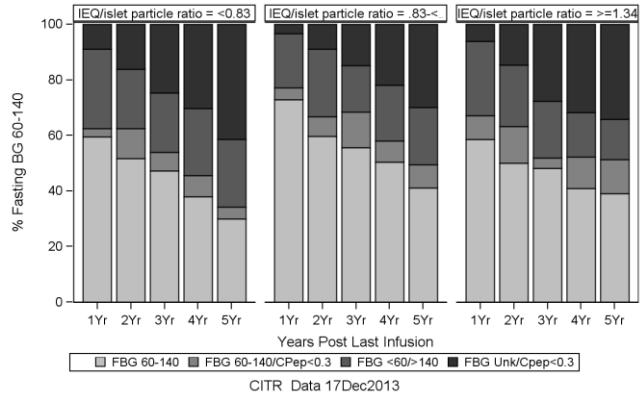
HTK p=0.02



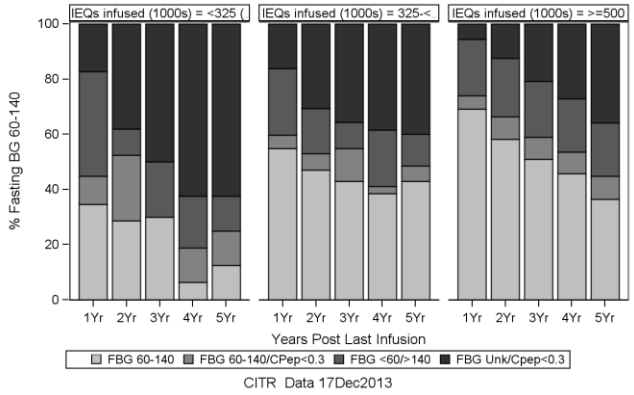
Islets cultured >6h p=0.03



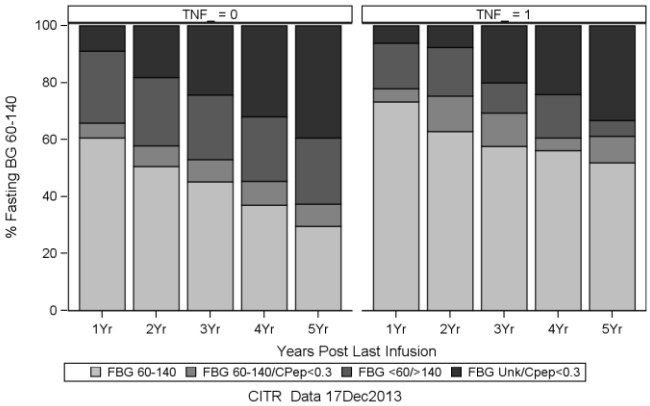
IEQ/particle ratio p=0.05



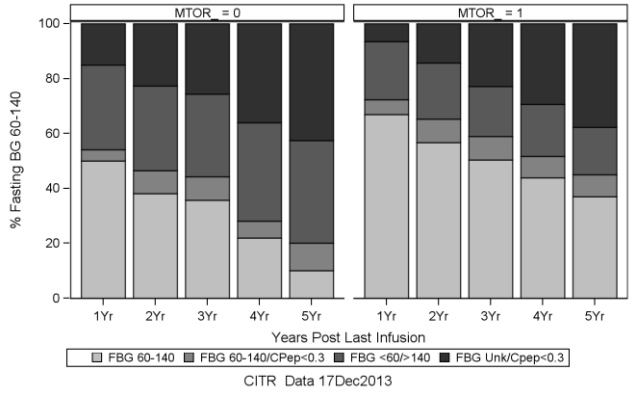
Total IEQs infused p=0.004



TNF-a Inhibitor p=0.009



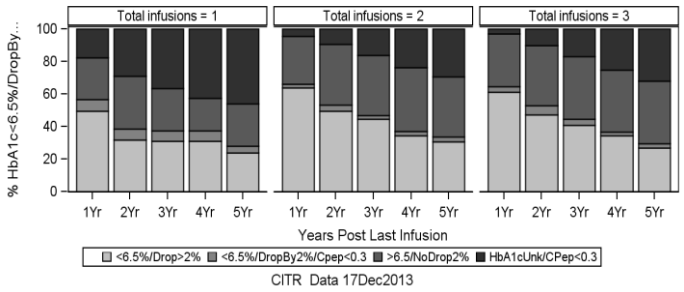
mTOR inhibitor p=0.001



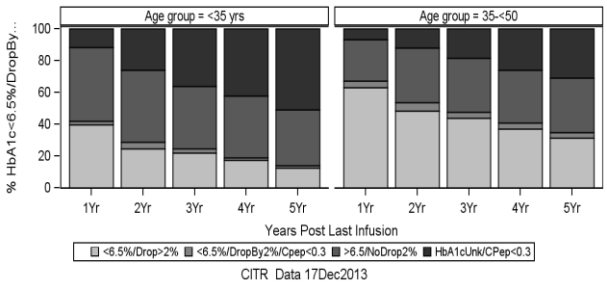
Factors associated with higher levels of HbA1c<6.5% or drop by 2% are shown in Exhibit 5-8.

Exhibit 5 – 8
HbA1c<6.5% or Drop by 2% Post Last Infusion

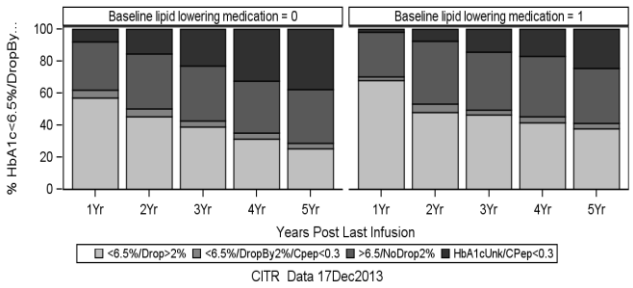
≥2 infusions p=0.01



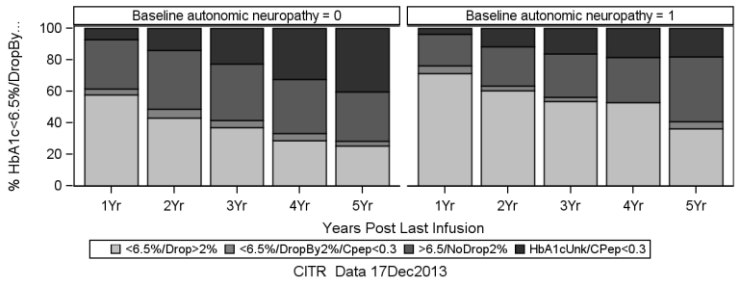
Age≥35 p<0.001



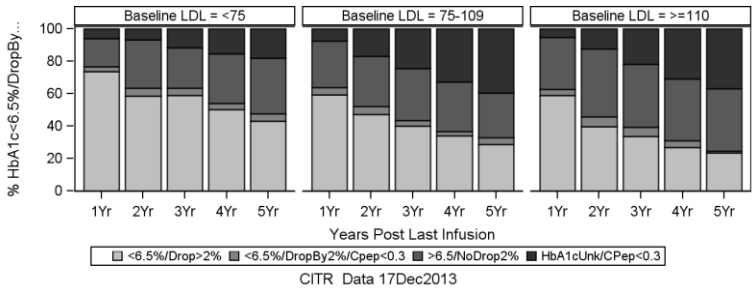
Baseline lipid-lowering medication p=0.02



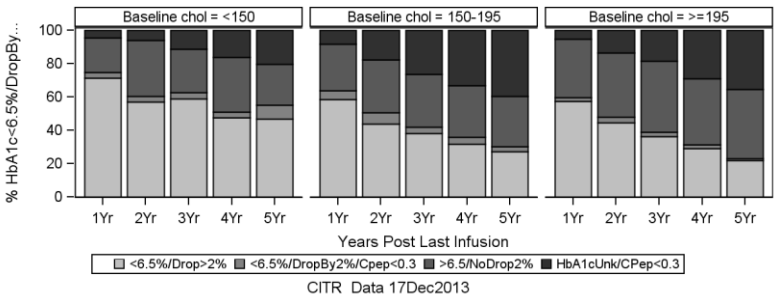
Baseline autonomic neuropathy p=0.003



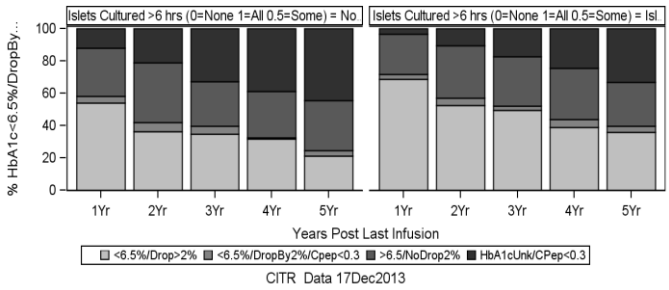
Baseline LDL<75 p<0.001



Baseline cholesterol<150 p=0.01



Islets cultured >6h p=0.01



Stimulation index>1.5 p=0.04

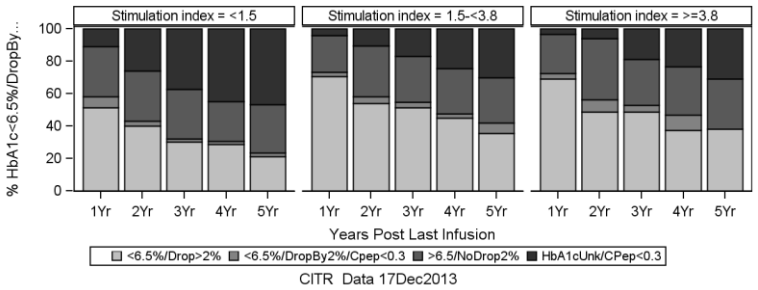
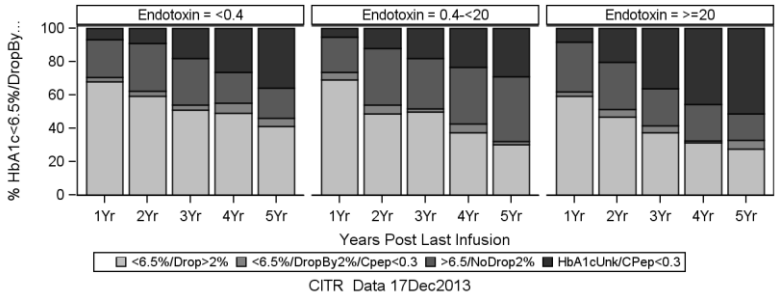
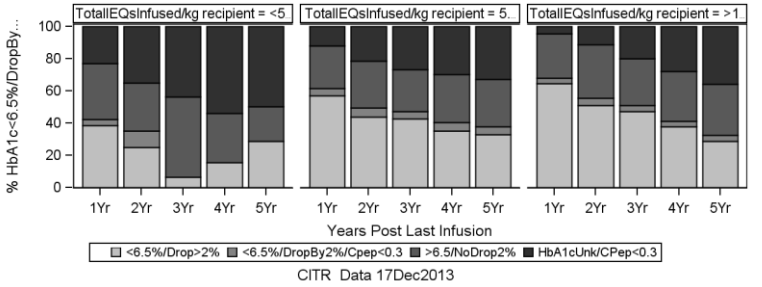


Exhibit 5 – 8 *(continued)*
HbA1c<6.5% or Drop by 2% Post Last Infusion

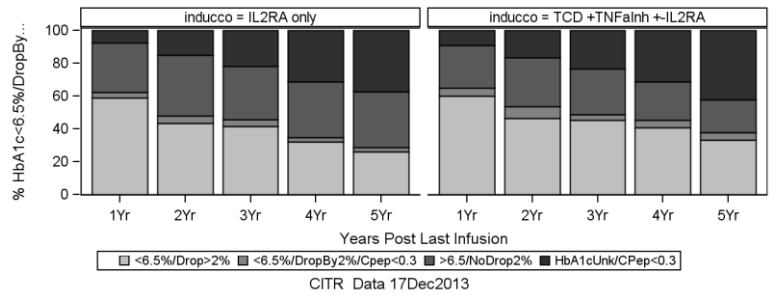
Endotoxin<0.4 p=0.02

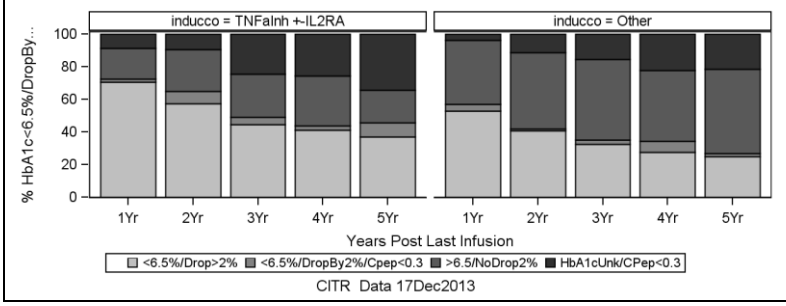


Total IEQs infused >5K/kg p=0.004

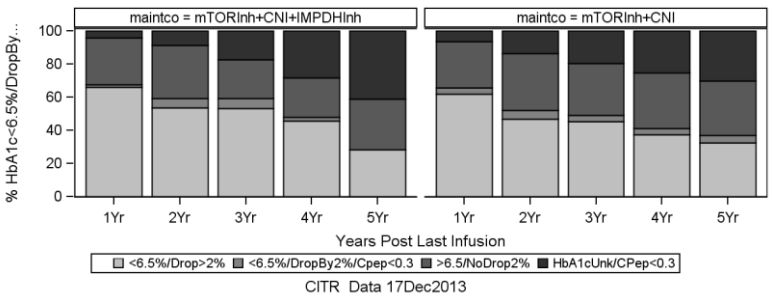


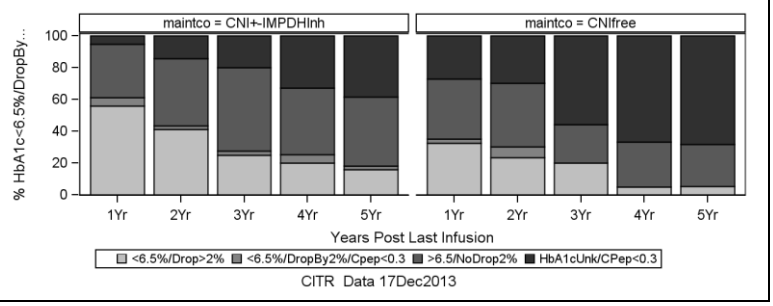
Induction with TCD and TNFa-inhibition p=0.04





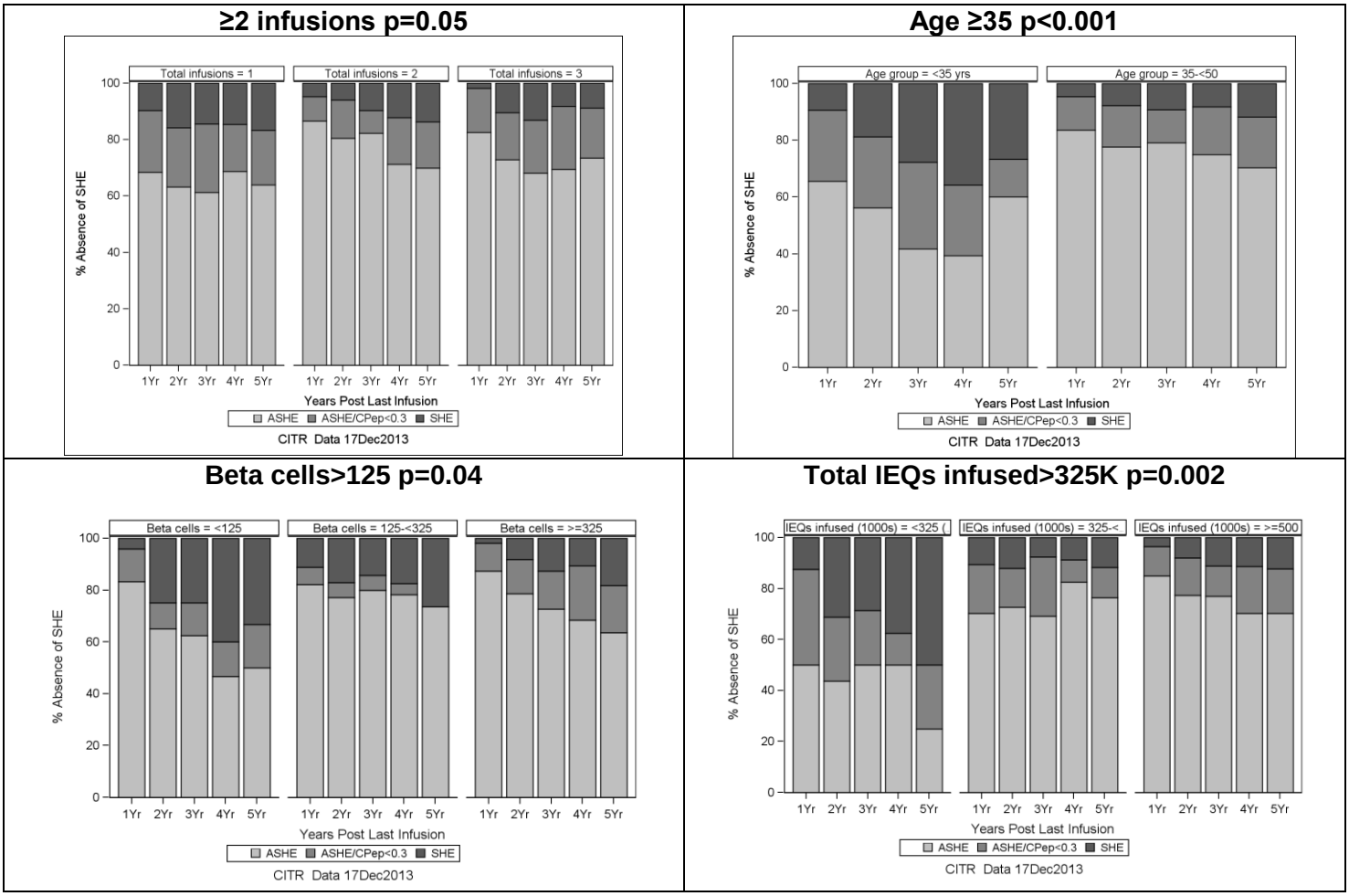
Maintenance with mTOR inhibitor and Calcineurin inhibitor p=0.04





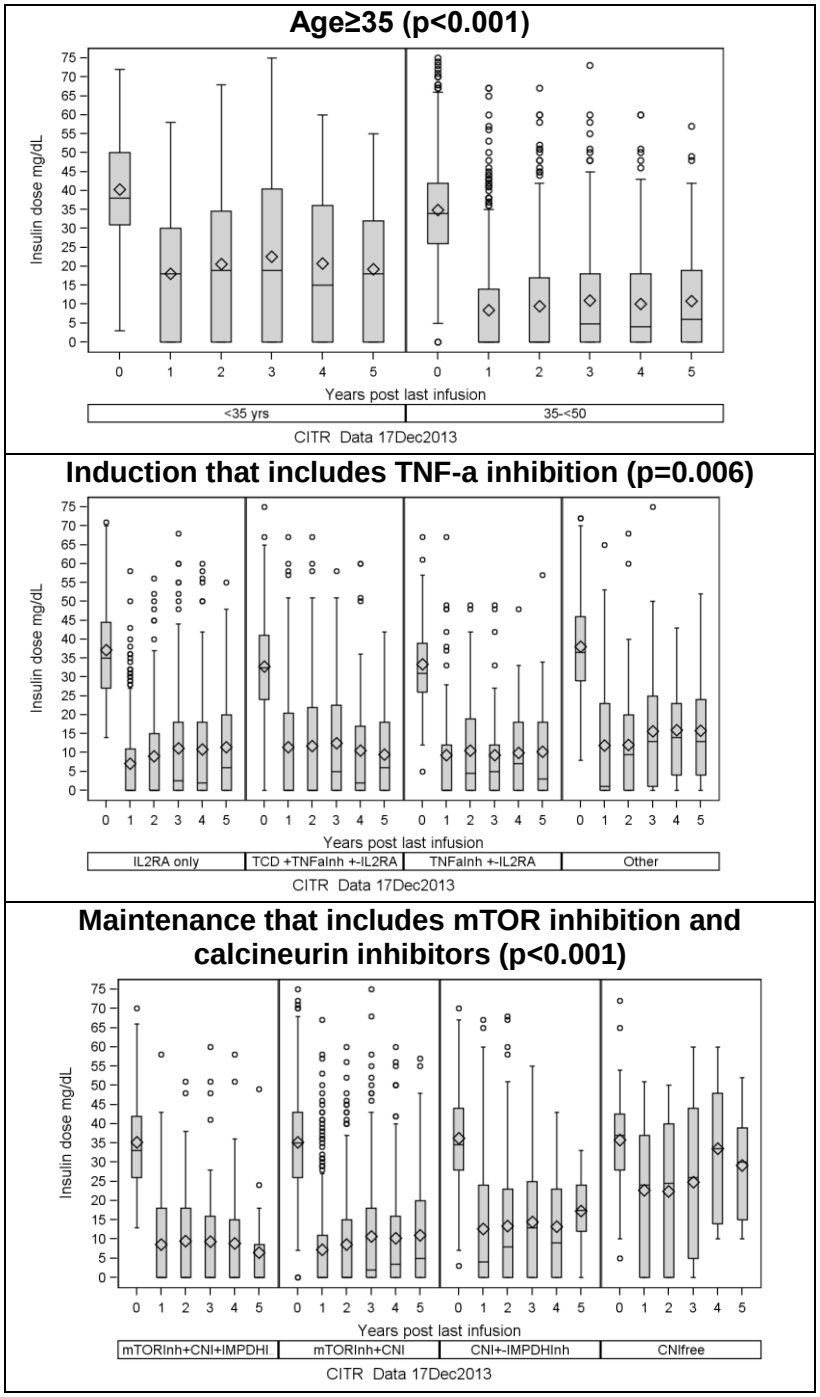
Factors associated with higher levels of absence of severe hypoglycemic events (ASHE) post allogeneic islet transplantation are shown in Exhibit 5-9. The light gray and medium-gray portions of the bars comprise ASHE: the medium-gray portion shows the percentage with ASHE when concurrent C-peptide was <0.03 ng/mL (that is, protection from SHE even without positive C-peptide). Overall, ASHE is maintained at about 90% throughout the first 5 years after last infusion, with or without positive C-peptide. Recipient age<35, lower beta cell counts in the islet preparation(s), and fewer than 325K total IEQs infused are the major factors that attenuate protection from SHE.

Exhibit 5 – 9
Absence of Severe Hypoglycemia Post Last Infusion



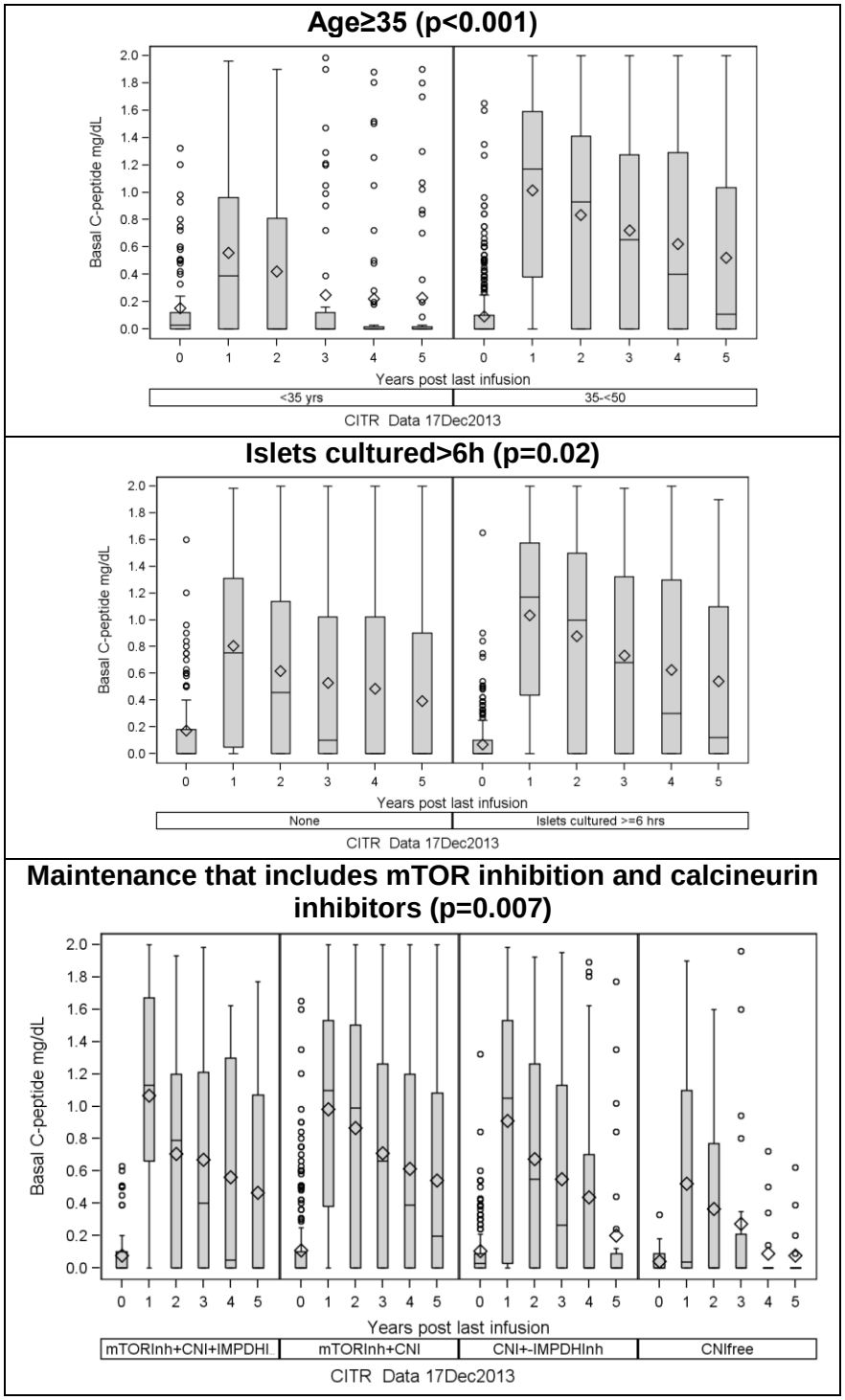
Levels of daily insulin requirement (U/day) declined dramatically in follow-up through 5-years after islet transplantation (Exhibit 5-10, p<0.001), with some return upwards over 5 years of follow-up. Factors associated with improved results are shown in Exhibit 5-10 and include: age≥35 (p<0.001); induction that includes TFN-a inhibition (p=0.006); and maintenance that includes mTOR inhibition and calcineurin inhibitors (p<0.001).

Exhibit 5 – 10
Insulin Dose (U/day) Post Last Infusion



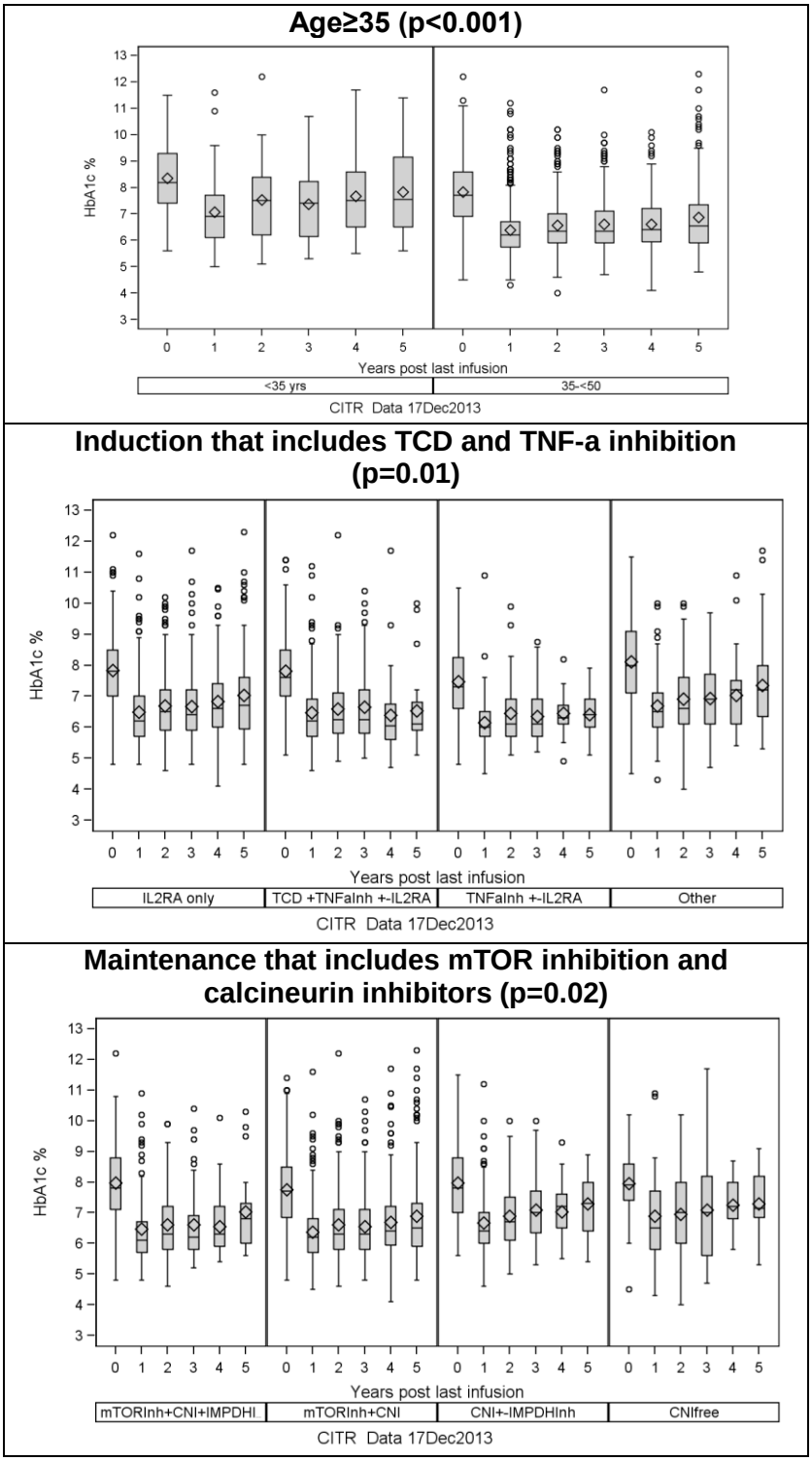
Fasting C-peptide rises dramatically after islet transplantation, with decline over 5 years although more than 50% retain C-peptide>0.3 ng/mL at 5-years post last infusion (Exhibit 5-11). Factors associated with improved results are shown in Exhibit 5-11 and include: age≥35 (p<0.001); islets cultured>6h (p=0.02); and maintenance that includes mTOR inhibition and calcineurin inhibitors (p=0.007).

Exhibit 5 – 11
Fasting C-peptide (ng/ml) Post Last Infusion



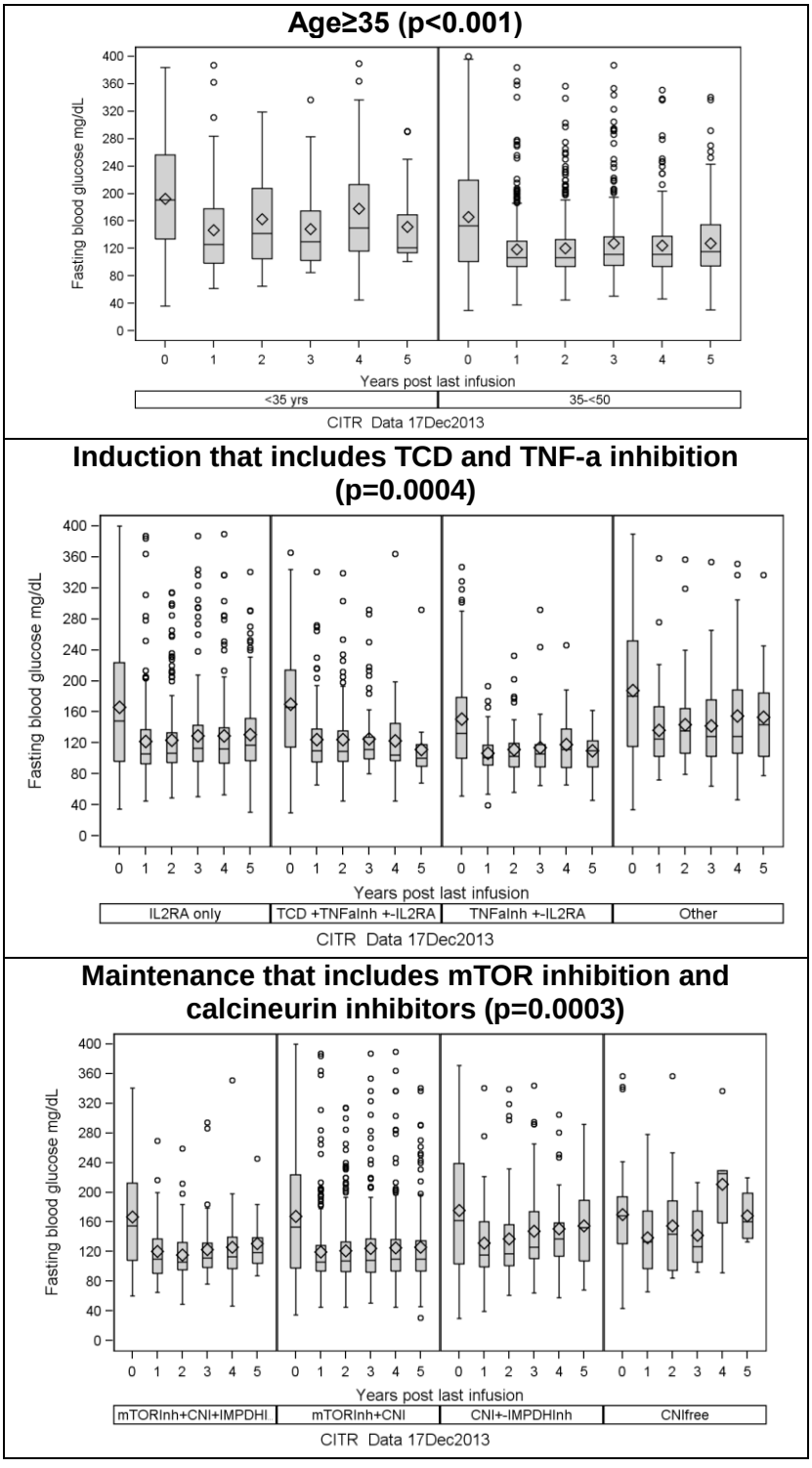
HbA1c declines sharply after islet transplantation, and does not return to pre-transplant levels (p<0.01, Exhibit 5-12). Factors associated with improved results are shown in Exhibit 5-12 and include: age≥35 (p=<0.001); induction that includes TCD and TNF-a inhibition (p=0.01); and maintenance that includes mTOR inhibition and calcineurin inhibitors (p=0.02).

Exhibit 5 – 12
HbA1c (%) Post Last Infusion



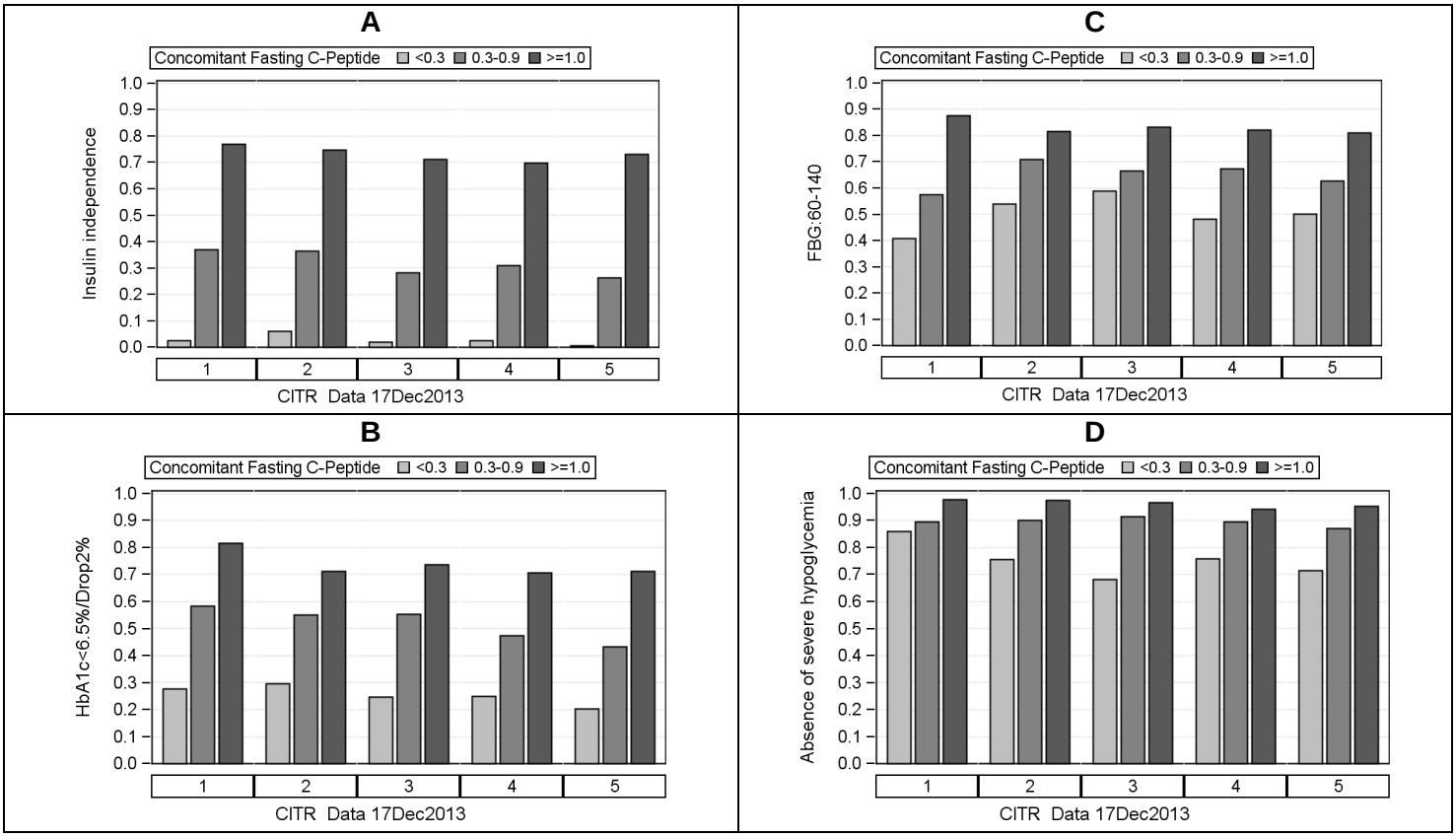
Fasting blood glucose also declines dramatically after islet transplantation and remains at levels of 80-120 mg/dL over 5 years (p<0.01, Exhibit 5-13). Factors associated with improved results are shown in Exhibit 5-13 and include: age≥35 (p=<0.001); induction that includes TCD and TNF-a inhibition (p=0.0004); and maintenance that includes mTOR inhibition and calcineurin inhibitors (p=0.0003).

Exhibit 5 – 13
Fasting Blood Glucose (mg/dl) Post Last Infusion



The higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<6.5% or drop by 2%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia (Exhibit 5-14). 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 – 14
Association of C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion



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. There are differences in change in ALT noted between ITA and IAK/SIK. Long-term recovery appears to be better in recipients aged<35 years. Induction with TCD or other non-IL2RA agent is associated with lower increase in ALT after islet transplantation.

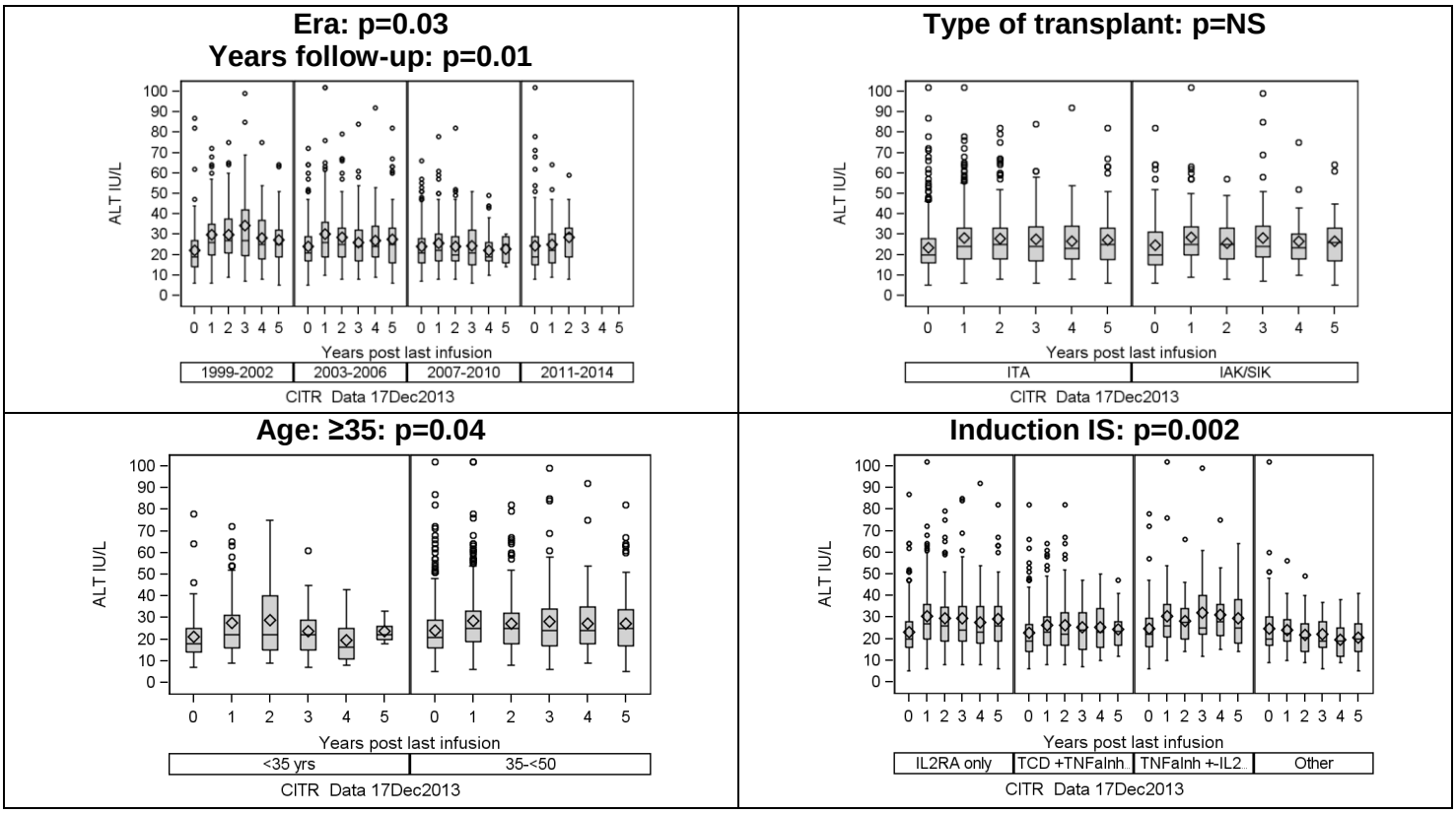


Exhibit 6 – 1B
AST (IU/L)

The same differences are seen with change in AST as in ALT.

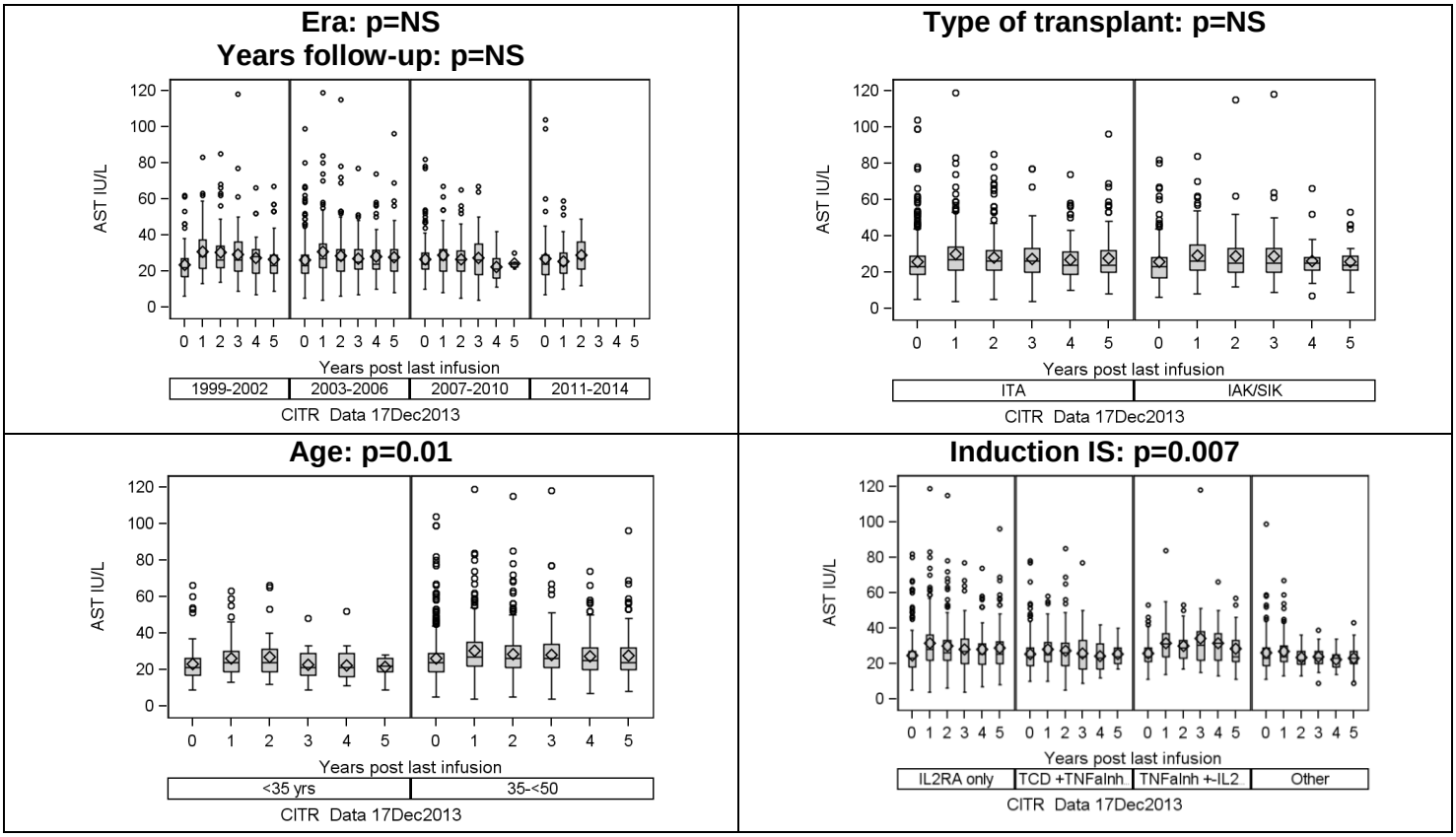


Exhibit 6 – 2
Alkaline Phosphatase

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.

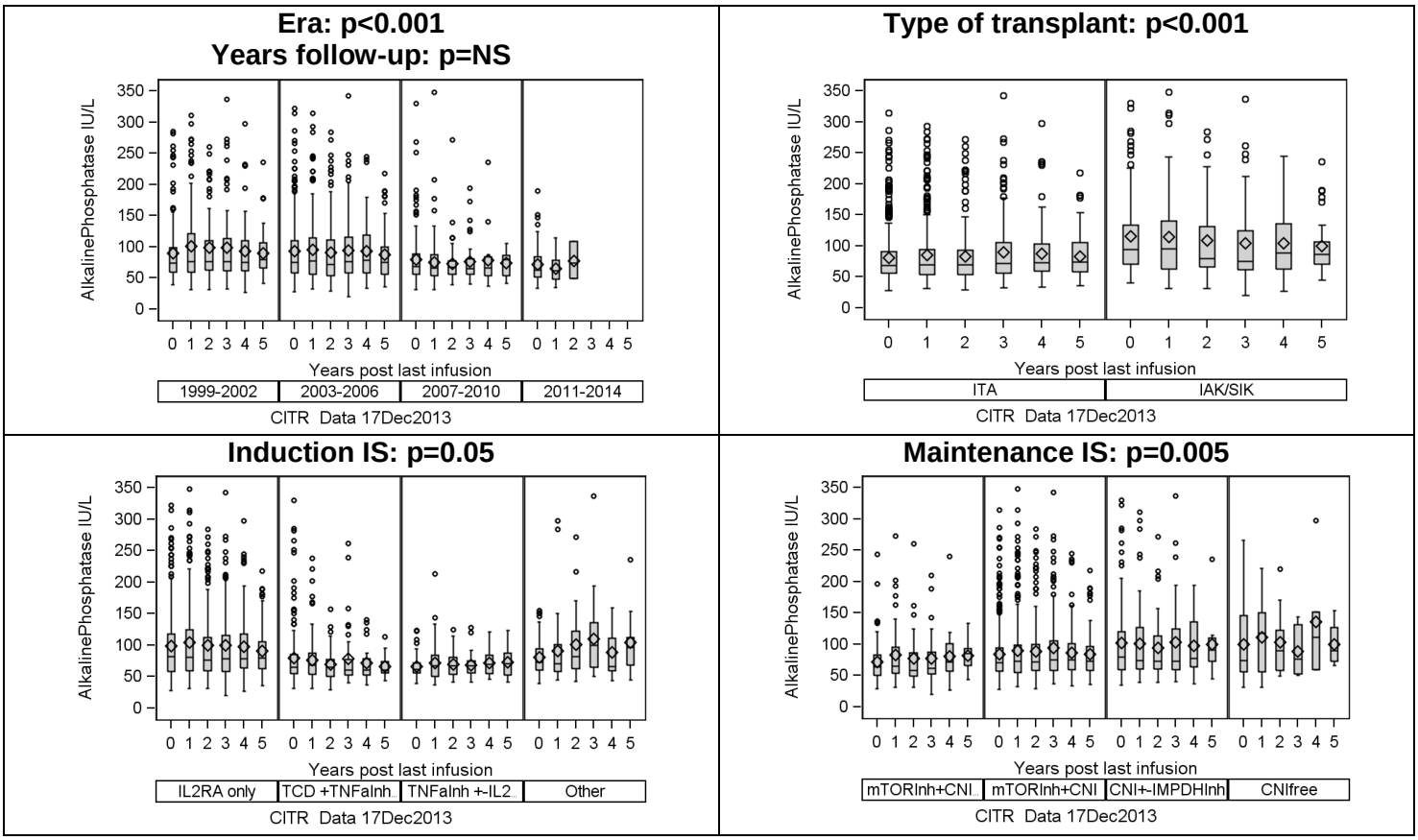


Exhibit 6 – 3
Total Bilirubin

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

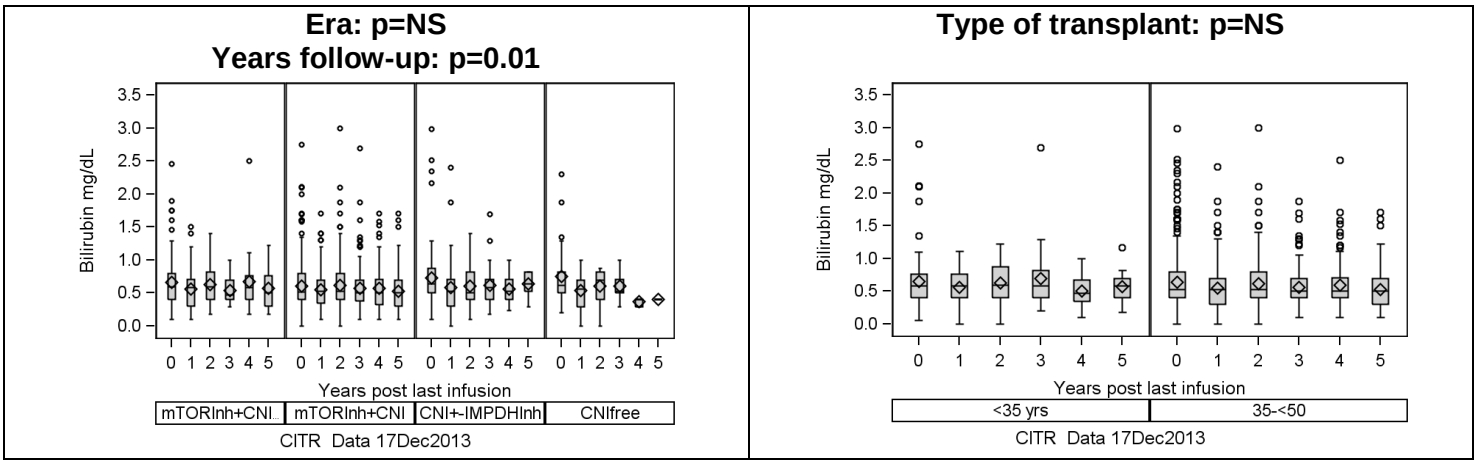


Exhibit 6 – 4
HDL Cholesterol

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. There were no differences by age or immunosuppression regimen.

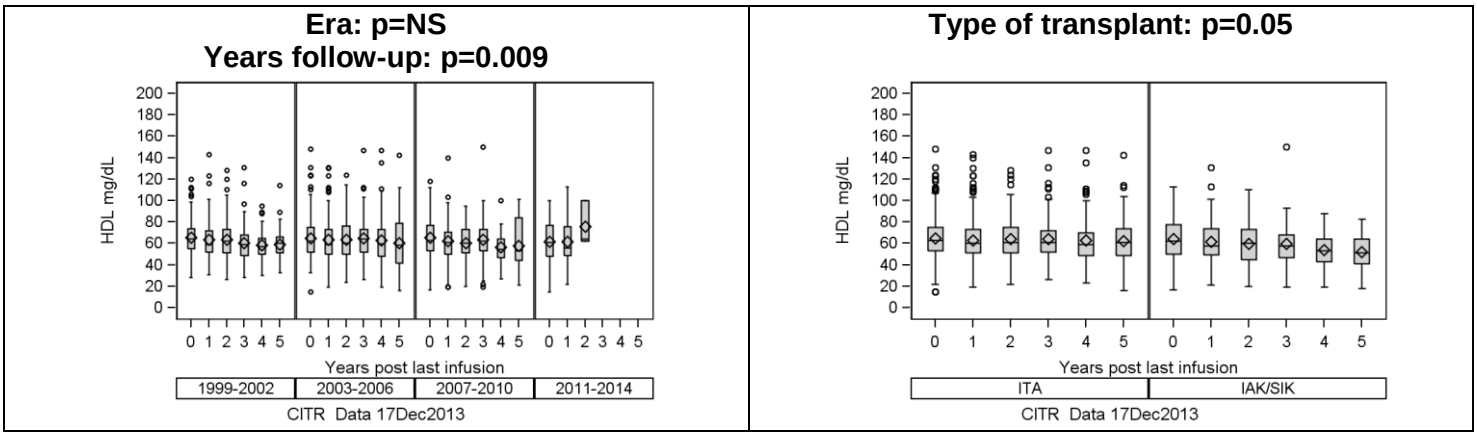
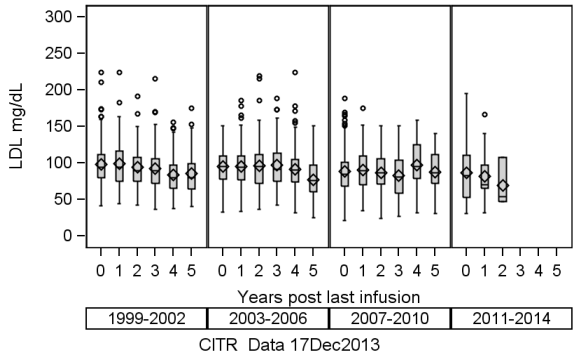


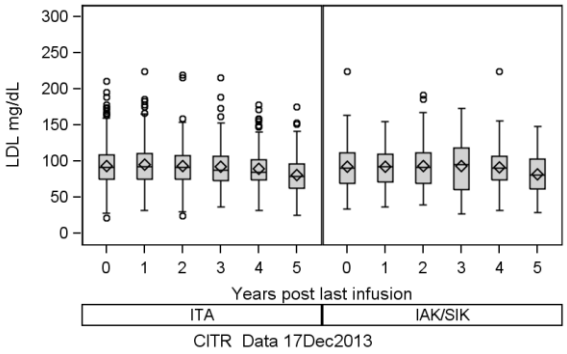
Exhibit 6 – 5
LDL Cholesterol

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.

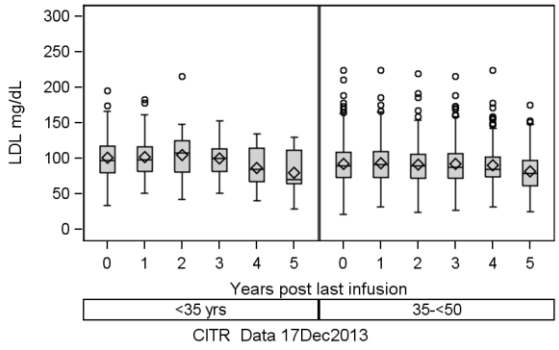
Era: p=0.003
Years follow-up: p<0.001



Type of transplant: p=NS



Age: p=0.004



Induction IS: p=0.002

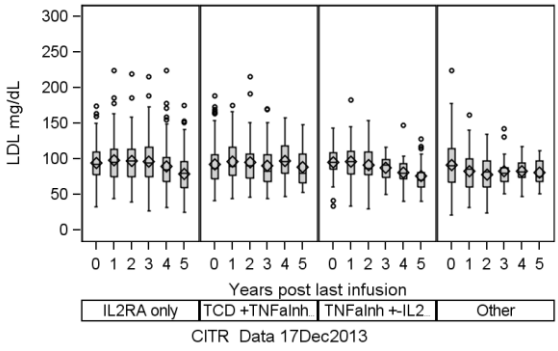
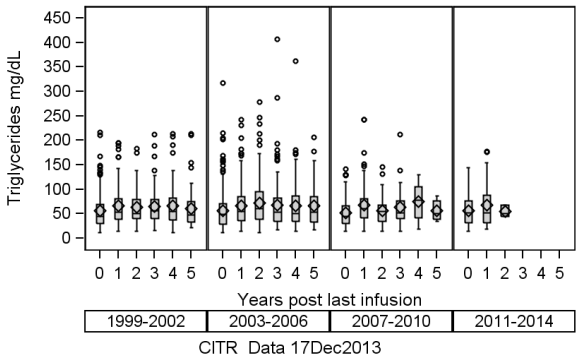


Exhibit 6 – 6
Triglycerides

Triglycerides rose somewhat following islet transplantation. Initial levels were higher in IAK/SIK recipients, though the subsequent rise was not different. There were no net effects of age or either induction or maintenance immunosuppression.

Era: p=NS
Years follow-up: p=0.001



Type of transplant: p=0.04

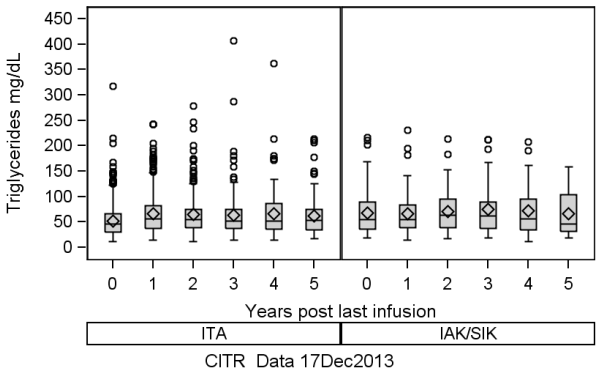
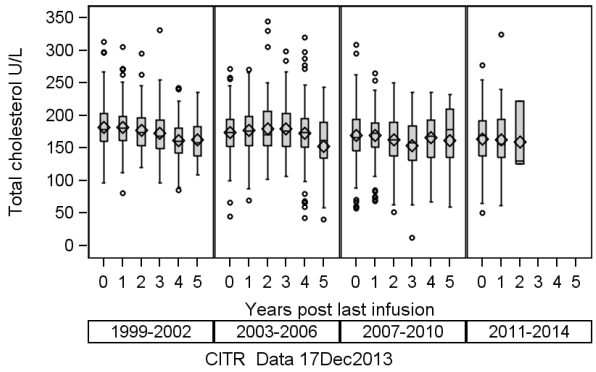


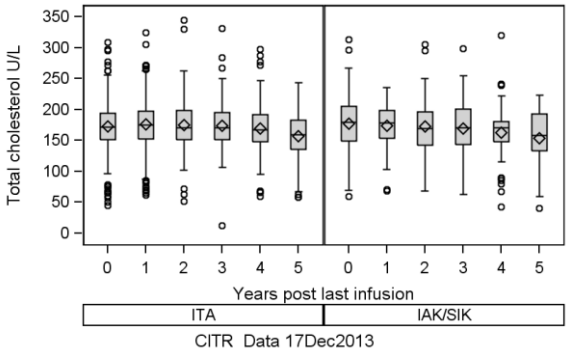
Exhibit 6 – 7
Total Cholesterol

Total cholesterol generally declined in follow-up after islet transplantation, though the pattern of change has varied by era. There were no notable differences between ITA and IAK/SIK, and borderline differences by age. Induction with TCD+TNFa inhibition is associated with significantly lower decline over follow-up. There were no notable effects of maintenance immunosuppression on changes in total cholesterol.

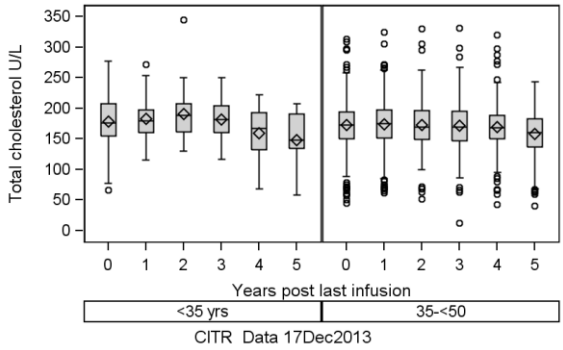
Era: p<0.001
Years follow-up: p<0.001



Type of transplant: p=NS



Age: p=0.05



Induction IS: p=0.002

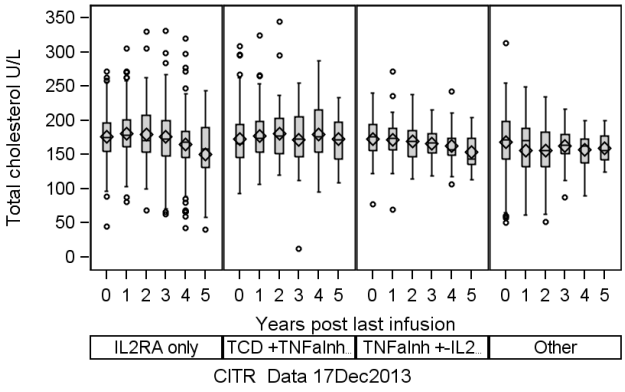
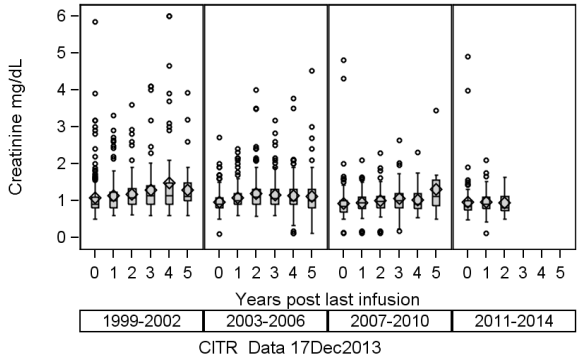


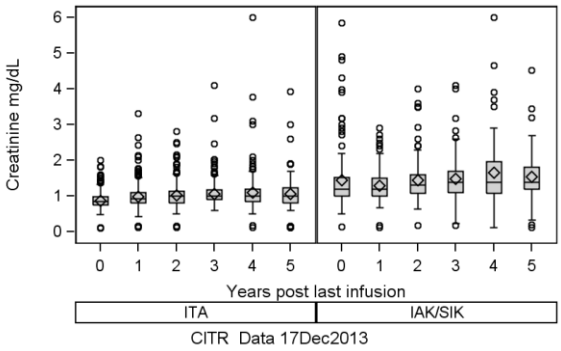
Exhibit 6 – 8
Serum Creatinine

Serum creatinine rose over years of follow-up after initial islet transplant, in both ITA and IAK/SIK. 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. Younger patients, both ITA and IAK/SIK, had lower initial levels of serum creatinine. There were no significant differences by immunosuppression regimen.

Era: p<0.001
Years of follow-up: p=0.001



Type of transplant: p<0.001



Age: p=0.01

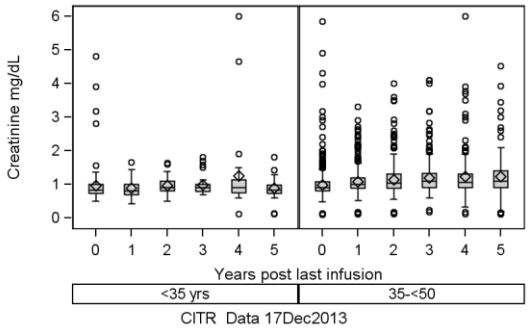
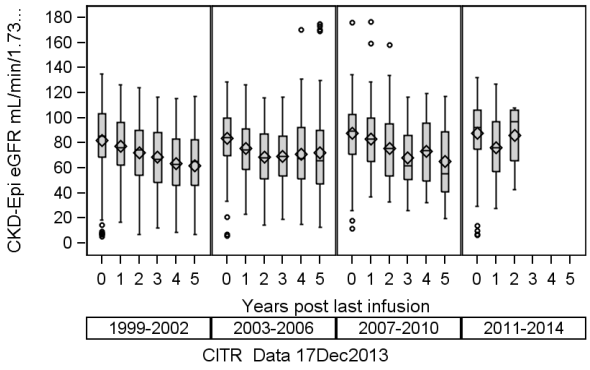


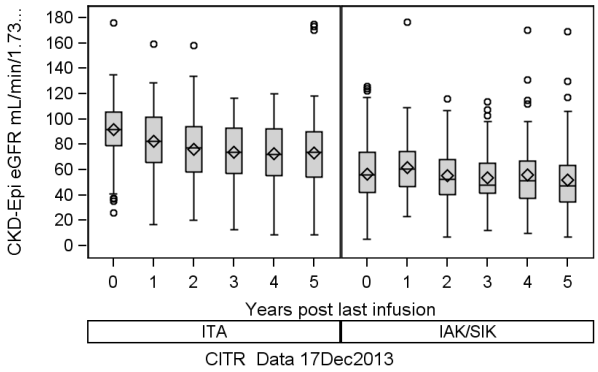
Exhibit 6 – 9
CKD-EPI eGFR

The decline in eGFR after islet transplantation is both statistically significant and clinically important. The differences by era are due to both higher pre-transplant levels and a more blunted decline in the most recent era. 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.

Era: p=0.004
Years of follow-up: p<0.001



Type of transplant: p<0.001



Age: p<0.001

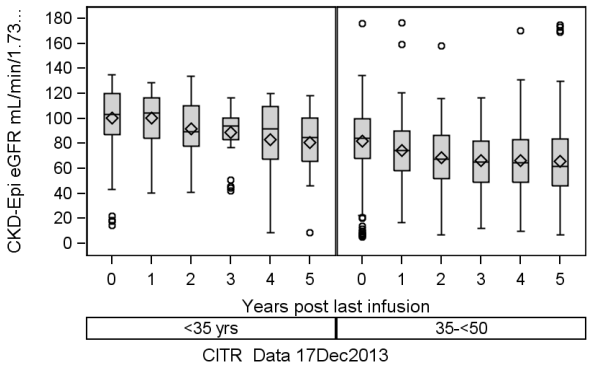
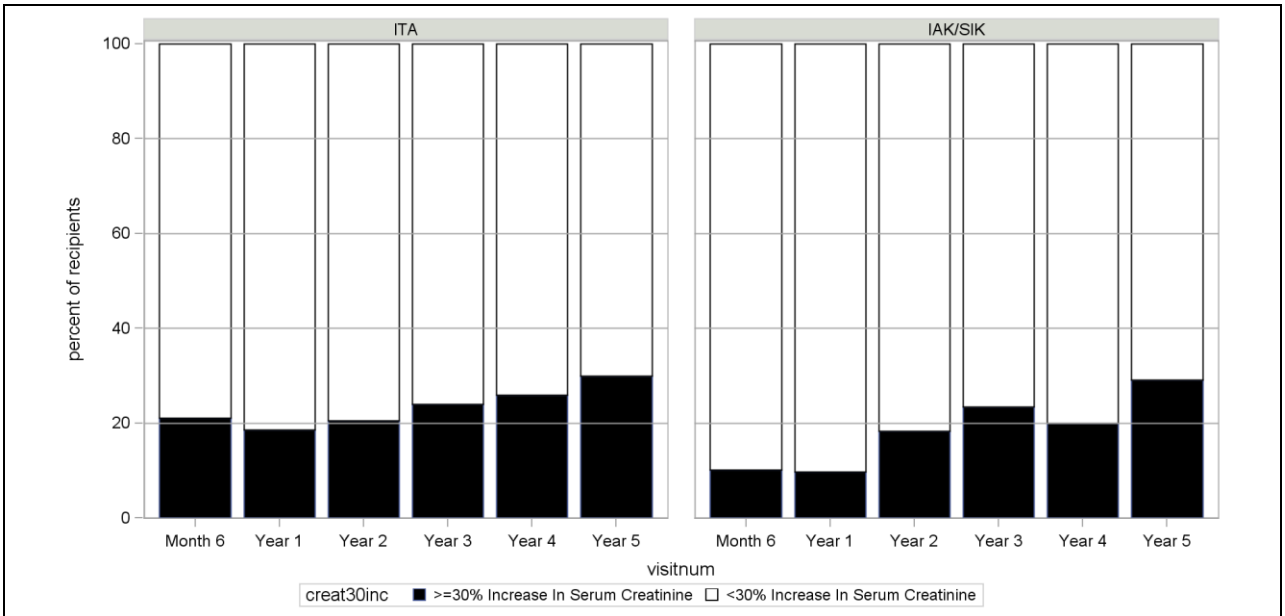
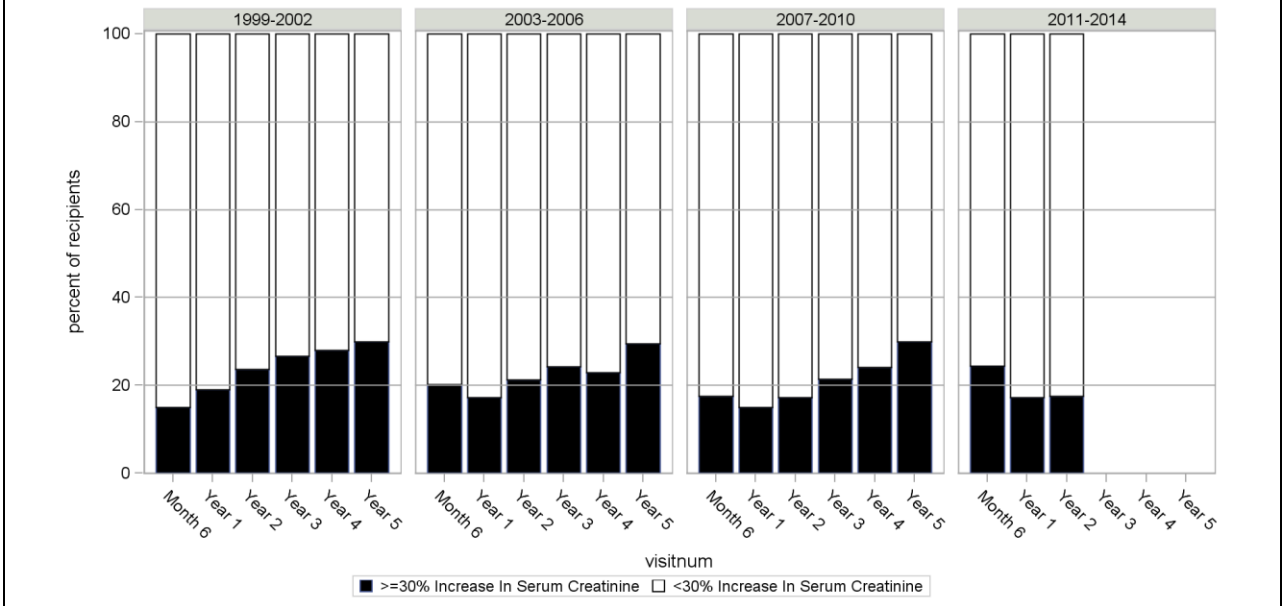


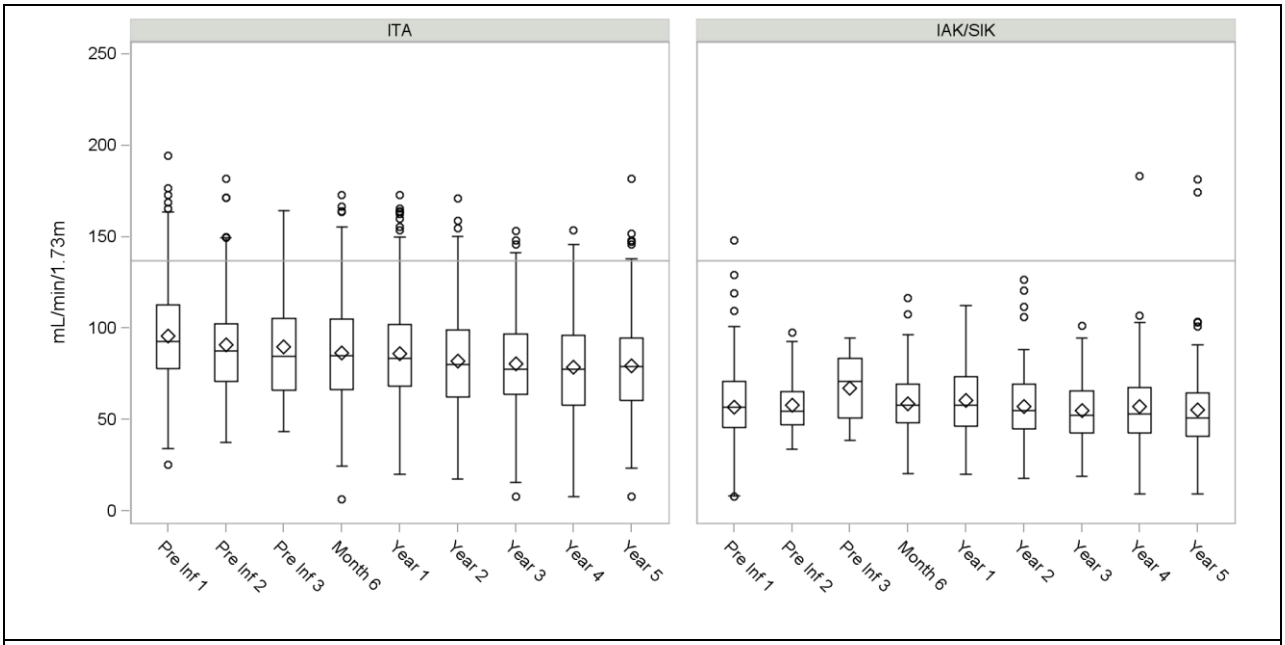
Exhibit 6 – 10
Percent of Recipients with a 30% increase in Serum Creatinine at each Follow-up Time Point by Infusion Type and Era

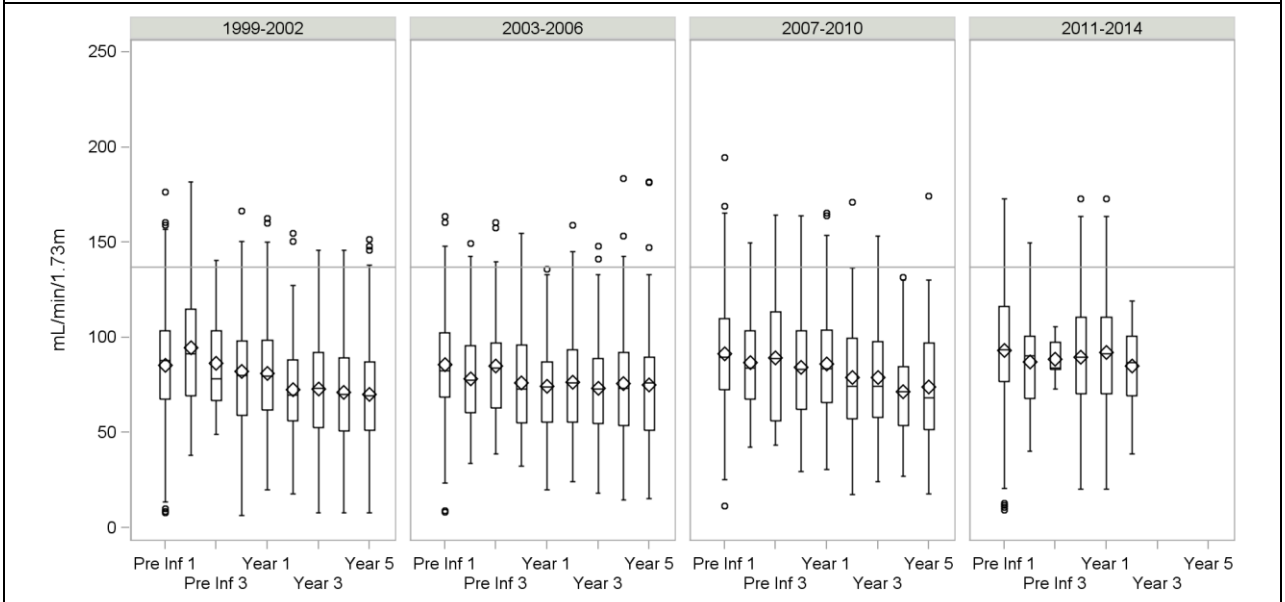




	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	507	506	430	376	285	251
IAK/SIK	118	123	109	98	85	86
1999-2002	121	137	114	120	104	107
2003-2006	178	181	193	186	166	173
2007-2010	211	200	192	168	100	57
2011-2014	115	111	40	.	.	.

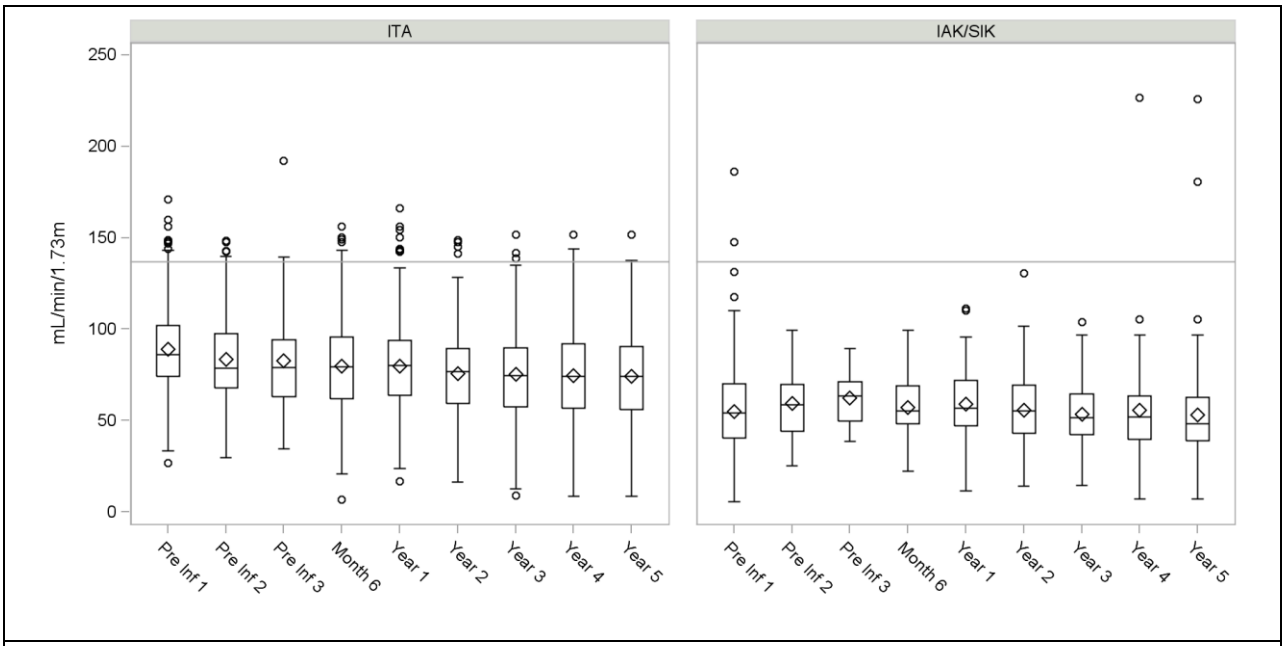
Exhibit 6 – 11
Cockgroft-Gault Calculated Clearance(mL/min/1.73m2) by Immunosuppression Categories

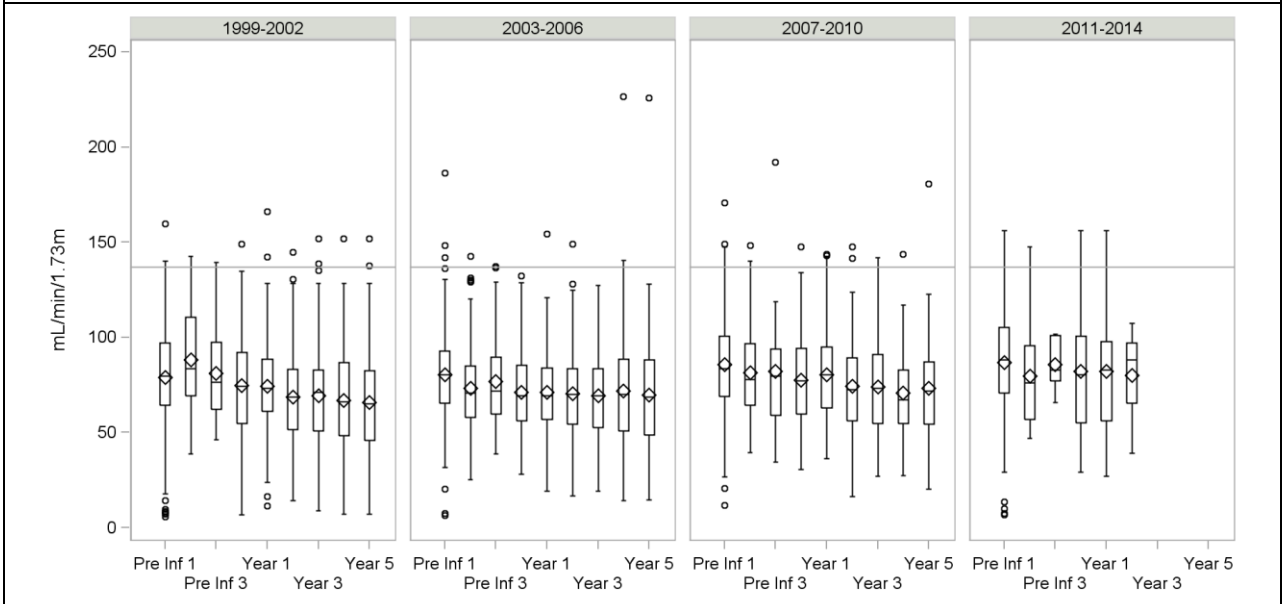




	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	545	191	78	370	378	304	288	216	199
IAK/SIK	134	48	15	77	84	85	79	70	72
1999-2002	178	37	21	103	111	98	101	93	94
2003-2006	247	97	40	146	151	163	154	131	134
2007-2010	173	74	24	142	152	113	112	62	43
2011-2014	81	31	8	56	48	15	.	.	.

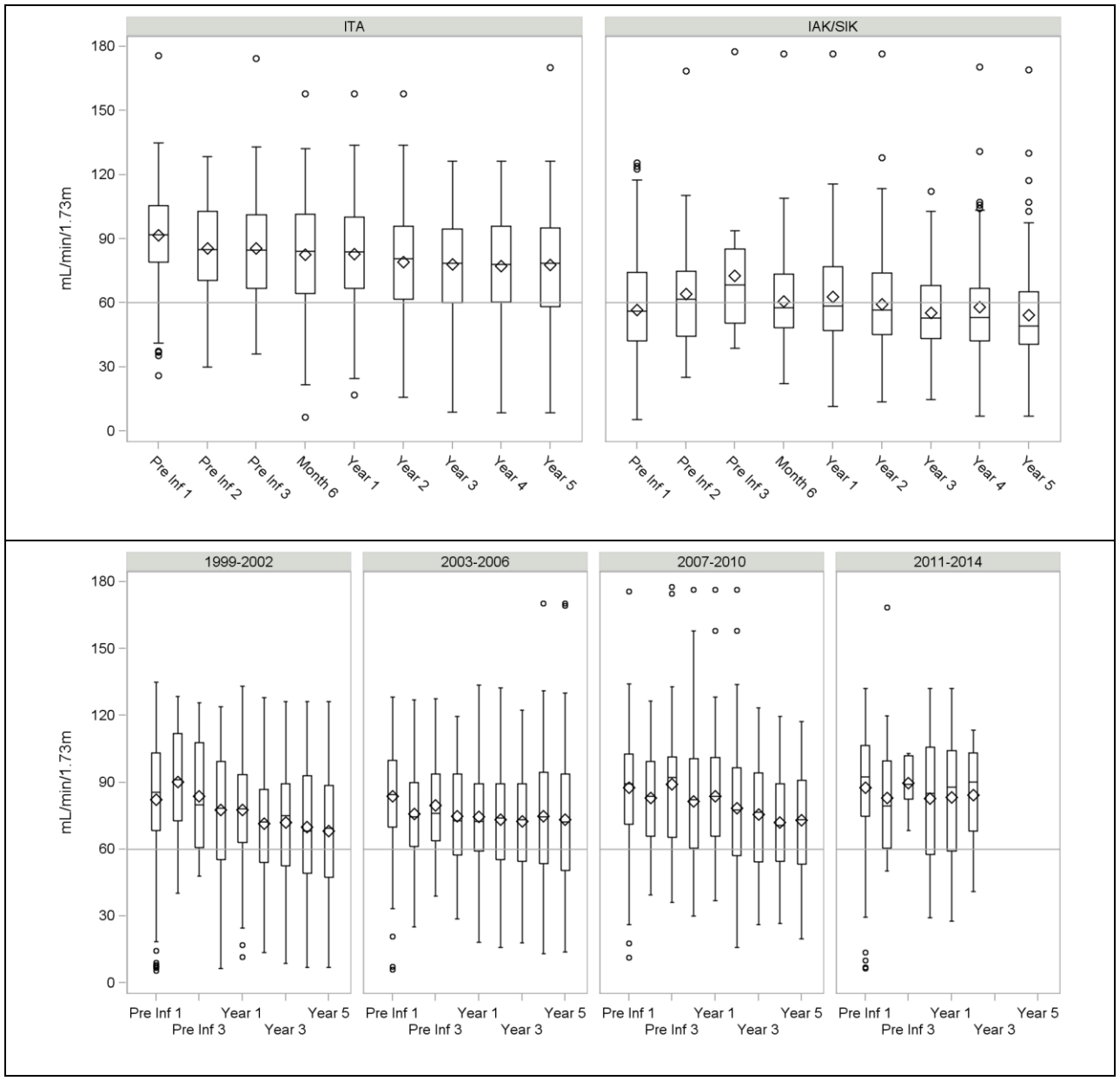
Exhibit 6 – 12
MDRD Estimated Cockgroft-Gault(mL/min/1.73m2) by Immunosuppression Categories





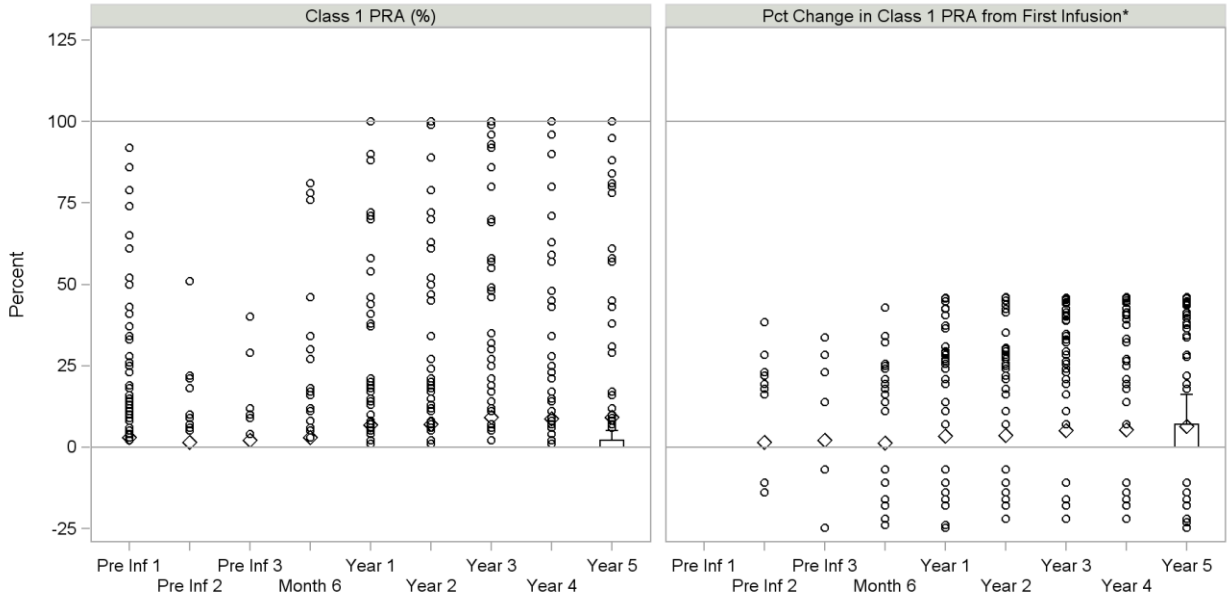
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	562	210	88	402	415	328	314	244	226
IAK/SIK	138	52	17	93	92	92	85	76	80
1999-2002	180	39	22	112	121	101	112	99	104
2003-2006	254	104	46	161	162	177	167	148	153
2007-2010	177	76	27	151	163	125	120	73	49
2011-2014	89	43	10	71	61	17	.	.	.

Exhibit 6 – 13
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR(mL/min/1.73m^2) by Immunosuppression Categories



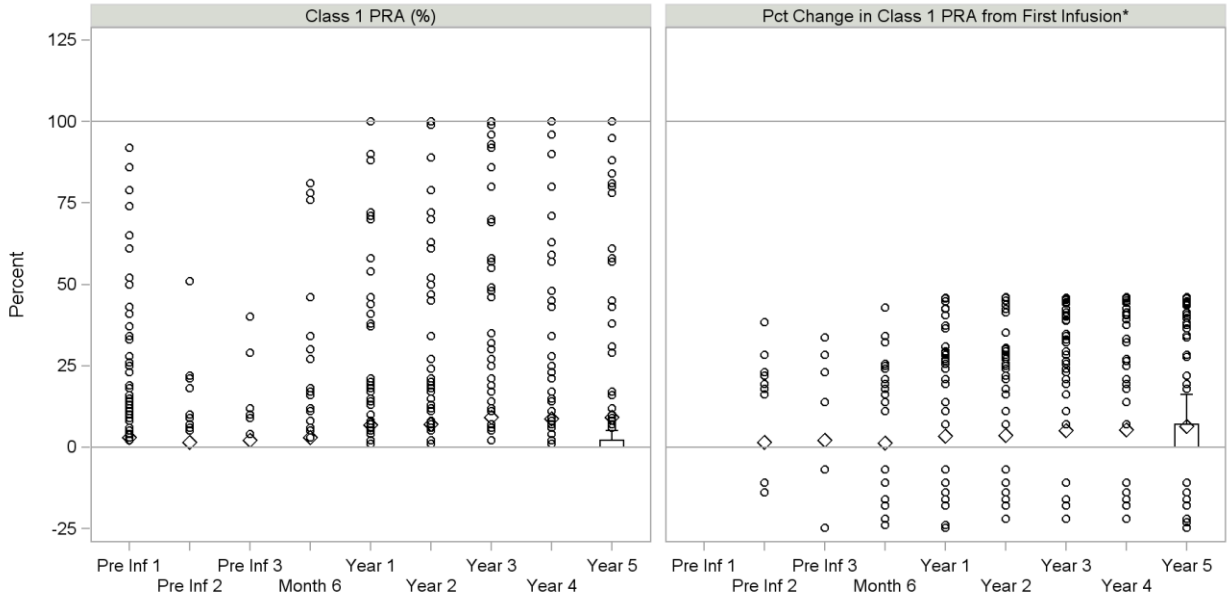
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
ITA	562	210	88	402	415	328	314	244	226
IAK/SIK	138	52	17	93	92	92	85	76	80
1999-2002	180	39	22	112	121	101	112	99	104
2003-2006	254	104	46	161	162	177	167	148	153
2007-2010	177	76	27	151	163	125	120	73	49
2011-2014	89	43	10	71	61	17	.	.	.

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 (%)	439	102	49	182	207	200	173	141	132
Pct Change in Class 1 PRA from First Infusion	.	92	45	175	197	188	158	128	120

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	20	36	46	43	31	33
without Complete Graft Loss	98	100	83	61	53	40

Chapter 7
Adverse Events

Introduction

In the first 30 days following islet transplantation, about 31% of recipients experienced a reportable adverse event (Exhibit 7-1A), which occurred less frequently in IAK/SIK (24%) than ITA (33%). Roughly half of these events were adjudicated by the local investigator as possibly to definitely related to either the infusion procedure or the immunosuppression (IS). The vast majority was not unexpected, such as abnormal lymphocyte count and increased liver function. Very few were infections. The instances of peritoneal hemorrhage seen in the early era 1999-2002 have been drastically reduced in the recent eras.

About 20% of all recipients experienced a serious adverse event in the first 30 days (Exhibit 7-1B), which occurred about equally in IAK/SIK as in ITA, and have declined somewhat over the eras.

In the first year after islet transplantation, which includes the vast majority of the re-infusions that were performed, about 48% of all recipients experienced a reportable adverse event (Exhibit 7-2A), with a decline in the most recent era. About one-third have experienced a serious adverse event within the first year (Exhibit 7-2B), with a significant decline in the most recent era. This pattern is also seen for all adverse events in all follow-up after islet transplantation (Exhibit 7-3).

The outcomes of the reported adverse events have improved over the decade, with fewer patients experiencing long-term sequelae of their adverse events in the most recent era (Exhibit 7-4). Many adverse events seen in this population are unrelated to islet transplantation but not unexpected in a cohort of older T1D with significant co-morbidity. Overall, 16% of all recipients failed to recover completely from an adverse event (Exhibit 7-5).

Expressed as events per person-year of follow-up, both non-serious and serious reportable adverse events occur with a frequency of about 0.1 event per person-year, with a concentration in 1999 (Exhibit 7-7). AEs related to immunosuppression (IS) are also most frequent in the first year of follow-up (Exhibits 7-7B and 7-8B) and then decline rapidly after the first year.

Exhibit 7-9 displays trends in AE and SAE incidence according to type of transplant, era and relatedness to the infusion procedure and immunosuppression. While marginally significant differences are noted by era (see above), there may be differences according to immunosuppression strategies and patient characteristics that deserve further investigation.

There have been 21 instances in 17 patients of basal or squamous carcinoma of the skin (Exhibit 7-10). There have been 16 recipients who developed non-skin cancers, of whom 8 (57%) recovered completely, 2 recovered with sequelae, 5 did not recover, and one died. In recent reports, malignancy may be increased with either diabetes or with the use of immunosuppression. It is difficult with these few cases to definitively determine if the reported neoplasms are related to islet transplantation.

There have been 25 or 2.9% deaths, with 15 in the early cohort 1999-2003 (Exhibit 7-11), although cumulative mortality rates by era are not different. Of the 25 reported deaths, two were deemed possibly related and three were deemed definitely related to islet transplantation or immunosuppression (Exhibit 7-11).

Life-threatening events have occurred in 24% of recipients in 1999-2003 and only 4% in 2011-2014 ($p<0.001$, Exhibit 7-12). Most involved neutropenia and abnormal liver function. The vast majority recovered, 5 died (included above), 7 did not recover, and 12 recovered with sequelae.

Exhibit 7 – 1A
Adverse Events (AEs) in Days 0-30 Post First Infusion

Percent of Recipients with:	Type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Any AE in Day 0-30	227	33.1	42	23.6	67	32.1	98	36.2	80	34.8	24	15.6
Any AE related to infusion in Day 0-30	126	18.4	22	12.4	45	21.5	58	21.4	37	16.1	8	5.2
Any AE related to IS in Day 0-30	129	18.8	18	10.1	37	17.7	55	20.3	47	20.4	8	5.2
Any AE related to both in Day 0-30	35	5.1	6	3.4	15	7.2	12	4.4	12	5.2	2	1.3
Any AE related to neither in Day 0-30	63	9.2	14	7.9	9	4.3	16	5.9	36	15.7	16	10.4

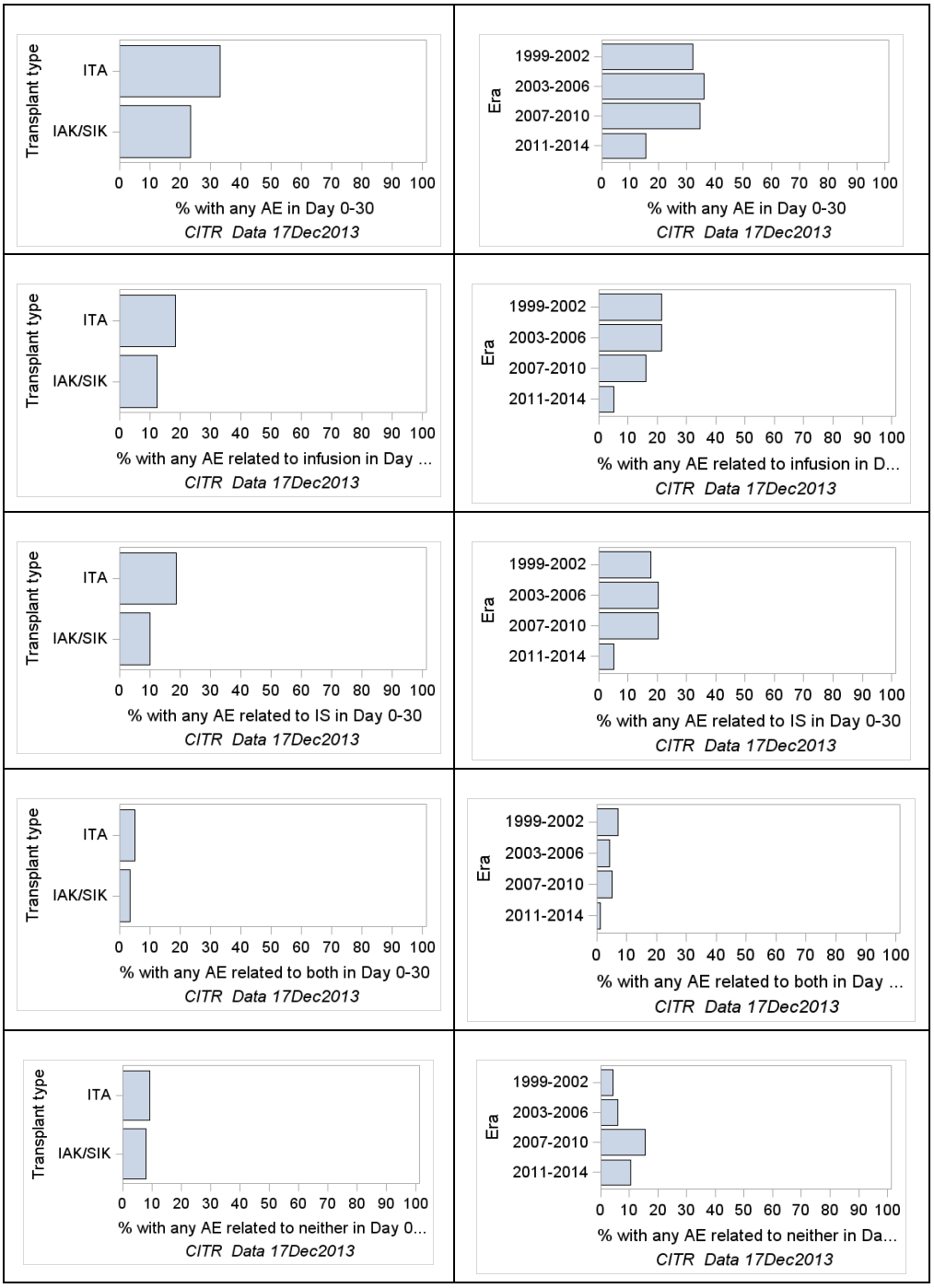


Exhibit 7 – 1A *(continued)*
Adverse Events (AEs) in Days 0-30 Post First Infusion
(Counts by AE Category)

		Overall	Transplant type		Era			
			ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
System/Organ Class	Preferred term							
Blood and lymphatic system disorders	Anaemia	9	6	3	1	4	4	.
	Blood disorder	2	2	.	.	.	1	1
	Febrile neutropenia	2	2	.	.	.	2	.
	Leukopenia	2	1	1	.	.	2	.
	Lymphopenia	37	35	2	.	10	22	5
	Neutropenia	8	8	.	.	.	7	1
	Platelet disorder	2	2	.	.	1	1	.
Cardiac disorders	Arrhythmia supraventricular	2	2	.	.	.	2	.
	Cardiac disorder	1	1	.	.	.	1	.
	Myocardial ischaemia	3	2	1	1	1	1	.
Gastrointestinal disorders	Ascites	1	1	.	1	.	.	.
	Diarrhoea	5	4	1	.	4	1	.
	Gastrointestinal disorder	1	1	.	.	1	.	.
	Gastrointestinal haemorrhage	3	1	2	1	2	.	.
	Gastrointestinal obstruction	1	1	.	.	.	1	.
	Gastrointestinal perforation	1	1	.	.	.	1	.
	Haemorrhoids	1	1	.	.	1	.	.
	Ileus	1	1	.	1	.	.	.
	Nausea	5	3	2	.	3	1	1
	Peritoneal haemorrhage	18	12	6	8	5	5	.
	Vomiting	8	5	3	2	.	4	2
General disorders and administration site conditions	Mucosal inflammation	1	1	.	.	1	.	.
	Oedema peripheral	1	1	.	.	.	1	.
	Pain	11	11	.	2	3	4	2
	Pyrexia	1	1	.	.	1	.	.
Hepatobiliary disorders	Cholecystitis	3	2	1	.	1	2	.
	Portal vein thrombosis	6	6	.	2	3	1	.
Immune system disorders	Cytokine release syndrome	1	1	.	.	.	1	.
	Hypersensitivity	2	2	.	.	2	.	.
Infections and infestations	Infection	8	5	3	1	6	1	.
Injury, poisoning and procedural complications	Fracture	1	1	.	.	1	.	.
	Toxicity to various agents	1	1	.	.	.	1	.
	Wound complication	1	1	.	.	.	1	.
	Wound dehiscence	1	1	.	.	.	1	.

Exhibit 7 – 1A *(continued)*
Adverse Events (AEs) in Days 0-30 Post First Infusion
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Investigations	**Activated partial thromboplastin time**	1	1	.	1	.	.	.
	Alanine aminotransferase increased	6	6	.	.	.	4	2
	Aspartate aminotransferase increased	5	5	.	.	.	4	1
	Blood alkaline phosphatase	14	13	1	3	9	2	.
	Blood phosphorus decreased	2	2	.	.	.	2	.
	Gamma-glutamyltransferase	6	5	1	1	3	2	.
	Gamma-glutamyltransferase increased	2	2	.	.	.	1	1
	Granulocytes abnormal	101	100	1	29	47	19	6
	Haemoglobin decreased	1	1	.	.	.	1	.
	Hepatic enzyme increased	3	3	.	.	.	2	1
	Lipase	4	1	3	1	3	.	.
	Liver function test abnormal	94	91	3	35	38	16	5
	Low density lipoprotein increased	1	1	.	.	.	1	.
	Neutrophil count	2	2	.	.	.	2	.
	Neutrophil count decreased	8	8	.	.	.	7	1
	Transaminases	3	3	.	.	.	3	.
	Transaminases increased	2	2	.	.	.	1	1
	Troponin T	1	1	.	.	.	1	.
Metabolism and nutrition disorders	**Hyperglycaemia**	6	.	6	.	.	.	6
	Hyperkalaemia	1	1	.	1	.	.	.
	Hypoalbuminaemia	2	2	.	1	.	1	.
	Hypocalcaemia	1	1	.	.	.	1	.
	Hypoglycaemia	18	16	2	4	7	5	2
	Hypokalaemia	7	6	1	.	1	5	1
	Hyponatraemia	2	1	1	.	1	1	.
	Hypophosphataemia	9	7	2	.	.	7	2
	Ketoacidosis	15	13	2	4	9	2	.
Musculoskeletal and connective tissue disorders	**Muscular weakness**	1	1	.	.	1	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	2	1	1	.	2	.	.
Nervous system disorders	**Cerebral ischaemia**	1	.	1	1	.	.	.
	Dyskinesia	1	1	.	.	.	1	.
	Headache	2	2	.	.	.	2	.
	Hypoglycaemic seizure	1	.	1	.	.	.	1
	Presyncope	1	1	.	.	.	1	.

Exhibit 7 – 1A *(continued)*
Adverse Events (AEs) in Days 0-30 Post First Infusion
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Respiratory, thoracic and mediastinal disorders	**Aspiration**	1	1	.	.	.	1	.
	Dyspnoea	2	1	1	1	.	1	.
	Haemothorax	1	.	1	.	1	.	.
	Hypoxia	2	2	.	.	.	2	.
	Lung disorder	1	.	1	.	1	.	.
	Pleural effusion	1	1	.	.	.	1	.
	Pneumonitis	1	.	1	1	.	.	.
	Pulmonary hypertension	1	1	.	.	.	1	.
Skin and subcutaneous tissue disorders	**Exfoliative rash**	2	2	.	.	.	2	.
Surgical and medical procedures	**Surgery**	1	1	.	1	.	.	.
Vascular disorders	**Haematoma**	7	5	2	1	3	1	2
	Haemorrhage	7	4	3	1	2	1	3
	Hypertension	2	.	2	.	1	1	.
	Hypotension	3	3	.	.	.	3	.
	Thrombosis	2	.	2	2	.	.	.

Exhibit 7 – 1B
Serious Adverse Events (SAEs) in Days 0-30 Post First Infusion

Percent of Recipients with:	Type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE in Day 0-30	110	16.0	28	15.7	32	15.3	54	19.9	38	16.5	14	9.1
Any SAE related to infusion in Day 0-30	66	9.6	17	9.6	23	11.0	35	12.9	18	7.8	7	4.5
Any SAE related to IS in Day 0-30	54	7.9	11	6.2	6	2.9	26	9.6	26	11.3	7	4.5
Any SAE related to both in Day 0-30	12	1.7	3	1.7	1	0.5	5	1.8	7	3.0	2	1.3
Any SAE related to neither in Day 0-30	11	1.6	7	3.9	5	2.4	5	1.8	5	2.2	3	1.9

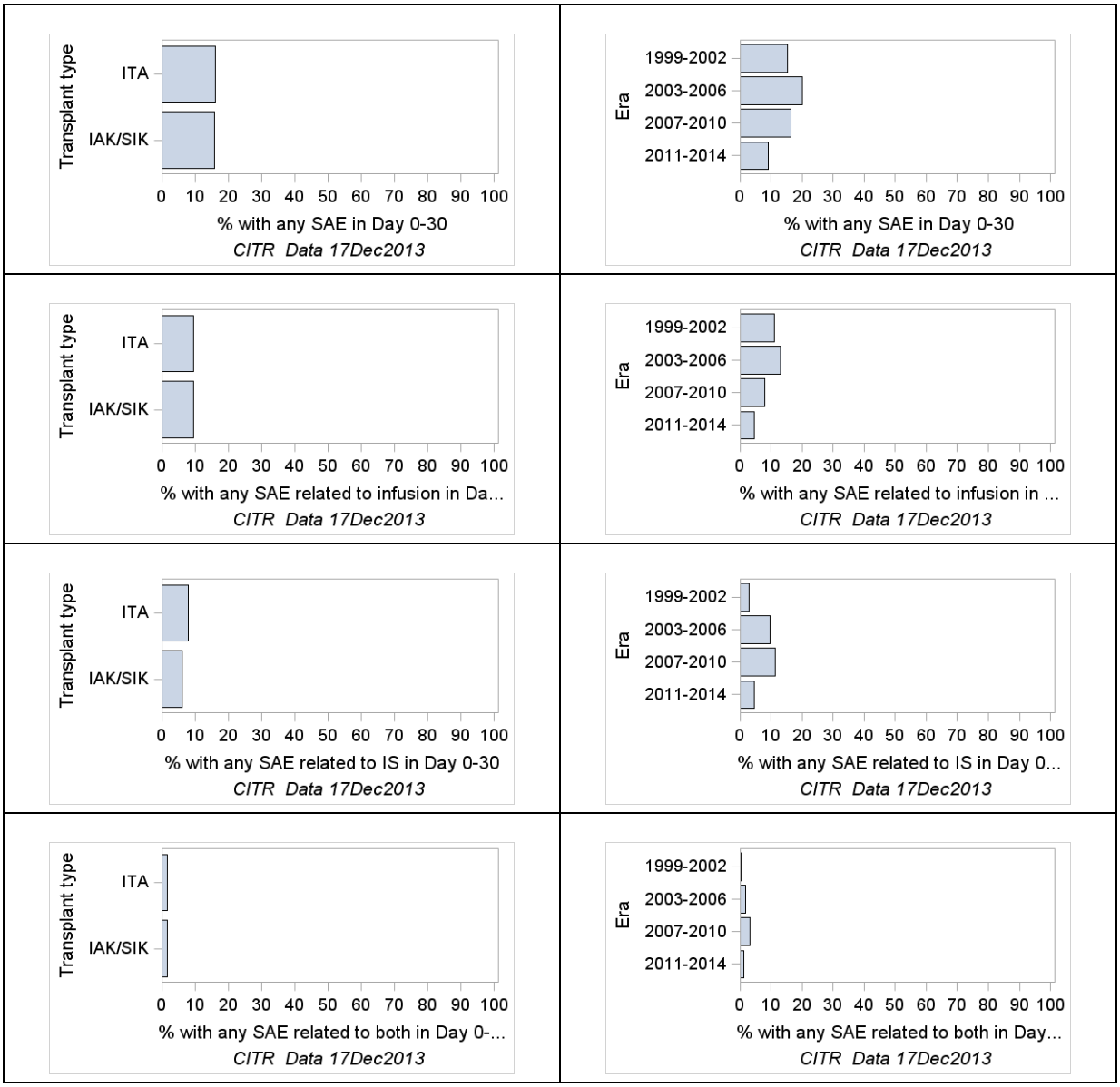


Exhibit 7 – 1B *(continued)*
Serious Adverse Events (SAEs) in Days 0-30 Post First Infusion

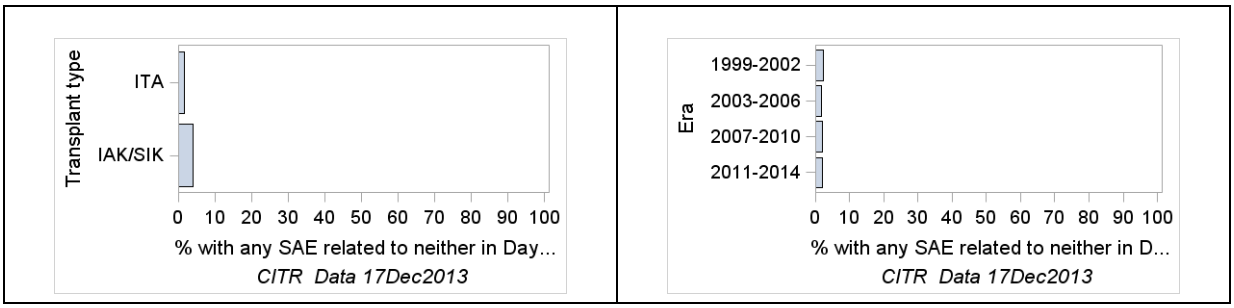


Exhibit 7 – 1B *(continued)*
Serious Adverse Events (SAEs) in Days 0-30 Post First Infusion
(Counts by SAE Category)

		Overall	Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
System/Organ Class	**Preferred term**							
Blood and lymphatic system disorders	**Anaemia**	4	2	2	.	2	2	.
	Blood disorder	1	1	.	.	.	1	.
	Febrile neutropenia	1	1	.	.	.	1	.
	Lymphopenia	6	5	1	.	4	2	.
	Neutropenia	2	2	.	.	.	2	.
	Platelet disorder	1	1	.	.	1	.	.
Cardiac disorders	**Arrhythmia supraventricular**	1	1	.	.	.	1	.
	Cardiac disorder	1	1	.	.	.	1	.
	Myocardial ischaemia	3	2	1	1	1	1	.
Gastrointestinal disorders	**Diarrhoea**	3	2	1	.	2	1	.
	Gastrointestinal disorder	1	1	.	.	1	.	.
	Gastrointestinal haemorrhage	3	1	2	1	2	.	.
	Gastrointestinal obstruction	1	1	.	.	.	1	.
	Gastrointestinal perforation	1	1	.	.	.	1	.
	Haemorrhoids	1	1	.	.	1	.	.
	Ileus	1	1	.	1	.	.	.
	Nausea	3	2	1	.	1	1	1
	Peritoneal haemorrhage	13	9	4	6	4	3	.
	Vomiting	7	4	3	1	.	4	2
General disorders and administration site conditions	**Mucosal inflammation**	1	1	.	.	1	.	.
	Pain	7	7	.	2	1	2	2
	Pyrexia	1	1	.	.	1	.	.
Hepatobiliary disorders	**Cholecystitis**	3	2	1	.	1	2	.
	Portal vein thrombosis	6	6	.	2	3	1	.
Immune system disorders	**Cytokine release syndrome**	1	1	.	.	.	1	.
	Hypersensitivity	1	1	.	.	1	.	.
Infections and infestations	**Infection**	8	5	3	1	6	1	.
Injury, poisoning and procedural complications	**Toxicity to various agents**	1	1	.	.	.	1	.

Exhibit 7 – 1B *(continued)*
Serious Adverse Events (SAEs) in Days 0-30 Post First Infusion
(Counts by SAE Category)

		Overall	Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Investigations	**Blood alkaline phosphatase**	8	8	.	2	6	.	.
	Granulocytes abnormal	21	21	.	4	9	6	2
	Liver function test abnormal	27	27	.	12	15	.	.
	Neutrophil count	1	1	.	.	.	1	.
	Neutrophil count decreased	1	1	.	.	.	1	.
	Troponin T	1	1	.	.	.	1	.
Metabolism and nutrition disorders	**Hyperglycaemia**	6	.	6	.	.	.	6
	Hypoglycaemia	5	4	1	2	1	1	1
	Ketoacidosis	1	1	.	.	.	1	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	1	1	.	.	1	.	.
Nervous system disorders	**Cerebral ischaemia**	1	.	1	1	.	.	.
	Headache	2	2	.	.	.	2	.
	Hypoglycaemic seizure	1	.	1	.	.	.	1
Respiratory, thoracic and mediastinal disorders	**Aspiration**	1	1	.	.	.	1	.
	Dyspnoea	2	1	1	1	.	1	.
	Haemothorax	1	.	1	.	1	.	.
	Hypoxia	1	1	.	.	.	1	.
	Lung disorder	1	.	1	.	1	.	.
	Pleural effusion	1	1	.	.	.	1	.
	Pneumonitis	1	.	1	1	.	.	.
	Pulmonary hypertension	1	1	.	.	.	1	.
Skin and subcutaneous tissue disorders	**Exfoliative rash**	1	1	.	.	.	1	.
Surgical and medical procedures	**Surgery**	1	1	.	1	.	.	.
Vascular disorders	**Haematoma**	7	5	2	1	3	1	2
	Haemorrhage	7	4	3	1	2	1	3
	Hypotension	2	2	.	.	.	2	.
	Thrombosis	2	.	2	2	.	.	.

Exhibit 7 – 2A
Adverse Event (AEs) in Year 1 Post First Infusion

Percent of Recipients with:	Type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
`Any AE in 1-year	343	50.0	83	46.6	114	54.5	160	59.0	113	49.1	39	25.3
Any AE related to infusion in 1-year	178	25.9	39	21.9	64	30.6	87	32.1	52	22.6	14	9.1
Any AE related to IS in 1-year	228	33.2	47	26.4	75	35.9	117	43.2	71	30.9	12	7.8
Any AE related to both in 1-year	58	8.5	10	5.6	25	12.0	23	8.5	17	7.4	3	1.9
Any AE related to neither in 1-year	140	20.4	35	19.7	37	17.7	48	17.7	60	26.1	30	19.5

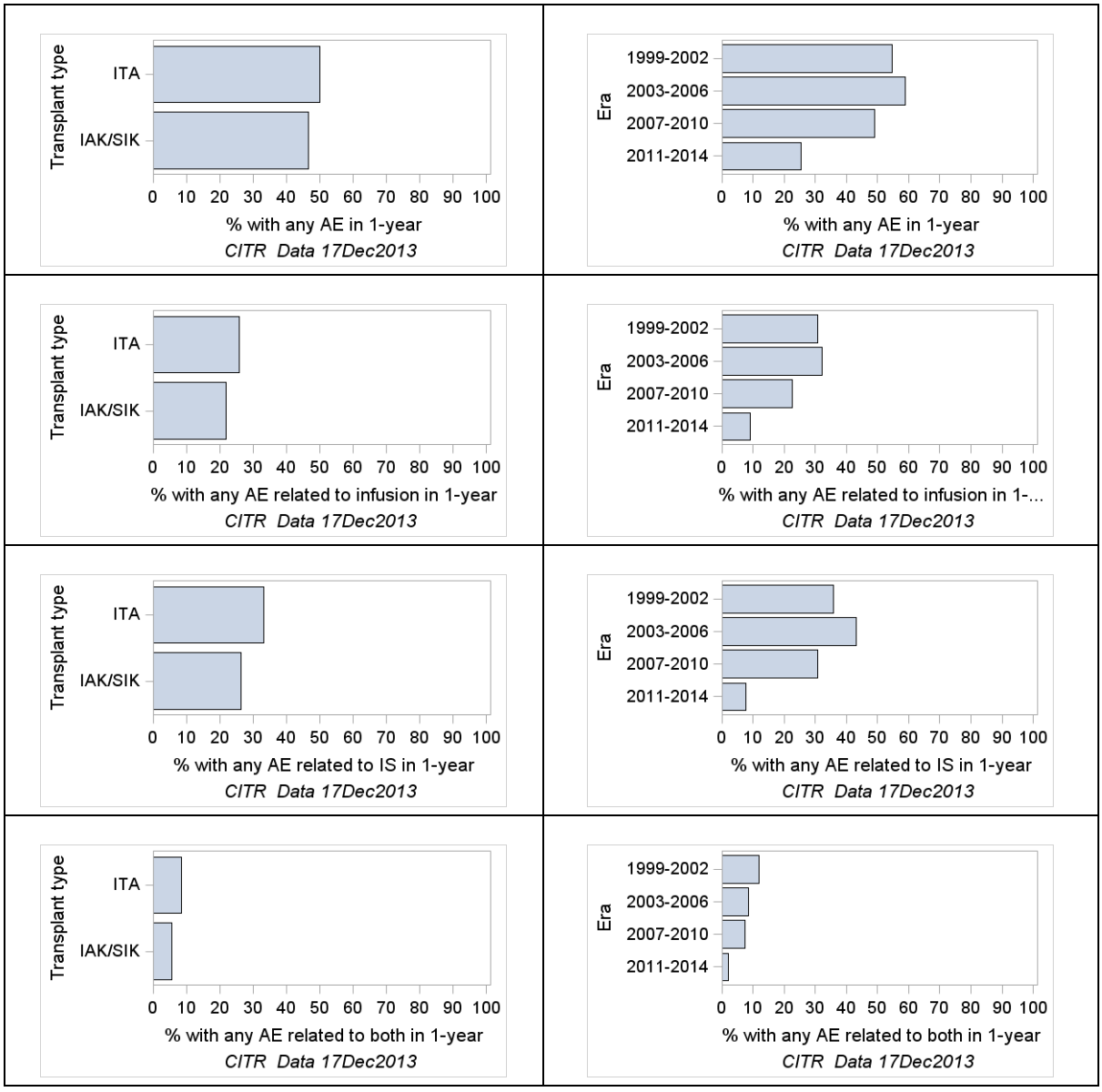


Exhibit 7 – 2A *(continued)*
Adverse Event (AEs) in Year 1 Post First Infusion

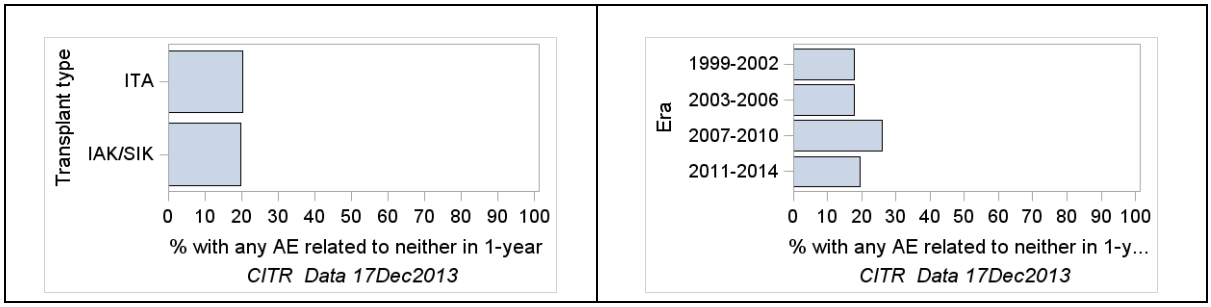


Exhibit 7 – 2A *(continued)*
Adverse Event (AEs) in Year 1 Post First Infusion

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
System/Organ Class	**Preferred term**							
Blood and lymphatic system disorders	**Anaemia**	32	25	7	7	15	9	1
	Blood disorder	5	2	3	2	1	1	1
	Febrile neutropenia	5	5	.	.	.	5	.
	Leukopenia	6	2	4	.	.	3	3
	Lymphatic disorder	1	1	.	.	1	.	.
	Lymphopenia	49	45	4	3	15	25	6
	Neutropenia	25	25	.	.	.	9	16
	Platelet disorder	3	3	.	1	1	1	.
Cardiac disorders	**Arrhythmia supraventricular**	2	2	.	.	.	2	.
	Cardiac disorder	1	1	.	.	.	1	.
	Myocardial ischaemia	4	3	1	1	1	2	.
Ear and labyrinth disorders	**Hearing impaired**	1	1	.	.	1	.	.
Endocrine disorders	**Endocrine disorder**	2	.	2	.	1	1	.
Eye disorders	**Eye disorder**	5	3	2	2	3	.	.
	Retinal detachment	1	1	.	1	.	.	.
Gastrointestinal disorders	**Ascites**	4	4	.	3	1	.	.
	Colitis	4	2	2	.	3	1	.
	Constipation	2	2	.	.	1	1	.
	Diarrhoea	25	23	2	2	15	7	1
	Dysphagia	2	2	.	.	2	.	.
	Gastritis	1	1	.	.	1	.	.
	Gastrointestinal disorder	11	8	3	2	8	1	.
	Gastrointestinal haemorrhage	5	2	3	2	3	.	.
	Gastrointestinal obstruction	3	3	.	.	2	1	.
	Gastrointestinal perforation	2	2	.	1	.	1	.
	Haemorrhoids	1	1	.	.	1	.	.
	Ileus	1	1	.	1	.	.	.
	Mouth ulceration	1	1	.	.	.	1	.
	Nausea	8	6	2	1	5	1	1
	Oral pain	1	1	.	.	.	1	.
	Pancreatitis	2	2	.	.	.	2	.
	Peritoneal haemorrhage	42	31	11	14	14	11	3
	Stomatitis	1	1	.	.	.	1	.
	Vomiting	16	13	3	4	3	7	2

Exhibit 7 – 2A *(continued)*
Adverse Event (AEs) in Year 1 Post First Infusion

		Overall	Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
General disorders and administration site conditions	**Chest pain**	5	5	.	.	.	2	3
	Death	3	.	3	3	.	.	.
	Fatigue	10	10	.	.	10	.	.
	Influenza like illness	1	1	.	.	.	1	.
	Injection site reaction	1	1	.	.	1	.	.
	Mucosal inflammation	17	14	3	3	9	4	1
	Oedema peripheral	6	4	2	2	2	2	.
	Pain	45	44	1	10	20	13	2
	Pyrexia	1	1	.	.	1	.	.
	Ulcer	1	1	.	.	.	1	.
Hepatobiliary disorders	**Biliary tract disorder**	1	1	.	.	1	.	.
	Cholecystitis	7	5	2	3	2	2	.
	Hepatic haemorrhage	2	2	.	.	.	.	2
	Portal vein thrombosis	10	8	2	3	5	1	1
Immune system disorders	**Autoimmune disorder**	1	1	.	.	.	1	.
	Cytokine release syndrome	1	1	.	.	.	1	.
	Hypersensitivity	14	11	3	3	8	2	1
Infections and infestations	**Clostridium difficile colitis**	1	1	.	.	.	1	.
	Cystitis	2	2	.	.	1	1	.
	Ear infection	1	1	.	.	.	1	.
	Infection	50	32	18	19	23	7	1
	Pneumonia	2	.	2	.	.	2	.
	Urinary tract infection	1	1	.	.	.	1	.
Injury, poisoning and procedural complications	**Fracture**	4	3	1	1	3	.	.
	Hepatic haematoma	2	2	.	.	.	2	.
	Post procedural haemorrhage	1	1	.	.	.	1	.
	Toxicity to various agents	1	1	.	.	.	1	.
	Wound complication	3	3	.	1	1	1	.
	Wound dehiscence	1	1	.	.	.	1	.

Exhibit 7 – 2A *(continued)*
Adverse Event (AEs) in Year 1 Post First Infusion

		Overall	Transplant type		Era			
			ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Investigations	**Activated partial thromboplastin time**	1	1	.	1	.	.	.
	Alanine aminotransferase increased	8	8	.	.	.	5	3
	Aspartate aminotransferase increased	6	6	.	.	.	4	2
	Blood albumin decreased	1	1	.	.	.	.	1
	Blood alkaline phosphatase	18	16	2	4	12	2	.
	Blood bilirubin	1	1	.	1	.	.	.
	Blood creatine phosphokinase	1	1	.	.	1	.	.
	Blood creatine phosphokinase increased	1	1	.	.	.	.	1
	Blood creatinine increased	4	4	.	.	.	2	2
	Blood phosphorus decreased	2	2	.	.	.	2	.
	Blood potassium increased	1	1	.	.	.	1	.
	Gamma-glutamyltransferase	8	7	1	1	3	4	.
	Gamma-glutamyltransferase increased	3	3	.	.	.	2	1
	Glomerular filtration rate	1	1	.	1	.	.	.
	Granulocytes abnormal	208	199	9	67	102	31	8
	Haemoglobin decreased	1	1	.	.	.	1	.
	Hepatic enzyme increased	3	3	.	.	.	2	1
	International normalised ratio increased	1	1	.	.	.	.	1
	Lipase	4	1	3	1	3	.	.
	Liver function test abnormal	114	110	4	44	46	17	7
	Low density lipoprotein abnormal	4	4	.	.	1	3	.
	Low density lipoprotein increased	5	5	.	.	.	4	1
	Neutrophil count	5	5	.	.	.	5	.
	Neutrophil count decreased	18	18	.	.	.	15	3
	Transaminases	3	3	.	.	.	3	.
	Transaminases increased	2	2	.	.	.	1	1
	Troponin T	1	1	.	.	.	1	.

Exhibit 7 – 2A *(continued)*
Adverse Event (AEs) in Year 1 Post First Infusion

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Metabolism and nutrition disorders	**Decreased appetite**	1	1	.	.	.	1	.
	Dehydration	8	7	1	1	1	4	2
	Hyperglycaemia	6	.	6	.	.	.	6
	Hyperkalaemia	5	4	1	2	1	2	.
	Hypoalbuminaemia	3	3	.	1	.	2	.
	Hypocalcaemia	2	2	.	.	.	1	1
	Hypoglycaemia	77	67	10	9	32	15	21
	Hypokalaemia	11	10	1	1	3	5	2
	Hypomagnesaemia	1	1	.	.	1	.	.
	Hyponatraemia	9	8	1	1	1	7	.
	Hypophosphataemia	15	13	2	1	4	8	2
	Ketoacidosis	65	62	3	42	19	4	.
Musculoskeletal and connective tissue disorders	**Arthritis**	1	1	.	.	.	1	.
	Muscular weakness	6	6	.	.	6	.	.
	Musculoskeletal disorder	2	2	.	1	1	.	.
	Musculoskeletal pain	2	2	.	.	.	.	2
	Rheumatoid arthritis	1	1	.	.	.	1	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	7	5	2	1	5	1	.
	Post transplant lymphoproliferative disorder	3	.	3	.	.	.	3
Nervous system disorders	**Ataxia**	2	2	.	.	1	1	.
	Cerebral ischaemia	1	.	1	1	.	.	.
	Cognitive disorder	1	1	.	.	.	1	.
	Convulsion	1	1	.	.	.	.	1
	Dizziness	1	1	.	.	1	.	.
	Dyskinesia	1	1	.	.	.	1	.
	Headache	2	2	.	.	.	2	.
	Hypoglycaemic seizure	1	.	1	.	.	.	1
	Presyncope	1	1	.	.	.	1	.
	Syncope	6	6	.	1	5	.	.
	Tremor	2	2	.	1	1	.	.
Psychiatric disorders	**Anxiety**	2	.	2	.	.	.	2
	Cognitive disorder	1	1	.	.	.	1	.
	Confusional state	1	1	.	1	.	.	.
	Insomnia	1	1	.	.	1	.	.
	Mood altered	2	2	.	.	2	.	.
	Psychogenic seizure	2	2	.	.	.	.	2

Exhibit 7 – 2A *(continued)*
Adverse Event (AEs) in Year 1 Post First Infusion

		Overall	Transplant type		Era			
			ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Renal and urinary disorders	**Haemoglobinuria**	1	1	.	1	.	.	.
	Micturition urgency	1	1	.	.	1	.	.
	Proteinuria	1	1	.	1	.	.	.
	Renal disorder	2	2	.	2	.	.	.
	Renal failure	10	5	5	5	4	1	.
	Urinary bladder haemorrhage	4	2	2	1	1	2	.
Reproductive system and breast disorders	**Sexual dysfunction**	3	3	.	.	2	1	.
Respiratory, thoracic and mediastinal disorders	**Acute respiratory distress syndrome**	1	.	1	1	.	.	.
	Aspiration	2	2	.	1	.	1	.
	Cough	2	1	1	1	.	1	.
	Dyspnoea	3	2	1	1	1	1	.
	Haemothorax	2	1	1	1	1	.	.
	Hypoxia	4	4	.	.	1	3	.
	Lung disorder	4	2	2	1	2	1	.
	Pleural effusion	3	2	1	.	1	2	.
	Pneumonitis	3	2	1	2	1	.	.
	Pulmonary hypertension	1	1	.	.	.	1	.
Skin and subcutaneous tissue disorders	**Dermatitis**	1	1	.	.	.	.	1
	Exfoliative rash	5	4	1	1	1	3	.
	Pruritus	1	1	.	.	.	1	.
Surgical and medical procedures	**Surgery**	2	2	.	2	.	.	.
Vascular disorders	**Haematoma**	10	6	4	2	5	1	2
	Haemorrhage	11	6	5	2	4	2	3
	Hypertension	7	3	4	.	3	4	.
	Hypotension	3	3	.	.	.	3	.
	Peripheral ischaemia	1	.	1	1	.	.	.
	Thrombosis	2	.	2	2	.	.	.

Exhibit 7 – 2B
Recipients with a Serious Adverse Event (SAE) in Year 1 Post First Infusion

Percent of Recipients with:	Type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE in 1-year	220	32.1	68	38.2	80	38.3	111	41.0	73	31.7	24	15.6
Any SAE related to infusion in 1-year	111	16.2	30	16.9	39	18.7	58	21.4	31	13.5	13	8.4
Any SAE related to IS in 1-year	133	19.4	35	19.7	41	19.6	68	25.1	48	20.9	11	7.1
Any SAE related to both in 1-year	26	3.8	5	2.8	7	3.3	10	3.7	11	4.8	3	1.9
Any SAE related to neither in 1-year	60	8.7	29	16.3	26	12.4	26	9.6	28	12.2	9	5.8

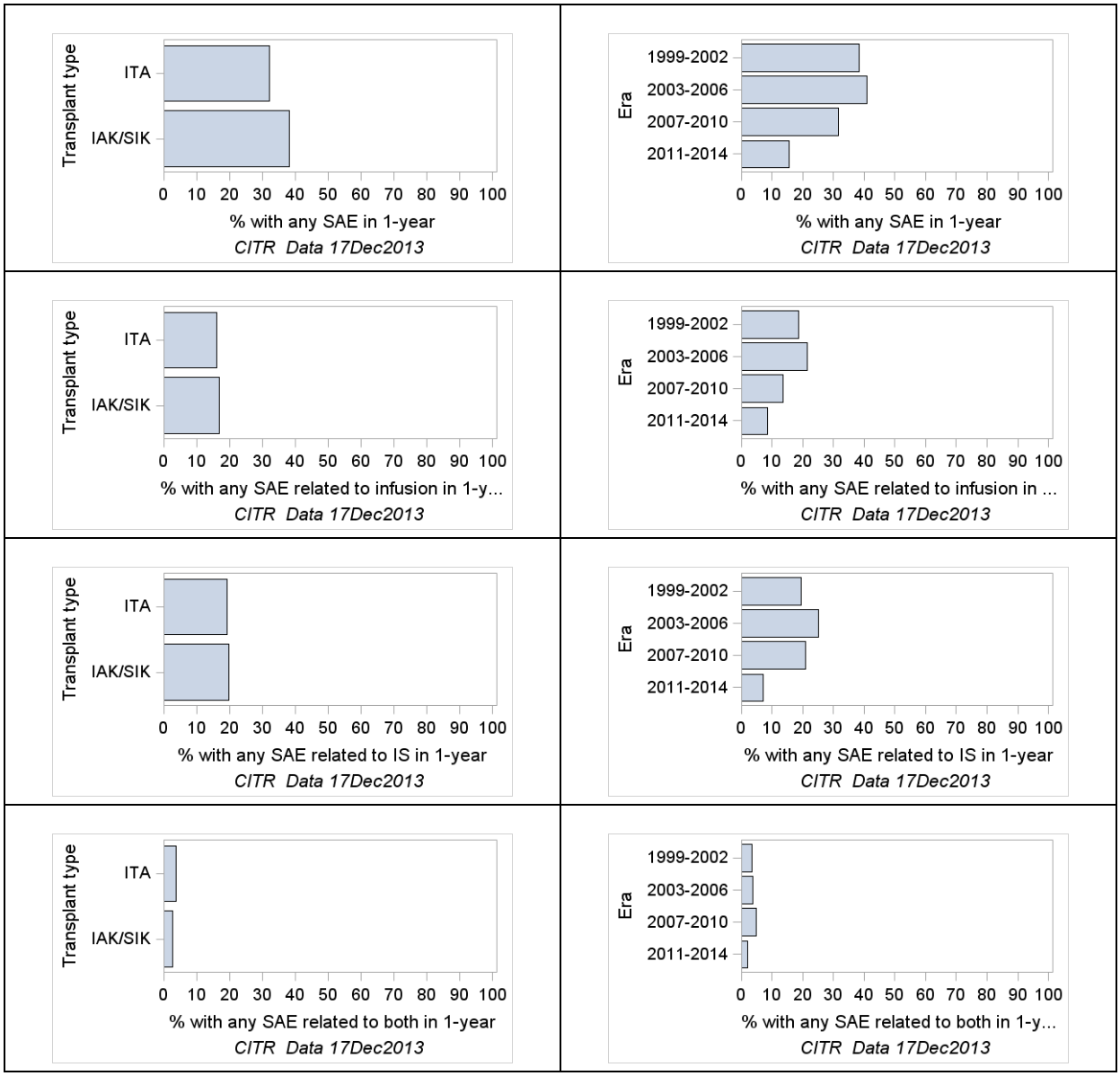


Exhibit 7 – 2B *(continued)*
Recipients with a Serious Adverse Event (SAE) in Year 1 Post First Infusion

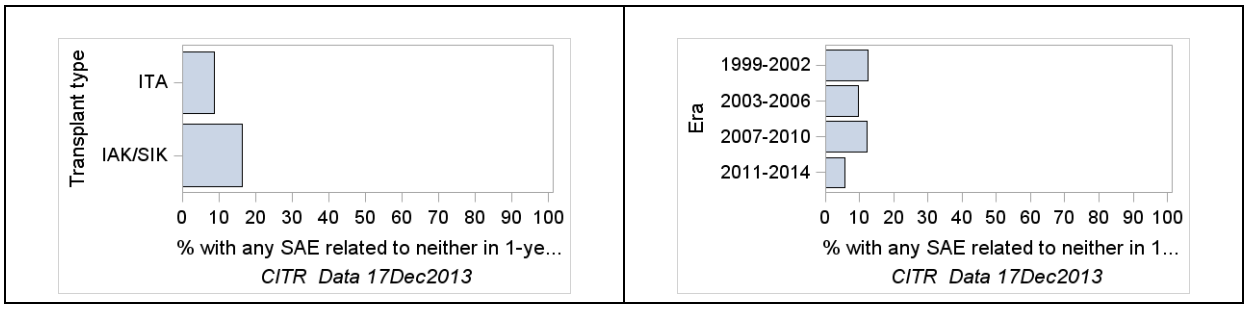


Exhibit 7 – 2B *(continued)*
Recipients with a Serious Adverse Event (SAE) in Year 1 Post First Infusion
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
System/Organ Class	**Preferred term**							
Blood and lymphatic system disorders	**Anaemia**	18	13	5	4	9	4	1
	Blood disorder	2	1	1	1	.	1	.
	Febrile neutropenia	4	4	.	.	.	4	.
	Leukopenia	3	.	3	.	.	.	3
	Lymphatic disorder	1	1	.	.	1	.	.
	Lymphopenia	8	6	2	1	5	2	.
	Neutropenia	15	15	.	.	.	3	12
	Platelet disorder	1	1	.	.	1	.	.
Cardiac disorders	**Arrhythmia supraventricular**	1	1	.	.	.	1	.
	Cardiac disorder	1	1	.	.	.	1	.
	Myocardial ischaemia	4	3	1	1	1	2	.
Endocrine disorders	**Endocrine disorder**	2	.	2	.	1	1	.
Eye disorders	**Eye disorder**	2	2	.	.	2	.	.
	Retinal detachment	1	1	.	1	.	.	.
Gastrointestinal disorders	**Ascites**	3	3	.	2	1	.	.
	Colitis	4	2	2	.	3	1	.
	Constipation	2	2	.	.	1	1	.
	Diarrhoea	9	7	2	1	3	5	.
	Dysphagia	1	1	.	.	1	.	.
	Gastrointestinal disorder	8	6	2	2	5	1	.
	Gastrointestinal haemorrhage	5	2	3	2	3	.	.
	Gastrointestinal obstruction	3	3	.	.	2	1	.
	Gastrointestinal perforation	2	2	.	1	.	1	.
	Haemorrhoids	1	1	.	.	1	.	.
	Ileus	1	1	.	1	.	.	.
	Nausea	6	5	1	1	3	1	1
	Pancreatitis	2	2	.	.	.	2	.
	Peritoneal haemorrhage	35	27	8	11	13	8	3
	Vomiting	14	11	3	3	2	7	2
General disorders and administration site conditions	**Chest pain**	5	5	.	.	.	2	3
	Death	3	.	3	3	.	.	.
	Mucosal inflammation	7	6	1	2	4	1	.
	Oedema peripheral	3	1	2	.	2	1	.
	Pain	21	21	.	5	8	6	2
	Pyrexia	1	1	.	.	1	.	.

Exhibit 7 – 2B *(continued)*
Recipients with a Serious Adverse Event (SAE) in Year 1 Post First Infusion
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Hepatobiliary disorders	**Biliary tract disorder**	1	1	.	.	1	.	.
	Cholecystitis	7	5	2	3	2	2	.
	Hepatic haemorrhage	2	2	.	.	.	.	2
	Portal vein thrombosis	9	7	2	3	5	1	.
Immune system disorders	**Autoimmune disorder**	1	1	.	.	.	1	.
	Cytokine release syndrome	1	1	.	.	.	1	.
	Hypersensitivity	11	8	3	3	7	1	.
Infections and infestations	**Clostridium difficile colitis**	1	1	.	.	.	1	.
	Cystitis	1	1	.	.	1	.	.
	Ear infection	1	1	.	.	.	1	.
	Infection	47	29	18	19	21	7	.
	Pneumonia	2	.	2	.	.	2	.
	Urinary tract infection	1	1	.	.	.	1	.
Injury, poisoning and procedural complications	**Fracture**	3	2	1	1	2	.	.
	Hepatic haematoma	2	2	.	.	.	2	.
	Post procedural haemorrhage	1	1	.	.	.	1	.
	Toxicity to various agents	1	1	.	.	.	1	.
	Wound complication	1	1	.	.	1	.	.
Investigations	**Blood alkaline phosphatase**	11	11	.	3	8	.	.
	Blood creatine phosphokinase	1	1	.	.	1	.	.
	Blood creatinine increased	2	2	.	.	.	2	.
	Granulocytes abnormal	53	47	6	17	20	12	4
	Liver function test abnormal	33	33	.	18	15	.	.
	Neutrophil count	1	1	.	.	.	1	.
	Neutrophil count decreased	2	2	.	.	.	2	.
	Troponin T	1	1	.	.	.	1	.
Metabolism and nutrition disorders	**Dehydration**	7	6	1	1	1	3	2
	Hyperglycaemia	6	.	6	.	.	.	6
	Hyperkalaemia	1	.	1	.	.	1	.
	Hypoglycaemia	21	13	8	4	4	8	5
	Hypomagnesaemia	1	1	.	.	1	.	.
	Hypophosphataemia	1	1	.	.	1	.	.
	Ketoacidosis	5	4	1	.	2	3	.
Musculoskeletal and connective tissue disorders	**Arthritis**	1	1	.	.	.	1	.
	Musculoskeletal disorder	2	2	.	1	1	.	.
	Musculoskeletal pain	2	2	.	.	.	.	2

Exhibit 7 – 2B *(continued)*
Recipients with a Serious Adverse Event (SAE) in Year 1 Post First Infusion
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	5	5	.	1	4	.	.
	Post transplant lymphoproliferative disorder	3	.	3	.	.	.	3
Nervous system disorders	**Ataxia**	1	1	.	.	.	1	.
	Cerebral ischaemia	1	.	1	1	.	.	.
	Convulsion	1	1	.	.	.	.	1
	Headache	2	2	.	.	.	2	.
	Hypoglycaemic seizure	1	.	1	.	.	.	1
	Tremor	1	1	.	.	1	.	.
Psychiatric disorders	**Anxiety**	2	.	2	.	.	.	2
	Confusional state	1	1	.	1	.	.	.
	Mood altered	2	2	.	.	2	.	.
	Psychogenic seizure	2	2	.	.	.	.	2
Renal and urinary disorders	**Renal disorder**	2	2	.	2	.	.	.
	Renal failure	10	5	5	5	4	1	.
	Urinary bladder haemorrhage	4	2	2	1	1	2	.
Reproductive system and breast disorders	**Sexual dysfunction**	3	3	.	.	2	1	.
Respiratory, thoracic and mediastinal disorders	**Acute respiratory distress syndrome**	1	.	1	1	.	.	.
	Aspiration	2	2	.	1	.	1	.
	Cough	1	.	1	1	.	.	.
	Dyspnoea	3	2	1	1	1	1	.
	Haemothorax	2	1	1	1	1	.	.
	Hypoxia	1	1	.	.	.	1	.
	Lung disorder	4	2	2	1	2	1	.
	Pleural effusion	2	1	1	.	1	1	.
	Pneumonitis	2	1	1	2	.	.	.
	Pulmonary hypertension	1	1	.	.	.	1	.
Skin and subcutaneous tissue disorders	**Exfoliative rash**	2	2	.	.	.	2	.
Surgical and medical procedures	**Surgery**	2	2	.	2	.	.	.
Vascular disorders	**Haematoma**	10	6	4	2	5	1	2
	Haemorrhage	11	6	5	2	4	2	3
	Hypertension	2	1	1	.	.	2	.
	Hypotension	2	2	.	.	.	2	.
	Peripheral ischaemia	1	.	1	1	.	.	.
	Thrombosis	2	.	2	2	.	.	.

Exhibit 7 – 3A
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation

Percent of Recipients with:	Type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Any AE	396	57.7	100	56.2	134	64.1	189	69.7	131	57.0	42	27.3
Any AE related to infusion	202	29.4	46	25.8	72	34.4	102	37.6	58	25.2	16	10.4
Any AE related to IS	280	40.8	58	32.6	94	45.0	144	53.1	87	37.8	13	8.4
Any AE related to both	74	10.8	11	6.2	26	12.4	32	11.8	23	10.0	4	2.6
Any AE related to neither	206	30.0	62	34.8	65	31.1	87	32.1	84	36.5	32	20.8

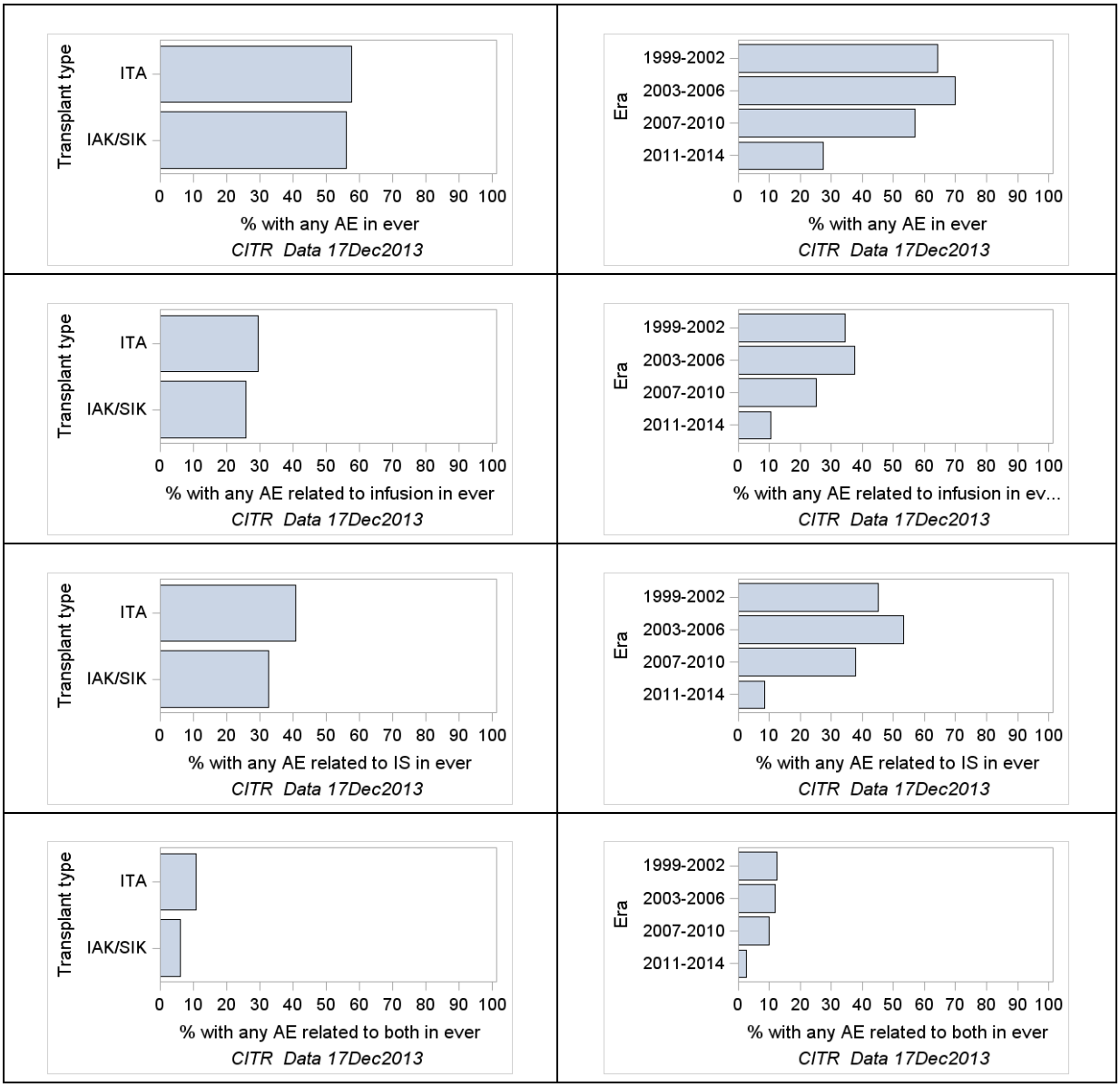


Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation

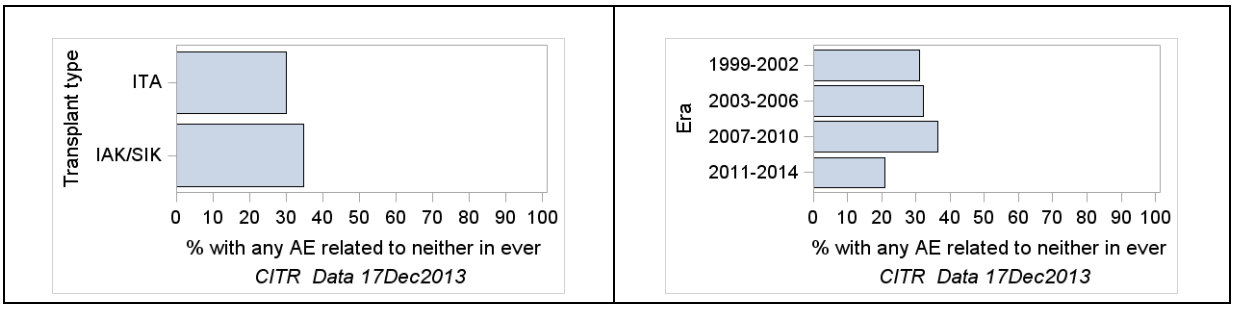


Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
System/Organ Class	**Preferred term**							
Blood and lymphatic system disorders	**Anaemia**	39	31	8	8	19	11	1
	Blood disorder	6	3	3	2	1	2	1
	Febrile neutropenia	5	5	.	.	.	5	.
	Haemolysis	1	1	.	.	1	.	.
	Leukopenia	10	6	4	.	.	3	7
	Lymphatic disorder	1	1	.	.	1	.	.
	Lymphopenia	58	52	6	3	20	27	8
	Neutropenia	25	25	.	.	.	9	16
	Platelet disorder	4	4	.	1	2	1	.
	Thrombocytopenia	5	5	.	.	.	5	.
Cardiac disorders	**Arrhythmia supraventricular**	3	3	.	.	1	2	.
	Cardiac disorder	2	2	.	1	.	1	.
	Cardio-respiratory arrest	2	.	2	1	1	.	.
	Myocardial ischaemia	16	8	8	5	7	4	.
	Pericardial effusion	3	1	2	2	1	.	.
	Pericarditis	1	1	.	.	1	.	.
Ear and labyrinth disorders	**Hearing impaired**	1	1	.	.	1	.	.
	Tinnitus	1	1	.	1	.	.	.
Endocrine disorders	**Endocrine disorder**	4	2	2	1	1	2	.
Eye disorders	**Eye disorder**	13	9	4	5	6	2	.
	Ocular surface disease	1	.	1	.	1	.	.
	Retinal detachment	4	3	1	1	1	2	.
	Uveitis	1	.	1	.	.	1	.

Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Gastrointestinal disorders	**Ascites**	5	5	.	3	2	.	.
	Colitis	8	5	3	1	5	2	.
	Constipation	2	2	.	.	1	1	.
	Diarrhoea	49	45	4	8	27	13	1
	Dysphagia	2	2	.	.	2	.	.
	Enteritis	1	1	.	.	1	.	.
	Gastritis	2	1	1	1	1	.	.
	Gastrointestinal disorder	21	14	7	2	18	1	.
	Gastrointestinal haemorrhage	5	2	3	2	3	.	.
	Gastrointestinal obstruction	10	6	4	1	8	1	.
	Gastrointestinal perforation	2	2	.	1	.	1	.
	Haemorrhoids	1	1	.	.	1	.	.
	Ileus	2	2	.	1	1	.	.
	Mouth ulceration	1	1	.	.	.	1	.
	Nausea	8	6	2	1	5	1	1
	Oral pain	1	1	.	.	.	1	.
	Pancreatitis	3	3	.	1	.	2	.
	Peritoneal haemorrhage	48	33	15	17	15	12	4
	Stomatitis	1	1	.	.	.	1	.
	Vomiting	29	22	7	8	8	11	2
General disorders and administration site conditions	**Chest discomfort**	2	2	.	.	.	.	2
	Chest pain	5	5	.	.	.	2	3
	Death	14	7	7	10	3	1	.
	Fatigue	15	15	.	1	12	2	.
	Influenza like illness	1	1	.	.	.	1	.
	Injection site reaction	1	1	.	.	1	.	.
	Mucosal inflammation	19	16	3	3	11	4	1
	Oedema peripheral	6	4	2	2	2	2	.
	Pain	73	62	11	18	38	15	2
	Pyrexia	6	5	1	3	2	1	.
	Systemic inflammatory response syndrome	2	.	2	.	.	2	.
	Ulcer	2	1	1	.	1	1	.
Hepatobiliary disorders	**Biliary tract disorder**	1	1	.	.	1	.	.
	Cholecystitis	13	10	3	6	5	2	.
	Hepatic haemorrhage	2	2	.	.	.	.	2
	Portal vein thrombosis	12	10	2	4	5	2	1
Immune system disorders	**Autoimmune disorder**	1	1	.	.	.	1	.
	Cytokine release syndrome	1	1	.	.	.	1	.
	Graft versus host disease	2	2	.	.	.	.	2
	Hypersensitivity	25	21	4	3	12	7	3
	Serum sickness	2	2	.	.	.	2	.

Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Infections and infestations	**Appendicitis**	4	4	.	.	.	.	4
	Appendicitis perforated	2	2	.	.	.	.	2
	Clostridium difficile colitis	1	1	.	.	.	1	.
	Cystitis	2	2	.	.	1	1	.
	Ear infection	1	1	.	.	.	1	.
	Enterocolitis infectious	1	1	.	.	.	1	.
	Gastrointestinal infection	1	1	.	.	.	.	1
	Herpes simplex	1	1	.	.	.	1	.
	Infection	97	60	37	36	44	16	1
	Opportunistic infection	3	2	1	.	1	2	.
	Pneumonia	5	2	3	.	.	5	.
	Pyelonephritis	2	2	.	.	.	.	2
	Urinary tract infection	3	1	2	.	.	1	2
Injury, poisoning and procedural complications	**Fracture**	12	10	2	6	5	1	.
	Hepatic haematoma	2	2	.	.	.	2	.
	Hip fracture	4	4	.	.	.	2	2
	Injury	2	1	1	1	1	.	.
	Laceration	1	1	.	.	.	1	.
	Post procedural haemorrhage	1	1	.	.	.	1	.
	Toxicity to various agents	1	1	.	.	.	1	.
	Upper limb fracture	1	1	.	.	.	1	.
	Wound complication	12	11	1	5	3	4	.
	Wound dehiscence	1	1	.	.	.	1	.

Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Investigations	**Activated partial thromboplastin time**	2	1	1	1	1	.	.
	Alanine aminotransferase increased	8	8	.	.	.	5	3
	Aspartate aminotransferase increased	6	6	.	.	.	4	2
	Blood albumin decreased	1	1	.	.	.	.	1
	Blood alkaline phosphatase	21	19	2	5	14	2	.
	Blood amylase	2	1	1	.	2	.	.
	Blood bilirubin	1	1	.	1	.	.	.
	Blood creatine phosphokinase	1	1	.	.	1	.	.
	Blood creatine phosphokinase increased	1	1	.	.	.	.	1
	Blood creatinine increased	4	4	.	.	.	2	2
	Blood phosphorus decreased	2	2	.	.	.	2	.
	Blood potassium increased	1	1	.	.	.	1	.
	Gamma-glutamyltransferase	13	12	1	6	3	4	.
	Gamma-glutamyltransferase increased	3	3	.	.	.	2	1
	Glomerular filtration rate	2	1	1	1	1	.	.
	Granulocytes abnormal	246	234	12	84	121	33	8
	Haemoglobin decreased	1	1	.	.	.	1	.
	Hepatic enzyme increased	3	3	.	.	.	2	1
	International normalised ratio increased	1	1	.	.	.	.	1
	Lipase	5	1	4	1	4	.	.
	Liver function test abnormal	125	120	5	50	51	17	7
	Low density lipoprotein abnormal	6	6	.	.	2	4	.
	Low density lipoprotein increased	6	6	.	.	.	5	1
	Neutrophil count	6	6	.	.	.	6	.
	Neutrophil count decreased	18	18	.	.	.	15	3
	Transaminases	4	4	.	.	.	4	.
	Transaminases increased	2	2	.	.	.	1	1
	Troponin I	1	.	1	.	1	.	.
	Troponin T	1	1	.	.	.	1	.
	Weight decreased	3	3	.	.	1	2	.

Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Metabolism and nutrition disorders	**Decreased appetite**	1	1	.	.	.	1	.
	Dehydration	11	8	3	2	3	4	2
	Hyperglycaemia	7	1	6	.	.	.	7
	Hyperkalaemia	11	10	1	6	3	2	.
	Hypoalbuminaemia	4	4	.	1	1	2	.
	Hypocalcaemia	2	2	.	.	.	1	1
	Hypoglycaemia	126	111	15	14	49	30	33
	Hypokalaemia	16	14	2	1	7	6	2
	Hypomagnesaemia	1	1	.	.	1	.	.
	Hyponatraemia	13	11	2	1	4	8	.
	Hypophosphataemia	17	14	3	1	6	8	2
	Ketoacidosis	107	98	9	67	34	6	.
Musculoskeletal and connective tissue disorders	**Arthritis**	3	3	.	.	1	2	.
	Arthropathy	1	1	.	.	.	1	.
	Back pain	1	1	.	.	.	.	1
	Muscular weakness	8	8	.	.	8	.	.
	Musculoskeletal disorder	5	5	.	3	2	.	.
	Musculoskeletal pain	2	2	.	.	.	.	2
	Myositis	1	1	.	.	1	.	.
	Rheumatoid arthritis	1	1	.	.	.	1	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Basal cell carcinoma**	1	1	.	.	.	1	.
	Neoplasm malignant	37	25	12	18	17	2	.
	Post transplant lymphoproliferative disorder	3	.	3	.	.	.	3
Nervous system disorders	**Ataxia**	2	2	.	.	1	1	.
	Cerebral ischaemia	7	1	6	3	2	2	.
	Cognitive disorder	1	1	.	.	.	1	.
	Convulsion	1	1	.	.	.	.	1
	Dizziness	5	5	.	.	4	1	.
	Dyskinesia	1	1	.	.	.	1	.
	Frontotemporal dementia	1	1	.	.	.	1	.
	Headache	2	2	.	.	.	2	.
	Hypoglycaemic seizure	1	.	1	.	.	.	1
	Presyncope	1	1	.	.	.	1	.
	Spinal cord compression	2	2	.	.	.	.	2
	Syncope	10	10	.	1	7	1	1
	Tremor	3	3	.	2	1	.	.

Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Psychiatric disorders	**Alcoholism**	1	1	.	.	.	1	.
	Anxiety	2	.	2	.	.	.	2
	Cognitive disorder	2	2	.	.	.	2	.
	Confusional state	4	4	.	1	.	3	.
	Insomnia	2	2	.	1	1	.	.
	Mood altered	5	5	.	2	3	.	.
	Psychogenic seizure	2	2	.	.	.	.	2
	Psychotic disorder	1	1	.	1	.	.	.
Renal and urinary disorders	**Albuminuria**	3	3	.	.	3	.	.
	Haemoglobinuria	1	1	.	1	.	.	.
	Micturition urgency	1	1	.	.	1	.	.
	Proteinuria	5	4	1	1	4	.	.
	Renal disorder	7	3	4	3	2	2	.
	Renal failure	18	9	9	10	7	1	.
	Tubulointerstitial nephritis	1	1	.	.	.	1	.
	Urinary bladder haemorrhage	5	3	2	1	2	2	.
Reproductive system and breast disorders	**Lactation disorder**	1	1	.	.	1	.	.
	Sexual dysfunction	9	8	1	2	6	1	.
Respiratory, thoracic and mediastinal disorders	**Acute respiratory distress syndrome**	2	1	1	1	1	.	.
	Aspiration	2	2	.	1	.	1	.
	Cough	3	1	2	1	1	1	.
	Dyspnoea	4	3	1	1	2	1	.
	Haemothorax	2	1	1	1	1	.	.
	Hypoxia	4	4	.	.	1	3	.
	Lung disorder	9	5	4	3	4	2	.
	Lung infiltration	4	4	.	.	.	4	.
	Pleural effusion	3	2	1	.	1	2	.
	Pneumonitis	8	4	4	3	3	2	.
	Pulmonary hypertension	3	1	2	.	.	3	.
Skin and subcutaneous tissue disorders	**Acne**	1	.	1	.	1	.	.
	Decubitus ulcer	2	.	2	.	2	.	.
	Dermatitis	1	1	.	.	.	.	1
	Exfoliative rash	7	6	1	2	2	3	.
	Pruritus	1	1	.	.	.	1	.
	Skin disorder	5	5	.	3	2	.	.
Surgical and medical procedures	**Abdominal hernia repair**	2	2	.	.	.	2	.
	Surgery	8	4	4	2	2	4	.

Exhibit 7 – 3A *(continued)*
Recipients with an Adverse Event (AE) Any Time Post Islet Transplantation
(Counts by AE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Vascular disorders	**Haematoma**	13	8	5	4	6	1	2
	Haemorrhage	14	7	7	2	6	3	3
	Hypertension	13	8	5	1	8	4	.
	Hypotension	4	3	1	.	.	4	.
	Peripheral ischaemia	5	.	5	3	2	.	.
	Thrombosis	4	2	2	3	1	.	.

Exhibit 7 – 3B
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation

Percent of Recipients with:	Type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE	289	42.1	89	50.0	105	50.2	150	55.4	93	40.4	30	19.5
Any SAE related to infusion	134	19.5	34	19.1	46	22.0	69	25.5	38	16.5	15	9.7
Any SAE related to IS	187	27.3	51	28.7	61	29.2	102	37.6	63	27.4	12	7.8
Any SAE related to both	40	5.8	6	3.4	8	3.8	17	6.3	17	7.4	4	2.6
Any SAE related to neither	125	18.2	57	32.0	51	24.4	65	24.0	52	22.6	14	9.1

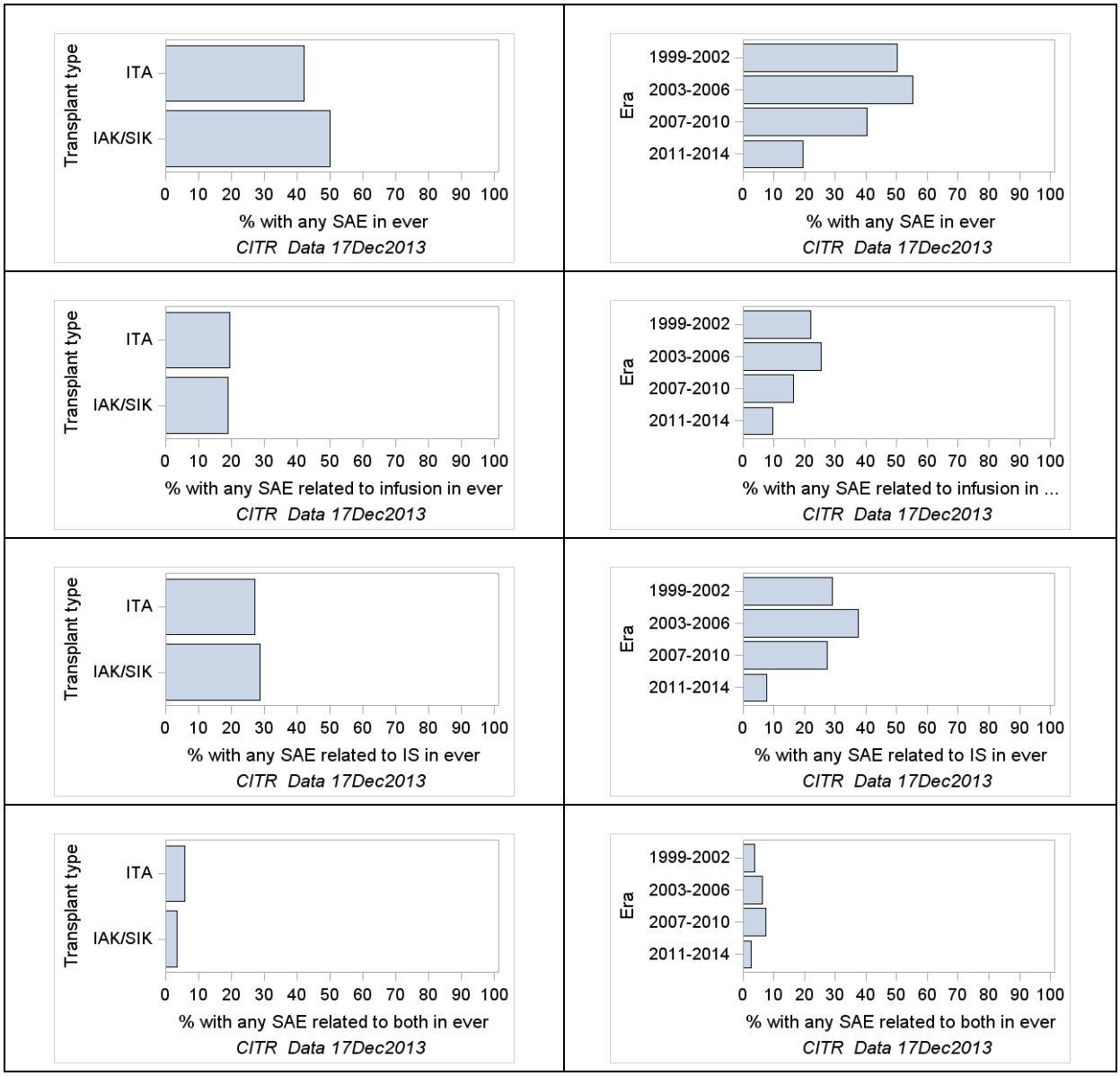


Exhibit 7 – 3B *(continued)*
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation

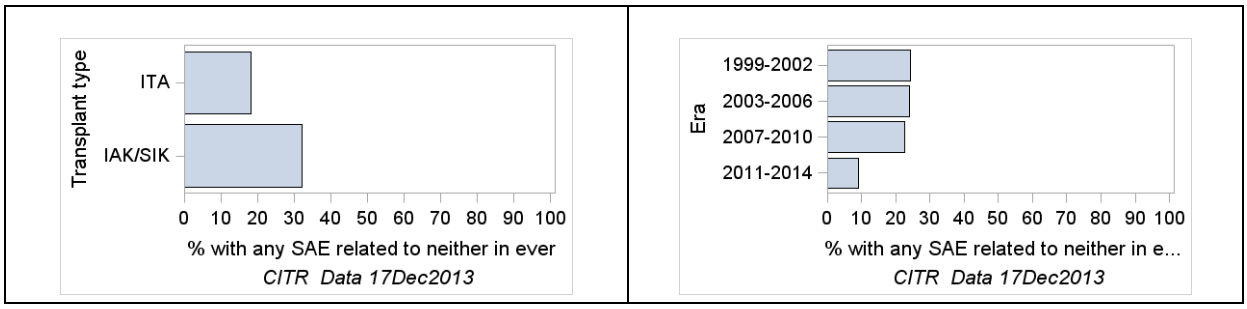


Exhibit 7 – 3B *(continued)*
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation
(Counts by SAE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
System/Organ Class	**Preferred term**							
Blood and lymphatic system disorders	**Anaemia**	23	17	6	5	12	5	1
	Blood disorder	2	1	1	1	.	1	.
	Febrile neutropenia	4	4	.	.	.	4	.
	Haemolysis	1	1	.	.	1	.	.
	Leukopenia	3	.	3	.	.	.	3
	Lymphatic disorder	1	1	.	.	1	.	.
	Lymphopenia	10	7	3	1	7	2	.
	Neutropenia	15	15	.	.	.	3	12
	Platelet disorder	1	1	.	.	1	.	.
	Thrombocytopenia	5	5	.	.	.	5	.
Cardiac disorders	**Arrhythmia supraventricular**	2	2	.	.	1	1	.
	Cardiac disorder	2	2	.	1	.	1	.
	Cardio-respiratory arrest	2	.	2	1	1	.	.
	Myocardial ischaemia	16	8	8	5	7	4	.
	Pericardial effusion	2	.	2	1	1	.	.
	Pericarditis	1	1	.	.	1	.	.
Endocrine disorders	**Endocrine disorder**	4	2	2	1	1	2	.
Eye disorders	**Eye disorder**	6	5	1	.	4	2	.
	Ocular surface disease	1	.	1	.	1	.	.
	Retinal detachment	4	3	1	1	1	2	.
	Uveitis	1	.	1	.	.	1	.

Exhibit 7 – 3B *(continued)*
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation
(Counts by SAE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Gastrointestinal disorders	**Ascites**	4	4	.	2	2	.	.
	Colitis	8	5	3	1	5	2	.
	Constipation	2	2	.	.	1	1	.
	Diarrhoea	29	26	3	7	12	10	.
	Dysphagia	1	1	.	.	1	.	.
	Enteritis	1	1	.	.	1	.	.
	Gastritis	1	.	1	1	.	.	.
	Gastrointestinal disorder	18	12	6	2	15	1	.
	Gastrointestinal haemorrhage	5	2	3	2	3	.	.
	Gastrointestinal obstruction	8	4	4	1	6	1	.
	Gastrointestinal perforation	2	2	.	1	.	1	.
	Haemorrhoids	1	1	.	.	1	.	.
	Ileus	2	2	.	1	1	.	.
	Nausea	6	5	1	1	3	1	1
	Pancreatitis	3	3	.	1	.	2	.
	Peritoneal haemorrhage	40	29	11	13	14	9	4
	Vomiting	26	20	6	7	6	11	2
General disorders and administration site conditions	**Chest discomfort**	2	2	.	.	.	.	2
	Chest pain	5	5	.	.	.	2	3
	Death	13	6	7	10	2	1	.
	Fatigue	2	2	.	1	.	1	.
	Mucosal inflammation	9	8	1	2	6	1	.
	Oedema peripheral	3	1	2	.	2	1	.
	Pain	41	32	9	11	22	6	2
	Pyrexia	5	4	1	3	1	1	.
	Systemic inflammatory response syndrome	2	.	2	.	.	2	.
	Ulcer	1	.	1	.	1	.	.
Hepatobiliary disorders	**Biliary tract disorder**	1	1	.	.	1	.	.
	Cholecystitis	12	9	3	5	5	2	.
	Hepatic haemorrhage	2	2	.	.	.	.	2
	Portal vein thrombosis	11	9	2	4	5	2	.
Immune system disorders	**Autoimmune disorder**	1	1	.	.	.	1	.
	Cytokine release syndrome	1	1	.	.	.	1	.
	Graft versus host disease	2	2	.	.	.	.	2
	Hypersensitivity	21	17	4	3	11	5	2
	Serum sickness	2	2	.	.	.	2	.

Exhibit 7 – 3B *(continued)*
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation
(Counts by SAE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Infections and infestations	**Appendicitis**	4	4	.	.	.	.	4
	Appendicitis perforated	2	2	.	.	.	.	2
	Clostridium difficile colitis	1	1	.	.	.	1	.
	Cystitis	1	1	.	.	1	.	.
	Ear infection	1	1	.	.	.	1	.
	Enterocolitis infectious	1	1	.	.	.	1	.
	Gastrointestinal infection	1	1	.	.	.	.	1
	Herpes simplex	1	1	.	.	.	1	.
	Infection	89	53	36	36	40	13	.
	Opportunistic infection	3	2	1	.	1	2	.
	Pneumonia	5	2	3	.	.	5	.
	Pyelonephritis	2	2	.	.	.	.	2
	Urinary tract infection	3	1	2	.	.	1	2
Injury, poisoning and procedural complications	**Fracture**	10	8	2	5	4	1	.
	Hepatic haematoma	2	2	.	.	.	2	.
	Hip fracture	4	4	.	.	.	2	2
	Injury	2	1	1	1	1	.	.
	Post procedural haemorrhage	1	1	.	.	.	1	.
	Toxicity to various agents	1	1	.	.	.	1	.
	Wound complication	9	8	1	3	3	3	.
Investigations	**Blood alkaline phosphatase**	14	14	.	4	10	.	.
	Blood creatine phosphokinase	1	1	.	.	1	.	.
	Blood creatinine increased	2	2	.	.	.	2	.
	Glomerular filtration rate	1	.	1	.	1	.	.
	Granulocytes abnormal	65	57	8	22	26	13	4
	Liver function test abnormal	36	36	.	19	17	.	.
	Low density lipoprotein abnormal	1	1	.	.	1	.	.
	Neutrophil count	1	1	.	.	.	1	.
	Neutrophil count decreased	2	2	.	.	.	2	.
	Troponin I	1	.	1	.	1	.	.
	Troponin T	1	1	.	.	.	1	.
	Weight decreased	1	1	.	.	1	.	.

Exhibit 7 – 3B *(continued)*
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation
(Counts by SAE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Metabolism and nutrition disorders	**Dehydration**	9	7	2	2	2	3	2
	Hyperglycaemia	6	.	6	.	.	.	6
	Hyperkalaemia	1	.	1	.	.	1	.
	Hypoglycaemia	50	38	12	6	18	11	15
	Hypokalaemia	1	1	.	.	1	.	.
	Hypomagnesaemia	1	1	.	.	1	.	.
	Hypophosphataemia	1	1	.	.	1	.	.
	Ketoacidosis	15	12	3	3	7	5	.
Musculoskeletal and connective tissue disorders	**Arthritis**	3	3	.	.	1	2	.
	Arthropathy	1	1	.	.	.	1	.
	Musculoskeletal disorder	5	5	.	3	2	.	.
	Musculoskeletal pain	2	2	.	.	.	.	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	22	17	5	8	13	1	.
	Post transplant lymphoproliferative disorder	3	.	3	.	.	.	3
Nervous system disorders	**Ataxia**	1	1	.	.	.	1	.
	Cerebral ischaemia	7	1	6	3	2	2	.
	Convulsion	1	1	.	.	.	.	1
	Dizziness	3	3	.	.	2	1	.
	Frontotemporal dementia	1	1	.	.	.	1	.
	Headache	2	2	.	.	.	2	.
	Hypoglycaemic seizure	1	.	1	.	.	.	1
	Spinal cord compression	2	2	.	.	.	.	2
	Syncope	3	3	.	.	2	1	.
	Tremor	2	2	.	1	1	.	.
Psychiatric disorders	**Anxiety**	2	.	2	.	.	.	2
	Cognitive disorder	1	1	.	.	.	1	.
	Confusional state	4	4	.	1	.	3	.
	Insomnia	1	1	.	1	.	.	.
	Mood altered	4	4	.	2	2	.	.
	Psychogenic seizure	2	2	.	.	.	.	2
	Psychotic disorder	1	1	.	1	.	.	.
Renal and urinary disorders	**Proteinuria**	2	1	1	.	2	.	.
	Renal disorder	7	3	4	3	2	2	.
	Renal failure	17	8	9	9	7	1	.
	Tubulointerstitial nephritis	1	1	.	.	.	1	.
	Urinary bladder haemorrhage	4	2	2	1	1	2	.
Reproductive system and breast disorders	**Lactation disorder**	1	1	.	.	1	.	.
	Sexual dysfunction	9	8	1	2	6	1	.

Exhibit 7 – 3B *(continued)*
Serious Adverse Events (SAEs) Any Time Post Islet Transplantation
(Counts by SAE Category)

			Transplant type		Era			
		Overall	ITA	IAK/SIK	1999-2002	2003-2006	2007-2010	2011-2014
		N	N	N	N	N	N	N
Respiratory, thoracic and mediastinal disorders	**Acute respiratory distress syndrome**	2	1	1	1	1	.	.
	Aspiration	2	2	.	1	.	1	.
	Cough	2	.	2	1	1	.	.
	Dyspnoea	3	2	1	1	1	1	.
	Haemothorax	2	1	1	1	1	.	.
	Hypoxia	1	1	.	.	.	1	.
	Lung disorder	8	4	4	2	4	2	.
	Lung infiltration	4	4	.	.	.	4	.
	Pleural effusion	2	1	1	.	1	1	.
	Pneumonitis	5	1	4	3	1	1	.
	Pulmonary hypertension	3	1	2	.	.	3	.
Skin and subcutaneous tissue disorders	**Decubitus ulcer**	2	.	2	.	2	.	.
	Exfoliative rash	2	2	.	.	.	2	.
	Skin disorder	1	1	.	1	.	.	.
Surgical and medical procedures	**Abdominal hernia repair**	2	2	.	.	.	2	.
	Surgery	8	4	4	2	2	4	.
Vascular disorders	**Haematoma**	13	8	5	4	6	1	2
	Haemorrhage	14	7	7	2	6	3	3
	Hypertension	4	2	2	1	1	2	.
	Hypotension	3	2	1	.	.	3	.
	Peripheral ischaemia	4	.	4	3	1	.	.
	Thrombosis	2	.	2	2	.	.	.

Exhibit 7 – 4
Worst Outcome of Adverse Events (per Recipient)

	Total		Transplant type				Era							
			ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	864	100.0	686	100.0	178	100.0	209	100.0	271	100.0	230	100.0	154	100.0
No AE	368	42.6	290	42.3	78	43.8	75	35.9	82	30.3	99	43.0	112	72.7
Recovered	331	38.3	271	39.5	60	33.7	93	44.5	126	46.5	86	37.4	26	16.9
Sequelae	116	13.4	95	13.8	21	11.8	20	9.6	48	17.7	33	14.3	15	9.7
Disability	28	3.2	21	3.1	7	3.9	7	3.3	9	3.3	11	4.8	1	0.6
Death	21	2.4	9	1.3	12	6.7	14	6.7	6	2.2	1	0.4	.	.

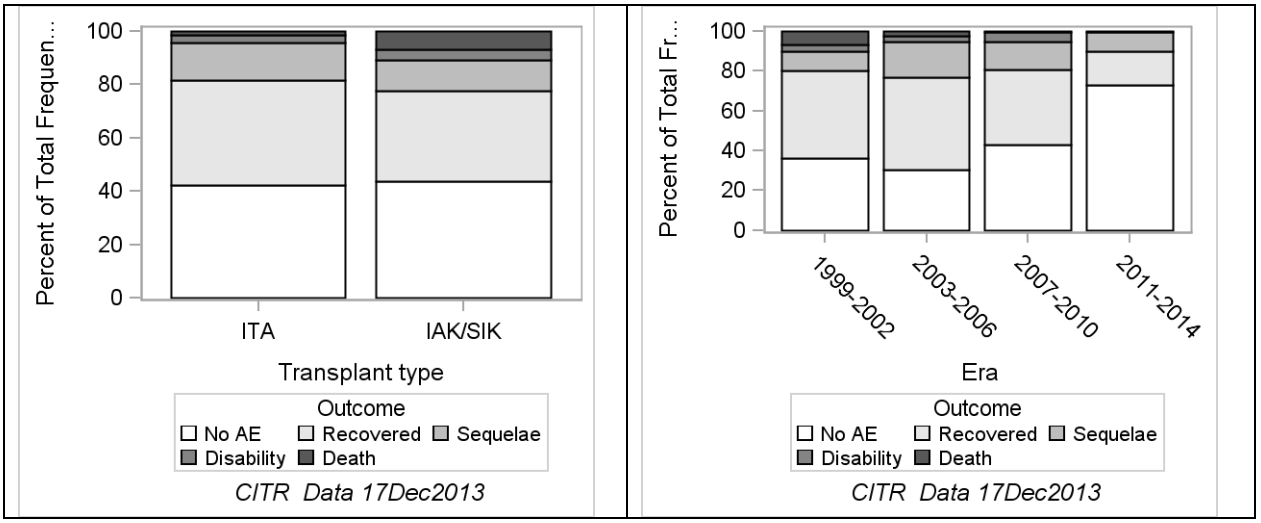


Exhibit 7 – 5
All Adverse Events (AEs) Following Islet Transplantation
(in order by frequency, with final outcomes)

	Total	Outcome				
		0-Unknown	1-Recover	2-Sequela	3-Disabil	4-Death
	N	%	%	%	%	%
Total adverse events following islet transplantation	1,878	0.7	84.2	12.2	1.7	1.2

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
Order by frequency	**Adverse event**						
1	**Granulocytes abnormal**	246	.	94.7	4.9	0.4	.
2	**Hypoglycaemia**	126	1.6	95.2	2.4	0.8	.
3	**Liver function test abnormal**	125	0.8	96.0	3.2	.	.
4	**Ketoacidosis**	107	.	96.3	3.7	.	.
5	**Infection**	97	.	79.4	14.4	4.1	2.1
6	**Pain**	73	.	80.8	19.2	.	.
7	**Lymphopenia**	58	1.7	87.9	10.3	.	.
8	**Diarrhoea**	49	.	75.5	22.4	2.0	.
9	**Peritoneal haemorrhage**	48	.	91.7	8.3	.	.
10	**Anaemia**	39	.	100.0	.	.	.
11	**Neoplasm malignant**	37	2.7	64.9	29.7	2.7	.
12	**Vomiting**	29	.	82.8	17.2	.	.
13	**Hypersensitivity**	25	4.0	52.0	40.0	.	4.0
14	**Neutropenia**	25	.	72.0	28.0	.	.
15	**Blood alkaline phosphatase**	21	.	90.5	9.5	.	.
16	**Gastrointestinal disorder**	21	.	95.2	4.8	.	.
17	**Mucosal inflammation**	19	.	84.2	10.5	5.3	.
18	**Neutrophil count decreased**	18	.	100.0	.	.	.
19	**Renal failure**	18	.	66.7	22.2	11.1	.
20	**Hypophosphataemia**	17	.	100.0	.	.	.
21	**Hypokalaemia**	16	.	93.8	.	6.3	.
22	**Myocardial ischaemia**	16	6.3	62.5	25.0	6.3	.
23	**Fatigue**	15	.	93.3	.	6.7	.
24	**Death**	14	7.1	.	.	.	92.9
25	**Haemorrhage**	14	.	85.7	7.1	.	7.1
26	**Cholecystitis**	13	.	92.3	.	7.7	.
27	**Eye disorder**	13	.	61.5	7.7	30.8	.
28	**Gamma-glutamyltransferase**	13	.	84.6	15.4	.	.
29	**Haematoma**	13	.	84.6	15.4	.	.
30	**Hypertension**	13	.	69.2	30.8	.	.
31	**Hyponatraemia**	13	.	84.6	15.4	.	.
32	**Fracture**	12	.	58.3	41.7	.	.
33	**Portal vein thrombosis**	12	.	83.3	8.3	8.3	.

Exhibit 7 – 5 *(continued)*
All Adverse Events (AEs) Following Islet Transplantation
(in order by frequency, with final outcomes)

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
34	**Wound complication**	12	.	100.0	.	.	.
35	**Dehydration**	11	.	90.9	9.1	.	.
36	**Hyperkalaemia**	11	.	81.8	18.2	.	.
37	**Gastrointestinal obstruction**	10	.	60.0	40.0	.	.
38	**Leukopenia**	10	.	90.0	10.0	.	.
39	**Syncope**	10	.	90.0	.	10.0	.
40	**Lung disorder**	9	.	77.8	22.2	.	.
41	**Sexual dysfunction**	9	.	88.9	11.1	.	.
42	**Alanine aminotransferase increased**	8	.	100.0	.	.	.
43	**Colitis**	8	.	75.0	25.0	.	.
44	**Muscular weakness**	8	.	62.5	37.5	.	.
45	**Nausea**	8	.	87.5	12.5	.	.
46	**Pneumonitis**	8	.	87.5	.	.	12.5
47	**Surgery**	8	.	62.5	12.5	25.0	.
48	**Cerebral ischaemia**	7	14.3	14.3	42.9	14.3	14.3
49	**Exfoliative rash**	7	.	85.7	14.3	.	.
50	**Hyperglycaemia**	7	.	57.1	42.9	.	.
51	**Renal disorder**	7	.	85.7	.	14.3	.
52	**Aspartate aminotransferase increased**	6	.	100.0	.	.	.
53	**Blood disorder**	6	.	100.0	.	.	.
54	**Low density lipoprotein abnormal**	6	.	66.7	33.3	.	.
55	**Low density lipoprotein increased**	6	.	83.3	16.7	.	.
56	**Neutrophil count**	6	.	100.0	.	.	.
57	**Oedema peripheral**	6	.	100.0	.	.	.
58	**Pyrexia**	6	.	100.0	.	.	.
59	**Ascites**	5	.	100.0	.	.	.
60	**Chest pain**	5	.	60.0	40.0	.	.
61	**Dizziness**	5	.	100.0	.	.	.
62	**Febrile neutropenia**	5	.	80.0	20.0	.	.
63	**Gastrointestinal haemorrhage**	5	.	100.0	.	.	.
64	**Lipase**	5	.	100.0	.	.	.
65	**Mood altered**	5	.	20.0	60.0	20.0	.
66	**Musculoskeletal disorder**	5	.	60.0	20.0	20.0	.
67	**Peripheral ischaemia**	5	.	60.0	40.0	.	.
68	**Pneumonia**	5	.	60.0	40.0	.	.
69	**Proteinuria**	5	.	20.0	80.0	.	.
70	**Skin disorder**	5	20.0	80.0	.	.	.
71	**Thrombocytopenia**	5	.	20.0	80.0	.	.
72	**Urinary bladder haemorrhage**	5	.	80.0	20.0	.	.
73	**Appendicitis**	4	.	50.0	50.0	.	.
74	**Blood creatinine increased**	4	.	75.0	25.0	.	.

Exhibit 7 – 5 *(continued)*
All Adverse Events (AEs) Following Islet Transplantation
(in order by frequency, with final outcomes)

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
75	**Confusional state**	4	25.0	50.0	25.0	.	.
76	**Dyspnoea**	4	.	100.0	.	.	.
77	**Endocrine disorder**	4	.	100.0	.	.	.
78	**Hip fracture**	4	.	75.0	25.0	.	.
79	**Hypoalbuminaemia**	4	.	100.0	.	.	.
80	**Hypotension**	4	.	75.0	25.0	.	.
81	**Hypoxia**	4	.	100.0	.	.	.
82	**Lung infiltration**	4	.	25.0	75.0	.	.
83	**Platelet disorder**	4	.	100.0	.	.	.
84	**Retinal detachment**	4	.	50.0	25.0	25.0	.
85	**Thrombosis**	4	.	75.0	25.0	.	.
86	**Transaminases**	4	.	100.0	.	.	.
87	**Albuminuria**	3	.	33.3	66.7	.	.
88	**Arrhythmia supraventricular**	3	.	100.0	.	.	.
89	**Arthritis**	3	.	.	.	100.0	.
90	**Cognitive disorder**	3	.	100.0	.	.	.
91	**Cough**	3	.	100.0	.	.	.
92	**Gamma-glutamyltransferase increased**	3	.	100.0	.	.	.
93	**Hepatic enzyme increased**	3	.	100.0	.	.	.
94	**Opportunistic infection**	3	.	100.0	.	.	.
95	**Pancreatitis**	3	.	66.7	33.3	.	.
96	**Pericardial effusion**	3	.	100.0	.	.	.
97	**Pleural effusion**	3	.	66.7	33.3	.	.
98	**Post transplant lymphoproliferative disorder**	3	.	.	100.0	.	.
99	**Pulmonary hypertension**	3	33.3	33.3	33.3	.	.
100	**Tremor**	3	.	100.0	.	.	.
101	**Urinary tract infection**	3	.	33.3	66.7	.	.
102	**Weight decreased**	3	.	100.0	.	.	.
103	**Abdominal hernia repair**	2	.	50.0	50.0	.	.
104	**Activated partial thromboplastin time**	2	.	100.0	.	.	.
105	**Acute respiratory distress syndrome**	2	.	.	.	.	100.0
106	**Anxiety**	2	.	50.0	50.0	.	.
107	**Appendicitis perforated**	2	.	100.0	.	.	.
108	**Aspiration**	2	.	100.0	.	.	.
109	**Ataxia**	2	.	100.0	.	.	.
110	**Blood amylase**	2	.	100.0	.	.	.
111	**Blood phosphorus decreased**	2	.	100.0	.	.	.
112	**Cardiac disorder**	2	.	100.0	.	.	.
113	**Cardio-respiratory arrest**	2	.	50.0	.	.	50.0
114	**Chest discomfort**	2	.	50.0	50.0	.	.

Exhibit 7 – 5 *(continued)*
All Adverse Events (AEs) Following Islet Transplantation
(in order by frequency, with final outcomes)

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
115	Constipation	2	.	50.0	.	50.0	.
116	Cystitis	2	.	100.0	.	.	.
117	Decubitus ulcer	2	.	.	100.0	.	.
118	Dysphagia	2	.	50.0	50.0	.	.
119	Gastritis	2	.	100.0	.	.	.
120	Gastrointestinal perforation	2	.	100.0	.	.	.
121	Glomerular filtration rate	2	.	50.0	50.0	.	.
122	Graft versus host disease	2	.	.	100.0	.	.
123	Haemothorax	2	.	100.0	.	.	.
124	Headache	2	.	100.0	.	.	.
125	Hepatic haematoma	2	.	50.0	50.0	.	.
126	Hepatic haemorrhage	2	.	100.0	.	.	.
127	Hypocalcaemia	2	.	100.0	.	.	.
128	Ileus	2	.	100.0	.	.	.
129	Injury	2	.	50.0	50.0	.	.
130	Insomnia	2	.	50.0	50.0	.	.
131	Musculoskeletal pain	2	.	50.0	50.0	.	.
132	Psychogenic seizure	2	.	50.0	50.0	.	.
133	Pyelonephritis	2	.	50.0	50.0	.	.
134	Serum sickness	2	.	50.0	50.0	.	.
135	Spinal cord compression	2	50.0	50.0	.	.	.
136	Systemic inflammatory response syndrome	2	.	100.0	.	.	.
137	Transaminases increased	2	.	100.0	.	.	.
138	Ulcer	2	.	100.0	.	.	.
139	Acne	1	.	100.0	.	.	.
140	Alcoholism	1	.	100.0	.	.	.
141	Arthropathy	1	.	100.0	.	.	.
142	Autoimmune disorder	1	.	100.0	.	.	.
143	Back pain	1	.	100.0	.	.	.
144	Basal cell carcinoma	1	.	100.0	.	.	.
145	Biliary tract disorder	1	.	100.0	.	.	.
146	Blood albumin decreased	1	.	100.0	.	.	.
147	Blood bilirubin	1	.	100.0	.	.	.
148	Blood creatine phosphokinase	1	.	100.0	.	.	.
149	Blood creatine phosphokinase increased	1	.	.	100.0	.	.
150	Blood potassium increased	1	.	100.0	.	.	.
151	Clostridium difficile colitis	1	.	100.0	.	.	.
152	Convulsion	1	.	.	100.0	.	.
153	Cytokine release syndrome	1	.	100.0	.	.	.
154	Decreased appetite	1	.	100.0	.	.	.

Exhibit 7 – 5 *(continued)*
All Adverse Events (AEs) Following Islet Transplantation
(in order by frequency, with final outcomes)

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
155	Dermatitis	1	.	100.0	.	.	.
156	Dyskinesia	1	.	100.0	.	.	.
157	Ear infection	1	.	.	100.0	.	.
158	Enteritis	1	.	100.0	.	.	.
159	Enterocolitis infectious	1	.	100.0	.	.	.
160	Frontotemporal dementia	1	.	100.0	.	.	.
161	Gastrointestinal infection	1	.	100.0	.	.	.
162	Haemoglobin decreased	1	.	100.0	.	.	.
163	Haemoglobinuria	1	.	100.0	.	.	.
164	Haemolysis	1	.	100.0	.	.	.
165	Haemorrhoids	1	.	100.0	.	.	.
166	Hearing impaired	1	.	.	100.0	.	.
167	Herpes simplex	1	.	100.0	.	.	.
168	Hypoglycaemic seizure	1	.	100.0	.	.	.
169	Hypomagnesaemia	1	.	100.0	.	.	.
170	Influenza like illness	1	.	100.0	.	.	.
171	Injection site reaction	1	.	100.0	.	.	.
172	International normalised ratio increased	1	.	100.0	.	.	.
173	Laceration	1	.	100.0	.	.	.
174	Lactation disorder	1	.	100.0	.	.	.
175	Lymphatic disorder	1	.	100.0	.	.	.
176	Micturition urgency	1	.	100.0	.	.	.
177	Mouth ulceration	1	.	100.0	.	.	.
178	Myositis	1	.	100.0	.	.	.
179	Ocular surface disease	1	.	100.0	.	.	.
180	Oral pain	1	.	100.0	.	.	.
181	Pericarditis	1	.	100.0	.	.	.
182	Post procedural haemorrhage	1	.	.	100.0	.	.
183	Presyncope	1	.	100.0	.	.	.
184	Pruritus	1	.	.	100.0	.	.
185	Psychotic disorder	1	.	100.0	.	.	.
186	Rheumatoid arthritis	1	.	100.0	.	.	.
187	Stomatitis	1	.	100.0	.	.	.
188	Tinnitus	1	.	.	100.0	.	.
189	Toxicity to various agents	1	.	100.0	.	.	.
190	Troponin I	1	.	100.0	.	.	.
191	Troponin T	1	.	100.0	.	.	.
192	Tubulointerstitial nephritis	1	.	100.0	.	.	.
193	Upper limb fracture	1	.	100.0	.	.	.
194	Uveitis	1	.	.	100.0	.	.
195	Wound dehiscence	1	.	100.0	.	.	.

Exhibit 7 – 6
SAE Criteria

	Transplant type				Era							
	ITA		IAK/SIK		1999-2002		2003-2006		2007-2010		2011-2014	
	N	%	N	%	N	%	N	%	N	%	N	%
Total recipients (N)	686	100.0	178	100.0	209	100.0	271	100.0	230	100.0	154	100.0
Death	9	1.3	12	6.7	14	6.7	6	2.2	1	0.4	.	.
Life Threatening	108	15.7	38	21.3	50	23.9	74	27.3	16	7.0	6	3.9
Hospitalization	217	31.6	79	44.4	95	45.5	128	47.2	64	27.8	9	5.8
Congenital abnormality	1	0.1	.	.	.	.	1	0.4	.	.	.	.
Long term disability	21	3.1	8	4.5	8	3.8	9	3.3	11	4.8	1	0.6
PI Indicated Serious	67	9.8	20	11.2	19	9.1	40	14.8	25	10.9	3	1.9

Exhibit 7 – 7A
CITR ITA: Incidence of Post-Transplant AEs Related to Infusion Procedure

By Calendar Year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.9	1	0.34	0.01 - 1.92	1	0.34	0.01 - 1.92
2000	12.6	5	0.40	0.13 - 0.93	2	0.16	0.02 - 0.57
2001	38.7	13	0.34	0.18 - 0.57	5	0.13	0.04 - 0.30
2002	102.6	58	0.57	0.43 - 0.73	31	0.30	0.21 - 0.43
2003	175.8	46	0.26	0.19 - 0.35	22	0.13	0.08 - 0.19
2004	222.5	26	0.12	0.08 - 0.17	14	0.06	0.03 - 0.11
2005	291.1	50	0.17	0.13 - 0.23	30	0.10	0.07 - 0.15
2006	346.1	27	0.08	0.05 - 0.11	20	0.06	0.04 - 0.09
2007	378.5	17	0.04	0.03 - 0.07	10	0.03	0.01 - 0.05
2008	412.5	21	0.05	0.03 - 0.08	12	0.03	0.02 - 0.05
2009	464.4	26	0.06	0.04 - 0.08	11	0.02	0.01 - 0.04
2010	523.0	22	0.04	0.03 - 0.06	16	0.03	0.02 - 0.05
2011	587.9	14	0.02	0.01 - 0.04	13	0.02	0.01 - 0.04
2012	647.7	15	0.02	0.01 - 0.04	13	0.02	0.01 - 0.03

By year of follow-up post first infusion

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	638.2	284	0.45	0.39 - 0.50	157	0.25	0.21 - 0.29
2	576.8	27	0.05	0.03 - 0.07	22	0.04	0.02 - 0.06
3	503.5	13	0.03	0.01 - 0.04	7	0.01	0.01 - 0.03
4	454.0	11	0.02	0.01 - 0.04	9	0.02	0.01 - 0.04
5	391.6	4	0.01	0.00 - 0.03	3	0.01	0.00 - 0.02
6	356.8	1	0.00	0.00 - 0.02	1	0.00	0.00 - 0.02
7	314.1	0	0.00	0.00 - 0.01	0	0.00	0.00 - 0.01
8	290.6	0	0.00	0.00 - 0.01	0	0.00	0.00 - 0.01
9	255.1	0	0.00	0.00 - 0.01	0	0.00	0.00 - 0.01
10	231.8	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
11	171.3	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
12	150.9	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
13	115.8	0	0.00	0.00 - 0.03	0	0.00	0.00 - 0.03
14	98.5	0	0.00	0.00 - 0.04	0	0.00	0.00 - 0.04

Exhibit 7 – 7B
ITA: Incidence of Post-Transplant AEs Related to Immunosuppression Therapy

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	2.9	5	1.72	0.56 - 4.02	5	1.72	0.56 - 4.02
2000	12.6	7	0.56	0.22 - 1.14	2	0.16	0.02 - 0.57
2001	38.7	15	0.39	0.22 - 0.64	2	0.05	0.01 - 0.19
2002	102.6	87	0.85	0.68 - 1.05	32	0.31	0.21 - 0.44
2003	175.8	80	0.46	0.36 - 0.57	22	0.13	0.08 - 0.19
2004	222.5	81	0.36	0.29 - 0.45	27	0.12	0.08 - 0.18
2005	291.1	140	0.48	0.40 - 0.57	62	0.21	0.16 - 0.27
2006	346.1	79	0.23	0.18 - 0.28	33	0.10	0.07 - 0.13
2007	378.5	40	0.11	0.08 - 0.14	25	0.07	0.04 - 0.10
2008	412.5	60	0.15	0.11 - 0.19	33	0.08	0.06 - 0.11
2009	464.4	72	0.16	0.12 - 0.20	30	0.06	0.04 - 0.09
2010	523.0	47	0.09	0.07 - 0.12	37	0.07	0.05 - 0.10
2011	587.9	40	0.07	0.05 - 0.09	32	0.05	0.04 - 0.08
2012	647.7	23	0.04	0.02 - 0.05	16	0.02	0.01 - 0.04

By follow-up year

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	638.2	525	0.82	0.75 - 0.90	216	0.34	0.29 - 0.39
2	576.8	124	0.21	0.18 - 0.26	55	0.10	0.07 - 0.12
3	503.5	54	0.11	0.08 - 0.14	37	0.07	0.05 - 0.10
4	454.0	33	0.07	0.05 - 0.10	24	0.05	0.03 - 0.08
5	391.6	18	0.05	0.03 - 0.07	12	0.03	0.02 - 0.05
6	356.8	12	0.03	0.02 - 0.06	7	0.02	0.01 - 0.04
7	314.1	4	0.01	0.00 - 0.03	3	0.01	0.00 - 0.03
8	290.6	2	0.01	0.00 - 0.02	1	0.00	0.00 - 0.02
9	255.1	1	0.00	0.00 - 0.02	0	0.00	0.00 - 0.01
10	231.8	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
11	171.3	1	0.01	0.00 - 0.03	1	0.01	0.00 - 0.03
12	150.9	0	0.00	0.00 - 0.02	0	0.00	0.00 - 0.02
13	115.8	0	0.00	0.00 - 0.03	0	0.00	0.00 - 0.03
14	98.5	0	0.00	0.00 - 0.04	0	0.00	0.00 - 0.04

Exhibit 7 – 8A
IAKSIK: Incidence of Post-Transplant AEs Related to Infusion Procedure

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	7.5	1	0.13	0.00 - 0.74	1	0.13	0.00 - 0.74
2000	24.3	3	0.12	0.03 - 0.36	3	0.12	0.03 - 0.36
2001	34.9	4	0.11	0.03 - 0.29	2	0.06	0.01 - 0.21
2002	43.5	6	0.14	0.05 - 0.30	3	0.07	0.01 - 0.20
2003	61.1	13	0.21	0.11 - 0.36	11	0.18	0.09 - 0.32
2004	74.8	5	0.07	0.02 - 0.16	2	0.03	0.00 - 0.10
2005	86.4	8	0.09	0.04 - 0.18	2	0.02	0.00 - 0.08
2006	97.9	6	0.06	0.02 - 0.13	3	0.03	0.01 - 0.09
2007	106.8	3	0.03	0.01 - 0.08	3	0.03	0.01 - 0.08
2008	112.6	3	0.03	0.01 - 0.08	3	0.03	0.01 - 0.08
2009	117.2	1	0.01	0.00 - 0.05	1	0.01	0.00 - 0.05
2010	129.5	2	0.02	0.00 - 0.06	2	0.02	0.00 - 0.06
2011	145.4	1	0.01	0.00 - 0.04	1	0.01	0.00 - 0.04
2012	157.5	8	0.05	0.02 - 0.10	8	0.05	0.02 - 0.10

By follow-up year

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	144.8	54	0.37	0.28 - 0.49	39	0.27	0.19 - 0.37
2	129.8	3	0.02	0.00 - 0.07	2	0.02	0.00 - 0.06
3	113.5	3	0.03	0.01 - 0.08	0	0.00	0.00 - 0.03
4	110.7	2	0.02	0.00 - 0.07	2	0.02	0.00 - 0.07
5	105.6	2	0.02	0.00 - 0.07	2	0.02	0.00 - 0.07
6	99.1	0	0.00	0.00 - 0.04	0	0.00	0.00 - 0.04
7	86.0	0	0.00	0.00 - 0.04	0	0.00	0.00 - 0.04
8	75.8	0	0.00	0.00 - 0.05	0	0.00	0.00 - 0.05
9	64.5	0	0.00	0.00 - 0.06	0	0.00	0.00 - 0.06
10	59.1	0	0.00	0.00 - 0.06	0	0.00	0.00 - 0.06
11	45.2	0	0.00	0.00 - 0.08	0	0.00	0.00 - 0.08
12	43.1	0	0.00	0.00 - 0.09	0	0.00	0.00 - 0.09
13	33.2	0	0.00	0.00 - 0.11	0	0.00	0.00 - 0.11
14	29.7	0	0.00	0.00 - 0.12	0	0.00	0.00 - 0.12

Exhibit 7 – 8B
IAKSIK: Incidence of Post-Transplant AEs Related to Immunosuppression Therapy

By calendar year

Study Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1999	7.5	0	0.00	0.00 - 0.49	0	0.00	0.00 - 0.49
2000	24.3	3	0.12	0.03 - 0.36	3	0.12	0.03 - 0.36
2001	34.9	5	0.14	0.05 - 0.33	4	0.11	0.03 - 0.29
2002	43.5	11	0.25	0.13 - 0.45	6	0.14	0.05 - 0.30
2003	61.1	13	0.21	0.11 - 0.36	10	0.16	0.08 - 0.30
2004	74.8	23	0.31	0.19 - 0.46	17	0.23	0.13 - 0.36
2005	86.4	14	0.16	0.09 - 0.27	8	0.09	0.04 - 0.18
2006	97.9	18	0.18	0.11 - 0.29	12	0.12	0.06 - 0.21
2007	106.8	9	0.08	0.04 - 0.16	9	0.08	0.04 - 0.16
2008	112.6	8	0.07	0.03 - 0.14	6	0.05	0.02 - 0.12
2009	117.2	6	0.05	0.02 - 0.11	4	0.03	0.01 - 0.09
2010	129.5	7	0.05	0.02 - 0.11	4	0.03	0.01 - 0.08
2011	145.4	8	0.06	0.02 - 0.11	7	0.05	0.02 - 0.10
2012	157.5	15	0.10	0.05 - 0.16	15	0.10	0.05 - 0.16

By follow-up year

Recipient Follow-Up Year	Person-Years of Follow-Up During Year	Total AEs Reported Occurring During Year	Incidence of AEs (AEs/Person-Yr)	95% CI	Total SAEs Reported Occurring During Year	Incidence of SAEs (SAEs/Person-Yr)	95% CI
1	144.8	77	0.53	0.42 - 0.66	55	0.38	0.29 - 0.49
2	129.8	17	0.13	0.08 - 0.21	15	0.12	0.06 - 0.19
3	113.5	19	0.17	0.10 - 0.26	15	0.13	0.07 - 0.22
4	110.7	7	0.06	0.03 - 0.13	5	0.05	0.01 - 0.11
5	105.6	4	0.04	0.01 - 0.10	4	0.04	0.01 - 0.10
6	99.1	3	0.03	0.01 - 0.09	1	0.01	0.00 - 0.06
7	86.0	5	0.06	0.02 - 0.14	4	0.05	0.01 - 0.12
8	75.8	1	0.01	0.00 - 0.07	1	0.01	0.00 - 0.07
9	64.5	1	0.02	0.00 - 0.09	1	0.02	0.00 - 0.09
10	59.1	2	0.03	0.00 - 0.12	2	0.03	0.00 - 0.12
11	45.2	1	0.02	0.00 - 0.12	1	0.02	0.00 - 0.12
12	43.1	0	0.00	0.00 - 0.09	0	0.00	0.00 - 0.09
13	33.2	0	0.00	0.00 - 0.11	0	0.00	0.00 - 0.11
14	29.7	0	0.00	0.00 - 0.12	0	0.00	0.00 - 0.12

Exhibit 7 – 9
Incidence of AEs and SAEs per Recipient by type of Transplant and Era

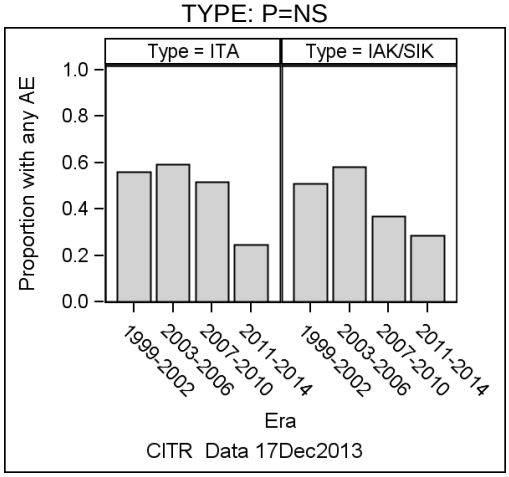
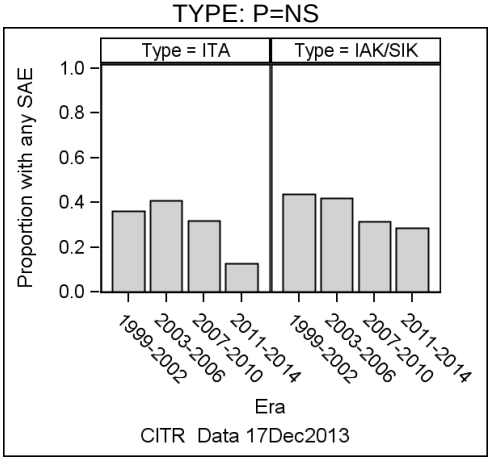
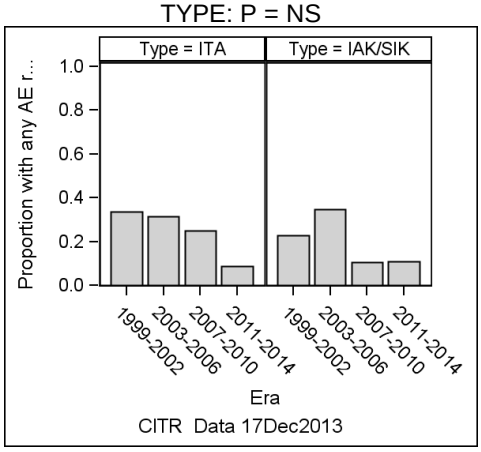
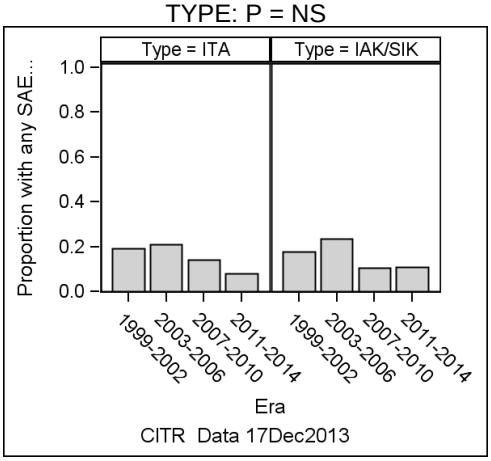
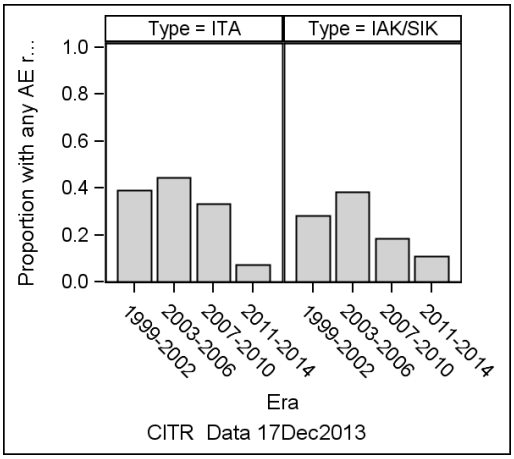
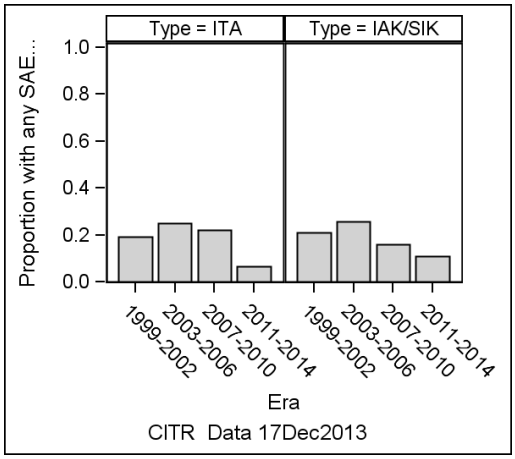
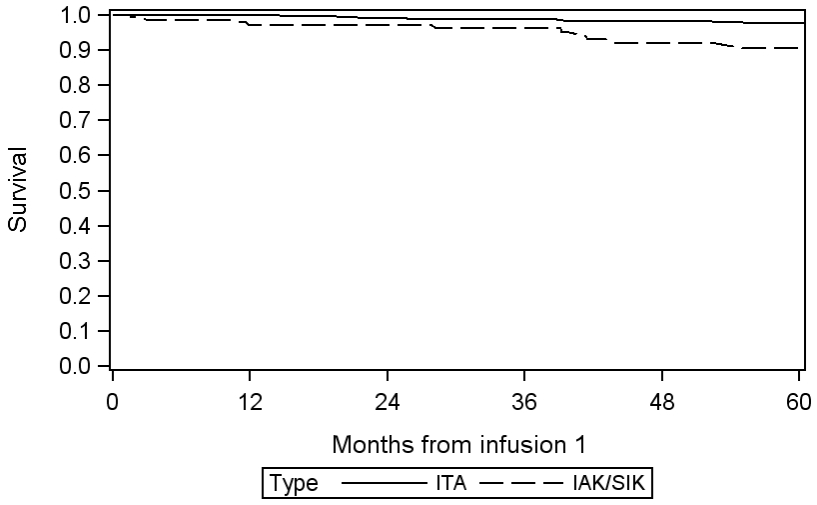
	ANY AE	ANY SAE
PROPORTION WITH ANY AE IN FIRST YEAR POST TRANSPLANT	ERA: P<0.001 TYPE: P=NS 	ERA: P<0.001 TYPE: P=NS 
PROPORTION WITH ANY AE IN FIRST YEAR POST TRANSPLANT RELATED TO INFUSION	ERA: P<0.001 TYPE: P = NS 	ERA: P<0.001 TYPE: P = NS 
PROPORTION WITH ANY AE IN FIRST YEAR POST TRANSPLANT RELATED TO IMMUNOSUPPRESSION	ERA: P<0.001 TYPE: P=0.02 	ERA: P<0.001 TYPE: P = NS 

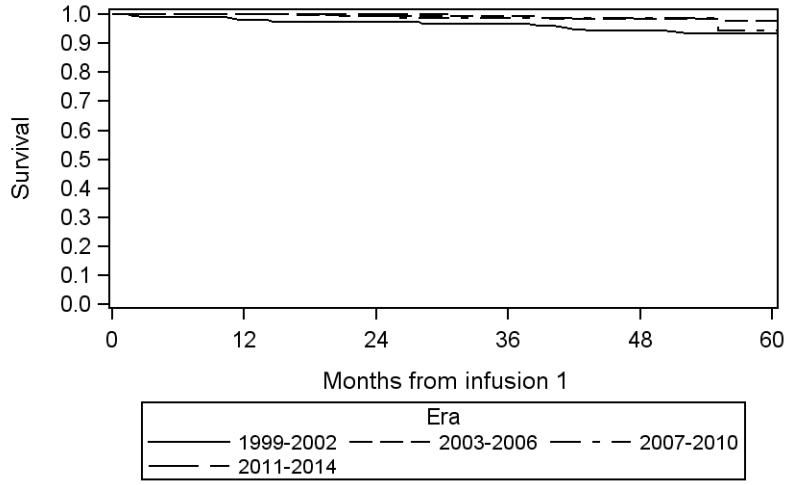
Exhibit 7 – 10
Summary of Neoplasms Reported Post Islet Transplantation

Total recipients of Allo-ITx with first infusion as of 12/31/2012	**N= 864 (686 ITA; 178 IAK/SIK)**
Mean follow-up / recipient	**6.7 (0.2-14.3)**
Total person-years follow-up	**5,762 years**
Post-ITx incidence of neoplasm	**41 instances / 32 recipients** (4 instances in 1 recipient, 3 instances each in 2 recipients, 2 instances each in 2 recipients)
Incidence rate	**0.007 events / person-year of follow-up**
Related to immunosuppression	**35 (85%) possibly related** **4 (9.8%) not related** **1 (2.4%) unlikely related** **1 (2.4%) unknown**
Neoplasms	- 21 instances in 17 patients (1 in 15 recipients, 2 in 1 recipient, and 4 in another) of basal or squamous cell carcinoma of the skin. Of the 15 patients with a single instance, 11 recovered, 1 recovered with sequelae, 1 is recovering, and 1 has an unknown recovery status. The recipient with 4 instances recovered with sequelae and the recipient with 2 instances has not recovered. - 6 instances of malignant ovarian cysts, 4 instances of breast cancer (2 instances in 1 recipient), 2 instances of lung cancer, 2 instances of thyroid cancer, and 3 instances of PTLD. Of the 16 recipients with non-skin cancers, 8 recovered, 2 recovered with sequelae, 5 have not recovered, and 1 died (lung cancer). For 3 instances of cancer, there were no types specified (2 instances in 1 recipient). Both of these recipients recovered.

Exhibit 7 – 11
Deaths



	ITA	IAK/SIK
Deaths/N	12 / 686 (1.7%)	13 / 178 (7.3%)



	Era			
	1999-2002	2003-2006	2007-2010	2011-2014
Deaths / N	15 / 209 (7.2%)	7 / 271 (2.6%)	3 / 230 (1.3%)	0

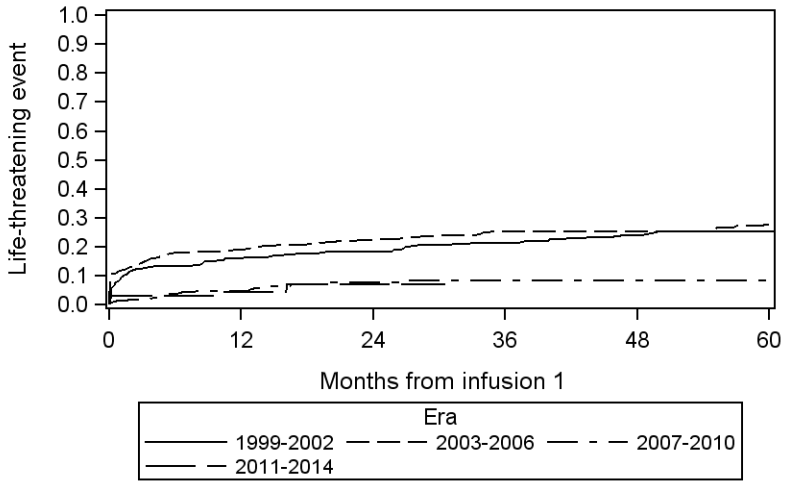
Exhibit 7 – 11 *(continued)*
Deaths by Cause and Relatedness to Procedure or Immunosuppression

	Type of Transplant	Years post infusion 1	Year of Transplant	MedDRA Primary Cause of Death	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Active Immunosuppression
1	ITA	1.2	2002		Missing Information	Missing Information	
2	ITA	1.4	2005	Atherosclerotic Coronary Artery Disease	Not related	Not related	Yes
3	ITA	1.7	2008	Multi-organ failure of unknown etiology	Possibly related	Possibly related	Yes
4	ITA	1.8	2003	Acute Methadone and Diphenhydramine Toxicity	Not related	Not related	Yes
5	ITA	2.1	2009		Missing Information	Missing Information	Yes
6	ITA	3.2	2002	Viral meningitis	Not related	Possibly related	Yes
7	ITA	3.3	2006		Missing Information	Missing Information	Yes
8	ITA	4.4	2001	Unknown	Not related	Unlikely related	Yes
9	ITA	4.6	2006	Cardiac failure	Related	Not related	Yes
10	ITA	5.3	2003	Infection	Not related	Unlikely related	
11	ITA	6.5	2000	Diabetic Ketoacidosis due to Diabetes Mellitus	Not related	Not related	Yes
12	ITA	8.2	2000	Pneumonia	Not related	Not related	Yes
13	IAK/SIK	0.1	2002	Infectious pneumopathy	Missing Information	Related	Yes
14	IAK/SIK	0.3	2001	Cardio-respiratory arrest	Unlikely related	Unlikely related	Yes
15	IAK/SIK	0.9	2001	respiratory arrest after therapy withdrawal	Not related	Related	Yes
16	IAK/SIK	1	2000	Unknown	Not related	Unlikely related	Yes
17	IAK/SIK	2.3	1999	Congestive heart failure	Not related	Not related	
18	IAK/SIK	3.3	2004	Brain hemorrhage	Not related	Not related	Yes
19	IAK/SIK	3.4	2000		Not related	Not related	Yes
20	IAK/SIK	3.5	2001	Massive Hemorrhagic Infarct	Not related	Not related	Yes
21	IAK/SIK	3.7	2002	Subarachnoid hemorrhage mesencephalic	Not related	Not related	Yes
22	IAK/SIK	4.6	2007	Severe chronic cardiovascular complications	Missing Information	Missing Information	Yes
23	IAK/SIK	6.2	2000	Unknown	Not related	Unlikely related	Yes
24	IAK/SIK	6.3	2003	Pneumonia	Not related	Not related	Yes
25	IAK/SIK	8.8	1999	Lung Carcinoma Non-small cell poorly differentiate	Not related	Unlikely related	Yes

There have been 25 deaths reported to the Registry: 12 / 686 ITA's (1.7%) and 13 / 178 (7.3%) IAK/SIK.

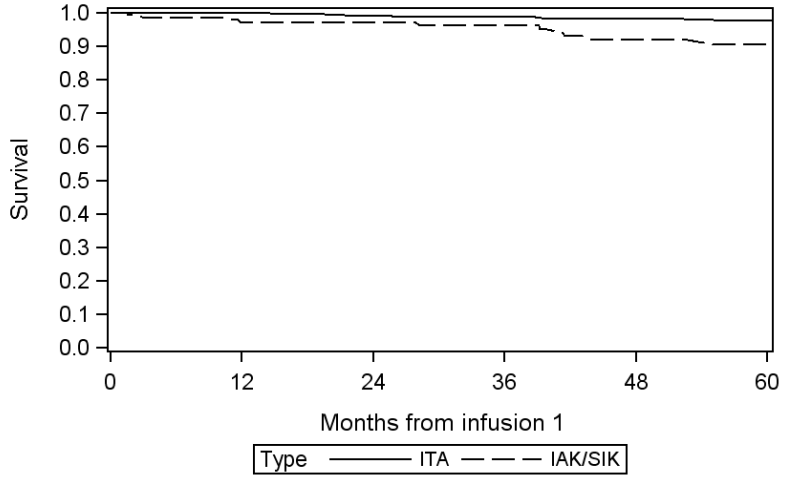
Exhibit 7 – 12
Life-Threatening Events

By Era



	Era			
	1999-2002	*2003-2006*	*2007-2010*	*2011-2014*
Life-threatening events	50 / 209	74 / 271	16 / 230	6 / 154

By Type of Transplant



	Transplant type	
	ITA	*IAK/SIK*
Life-threatening event	12 / 686	13 / 178

Exhibit 7 – 12 *(continued)*
Life-Threatening Events (in System/Organ Class Order)

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
Blood and lymphatic system disorders	Anaemia	IAK/SIK	2003-2006	0.9	Possibly related	Unlikely related
	Anaemia	ITA	2003-2006	1.9	Unlikely related	Unlikely related
	Anaemia	IAK/SIK	1999-2002	46.6	Not related	Possibly related
	Blood disorder	IAK/SIK	1999-2002	8.5	Not related	Unlikely related
	Lymphopenia	ITA	2003-2006	0.0	Not related	Related
	Lymphopenia	ITA	2003-2006	0.0	Not related	Related
	Lymphopenia	ITA	2003-2006	-1.2	Not related	Related
	Lymphopenia	ITA	2003-2006	0.0	Not related	Related
	Lymphopenia	IAK/SIK	2003-2006	18.6	Unlikely related	Possibly related
Cardiac disorders	Cardio-respiratory arrest	IAK/SIK	2003-2006	55.2	Unlikely related	Unlikely related
	Cardio-respiratory arrest	IAK/SIK	1999-2002	28.2	Not related	Not related
	Myocardial ischaemia	ITA	2003-2006	0.0	Possibly related	Possibly related
	Myocardial ischaemia	IAK/SIK	2007-2010	26.7	Unlikely related	Unlikely related
	Myocardial ischaemia	ITA	2007-2010	4.1	Not related	Unlikely related
	Myocardial ischaemia	IAK/SIK	2003-2006	59.8	Not related	Not related
	Myocardial ischaemia	IAK/SIK	2003-2006	67.2	Missing Information	Missing Information
	Myocardial ischaemia	IAK/SIK	1999-2002	40.0	Unlikely related	Unlikely related
	Myocardial ischaemia	ITA	2007-2010	0.7	Not related	Not related
Gastrointestinal disorders	Gastrointestinal haemorrhage	IAK/SIK	2003-2006	0.0	Related	Unlikely related
	Gastrointestinal obstruction	ITA	2003-2006	1.6	Related	Not related
	Peritoneal haemorrhage	ITA	1999-2002	1.1	Related	Possibly related
	Peritoneal haemorrhage	IAK/SIK	1999-2002	0.0	Related	Not related
	Peritoneal haemorrhage	ITA	1999-2002	1.0	Related	Unlikely related
	Peritoneal haemorrhage	ITA	2003-2006	0.0	Related	Not related
	Peritoneal haemorrhage	ITA	2007-2010	6.7	Related	Unlikely related
	Peritoneal haemorrhage	IAK/SIK	2003-2006	15.2	Related	Not related
	Peritoneal haemorrhage	IAK/SIK	1999-2002	1.8	Related	Not related
	Peritoneal haemorrhage	ITA	1999-2002	17.2	Related	Not related
	Peritoneal haemorrhage	ITA	2007-2010	8.2	Related	Not related
	Peritoneal haemorrhage	ITA	2011-2014	16.2	Related	Not related
	Vomiting	ITA	2007-2010	5.6	Not related	Unlikely related
General disorders and administration site conditions	Death	ITA	2003-2006	55.1	Related	Not related
	Death	IAK/SIK	1999-2002	43.9	Not related	Not related
	Death	ITA	2007-2010	19.8	Possibly related	Possibly related
Hepatobiliary disorders	Cholecystitis	ITA	1999-2002	12.4	Possibly related	Unlikely related
	Portal vein thrombosis	ITA	2003-2006	3.3	Related	Not related
	Portal vein thrombosis	ITA	2003-2006	0.0	Related	Not related
Immune system disorders	Hypersensitivity	ITA	2003-2006	29.7	Not related	Related
	Hypersensitivity	IAK/SIK	2003-2006	34.0	Unlikely related	Possibly related
	Hypersensitivity	IAK/SIK	1999-2002	10.5	Not related	Unlikely related
Infections and infestations	Infection	IAK/SIK	1999-2002	106.8	Not related	Not related
	Infection	ITA	2003-2006	20.7	Not related	Possibly related
	Infection	ITA	2003-2006	33.9	Not related	Possibly related
	Infection	ITA	2003-2006	1.6	Related	Not related
	Infection	ITA	2003-2006	5.9	Possibly related	Possibly related
	Infection	ITA	1999-2002	33.2	Unlikely related	Possibly related
	Opportunistic infection	ITA	2003-2006	60.3	Unlikely related	Related
	Opportunistic infection	IAK/SIK	2007-2010	12.8	Not related	Possibly related

Exhibit 7 – 12 *(continued)*
Life-Threatening Events (in System/Organ Class Order)

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
Investigations	Blood alkaline phosphatase	ITA	1999-2002	0.2	Possibly related	Unlikely related
	Blood alkaline phosphatase	ITA	2003-2006	0.1	Possibly related	Unlikely related
	Blood alkaline phosphatase	ITA	2003-2006	0.1	Possibly related	Unlikely related
	Granulocytes abnormal	ITA	1999-2002	1.9	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	37.8	Not related	Related
	Granulocytes abnormal	ITA	1999-2002	2.5	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	26.7	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	1.4	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	9.8	Not related	Related
	Granulocytes abnormal	ITA	1999-2002	4.1	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	1.7	Not related	Possibly related
	Granulocytes abnormal	IAK/SIK	1999-2002	3.1	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	49.2	Not related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	0.9	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	1999-2002	0.5	Not related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	19.7	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	0.1	Unlikely related	Possibly related
	Granulocytes abnormal	IAK/SIK	2003-2006	3.8	Not related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	0.1	Related	Related
	Granulocytes abnormal	IAK/SIK	2003-2006	2.5	Not related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	0.2	Not related	Related
	Granulocytes abnormal	ITA	2003-2006	0.1	Unlikely related	Related
	Granulocytes abnormal	ITA	2003-2006	3.4	Not related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	0.7	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	0.3	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	0.7	Not related	Related
	Granulocytes abnormal	IAK/SIK	2003-2006	7.9	Not related	Possibly related
	Granulocytes abnormal	ITA	2003-2006	5.2	Not related	Related
	Granulocytes abnormal	ITA	2003-2006	3.6	Not related	Related
	Granulocytes abnormal	ITA	2007-2010	4.8	Unlikely related	Related
	Granulocytes abnormal	ITA	2007-2010	0.1	Unlikely related	Possibly related
	Granulocytes abnormal	ITA	2007-2010	1.8	Not related	Possibly related
	Granulocytes abnormal	ITA	2011-2014	0.1	Possibly related	Related
	Granulocytes abnormal	ITA	2011-2014	0.1	Unlikely related	Related
	Granulocytes abnormal	IAK/SIK	2011-2014	10.0	Unlikely related	Possibly related
	Liver function test abnormal	ITA	1999-2002	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	1.1	Related	Related
	Liver function test abnormal	ITA	2003-2006	0.0	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.0	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	1999-2002	0.1	Related	Not related
	Liver function test abnormal	ITA	2003-2006	12.9	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.1	Possibly related	Unlikely related

Exhibit 7 – 12 *(continued)*
Life-Threatening Events (in System/Organ Class Order)

System/Organ Class	MedDRA Preferred Term	Type of Transplant	Era	Months post infusion 1	Related to Infusion Procedure?	Related to Immunosuppression Therapy?
	Liver function test abnormal	ITA	2003-2006	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.1	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.3	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.2	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.0	Possibly related	Unlikely related
	Liver function test abnormal	ITA	2003-2006	0.2	Possibly related	Possibly related
	Liver function test abnormal	ITA	2003-2006	0.1	Possibly related	Possibly related
	Liver function test abnormal	ITA	2003-2006	0.0	Possibly related	Unlikely related
	Troponin I	IAK/SIK	2003-2006	57.1	Not related	Not related
Metabolism and nutrition disorders	Hypoglycaemia	ITA	2003-2006	26.9	Not related	Not related
	Hypoglycaemia	ITA	1999-2002	8.7	Not related	Not related
	Hypoglycaemia	ITA	1999-2002	14.9	Not related	Not related
	Hypoglycaemia	ITA	2003-2006	11.1	Not related	Not related
	Hypoglycaemia	ITA	2003-2006	34.9	Not related	Not related
	Hypoglycaemia	ITA	1999-2002	0.4	Missing Information	Unlikely related
	Hypoglycaemia	ITA	2003-2006	12.4	Not related	Not related
	Hypoglycaemia	ITA	2003-2006	11.3	Not related	Possibly related
	Hypoglycaemia	ITA	2003-2006	2.6	Related	Not related
	Hypoglycaemia	ITA	2003-2006	-8.1	Not related	Not related
	Hypoglycaemia	ITA	2003-2006	0.0	Unlikely related	Unlikely related
	Hypoglycaemia	ITA	2007-2010	16.5	Unlikely related	Unlikely related
	Hypophosphataemia	ITA	2003-2006	2.3	Not related	Possibly related
	Ketoacidosis	ITA	2007-2010	4.5	Possibly related	Unlikely related
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	ITA	1999-2002	26.9	Not related	Possibly related
	Neoplasm malignant	ITA	2003-2006	4.4	Not related	Not related
	Neoplasm malignant	ITA	2003-2006	22.9	Not related	Possibly related
	Neoplasm malignant	ITA	2003-2006	4.6	Unlikely related	Possibly related
	Neoplasm malignant	IAK/SIK	1999-2002	105.0	Not related	Possibly related
Nervous system disorders	Cerebral ischaemia	IAK/SIK	1999-2002	66.6	Unlikely related	Not related
	Cerebral ischaemia	IAK/SIK	2007-2010	13.2	Not related	Not related
	Cerebral ischaemia	IAK/SIK	1999-2002	0.2	Unlikely related	Unlikely related
Psychiatric disorders	Insomnia	ITA	1999-2002	19.7	Not related	Related
Renal and urinary disorders	Proteinuria	IAK/SIK	2003-2006	28.3	Not related	Possibly related
	Proteinuria	ITA	2003-2006	24.3	Not related	Related
	Renal failure	ITA	2003-2006	3.3	Unlikely related	Possibly related
	Renal failure	IAK/SIK	1999-2002	8.1	Unlikely related	Possibly related
Respiratory, thoracic and mediastinal disorders	Aspiration	ITA	2007-2010	0.1	Possibly related	Possibly related
	Pneumonitis	IAK/SIK	1999-2002	0.6	Not related	Related
Vascular disorders	Haematoma	ITA	2003-2006	0.0	Related	Not related
	Haematoma	IAK/SIK	2003-2006	0.0	Related	Not related
	Haematoma	IAK/SIK	1999-2002	25.8	Not related	Not related
	Haemorrhage	IAK/SIK	2003-2006	5.4	Related	Unlikely related
	Haemorrhage	IAK/SIK	1999-2002	0.0	Related	Unlikely related
	Haemorrhage	IAK/SIK	2011-2014	0.0	Related	Not related
	Hypertension	ITA	1999-2002	50.0	Not related	Possibly related

Exhibit 7 – 12 *(continued)*
Life-Threatening Events (in System/Organ Class Order)
Outcomes of life-threatening events

			AEOUT				
		Total	Fatal	Not recovered	Recovered	Recovered with seq	Unknown
		N	Row%	Row%	Row%	Row%	Row%
System/Organ Class	**Preferred Term**						
Blood and lymphatic system disorders	**Anaemia**	3	.	.	100.0	.	.
	Blood disorder	1	.	.	100.0	.	.
	Lymphopenia	5	.	.	100.0	.	.
Cardiac disorders	**Cardio-respiratory arrest**	2	50.0	.	50.0	.	.
	Myocardial ischaemia	7	.	.	71.4	28.6	.
Gastrointestinal disorders	**Gastrointestinal haemorrhage**	1	.	.	100.0	.	.
	Gastrointestinal obstruction	1	.	.	100.0	.	.
	Peritoneal haemorrhage	10	.	.	100.0	.	.
	Vomiting	1	.	.	100.0	.	.
General disorders and administration site conditions	**Death**	3	100.0	.	.	.	.
Hepatobiliary disorders	**Cholecystitis**	1	.	.	100.0	.	.
	Portal vein thrombosis	2	.	.	100.0	.	.
Immune system disorders	**Hypersensitivity**	3	.	.	33.3	33.3	33.3
Infections and infestations	**Infection**	6	.	.	50.0	50.0	.
	Opportunistic infection	2	.	.	100.0	.	.
Investigations	**Blood alkaline phosphatase**	3	.	.	100.0	.	.
	Granulocytes abnormal	32	.	3.1	96.9	.	.
	Liver function test abnormal	23	.	.	95.7	4.3	.
	Troponin I	1	.	.	100.0	.	.
Metabolism and nutrition disorders	**Hypoglycaemia**	12	.	.	100.0	.	.
	Hypophosphataemia	1	.	.	100.0	.	.
	Ketoacidosis	1	.	.	100.0	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	5	.	40.0	20.0	40.0	.
Nervous system disorders	**Cerebral ischaemia**	3	.	33.3	.	66.7	.
Psychiatric disorders	**Insomnia**	1	.	.	100.0	.	.
Renal and urinary disorders	**Proteinuria**	2	.	50.0	50.0	.	.
	Renal failure	2	.	.	50.0	50.0	.
Respiratory, thoracic and mediastinal disorders	**Aspiration**	1	.	.	100.0	.	.
	Pneumonitis	1	100.0	.	.	.	.
Vascular disorders	**Haematoma**	3	.	.	100.0	.	.
	Haemorrhage	3	.	.	100.0	.	.
	Hypertension	1	.	.	100.0	.	.

Chapter 8
Registry Data Quality Review

Introduction

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

Ns	Overall						JDRF						NorthAm					
	Post LastTx						Post LastTx						Post LastTx					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
1999 - 2002	209	413	202	199	195	197	86	166	81	80	78	78	123	247	121	119	117	119
2003 - 2006	271	546	262	258	255	244	105	213	103	102	101	100	166	333	159	156	154	144
2007 - 2010	230	462	217	193	120	64	95	190	93	81	55	32	135	272	124	112	65	32
2011 - 2014	154	285	52	.	.	.	62	110	18	.	.	.	92	175	34	.	.	.

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

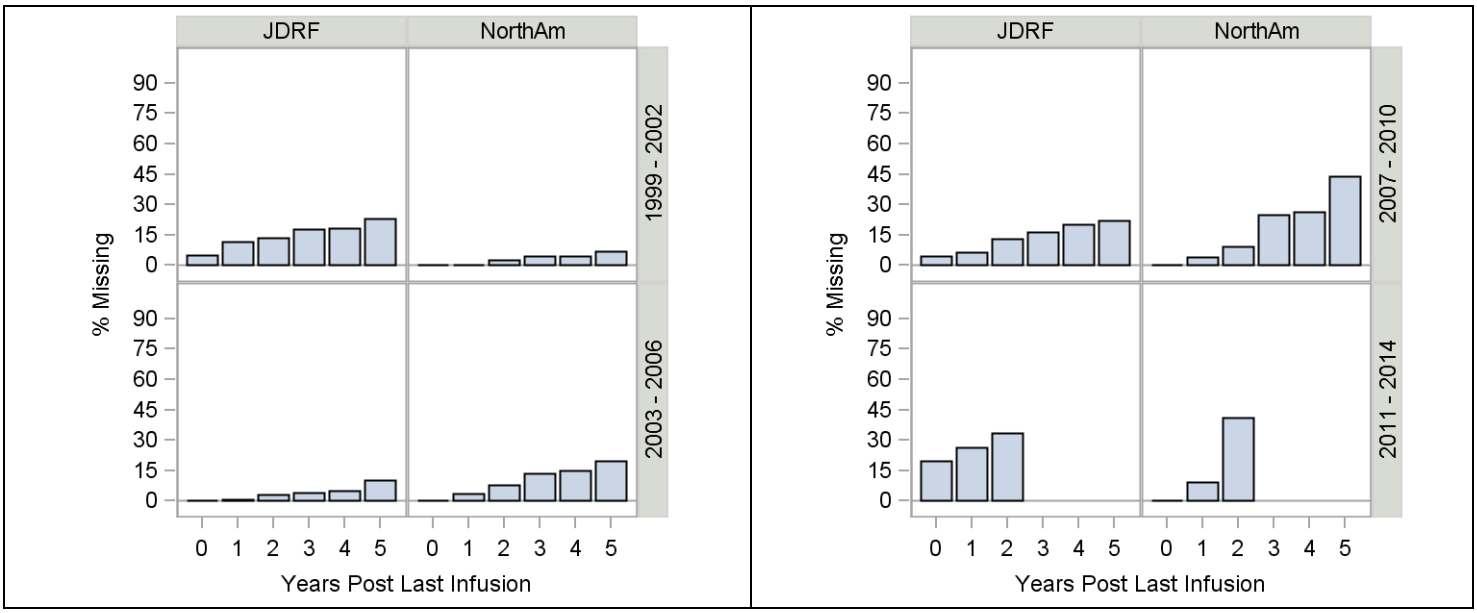


Exhibit 8 – 2
Missing Data for Fasting C-Peptide by Era and Continent

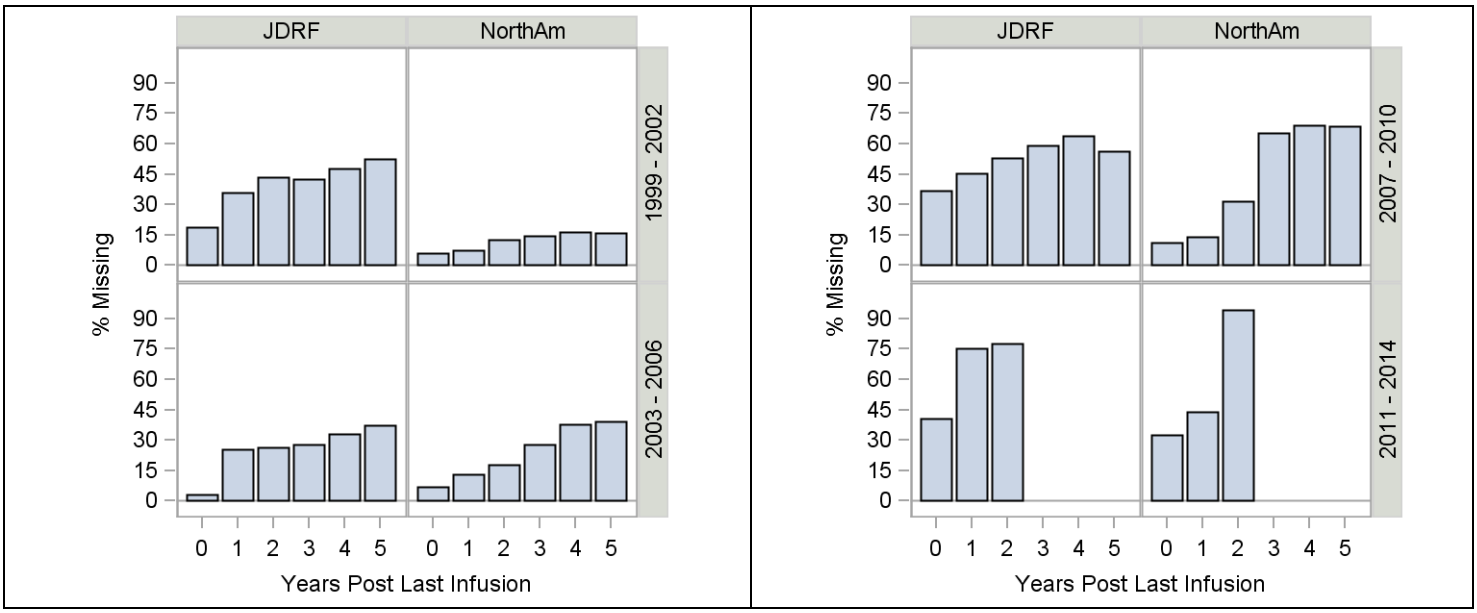


Exhibit 8 – 3
Missing Data for Hemoglobin A1c by Era and Continent

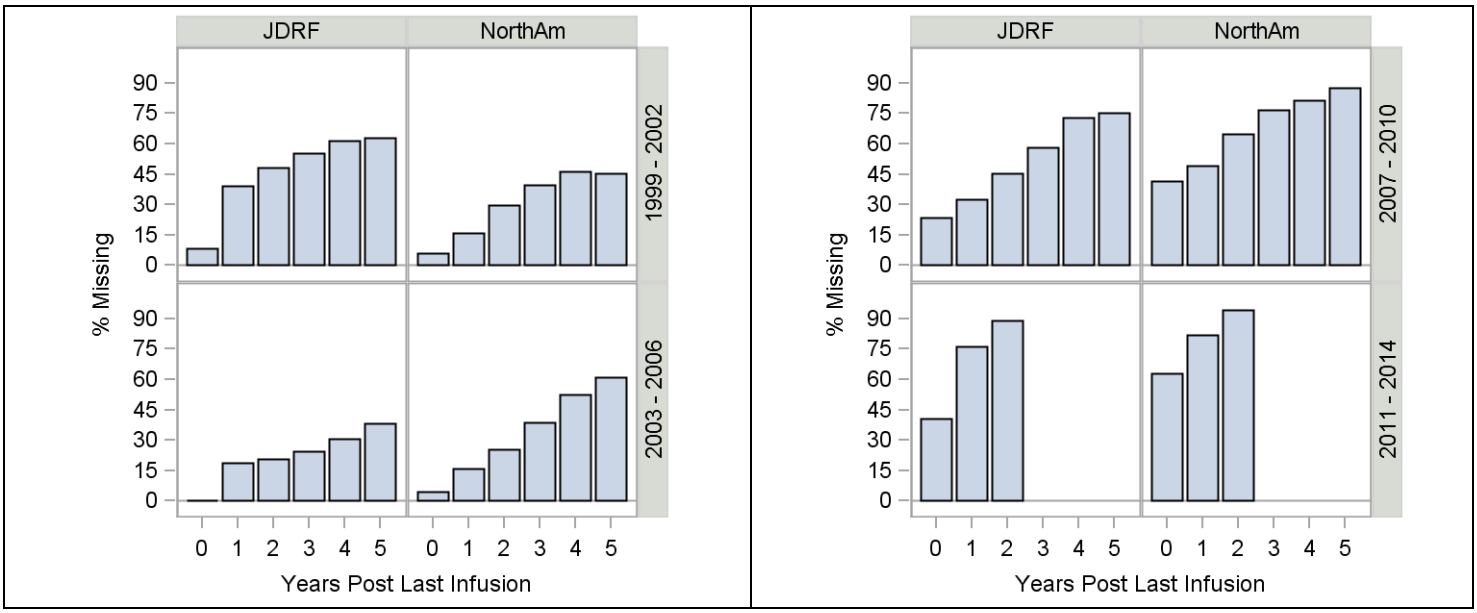


Exhibit 8 – 4
Missing Data for Fasting Blood Glucose by Era and Continent

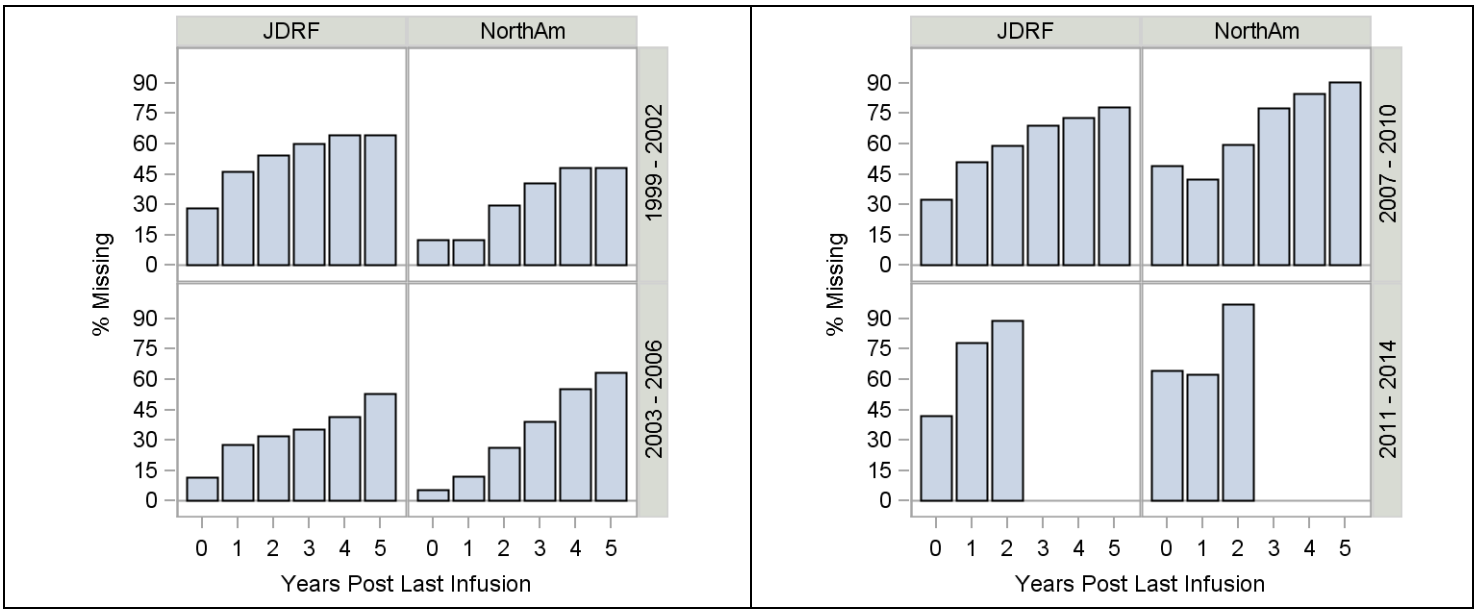


Exhibit 8 – 5
Missing Data for Severe HypoGlycemia by Era and Continent

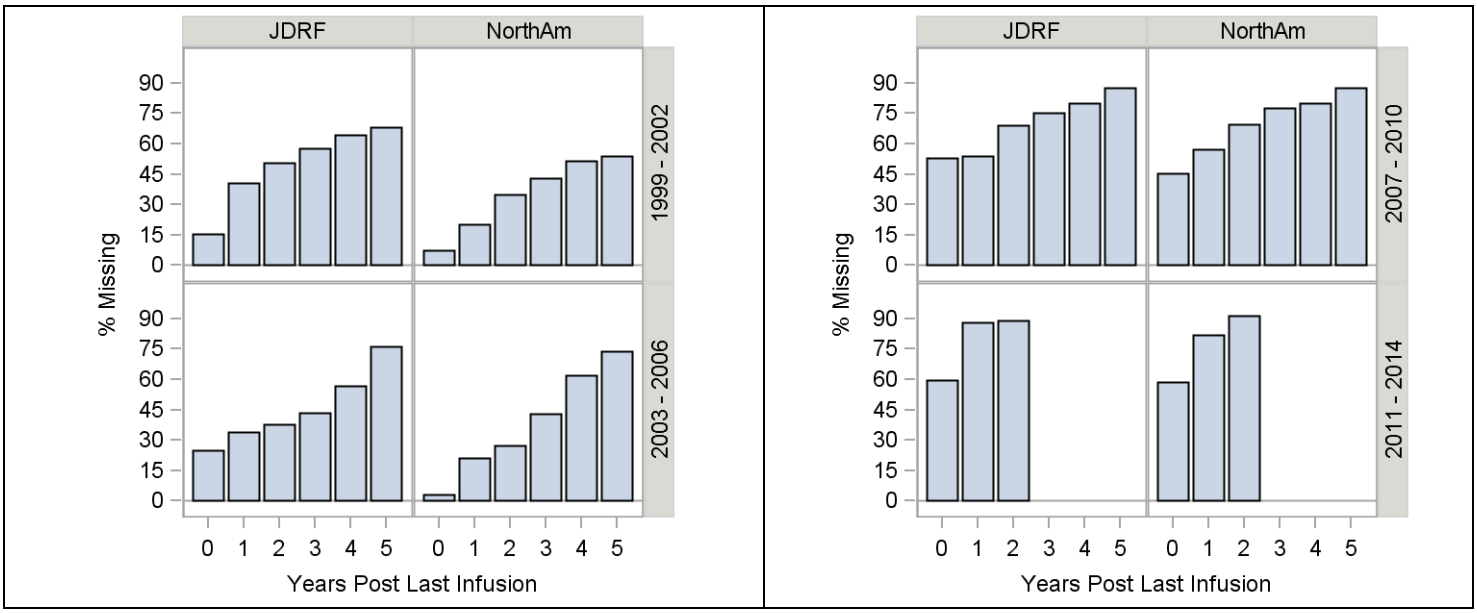


Exhibit 8 – 6
Missing Data for BMI by Era and Continent

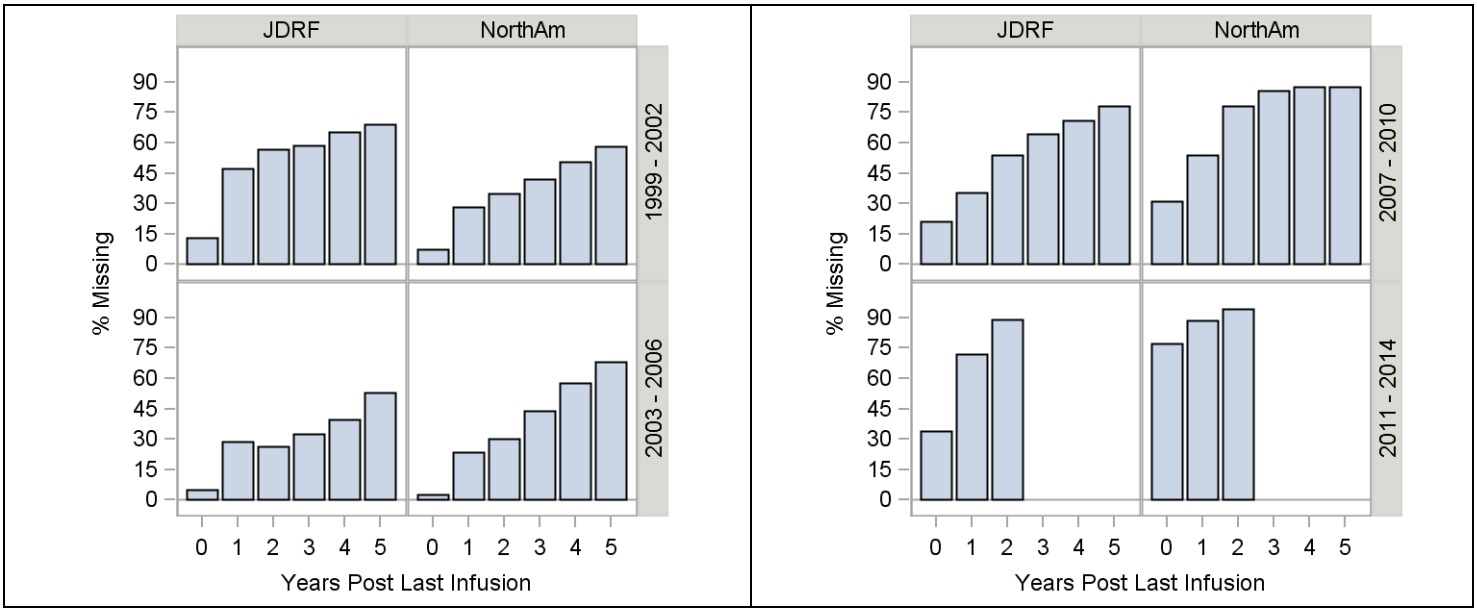


Exhibit 8 – 7
Missing Data for Clarke Score by Era and Continent

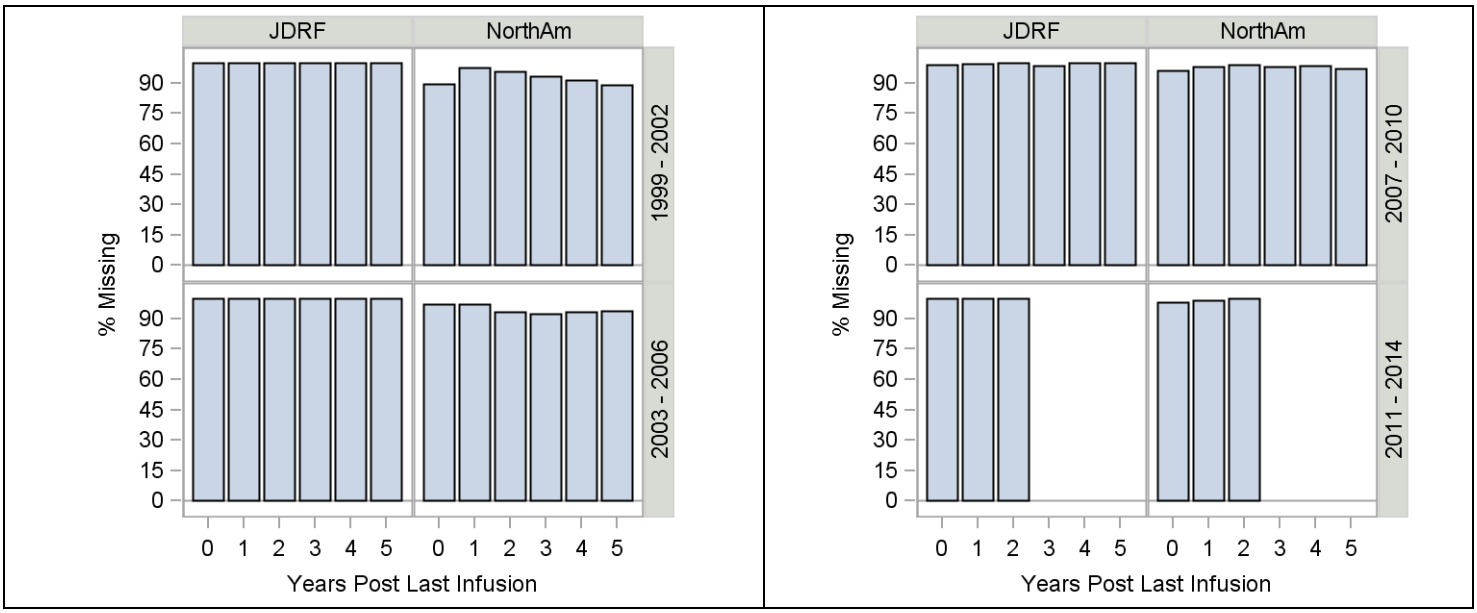


Exhibit 8 – 8
Missing Data for Ryan Hypo by Era and Continent

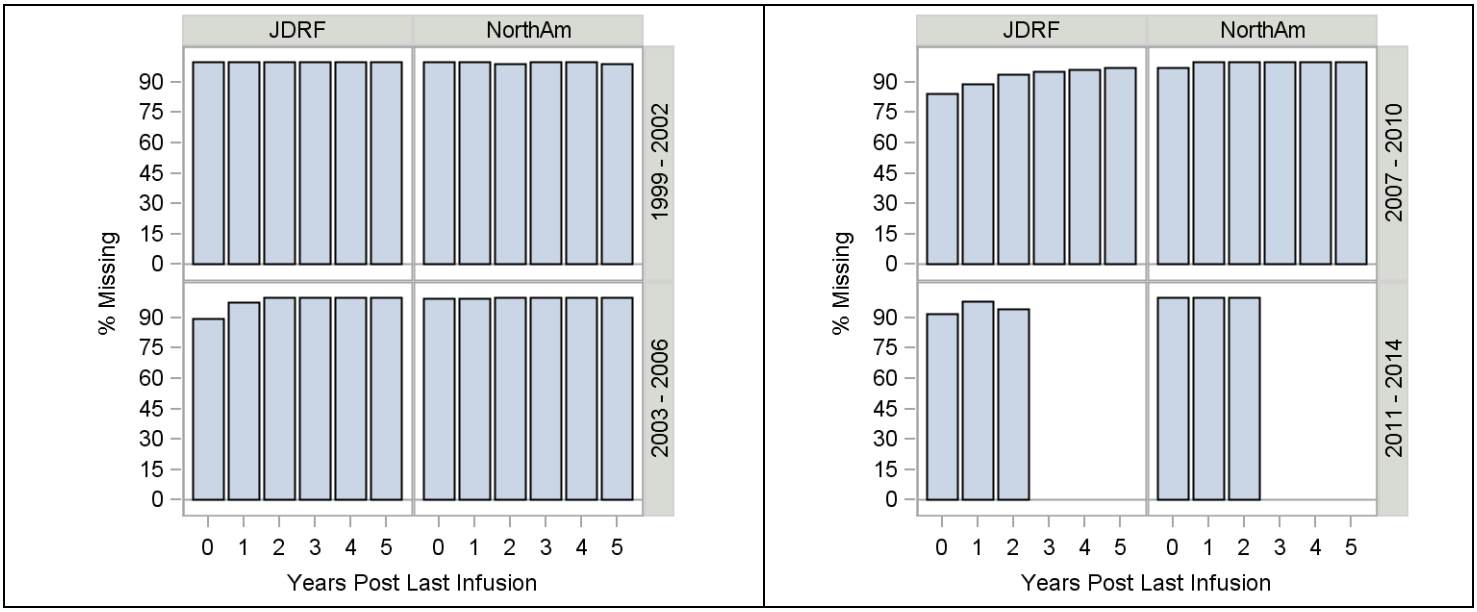


Exhibit 8 – 9
Missing Data for C-Peptide AUC by Era and Continent

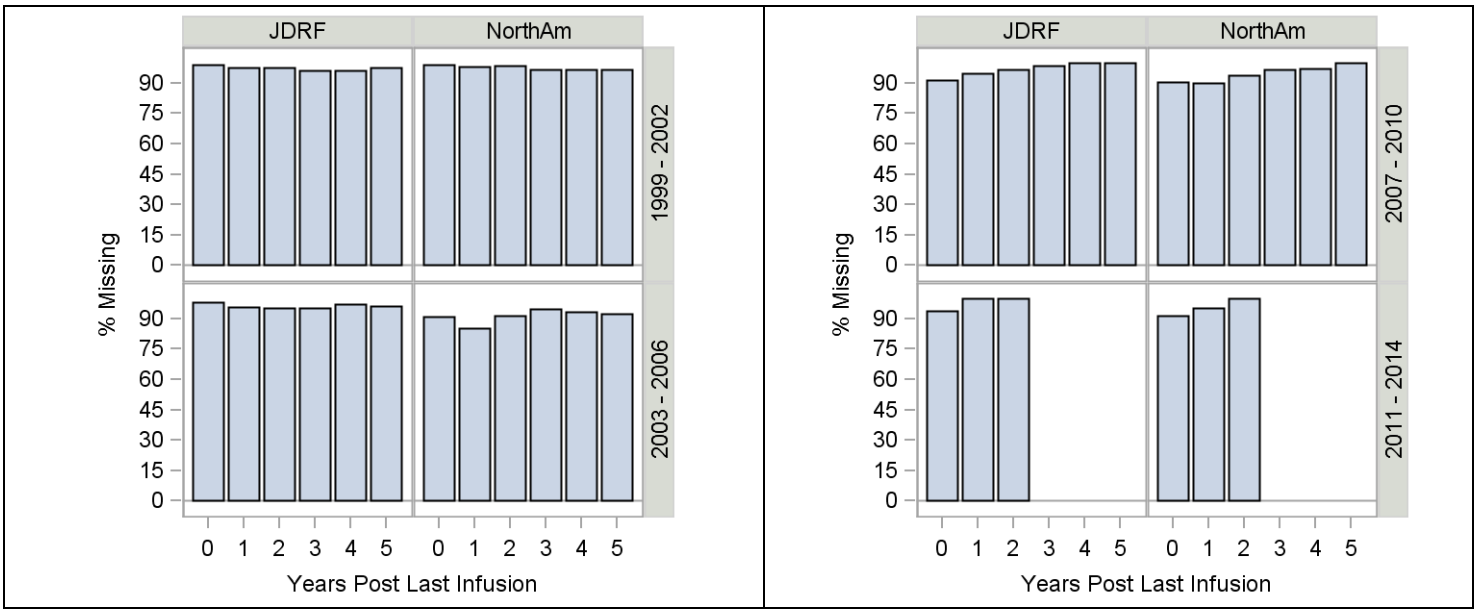


Exhibit 8 – 10
Missing Data for Cockcroft-Gaullt by Era and Continent

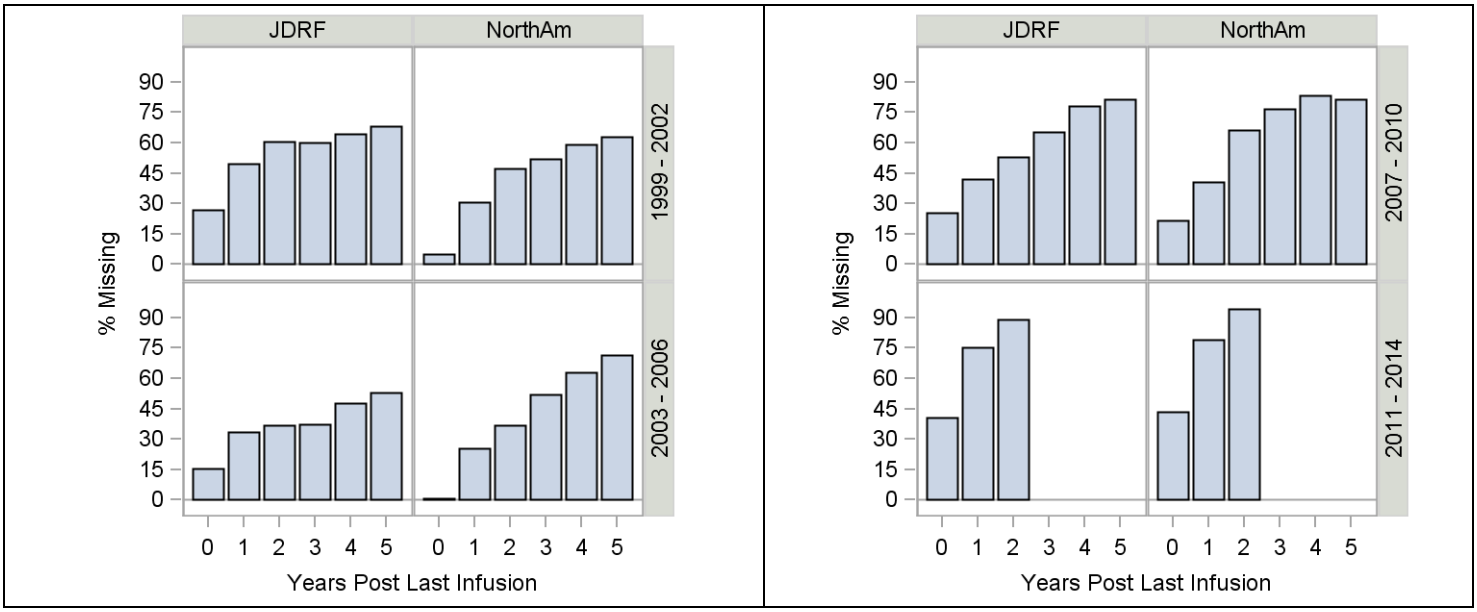


Exhibit 8 – 11
Missing Data for Creatinine by Era and Continent

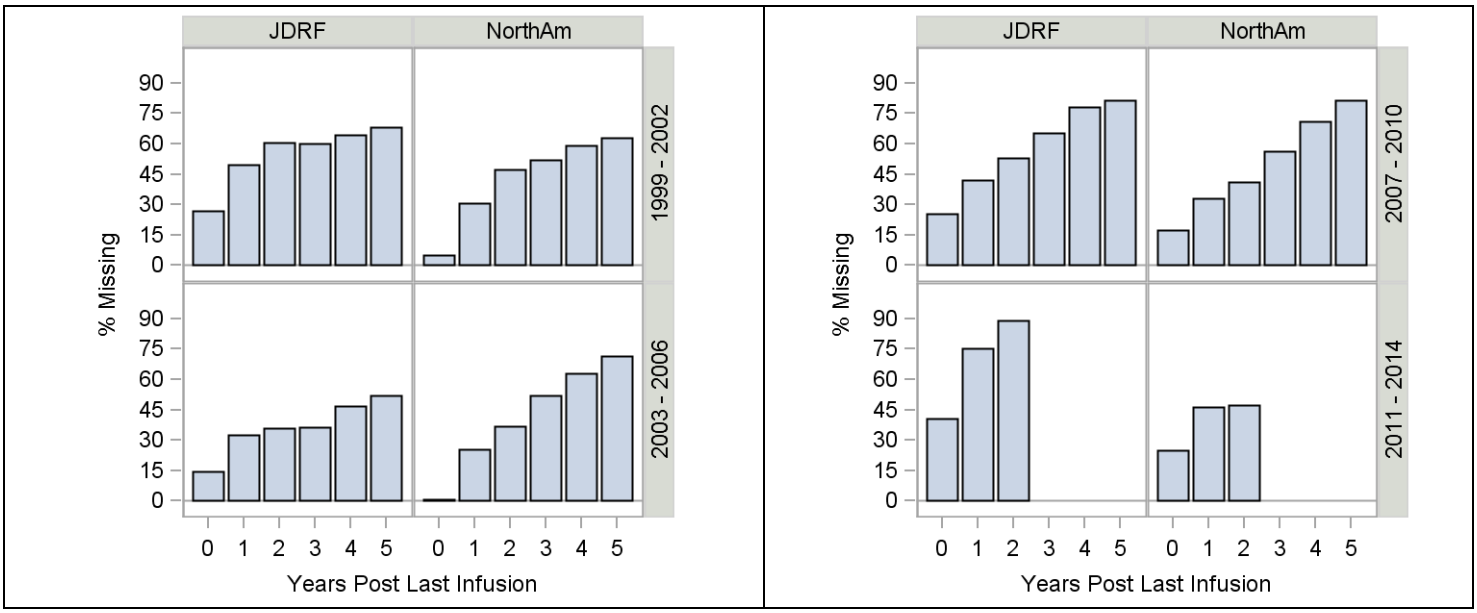


Exhibit 8 – 12
Missing Data for Cholesterol by Era and Continent

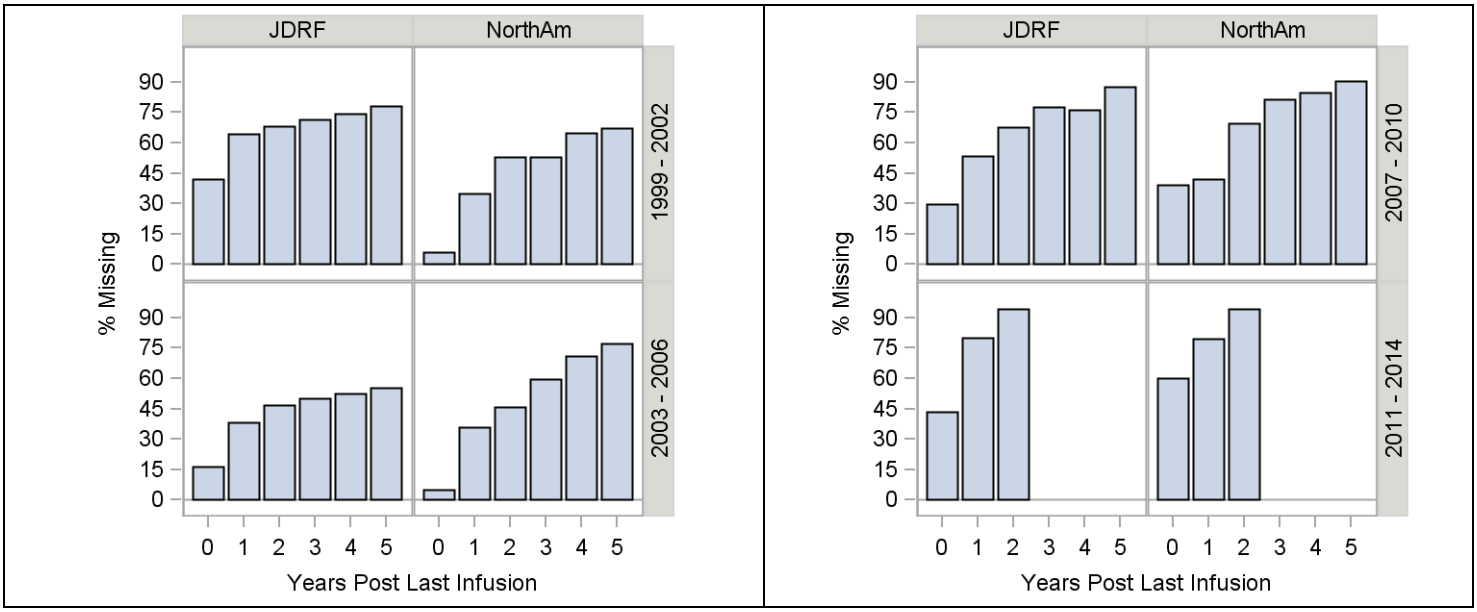


Exhibit 8 – 13
Missing Data for HDL by Era and Continent

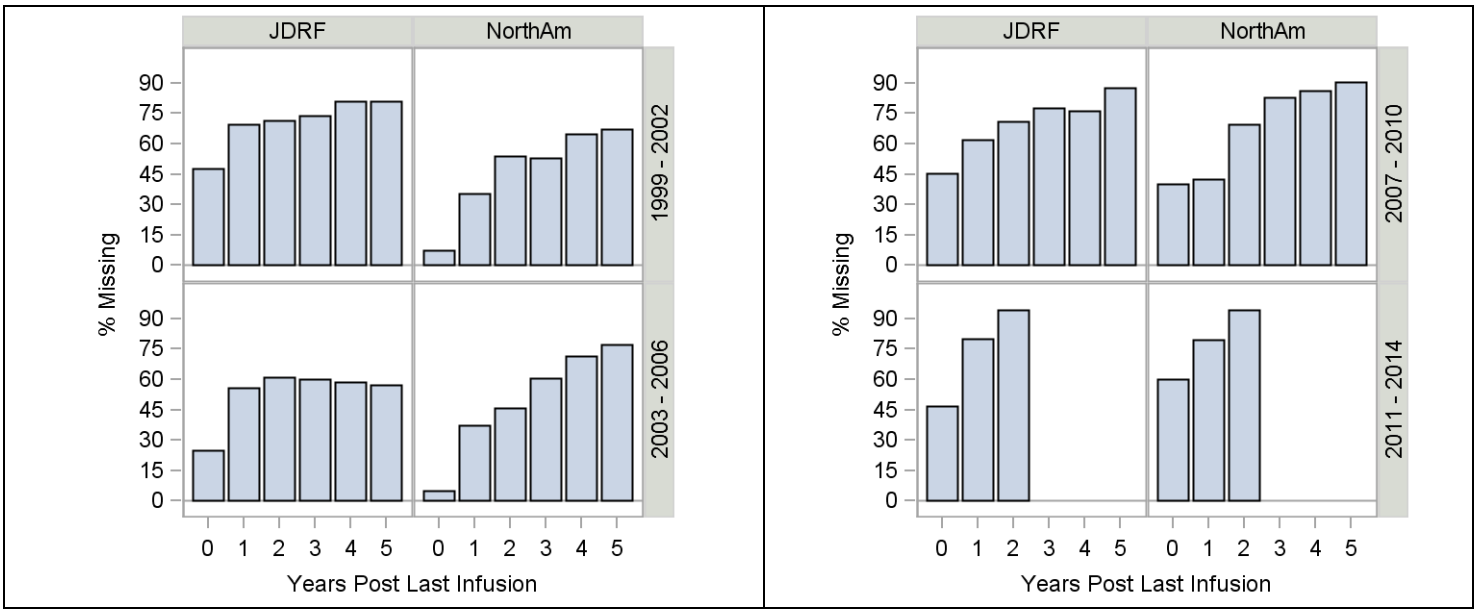


Exhibit 8 – 14
Missing Data for LDL by Era and Continent

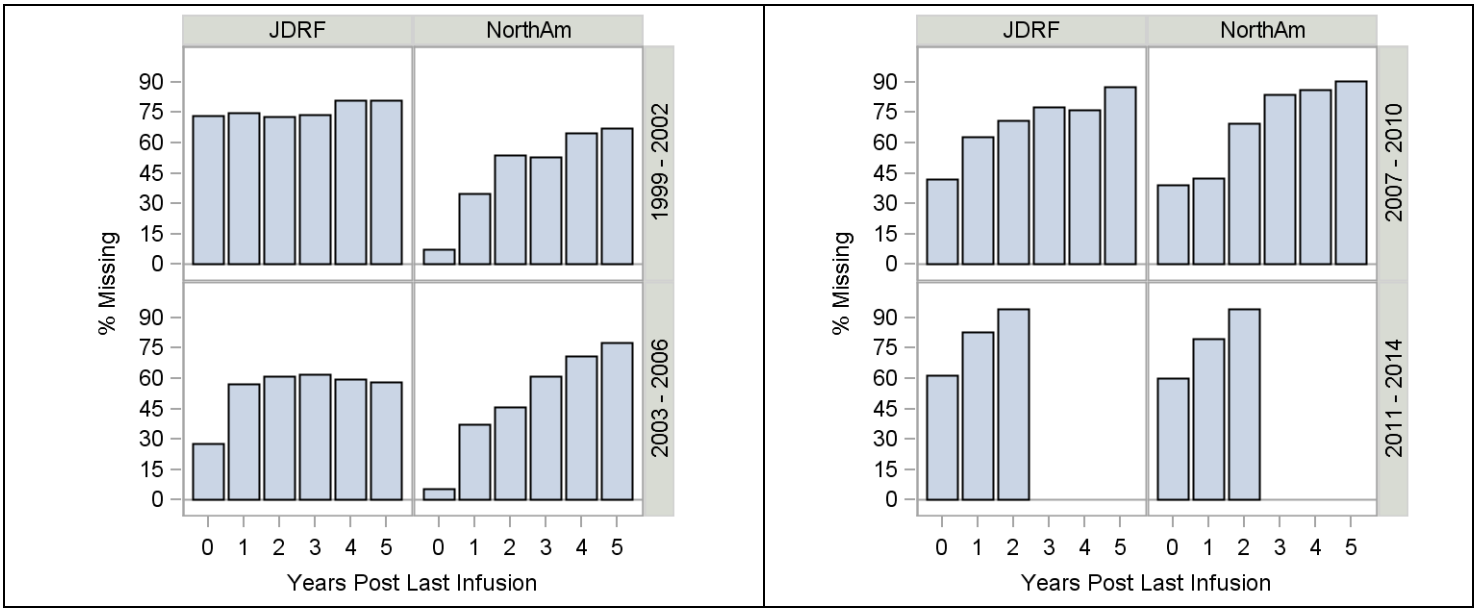


Exhibit 8 – 15
Missing Data for Triglicerides by Era and Continent -

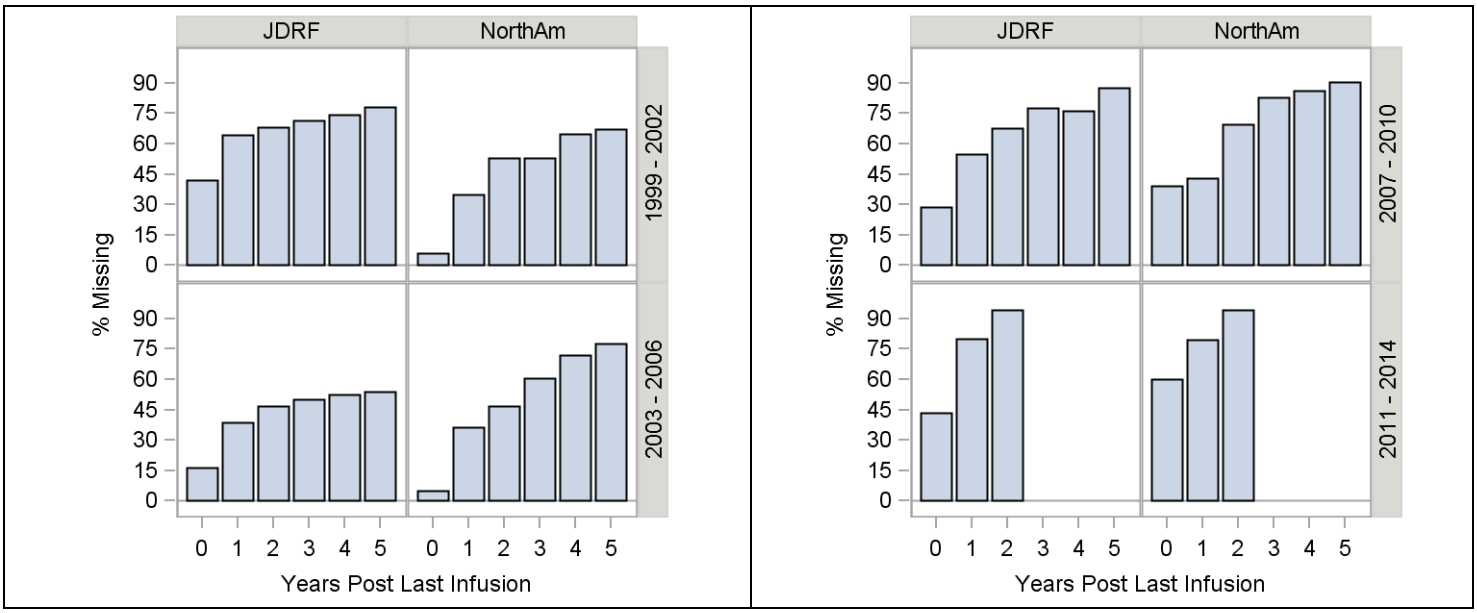


Exhibit 8 – 16
Missing Data for Bilirubin by Era and Continent

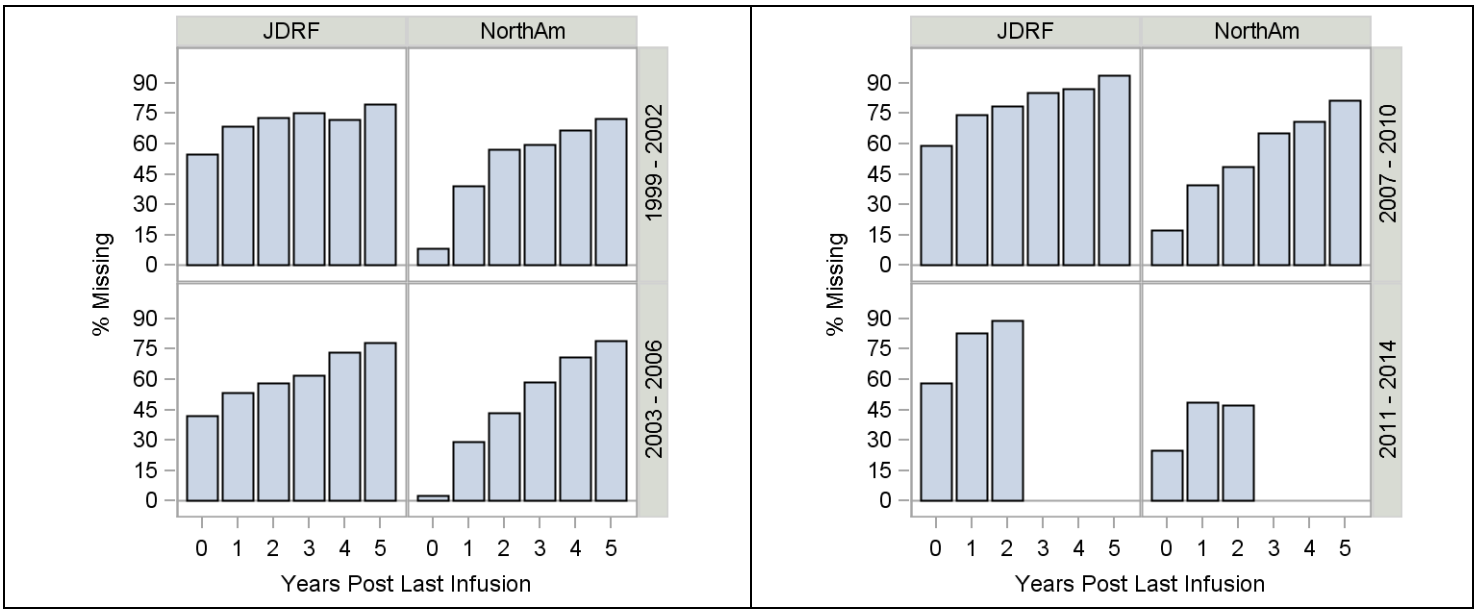


Exhibit 8 – 17
Missing Data for ALT by Era and Continent

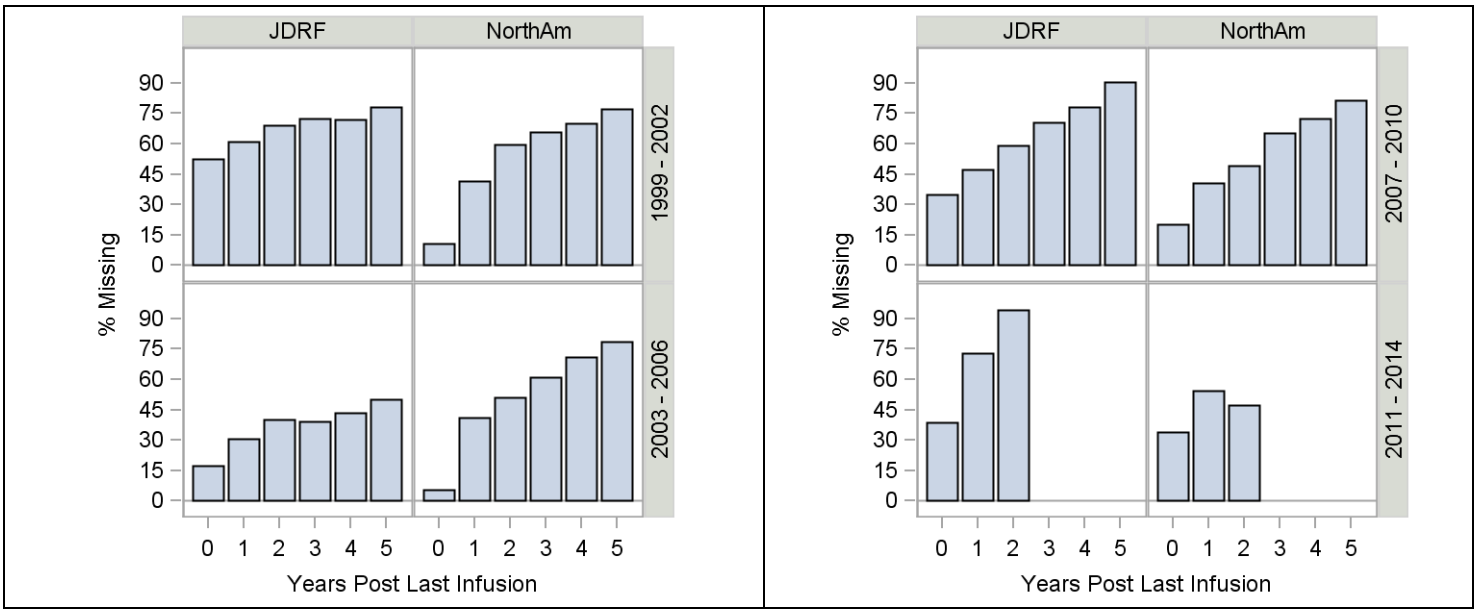


Exhibit 8 – 18
Missing Data for AST by Era and Continent

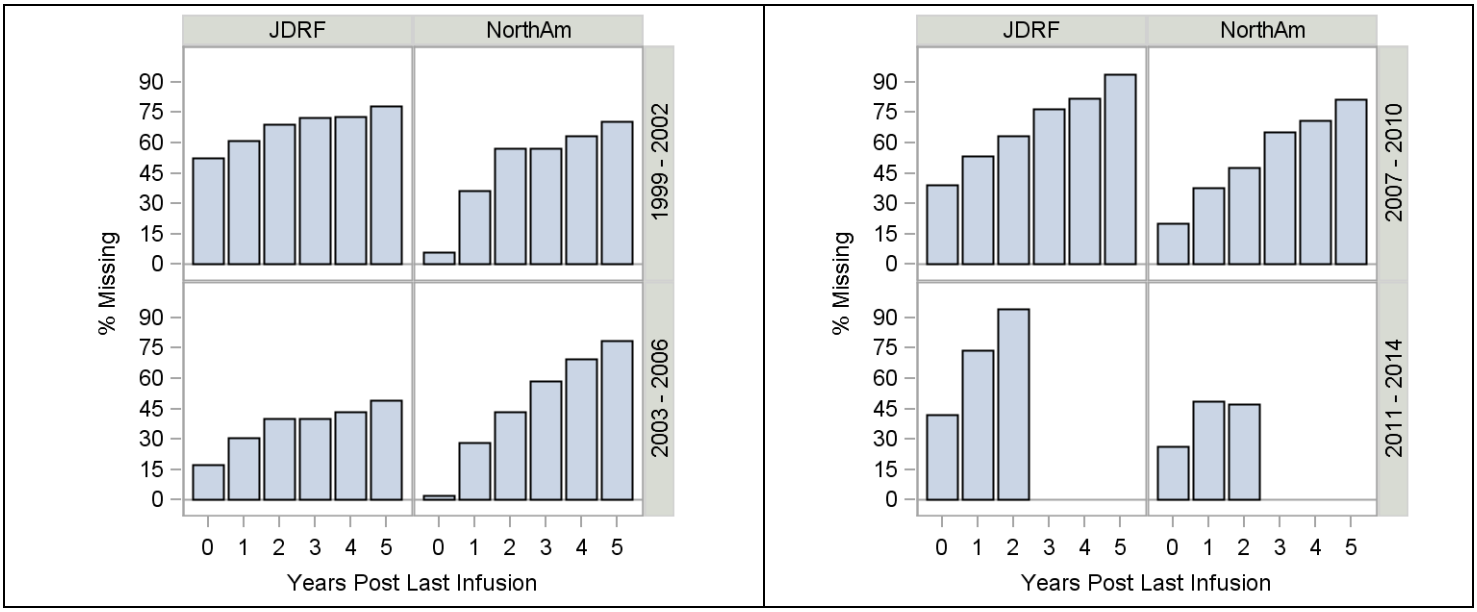
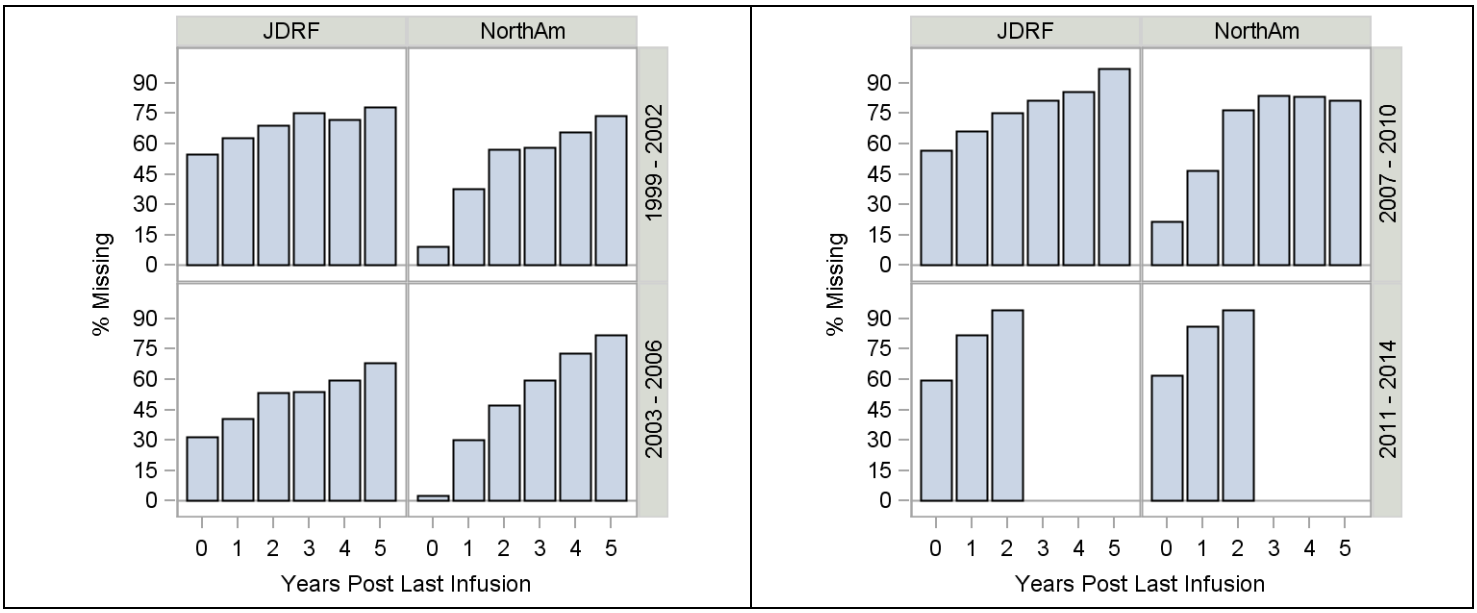


Exhibit 8 – 19
Missing Data for Alkaline Phosphate by Era and Continent



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