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Collaborative Islet Transplant Registry

Tenth Annual Report

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

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National Institutes of Health
US Department of Health and Human Services
Bethesda, MD

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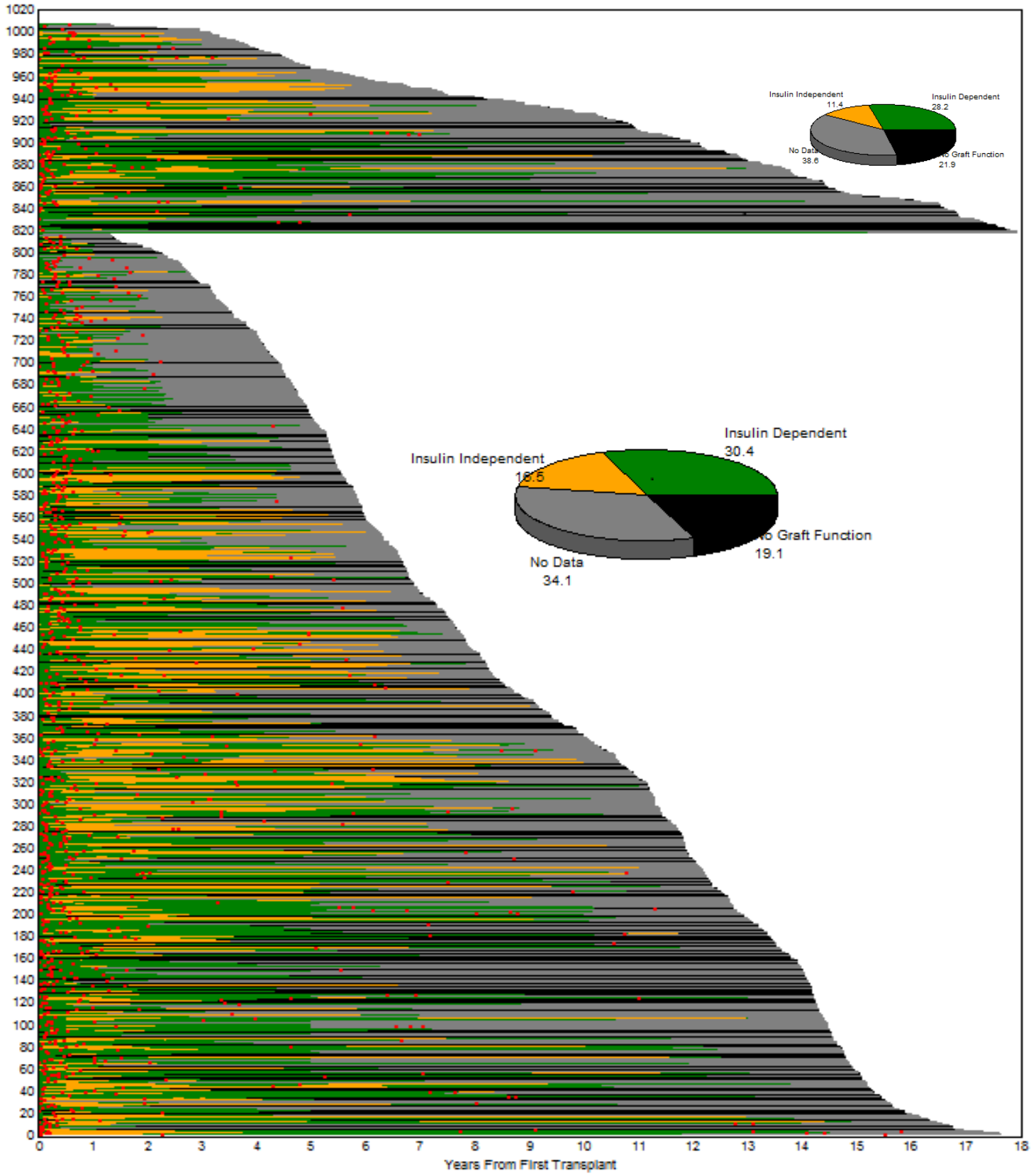
January 6, 2017



Collaborative Islet Transplant Registry 2015
TOP: Islet after kidney, simultaneous islet-kidney, or kidney after islet (IAK/SIK/KAI, N=209)
BOTTOM: Islet transplant alone (ITA, N=877)
Yellow: insulin independent; Green: insulin-using with graft function (50% average reduction in daily insulin use);
Black: no islet function (C-peptide<0.3 ng/ml); Gray: missing data; Red: re-infusions.
Pie charts show percent of all follow-up time

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

January 6, 2017

M E M O R A N D U M

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

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

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

SUBJECT: CITR Tenth Annual Report (2016)

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

We are pleased to present this Tenth Annual Report (infusions as of Sep 2015, follow-up as of Jan 2017) including data from the great majority of the islet transplant programs active in 1999-2016. We are privileged to have the ongoing collaboration of the United Network for Organ Sharing for the USA donor data, and the University of Iowa Clinical Trials Statistical Data Management Center for data from the Clinical Islet Transplantation Consortium (CIT; www.isletstudy.org; www.citisletstudy.org).

The 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.

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♦ 1-800-459-CITR or 301-251-1161 ♦ Fax 1-877-665-4596 ♦ www.citregistry.org ♦

NOTICE:

The CITR Annual Report details data received as of January 6, 2017 for all islet transplant recipients transplanted by September 15, 2016.

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

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Detailed Methods and Definitions

Background and Purpose

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

Status and History

This report focuses on 1,086 islet allograft recipients (877 islet alone, 183 islet after kidney, 24 simultaneous islet kidney, and 2 kidney after islet). Islet autografts are also conducted for other indications (principally pancreatitis) and centers may voluntarily report these data also to the Registry. As of September 30, 2015, a total of 827 autologous islet transplant recipients were registered in CITR. Results on the autograft transplants are summarized in a separate report.

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

CITR Annual Report (data through)	Allograft Recipients	Allograft Infusions	Allograft Donors
First (2004)	86	158	173
Second (2005)	138	256	266
Third (2006)	227	429	469
Fourth (2007)	292	579	634
Fifth (2008)	325	649	712
Sixth (2009)	412	828	905
Seventh (2011)	571	1,072	905
Eighth (2012)	864	1,679	2,146
Ninth (2013)	1,011	1,927	2,421
Tenth (2015)	1,086	2,150	2,619

The current report represents a 7% increase in the number of recipients, a 12% increase in the number of infusion procedures, and 8% increase in donors, compared to the 9th Report.

Data Sources

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

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

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

Study Endpoints

The primary endpoints presented in this report are:

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

Secondary endpoints include:

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

These are variously described by prevalence bar charts (frequency distributions) pre-infusion and post first and last infusion, accounting for all participants expected at each time point. For prevalence bar charts, all recipients expected at each follow-up time point based on the dates of their infusions and the report cut-off date are included in the analysis. Bar charts are intended to display prevalence and

generally represent 100% of data expected and available at each time point. Event analysis of incidence and persistence of specified endpoints are analyzed by Kaplan-Meier time-to-event or Survival estimates and by Cox proportional hazards regression using relevant baseline factors as stratifying or adjusting covariates.

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

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

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

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

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

Statistical Modeling

The Cox regressions and mixed effects models are used to comprehensively assess factors that may be predictive of the primary outcomes. In this report, generalized estimating equations (GEE) used in previous annual reports are replaced by mixed effects models, which estimate effects at a population level as do GEE, and allow analysis of individual trajectories of outcomes over longitudinal follow-up. Moreover, mixed effects models are robust to missing data -- common in registry studies. They assume data missing at random (MAR), whereas GEE assumes data missing completely at random (MCAR). In practice, it is difficult to meet the MCAR assumption. Univariate models are used first to identify possible effects. Any factor with an association at a nominal significance level of $p<0.05$ 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 $p<0.05$ but also strongly correlated with each other (Pearson $r>0.4$), were stepped into the multivariate model individually to test their effect. Of such correlated factors, the one with the greater effect was retained in the final model. The results of these models should be viewed as preliminary due to the relatively large number of factors, the effect of outliers and highly skewed distributions for many of the factors, and the associations among the factors.

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

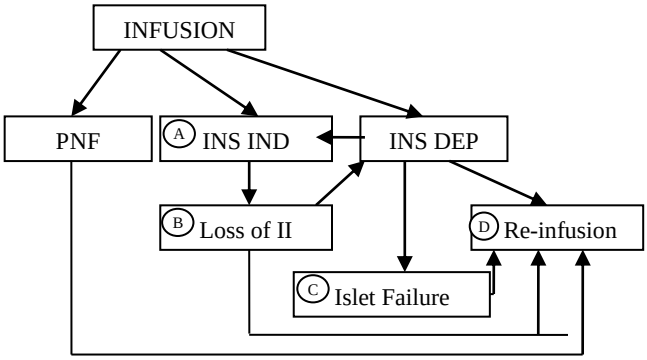

Figure 1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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

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

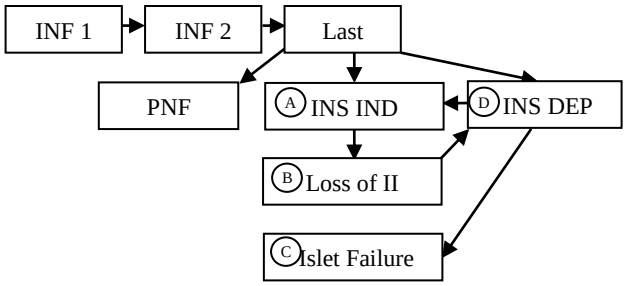

Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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

Limitations and Disclaimers

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

No center-specific information is presented in this report.

Data Quality Assurance and Closure

CITR adheres to strict quality control and assurance procedures. All data submitted are reviewed through several quality review processes. Islet transplant recipient data for this report reflect data entered by the islet transplant centers on participants receiving their first infusion from **January 1, 1999 through September 30, 2015**. 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 January 6, 2017 based on the recipients that had been registered for CITR at the September 30, 2015 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

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Introduction

From 1999 through 2015, 28 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored North American and 9 international European and Australian islet transplant centers (37 total) contributed data to the Collaborative Islet Transplant Registry (CITR). These sites registered 877 islet transplant alone (ITA) and 207 islet after kidney or simultaneous islet-kidney (IAK/SIK), and two kidney-after-islet allograft recipients consenting to have their data reported to the Registry, for a total of 1,086 allogeneic, human-to-human islet transplant recipients. In 2015, four North American sites performed allogeneic islet transplantation; all four participated in CITR. Exhibit 1-1A and 1-1B summarize the total allograft recipients, donors and infusions included in this report.

The Consortium for Islet Transplantation (CIT; www.citisletstudy.org/) enrolled 240 islet transplant patients from 2008 through 2012. All of the CIT sites also participate in CITR. Under collaborative agreements stipulated by the common sponsor, the NIDDK of the US National Institutes of Health (NIH), CITR-required data is transmitted to CITR for CITR-consenting patients.

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. Exhibits 1-3, 1-4, and 1-5 show the number of centers, recipients and infusions identified and captured by CITR. Overall, 586 (87.6%) of 669 islet allograft recipients and 1,146 (86.8%) of all islet allograft infusion procedures performed in North America from 1999-2015 are included in this report.

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.

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

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

Infusions

A summary of the total 2,150 North American and international islet allograft infusions by year of infusion is included in Exhibit 1-5. These infusions derived from 2,619 total donors: 1,882 (87.5%) were single donor preparations and 268 (12.5%) were multiple (2-3) donor preparations.

Three hundred eight (308) recipients (28.4%) have received a single islet infusion at the time of this report, 535 (49.3%) received a total of two infusions, 210 (19.3%) received three infusions, and 33 recipients (3.0%) received a total of four to six islet infusions (Exhibit 1-7).

Of the 1,086 islet allograft recipients presented in this report, 877 (80.8%) are islet alone recipients, 183 (16.9%) are islet after kidney recipients, 24 (2.2%) were islet simultaneous with kidney, and 2 (0.2%) were kidney after islet. Ten islet alone recipients later received a pancreas transplant subsequent to their islet graft failure.

CITR Allografts Overall

There has been a 7% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 12% increase in the total number of islet allograft infusion procedures reported.

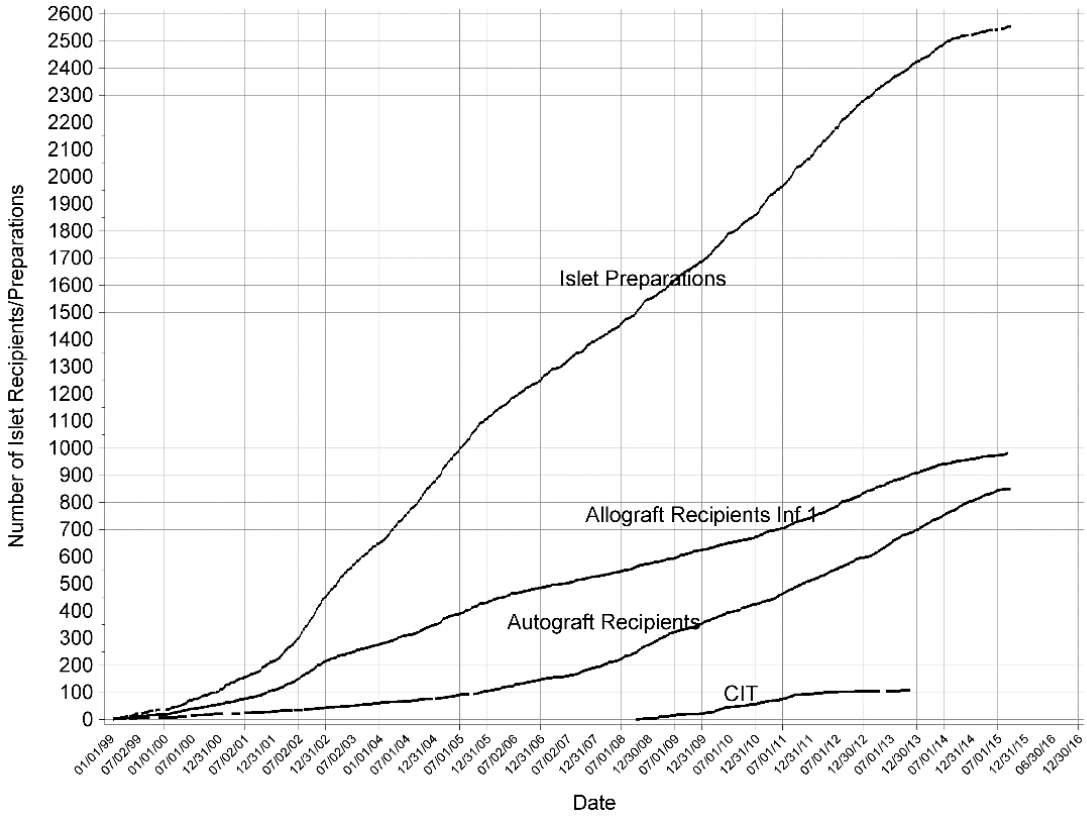
Autografts

Seven hundred fifty-four (754) North American and 65 international autograft consenting recipients have been registered in the Registry. A brief supplemental Annual Report will present analyses for autologous islet transplants.

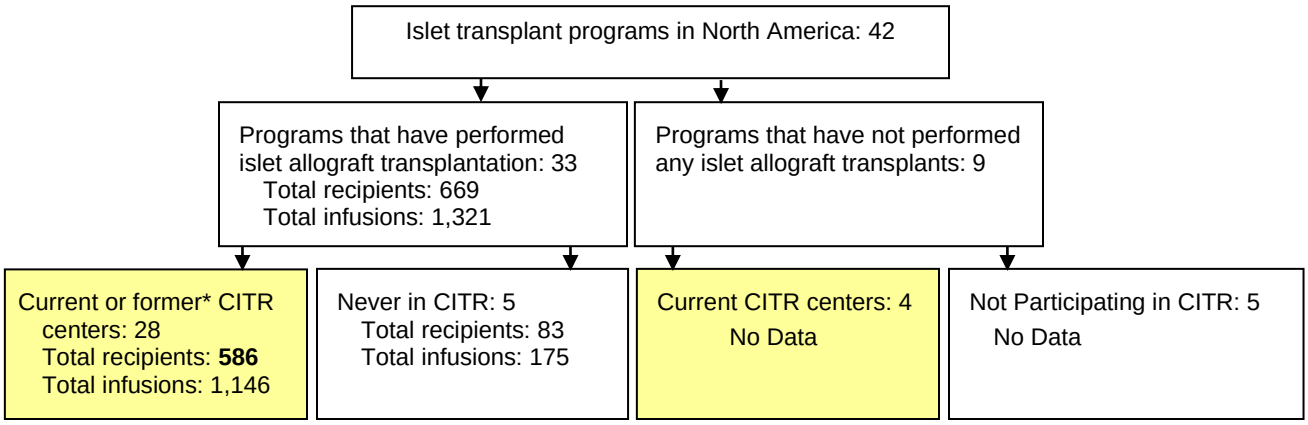
Exhibit 1 – 1A
CITR Allograft Recipients, Infusions and Donors by International Sites and by ITA/IAK/SIK/KAI Consented, Registered and First Infused in 1999-2015

	Islet Transplant Alone (ITA)			Islet After Kidney (IAK)			Simultaneous Islet Kidney (SIK)			Kidney After Islet (KAI)			
	Total	North America	Europe/ Australia/ Asia	Total	North America	Europe/ Australia/ Asia	Total	North America	Europe/ Australia/ Asia	Total	North America	Europe/ Australia/ Asia	GRAND TOTALS
Recipients	**877**	504	373	**183**	79	104	**24**	1	23	**2**	2	0	**1,086**
Infusions	**1,762**	1,002	760	**334**	138	196	**49**	1	48	**5**	5	0	**2,150**
Donors	**2,190**	1,061	1,129	**372**	147	225	**52**	1	51	**5**	5	0	**2,619**

Exhibit 1 – 1B
Cumulative Enrollment in CITR by Module



NORTH AMERICAN CENTERS
Total Performed and Total Reported to CITR 1999-2015



Four North American centers reported performing at least one islet allograft infusion procedure in 2015. All of these centers participated in and reported the information to CITR.

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

Exhibit 1 – 2A
Islet Transplant Centers Reporting Data to CITR
Participating North American Centers 1999-2015

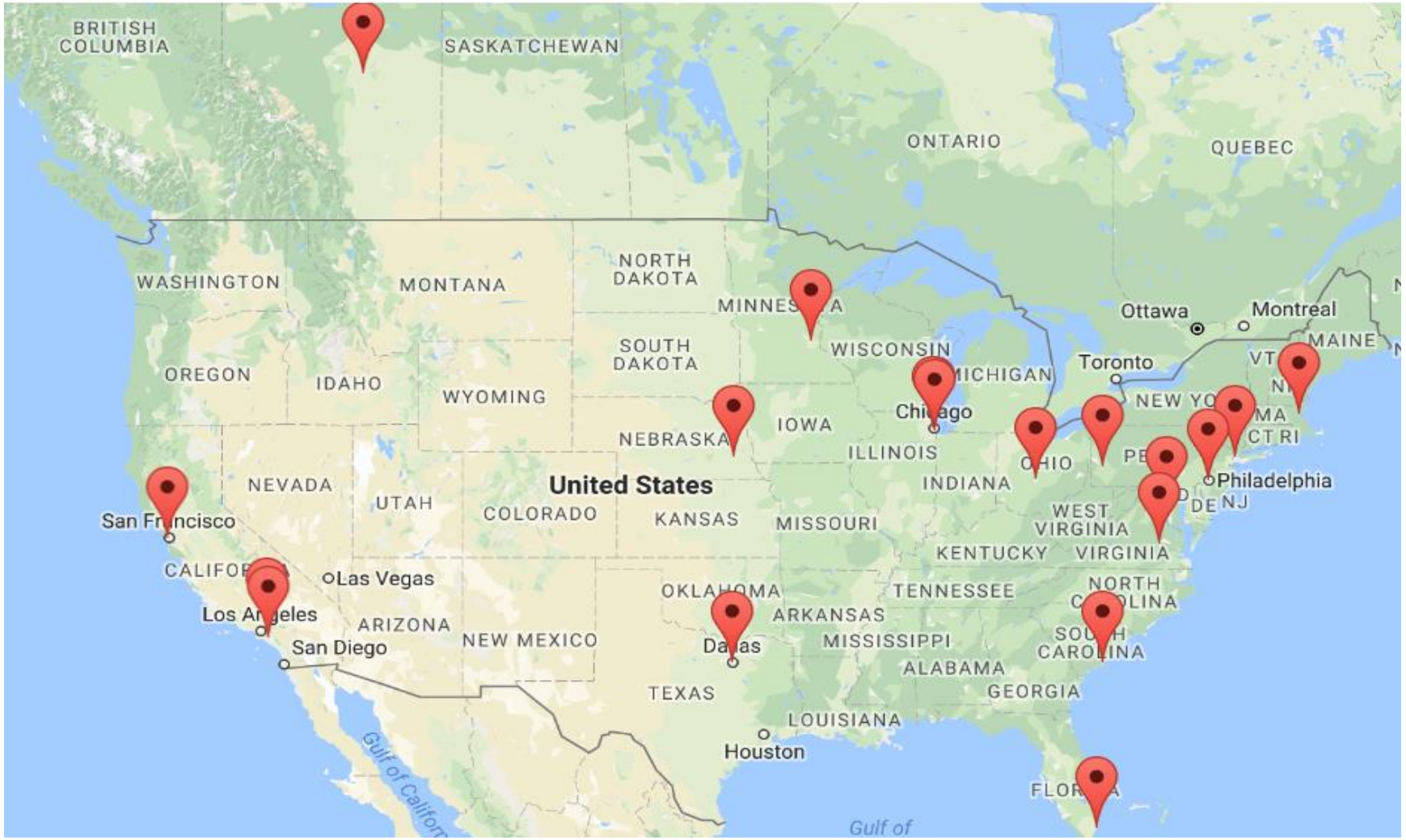
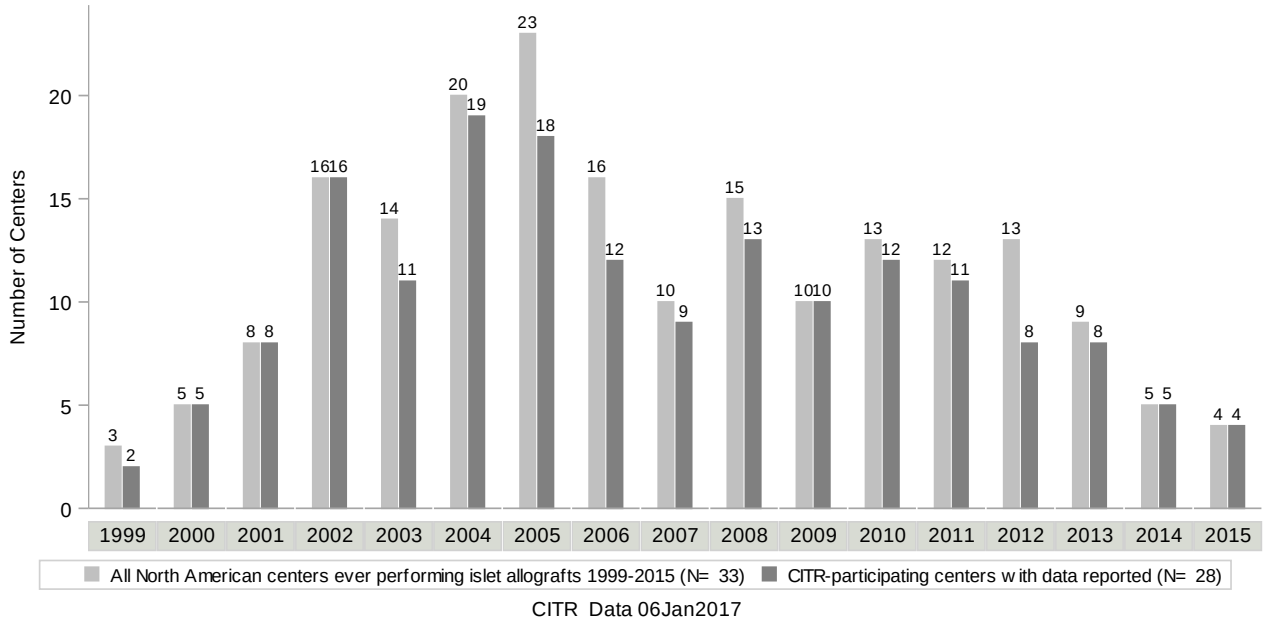


Exhibit 1 – 2B
Islet Transplant Centers Reporting Data to CITR
Participating European Centers 1999-2015

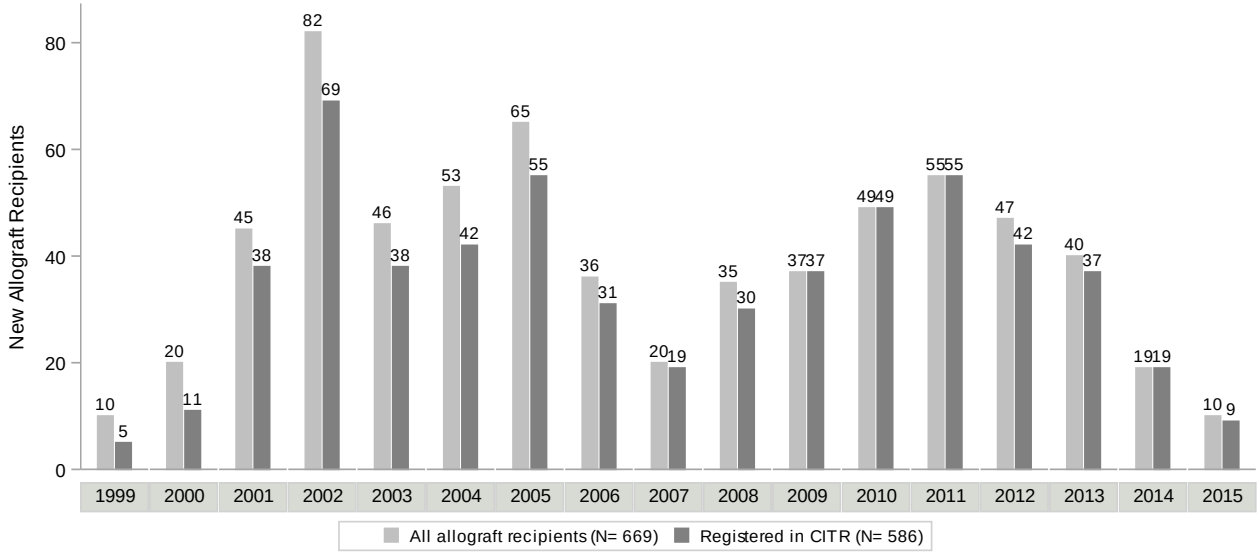
Exhibit 1 – 2C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2015

Exhibit 1 – 3
Number of Islet Transplantation Centers Performing Islet Allografts per Year and Number with Data Entered in CITR Database
All North American Islet Transplant Centers 1999-2015



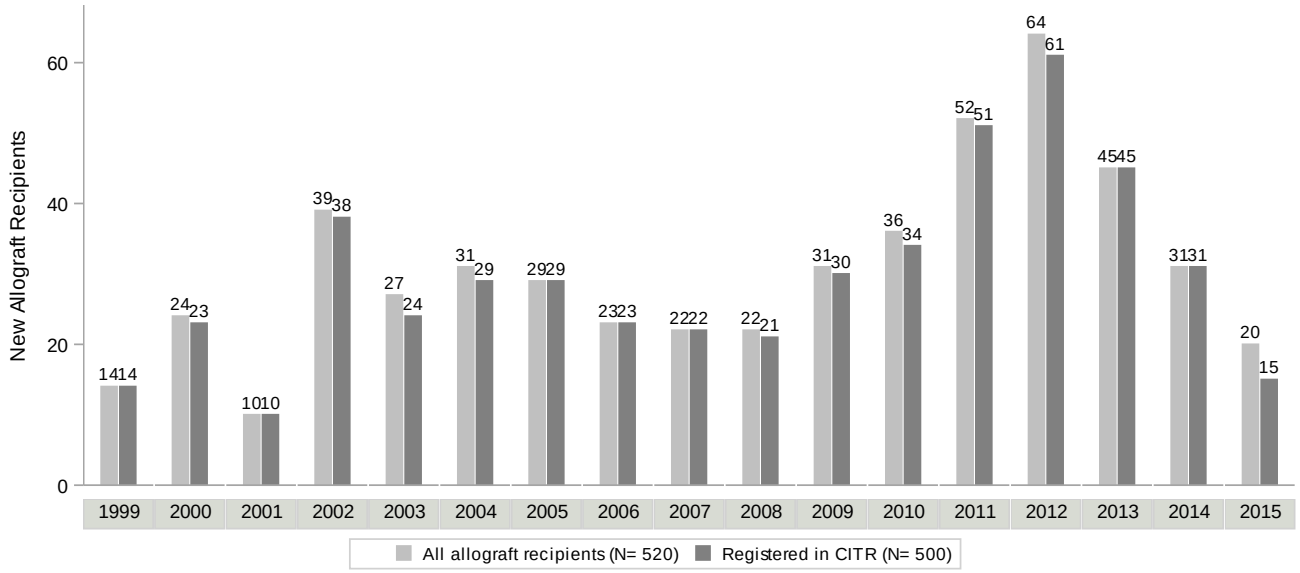
"All North American Centers Performing Islet Allografts" includes sites that reported performing at least one islet infusion procedure in the specified year. "CITR-Participating Centers with Data Entered" represents the number of islet transplant programs in the specified year that have contributed data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

Exhibit 1 – 4A
Total Number of Islet Allograft Recipients Receiving Their First Islet Allograft Infusion and Number with Data Reported to CITR: Allograft recipients at CITR-Participating North American Islet Transplant Centers 1999-2015



CITR Data 06Jan2017

Exhibit 1 – 4B
Total Number of Islet Allograft Recipients Receiving Their First Islet Allograft Infusion and Number with Data Reported to CITR: Allograft recipients at CITR-Participating European and Australian Islet Transplant Centers 1999-2015



CITR Data 06Jan2017

Exhibit 1 – 5A
Total Number of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number: CITR-Participating North American Islet Transplant Centers, 1999-2016

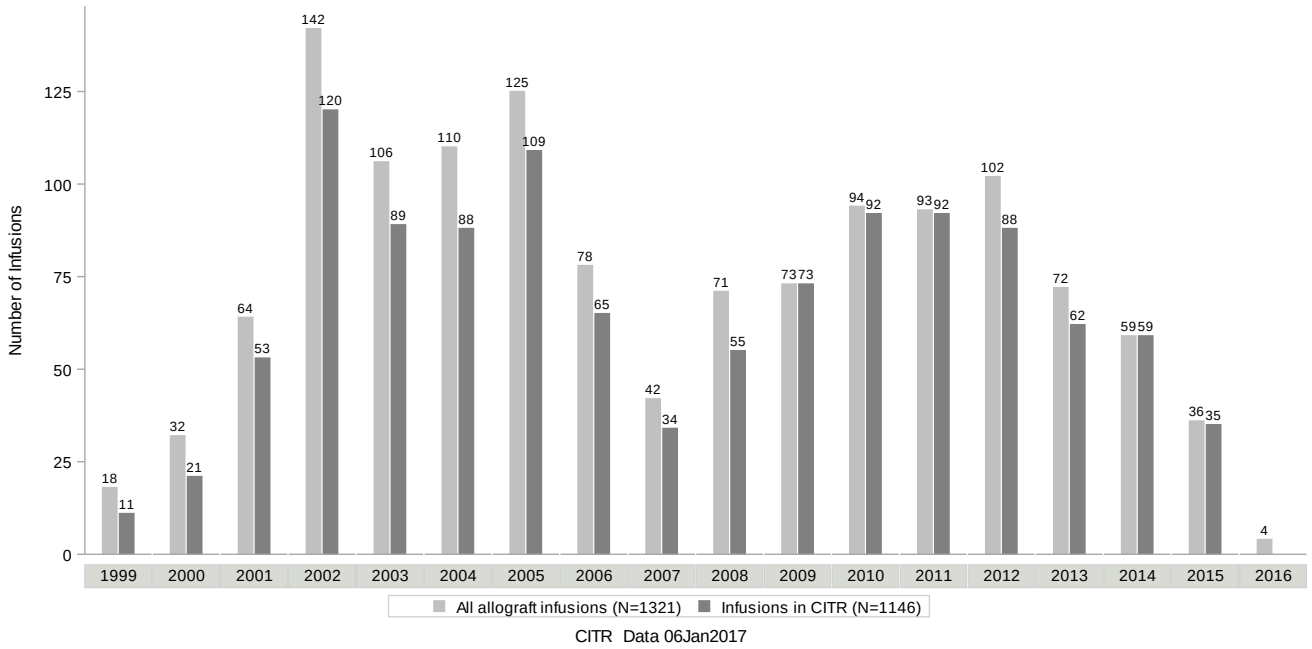


Exhibit 1 – 5B
Total Number of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number: CITR-Participating European and Australian Islet Transplant Centers, 1999-2016

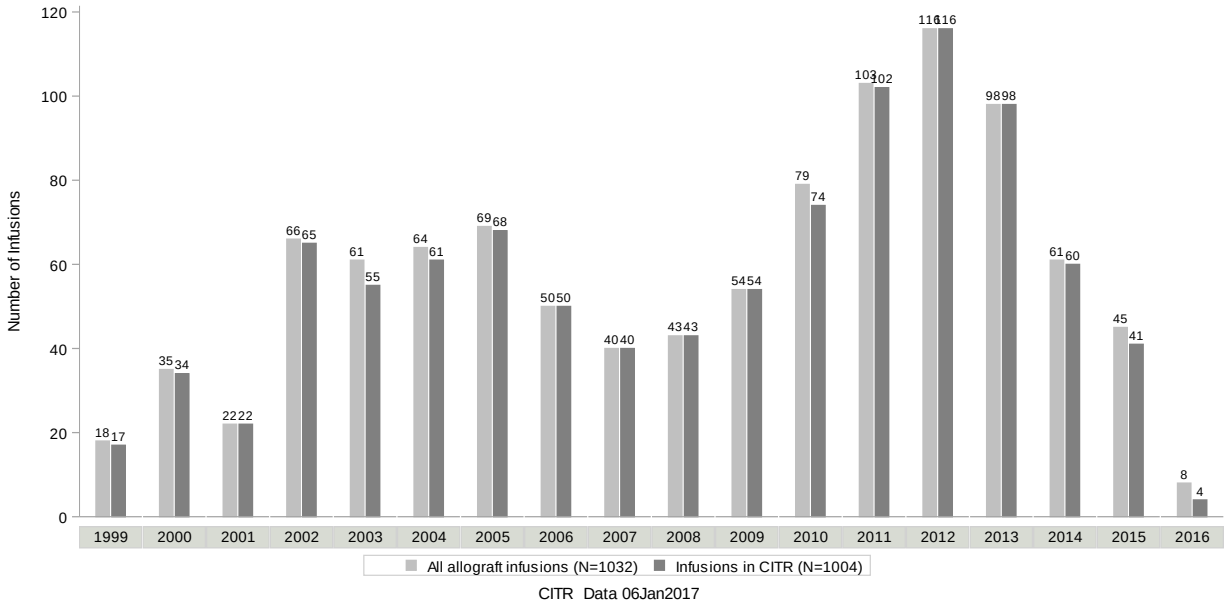


Exhibit 1 – 6A
Islet Allograft Infusions by Infusion Sequence Number and Year. CITR-Participating North American and International Centers, 1999-2016

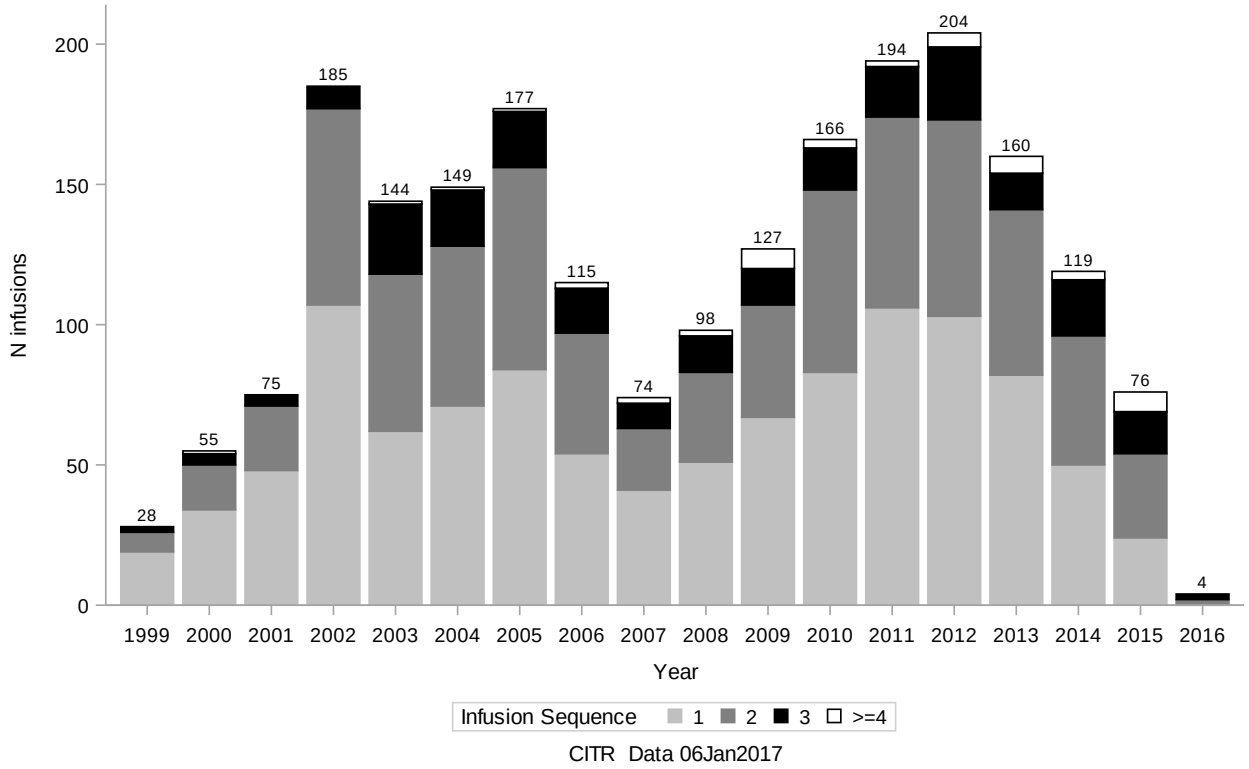


Exhibit 1 – 6B
Islet Allograft Recipients by Total Infusions to Date and Year. CITR-Participating North American and International Centers, 1999-2016

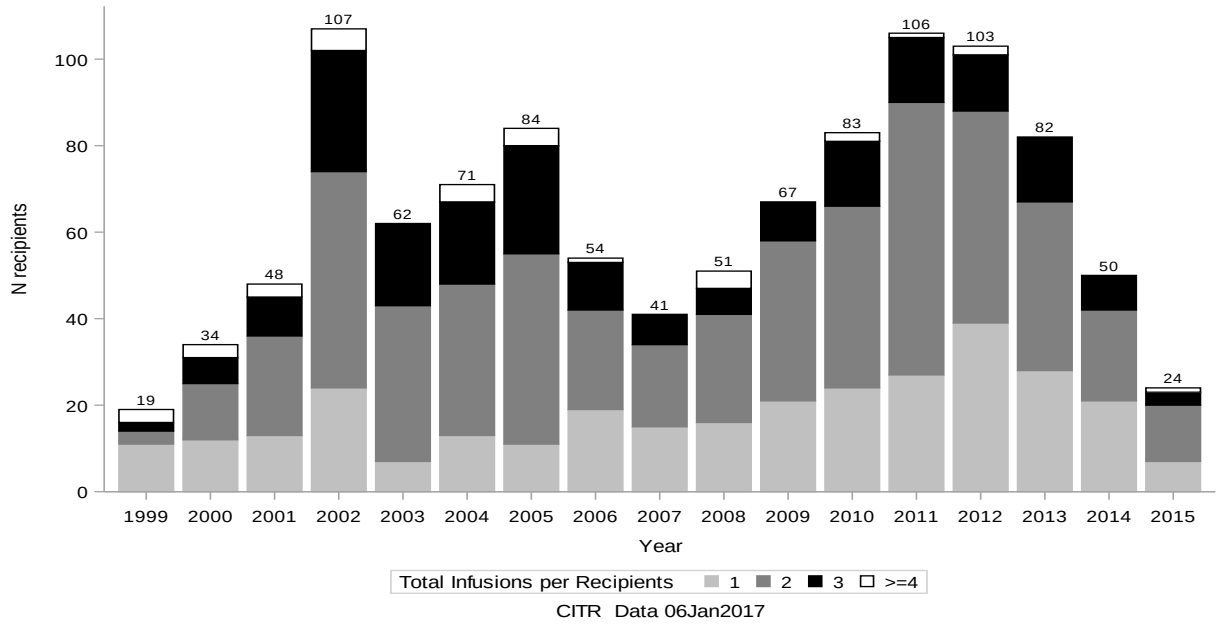


Exhibit 1 – 7
Total Number of Islet Allograft Infusion Procedures Per Recipient: CITR-Participating North American and International Centers, 1999-2016

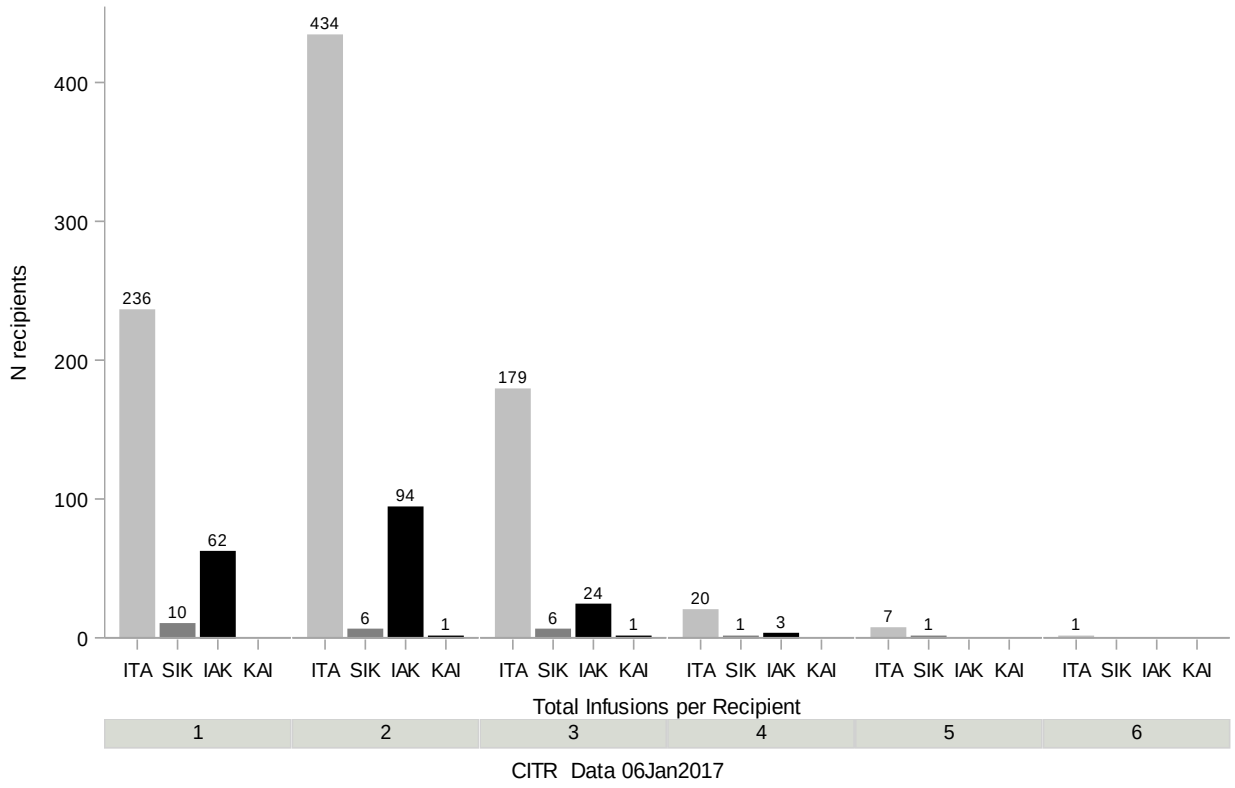
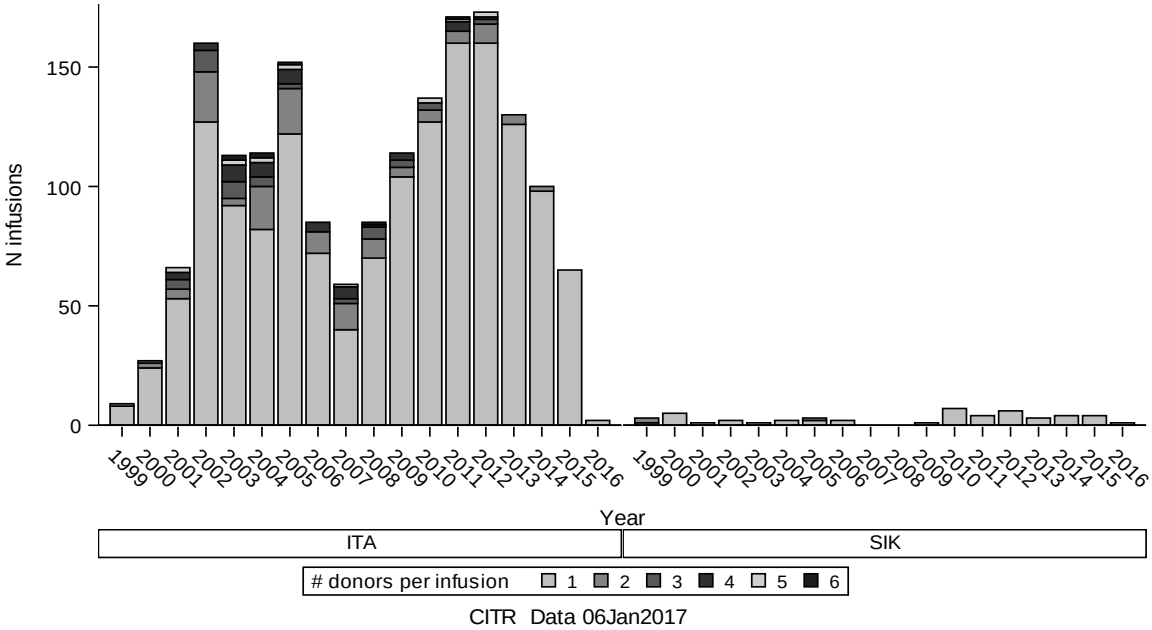
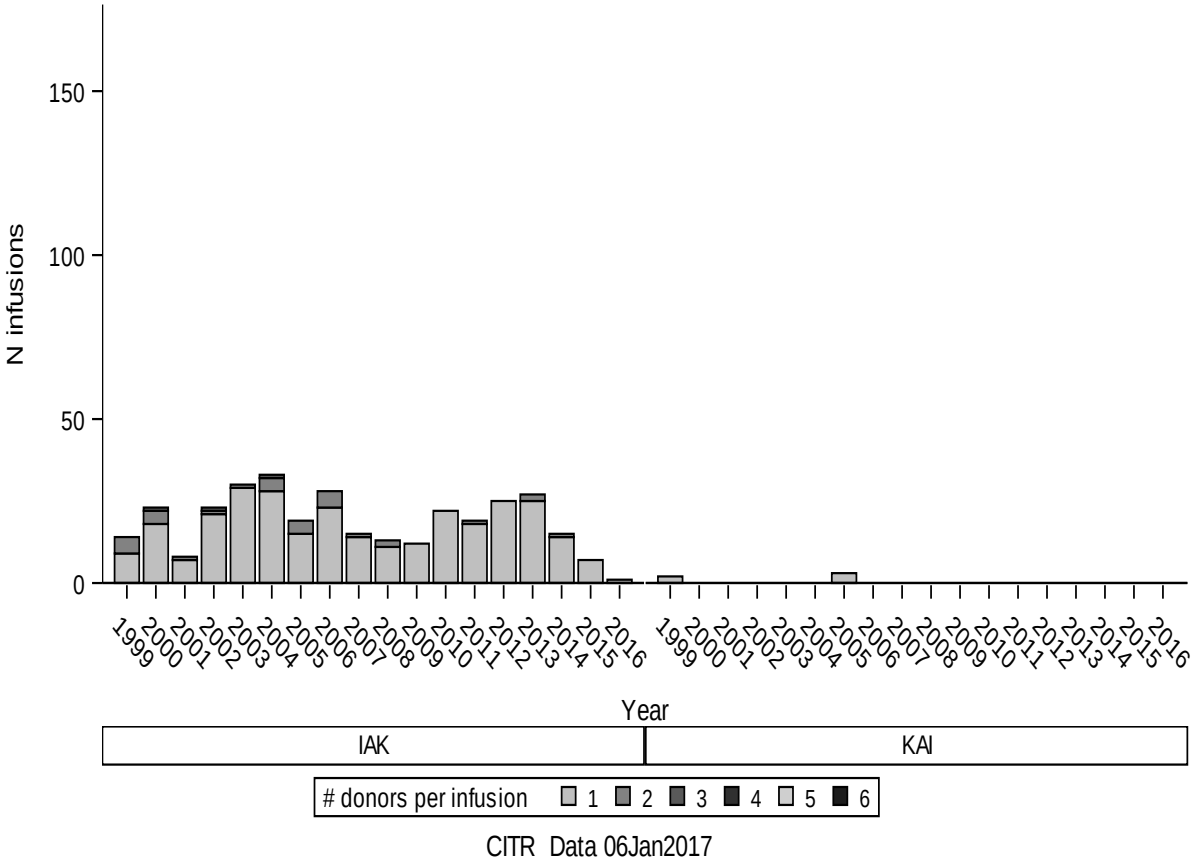


Exhibit 1 – 8
Total Number of Deceased Donors per Islet Allograft Infusion Procedure: CITR-Participating North American and International Centers, 1999-2016





Chapter 2
Recipient and Donor Characteristics

Table of Contents

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) and era (1999-2002, 2003-2006, 2007-2010, 2011-2014, and 2015-2018). In the first paired table per variable, the distribution of available data is shown and tested for differences by transplant type and era. Data availability is shown in the second, dimmed, paired table. Nominal p-values are calculated but are not based on experimental design.

In Exhibits 2-10 to 2-16, multiple donor information has been summarized over one to several donors/pancreata per islet infusion. There were 1,882 single-donor, 159 two-donor, 45 three-donor, 43 four-donor, 14 five-donor, and 7 six-donor, for a total of 2,619 donors and 2,150 infusions.

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

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

The following trends are observed among donors of allogeneic islets:

- Donor weight and BMI peaked in the 2007-2010 era and have since declined slightly
- Cold ischemia time and time from cross clamp to pancreas recovery both increased over the eras
- Transfusion during hospitalization has declined in the most recent eras
- Use of insulin during hospitalization peaked in 2007-2010 and has since declined
- Donor stimulated blood glucose has declined substantially over the eras

Exhibit 2-1
Recipient Demographics

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Gender	**Female**	530	60.5	100	54.9		112	56.3	158	59.4	146	61.9	199	59.6	15	65.2	
	Male	346	39.5	82	45.1		87	43.7	108	40.6	90	38.1	135	40.4	8	34.8	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gender	**Missing**	1	0.1	1	0.5		0.0	1	0.4	1	0.4		0.0		0.0
	Available	876	99.9	182	99.5	199	100.0	266	99.6	236	99.6	334	100.0	23	100.0

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Race	**American Indian**	2	0.3		0.0			0.0	1	0.5	1	0.5		0.0		0.0	***
	Asian	2	0.3		0.0			0.0		0.0		0.0	2	0.9		0.0	
	Black	5	0.8	2	1.6			0.0	1	0.5	5	2.7	1	0.5		0.0	
	Multiple	3	0.5		0.0		1	0.7		0.0		0.0		0.0	2	11.1	
	White	617	98.1	127	98.4		139	99.3	195	99.0	177	96.7	217	98.6	16	88.9	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Race	**Available**	629	71.7	129	70.5	140	70.4	197	73.8	183	77.2	220	65.9	18	78.3
	Missing	248	28.3	54	29.5	59	29.6	70	26.2	54	22.8	114	34.1	5	21.7

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Ethnicity	**Hispanic**	7	1.3	5	3.8		1	0.7	7	3.6	2	1.2	2	1.2		0.0	
	Not Hispanic	540	98.7	125	96.2		138	99.3	190	96.4	166	98.8	159	98.8	12	100.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Ethnicity	**Available**	547	62.4	130	71.0	139	69.8	197	73.8	168	70.9	161	48.2	12	52.2
	Missing	330	37.6	53	29.0	60	30.2	70	26.2	69	29.1	173	51.8	11	47.8

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

Exhibit 2-1 (continued)
Recipient Demographics

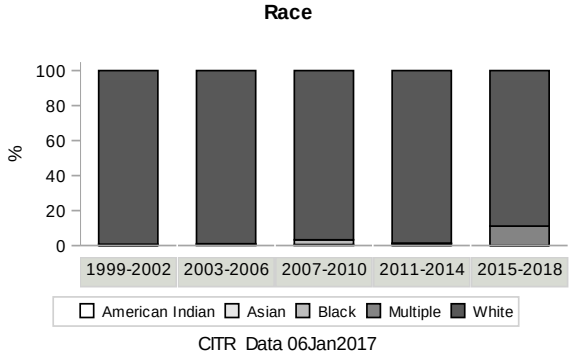
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Employment	**Full time**	292	55.9	31	36.0		85	63.9	111	53.6	54	49.5	66	45.2	7	53.8	
	Not applicable		0.0	1	1.2		1	0.8		0.0		0.0		0.0		0.0	
	Not working by choice	35	6.7	4	4.7		5	3.8	13	6.3	9	8.3	11	7.5	1	7.7	
	Not working disease	92	17.6	27	31.4		19	14.3	41	19.8	20	18.3	37	25.3	2	15.4	
	Not working no employ	2	0.4		0.0			0.0	1	0.5		0.0	1	0.7		0.0	
	Not working unknown	6	1.1	7	8.1		1	0.8	4	1.9	4	3.7	4	2.7		0.0	***
	Part time by choice	28	5.4	9	10.5		6	4.5	11	5.3	13	11.9	6	4.1	1	7.7	
	Part time by disease	25	4.8	4	4.7		11	8.3	9	4.3	3	2.8	4	2.7	2	15.4	
	Part time unknown	7	1.3		0.0		1	0.8	1	0.5		0.0	5	3.4		0.0	
	Retired	28	5.4	1	1.2		3	2.3	13	6.3	5	4.6	8	5.5		0.0	
	Student	7	1.3	2	2.3		1	0.8	3	1.4	1	0.9	4	2.7		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Employment	Missing	355	40.5	97	53.0	66	33.2	60	22.5	128	54.0	188	56.3	10	43.5
	Available	522	59.5	86	47.0	133	66.8	207	77.5	109	46.0	146	43.7	13	56.5

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

Race and ethnicity are not collected at the International sites.

Significant trends in patient characteristics from table above
By Era



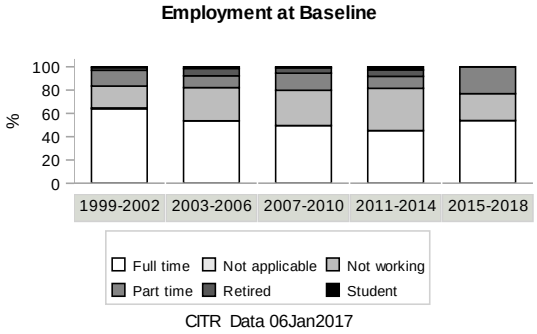


Exhibit 2-2
Indication for Islet Transplantation: Diabetes, Severe Hypoglycemia, and C-peptide

				ITA											
						Era									
				Total		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
				N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx				536	100.0	131	100.0	173	100.0	130	100.0	94	100.0	8	100.0
DiabHx	**SHE**	**C-peptide**	**Insulin**												
Cystic fibrosis	**ASHE**	**<0.3**	**On Insulin**	1	0.2	-	-	-	-	-	-	1	1.1	-	-
		>=0.5	**On Insulin**	1	0.2	-	-	1	0.6	-	-	-	-	-	-
Pancreatectomy	**SHE**	**0.3-0.4**	**On Insulin**	1	0.2	-	-	-	-	1	0.8	-	-	-	-
Type 1	**ASHE**	**<0.3**	**On Insulin**	86	16.0	25	19.1	28	16.2	10	7.7	21	22.3	2	25.0
		0.3-0.4	**On Insulin**	1	0.2	-	-	1	0.6	-	-	-	-	-	-
		>=0.5	**On Insulin**	4	0.7	2	1.5	-	-	2	1.5	-	-	-	-
	SHE	**<0.3**	**On Insulin**	406	75.7	88	67.2	130	75.1	112	86.2	70	74.5	6	75.0
		0.3-0.4	**On Insulin**	15	2.8	2	1.5	8	4.6	4	3.1	1	1.1	-	-
		>=0.5	**On Insulin**	21	3.9	14	10.7	5	2.9	1	0.8	1	1.1	-	-
Type 2	**ASHE**	**<0.3**	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-

				IAK											
						Era									
				Total		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
				N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx				138	100.0	35	100.0	52	100.0	22	100.0	28	100.0	1	100.0
DiabHx	**SHE**	**C-peptide**	**Insulin**												
Cystic fibrosis	**ASHE**	**<0.3**	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-
		>=0.5	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-
Pancreatectomy	**SHE**	**0.3-0.4**	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-
Type 1	**ASHE**	**<0.3**	**On Insulin**	52	37.7	16	45.7	21	40.4	10	45.5	5	17.9	-	-
		0.3-0.4	**On Insulin**	7	5.1	5	14.3	-	-	2	9.1	-	-	-	-
		>=0.5	**On Insulin**	8	5.8	3	8.6	5	9.6	-	-	-	-	-	-
	SHE	**<0.3**	**On Insulin**	66	47.8	10	28.6	24	46.2	10	45.5	21	75.0	1	100.0
		0.3-0.4	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-
		>=0.5	**On Insulin**	4	2.9	1	2.9	2	3.8	-	-	1	3.6	-	-
Type 2	**ASHE**	**<0.3**	**On Insulin**	1	0.7	-	-	-	-	-	-	1	3.6	-	-

	ITA											
			Era									
	TOTAL		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL	341	100.0	22	100.0	39	100.0	75	100.0	192	100.0	13	100.0

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

				ITA											
						Era									
				TOTAL		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
				N	%	N	%	N	%	N	%	N	%	N	%
DiabHx	SHE	C-peptide	Insulin												
Missing	Missing	Missing	Missing	52	15.2	-	-	-	-	9	12.0	34	17.7	9	69.2
			Available	12	3.5	-	-	-	-	12	16.0	-	-	-	-
		Available	Missing	10	2.9	-	-	-	-	-	-	10	5.2	-	-
			Available	20	5.9	-	-	14	35.9	4	5.3	2	1.0	-	-
	Available	Missing	Available	1	0.3	-	-	-	-	-	-	1	0.5	-	-
		Available	Available	1	0.3	-	-	-	-	-	-	1	0.5	-	-
Available	Missing	Missing	Missing	19	5.6	3	13.6	1	2.6	4	5.3	11	5.7	-	-
			Available	22	6.5	7	31.8	2	5.1	2	2.7	10	5.2	1	7.7
		Available	Missing	23	6.7	3	13.6	1	2.6	7	9.3	12	6.3	-	-
			Available	41	12.0	4	18.2	11	28.2	7	9.3	19	9.9	-	-
	Available	Missing	Missing	21	6.2	-	-	-	-	6	8.0	15	7.8	-	-
			Available	107	31.4	4	18.2	8	20.5	22	29.3	70	36.5	3	23.1
		Available	Missing	12	3.5	1	4.5	2	5.1	2	2.7	7	3.6	-	-

				IAK											
						Era									
				TOTAL		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
				N	%	N	%	N	%	N	%	N	%	N	%
TOTAL				45	100.0	11	100.0	3	100.0	10	100.0	20	100.0	1	100.0
DiabHx	SHE	C-peptide	Insulin												
Missing	Missing	Missing	Missing	14	31.1	3	27.3	-	-	3	30.0	8	40.0	-	-
			Available	-	-	-	-	-	-	-	-	-	-	-	-
		Available	Missing	2	4.4	1	9.1	-	-	-	-	1	5.0	-	-
			Available	-	-	-	-	-	-	-	-	-	-	-	-
	Available	Missing	Available	-	-	-	-	-	-	-	-	-	-	-	-
		Available	Available	-	-	-	-	-	-	-	-	-	-	-	-
Available	Missing	Missing	Missing	6	13.3	-	-	1	33.3	1	10.0	4	20.0	-	-
			Available	4	8.9	-	-	1	33.3	1	10.0	2	10.0	-	-
		Available	Missing	1	2.2	-	-	-	-	-	-	1	5.0	-	-
			Available	6	13.3	1	9.1	-	-	4	40.0	1	5.0	-	-
	Available	Missing	Missing	1	2.2	1	9.1	-	-	-	-	-	-	-	-
			Available	8	17.8	4	36.4	1	33.3	-	-	2	10.0	1	100.0
		Available	Missing	3	6.7	1	9.1	-	-	1	10.0	1	5.0	-	-

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

		ITA		IAK		p	1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		p
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	
Indication for ITx	**Cystic fibrosis**	8	1.0	-	-		-	-	1	0.4	2	1.0	5	1.8	-	-	
	Pancreatectomy	1	0.1	-	-		-	-	-	-	1	0.5	-	-	-	-	
	Type 1	771	98.7	166	99.4		195	100.0	252	99.6	206	98.6	270	97.5	14	100.0	
	Type 2	1	0.1	1	0.6		-	-	-	-	-	-	2	0.7	-	-	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx	**Missing**	96	10.9	16	8.7	4	2.0	14	5.2	28	11.8	57	17.1	9	39.1
	Available	781	89.1	167	91.3	195	98.0	253	94.8	209	88.2	277	82.9	14	60.9

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

Exhibit 2-3
Recipient Characteristics at First Infusion

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Age at transplant	877	46.2	0.4	183	47.2	0.6	
Days listed	542	320.4	15.6	117	373.1	46.3	
Duration of Diabetes (yrs)	698	29.0	0.4	137	34.0	0.7	***
Weight (kg)	791	67.6	0.4	162	63.9	0.8	***
Body mass index (kg/m2)	677	23.8	0.1	155	23.0	0.2	**
Daily insulin requirement prior to infusion (units)	740	37.1	0.6	156	35.8	1.1	
Duration of intensive therapy (yrs)	338	20.1	0.8	21	26.9	3.1	*
Avg daily insulin / kg recipient body weight	716	0.5	0.0	153	0.6	0.0	
Fasting plasma glucose (mg/dL)	640	172.3	3.5	129	172.1	8.0	
Basal C-Peptide (ng/mL)	643	0.1	0.0	150	0.2	0.1	***
HbA1C (%)	716	7.9	0.0	140	8.1	0.1	
Class I PRA (%)	411	3.6	0.6	70	0.9	0.6	
Class II PRA (%)	290	3.1	0.7	38	0.0	0.0	

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Age at transplant	199	41.6	0.6	267	44.6	0.6	237	48.3	0.6	334	49.3	0.6	23	45.5	2.5	***
Days listed	163	239.9	21.9	226	319.2	22.8	110	487.1	53.9	149	340.3	31.9	11	162.7	49.7	**
Duration of Diabetes (yrs)	188	27.3	0.8	250	29.6	0.6	188	31.2	0.9	195	30.9	0.9	14	34.4	3.3	***
Weight (kg)	187	65.8	0.8	259	65.3	0.6	212	67.1	0.8	278	69.0	0.7	17	68.8	3.3	***
Body mass index (kg/m2)	180	23.4	0.2	258	23.4	0.2	198	23.9	0.2	180	24.1	0.3	16	23.8	0.8	**
Daily insulin requirement prior to infusion (units)	186	39.4	1.1	262	37.3	0.9	204	33.6	1.0	230	36.8	1.0	14	39.5	3.2	*
Duration of intensive therapy (yrs)	107	18.1	1.1	143	23.6	1.2	67	19.9	2.0	38	18.4	2.3	4	9.5	5.0	
Avg daily insulin / kg recipient body weight	184	0.6	0.0	257	0.6	0.0	201	0.5	0.0	214	0.5	0.0	13	0.6	0.0	***
Fasting plasma glucose (mg/dL)	161	183.1	7.4	246	173.0	5.9	177	153.4	5.8	177	178.4	6.6	8	212.9	30.2	
Basal C-Peptide (ng/mL)	177	0.2	0.0	253	0.1	0.0	177	0.1	0.0	177	0.1	0.0	9	0.0	0.0	*
HbA1C (%)	186	7.9	0.1	261	7.8	0.1	186	7.9	0.1	212	8.2	0.1	11	8.4	0.4	**
Class I PRA (%)	126	1.3	0.5	185	4.3	1.1	84	2.5	0.9	80	4.7	1.6	6	1.7	1.2	
Class II PRA (%)	74	1.7	1.3	103	2.8	1.1	65	3.5	1.5	80	3.0	1.4	6	1.2	1.2	

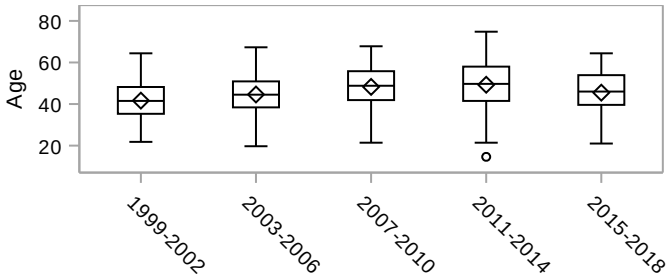
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

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

Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

Significant trends in patient characteristics from table above	
By ITA or IAK	**By Era**

Age



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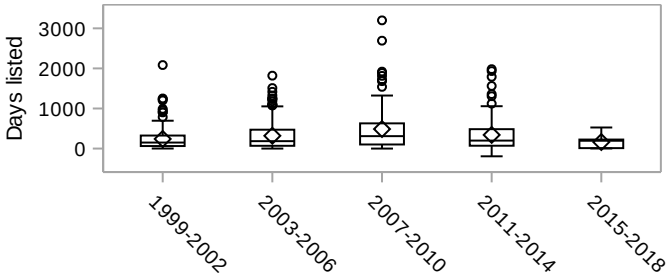
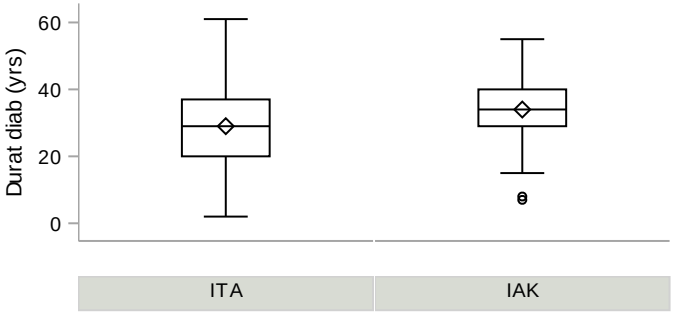
Days listed



CITR Data 06Jan2017

Durat diab (yrs)



CITR Data 06Jan2017

Durat diab (yrs)

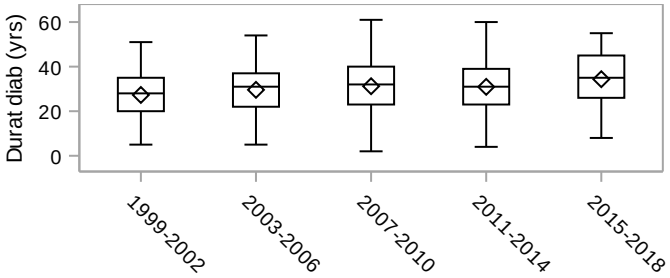


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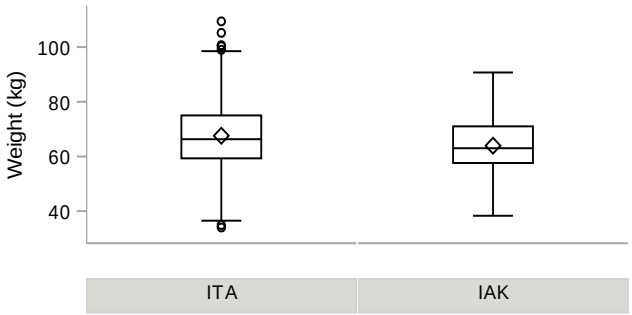
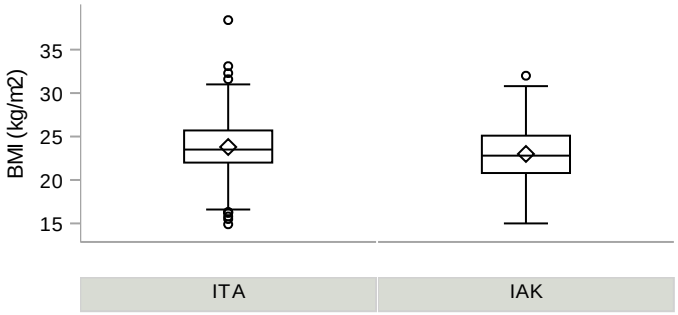
Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

Weight (kg)



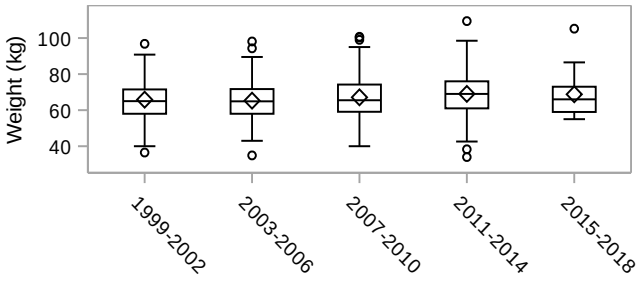
CITR Data 06Jan2017

BMI (kg/m2)



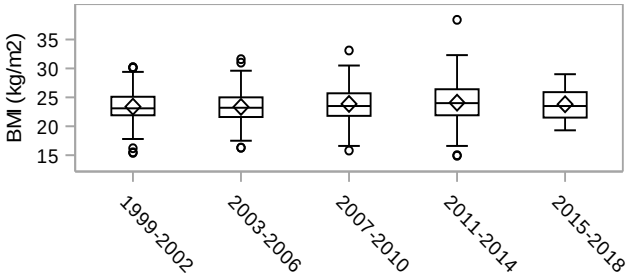
CITR Data 06Jan2017

Weight (kg)



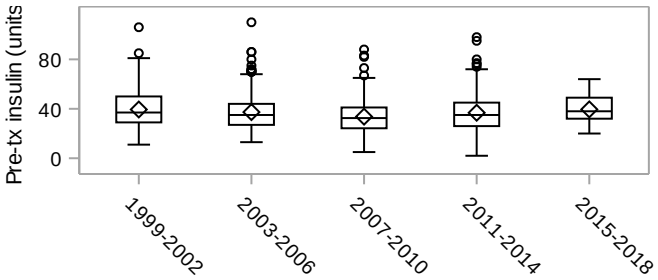
CITR Data 06Jan2017

BMI (kg/m2)



CITR Data 06Jan2017

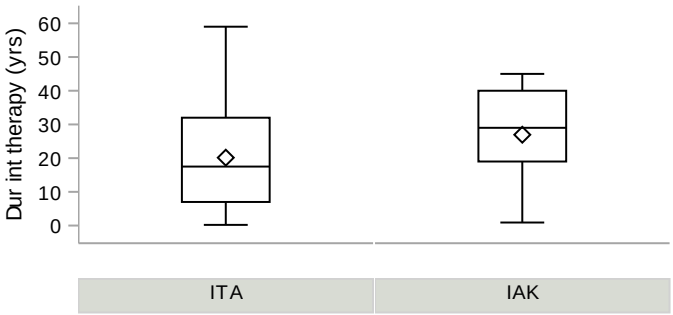
Pre-tx insulin (units)



CITR Data 06Jan2017

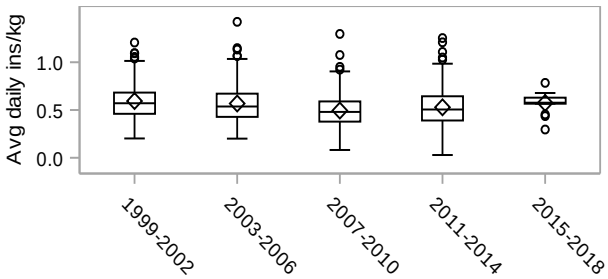
Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

Dur int therapy (yrs)



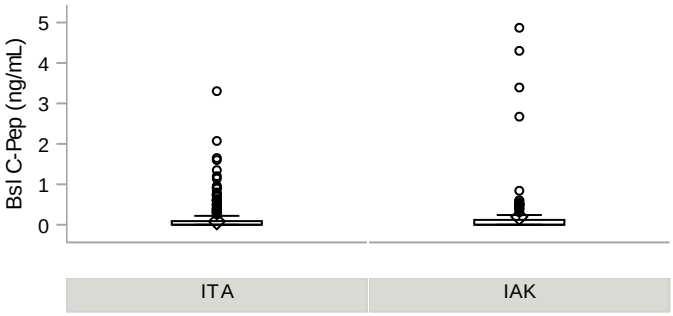
CITR Data 06Jan2017

Avg daily ins/kg



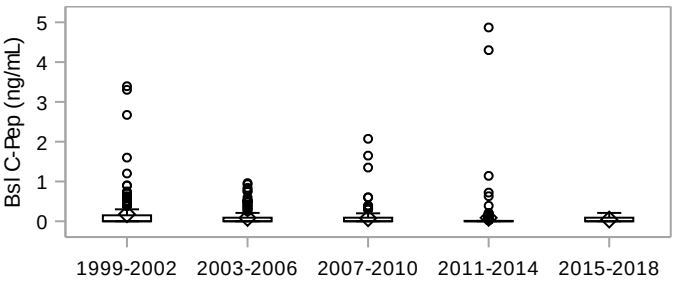
CITR Data 06Jan2017

Bsl C-Pep (ng/mL)



CITR Data 06Jan2017

Bsl C-Pep (ng/mL)



CITR Data 06Jan2017

Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

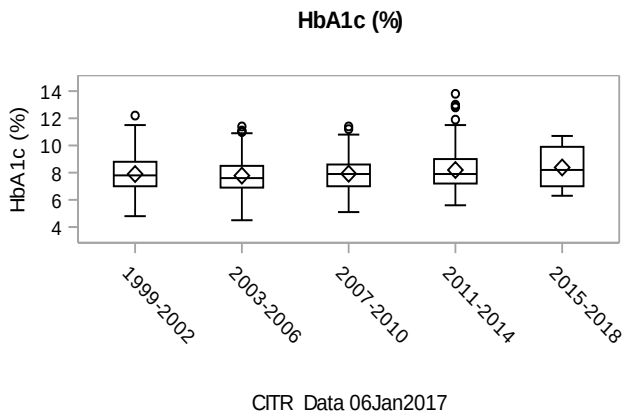


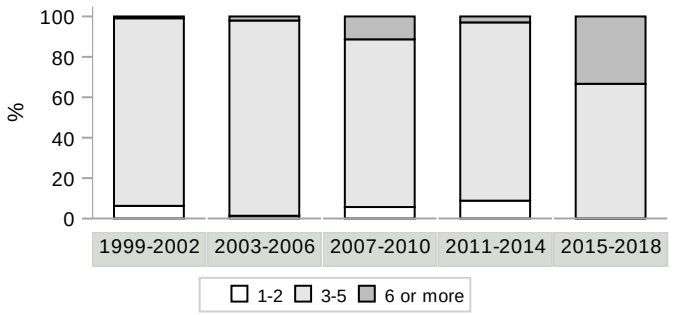
Exhibit 2-4
Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Number of injections per day	**1-2**	10	3.7	5	6.1		7	6.3	2	1.3	3	5.7	3	8.8		0.0	***
	3-5	250	92.9	74	90.2		104	92.9	144	96.6	44	83.0	30	88.2	2	66.7	
	6 or more	9	3.3	3	3.7		1	0.9	3	2.0	6	11.3	1	2.9	1	33.3	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Number of injections per day	Missing	608	69.3	101	55.2	87	43.7	118	44.2	184	77.6	300	89.8	20	87.0
	Available	269	30.7	82	44.8	112	56.3	149	55.8	53	22.4	34	10.2	3	13.0

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

Number of injections per day

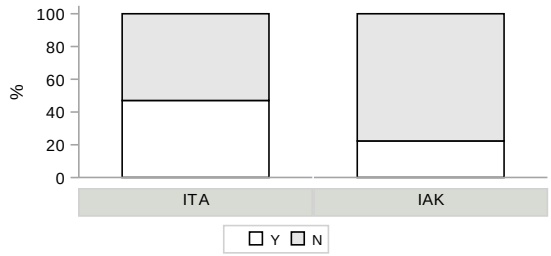


CITR Data 06Jan2017

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Use of insulin pump	**No**	312	53.0	101	77.7	***	126	69.2	163	62.2	65	46.8	54	43.9	5	38.5	***
	Yes	277	47.0	29	22.3		56	30.8	99	37.8	74	53.2	69	56.1	8	61.5	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Use of insulin pump	Missing	288	32.8	53	29.0	17	8.5	5	1.9	98	41.4	211	63.2	10	43.5
	Available	589	67.2	130	71.0	182	91.5	262	98.1	139	58.6	123	36.8	13	56.5

Use of insulin pump



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Use of insulin pump

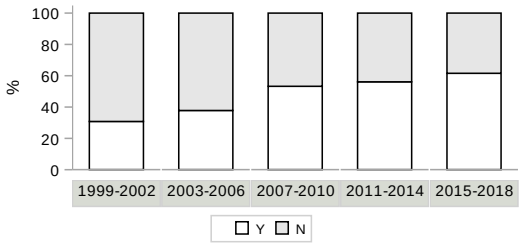

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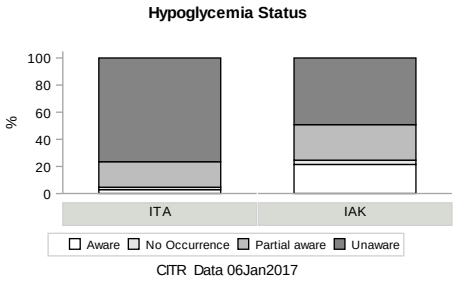
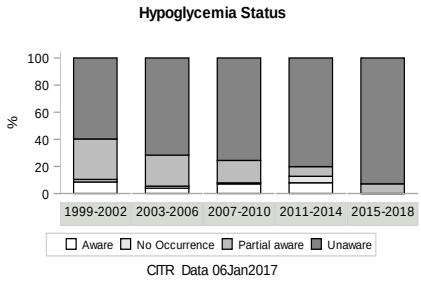
Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Hypoglycemia status	**Aware**	16	2.8	27	21.4		14	8.5	10	3.9	9	7.1	10	7.9		0.0	
	No Occurrence	10	1.8	4	3.2	***	3	1.8	4	1.6	1	0.8	6	4.8		0.0	***
	Partial aware	106	18.8	33	26.2		49	29.9	59	22.9	21	16.5	9	7.1	1	7.1	
	Unaware	431	76.6	62	49.2		98	59.8	185	71.7	96	75.6	101	80.2	13	92.9	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hypoglycemia status	Available	563	64.2	126	68.9	164	82.4	258	96.6	127	53.6	126	37.7	14	60.9
	Missing	314	35.8	57	31.1	35	17.6	9	3.4	110	46.4	208	62.3	9	39.1





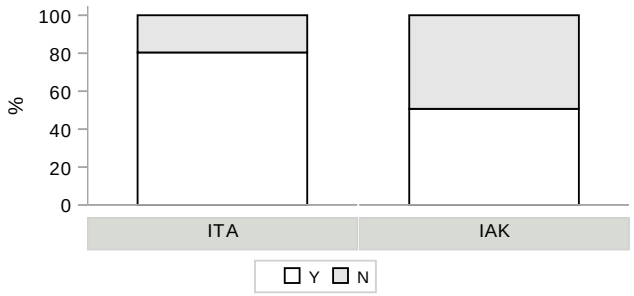
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Severe hypoglycemia	**No**	133	19.6	74	49.3	***	58	32.8	60	25.4	31	16.9	55	25.1	3	23.1	*
	Yes	545	80.4	76	50.7		119	67.2	176	74.6	152	83.1	164	74.9	10	76.9	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Severe hypoglycemia	Missing	199	22.7	33	18.0	22	11.1	31	11.6	54	22.8	115	34.4	10	43.5
	Available	678	77.3	150	82.0	177	88.9	236	88.4	183	77.2	219	65.6	13	56.5

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

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

Severe Hypoglycemia



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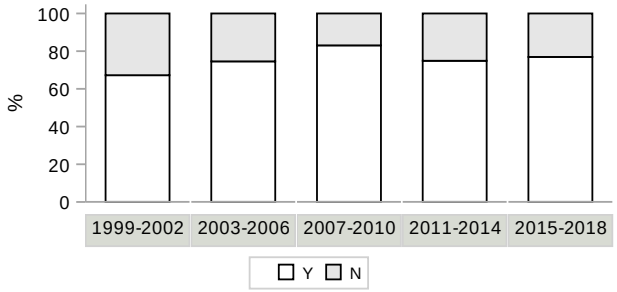
Severe Hypoglycemia

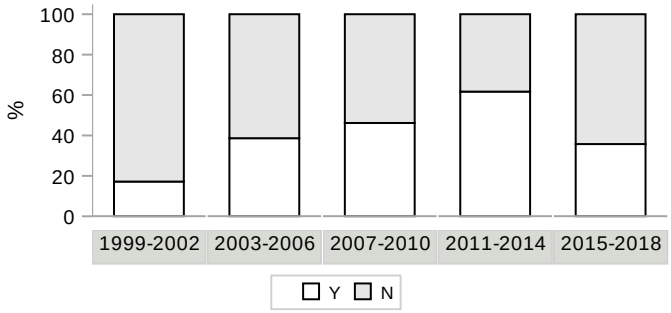


CITR Data 06Jan2017

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Lipid lowering medication	**No**	354	63.7	70	54.3		145	82.9	159	61.4	70	53.8	41	38.3	9	64.3	***
	Yes	202	36.3	59	45.7		30	17.1	100	38.6	60	46.2	66	61.7	5	35.7	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Lipid lowering medication	Missing	321	36.6	54	29.5	24	12.1	8	3.0	107	45.1	227	68.0	9	39.1
	Available	556	63.4	129	70.5	175	87.9	259	97.0	130	54.9	107	32.0	14	60.9

Lipid-lowering medication



CITR Data 06Jan2017

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

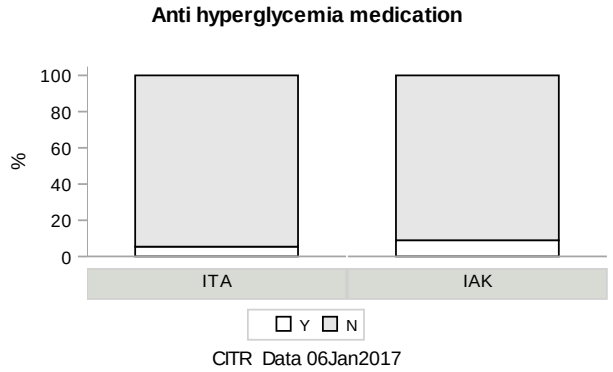
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Anti hypertension medication	**No**	354	63.3	35	27.1		112	62.6	153	59.1	67	50.4	48	46.2	9	69.2	
	Yes	205	36.7	94	72.9		67	37.4	106	40.9	66	49.6	56	53.8	4	30.8	

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

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anti hypertension medication	Missing	318	36.3	54	29.5	20	10.1	8	3.0	104	43.9	230	68.9	10	43.5
	Available	559	63.7	129	70.5	179	89.9	259	97.0	133	56.1	104	31.1	13	56.5

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Anti-hyperglycemia medication	**No**	228	94.6	51	91.1	***	37	94.9	78	98.7	80	93.0	77	91.7	7	77.8	*
	Yes	13	5.4	5	8.9		2	5.1	1	1.3	6	7.0	7	8.3	2	22.2	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anti-hyperglycemia medication	Missing	636	72.5	127	69.4	160	80.4	188	70.4	151	63.7	250	74.9	14	60.9
	Available	241	27.5	56	30.6	39	19.6	79	29.6	86	36.3	84	25.1	9	39.1



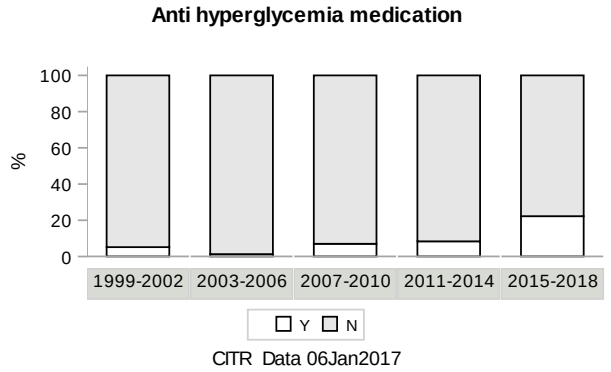
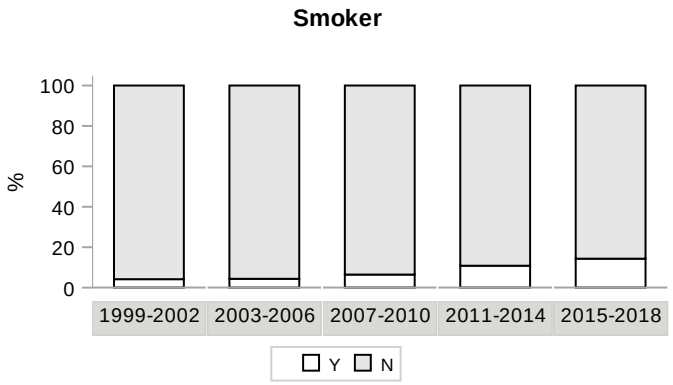


Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Smoker	**No**	589	93.2	79	95.2		139	95.9	221	95.7	131	93.6	165	89.2	12	85.7	*
	Yes	43	6.8	4	4.8		6	4.1	10	4.3	9	6.4	20	10.8	2	14.3	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Smoker	Missing	245	27.9	100	54.6	54	27.1	36	13.5	97	40.9	149	44.6	9	39.1
	Available	632	72.1	83	45.4	145	72.9	231	86.5	140	59.1	185	55.4	14	60.9

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



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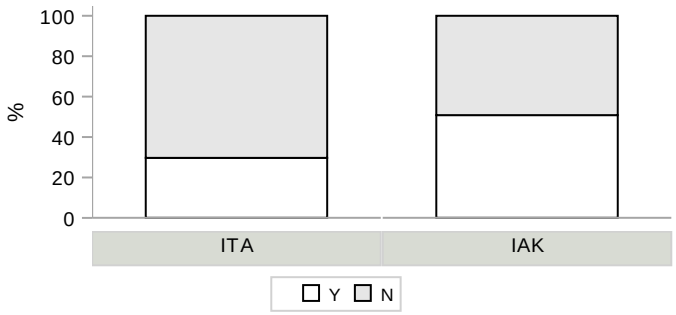
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Peripheral neuropathy	**No**	448	70.3	60	49.2	***	107	59.8	166	65.9	99	68.3	126	73.7	10	83.3	
	Yes	189	29.7	62	50.8		72	40.2	86	34.1	46	31.7	45	26.3	2	16.7	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Peripheral neuropathy	Missing	240	27.4	61	33.3	20	10.1	15	5.6	92	38.8	163	48.8	11	47.8
	Available	637	72.6	122	66.7	179	89.9	252	94.4	145	61.2	171	51.2	12	52.2

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

Peripheral neuropathy



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		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Autonomic neuropathy	**No**	458	83.6	76	67.9	***	129	75.9	193	81.1	99	81.8	104	86.0	9	90.0	
	Yes	90	16.4	36	32.1		41	24.1	45	18.9	22	18.2	17	14.0	1	10.0	

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

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Autonomic neuropathy	Missing	329	37.5	71	38.8	29	14.6	29	10.9	116	48.9	213	63.8	13	56.5
	Available	548	62.5	112	61.2	170	85.4	238	89.1	121	51.1	121	36.2	10	43.5

Autonomic neuropathy

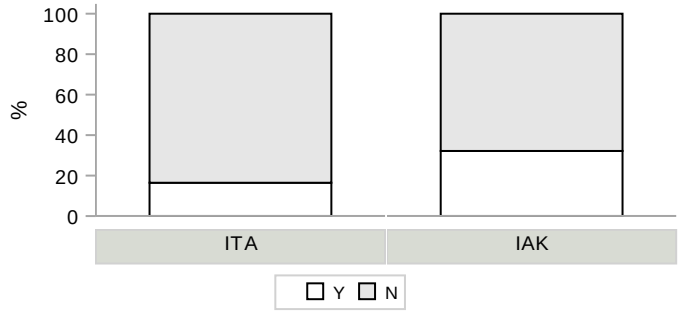

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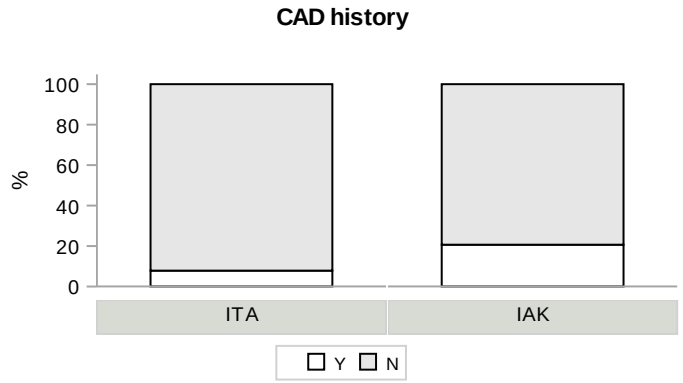
Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
CAD history	No	578	92.2	100	79.4	***	169	93.9	229	89.1	122	86.5	151	90.4	7	87.5	
	Yes	49	7.8	26	20.6		11	6.1	28	10.9	19	13.5	16	9.6	1	12.5	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
CAD history	Missing	250	28.5	57	31.1	19	9.5	10	3.7	96	40.5	167	50.0	15	65.2
	Available	627	71.5	126	68.9	180	90.5	257	96.3	141	59.5	167	50.0	8	34.8



CITR Data 06Jan2017

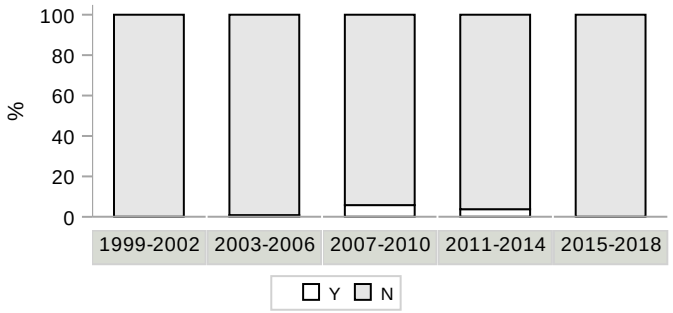
Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
CVA history	No	602	98.0	114	96.6		176	100.0	247	99.2	131	94.2	155	96.3	7	100.0	**
	Yes	12	2.0	4	3.4			0.0	2	0.8	8	5.8	6	3.7		0.0	

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

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
CVA history	Missing	263	30.0	65	35.5	23	11.6	18	6.7	98	41.4	173	51.8	16	69.6
	Available	614	70.0	118	64.5	176	88.4	249	93.3	139	58.6	161	48.2	7	30.4

CVA history

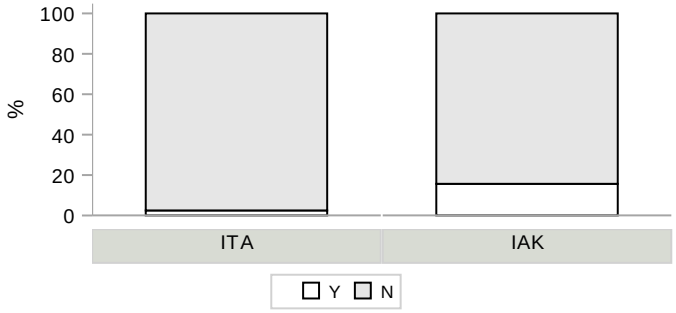


CITR Data 06Jan2017

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
PVD history	No	518	97.6	81	84.4	***	154	95.7	231	95.1	108	93.9	99	98.0	7	100.0	
	Yes	13	2.4	15	15.6		7	4.3	12	4.9	7	6.1	2	2.0		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
PVD history	Missing	346	39.5	87	47.5	38	19.1	24	9.0	122	51.5	233	69.8	16	69.6
	Available	531	60.5	96	52.5	161	80.9	243	91.0	115	48.5	101	30.2	7	30.4

PVD history



CITR Data 06Jan2017

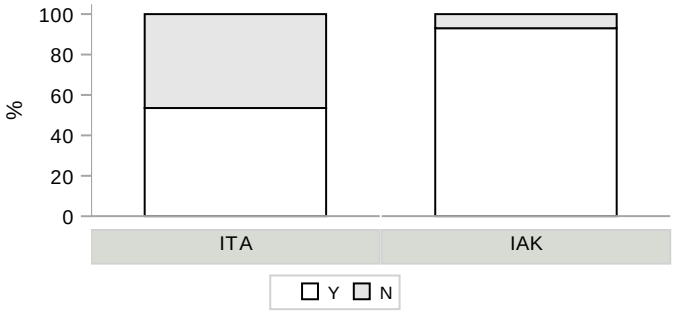
Exhibit 2-4 (continued)
Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Retinopathy	**No**	258	46.5	9	7.0	***	57	31.3	96	38.9	50	39.7	58	49.6	6	50.0	*
	Yes	297	53.5	120	93.0		125	68.7	151	61.1	76	60.3	59	50.4	6	50.0	

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

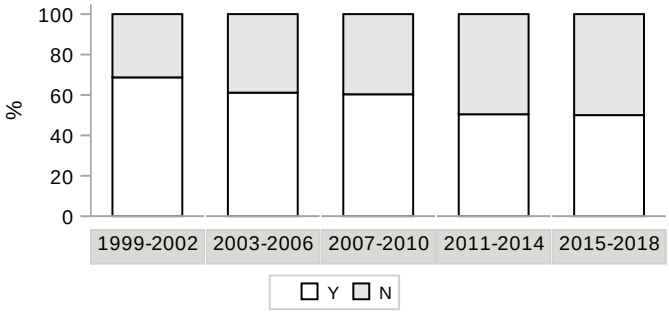
Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Retinopathy	Missing	322	36.7	54	29.5	17	8.5	20	7.5	111	46.8	217	65.0	11	47.8
	Available	555	63.3	129	70.5	182	91.5	247	92.5	126	53.2	117	35.0	12	52.2

Retinopathy



CITR Data 06Jan2017

Retinopathy



CITR Data 06Jan2017

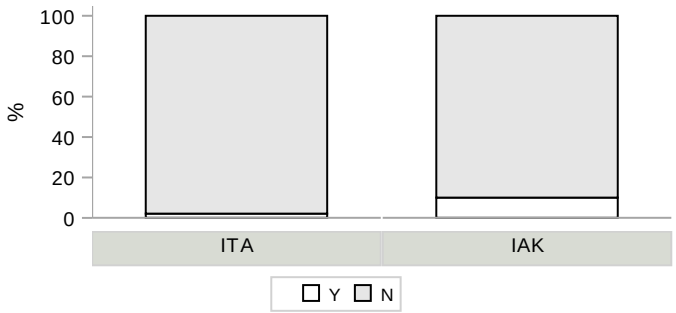
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Macular edema	**No**	473	97.9	72	90.0	***	136	97.1	205	96.7	94	95.9	103	97.2	7	100.0	
	Yes	10	2.1	8	10.0		4	2.9	7	3.3	4	4.1	3	2.8		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Macular edema	Missing	394	44.9	103	56.3	59	29.6	55	20.6	139	58.6	228	68.3	16	69.6
	Available	483	55.1	80	43.7	140	70.4	212	79.4	98	41.4	106	31.7	7	30.4

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

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

Macular edema

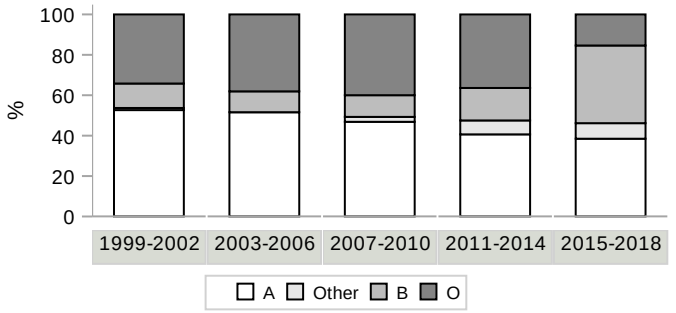


CITR Data 06Jan2017

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Blood group	**A**	355	46.8	82	50.3		100	52.6	130	51.6	96	46.8	106	40.6	5	38.5	
	A1		0.0	1	0.6		1	0.5		0.0		0.0		0.0		0.0	
	A1B	2	0.3		0.0			0.0		0.0		0.0	1	0.4	1	7.7	
	A2	1	0.1		0.0			0.0		0.0	1	0.5		0.0		0.0	***
	AB	18	2.4	4	2.5		1	0.5		0.0	4	2.0	17	6.5		0.0	
	B	98	12.9	20	12.3		23	12.1	26	10.3	22	10.7	42	16.1	5	38.5	
	O	284	37.5	56	34.4		65	34.2	96	38.1	82	40.0	95	36.4	2	15.4	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Blood group	**Available**	758	86.4	163	89.1	190	95.5	252	94.4	205	86.5	261	78.1	13	56.5
	Missing	119	13.6	20	10.9	9	4.5	15	5.6	32	13.5	73	21.9	10	43.5

Blood group

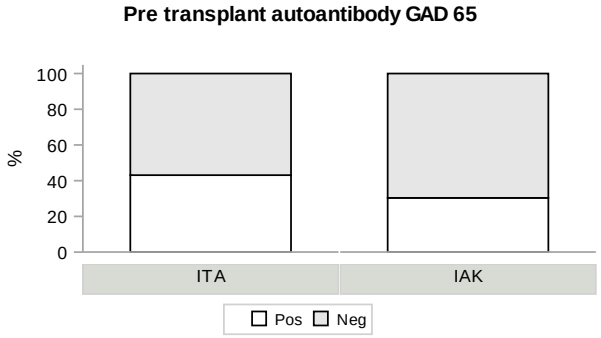


CITR Data 06Jan2017

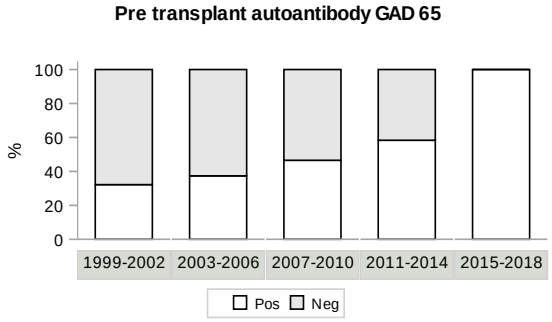
Exhibit 2-5
Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody GAD 65	**Negative**	230	56.9	62	69.7	*	99	67.8	114	62.6	54	53.5	25	41.7		0.0	***
	Positive	174	43.1	27	30.3		47	32.2	68	37.4	47	46.5	35	58.3	4	100.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody GAD 65	Missing	473	53.9	94	51.4	53	26.6	85	31.8	136	57.4	274	82.0	19	82.6
	Available	404	46.1	89	48.6	146	73.4	182	68.2	101	42.6	60	18.0	4	17.4



CITR Data 06Jan2017



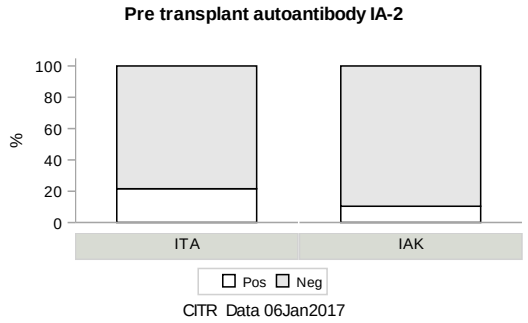
CITR Data 06Jan2017

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

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody IA-2	**Negative**	491	78.4	121	89.6	**	157	82.2	217	81.9	123	76.9	104	78.8	11	84.6	
	Positive	135	21.6	14	10.4		34	17.8	48	18.1	37	23.1	28	21.2	2	15.4	

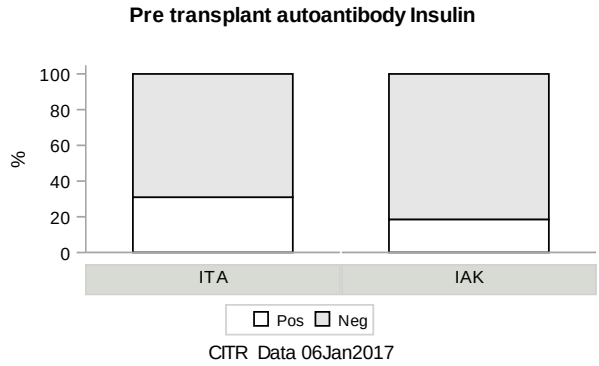
Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody IA-2	Missing	251	28.6	48	26.2	8	4.0	2	0.7	77	32.5	202	60.5	10	43.5
	Available	626	71.4	135	73.8	191	96.0	265	99.3	160	67.5	132	39.5	13	56.5

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



		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody Insulin	**Negative**	433	69.1	110	81.5	**	128	67.0	155	58.5	131	81.4	116	87.9	13	100.0	***
	Positive	194	30.9	25	18.5		63	33.0	110	41.5	30	18.6	16	12.1		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody Insulin	Missing	250	28.5	48	26.2	8	4.0	2	0.7	76	32.1	202	60.5	10	43.5
	Available	627	71.5	135	73.8	191	96.0	265	99.3	161	67.9	132	39.5	13	56.5



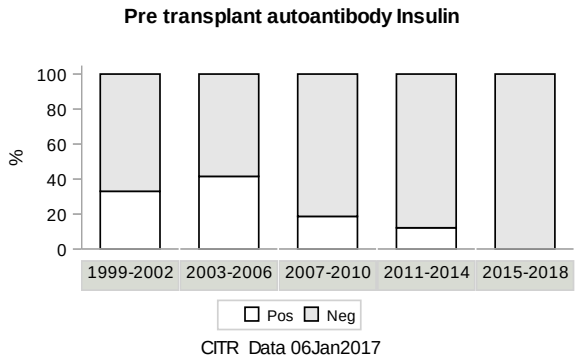


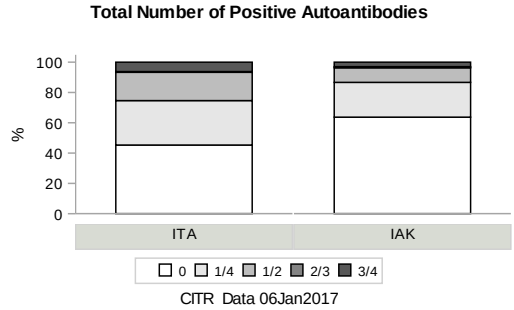
Exhibit 2-5 (continued)
Recipient Autoantibody and Sensitization at First Infusion

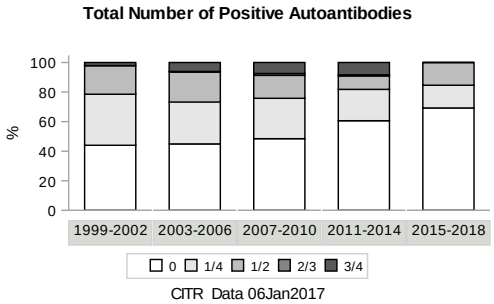
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Total Number of Positive Autoantibodies	**0**	284	45.3	86	63.7		84	44.0	119	44.9	78	48.4	80	60.6	9	69.2	
	1/4	184	29.3	31	23.0		66	34.6	75	28.3	44	27.3	28	21.2	2	15.4	
	1/2	117	18.7	13	9.6	*	37	19.4	54	20.4	25	15.5	12	9.1	2	15.4	**
	2/3	3	0.5	1	0.7			0.0	1	0.4	2	1.2	1	0.8		0.0	
	3/4	39	6.2	4	3.0		4	2.1	16	6.0	12	7.5	11	8.3		0.0	

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

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total Number of Positive Autoantibodies	Missing	250	28.5	48	26.2	8	4.0	2	0.7	76	32.1	202	60.5	10	43.5
	Available	627	71.5	135	73.8	191	96.0	265	99.3	161	67.9	132	39.5	13	56.5

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





		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
PRA-Class I	**Equ**	2	0.5		0.0			0.0		0.0		0.0		0.0	2	25.0	
	Neg	330	79.3	64	91.4		111	88.1	154	82.8	65	76.5	60	74.1	4	50.0	***
	Pos	84	20.2	6	8.6		15	11.9	32	17.2	20	23.5	21	25.9	2	25.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
PRA-Class I	Missing	461	52.6	113	61.7	73	36.7	81	30.3	152	64.1	253	75.7	15	65.2
	Available	416	47.4	70	38.3	126	63.3	186	69.7	85	35.9	81	24.3	8	34.8

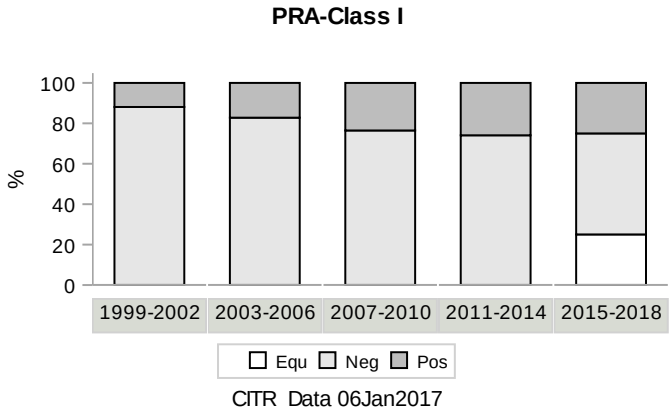


Exhibit 2-5 (continued)
Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
PRA-Class II	Equ	2	0.7		0.0			0.0		0.0	2	2.9		0.0		0.0	
	Neg	250	84.5	36	94.7		71	95.9	92	89.3	56	82.4	62	77.5	5	55.6	***
	Pos	44	14.9	2	5.3		3	4.1	11	10.7	10	14.7	18	22.5	4	44.4	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
PRA-Class II	Missing	581	66.2	145	79.2	125	62.8	164	61.4	169	71.3	254	76.0	14	60.9
	Available	296	33.8	38	20.8	74	37.2	103	38.6	68	28.7	80	24.0	9	39.1

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

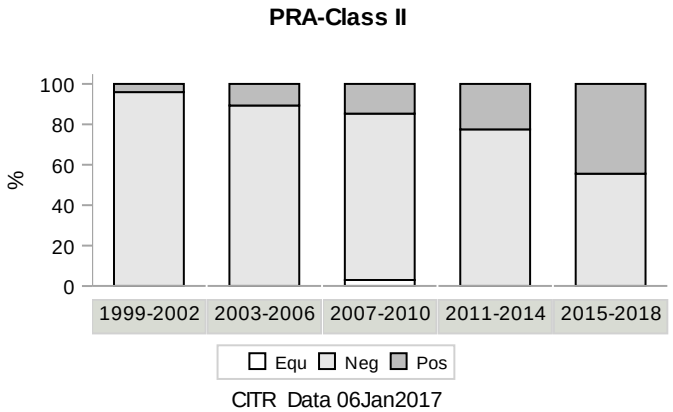


Exhibit 2-6
Recipient Infectious Disease Testing at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HIV	NEG	690	100.0	113	99.1		170	100.0	242	100.0	171	99.4	211	100.0	9	100.0	
	POS	-	0.0	1	0.9		-	0.0	-	0.0	1	0.6	-	0.0	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HIV	Available	690	78.7	114	62.3	170	85.4	242	90.6	172	72.6	211	63.2	9	39.1
	Missing	187	21.3	69	37.7	29	14.6	25	9.4	65	27.4	123	36.8	14	60.9

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
CMV-IgG	NEG	406	57.2	48	40.7		91	52.9	134	54.7	104	54.5	118	56.2	7	70.0	
	POS	304	42.8	70	59.3		81	47.1	111	45.3	87	45.5	92	43.8	3	30.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgG	Available	710	81.0	118	64.5	172	86.4	245	91.8	191	80.6	210	62.9	10	43.5
	Missing	167	19.0	65	35.5	27	13.6	22	8.2	46	19.4	124	37.1	13	56.5

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
CMV-IgM	NEG	493	92.5	71	88.8		102	96.2	161	97.0	126	93.3	168	84.8	7	87.5	
	POS	40	7.5	9	11.3		4	3.8	5	3.0	9	6.7	30	15.2	1	12.5	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgM	Available	533	60.8	80	43.7	106	53.3	166	62.2	135	57.0	198	59.3	8	34.8
	Missing	344	39.2	103	56.3	93	46.7	101	37.8	102	43.0	136	40.7	15	65.2

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Hepatitis B Core	NEG	535	97.6	87	95.6		125	98.4	200	98.0	140	95.9	150	96.8	7	100.0	
	POS	13	2.4	4	4.4		2	1.6	4	2.0	6	4.1	5	3.2	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Core	Available	548	62.5	91	49.7	127	63.8	204	76.4	146	61.6	155	46.4	7	30.4
	Missing	329	37.5	92	50.3	72	36.2	63	23.6	91	38.4	179	53.6	16	69.6

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

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

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Hepatitis B Surface	**NEG**	193	79.4	29	69.0		23	74.2	33	82.5	55	67.1	103	84.4	8	80.0	
	POS	50	20.6	13	31.0		8	25.8	7	17.5	27	32.9	19	15.6	2	20.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Surface	Available	243	27.7	42	23.0	31	15.6	40	15.0	82	34.6	122	36.5	10	43.5
	Missing	634	72.3	141	77.0	168	84.4	227	85.0	155	65.4	212	63.5	13	56.5

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HCV	**NEG**	669	99.3	118	96.7		162	97.6	243	99.6	170	99.4	203	98.5	9	100.0	
	POS	5	0.7	4	3.3		4	2.4	1	0.4	1	0.6	3	1.5	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HCV	Available	674	76.9	122	66.7	166	83.4	244	91.4	171	72.2	206	61.7	9	39.1
	Missing	203	23.1	61	33.3	33	16.6	23	8.6	66	27.8	128	38.3	14	60.9

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
EBV-IgG	**NEG**	68	10.7	5	4.4		10	6.1	17	7.6	18	11.7	27	13.6	1	11.1	
	POS	568	89.3	109	95.6		155	93.9	207	92.4	136	88.3	171	86.4	8	88.9	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgG	Available	636	72.5	114	62.3	165	82.9	224	83.9	154	65.0	198	59.3	9	39.1
	Missing	241	27.5	69	37.7	34	17.1	43	16.1	83	35.0	136	40.7	14	60.9

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
EBV-IgM	**NEG**	349	78.1	69	88.5		79	78.2	128	88.9	85	85.9	120	69.0	6	85.7	
	POS	98	21.9	9	11.5		22	21.8	16	11.1	14	14.1	54	31.0	1	14.3	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgM	Available	447	51.0	78	42.6	101	50.8	144	53.9	99	41.8	174	52.1	7	30.4
	Missing	430	49.0	105	57.4	98	49.2	123	46.1	138	58.2	160	47.9	16	69.6

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

No Testing

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

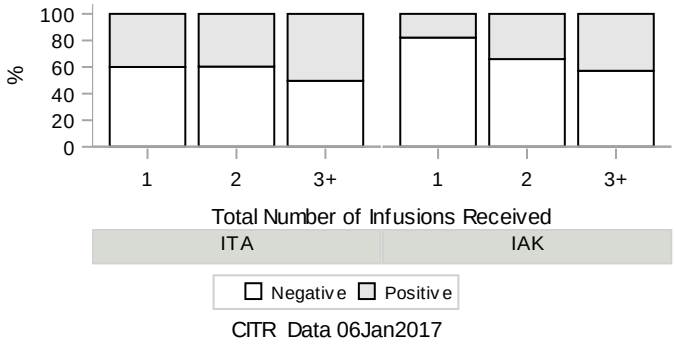
	ITA									IAK								
	Total Number of Infusions Received									Total Number of Infusions Received								
	One Infusion			Two Infusions			>= Three Infusions			One Infusion			Two Infusions			>= Three Infusions		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Age (yrs)	236	46.3	0.7	434	46.8	0.5	207	44.7	0.7	62	47.1	1.1	94	47.9	0.9	27	45.0	1.4
Duration of Diabetes (yrs)	181	29.0	0.9	352	29.8	0.6	165	27.2	0.9	46	33.5	1.4	71	34.5	1.0	20	33.3	1.2
Weight (kg)	204	66.1	0.8	395	67.7	0.6	192	68.8	0.8	53	63.0	1.6	84	63.4	1.1	25	67.5	1.6
Body Mass Index (kg/m2)	172	23.3	0.2	329	24.0	0.2	176	23.9	0.2	50	22.7	0.4	80	23.0	0.3	25	23.7	0.6
Daily insulin requirement (units)	184	34.4	1.0	371	36.6	0.8	185	40.6	1.2	55	37.0	1.8	78	35.7	1.5	23	32.8	3.1
Average daily insulin / kg recipient body weight	180	0.5	0.0	357	0.5	0.0	179	0.6	0.0	52	0.6	0.0	78	0.6	0.0	23	0.5	0.0
Duration of intensive insulin therapy (yrs)	67	17.4	1.9	172	21.4	1.1	99	19.9	1.2	11	30.5	3.8	9	25.4	4.7	1	0.9	-
Fasting plasma glucose (mg/dL)	165	158.6	6.8	303	175.2	5.1	172	180.3	6.8	39	172.7	14.5	70	167.9	9.5	20	185.7	28.7
Basal C-Peptide (ng/mL)	166	0.1	0.0	299	0.1	0.0	178	0.1	0.0	49	0.2	0.1	78	0.2	0.1	23	0.1	0.0
HbA1C (%)	179	7.8	0.1	349	7.9	0.1	188	7.9	0.1	44	8.1	0.2	74	8.2	0.1	22	8.0	0.3

Exhibit 2-8
Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK					
		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**	51	60.0	117	60.3	62	49.6	23	82.1	31	66.0	8	57.1
	Positive	34	40.0	77	39.7	63	50.4	5	17.9	16	34.0	6	42.9

Data completeness		ITA						IAK					
		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**	151	64.0	240	55.3	82	39.6	34	54.8	47	50.0	13	48.1
	Available	85	36.0	194	44.7	125	60.4	28	45.2	47	50.0	14	51.9

Pre transplant autoantibody - GAD 65

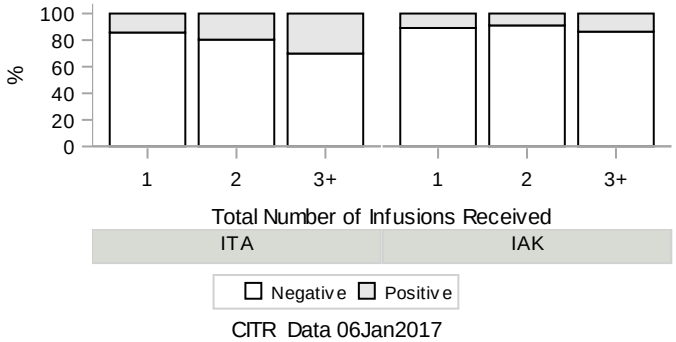


		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - IA-2	**Negative**	120	85.7	241	80.3	130	69.9	41	89.1	61	91.0	19	86.4
	Positive	20	14.3	59	19.7	56	30.1	5	10.9	6	9.0	3	13.6

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

Data completeness		ITA						IAK					
		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	96	40.7	134	30.9	21	10.1	16	25.8	27	28.7	5	18.5
	Available	140	59.3	300	69.1	186	89.9	46	74.2	67	71.3	22	81.5

Pre transplant autoantibody - IA-2



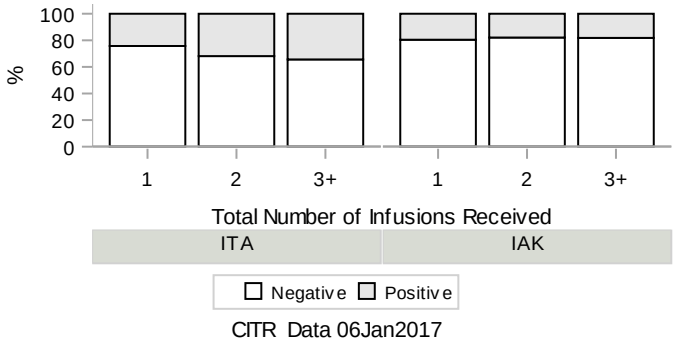
CITR Data 06Jan2017

		ITA						IAK					
		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**	106	75.7	205	68.1	122	65.6	37	80.4	55	82.1	18	81.8
	Positive	34	24.3	96	31.9	64	34.4	9	19.6	12	17.9	4	18.2

Data completeness		ITA						IAK					
		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	96	40.7	133	30.6	21	10.1	16	25.8	27	28.7	5	18.5
	Available	140	59.3	301	69.4	186	89.9	46	74.2	67	71.3	22	81.5

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

Pre transplant autoantibody - Insulin



		ITA						IAK					
		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**	72	51.4	139	46.2	73	39.2	33	71.7	40	59.7	13	59.1
	1/4	42	30.0	89	29.6	53	28.5	7	15.2	19	28.4	5	22.7
	1/2	16	11.4	62	20.6	39	21.0	5	10.9	7	10.4	1	4.5
	2/3	-	-	1	0.3	2	1.1	-	-	-	-	1	4.5
	3/4	10	7.1	10	3.3	19	10.2	1	2.2	1	1.5	2	9.1

Data completeness		ITA						IAK					
		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**	96	40.7	133	30.6	21	10.1	16	25.8	27	28.7	5	18.5
	Available	140	59.3	301	69.4	186	89.9	46	74.2	67	71.3	22	81.5

Total Number of Positive Autoantibodies

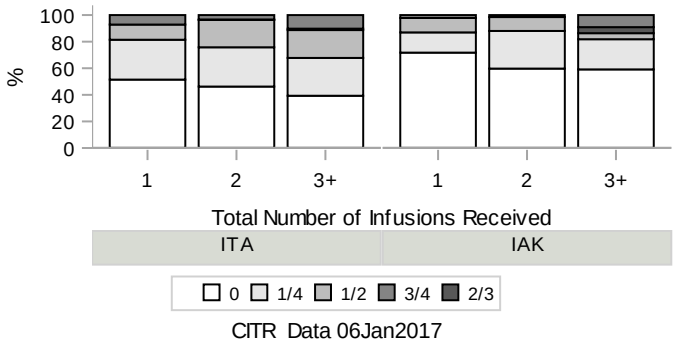


Exhibit 2-9
Recipient Laboratory Values at First Infusion

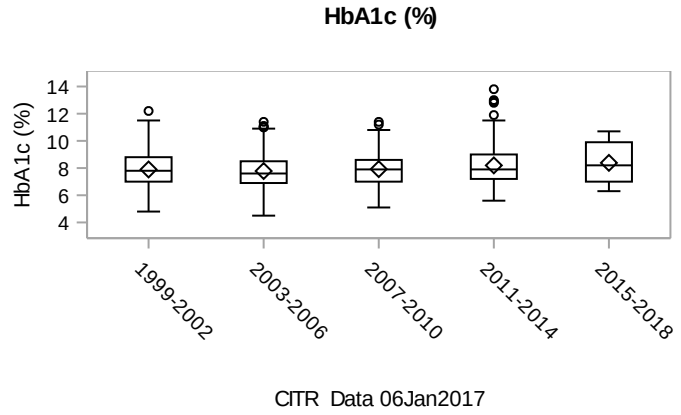
	ITA			IAK				1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
HbA1C (%)	716	7.9	0.0	140	8.1	0.1		186	7.9	0.1	261	7.8	0.1	186	7.9	0.1	212	8.2	0.1	11	8.4	0.4	**
Basal C-Peptide (ng/mL)	643	0.1	0.0	150	0.2	0.1	***	177	0.2	0.0	253	0.1	0.0	177	0.1	0.0	177	0.1	0.0	9	0.0	0.0	*
Fasting blood glucose (mg/dL)	640	172.3	3.5	129	172.1	8.0		161	183.1	7.4	246	173.0	5.9	177	153.4	5.8	177	178.4	6.6	8	212.9	30.2	
ALT (U/L)	683	24.2	0.6	125	24.5	1.2		141	22.1	1.1	240	24.2	0.7	185	26.3	1.5	233	24.2	1.0	9	19.8	3.0	
AST (U/L)	632	27.7	0.9	127	26.6	1.2		148	23.6	0.7	246	26.3	0.7	168	32.9	2.8	191	27.5	1.5	6	20.2	3.3	*
Alkaline phosphatase (U/L)	579	79.7	1.8	119	113.4	7.4	***	142	90.9	4.7	230	99.3	4.5	156	76.3	3.0	162	69.9	2.4	8	81.1	8.9	***
Total bilirubin (mg/dL)	574	0.7	0.0	122	0.5	0.0	*	142	0.6	0.0	219	0.6	0.0	153	0.7	0.0	176	0.8	0.1	6	0.4	0.1	
Total cholesterol (mg/dL)	641	169.2	1.7	126	173.2	3.8		157	181.5	2.8	242	173.3	2.1	174	166.5	3.5	185	158.4	3.8	9	173.8	12.2	***
HDL (mg/dL)	618	64.2	0.8	115	62.8	1.8		150	65.3	1.4	233	64.9	1.3	158	63.6	1.6	183	62.0	1.7	9	59.9	5.8	
LDL (mg/dL)	605	90.3	1.3	100	89.3	3.1		134	99.4	2.5	229	94.4	1.7	162	87.2	2.5	172	80.0	2.6	8	93.6	11.7	***
Triglycerides (mg/dL)	642	52.5	1.4	126	68.7	3.8	***	157	55.8	3.0	242	57.0	2.6	175	53.7	2.3	185	53.3	2.6	9	63.3	17.8	
eGFR-CKD (mL/min/1.73m2)	728	88.5	1.0	161	64.1	2.1	***	170	85.7	1.9	250	84.9	1.5	201	84.2	2.1	260	81.9	2.0	8	96.1	7.6	

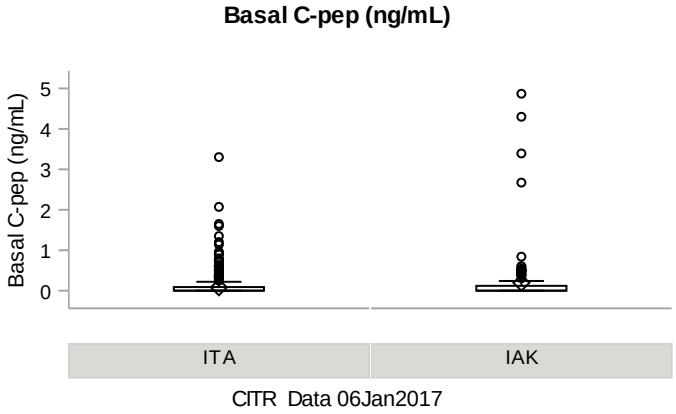
* p < 0.05 ** p < 0.01 *** p < 0.001

Significant trends in recipient laboratory values at first infusion from table above

By ITA or IAK

By Era





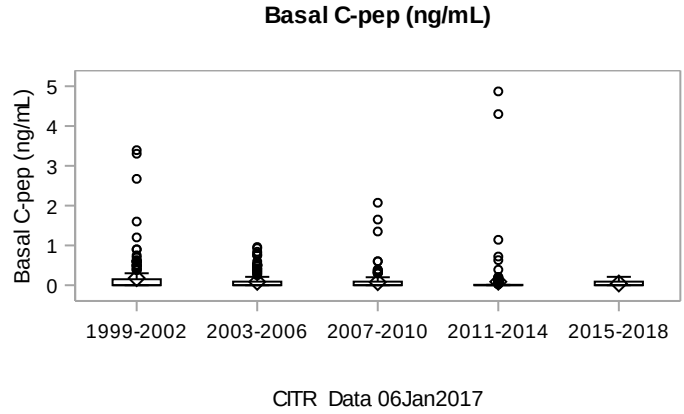
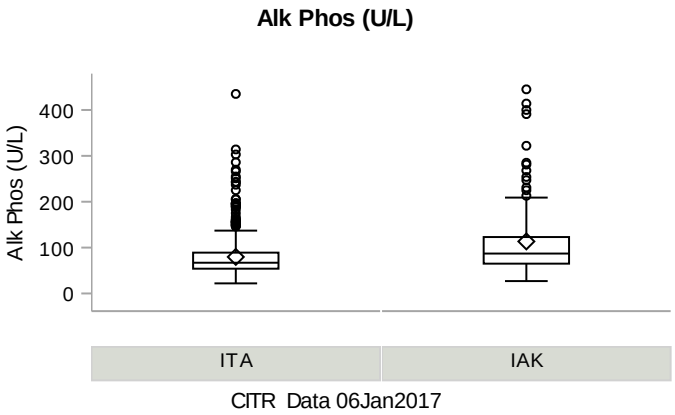
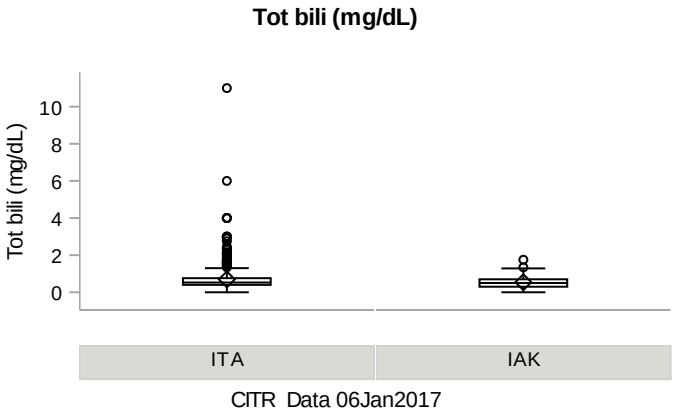
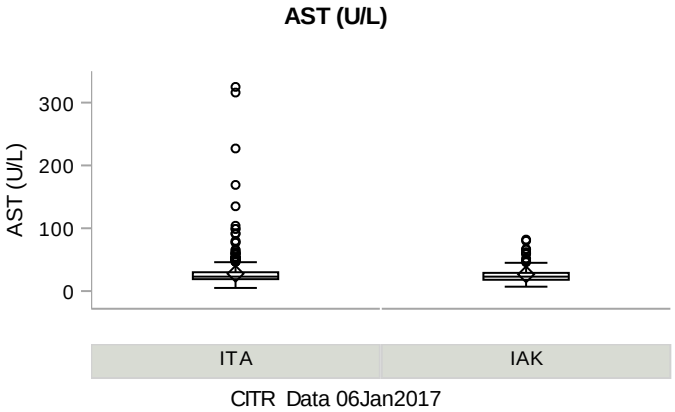
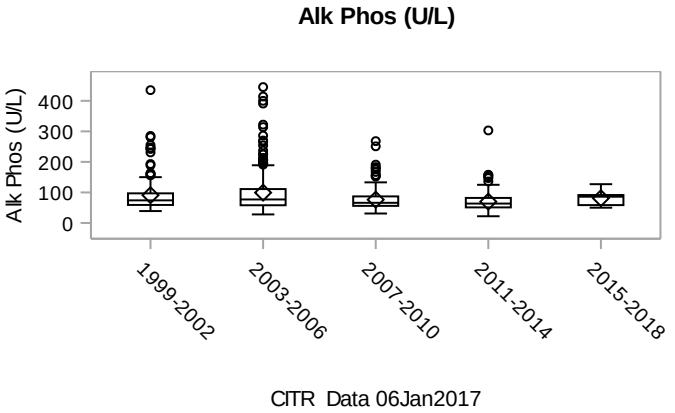


Exhibit 2-9 (continued)
Recipient Laboratory Values at First Infusion









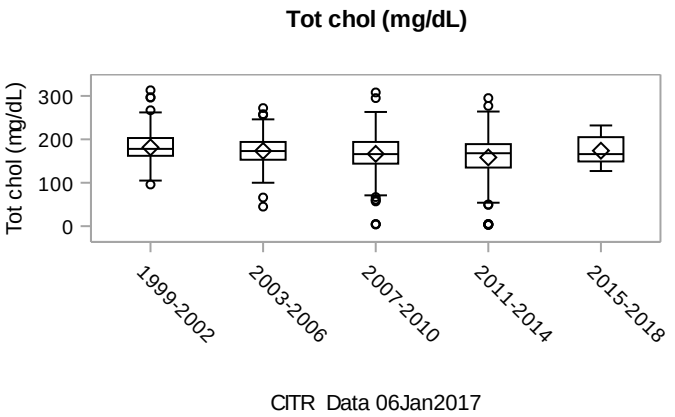
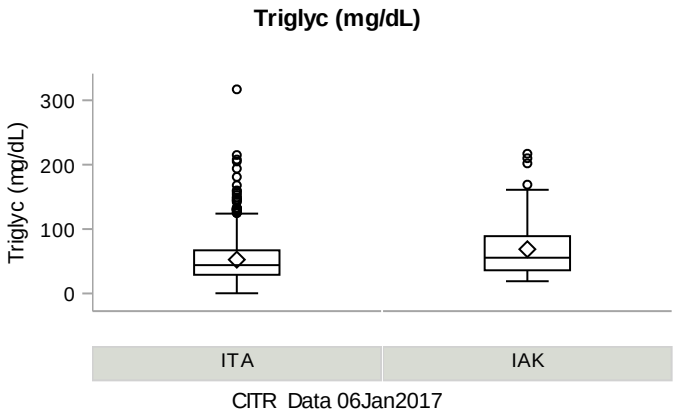
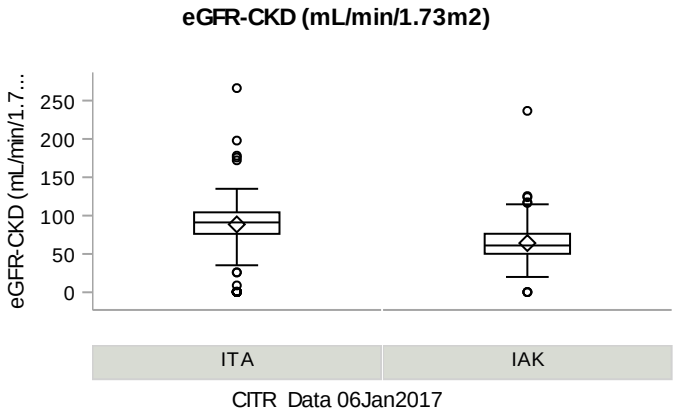


Exhibit 2-9 (continued)
Recipient Laboratory Values at First Infusion





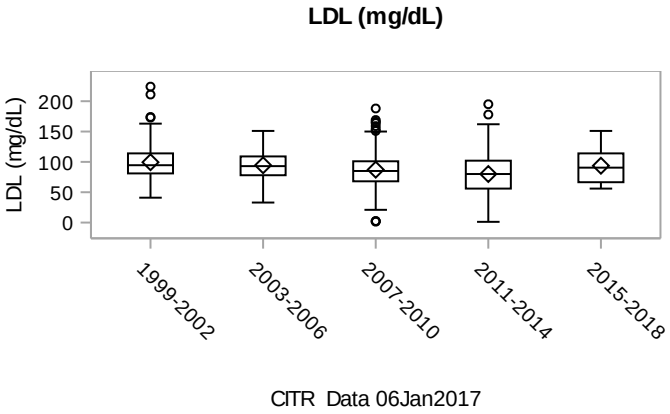


Exhibit 2-10
Donor Demographics (per Infusion)

	ITA			IAK			
	N	Mean	StdErr	N	Mean	StdErr	p
Age (yrs)	1188	44.0	0.3	209	44.1	0.8	

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	p
Age (yrs)	284	43.8	0.7	393	43.5	0.6	367	44.4	0.6	339	44.3	0.6	14	45.9	3.7	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Gender	**Female**	508	38.5	101	35.2		132	37.3	186	38.7	147	37.8	142	38.5	2	15.4	
	Mixed	58	4.4	13	4.5		15	4.2	23	4.8	30	7.7	3	0.8		0.0	
	Male	753	57.1	173	60.3		207	58.5	272	56.5	212	54.5	224	60.7	11	84.6	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gender	Missing	431	24.6	45	13.6	67	15.9	90	15.8	61	13.6	237	39.1	21	61.8
	Available	1319	75.4	287	86.4	354	84.1	481	84.2	389	86.4	369	60.9	13	38.2

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Race	**White**	803	89.0	117	87.3		221	92.1	239	86.0	214	89.2	242	88.3	4	100.0	
	Mixed	5	0.6		0.0			0.0	3	1.1	1	0.4	1	0.4		0.0	
	Non-white	94	10.4	17	12.7		19	7.9	36	12.9	25	10.4	31	11.3		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Race	Missing	848	48.5	198	59.6	181	43.0	293	51.3	210	46.7	332	54.8	30	88.2
	Available	902	51.5	134	40.4	240	57.0	278	48.7	240	53.3	274	45.2	4	11.8

Exhibit 2-10 (continued)
Donor Demographics (per Infusion)

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Ethnicity	**Non-Hispanic**	225	82.1	25	65.8		81	98.8	49	71.0	70	76.9	48	70.6	2	100.0	
	Hispanic	49	17.9	13	34.2		1	1.2	20	29.0	21	23.1	20	29.4		0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	
Ethnicity	Missing	1476	84.3	294	88.6		339	80.5	502	87.9	359	79.8	538	88.8	32	94.1	
	Available	274	15.7	38	11.4		82	19.5	69	12.1	91	20.2	68	11.2	2	5.9	

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

Exhibit 2-11
Donor Characteristics

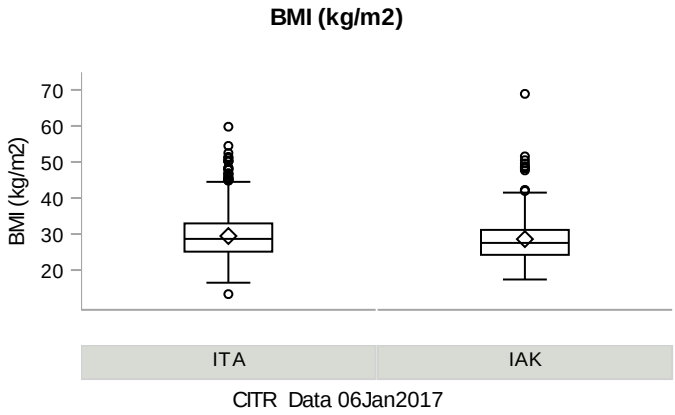
	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Donor age (yrs)	1188	44.0	0.3	209	44.1	0.8	
Weight (kg)	1451	88.1	0.5	288	86.5	1.2	
Height (cm)	1449	172.9	0.3	288	173.8	0.5	
Body Mass Index(kg/m2)	1449	29.4	0.2	288	28.6	0.4	*

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Donor age (yrs)	284	43.8	0.7	393	43.5	0.6	367	44.4	0.6	339	44.3	0.6	14	45.9	3.7	
Weight (kg)	354	83.9	1.1	489	87.7	0.9	418	90.9	1.0	464	88.7	0.9	14	78.9	4.6	**
Height (cm)	352	172.9	0.5	489	173.6	0.4	418	173.1	0.5	464	172.6	0.5	14	174.9	1.8	
Body Mass Index(kg/m2)	352	28.0	0.3	489	29.1	0.3	418	30.2	0.3	464	29.7	0.3	14	25.6	1.1	***

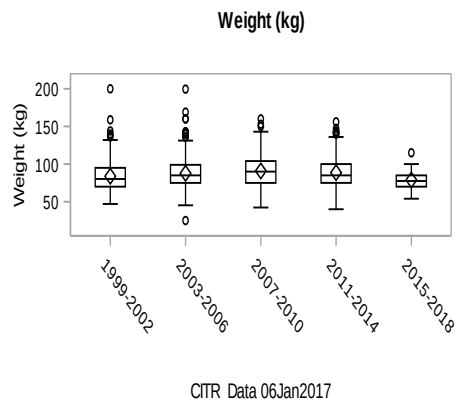
* $p < 0.05$ ** $p < 0.01$ *** $p < 0.001$

Significant trends in donor characteristics from table above

By ITA or IAK



By Era



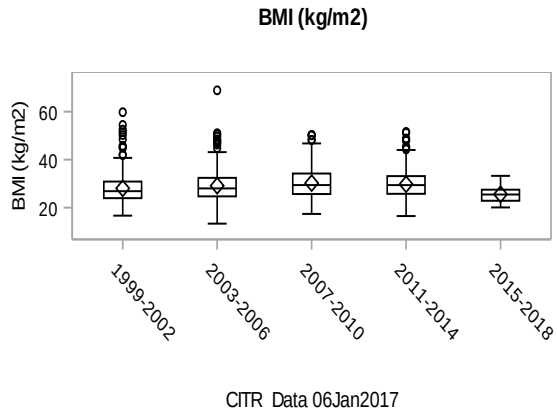
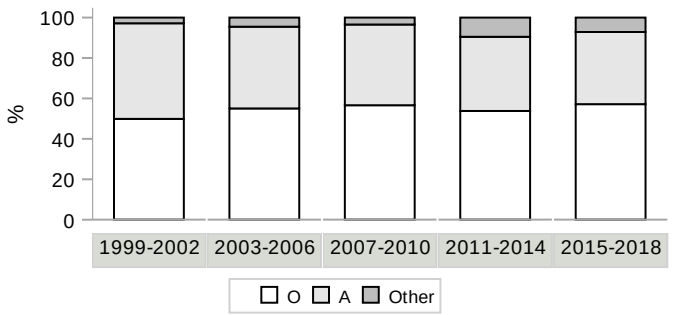


Exhibit 2-11 (continued)
Donor Characteristics

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Donor Blood Type	**O**	767	53.3	166	57.4		177	49.9	268	55.0	231	56.6	249	53.8	8	57.1	
	A	591	41.1	112	38.8		168	47.3	197	40.5	163	40.0	170	36.7	5	35.7	*
	Other	80	5.6	11	3.8		10	2.8	22	4.5	14	3.4	44	9.5	1	7.1	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Donor Blood Type	Missing	312	17.8	43	13.0	66	15.7	84	14.7	42	9.3	143	23.6	20	58.8
	Available	1438	82.2	289	87.0	355	84.3	487	85.3	408	90.7	463	76.4	14	41.2

Donor Blood Type



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		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Hx Hypertension	**No**	856	65.8	144	64.9		174	64.7	290	65.8	238	62.6	287	68.7	11	78.6	
	Yes	444	34.2	78	35.1		95	35.3	151	34.2	142	37.4	131	31.3	3	21.4	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hx Hypertension	Missing	450	25.7	110	33.1	152	36.1	130	22.8	70	15.6	188	31.0	20	58.8
	Available	1300	74.3	222	66.9	269	63.9	441	77.2	380	84.4	418	69.0	14	41.2

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Hx Alcohol	**No**	1094	86.1	190	86.4		215	83.3	369	84.8	329	87.7	358	87.7	13	92.9	
	Yes	176	13.9	30	13.6		43	16.7	66	15.2	46	12.3	50	12.3	1	7.1	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hx Alcohol	Missing	480	27.4	112	33.7	163	38.7	136	23.8	75	16.7	198	32.7	20	58.8
	Available	1270	72.6	220	66.3	258	61.3	435	76.2	375	83.3	408	67.3	14	41.2

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

Exhibit 2-11 (continued)
Donor Characteristics

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Hx Diabetes	**No**	1351	99.6	226	99.6		319	99.7	453	99.8	380	100.0	411	98.8	14	100.0	
	Yes	6	0.4	1	0.4		1	0.3	1	0.2		0.0	5	1.2		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hx Diabetes	Missing	393	22.5	105	31.6	101	24.0	117	20.5	70	15.6	190	31.4	20	58.8
	Available	1357	77.5	227	68.4	320	76.0	454	79.5	380	84.4	416	68.6	14	41.2

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

Exhibit 2-12
Characteristics of Hospitalization and Organ Procurement

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Time from admission to brain death (hrs)	739	57.3	2.7	121	49.5	4.7	
Time from cross clamp to pancreas recovery (hrs)	692	0.9	0.0	162	0.9	0.0	
Cold ischemia time (hrs)	891	7.8	0.2	157	7.7	0.7	

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Time from admission to brain death (hrs)	205	47.4	4.2	301	52.2	3.8	195	58.8	4.3	155	73.0	7.7	4	29.0	7.0	***
Time from cross clamp to pancreas recovery (hrs)	180	0.6	0.0	356	0.9	0.1	164	1.0	0.1	142	1.1	0.1	12	0.9	0.1	***
Cold ischemia time (hrs)	297	7.4	0.2	407	7.2	0.2	205	8.0	0.6	125	9.4	0.7	14	11.2	2.0	***

		ITA		IAK		
		N	%	N	%	p
Cause of death	**CVA**	818	58.8	163	66.0	
	Trauma	385	27.7	58	23.5	
	Other	187	13.5	26	10.5	

		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	N	%	N	%	N	%	p
Cause of death	**CVA**	195	59.5	280	60.1	243	61.4	255	58.9	8	57.1	
	Trauma	89	27.1	133	28.5	111	28.0	104	24.0	6	42.9	
	Other	44	13.4	53	11.4	42	10.6	74	17.1	-	0.0	

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

Significant trends in characteristics of hospitalization and organ procurement from table above

By ITA or IAK	By Era

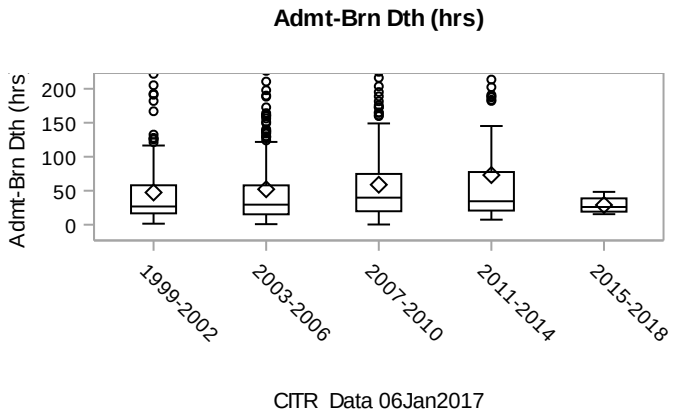
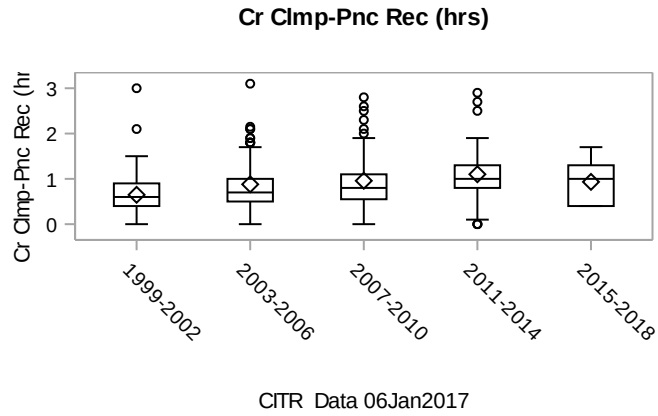
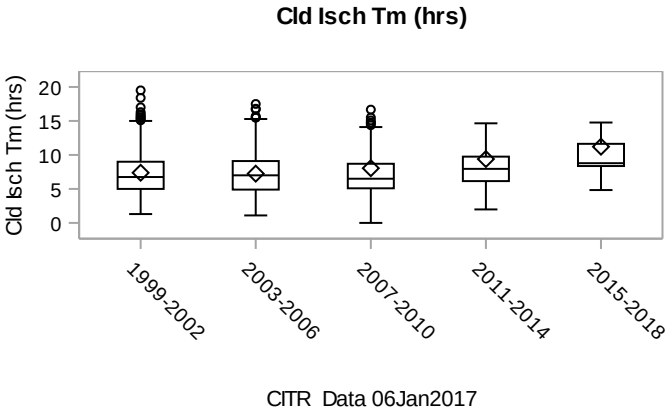


Exhibit 2-12 (continued)
Characteristics of Hospitalization and Organ Procurement





		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Vasopressors used	**No**	69	5.6	12	5.8		10	3.4	10	2.2	26	8.1	35	9.9		0.0	***
	Yes	1164	94.4	195	94.2		288	96.6	445	97.8	295	91.9	318	90.1	13	100.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Vasopressors used	**Missing**	517	29.5	125	37.7	123	29.2	116	20.3	129	28.7	253	41.7	21	61.8
	Available	1233	70.5	207	62.3	298	70.8	455	79.7	321	71.3	353	58.3	13	38.2

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

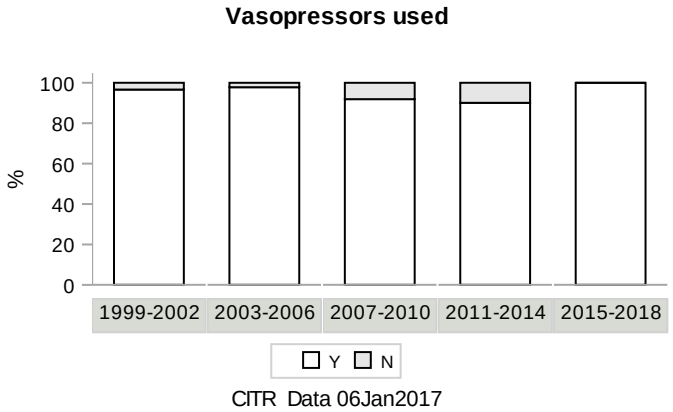
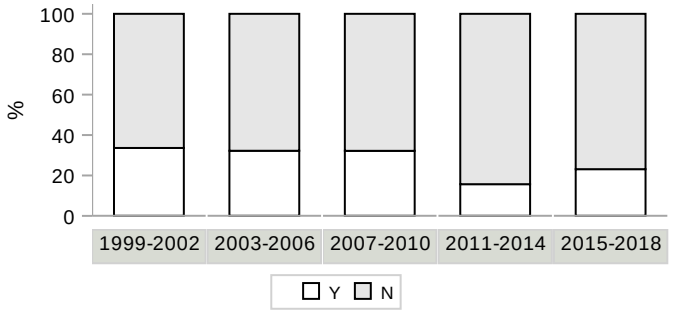


Exhibit 2-12 (continued)
Characteristics of Hospitalization and Organ Procurement

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Transfusions during hospitalization	**No**	638	70.3	110	71.0		174	66.4	278	67.8	135	67.8	151	84.4	10	76.9	***
	Yes	270	29.7	45	29.0		88	33.6	132	32.2	64	32.2	28	15.6	3	23.1	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Transfusions during hospitalization	Missing	842	48.1	177	53.3	159	37.8	161	28.2	251	55.8	427	70.5	21	61.8
	Available	908	51.9	155	46.7	262	62.2	410	71.8	199	44.2	179	29.5	13	38.2

Transfus during hosp



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		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Transfusions intraoperatively	**No**	633	94.1	108	93.9		206	92.0	334	94.9	141	95.9	58	92.1	2	100.0	
	Yes	40	5.9	7	6.1		18	8.0	18	5.1	6	4.1	5	7.9		0.0	

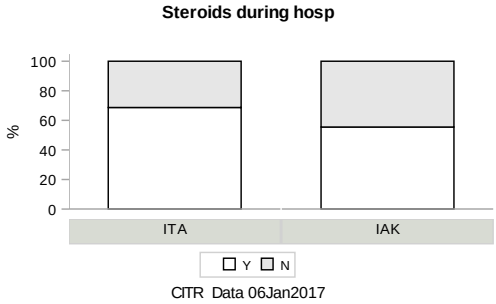
Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Transfusions intraoperatively	Missing	1077	61.5	217	65.4	197	46.8	219	38.4	303	67.3	543	89.6	32	94.1
	Available	673	38.5	115	34.6	224	53.2	352	61.6	147	32.7	63	10.4	2	5.9

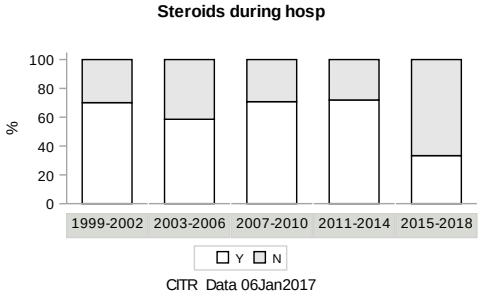
Exhibit 2-12 (continued)
Characteristics of Hospitalization and Organ Procurement

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Steroids given to donor during hospitalization	**No**	253	31.3	65	44.5	**	52	29.9	133	41.4	78	29.2	53	28.0	2	66.7	**
	Yes	555	68.7	81	55.5		122	70.1	188	58.6	189	70.8	136	72.0	1	33.3	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Steroids given to donor during hospitalization	Missing	942	53.8	186	56.0	247	58.7	250	43.8	183	40.7	417	68.8	31	91.2
	Available	808	46.2	146	44.0	174	41.3	321	56.2	267	59.3	189	31.2	3	8.8

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





		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Insulin given to donor during hospitalization	**No**	581	52.6	94	50.8		170	66.4	228	54.5	146	42.7	129	47.6	2	66.7	***
	Yes	524	47.4	91	49.2		86	33.6	190	45.5	196	57.3	142	52.4	1	33.3	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Insulin given to donor during hospitalization	Missing	645	36.9	147	44.3	165	39.2	153	26.8	108	24.0	335	55.3	31	91.2
	Available	1105	63.1	185	55.7	256	60.8	418	73.2	342	76.0	271	44.7	3	8.8

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

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

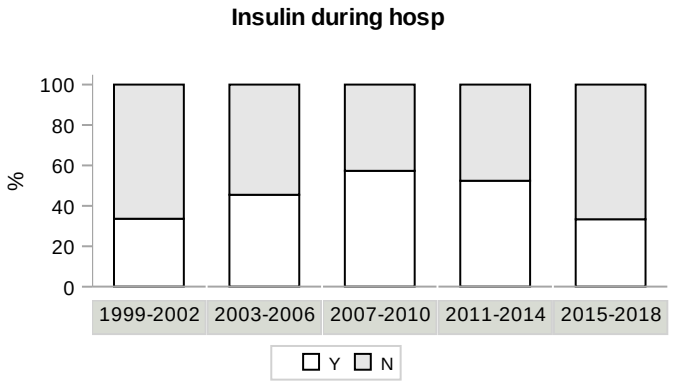


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Exhibit 2-13
Donor Serology

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HIV	NEG	1395	100.0	243	100.0		330	100.0	463	100.0	399	100.0	432	100.0	14	100.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HIV	Missing	355	20.3	89	26.8	91	21.6	108	18.9	51	11.3	174	28.7	20	58.8
	Available	1395	79.7	243	73.2	330	78.4	463	81.1	399	88.7	432	71.3	14	41.2

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HTLV	NEG	1078	100.0	196	100.0		285	100.0	418	100.0	306	100.0	254	100.0	11	100.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HTLV	Missing	672	38.4	136	41.0	136	32.3	153	26.8	144	32.0	352	58.1	23	67.6
	Available	1078	61.6	196	59.0	285	67.7	418	73.2	306	68.0	254	41.9	11	32.4

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
VDRL	NEG	1086	99.8	216	100.0		294	100.0	427	99.8	320	100.0	259	99.6	2	100.0	
	POS	2	0.2	-	0.0		-	0.0	1	0.2	-	0.0	1	0.4	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
VDRL	Missing	662	37.8	116	34.9	127	30.2	143	25.0	130	28.9	346	57.1	32	94.1
	Available	1088	62.2	216	65.1	294	69.8	428	75.0	320	71.1	260	42.9	2	5.9

Exhibit 2-13 (continued)
Donor Serology

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
CMV	NEG	605	44.9	109	45.2		124	39.5	204	45.8	170	43.7	211	49.4	5	38.5	
	POS	742	55.1	132	54.8		190	60.5	241	54.2	219	56.3	216	50.6	8	61.5	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV	Missing	403	23.0	91	27.4	107	25.4	126	22.1	61	13.6	179	29.5	21	61.8
	Available	1347	77.0	241	72.6	314	74.6	445	77.9	389	86.4	427	70.5	13	38.2

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

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HBSag	NEG	1382	99.9	239	100.0		325	100.0	462	99.8	392	100.0	429	99.8	13	100.0	
	POS	2	0.1	-	0.0		-	0.0	1	0.2	-	0.0	1	0.2	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HBSag	Missing	366	20.9	93	28.0	96	22.8	108	18.9	58	12.9	176	29.0	21	61.8
	Available	1384	79.1	239	72.0	325	77.2	463	81.1	392	87.1	430	71.0	13	38.2

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HBC	NEG	1306	99.2	226	99.6		301	98.7	457	99.6	366	98.7	395	100.0	13	100.0	
	POS	10	0.8	1	0.4		4	1.3	2	0.4	5	1.3	-	0.0	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HBC	Missing	434	24.8	105	31.6	116	27.6	112	19.6	79	17.6	211	34.8	21	61.8
	Available	1316	75.2	227	68.4	305	72.4	459	80.4	371	82.4	395	65.2	13	38.2

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
HCV	NEG	1264	99.9	210	99.5		320	99.7	454	100.0	366	99.7	329	100.0	5	100.0	
	POS	1	0.1	1	0.5		1	0.3	-	0.0	1	0.3	-	0.0	-	0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
HCV	Missing	485	27.7	121	36.4	100	23.8	117	20.5	83	18.4	277	45.7	29	85.3
	Available	1265	72.3	211	63.6	321	76.2	454	79.5	367	81.6	329	54.3	5	14.7

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

Exhibit 2-14
Donor Laboratory Data

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Serum creatinine (mg/dL)	1111	1.1	0.0	231	1.1	0.1	
BUN (mg/dL)	774	15.3	0.3	211	15.1	0.6	
Total bilirubin (mg/dL)	994	0.9	0.0	215	0.8	0.0	
AST (U/L)	1048	74.2	5.6	223	70.9	11.3	
ALT (U/L)	1144	64.9	4.5	227	59.3	8.5	
Serum lipase (mKat/L)	982	1.0	0.1	190	0.9	0.1	
Serum amylase (mKat/L)	1010	2.2	0.1	217	2.1	0.2	
Minimum pre-insulin blood glucose (mg/dL)	902	128.4	1.3	189	127.7	2.7	
Maximum blood glucose (mg/dL)	991	222.0	2.5	195	237.2	6.0	*

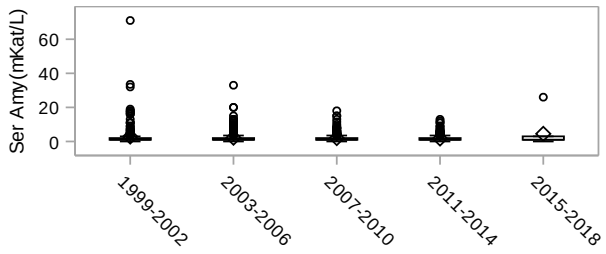
	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Serum creatinine (mg/dL)	250	1.2	0.1	432	1.2	0.0	333	1.1	0.0	313	1.1	0.0	14	0.9	0.1	
BUN (mg/dL)	190	15.1	0.6	325	14.8	0.5	238	16.2	0.6	219	15.5	0.7	13	11.8	1.1	
Total bilirubin (mg/dL)	206	0.8	0.0	358	0.9	0.0	326	0.8	0.0	305	0.8	0.0	14	1.0	0.2	
AST (U/L)	214	98.6	20.4	368	62.5	5.6	342	82.0	10.3	333	61.5	6.5	14	66.4	12.0	
ALT (U/L)	215	78.0	17.1	373	50.3	4.3	369	71.1	8.2	400	63.5	5.4	14	40.6	10.6	
Serum lipase (mKat/L)	239	0.9	0.1	354	1.1	0.1	291	1.1	0.1	275	1.0	0.1	13	0.5	0.2	
Serum amylase (mKat/L)	246	2.9	0.4	421	2.2	0.1	301	2.0	0.1	251	1.7	0.1	8	4.5	3.1	**
Minimum pre-insulin blood glucose (mg/dL)	268	129.4	2.3	389	124.7	1.9	175	125.0	2.9	247	135.2	2.6	12	124.5	11.9	
Maximum blood glucose (mg/dL)	237	245.6	6.3	413	226.3	3.9	241	219.6	4.5	282	208.6	4.2	13	217.6	18.7	***

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

Significant trends in donor laboratory data
from table above

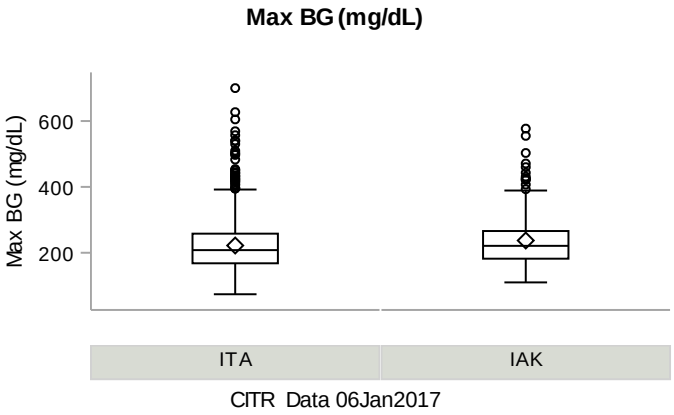
By ITA or IAK	By Era

Ser Amy(mKat/L)



CITR Data 06Jan2017

Exhibit 2-14 (continued)
Donor Laboratory Data



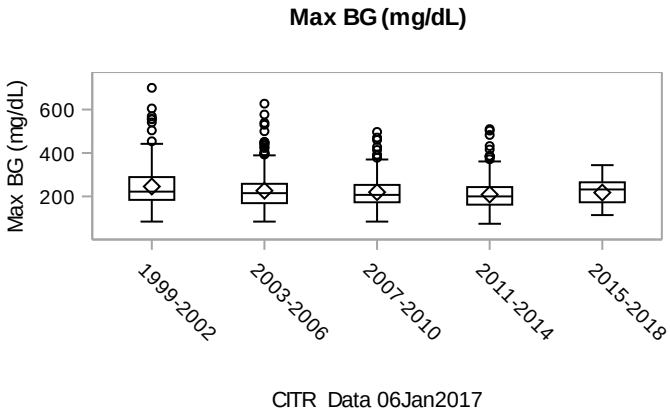


Exhibit 2-15
Organ Crossmatch Results

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Positive cross match	**No**	665	97.2	169	98.3		177	99.4	305	96.5	198	97.1	141	97.2	13	100.0	
	Yes	19	2.8	3	1.7		1	0.6	11	3.5	6	2.9	4	2.8		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Positive cross match	**Missing**	1066	60.9	160	48.2	243	57.7	255	44.7	246	54.7	461	76.1	21	61.8
	Available	684	39.1	172	51.8	178	42.3	316	55.3	204	45.3	145	23.9	13	38.2

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

Chapter 3
Pancreas Procurement, Islet Processing, and Infusion Characteristics

Table of Contents

Introduction

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

For the roughly 12% 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 and by era (1999-2002, 2003-2006, 2007-2010, 2011-2014, and 2015-2018).

Exhibits 3-5 to 3-6 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 3-5, while those that are continuous are shown as correlations with the islet product characteristics in Exhibit 3-6.

Over the duration of the Registry, the proportion of islet processing centers that were unrelated to the islet transplant center rose appreciably from 0% in 1999-2002 to 15% in 2007-2010 and has since declined, while the proportion of procurement teams unrelated to the islet transplant center has declined steadily from 31% in 1999-2002 to 9% in 2015-2018 (p. 3-3). The detailed patterns regarding transplant type, continent and other factors will be described in a separate report.

Islet processing practices including preservation and digestion have undergone substantial evolution over the last decade particularly. The CITR data collection system is currently being updated to allow collection of this detailed information. Hence, these factors have not been analyzed in this Annual Report. These will be the focus of a separate detailed analysis.

The following trends are observed among pancreas procurement and islet processing practices, transplant procedures, and final islet products:

- Islet preparations were cultured more frequently in the recent eras (100% in 2015-2018 vs. 35% in 1999-2002) and mean
  culture time has increased over the eras (Exhibit 3-1A).
- Total cell volume infused has declined appreciably over the eras, while total IEQs and IEQ/Kg recipient have remained remarkably stable (Exhibit 3-4A).
- Total Beta cells and β-cells/kg recipient have increased substantially over the eras, and were higher for IAK (Exhibit 3-4A).
- Endotoxin (both total and /kg) has declined sharply over the eras (Exhibit 3-4A).
- Stimulation index was higher for ITA than IAK, and has declined over the eras (Exhibit 3-4A).
- For ITA, total cell volume and IEQs/kg recipient have decreased notably with subsequent infusions (Exhibit 3-4B).
- For IAK, total IEQs/recipient has declined notably with subsequent infusion sequence (Exhibit 3-4B).
- Other differences that are nominally statistically significant may not indicate any clinically important trends.
-

Exhibit 3-1A
Islet Processing Summary

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Procurement Team	**Unrelated**	310	27.4	45	19.7		81	30.6	157	32.6	73	23.4	42	15.2	2	8.7	
	Procurement/ transplant centers related	765	67.7	171	75.0	*	170	64.2	301	62.4	226	72.4	218	79.0	21	91.3	***
	Mixed	26	2.3	4	1.8		7	2.6	14	2.9	8	2.6	1	0.4		0.0	
	Unknown	29	2.6	8	3.5		7	2.6	10	2.1	5	1.6	15	5.4		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Procurement Team	Missing	632	35.9	106	31.7	65	19.7	92	16.0	145	31.7	384	58.2	52	69.3
	Available	1130	64.1	228	68.3	265	80.3	482	84.0	312	68.3	276	41.8	23	30.7

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Islet processing center	**Processing/transplant centers related**	1087	93.1	258	95.6		265	100.0	493	98.2	322	85.0	243	90.7	22	95.7	***
	Unrelated	78	6.7	11	4.1			0.0	9	1.8	55	14.5	24	9.0	1	4.3	
	Mixed	2	0.2	1	0.4			0.0		0.0	2	0.5	1	0.4		0.0	

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Islet processing center	Missing	595	33.8	64	19.2	65	19.7	72	12.5	78	17.1	392	59.4	52	69.3
	Available	1167	66.2	270	80.8	265	80.3	502	87.5	379	82.9	268	40.6	23	30.7

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

Exhibit 3-1A (continued)
Islet Processing Summary

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Cultured	**Islets cultured >=6 hrs**	700	70.4	124	74.3		82	35.3	261	62.4	196	88.7	263	97.8	22	100.0	***
	None	295	29.6	43	25.7		150	64.7	157	37.6	25	11.3	6	2.2		0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	
Cultured	Missing	767	43.5	167	50.0		98	29.7	156	27.2	236	51.6	391	59.2	53	70.7	
	Available	995	56.5	167	50.0		232	70.3	418	72.8	221	48.4	269	40.8	22	29.3	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	p
Gradient type	**Continuous**	953	89.4	174	87.4		176	79.6	379	82.8	268	95.7	283	99.6	21	95.5	
	Discontinuous	33	3.1	16	8.0		19	8.6	28	6.1	1	0.4	1	0.4		0.0	
	Both	65	6.1	6	3.0	**	24	10.9	39	8.5	7	2.5		0.0	1	4.5	***
	Mixed	14	1.3	3	1.5		2	0.9	11	2.4	4	1.4		0.0		0.0	
	None	1	0.1		0.0			0.0	1	0.2		0.0		0.0		0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	
Gradient type	Missing	696	39.5	135	40.4		109	33.0	116	20.2	177	38.7	376	57.0	53	70.7	
	Available	1066	60.5	199	59.6		221	67.0	458	79.8	280	61.3	284	43.0	22	29.3	

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

Exhibit 3-1B
Final Islet Preparation Microbiology

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gram stain	**Negative**	971	99.8	156	100.0	206	100.0	387	100.0	230	100.0	282	99.3	22	100.0
	Positive	2	0.2	-	0.0	-	0.0	-	0.0	-	0.0	2	0.7	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Gram stain	Missing	789	44.8	178	53.3	124	37.6	187	32.6	227	49.7	376	57.0	53	70.7
	Available	973	55.2	156	46.7	206	62.4	387	67.4	230	50.3	284	43.0	22	29.3

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Aerobic culture	**Negative**	1040	98.4	188	98.4	220	97.3	441	99.3	278	97.9	269	98.5	20	95.2
	Positive	17	1.6	3	1.6	6	2.7	3	0.7	6	2.1	4	1.5	1	4.8

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Aerobic culture	Missing	705	40.0	143	42.8	104	31.5	130	22.6	173	37.9	387	58.6	54	72.0
	Available	1057	60.0	191	57.2	226	68.5	444	77.4	284	62.1	273	41.4	21	28.0

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anaerobic culture	**Negative**	929	99.0	164	100.0	170	97.7	356	99.7	275	100.0	272	98.9	20	95.2
	Positive	9	1.0	-	0.0	4	2.3	1	0.3	-	0.0	3	1.1	1	4.8

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anaerobic culture	Missing	824	46.8	170	50.9	156	47.3	217	37.8	182	39.8	385	58.3	54	72.0
	Available	938	53.2	164	49.1	174	52.7	357	62.2	275	60.2	275	41.7	21	28.0

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Fungal Culture	**Negative**	1012	98.7	185	98.4	221	100.0	448	99.1	263	99.6	246	95.7	19	100.0
	Positive	13	1.3	3	1.6	-	0.0	4	0.9	1	0.4	11	4.3	-	0.0

Exhibit 3-1B (continued)
Final Islet Preparation Microbiology

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Fungal Culture	Missing	737	41.8	146	43.7	109	33.0	122	21.3	193	42.2	403	61.1	56	74.7
	Available	1025	58.2	188	56.3	221	67.0	452	78.7	264	57.8	257	38.9	19	25.3

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014	
		N	%	N	%	N	%	N	%	N	%	N	%
Mycoplasma	**Negative**	632	99.8	56	100.0	170	99.4	247	100.0	122	100.0	149	100.0
	Positive	1	0.2	-	0.0	1	0.6	-	0.0	-	0.0	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mycoplasma	Missing	1129	64.1	278	83.2	159	48.2	327	57.0	335	73.3	511	77.4	75	100.0
	Available	633	35.9	56	16.8	171	51.8	247	43.0	122	26.7	149	22.6	-	0.0

Exhibit 3-2
Cold Ischemia Information

	Transplant type						p	Era															p
	ITA			IAK				1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SD	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)	695	0.9	1.2	162	0.9	0.4		138	0.6	0.4	353	0.9	1.4	186	0.9	1.1	160	1.1	0.9	20	1.0	0.5	**
Duration of cold ischemia (hrs)	894	7.8	4.9	157	7.7	8.2		228	7.3	3.4	421	7.2	3.2	244	8.2	7.9	135	9.0	7.8	23	10.7	7.2	***
Time from brain death to pancreas recovery (hrs)	640	19.7	8.4	145	18.4	9.2		128	17.0	7.0	313	19.3	8.7	169	21.2	9.3	155	20.3	8.3	20	18.5	7.0	**
Culture time (hrs)	994	20.1	18.0	167	21.2	17.8		232	11.0	17.5	418	17.6	17.9	221	26.5	17.6	268	27.5	14.5	22	18.6	3.5	***

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

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

Infusions	Transplant type						p	Era															p
	ITA			IAK				1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	536	7.3	0.2	91	7.3	0.6		137	8.5	0.4	202	8.2	0.3	127	7.0	0.4	146	5.3	0.3	15	5.3	0.9	***
Total islet particles (final preparation)	454	793.8	19.3	96	788.7	41.2		125	922.4	43.1	185	847.2	27.5	102	711.5	37.8	131	667.4	30.9	7	581.5	130.1	***
Embedded islets (%)	396	16.2	0.7	57	15.2	1.7		92	14.1	1.5	140	16.3	1.3	85	15.7	1.6	129	17.1	1.2	7	22.2	7.2	
Islet equivalents (1000s)	561	824.4	16.8	97	757.9	33.9		134	897.4	37.8	189	864.7	28.0	125	829.4	35.5	201	713.4	23.6	9	584.1	105.9	***
Islet equivalents(1000s)/kg recipient	597	13.0	0.2	136	12.0	0.4		155	14.1	0.5	220	13.6	0.4	177	12.2	0.4	168	11.5	0.4	13	11.7	1.9	***
Beta cells (x10^6)	205	421.7	22.4	22	426.5	76.9		60	456.3	42.0	81	436.9	37.4	26	469.8	66.5	60	347.6	37.9	0	-	-	
Beta cells/kg recipient weight	167	6.4	0.4	15	8.5	1.8		57	6.9	0.6	75	6.8	0.7	16	5.5	0.9	34	6.1	0.8	0	-	-	
Insulin content (1000s micrograms)	154	6.2	0.3	16	5.3	0.8		65	6.4	0.5	91	6.0	0.4	7	5.1	1.1	6	5.5	1.3	1	8.1	-	
Total Endotoxin units	488	30.4	3.9	101	28.8	6.3		119	46.4	7.3	190	52.2	8.8	153	10.3	2.5	119	5.7	1.7	8	5.1	3.9	***
Endotoxin units/kg recipient weight	455	0.5	0.1	95	0.5	0.1		113	0.8	0.1	182	0.8	0.1	143	0.2	0.0	106	0.1	0.0	6	0.1	0.1	***
Islet potency: Stimulation index	454	3.0	0.1	89	2.8	0.2		129	3.4	0.3	186	3.2	0.2	97	2.7	0.2	126	2.5	0.1	5	2.4	0.3	***
Islet viability	530	89.7	0.3	102	91.6	0.5	**	123	90.7	0.5	200	91.1	0.4	115	89.9	0.5	185	88.4	0.4	9	90.7	1.4	***
Purity	452	62.0	0.7	104	60.7	1.5		132	60.5	1.3	206	62.1	1.0	102	64.0	1.5	109	60.4	1.3	7	61.2	4.7	
Total DNA	237	20.1	1.2	26	16.9	2.6		64	17.1	1.8	97	20.7	1.9	32	20.3	3.1	69	21.0	2.1	1	3.2	-	

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

Exhibit 3-4A
Islet Product Characteristics (Per Infusion)

Infusions	Transplant type						p	Era															p
	ITA			IAK				1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	1071	3.6	0.1	168	4.0	0.2	*	227	4.0	0.1	426	3.9	0.1	254	3.8	0.2	286	3.1	0.1	46	3.1	0.2	***
Total islet particles (final preparation)	924	390.0	5.4	181	418.3	14.3	*	204	416.1	12.4	386	413.2	8.8	226	363.3	10.0	269	382.6	10.3	20	335.8	40.7	**
Embedded islets (%)	780	16.3	0.6	83	14.9	1.4		137	13.5	1.5	274	16.6	1.2	187	16.9	1.3	247	16.3	0.9	18	18.5	4.1	
Islet equivalents (1000s)	1103	419.3	4.4	183	401.7	12.7		218	419.2	10.4	391	411.0	7.8	261	420.8	8.8	394	420.4	7.8	22	383.9	21.5	
Islet equivalents (1000s)/kg recipient	1205	6.5	0.1	245	6.7	0.2		252	6.6	0.2	470	6.5	0.1	343	6.6	0.1	344	6.4	0.1	41	6.5	0.3	
Beta cells (x10^6)	362	238.8	10.7	33	284.3	32.3		91	191.4	18.4	140	240.0	16.1	60	293.7	28.2	104	261.4	21.5	0	-	-	**
Beta cells/kg recipient weight	299	3.6	0.2	24	5.3	0.6	*	85	3.0	0.3	128	3.8	0.3	46	3.9	0.4	64	4.5	0.4	0	-	-	**
Insulin content (1000s micrograms)	275	3.5	0.1	29	2.9	0.4		105	3.4	0.2	170	3.6	0.2	17	2.2	0.3	10	2.8	0.5	2	6.4	1.7	
Total Endotoxin units	902	16.4	1.6	171	17.0	3.1		161	27.8	4.6	390	27.5	3.1	290	5.6	1.2	210	4.1	1.1	22	2.1	1.4	***
Endotoxin units/kg recipient weight	847	0.3	0.0	162	0.3	0.1		153	0.5	0.1	372	0.4	0.0	272	0.1	0.0	192	0.1	0.0	20	0.0	0.0	***
Islet potency: Stimulation index	877	3.1	0.1	149	2.8	0.2		208	3.6	0.3	376	3.1	0.2	204	2.5	0.1	228	2.8	0.2	10	2.0	0.2	***
Islet viability	1028	89.5	0.2	192	91.3	0.4	***	169	90.9	0.5	435	91.3	0.3	247	89.2	0.4	346	87.7	0.4	23	91.2	1.0	***
Purity	874	61.9	0.6	197	59.9	1.3		182	60.2	1.4	451	62.0	0.9	211	63.1	1.1	207	60.2	1.1	20	61.2	3.0	
Total DNA	446	10.7	0.5	42	10.5	1.4		97	6.1	0.7	184	10.1	0.9	80	12.0	1.1	125	14.2	1.0	2	5.5	2.3	***

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

Exhibit 3-4B
Islet Product Characteristics by Infusion Sequence

Transplant type ITA

	Infusion Number									p
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	500	3.8	0.1	392	3.6	0.1	179	3.3	0.1	*
Total islet particles (final preparation)	434	397.5	8.4	340	387.7	8.5	150	373.8	11.9	
Embedded islets (%)	366	16.3	0.9	285	16.3	1.1	129	16.1	1.6	
Islet equivalents (1000s)	535	424.7	6.6	405	415.3	7.0	163	411.4	10.9	
Islet equivalents(1000s)/kg recipient	592	6.7	0.1	435	6.3	0.1	178	6.1	0.2	**
Beta cells (x10^6)	170	233.5	16.1	137	231.7	16.5	55	272.9	27.5	
Beta cells/kg recipient weight	135	3.5	0.3	115	3.5	0.3	49	3.9	0.4	
Insulin content (1000s micrograms)	140	3.6	0.2	106	3.2	0.2	29	4.0	0.4	
Total Endotoxin units	453	13.6	1.6	320	19.2	3.2	129	19.4	5.2	
Endotoxin units/kg recipient weight	425	0.2	0.0	302	0.3	0.0	120	0.3	0.1	
Islet potency: Stimulation index	425	3.0	0.1	316	3.3	0.2	136	2.7	0.2	
Islet viability	492	89.8	0.3	374	89.7	0.3	162	88.6	0.7	
Purity	412	62.1	0.8	319	62.0	1.0	143	61.3	1.5	
Total DNA	206	10.9	0.8	169	9.8	0.7	71	12.0	1.4	

Transplant type IAK

	Infusion Number									p
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	83	4.2	0.3	67	3.6	0.3	18	4.0	0.4	
Total islet particles (final preparation)	89	447.1	22.9	69	387.7	18.9	23	398.7	37.9	
Embedded islets (%)	45	15.6	2.1	33	13.3	2.1	5	18.2	5.1	
Islet equivalents (1000s)	90	438.0	20.9	68	372.5	16.3	25	350.7	27.0	**
Islet equivalents(1000s)/kg recipient	132	7.2	0.2	89	6.3	0.3	24	5.3	0.4	***
Beta cells (x10^6)	17	292.9	47.5	12	272.5	47.9	4	283.5	123.5	
Beta cells/kg recipient weight	11	5.0	0.9	9	6.0	0.9	4	4.5	2.0	
Insulin content (1000s micrograms)	11	3.1	0.5	12	3.1	0.7	6	2.2	0.5	
Total Endotoxin units	93	18.1	4.3	62	15.9	5.2	16	14.8	10.6	
Endotoxin units/kg recipient weight	87	0.3	0.1	60	0.2	0.1	15	0.2	0.2	
Islet potency: Stimulation index	78	3.0	0.3	55	2.6	0.3	16	2.2	0.3	
Islet viability	97	91.6	0.6	73	91.2	0.7	22	90.5	1.2	
Purity	101	60.5	1.8	75	59.6	2.0	21	57.9	5.0	
Total DNA	21	10.2	1.8	16	11.9	2.9	5	6.9	2.6	

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

Exhibit 3-5
Relationship between (Categorical) Islet Predictors and Final Islet Product Characteristics

p<0.05 (regression coefficient)	Islet characteristics													
	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg recipient	Total beta cells	Beta cells/kg recipient	Insulin content	Total endotoxin	Endotoxin/ kg recipient	Stimulation index	Viability	Purity	DNA content
Islet predictors	0.045 (0.346)	0.04 (28.3)					0.01 (1.71)					0.0007 (1.80)		
ITA vs IAK														
Year	<0.0001 (-0.077)	0.002 (-3.72)		0.02 (2.15)		0.004 (6.60)	0.004 (0.114)		<0.0001 (-2.72)	<0.0001 (-0.044)	<0.0001 (-0.087)	<0.0001 (-0.316)		<0.0001 (0.632)
Donor gender		<0.0001 (42.0)		<0.0001 (41.6)	0.0001 (0.525)									
Donor blood type A	0.001 (-0.409)		0.0007 (-4.07)											
Donor CMV			0.02 (2.82)						0.03 (6.30)					
Donor Hx HPT		0.03 (23.9)	0.007 (-3.44)						0.02 (7.21)	0.03 (0.109)				
Donor Hx ETOH														
Donor hospital transfusion									0.01 (9.94)	0.04 (0.128)		0.02 (1.15)	0.048 (2.54)	0.04 (-2.48)
Donor intra-op transfusion														
Donor given steroid				<0.0001 (69.3)	<0.0001 (0.912)	0.006 (112)	0.02 (1.66)		0.04 (9.75)				<0.0001 (7.27)	
Donor given insulin				0.0003 (33.0)	0.008 (0.403)	0.0002 (79.1)	0.005 (1.06)		0.04 (6.62)	0.04 (0.102)				0.001 (3.39)
Procurement team related		0.04 (-8.58)		0.03 (0.057)										
Gradient type	0.01 (-0.418)			0.01 (30.6)	0.03 (0.425)	0.004 (-109)	0.0004 (-2.27)							<0.0001 (-6.93)

Exhibit 3-6
Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

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

	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg donor	Total beta cells	Beta cells/kg donor	Insulin content	Total endo-toxin	Endotoxin/kg donor	Stimulation index
	pckclvol	TOTPARTICLES	TOTTRAP	totieq	ieqinfkg	totalbeta	totbetakg	totalinsulin	totalendo	TOTENDOKG	isstimin_mean
Mean donor age (yrs)	-0.10244 0.0018 927	0.06591 0.0566 837	-0.16023 <.0001 658	-0.06441 0.0433 985	-0.10288 0.0006 1113	-0.02491 0.6848 268	-0.06354 0.3229 244	0.05607 0.3525 277	0.03218 0.3139 981	0.02379 0.4683 932	-0.13700 <.0001 830
Donor Weight (kg)	0.05791 0.0470 1177	0.08170 0.0066 1103	-0.01649 0.6291 860	0.32915 <.0001 1283	0.30730 <.0001 1378	0.04294 0.3959 393	0.01024 0.8550 321	0.02001 0.7291 302	0.01710 0.5764 1069	0.00546 0.8627 1005	0.04722 0.1314 1022
Donor height	0.01491 0.6097 1175	0.12521 <.0001 1101	-0.03014 0.3779 858	0.15739 <.0001 1281	0.16380 <.0001 1376	-0.06198 0.2208 392	-0.07978 0.1545 320	0.12352 0.0322 301	-0.05209 0.0887 1069	-0.05612 0.0754 1005	0.01776 0.5708 1021
Donor Body Mass Index (kg/m2)	0.04123 0.1578 1175	0.01691 0.5751 1101	-0.00793 0.8167 858	0.27150 <.0001 1281	0.25159 <.0001 1376	0.06925 0.1712 392	0.05114 0.3619 320	-0.02764 0.6329 301	0.04242 0.1658 1069	0.03280 0.2989 1005	0.04919 0.1162 1021
Pre-ins donor glucose	-0.05717 0.0965 846	-0.01736 0.6183 826	0.06439 0.1058 632	-0.05252 0.1269 846	-0.05923 0.0649 972	-0.03983 0.4941 297	-0.02210 0.7255 255	0.04582 0.4576 265	0.05103 0.1390 842	0.05744 0.1047 799	0.03036 0.3876 812
Max donor glucose	0.03619 0.2749 912	-0.03727 0.2642 899	0.00644 0.8663 686	0.06436 0.0507 922	0.09751 0.0017 1036	0.11679 0.0377 317	0.15494 0.0122 261	-0.04133 0.5365 226	0.07451 0.0262 890	0.06878 0.0465 838	0.03384 0.3216 860
Donor creatinine	0.08251 0.0092 995	0.03569 0.2705 955	-0.02819 0.4418 747	0.17040 <.0001 1010	0.15080 <.0001 1129	-0.05362 0.3421 316	-0.05320 0.4032 249	0.04148 0.5491 211	0.00099 0.9755 969	-0.00518 0.8761 907	0.08395 0.0113 909
Donor BUN	0.09176 0.0145 710	0.04702 0.2270 662	-0.05668 0.2312 448	0.13906 0.0002 694	0.11684 0.0006 850	-0.04689 0.5662 152	-0.07719 0.4250 109	0.06010 0.4650 150	-0.06058 0.0839 815	-0.06523 0.0729 757	0.10303 0.0072 679
Donor bilirubin	0.06635 0.0500 873	0.07056 0.0421 830	-0.06506 0.1033 628	0.13765 <.0001 878	0.12812 <.0001 1004	0.01314 0.8373 247	0.07385 0.3165 186	0.09265 0.2594 150	0.01802 0.5930 882	0.01345 0.7001 822	0.06701 0.0569 808

Exhibit 3-6 (continued)
Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations											
	Packed cell volume	**Total particle count**	**Trapped islets**	**Total IEQs infused**	**IEQs/kg donor**	**Total beta cells**	**Beta cells/kg donor**	**Insulin content**	**Total endo-toxin**	**Endotoxin/kg donor**	**Stimulation index**
	pckclvol	**TOTPARTICLES**	**TOTTRAP**	**totieq**	**ieqinfkg**	**totalbeta**	**totbetakg**	**totalinsulin**	**totalendo**	**TOTENDOKG**	**isstimin_mean**
Donor AST	0.02494 0.4573 890	0.00714 0.8351 853	0.01657 0.6756 640	0.00626 0.8493 922	0.00309 0.9213 1026	-0.04057 0.5223 251	-0.01814 0.8033 191	0.09775 0.2188 160	-0.03269 0.3269 901	-0.02571 0.4565 841	0.01669 0.6300 835
Donor ALT	0.06089 0.0676 902	0.03369 0.3223 865	0.00916 0.8151 654	0.09764 0.0022 981	0.08996 0.0034 1060	-0.00150 0.9809 257	0.00056 0.9938 196	0.06920 0.3756 166	-0.02818 0.3883 939	-0.02645 0.4337 878	0.05274 0.1249 848
Donor lipase	0.03542 0.3038 845	0.00526 0.8817 803	-0.02239 0.5746 631	0.05765 0.0926 852	0.06431 0.0435 986	-0.05254 0.3760 286	-0.03401 0.6071 231	-0.00844 0.9032 210	-0.01199 0.7222 882	-0.01776 0.6093 830	0.04198 0.2307 817
Donor serum amylase	0.04944 0.1383 900	0.04935 0.1486 858	0.02186 0.5754 659	-0.01921 0.5645 902	-0.02488 0.4220 1044	-0.09637 0.1076 280	-0.11505 0.0887 220	0.08980 0.1982 207	-0.03039 0.3640 894	-0.02859 0.4070 843	0.04843 0.1638 828
Time from cross clamp to pancreas recovery (hrs)	-0.07292 0.0492 728	-0.00035 0.9925 718	-0.04212 0.3294 538	-0.09971 0.0063 750	-0.08669 0.0193 728	-0.07467 0.2563 233	-0.00544 0.9416 184	-0.00519 0.9414 203	-0.26789 <.0001 660	-0.28255 <.0001 604	-0.00809 0.8339 675
Time from brain death to pancreas recovery (hrs)	0.03173 0.4137 666	-0.03688 0.3471 652	0.03307 0.4661 488	0.13505 0.0004 685	0.07040 0.0699 664	0.12935 0.0571 217	0.08721 0.2539 173	-0.00255 0.9718 195	0.08461 0.0343 626	0.07666 0.0669 572	0.14774 0.0002 636
Cold ischemic time (hrs)	-0.10122 0.0025 893	0.05999 0.0778 865	-0.10880 0.0059 640	0.02369 0.4808 888	-0.01186 0.7229 896	-0.01964 0.7426 282	-0.02989 0.6354 254	0.03750 0.5183 299	-0.01693 0.6242 840	-0.02747 0.4433 781	-0.04882 0.1590 834
Culture time (hrs)	-0.16062 <.0001 1010	0.02360 0.4564 998	0.00928 0.7937 797	0.08683 0.0048 1053	-0.00971 0.7589 1001	0.22339 <.0001 387	0.22965 <.0001 315	-0.01075 0.8536 297	0.03751 0.2816 826	0.04767 0.1881 764	-0.00942 0.7736 936

Exhibit 3-7
Islet Product and Infusion Characteristics by Infusion Sequence

	ITA									IAK								
	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)	637	443.4	6.3	467	422.7	7.1	191	415.8	10.1	145	456.8	13.3	97	396.4	14.7	26	366.3	31.4
Islet equivalents infused(1000s)/donor kg	592	6.7	0.1	435	6.3	0.1	178	6.1	0.2	132	7.2	0.2	89	6.3	0.3	24	5.3	0.4
Embedded islets (%)	366	16.3	0.9	285	16.3	1.1	129	16.1	1.6	45	15.6	2.1	33	13.3	2.1	5	18.2	5.1
Cell volume (mL)	500	3.8	0.1	392	3.6	0.1	179	3.3	0.1	83	4.2	0.3	67	3.6	0.3	18	4.0	0.4
Time since first infusion (weeks)	641	29.6	1.8	641	29.6	1.8	244	16.5	1.3	121	29.3	4.7	121	29.3	4.7	30	31.5	13.7
Time since second infusion (weeks)	207	88.5	8.8	207	88.5	8.8	244	94.4	8.3	27	52.3	13.7	27	52.3	13.7	30	56.2	13.2
Time since third infusion (weeks)	28	152.7	41.2	28	152.7	41.2	65	165.6	28.0	3	8.4	4.5	3	8.4	4.5	6	8.4	2.8

Chapter 4
Immunosuppression and Other Medications

Table of Contents

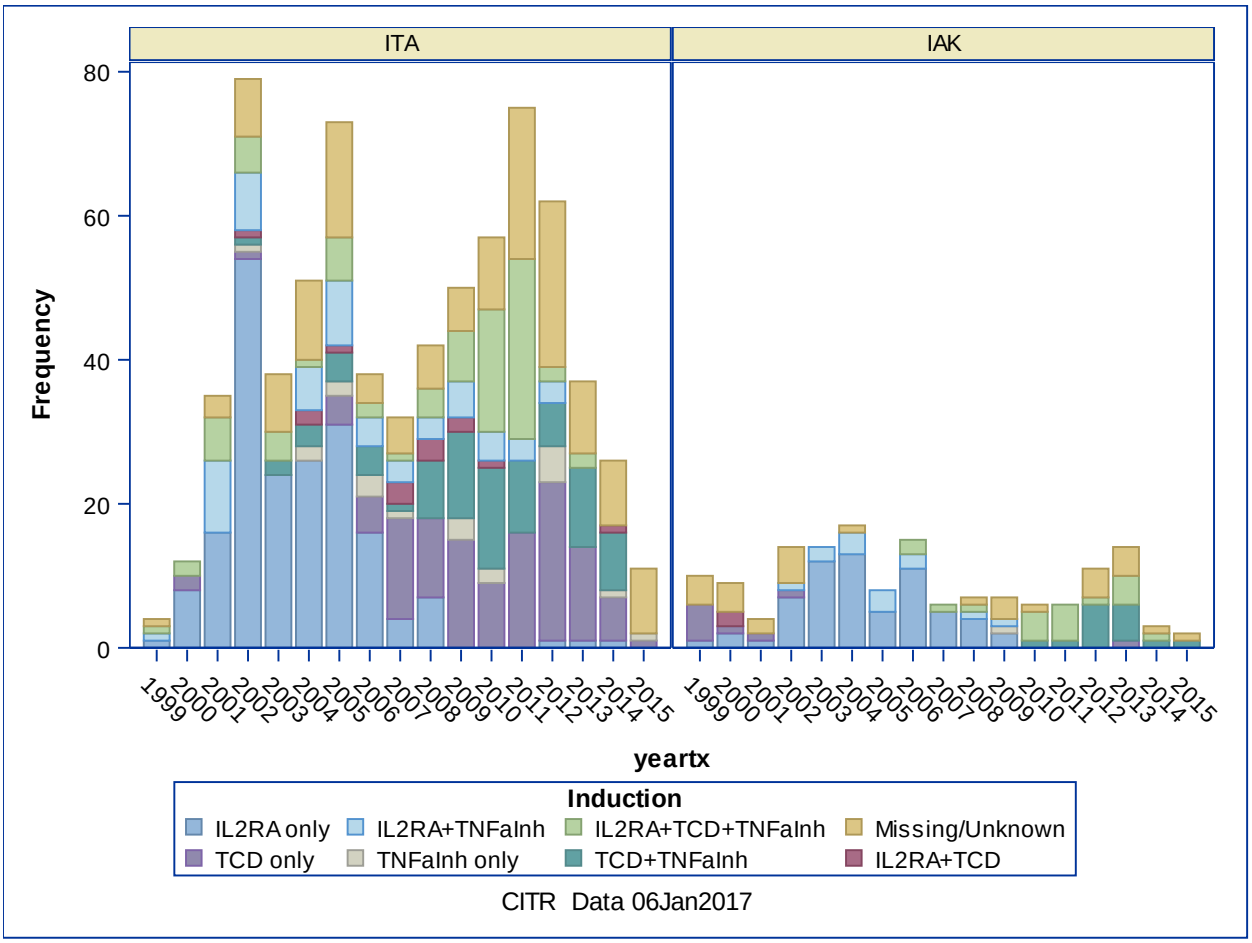
Introduction

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

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

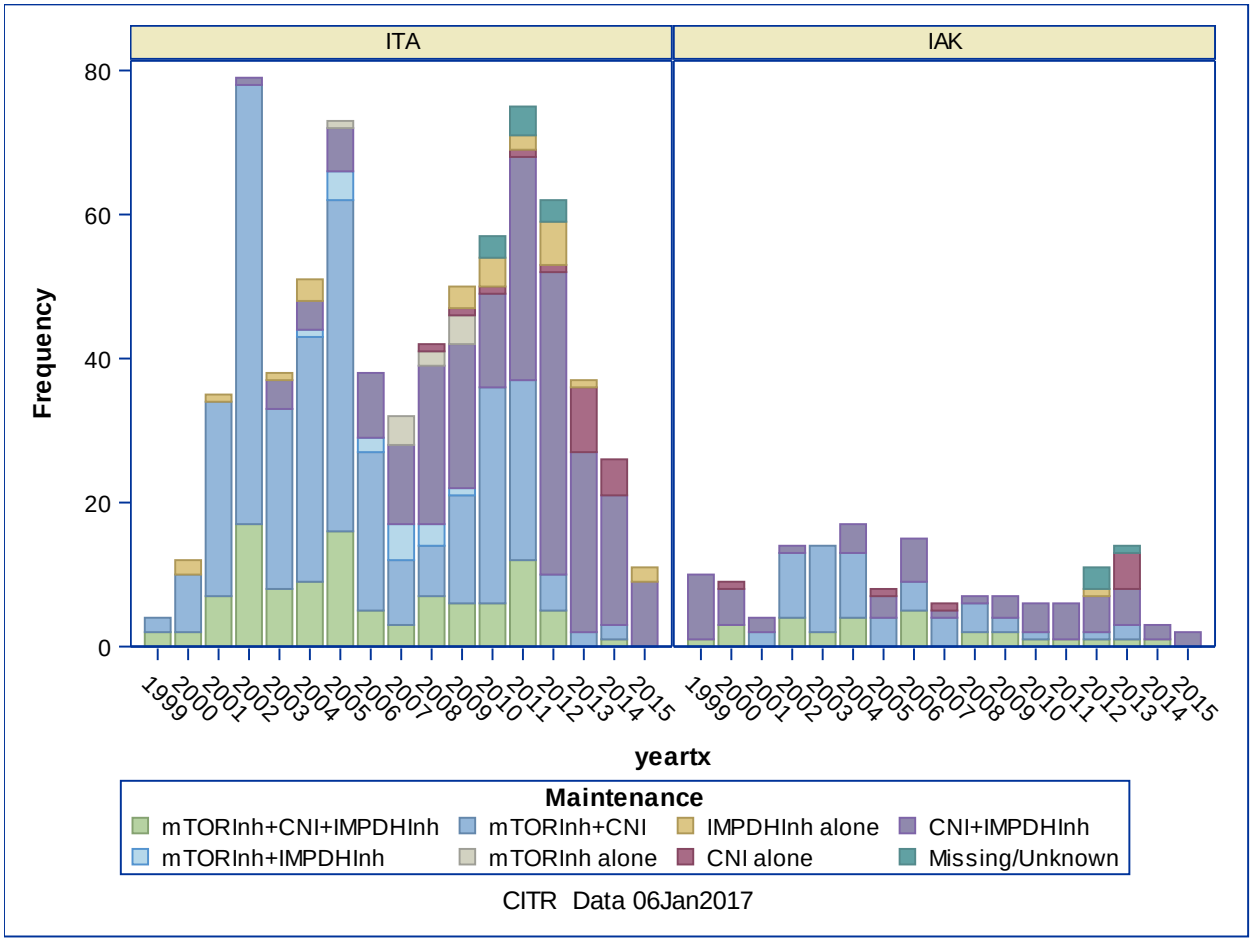
Multiple induction and maintenance agents may have been administered peri- and post- several infusions in the same recipient. In displays of results post last infusion, the cumulated induction agents are classified into the appropriate class combination (e.g., TCD+IL2RA – these could have been given at the same or different infusions in the recipient). For analysis of outcomes post last infusion, the induction and maintenance agents are cumulated over multiple infusions and the resulting combination is carried forward through the patient's follow-up post last infusion. These cumulative categories are shown in this Chapter by type of transplant and year of first infusion (era). In both ITA and IAK, 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 4-1). A Calcineurin inhibitor+mTOR inhibitor regimen ("Edmonton protocol") comprised the abundant majority of maintenance immunosuppression in the early eras 1999-2006. Increasingly it has been replaced with a CNI+IMPDH inhibitor combination in the recent eras in both ITA and IAK (Exhibit 4-2).

Exhibit 4 – 1
Induction Immunosuppression by Transplant Type and Era



	Type of transplant				Era									
	ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Induction														
IL2RA only	190	26.3	63	41.2	90	53.9	138	54.3	22	10.6	3	1.3	.	.
TCD only	119	16.5	9	5.9	11	6.6	9	3.5	49	23.7	58	24.8	1	7.7
TNFaInh only	21	2.9	1	0.7	1	0.6	7	2.8	7	3.4	6	2.6	1	7.7
TCD+TNFaInh	84	11.6	15	9.8	1	0.6	13	5.1	36	17.4	48	20.5	1	7.7
IL2RA+TCD	14	1.9	2	1.3	3	1.8	3	1.2	9	4.3	1	0.4	.	.
IL2RA+TNFaInh	59	8.2	13	8.5	20	12.0	29	11.4	17	8.2	6	2.6	.	.
IL2RA+TCD+TNFaInh	85	11.8	19	12.4	14	8.4	15	5.9	35	16.9	40	17.1	.	.
Missing/Unknown	150	20.8	31	20.3	27	16.2	40	15.7	32	15.5	72	30.8	10	76.9
TOTAL	722	100.0	153	100.0	167	100.0	254	100.0	207	100.0	234	100.0	13	100.0

Exhibit 4 – 2
Maintenance Immunosuppression by Transplant Type and Era



	Type of transplant				Era									
	ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Maintenance														
mTORInh+CNI+IMPDHInh	106	14.7	28	18.3	36	21.6	49	19.3	27	13.0	22	9.4	.	.
mTORInh+CNI	320	44.3	54	35.3	109	65.3	156	61.4	72	34.8	37	15.8	.	.
mTORInh+IMPDHInh	16	2.2	.	.	.	.	7	2.8	9	4.3	.	.	.	.
CNI+IMPDHInh	215	29.8	58	37.9	18	10.8	36	14.2	75	36.2	133	56.8	11	84.6
mTORInh alone	11	1.5	.	.	.	.	1	0.4	10	4.8	.	.	.	.
CNI alone	19	2.6	8	5.2	1	0.6	1	0.4	4	1.9	21	9.0	.	.
IMPDHInh alone	25	3.5	1	0.7	3	1.8	4	1.6	7	3.4	10	4.3	2	15.4
Missing/Unknown	10	1.4	4	2.6	.	.	.	.	3	1.4	11	4.7	.	.
TOTAL	722	100.0	153	100.0	167	100.0	254	100.0	207	100.0	234	100.0	13	100.0

Chapter 5
Graft Function

Table of Contents

Introduction

Summary

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

The analytical process evolved as follows, and was conducted for the ITA and IAK transplant groups separately. First, every variable available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome (insulin independence, HBa1c, etc.). Those variables significant at $p<0.05$ were then stepped into multivariate models to eliminate duplicative effects and narrow down the final effects. While some predictive variables (factors) consistently exerted a clear beneficial effect across outcomes, each outcome within ITA yielded a slightly different set of significant favorable factors. To facilitate interpretation for translation into clinical practice, the set of favorable factors that were common to all the outcomes within ITA were selected, and subgroups comprising all those with the favorable common factors is compared to the remainder (who may have none, one or more, but not all the favorable factors). These final results of the common favorable factors on the primary outcomes are exhibited together (Exhibit 5-9.) Targeting the common favorable factors somewhat dilutes the largest differences seen univariately for each outcome; however, this method identifies the factors that are clinically most relevant to the recipients. These then comprise best practices in terms of patient selection and medical management for allogeneic islet transplantation. That said, some leeway in applying these guidelines should always prevail in the management of specific patients who may benefit from islet transplantation.

Remarkably, only a handful of common favorable factors emerge, and their combined effects appear to be additive, as exhibited by the final multivariate models of the various primary endpoints (Exhibit 5-9). These salutary factors include:

For islet alone:

- Selection of patients aged 35 years or older. The remarkable consistency of this result runs across most of the primary outcomes including achievement and long-term retention of insulin independence or reduction in daily insulin requirement, higher levels of basal C-peptide, lowered HbA1c levels, and near elimination of severe hypoglycemia. As islet transplantation is not life-saving, this selection factor helps optimize use of scarce donor pancreas resources. Obviously, clinical judgment should drive the process: all other favorable factors being in place, someone younger than 35 may still be a good candidate for an islet transplant.
- Use of T-cell depletion, TNF-a inhibition, MTOR inhibition and calcineurin inhibitors continue to be associated with improved clinical outcomes with accruing data in CITR. A major limitation from the CITR data is that these strategies were not assigned at random and independently of each other; hampering the ability to isolate the effects of each factor separately. Nonetheless,

from analyses of each factor alone (yes/no) and as combinations of induction and maintenance immunosuppression, the benefit of these agents continues to be well supported by the data.

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

For islet-after-kidney:

No one common set of factors emerged as being beneficial for all primary outcomes among IAK. Further analysis of favorable factors for IAK is the focus topic of a CITR manuscript currently in progress.

The islet processing practices including preservation and digestion have undergone substantial evolution over the last decade particularly. The CITR data collection system is currently being updated to allow collection of this detailed information. Hence, little analysis of the effects of these factors on clinical outcomes of islet transplantation are included in this Annual Report.

The hallmark effect of islet transplantation as exhibited in these data is the remarkably effective and durable resolution of severe hypoglycemic events (Exhibits 5-7 and 5-9). While many IAK recipients never had SHE before transplantation, and fewer ITA recipients without SHE pre-infusion were transplanted in later eras, this remarkable and important benefit of islet transplantation in T1D could serve as a stand-alone indication for ITx in well-selected recipients.

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

Salient results are presented in Chapter 5 Exhibits. Detailed results are available in supplements online at www.citregistry.org / Reports / CITR 10th Annual Report / Supplemental Exhibits. The following table relates the Chapter 5 exhibits to the supplemental exhibits.

	Chapter 5 Exhibit	**Supplemental Exhibit a=ITA | b=IAK**
Achievement of insulin independence post first infusion (Kaplan-Meier)	5-1	A-1
Insulin independence post last infusion (Prevalence / Bar charts)	5-2	A-2a | A-2b
Retention of C-peptide ≥0.3 ng/mL post last infusion (Kaplan-Meier and Cox models on complete graft loss (CGL))	5-3	A-3a | A-3b
Fasting C-peptide ≥0.3 ng/mL post last infusion (Prevalence / Bar charts)	5-4	A-4a | A-4b
Fasting blood glucose 60-140 mg/mL post last infusion (Prevalence / Bar charts)	5-5	A-5a | A-5b
HbA1c<7.0% Post Last Infusion (Prevalence / Bar charts)	5-6	A-6a | A-6b
Absence of severe hypoglycemia (Prevalence / Bar charts)	5-7	A-7a | A-7b

	Chapter 5 Exhibit	Supplemental Exhibit a=ITA | b=IAK
HbA1c<7.0% and Absence of Severe Hypoglycemic Events (Prevalence / Bar charts)	5 – 8	A-8a | A-8b
Combined Effect of Common Favorable Factors on Primary Outcomes Post Last Infusion, ITA (Prevalence / Bar charts)	5-9	—
Insulin dose post last infusion (Box plots and generalized estimating equations)	5-10	—
Fasting C-peptide levels post last infusion (Box plots and generalized estimating equations)	5-11	—
HbA1c levels post last infusion (Box plots and generalized estimating equations)	5-12	—
Fasting blood glucose levels post last infusion (Box plots and generalized estimating equations)	5-13	—
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years1-5 Post Last Infusion	5-14	—
Reinfusion (Bar charts and Kaplan-Meier)	5-15	—

Insulin Independence

First achievement of insulin independence is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft function or loss, islet resource availability for re-infusion, individual tolerance of immunosuppression, patient/doctor decisions, and myriad other factors, some of which are characterized in the CITR data and others not. Notably, the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope. Using all the information in the Registry over the eras, factors predictive of first achievement of insulin independence in ITA and IAK were identified. These were induction immunosuppression with IL2RA inhibitor ($p<0.0001$) and recipient age ≥ 35 years ($p=0.006$). In IAK patients predictive factors were time from donor death to transplant < 36 hours ($p<0.0001$) and recipient BMI < 21 ($p=0.04$) . From both Cox modeling and by subgroup analysis, ITA recipients with these favorable factors exhibited 3-fold higher likelihood of achieving insulin independence following allo-islet transplantation IAK with their respective common factors exhibit a 2-fold higher likelihood of achieving insulin independence relative to the comparator with all unfavorable factors (Figure 5-1 left panel). The individual effects of the predictive factors are shown in Exhibit 5-1, B1-B3 for ITA and C1-C2 for IAK.

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

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

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-9, stratified for ITA.

C-peptide≥0.3 ng/mL

Of all 2,082 allogeneic islet infusions with C-peptide data, 89 (4.3%) resulted in primary non-function (C-peptide never ≥ 0.3 ng/mL up to reinfusion: 3.1% in 1999-2002, 3.0% in 2003-2006, 3.6% in 2007-2010, 6.4% in 2011-2014, and 11.8% in 2015-2018).

Retention of graft function (C-peptide ≥0.3 ng/mL; Exhibit 5-3) post last infusion – modeled as time to complete graft loss (CGL) -- is maximized in ITA patients by recipient age ≥ 35 ($p<0.0001$), total infusions > 1 ($p=0.0112$), induction immunosuppression with T-cell depletion ($p=0.0395$), maintenance immunosuppression with calcineurin inhibitor ($p<0.0001$), and islets cultured ≥ 6 hours ($p<0.0001$) and in IAK patients by total IEQs infused ≥325K ($p=0.0032$) and transplant era 2003 or later ($p=0.0002$). With these their respective favorable factors combined, graft retention rate remained at 80% through 8 years in both ITA and IAK groups.

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

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-9, stratified for ITA.

Persistence of Primary Outcomes

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

The raw, unadjusted prevalence of HbA1c<7.0% stratified by transplant type is shown in Exhibit 5-6A. Prevalence of HbA1c<7.0% was maintained in 60% of ITA patients and just under 50% of IAK patients

over 5 years of follow-up time. Individual factors that were significantly ($p<0.05$) associated with maintaining HbA1c<7.0% at significantly higher levels through 5 years are presented in Exhibit 5-6B for ITA and Exhibit 5-6C for IAK. The factors which were significant differed substantially between the transplant type groups.

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

The raw, unadjusted prevalence of combined HbA1c<7.0% with Absence of Severe Hypoglycemic Events (ASHE) stratified by transplant type is shown in Exhibit 5-8A. For ITA patients, prevalence of HbA1c<7.0% with ASHE was maintained in around 50% of patients over 5 years of follow-up time. For IAK patients, prevalence was maintained in just above 30% at 5 years. Factors that were significantly ($p<0.05$) associated with maintaining ASHE at higher levels through 5 years are presented in Exhibit 5-8B for ITA and Exhibit 5-8C for IAK. The factors which were significant resulted in substantial differences in outcome prevalence between ITA and IAK.

The combined effect of the most important favorable factors common to all endpoints is shown in Exhibit 5-9, stratified for ITA.

Levels of daily insulin requirement (U/day) declined dramatically in follow-up through 5-years after islet transplantation, with some return upwards over 5 years of follow-up for both ITA and IAK patients (Exhibit 5-10). Factors associated with improved results for each group are shown in Exhibit 5-9. Among ITA's favorable factors included age ≥35 ($p<0.0001$); induction immunosuppression with TCD and/or TNF alpha ($p=0.009$); and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p<0.0001$). Among IAK's favorable factors included maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p=0.0007$).

Fasting C-peptide rises dramatically after islet transplantation with decline over 5 years although more than 50% retain C-peptide >0.3 ng/mL at 5 years post last infusion in both ITA and IAK groups (Exhibit 5-11). Factors associated with improved results for each group are shown in Exhibit 5-10. Among ITA's favorable factors included Islets Cultured ≥ 6 hours ($p=0.03$) and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p=0.008$).

HbA1c in both ITA and IAK groups declines sharply after islet transplantation, and does not return to pre-transplant levels (Exhibit 5-12). Factors associated with improved results in each group are shown in Exhibit 5-12. Among ITA's favorable factors included age ≥35 ($p<0.0001$); induction immunosuppression with T-cell depletion and/or TNF-a inhibition ($p=0.003$) and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p<0.0001$).

Fasting blood glucose also declines dramatically after islet transplantation and in over 70% of ITA patients and almost 60% of IAK patient remains at levels of 60-140 mg/dL (Exhibits 5-13 and 5-5). Factors associated with improved results in each group are shown in Exhibit 5-13. Among ITA's favorable factors included age ≥ 35 ($p<0.0001$); induction immunosuppression with TCD and/or TNF alpha ($p=0.003$); and maintenance immunosuppression with mTOR inhibition and calcineurin inhibitors ($p<0.0001$).

The higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c <7.0%, fasting blood glucose of 60-140 mg/dL, and the lower the likelihood of severe hypoglycemia (Exhibit 5-14). This holds true for both ITA and IAK patients. Even partial graft function, i.e., fasting C-peptide of 0.3-0.5 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced over all follow-up even with C-peptide <0.3 ng/mL. While these strong associations among the co-primary outcomes are highly significant, any causal relationships cannot be deduced just from the associations; a temporal analysis is a separate focus topic.

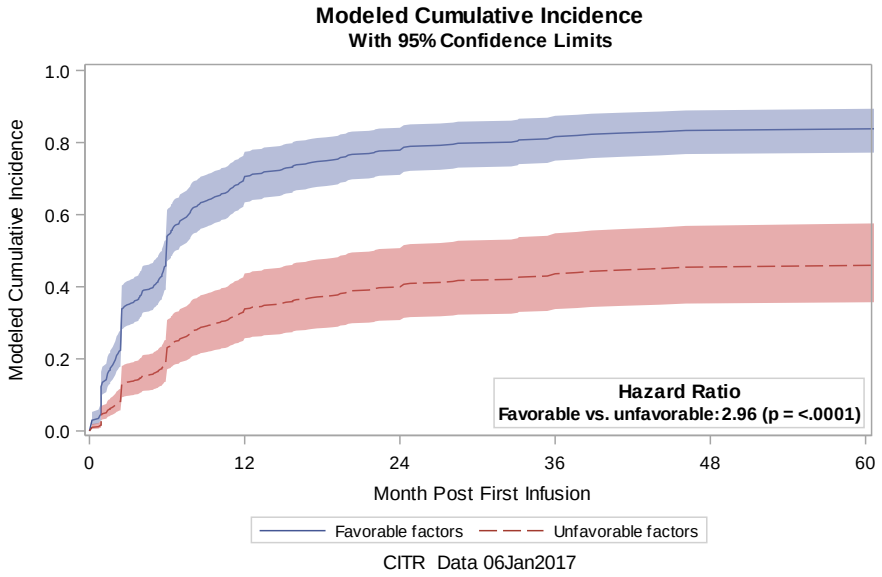
Re-infusion

Re-infusion may have been conducted without (781/1592=49.1%) or after (188/412=45.6%) complete graft failure (fasting C-peptide<0.3 ng/mL without recovery, Exhibit 5-4A). Viewed as time-to-event, reinfusion was no more likely with a functioning graft than with a lost graft (p=0.11). A number of re-infusions were conducted while the patient was not only C-peptide positive but also insulin independent (Exhibit 5-14B, 53/287=18.5%, for all infusions): re-infusion was much more likely when the patient had not yet achieved insulin independence (p<0.0001, Exhibit 5-14B). Second infusion rates have been remarkably constant over the whole history of the CITR (p=0.04, Exhibit 5-15C) and do not differ significantly by transplant type (p=0.3, Exhibit 5-15D).

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

A1. ITA

Factors	p-value	Hazard Ratio
Recipient Age (1= ≥35, 0= <35)	0.006	1.579
Induction Immunosuppression with IL2RA (1=Given, 0=Not Given)	<0.0001	1.874



A2. IAK

Factors	p-value	Hazard Ratio
Time from donor death to transplant (1= <36 hrs, 0= ≥36 hrs)	<0.0001	4.160
Recipient BMI (1= <21, 0= ≥21)	0.0441	1.927

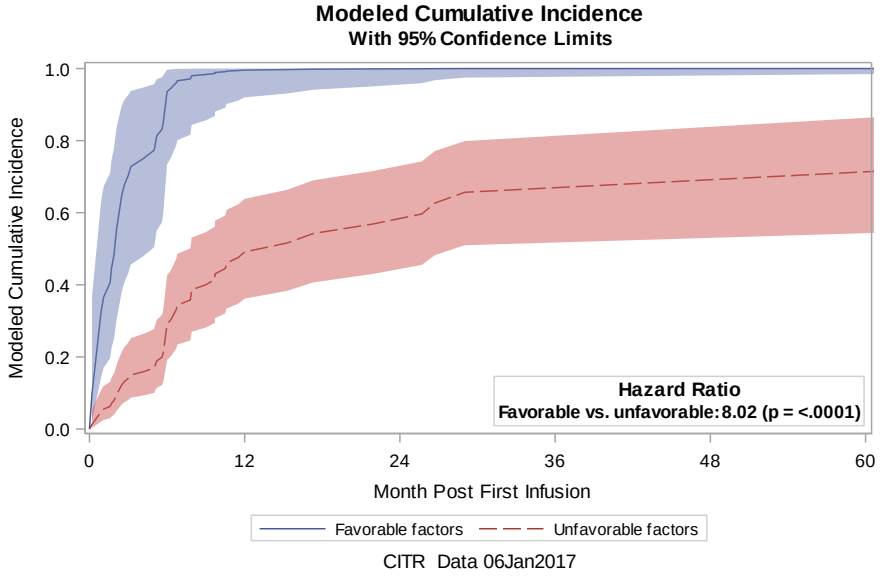
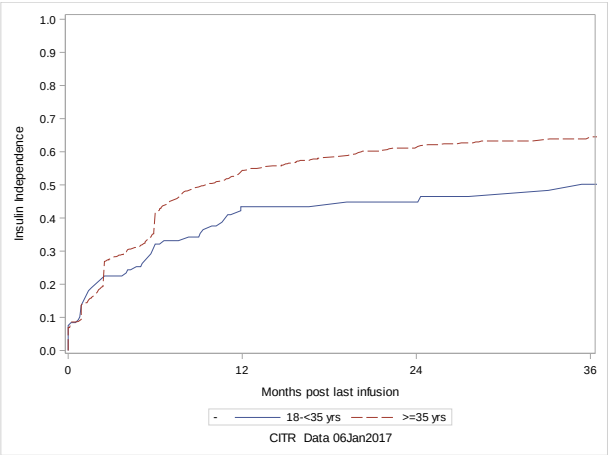


Exhibit 5 – 1 (continued)
First Achievement of Insulin Independence Post First Infusion, ITA and IAK Recipients Separately

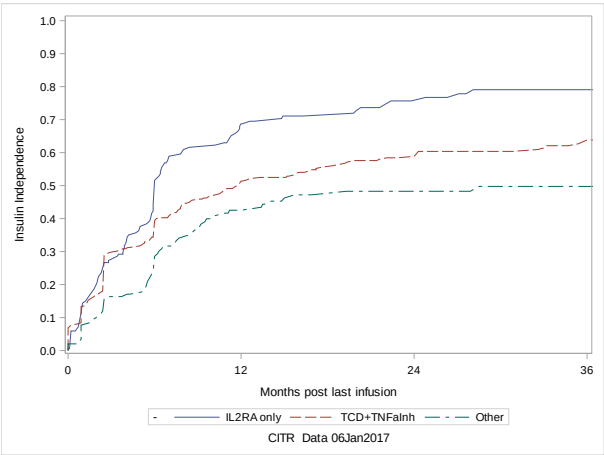
Effects of Individual factors

ITA

B1. Recipient Age ≥ 35 favorable

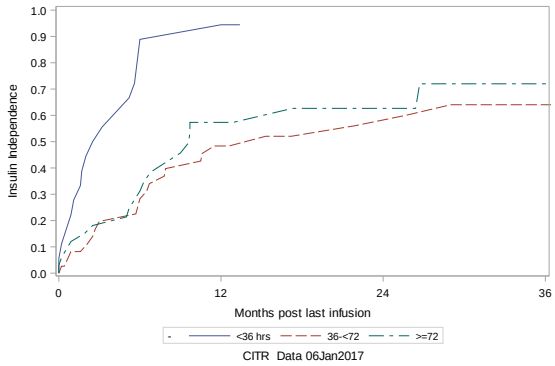


C1. Induction Immunosuppression with IL2RA favorable



IAK

B2. Time from donor death to transplant <36 hours favorable



C2. Recipient BMI < 21 favorable

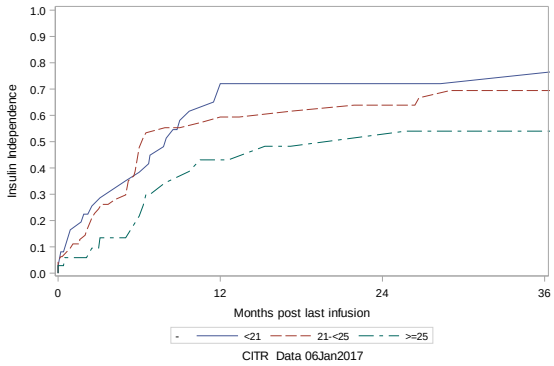
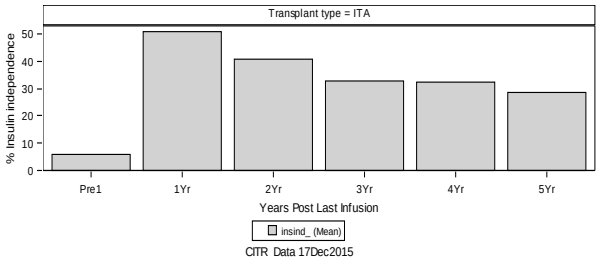


Exhibit 5 – 2A
Unadjusted Prevalence of Insulin Independence Post Last Infusion

ITA



IAK

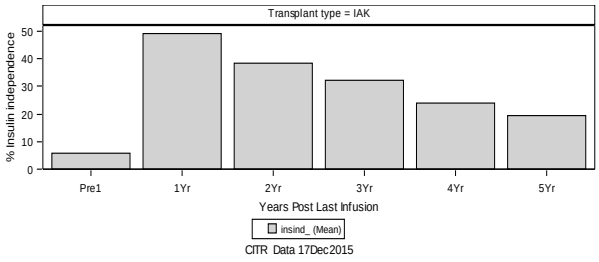
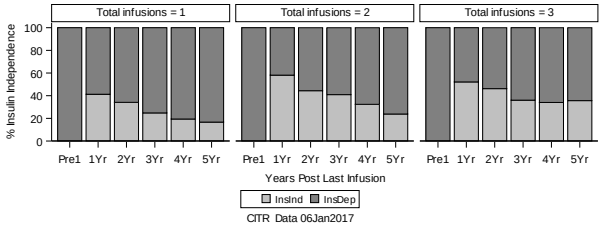
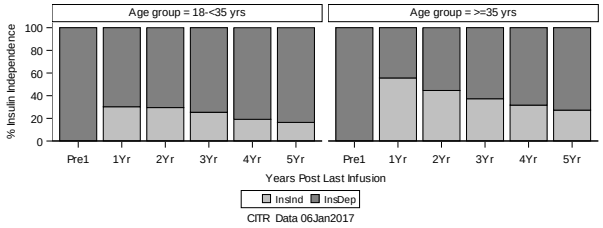


Exhibit 5 – 2B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

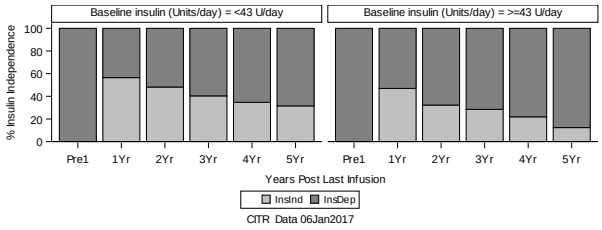
A. Total infusions ≥3 favorable (p=0.0144)



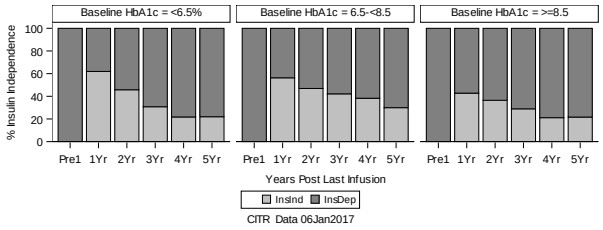
B. Recipient Age ≥ 35 years favorable (p=0.0023)



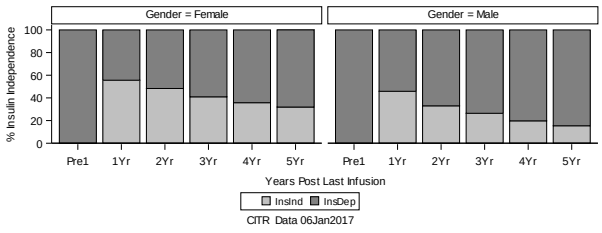
C. Baseline Insulin <43 units/day favorable (p=0.0042)



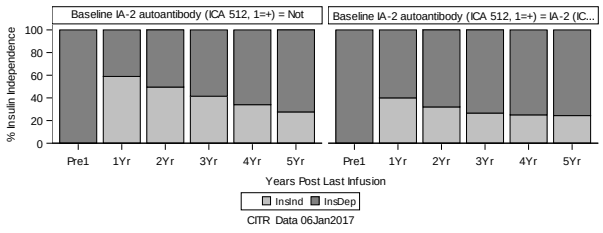
D. Baseline HbA1c <8.5 favorable (p=0.0216)



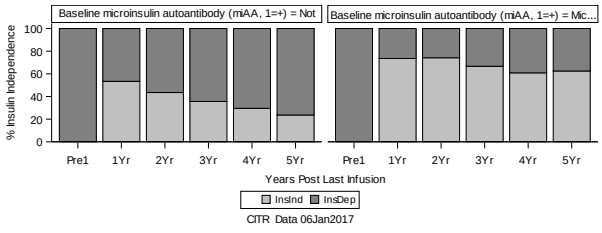
E. Recipient Gender female favorable (p=0.0007)



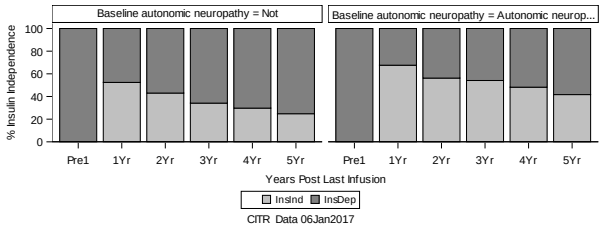
F. IA-2 (ICA 512) negative at baseline favorable (p=0.0042)



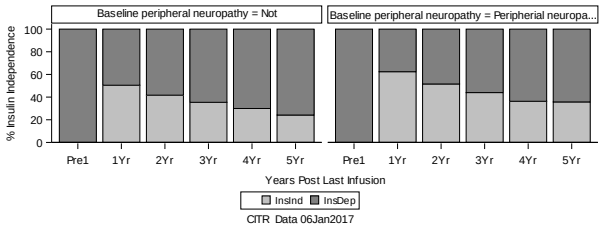
G. Microinsulin (mIAA) positive at baseline favorable (p<0.0001)



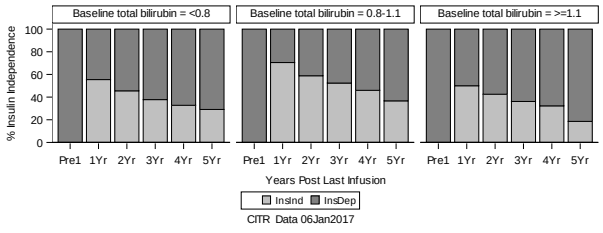
H. Autonomic neuropathy at baseline favorable (p=0.0024)



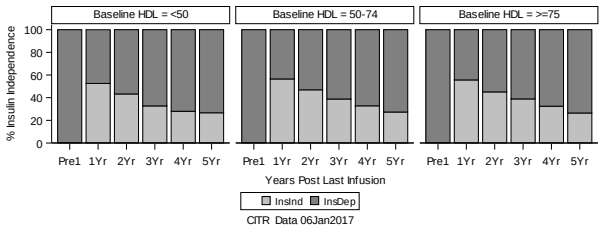
I. Baseline peripheral neuropathy favorable (p=0.0253)



J. Baseline total bilirubin <1.1 favorable (p=0.0317)



K. Baseline LDL < 75 favorable (p=0.0363)



L. Baseline triglycerides < 30 favorable (p=0.0014)

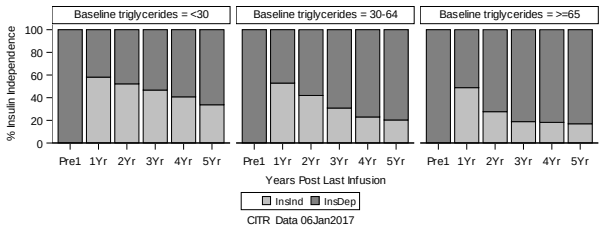
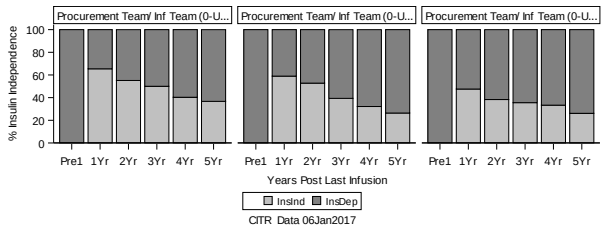
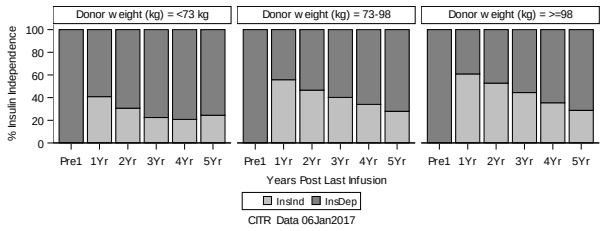


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

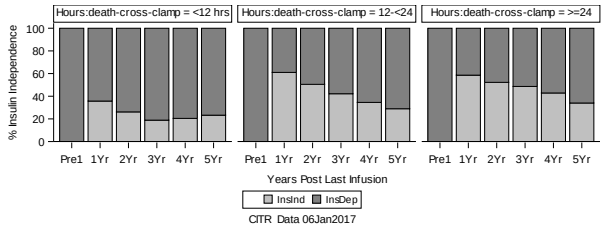
M. Procurement Team/ Inf Team unrelated favorable (p=0.0235)



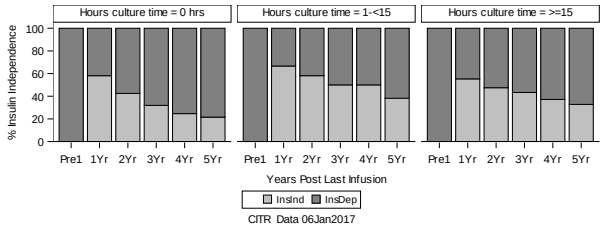
N. Donor Weight ≥ 98 kg favorable (p=0.0238)



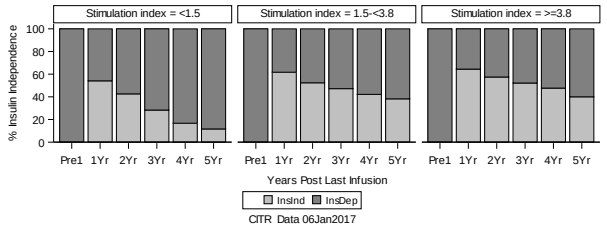
O. Hours from Death to Cross-Clamp ≥ 12 favorable (p=0.0040)



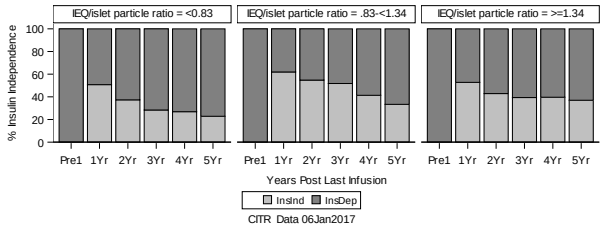
P. Hours culture time 1-<15 favorable (p=0.0453)



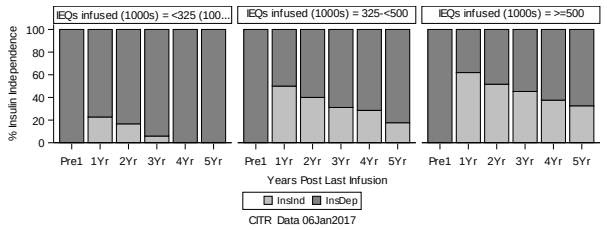
Q. Stimulation Index ≥ 1.5 favorable (p=0.0159)



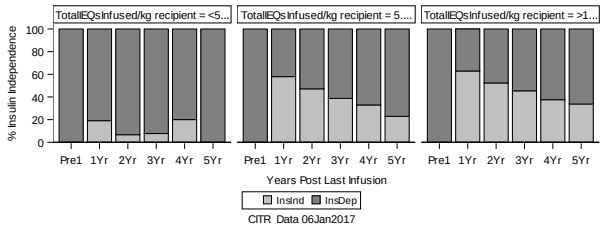
R. IEQ/islet particle ratio ≥ 0.83 favorable (p=0.0274)



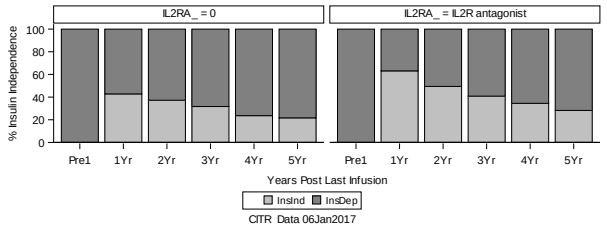
S. Total IEQs infused ≥ 500 favorable (p=0.0009)



T. Total IEQs infused/kg recipient weight >5.15 favorable (p=0.0038)



U. Induction Immunosuppression with IL2R antagonist favorable (p=0.0019)



V. Induction Immunosuppression with TNF-a-blockade favorable (p=0.0025)

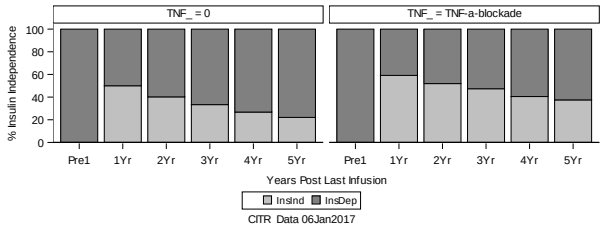
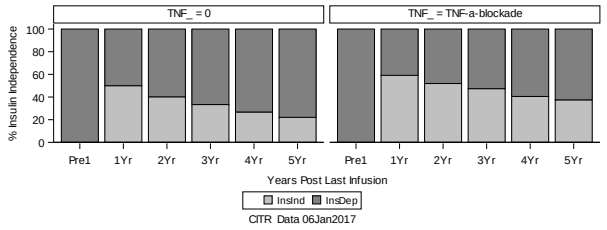
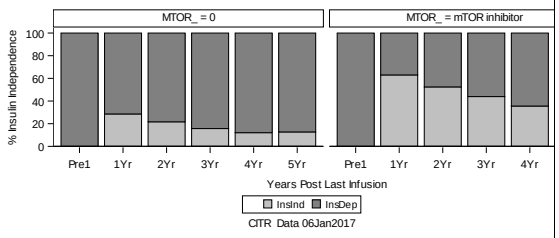


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

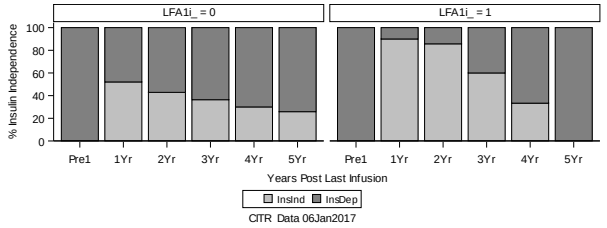
W. Maintenance Immunosuppression with Calcineurin Inhibitor favorable (p=0.0160)



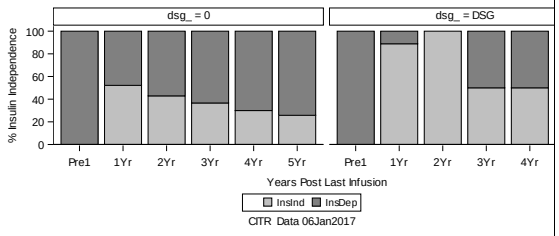
X. Maintenance Immunosuppression with mTOR Inhibitor favorable (p<0.0001)



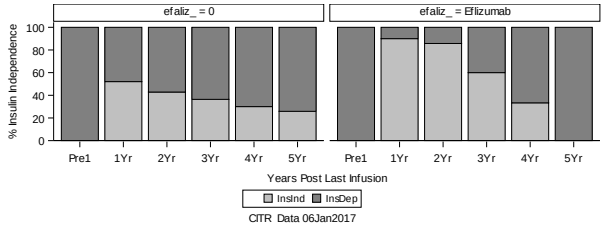
Y. Maintenance Immunosuppression with LFA1i favorable (p=0.0002)



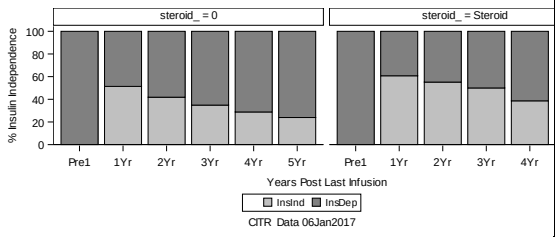
Z. Maintenance Immunosuppression with DSG favorable (p<0.0001)



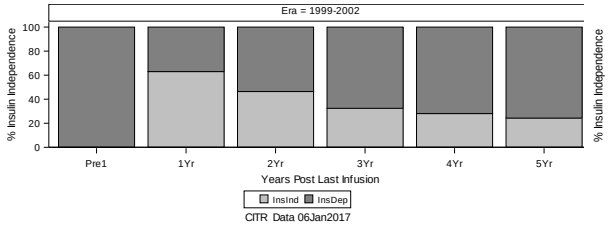
AA. Maintenance Immunosuppression with Maintenance Immunosuppression with Eflizumab favorable (p=0.0002)

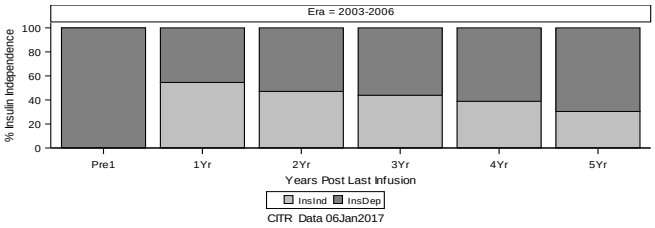


BB. Maintenance Immunosuppression with Steroid favorable (p=0.0172)



CC. Era (p=0.0040)





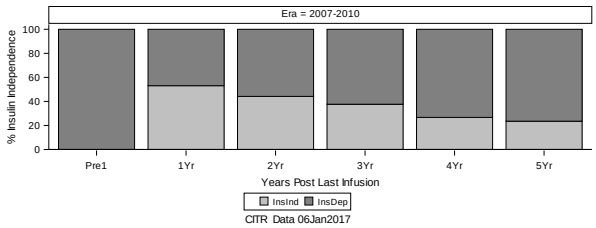


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

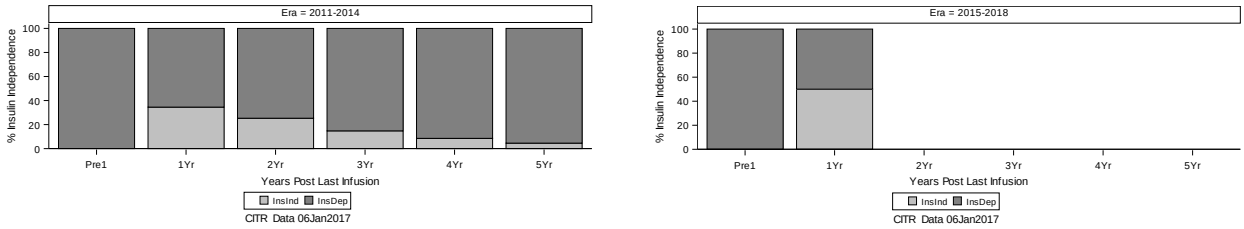
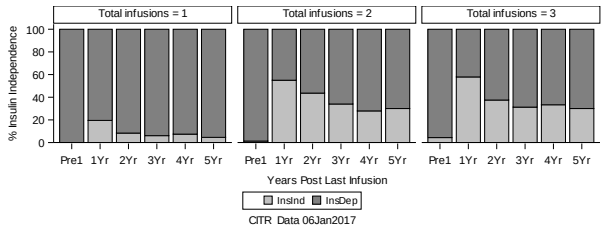
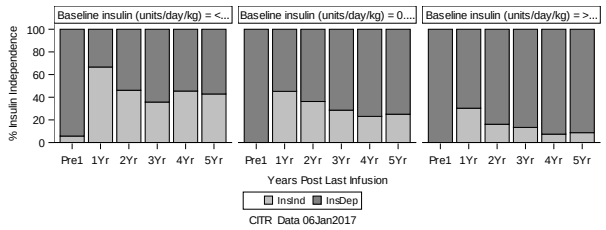


Exhibit 5 – 2C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

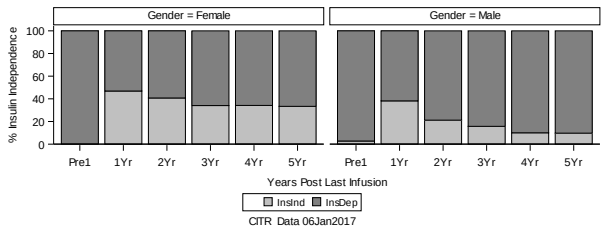
A. Total infusions ≥ 2 favorable (p=0.0029)



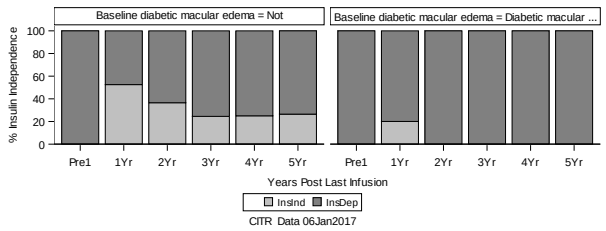
B. Baseline insulin <0.66 units/day/kg recipient weight favorable (p=0.0128)



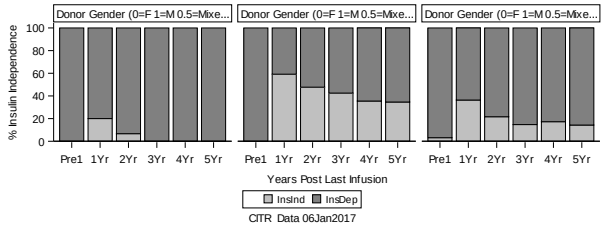
C. Recipient gender female favorable (p=0.0255)



D. Baseline diabetic macular edema unfavorable (p=0.0308)



E. Donor gender mixed favorable (p=0.0003)



F. Donor given transfusions prior to surgery favorable (p=0.0198)

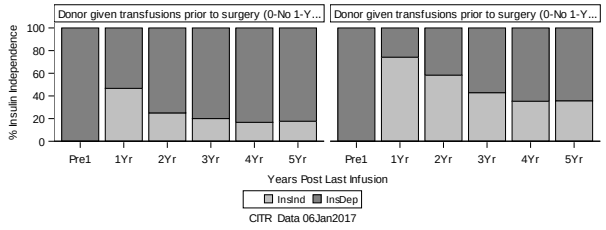
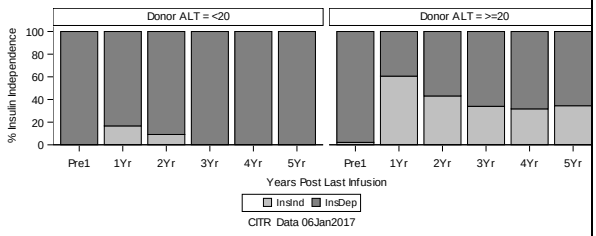
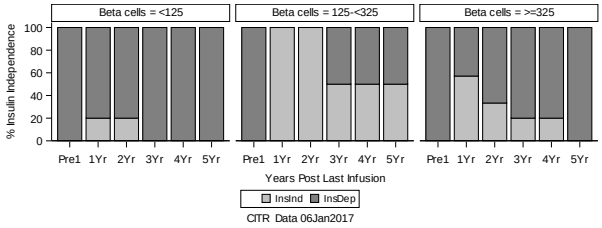


Exhibit 5 – 2C (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

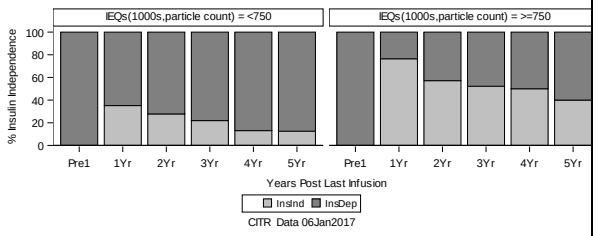
G. Donor ALT ≥ 20 favorable (p=0.0099)



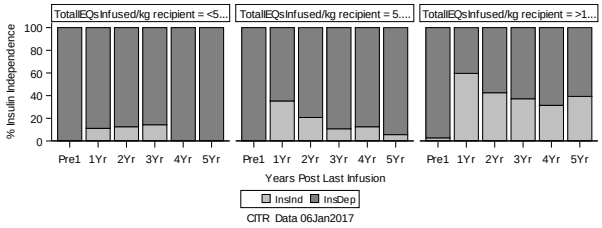
H. Beta cells 125-<325 favorable (p=0.0346)



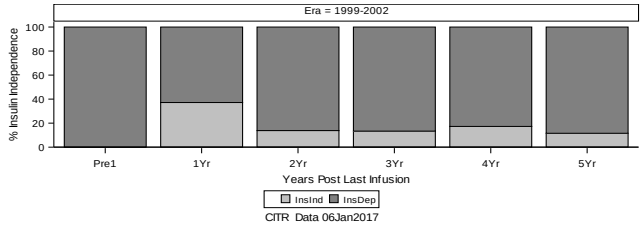
I. IEQ particle count ≥ 750 (1000s) favorable (p=0.0017)

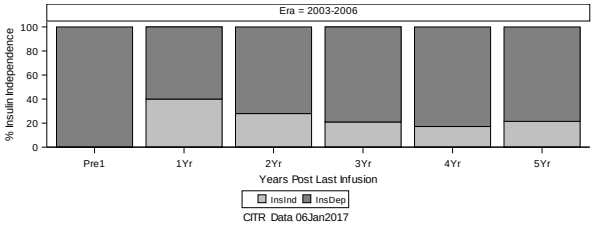


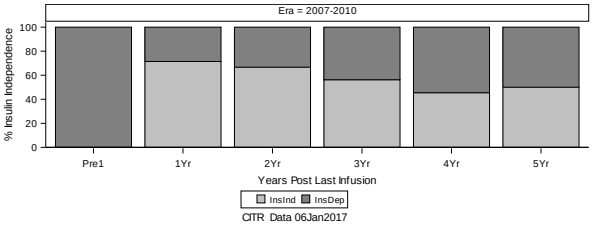
J. IEQs infused per kg recipient weight > 10.45 favorable (p=0.0106)

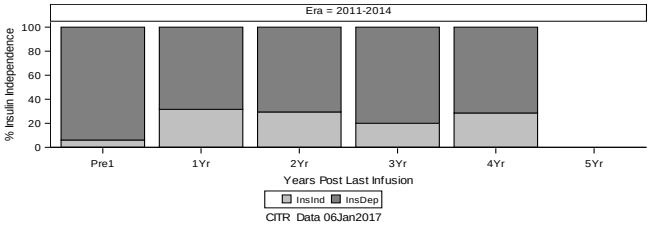


K. Era (p=0.0005)









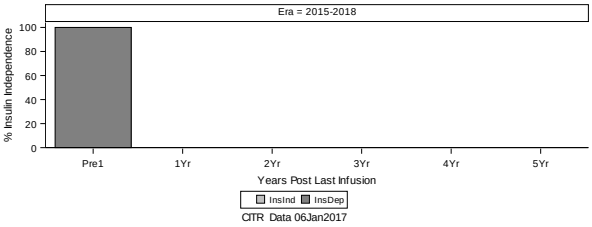
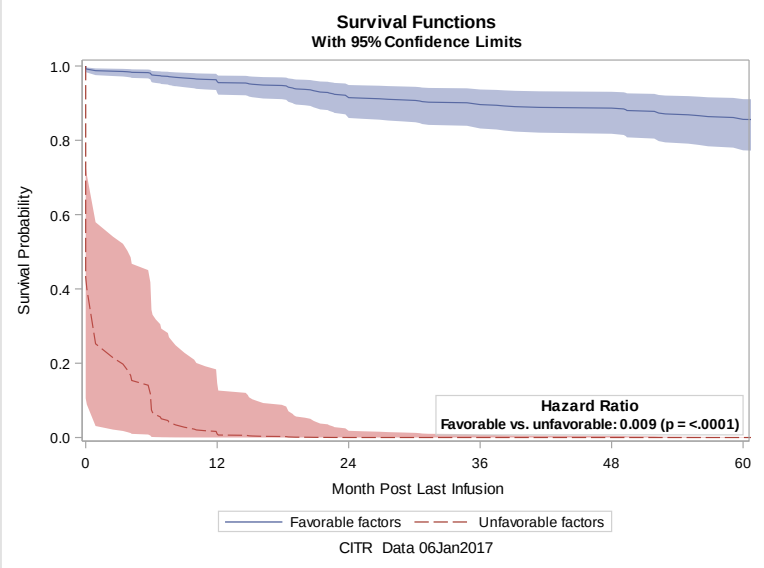


Exhibit 5 – 3
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion

A1. ITA		
Factors	**p-value**	**Hazard Ratio**
Recipient Age (1= ≥35, 0= <35)	<0.0001	0.326
Number of Infusions (1=two or more, 0=one)	0.0112	0.588
T-cell Depletion (1=Yes, 0=No)	0.0395	0.576
Calcineurin Inhibitor (1=Yes, 0=No)	<0.0001	0.181
Islets Cultured ≥ 6 hours (1=Yes, 0=No)	<0.0001	0.457



A2. IAK		
Factors	**p-value**	**Hazard Ratio**
IEQs Infused (1=IEQs ≥325K, 0=IEQs <325K)	0.0032	0.231
Era (1=2003 or later, 0=1999-2002)	0.0002	0.263

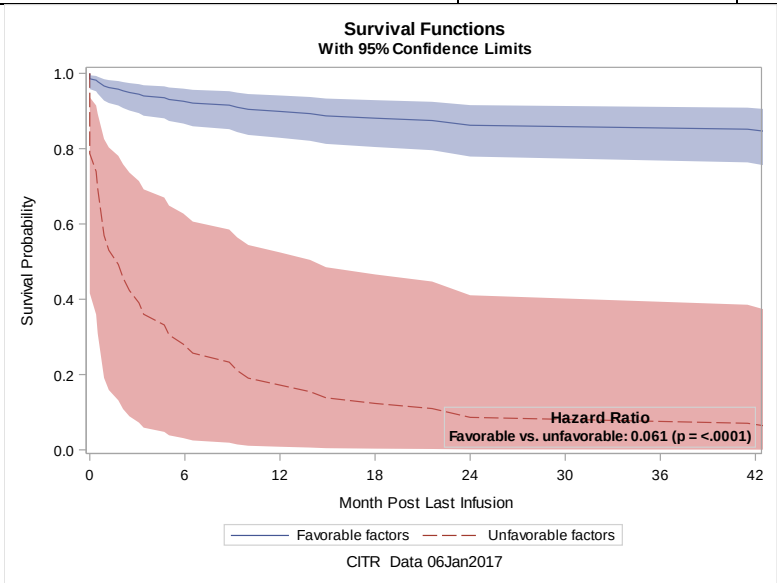
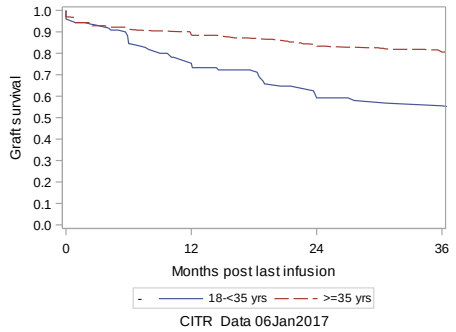


Exhibit 5 – 3 *(continued)*
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion

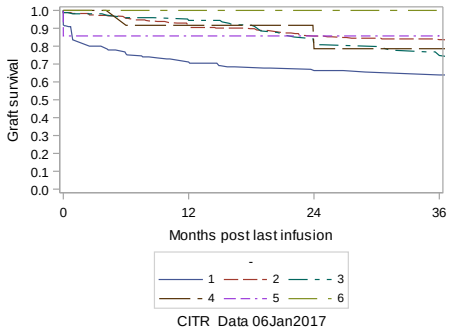
Effects of Individual factors

ITA

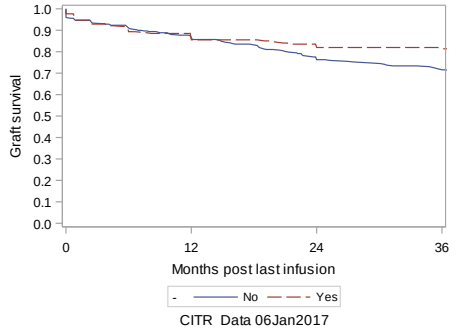
B1. Recipient Age ≥ 35 favorable



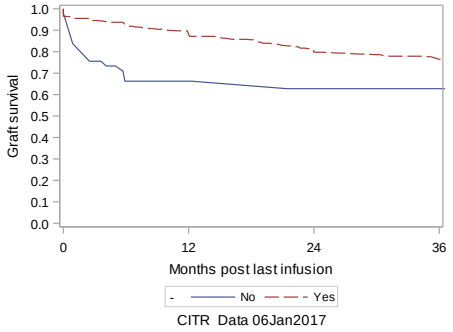
C1. Number of Infusions > 1 favorable



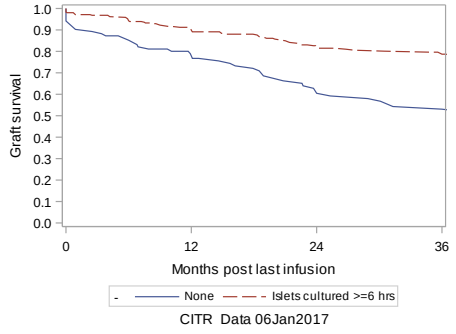
D1. Induction Immunosuppression with T-cell depletion favorable



E1. Maintenance Immunosuppression with calcineurin inhibitor favorable

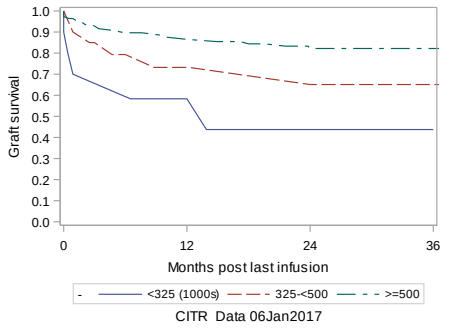


F1. Islets Cultured ≥ 6 hours favorable



IAK

B2. IEQs Infused ≥325,000 favorable



C2. Era 2003 or later favorable

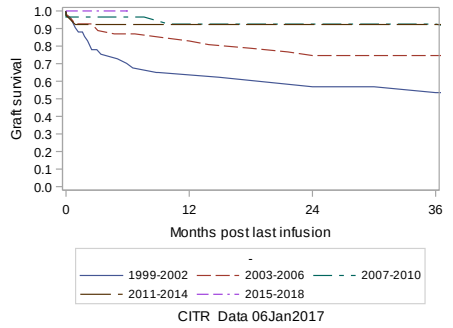


Exhibit 5-4A
Unadjusted Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion

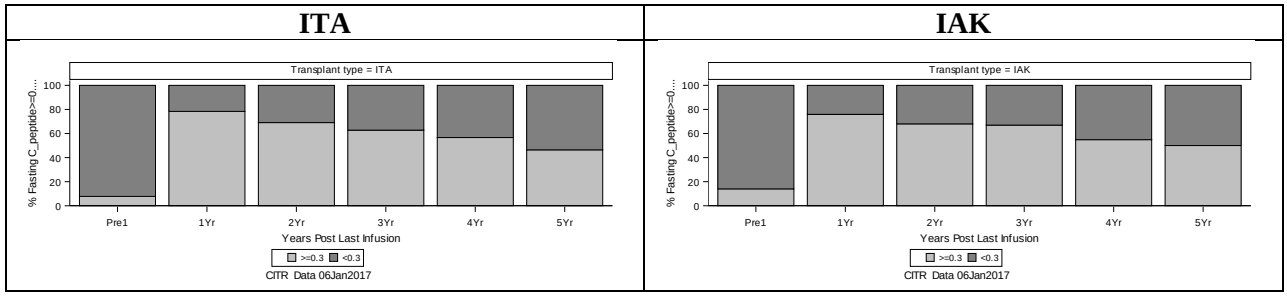


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among <u>ITA Recipients</u>

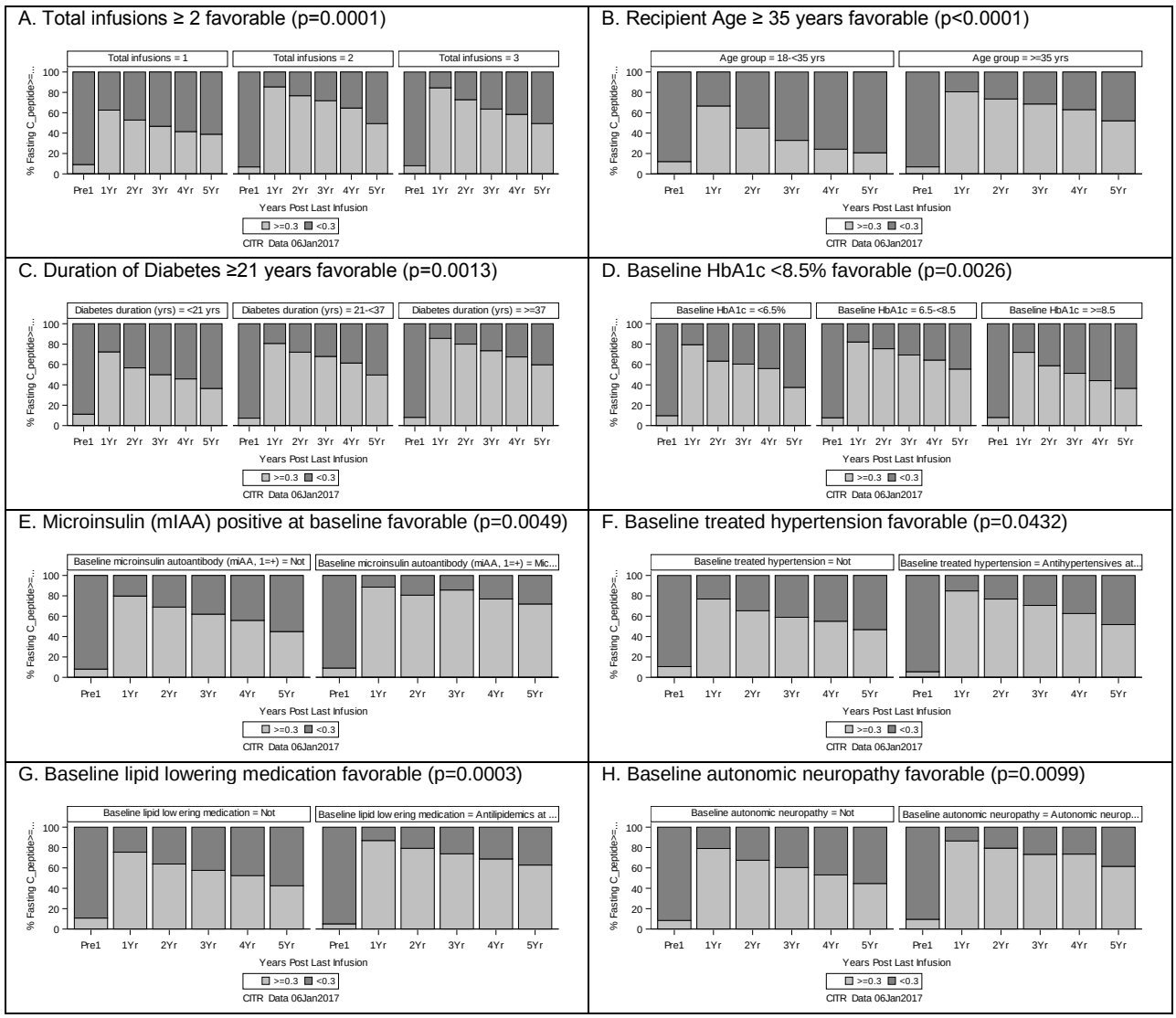
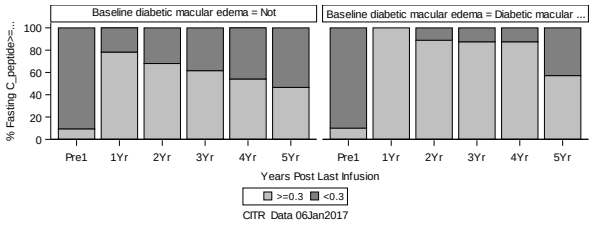
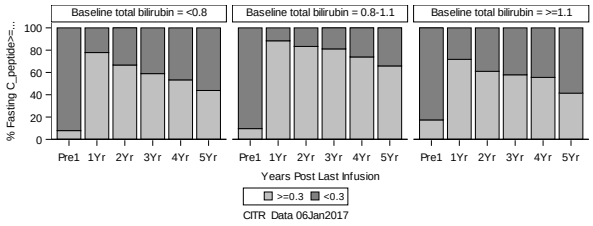


Exhibit 5-4B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

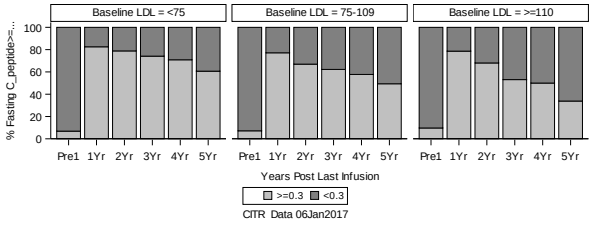
I. Baseline diabetic macular edema favorable (p=0.0049)



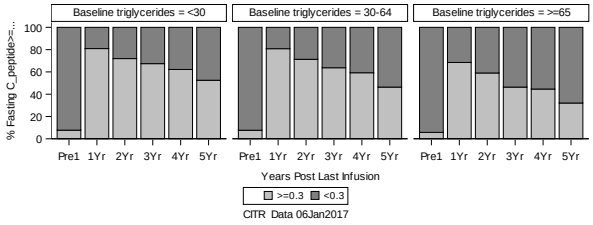
J. Baseline total bilirubin 0.8-1.1 favorable (p=0.0009)



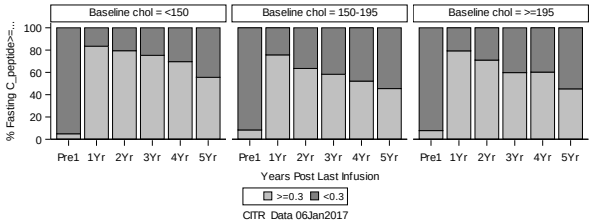
K. Baseline LDL <110 favorable (p=0.0216)



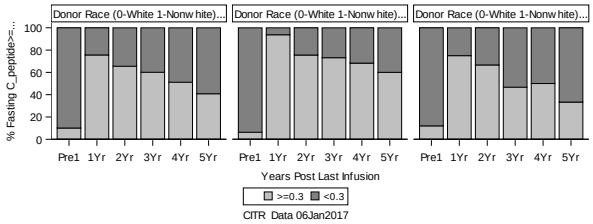
L. Baseline triglycerides < 65 favorable (p=0.0285)



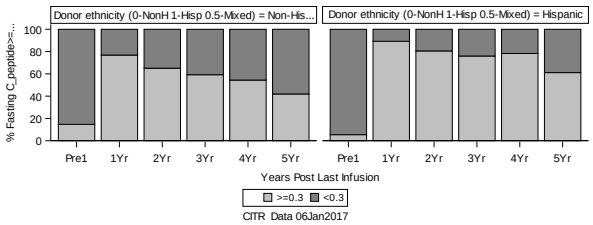
M. Baseline cholesterol <150 favorable (p=0.0145)



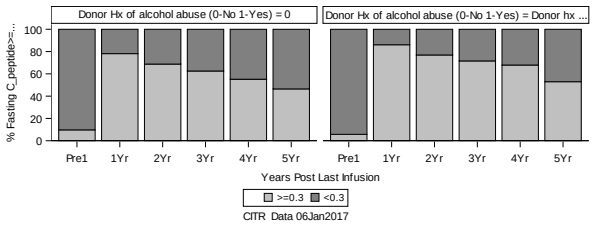
N. Donor race mixed favorable (p=0.0170)



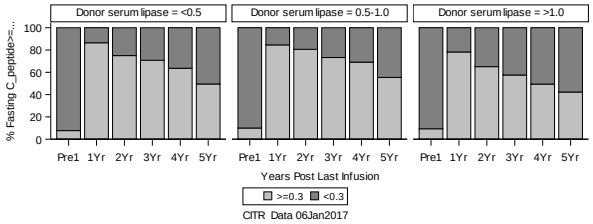
O. Donor ethnicity Hispanic favorable (p=0.0310)



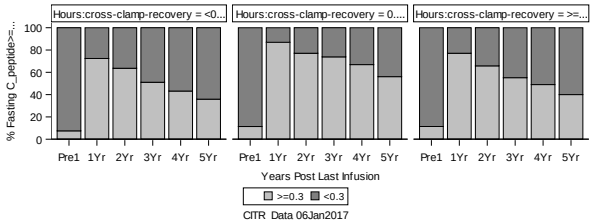
P Donor Hx of alcohol abuse favorable (p=0.0422)



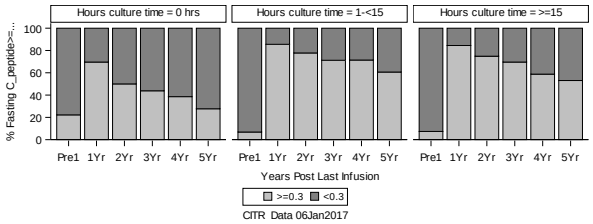
Q. Donor serum lipase ≤ 1.0 favorable (p=0.0411)



R. Hours: cross-clamp-recovery 0.5-<1.0 favorable (p=0.0078)



S. Hours culture time > 0 favorable (p=0.0007)



T. Trapped cells ≥ 5 favorable (p=0.0314)

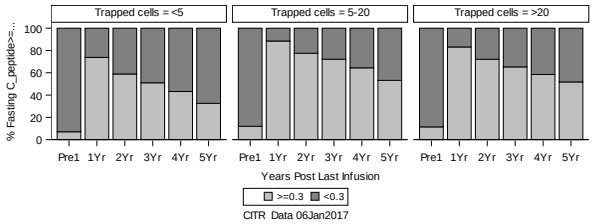
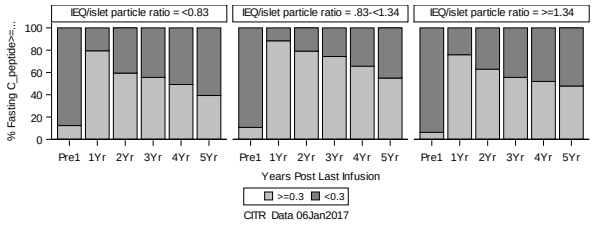
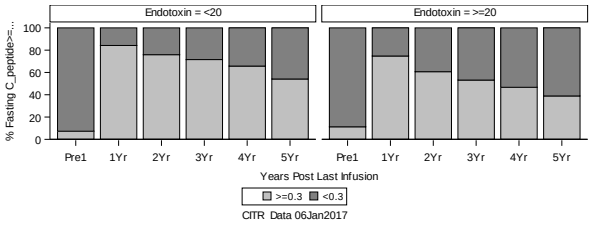


Exhibit 5-4B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

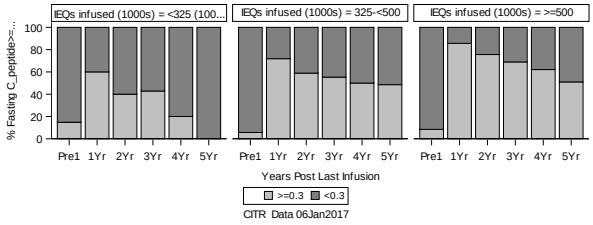
U. IEQ/islet particle ratio 0.83-<1.34 favorable (p=0.0091)



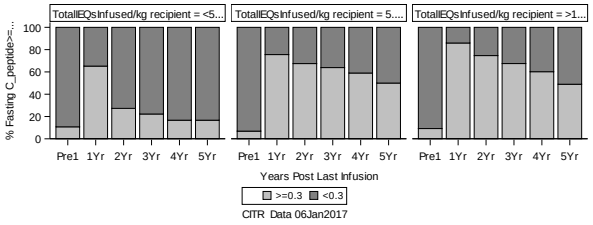
V. Endotoxin < 20 favorable (p=0.0065)



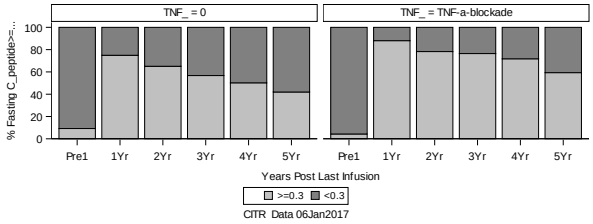
W. IEQs infused ≥500 (1000s) favorable (p=0.0109)



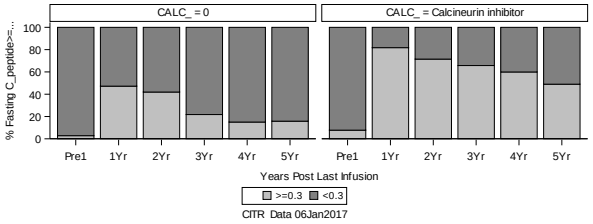
X. Total IEQs Infused/kg recipient >10.45 favorable (p=0.0498)



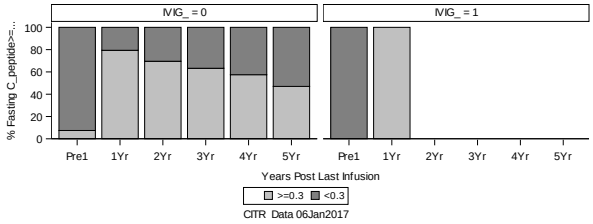
Y. Induction Immunosuppression with TNF-a-blockade favorable (p<0.0001)



Z. Maintenance Immunosuppression with Calcineurin Inhibitor favorable (p=0.0013)



AA. Maintenance Immunosuppression with IVIG favorable (p<0.0001)



BB. Maintenance Immunosuppression with DSG favorable (p=<0.0001)

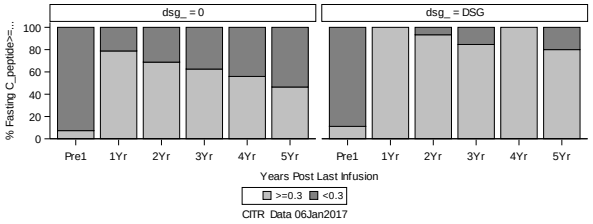
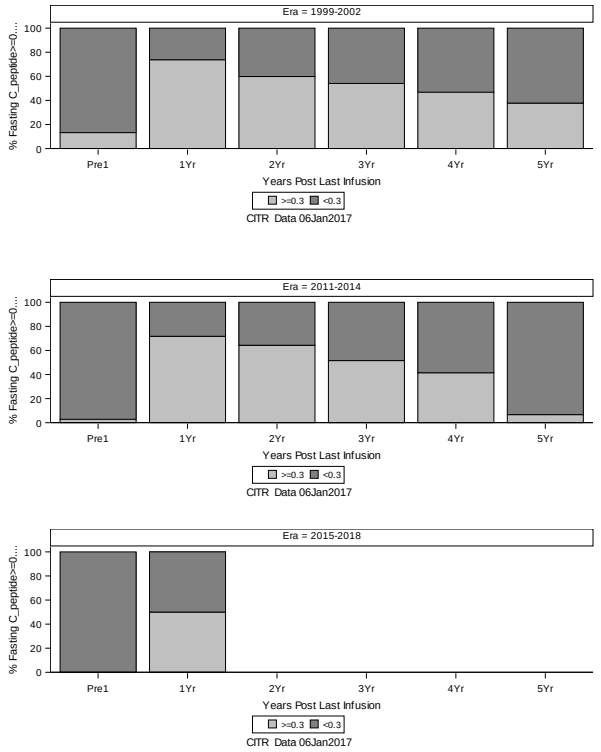
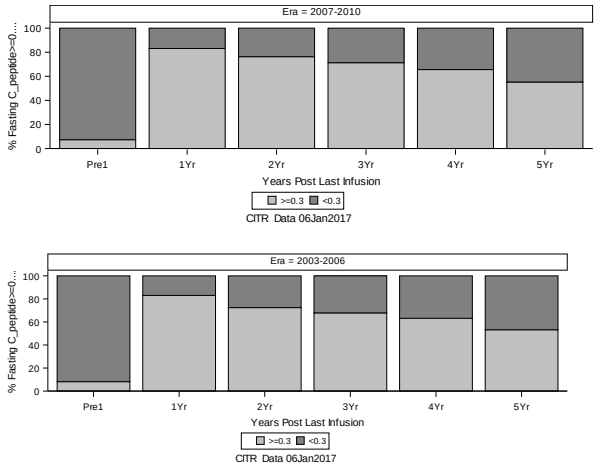


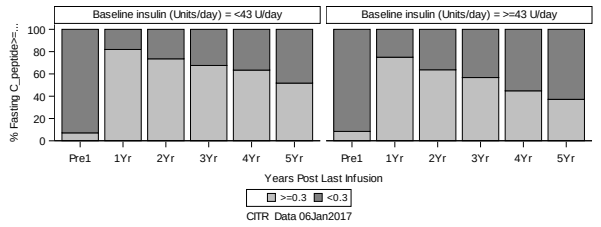
Exhibit 5-4B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

CC. Era (p=0.0063)





DD. Baseline insulin (Units/day) <43 favorable (p=0.0172)



EE. Islets Cultured >6 hrs favorable (p=0.0004)

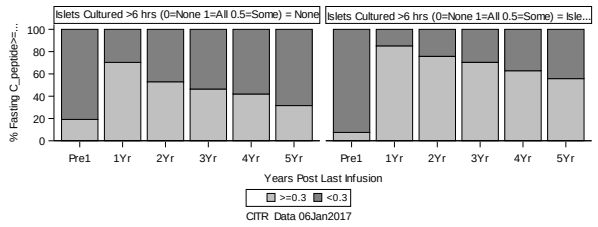
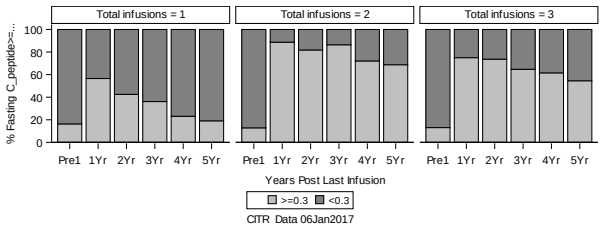
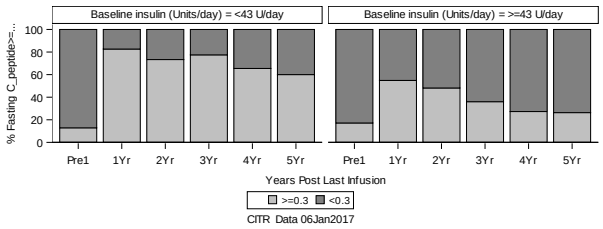


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

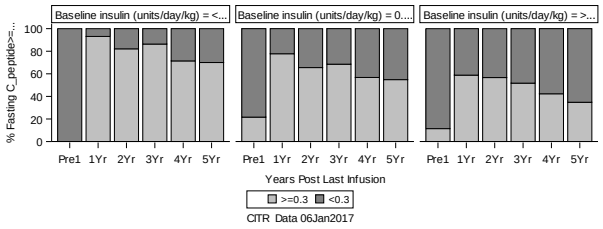
A. Total infusions ≥ 2 favorable (p=0.0002)



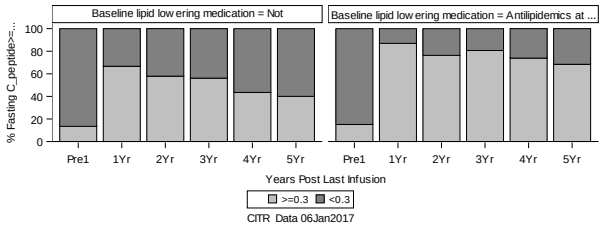
B. Baseline insulin <43 units/day favorable (p=0.0066)



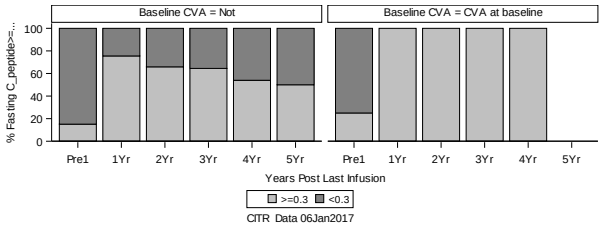
C. Baseline insulin <0.66 units/day/kg recipient weight favorable (p=0.0140)



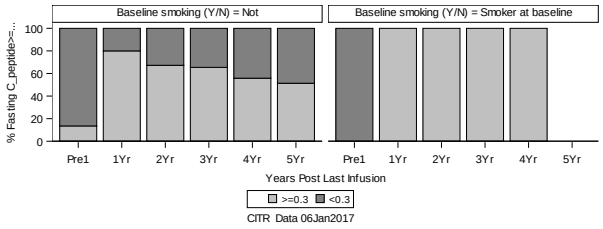
D. Baseline lipid lowering medication favorable (p=0.0087)



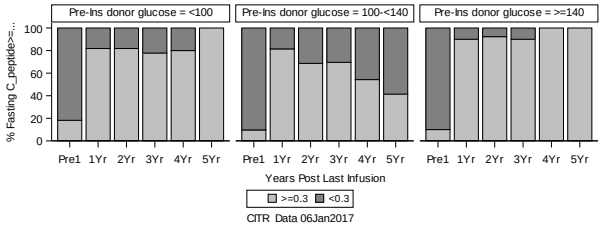
E. Baseline CVA favorable (p<0.0001)



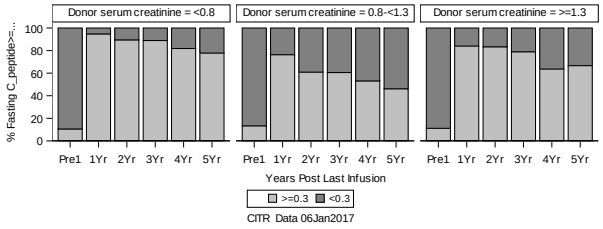
F. Baseline Smoking favorable (p<0.0001)



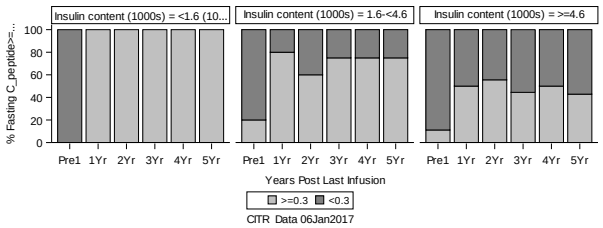
G. Pre-Ins donor glucose ≥140 favorable (p=0.0035)



H. Donor serum creatinine <0.8 favorable (p=0.0326)



I. Insulin content (1000s) 1.5-<4.6 favorable (p=0.0402)



J. Packed cell volume (mL) 2.5 - < 5 favorable (p=0.0001)

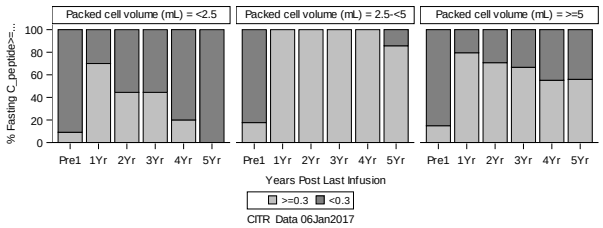
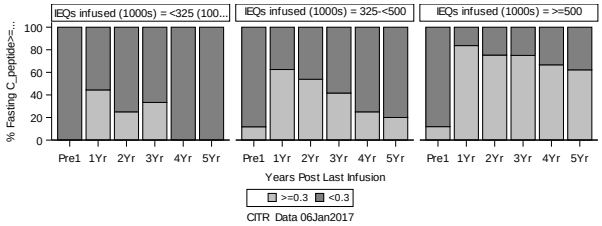
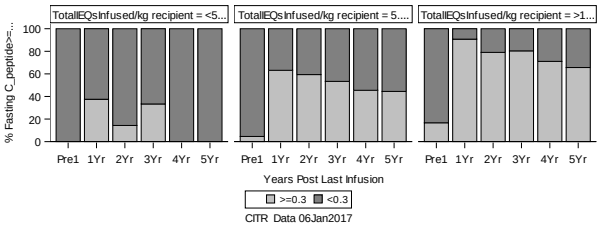


Exhibit 5-4C (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

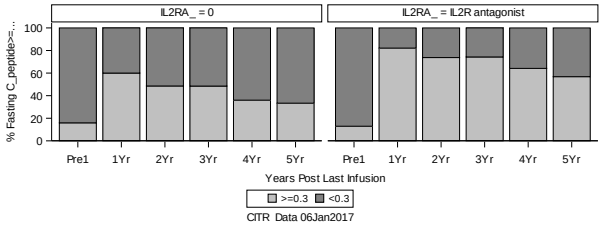
K. IEQs infused ≥500 (1000s) favorable (p=0.0153)



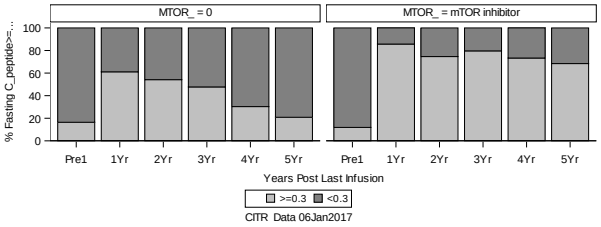
L. IEQs infused per kg recipient weight >10.45 (1000s) favorable (p=0.0043)



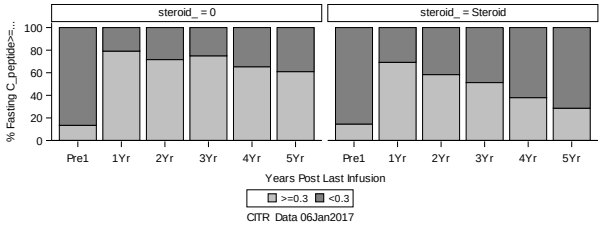
M. Induction Immunosuppression with IL2R antagonist favorable (p=0.0198)



N. Maintenance Immunosuppression with mTOR Inhibitor favorable (p=0.0012)



O. Steroid unfavorable (p=0.0369)



P. Era (p=0.0045)

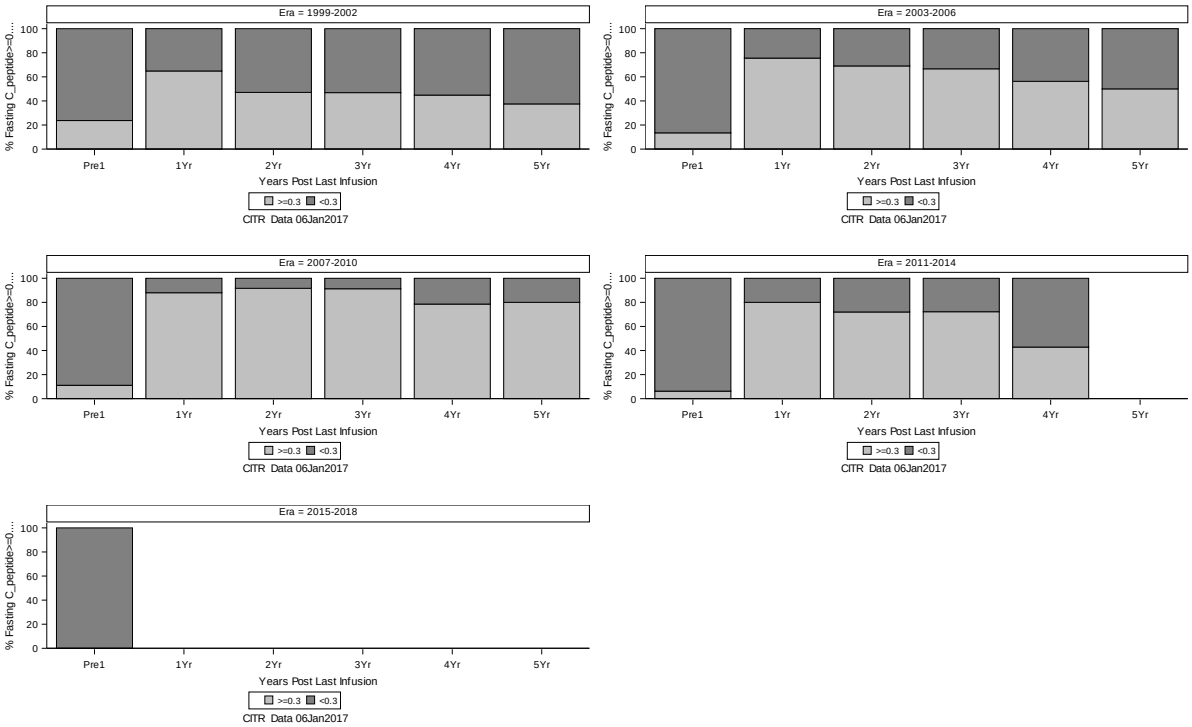


Exhibit 5-5A
Unadjusted Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion

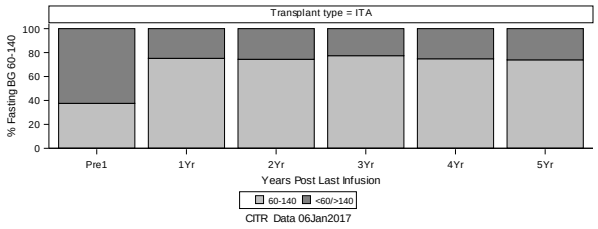
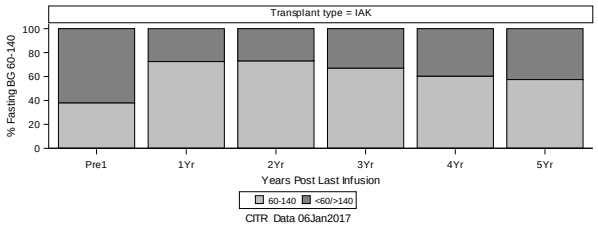
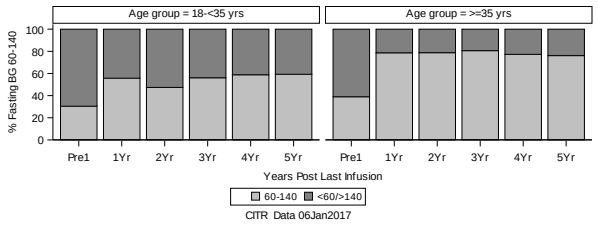
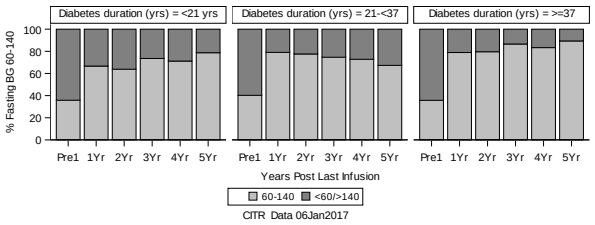
ITA	IAK
	

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

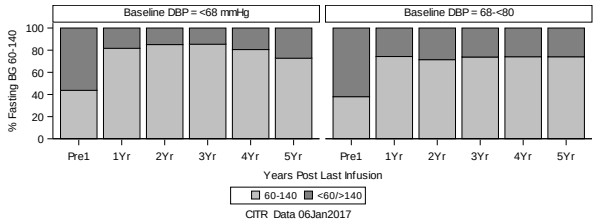
A. Recipient Age ≥35 years favorable (p<0.0001)



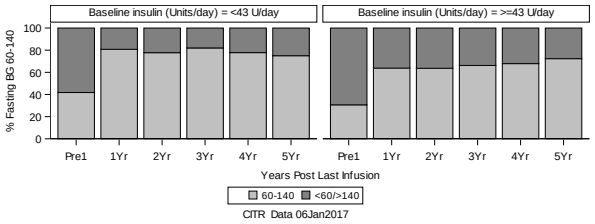
B. Duration of diabetes ≥ 37 years favorable (p=0.0099)



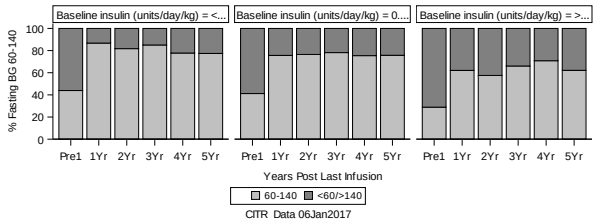
C. Baseline DBP <68 mmHg favorable (p=0.0101)



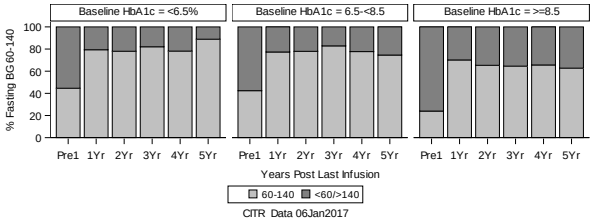
D. Baseline Insulin <43 units/day favorable (p=0.0014)



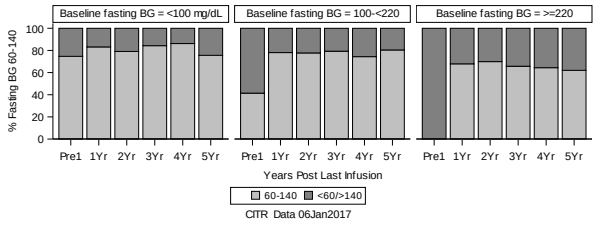
E. Baseline Insulin <0.66 units/day per kg recipient weight favorable (p=0.0009)



F. Baseline HbA1c < 8.5% favorable (p=0.0112)



G. Baseline Fasting Blood Glucose < 220 favorable (p=0.0091)



H. Baseline insulin autoantibody negative favorable (p=0.0007)

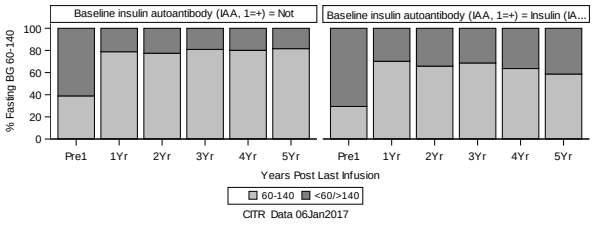
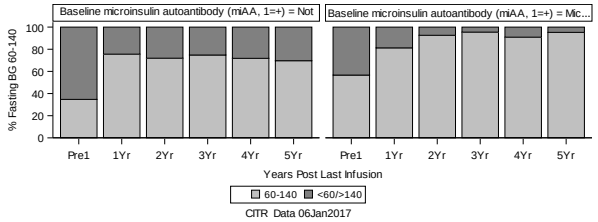
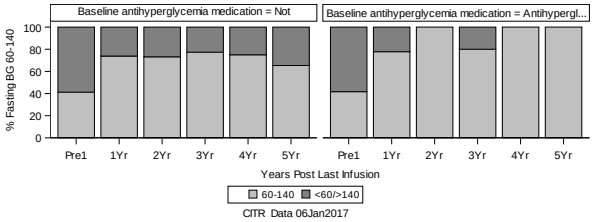


Exhibit 5-5B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

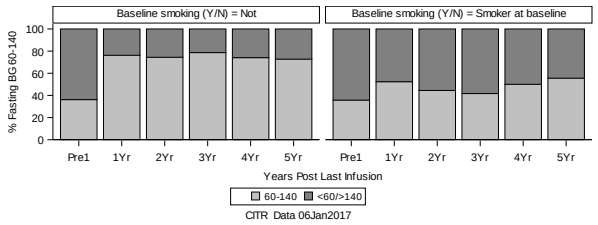
I. Baseline microinsulin autoantibody positive favorable (p<0.0001)



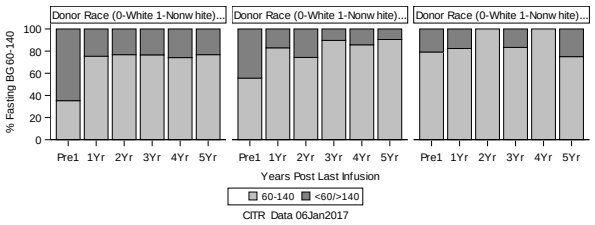
J. Baseline antihyperglycemia medication favorable (p=0.0102)



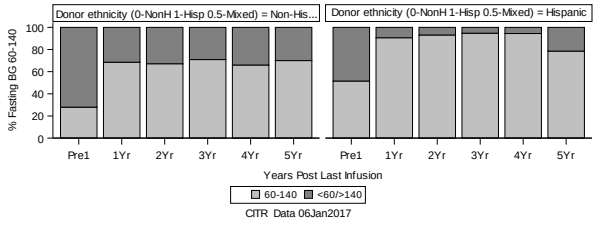
K. Baseline nonsmoker favorable (p=0.0284)



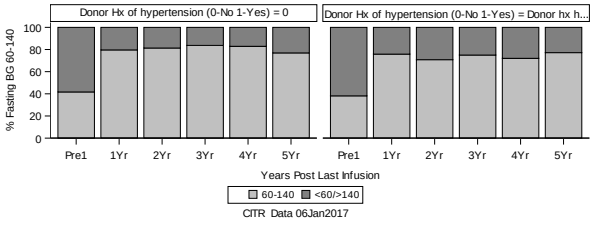
L. Donor Race: Mix favorable (p=0.0120)



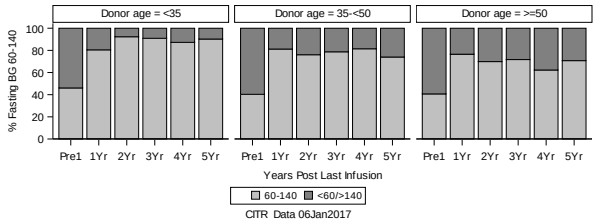
M. Donor Ethnicity: Hispanic favorable (p<0.0001)



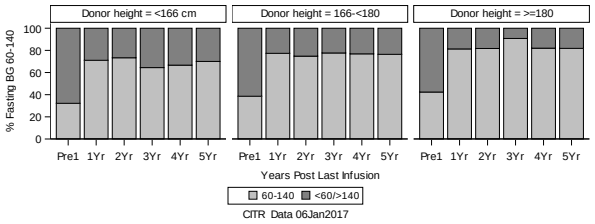
N. Donor with no history of hypertension favorable (p=0.0263)



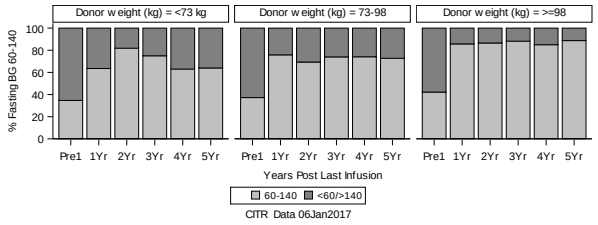
O. Donor age < 35 favorable (p=0.0029)



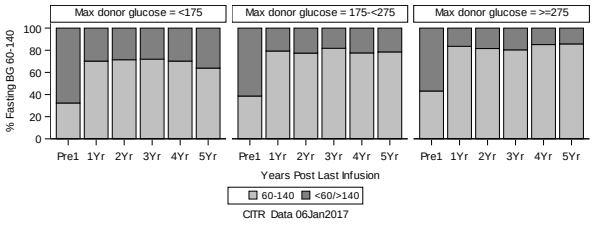
P. Donor height ≥ 180 cm favorable (p=0.0214)



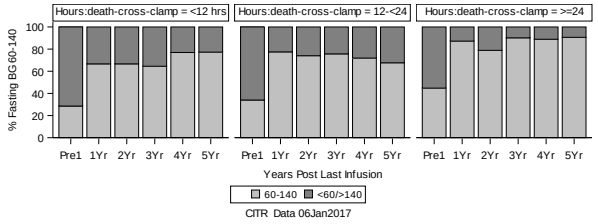
Q. Donor weight ≥98 kg favorable (p<0.0001)



R. Max donor glucose ≥ 275 favorable (p=0.0441)



S. Hours from Death to Cross-Clamp ≥ 24 favorable (p=0.0007)



T. Hours: death-recovery ≥ 24 favorable (p=0.0244)

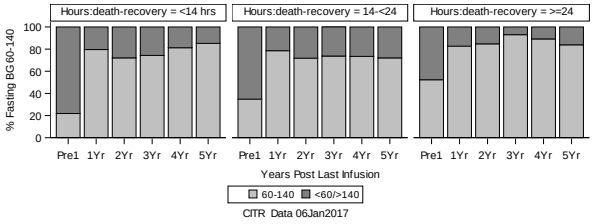
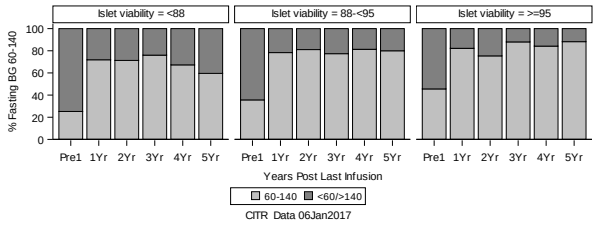
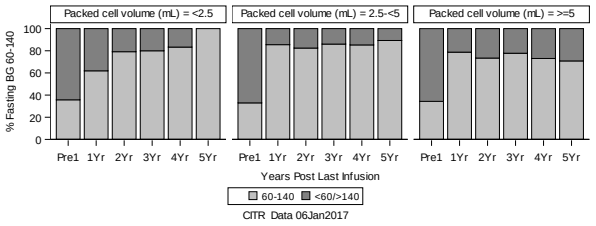


Exhibit 5-5B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

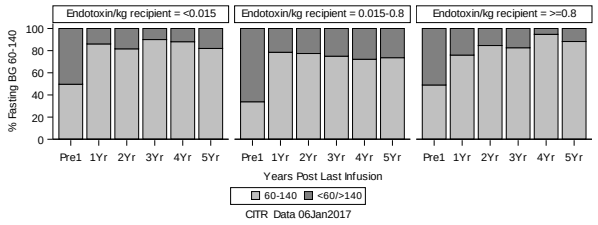
U. Islet viability ≥ 95 favorable (p=0.0191)



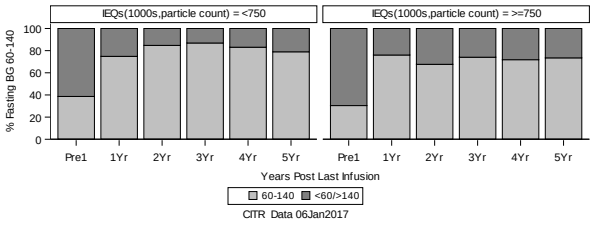
V. Packed cell volume (mL) 2.5-<5 favorable (p=0.0143)



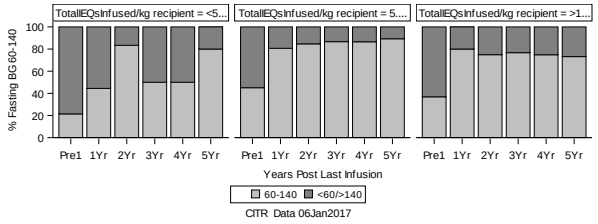
W. Endotoxin/kg recipient ≥ 0.8 favorable (p=0.0179)



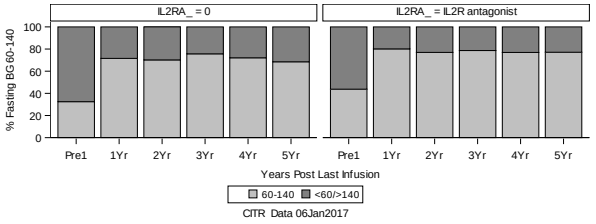
X. IEQs(1000s,particle count) <750 favorable (p=0.0167)



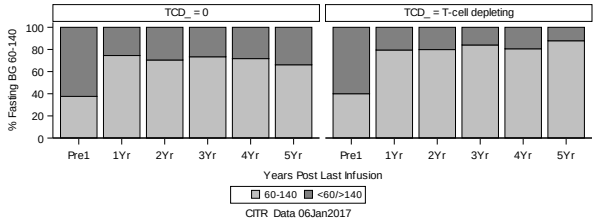
Y. Total IEQs Infused/kg recipient ≥ 5.15K favorable (p=0.0029)



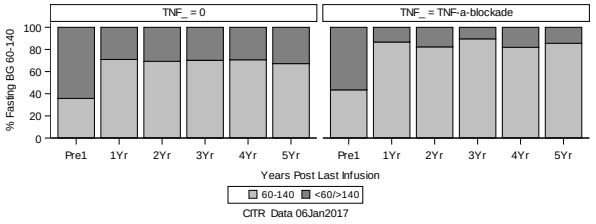
Z. Induction Immunosuppression with IL2RA favorable (p=0.0420)



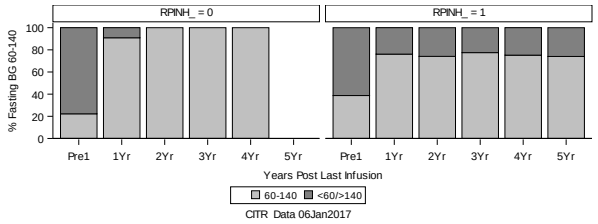
AA. Induction Immunosuppression with T-cell depletion favorable (p=0.0014)



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



CC. Maintenance Immunosuppression with RPINH unfavorable (p=0.0109)



DD. Maintenance Immunosuppression with mTOR inhibitor favorable (p=0.0005)

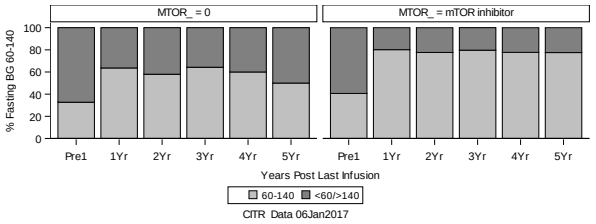
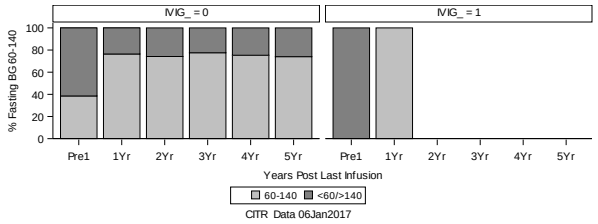
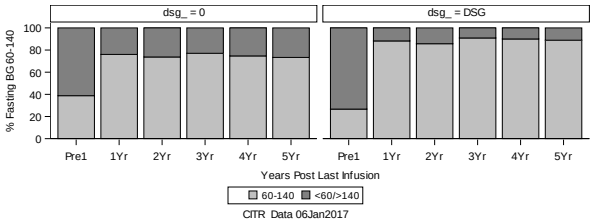


Exhibit 5-5B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

EE. Maintenance Immunosuppression with IVIG favorable (p<0.0001)



FF. Maintenance Immunosuppression with DSG favorable (p=0.0125)



GG. Steroid favorable (p=0.0175)

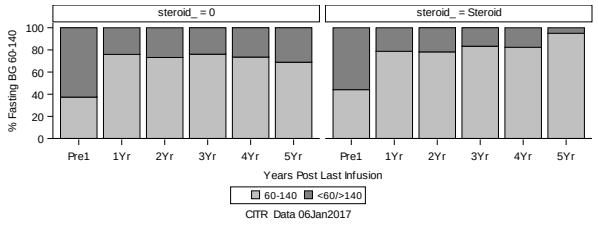
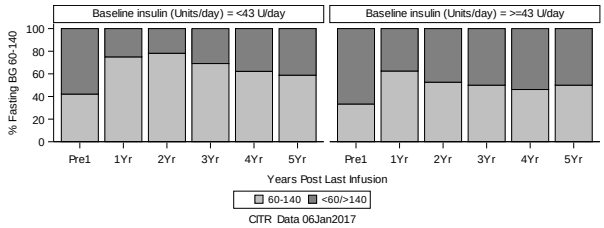
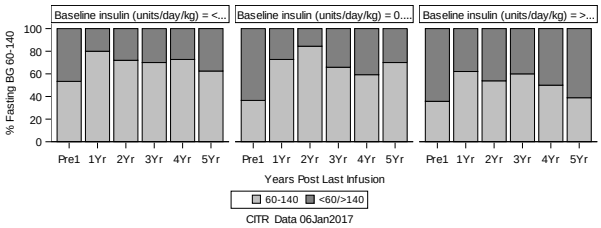


Exhibit 5-5C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

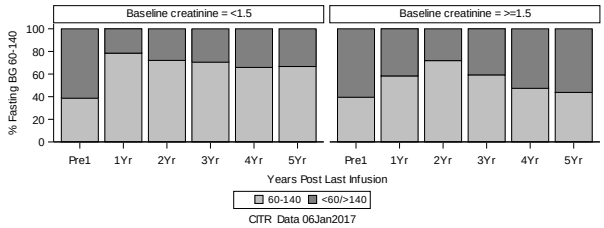
A. Baseline insulin <43 units/day favorable (p=0.0340)



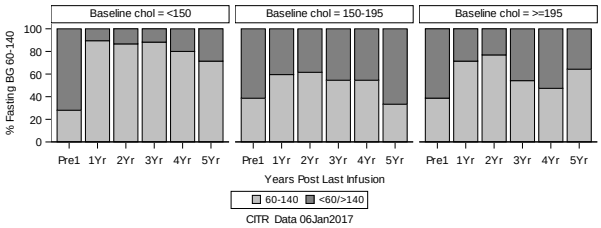
B. Baseline insulin (units/day/kg) < 0.66 favorable (p=0.0496)



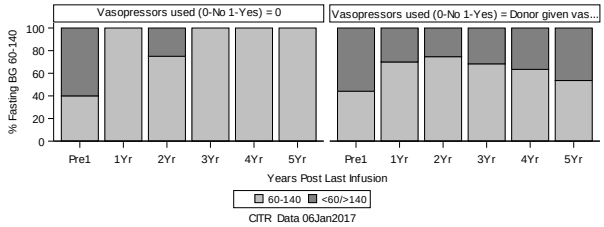
C. Baseline creatinine < 1.5 favorable (p=0.0424)



D. Baseline cholesterol < 150 favorable (p=0.0002)



E. Donor given vasopressors unfavorable (p=0.0090)



F. Pre-Ins donor glucose < 100 favorable (p=0.0038)

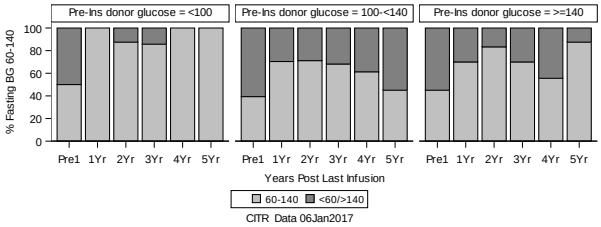
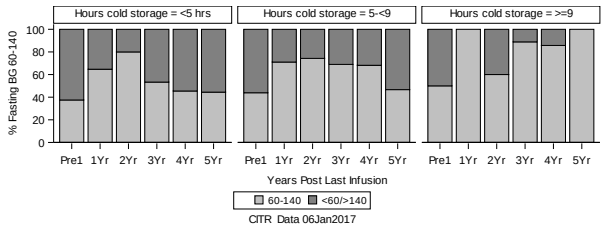
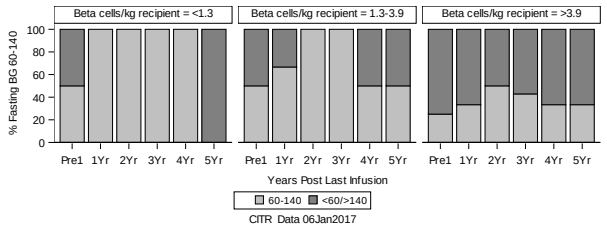


Exhibit 5-5C (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

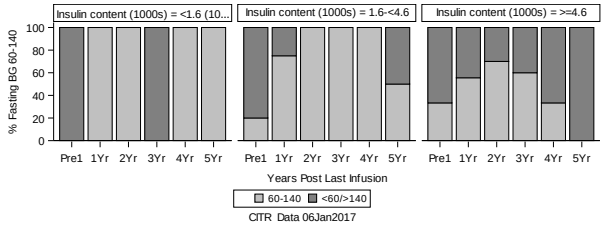
G. Hours cold storage ≥ 9 favorable (p=0.0444)



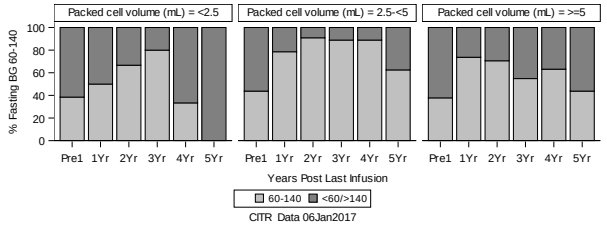
H. Beta cells/kg recipient < 1.3 favorable (p=0.0112)



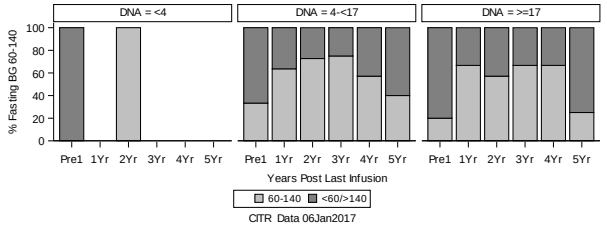
I. Insulin content <4.6 (1000s) favorable (p=0.0066)



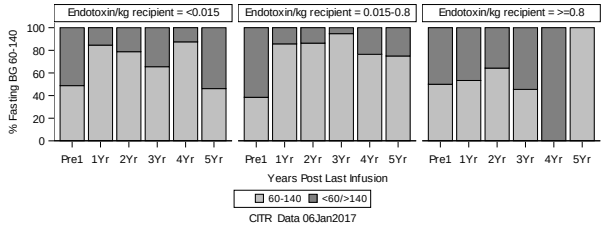
J. Packed cell volume (mL) 2.5-<5 favorable (p=0.0480)



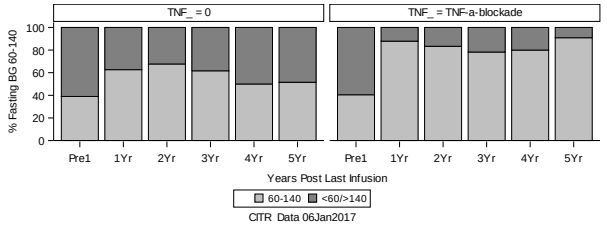
K. DNA < 17 favorable (p=0.0047)



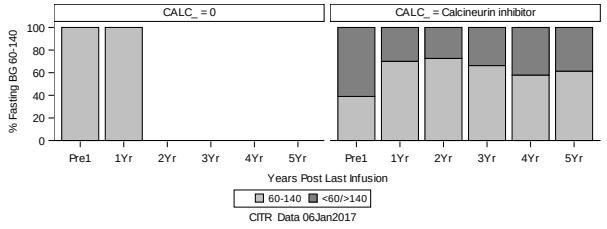
L. Endotoxin/kg recipient <0.8 favorable (p=0.0019)



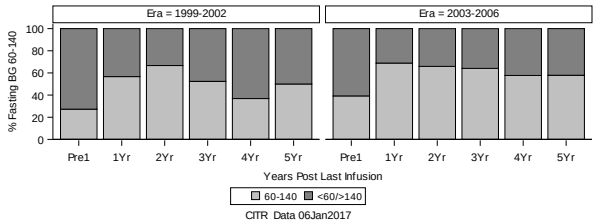
M. Induction Immunosuppression with TNF-a-blockade favorable (p=0.0001)



N. Maintenance Immunosuppression with Calcineurin inhibitor favorable (p<0.0001)



O. Era (p=0.0002)



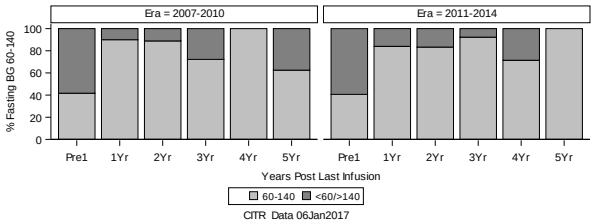
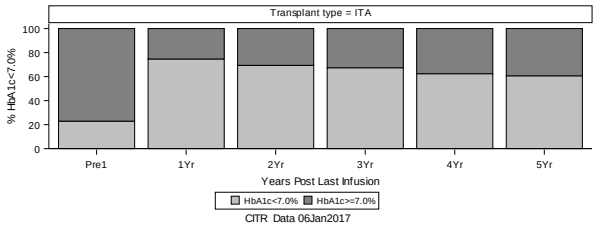


Exhibit 5-6A
Unadjusted Prevalence of HbA1c<7.0% Post Last Infusion

ITA



IAK

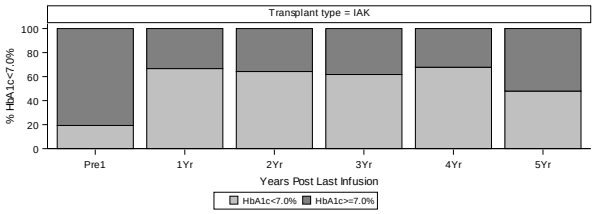
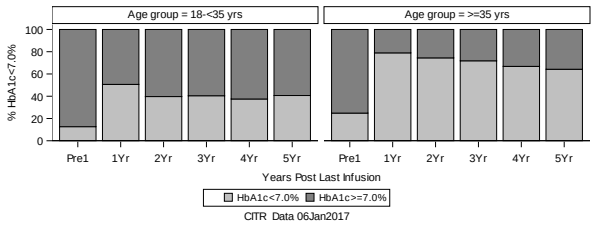
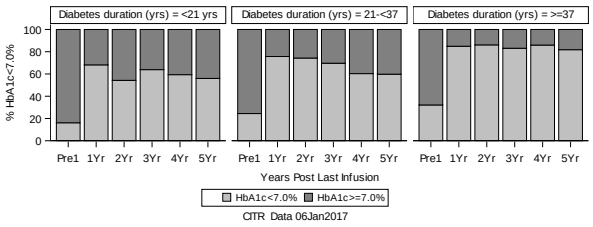


Exhibit 5 – 6B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% Post Last Infusion among <u>ITA Recipients</u>

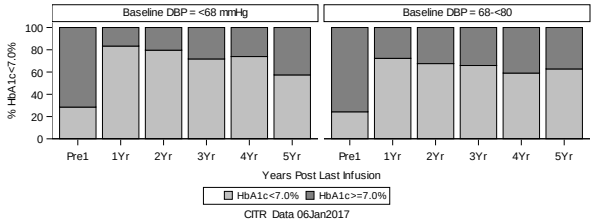
A. Recipient Age ≥ 35 years favorable (p<0.0001)



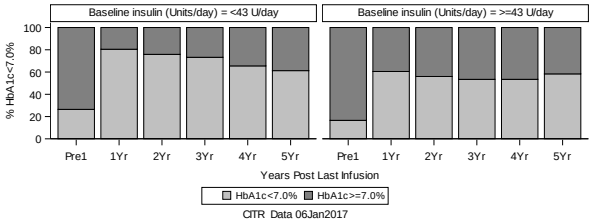
B. Duration of diabetes ≥ 37 favorable (p<0.0001)



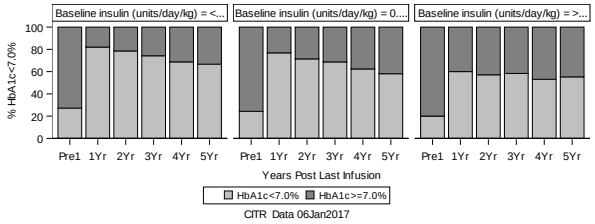
C. Baseline DBP <68 mmHg favorable (p=0.0211)



D. Baseline insulin <43 units/day favorable (p=0.0009)



E. Baseline insulin <0.66 units/day per kg recipient weight favorable (p=0.0081)



F. Baseline HbA1c <6.5% favorable (p<0.0001)

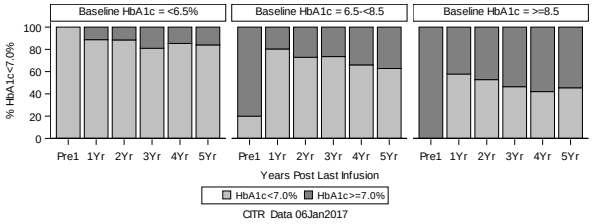
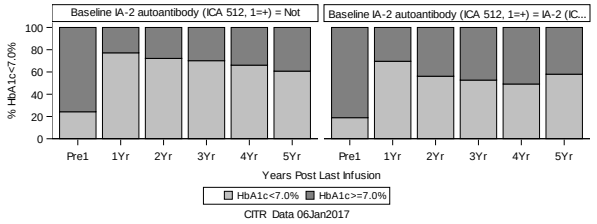
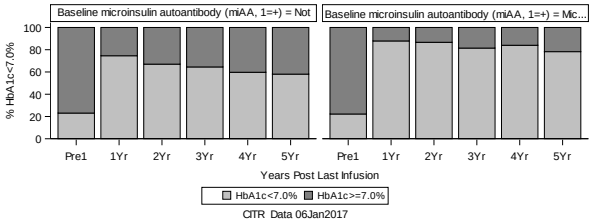


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

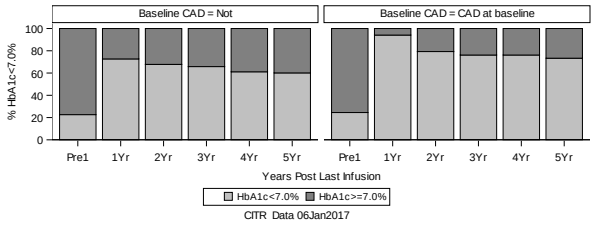
G. Baseline IA-2 autoantibody negative favorable (p=0.0170)



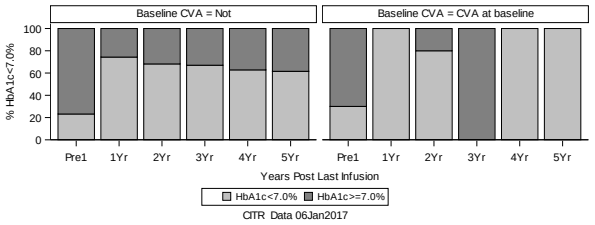
H. Baseline microinsulin autoantibody positive favorable (p=0.0002)



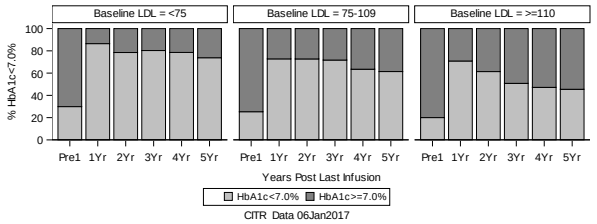
I. Baseline CAD favorable (p=0.0074)



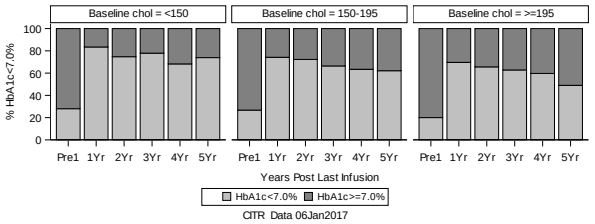
J. Baseline CVA favorable (p=0.0209)



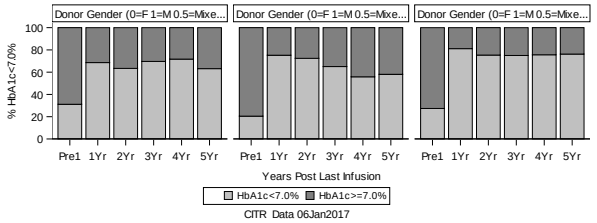
K. Baseline LDL < 75 favorable (p=0.0002)



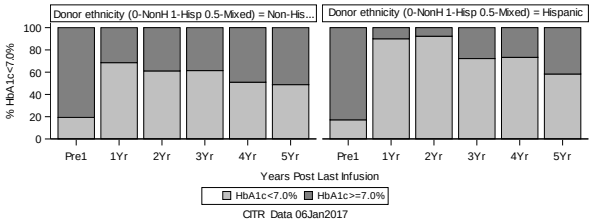
L. Baseline cholesterol < 150 favorable (p=0.0324)



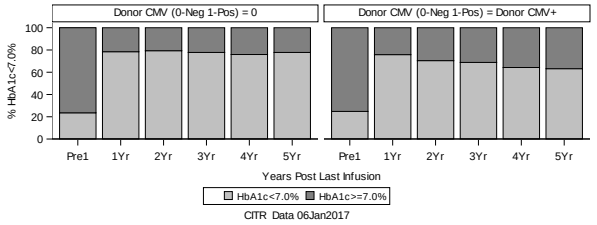
M. Donor gender male favorable (p=0.0388)



N. Donor ethnicity Hispanic favorable (p=0.0031)



O. Donor CMV negative favorable (p=0.0378)



P. CVA death of donor unfavorable (p=0.0126)

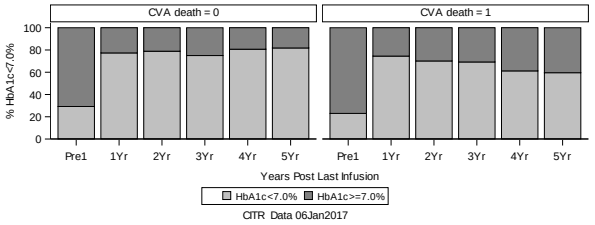
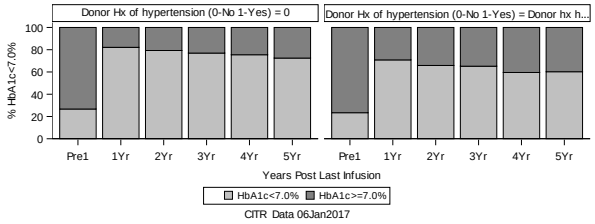
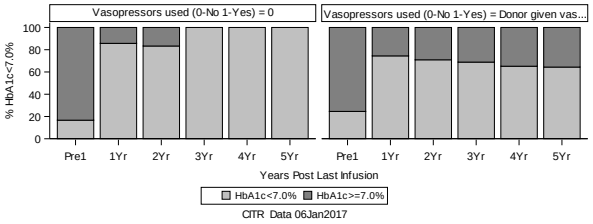


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

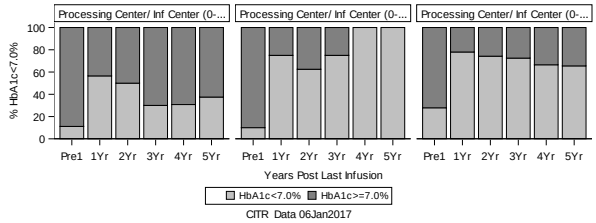
Q. No donor history of hypertension favorable (p=0.0007)



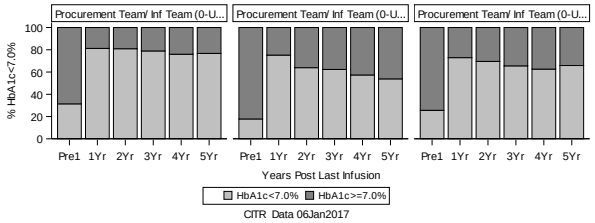
R. Donor given vasopressors unfavorable (p=0.0068)



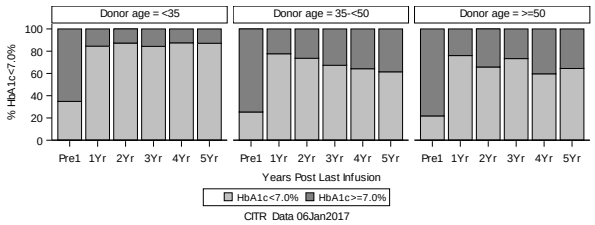
S. Processing Center/ Inf Center related favorable (p=0.0217)



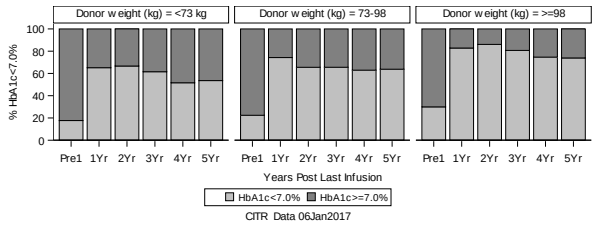
T. Procurement Team/ Inf Team unrelated favorable (p=0.0114)



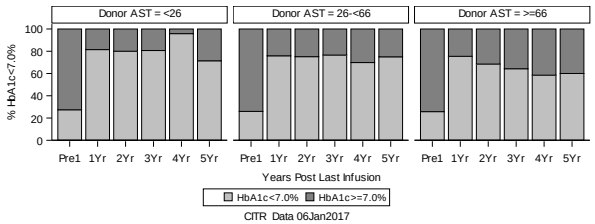
U. Donor age < 35 favorable (p=0.0004)



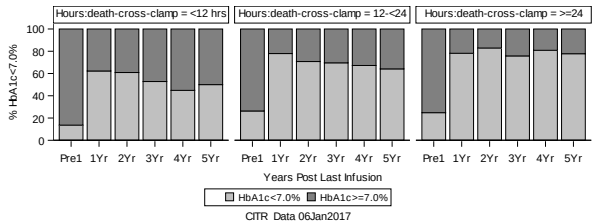
V. Donor weight (kg) ≥ 98 kg favorable (p=0.0003)



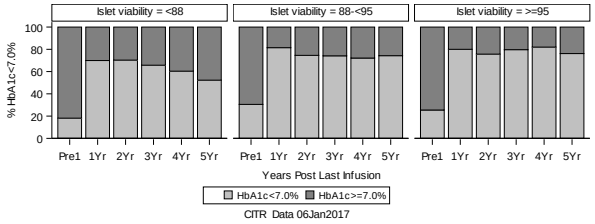
W. Donor AST < 26 favorable (p=0.0426)



X. Hours: death-cross-clamp ≥ 24 favorable (p=0.0099)



Y. Islet viability ≥ 88 favorable (p=0.0378)



Z. Beta cells/kg recipient < 1.3 favorable (p=0.0008)

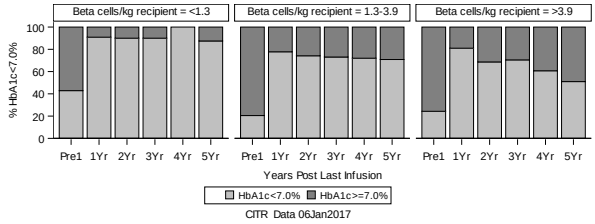
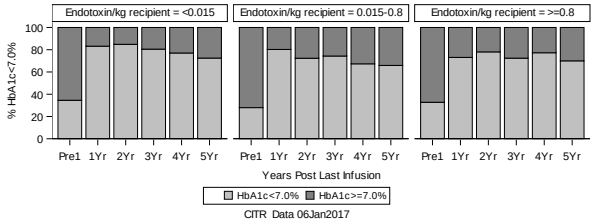
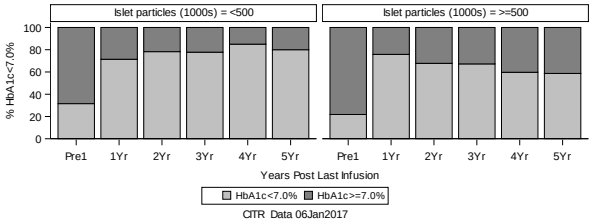


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

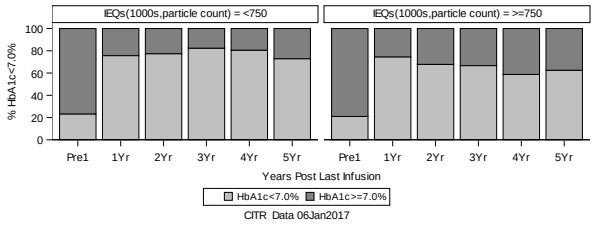
AA. Endotoxin / kg recipient weight <0.015 favorable (p=0.0008)



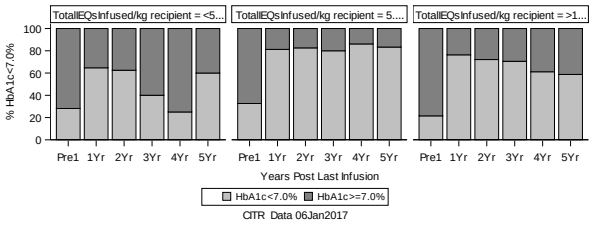
BB. Islet particles (1000s) <500 favorable (p=0.0373)



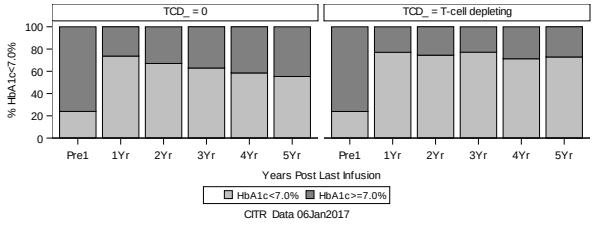
CC. IEQs (1000s,particle count) <750 favorable (p=0.0131)



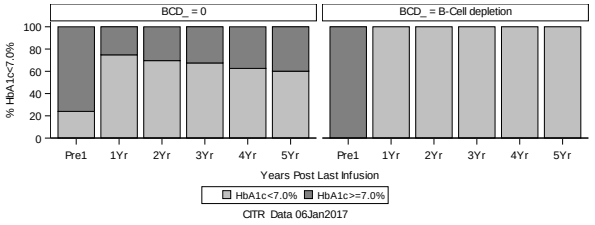
DD. Total IEQs Infused/kg recipient 5.15-10.45 favorable (p=0.0010)



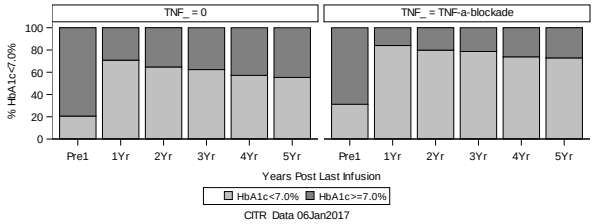
EE. Induction Immunosuppression with T-cell depletion favorable (p=0.0109)



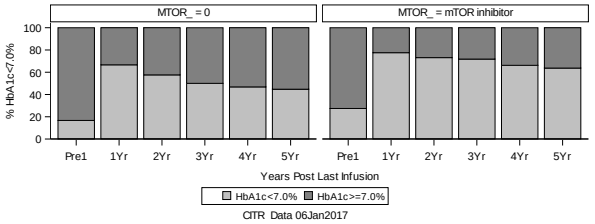
FF. Induction Immunosuppression B-Cell depletion favorable (p<0.0001)



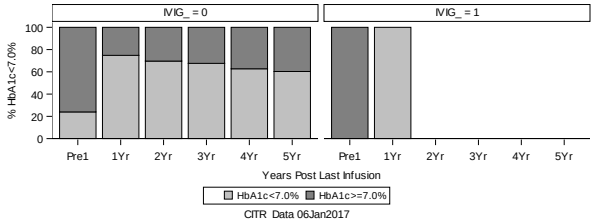
GG. Induction Immunosuppression with TNF-a-blockade favorable (p<0.0001)



HH. Maintenance Immunosuppression with mTOR inhibitor favorable (p=0.0016)



II. Maintenance Immunosuppression with IVIG favorable (p<0.0001)



JJ. Steroid favorable (p=0.0221)

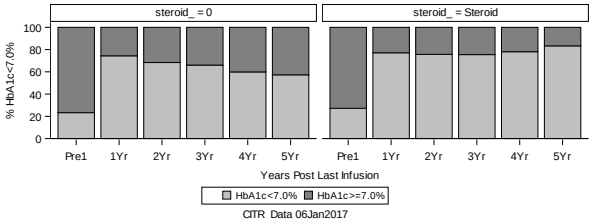
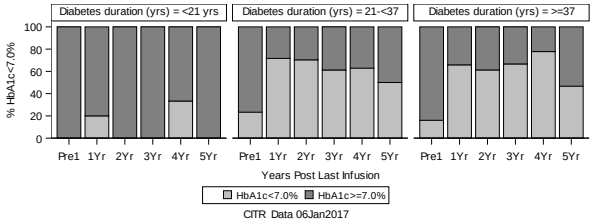
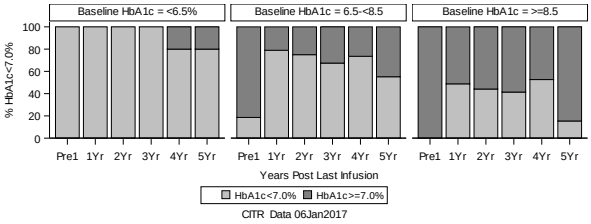


Exhibit 5 – 6C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

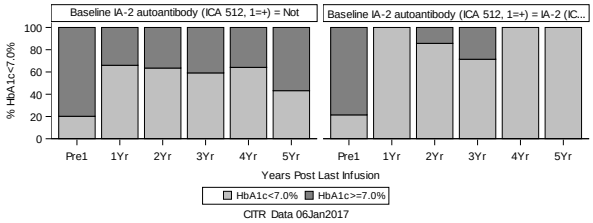
A. Duration of diabetes ≥ 37 favorable (p=0.0322)



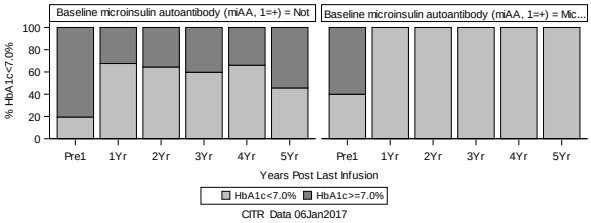
B. Baseline HbA1c <6.5% favorable (p<0.0001)



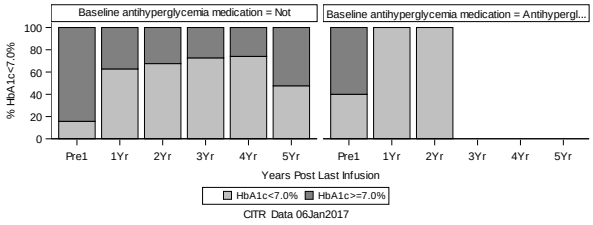
C. Baseline IA-2 autoantibody positive favorable (p=0.0009)



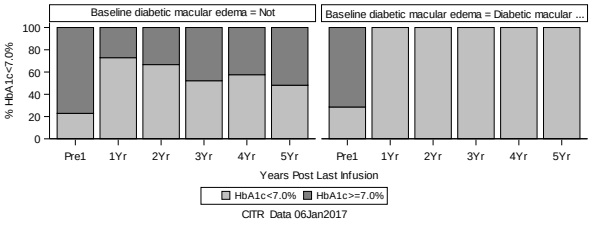
D. Baseline microinsulin autoantibody positive favorable (p<0.0001)



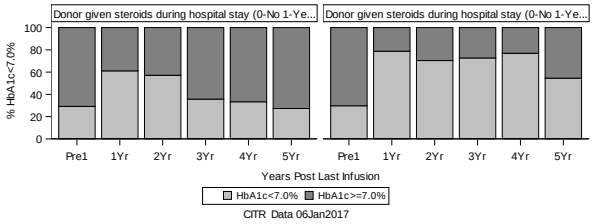
E. Baseline antihyperglycemia medication favorable (p<0.0001)



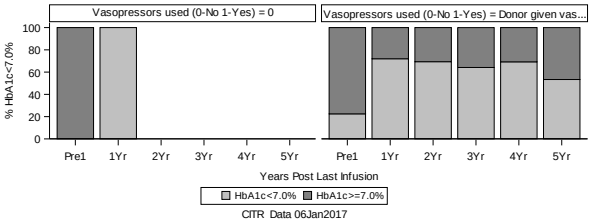
F. Baseline diabetic macular edema favorable (p<0.0001)



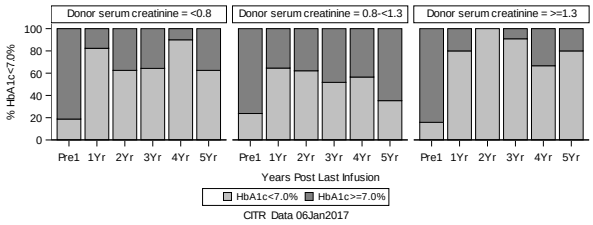
G. Donor given steroid favorable (p=0.0413)



H. Donor given vasopressors unfavorable (p<0.0001)



I. Donor serum creatinine ≥ 1.3 favorable (p=0.0115)



J. IEQs (1000s,particle count) ≥ 750 favorable (p=0.0126)

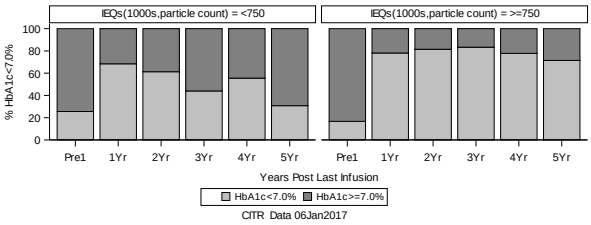
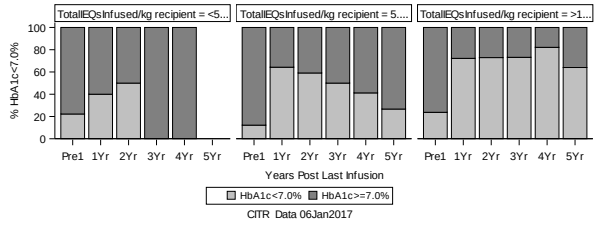


Exhibit 5 – 6C (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

K. Total IEQs Infused/kg recipient >10.45 favorable (p=0.0430)



L. Era (p=0.0367)

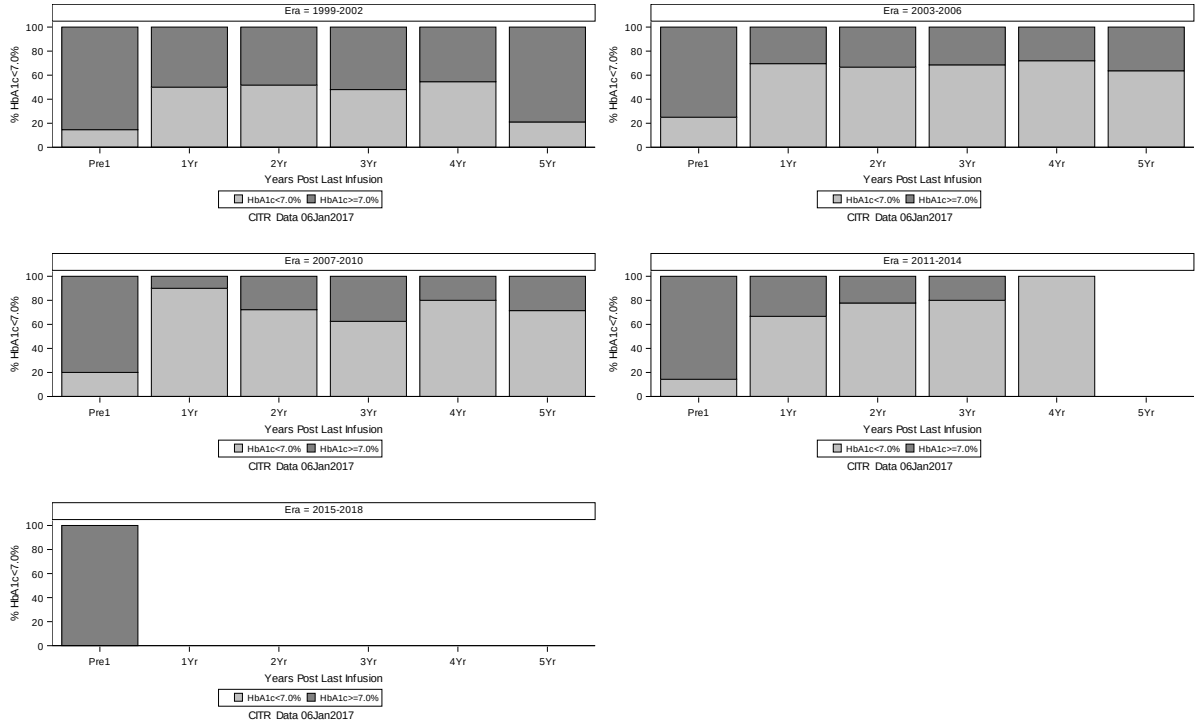
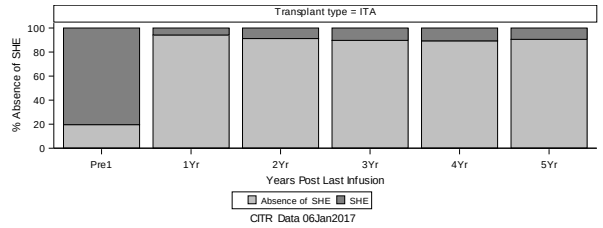


Exhibit 5 – 7A
Unadjusted Prevalence of Absence of Severe Hypoglycemia Events Post Last Infusion

ITA



IAK

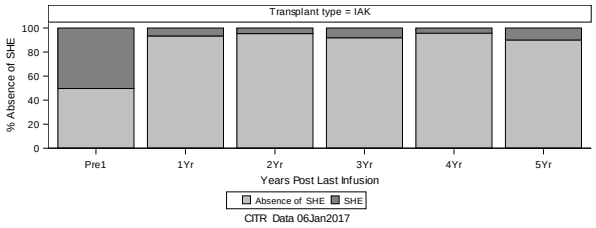
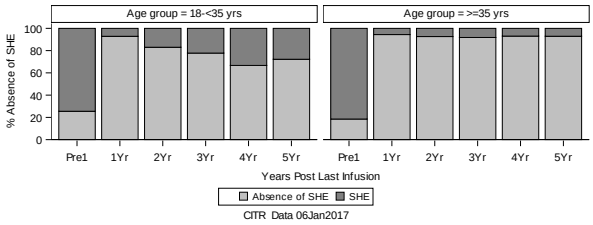
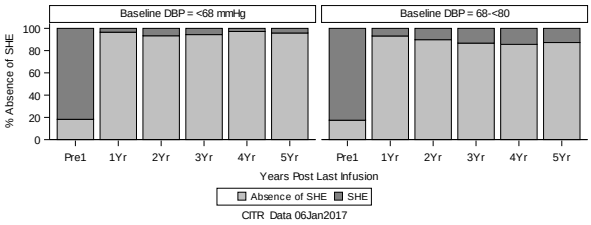


Exhibit 5 – 7B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among <u>ITA Recipient</u>

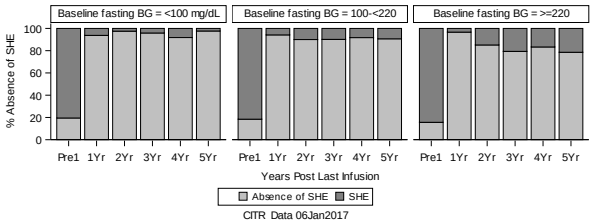
A. Recipient age ≥ 35 favorable (p=0.0142)



B. Baseline DBP <68 mmHg favorable (p=0.0042)



C. Baseline fasting BG < 220 favorable (p=0.0144)



D. Baseline hypoglycemia status partial/unaware favorable (p<0.0001)

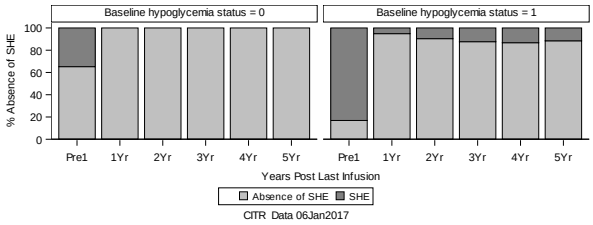
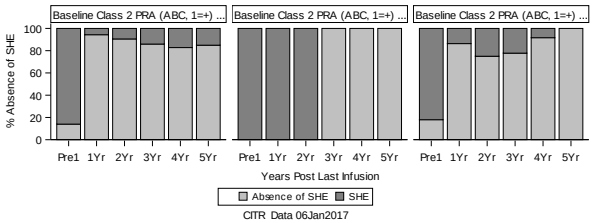
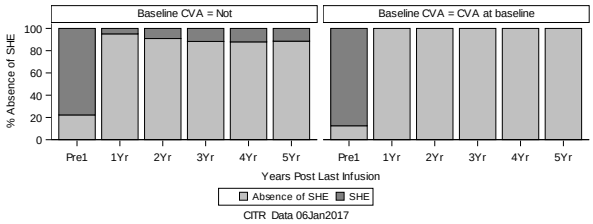


Exhibit 5 – 7B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipient

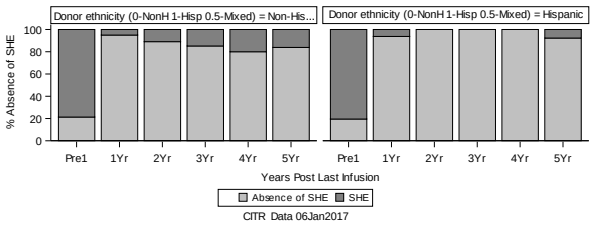
E. Baseline Class 2 PRA negative favorable (p<0.0001)



F. Baseline CVA favorable (p<0.0001)



G. Donor ethnicity Hispanic favorable (p=0.0119)



H. Donor AST 26-<66 favorable (p=0.0420)

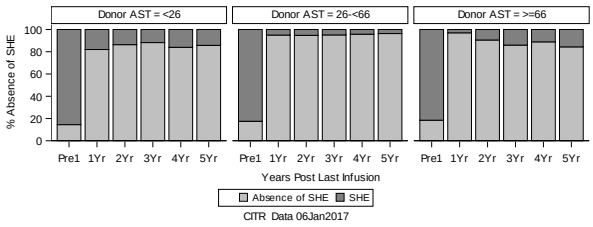
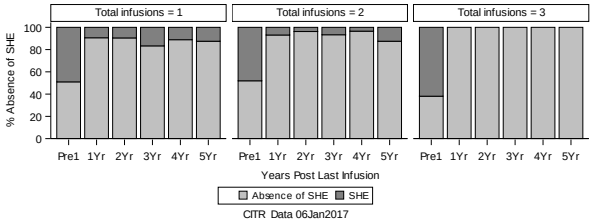
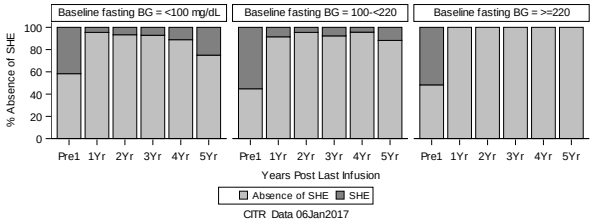


Exhibit 5 – 7C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

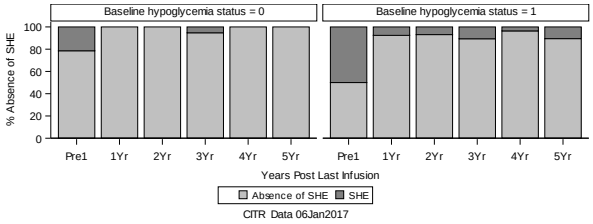
A. Total infusions ≥ 3 favorable (p=0.0009)



B. Baseline fasting BG ≥ 220 favorable (p=0.0065)



C. Baseline hypoglycemia status aware/none favorable (p=0.0129)



D. Intensive therapy at baseline unfavorable (p=0.0004)

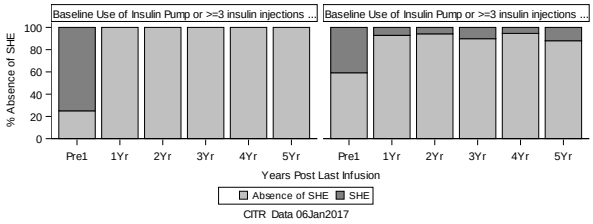
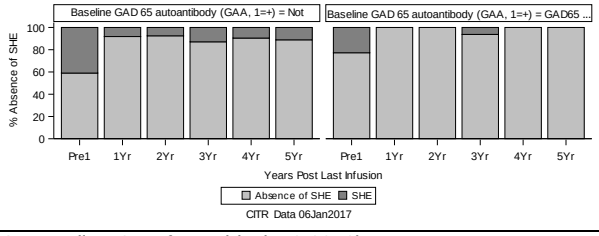
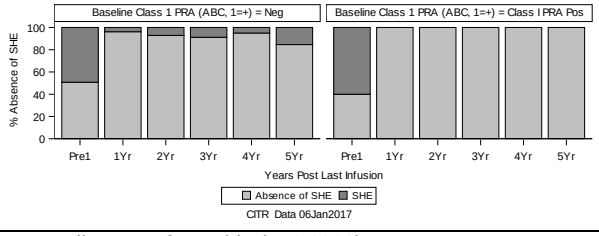


Exhibit 5 – 7C (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

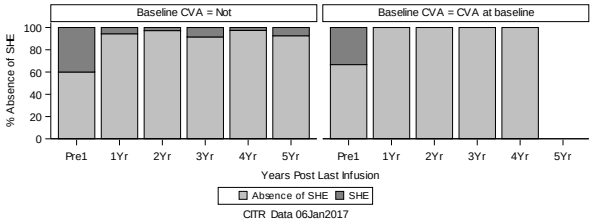
E. Baseline GAD 65 autoantibody positive favorable (p=0.0260)



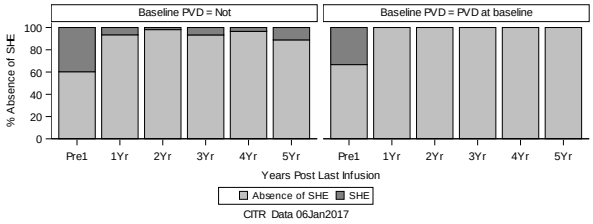
F. Baseline Class 1 PRA positive favorable (p=0.0129)



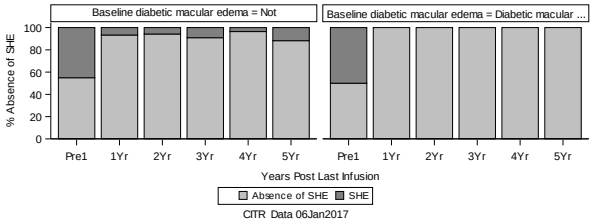
G. Baseline CVA favorable (p=0.0010)



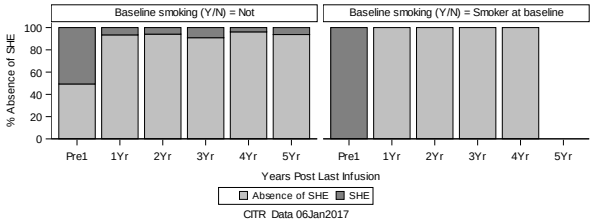
H. Baseline PVD favorable (p=0.0068)



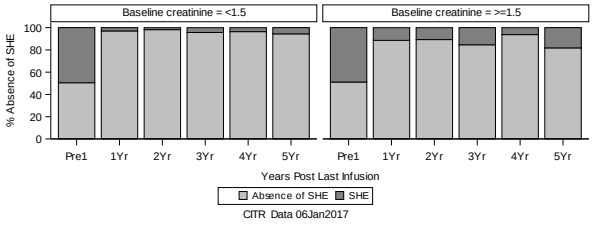
I. Baseline diabetic macular edema favorable (p=0.0059)



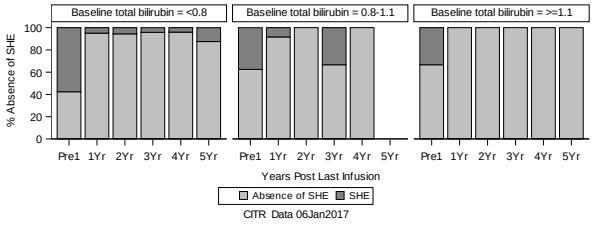
J. Baseline smoking favorable (p=0.0094)



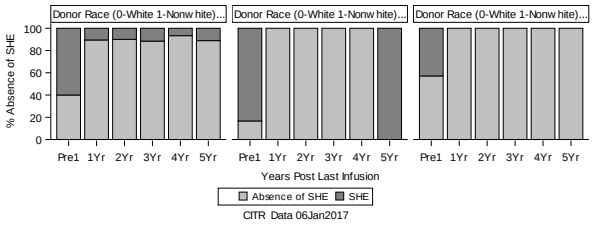
K. Baseline creatinine < 1.5 favorable (p=0.0471)



L. Baseline total bilirubin > 1.1 favorable (p=0.0259)



M. Donor Race Nonwhite favorable (p=0.0135)



N. Donor given transfusions intraoperatively favorable (p=0.0220)

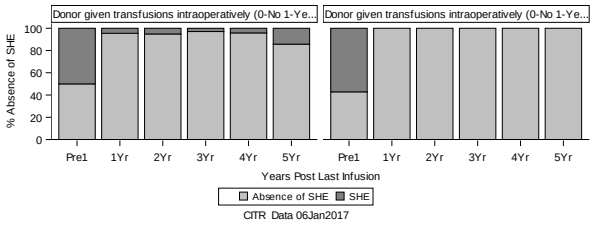
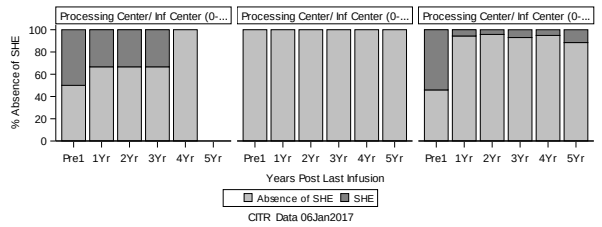
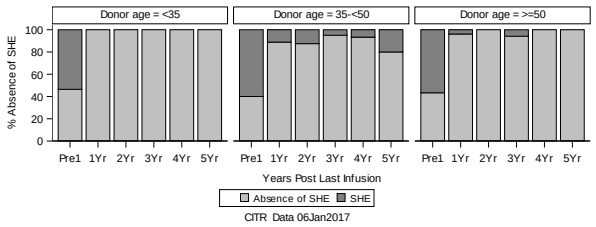


Exhibit 5 – 7C (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

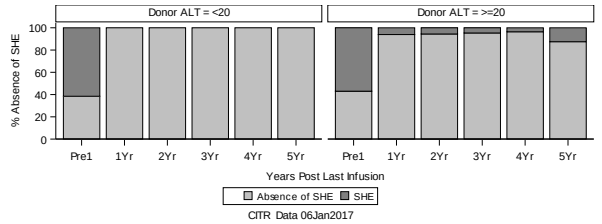
O. Processing Center/ Inf Center mixed favorable (p=0.0026)



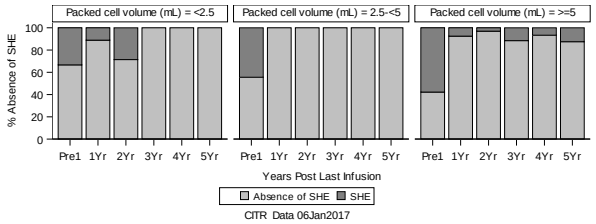
P. Donor age < 35 favorable (p=0.0275)



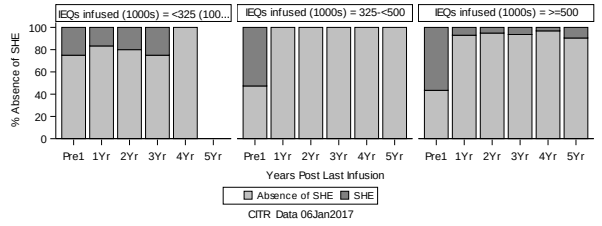
Q. Donor ALT < 20 favorable (p=0.0109)



R. Packed cell volume (mL) 2.5-<5 favorable (p=0.0396)



S. IEQs infused (1000s) ≥ 325 favorable (p=0.0027)



T. Maintenance Immunosuppression with RPINH unfavorable (p=0.0013)

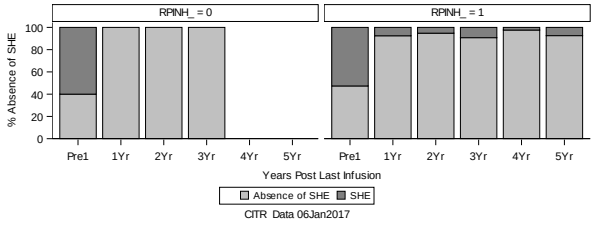
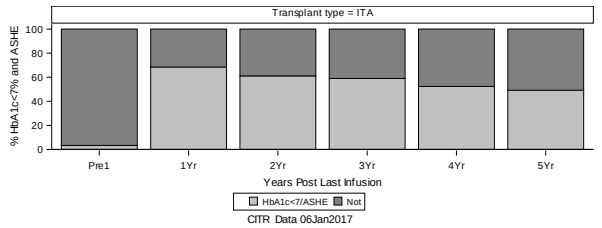


Exhibit 5 – 8A
HbA1c<7.0% <u>and</u> Absence of Severe Hypoglycemic Events (Prevalence / Bar charts)

ITA



IAK

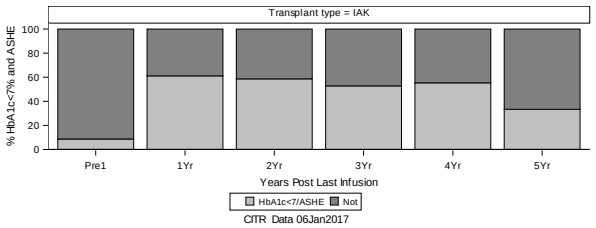
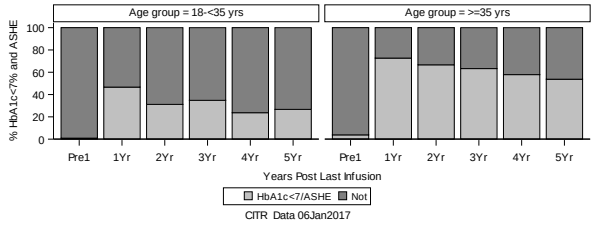
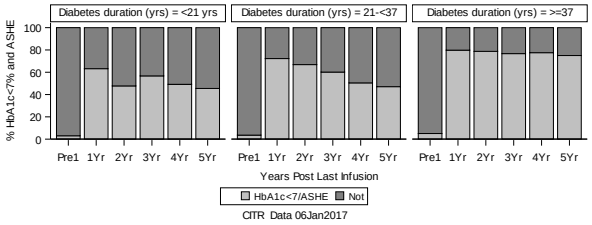


Exhibit 5 – 8B
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

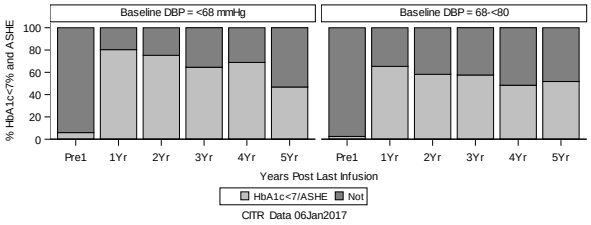
A. Recipient Age ≥ 35 favorable (p<0.0001)



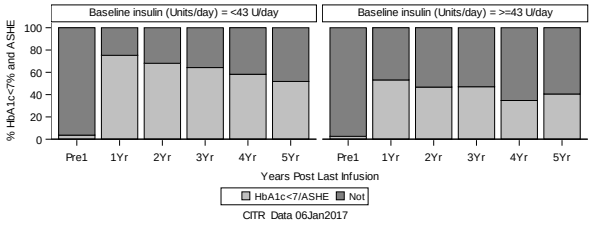
B. Diabetes duration ≥ 37 years favorable (p<0.0001)



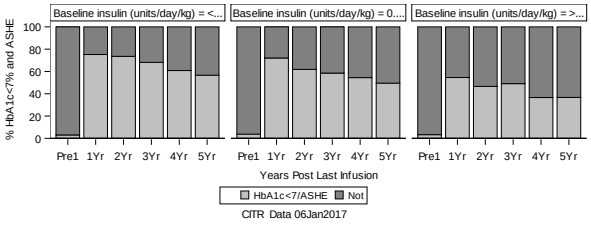
C. Baseline DBP <68 mmHg favorable (p=0.0038)



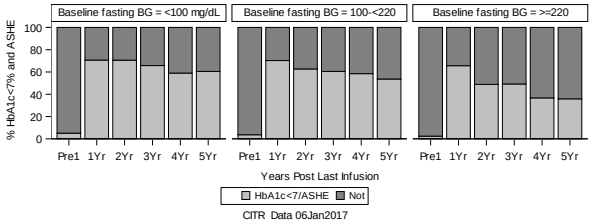
D. Baseline insulin (Units/day) < 43 favorable (p=0.0002)



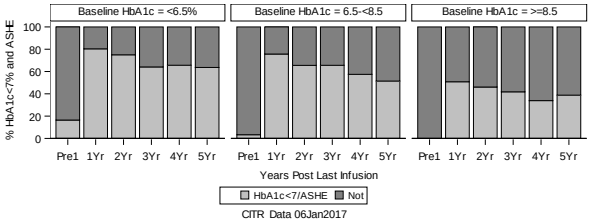
E. Baseline insulin (units/day/kg) <0.66 favorable (p=0.0029)



F. Baseline fasting Blood Glucose <220 mg/dL favorable (p=0.0285)



G. Baseline HbA1c <6.5% favorable (p<0.0001)



H. Baseline IA-2 autoantibody negative favorable (p=0.0047)

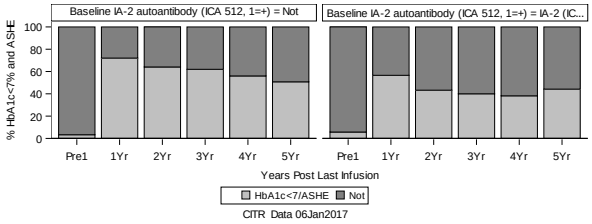
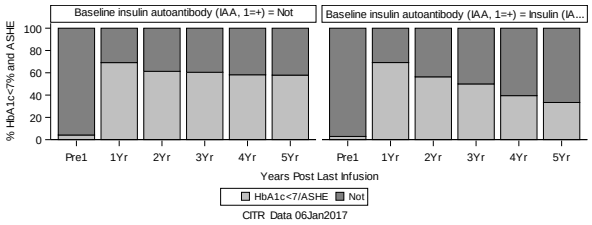
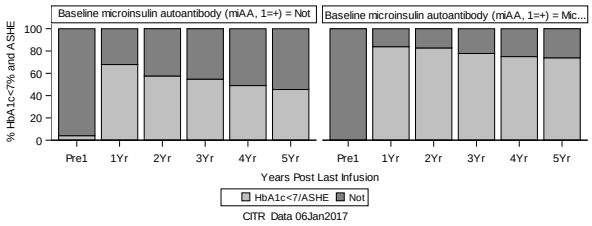


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

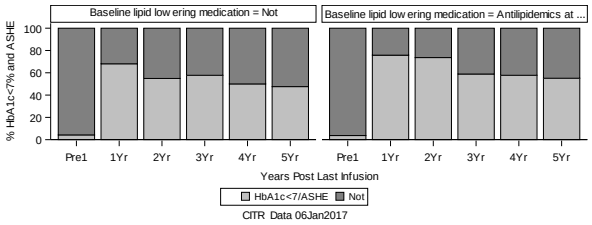
I. Baseline insulin autoantibody negative favorable (p=0.0467)



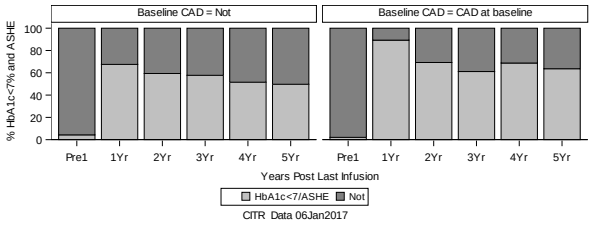
J. Baseline microinsulin autoantibody positive favorable (p<0.0001)



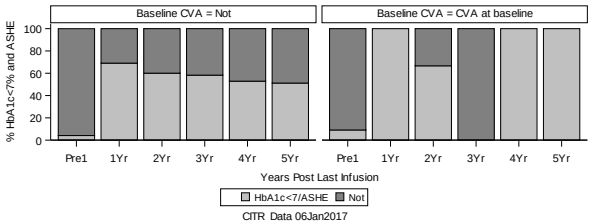
K. Baseline lipid lowering medication unfavorable (p=0.0435)



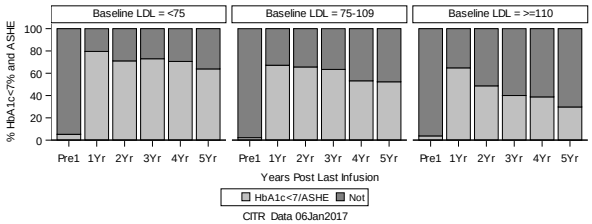
L. Baseline CAD favorable (p=0.0299)



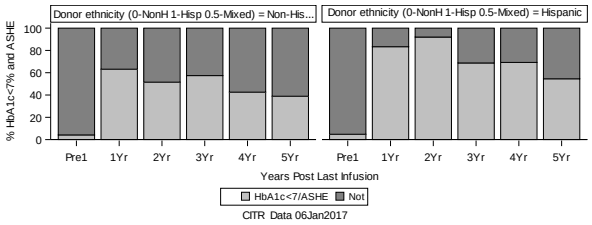
M. Baseline CVA favorable (p=0.0163)



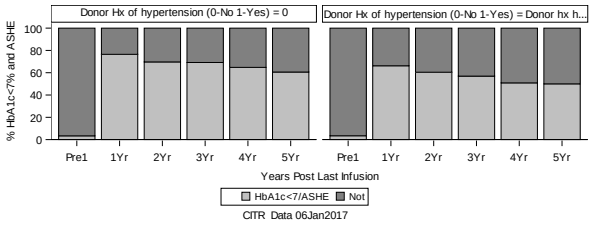
N. Baseline LDL <75 favorable (p=0.0004)



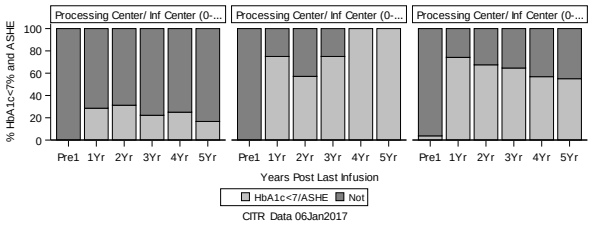
O. Donor ethnicity Hispanic favorable (p=0.0016)



P. Donor History of hypertension unfavorable (p=0.0084)



Q. Processing Center/ Inf Center mixed favorable (p=0.0388)



R. Procurement Team/ Inf Team unrelated favorable (p=0.0087)

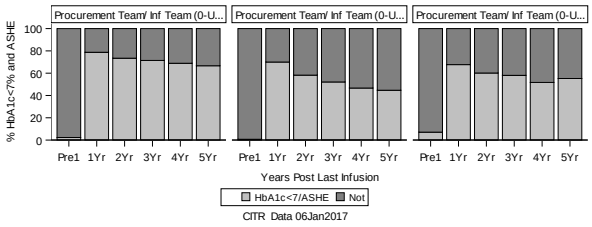
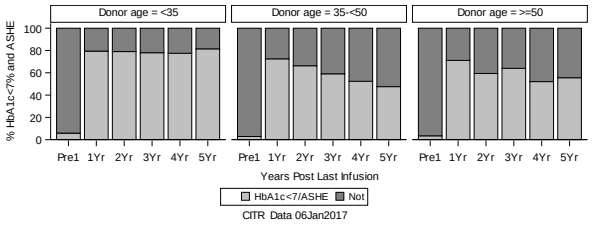


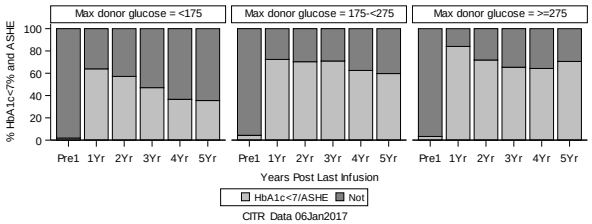
Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

S. Donor age < 35 favorable (p=0.0013)

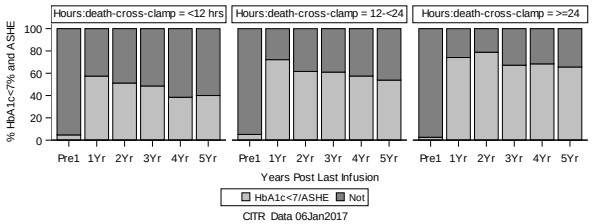


T. Donor weight (kg) ≥ 98kg favorable (p=0.0002)

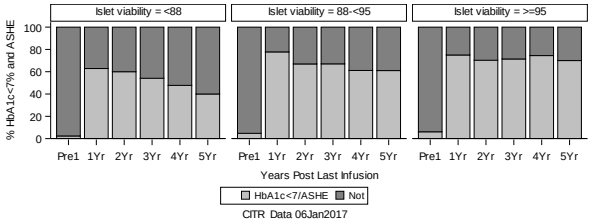
U. Max donor glucose ≥ 275 favorable (p=0.0071)



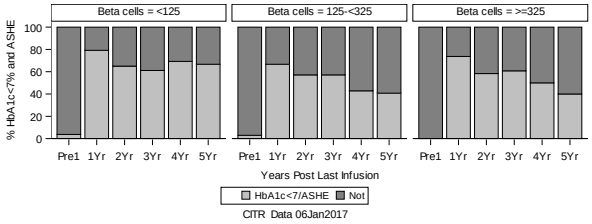
V. Hours:death-cross-clamp ≥ 24 favorable (p=0.0197)



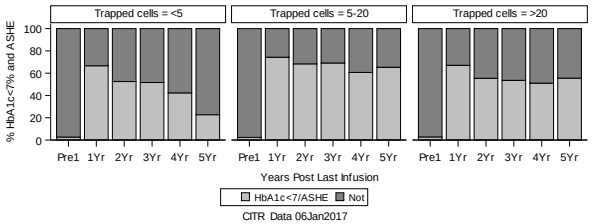
W. Islet viability ≥ 95 favorable (p=0.0125)



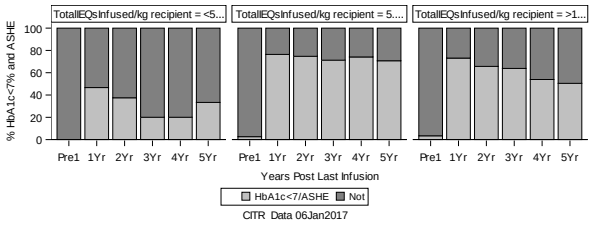
X. Beta cells/kg recipient <1.3 favorable (p=0.0237)



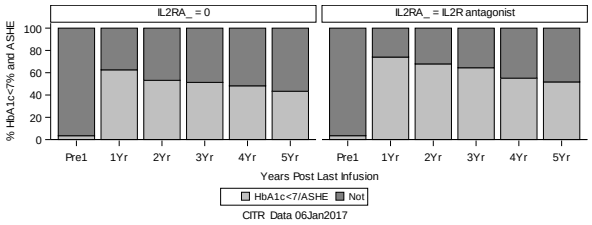
Y. Trapped cells 5-20% favorable (p=0.0253)



Z. Total IEQs Infused/kg recipient 5.15-10.45 favorable (p=0.0100)



AA. Induction Immunosuppression with IL2R antagonist favorable (p=0.0079)



BB. Induction Immunosuppression with T-cell depletion favorable (p=0.0023)

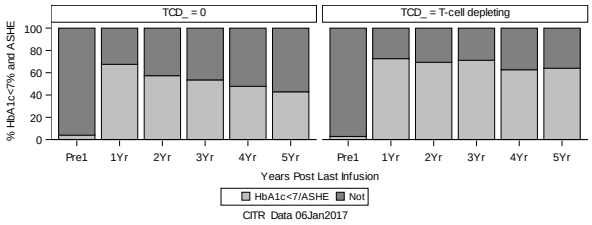
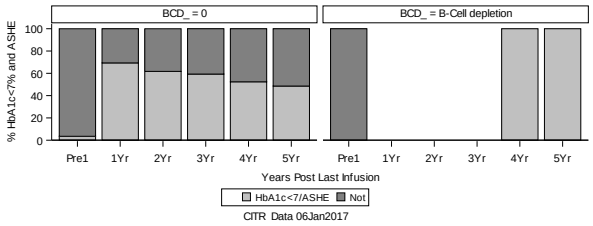
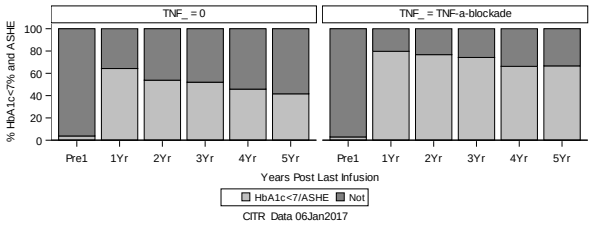


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

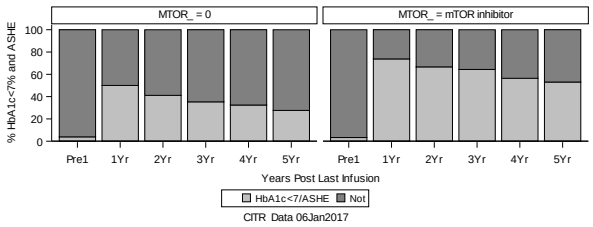
CC. Induction Immunosuppression with B-Cell depletion favorable (p<0.0001)



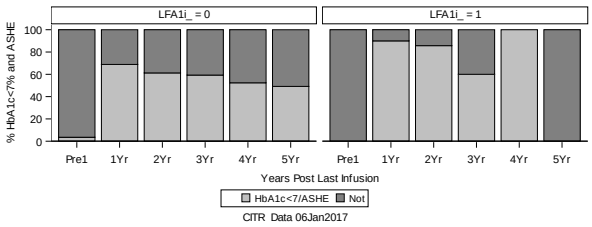
DD. Induction Immunosuppression with TNF-a-blockade (p<0.0001)



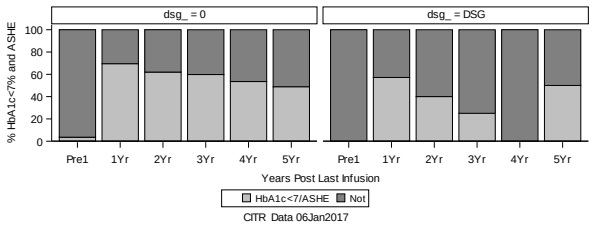
EE. Maintenance Immunosuppression with mTOR inhibitor favorable (p=0.0002)



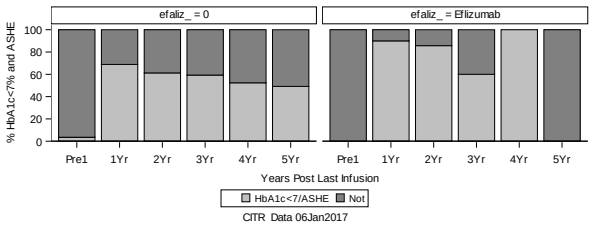
FF. Maintenance Immunosuppression with LFA1i favorable (p=0.0382)



GG. Maintenance Immunosuppression with DSG unfavorable (p=0.0491)



HH. Maintenance Immunosuppression with Eflizumab favorable (p=0.0382)



II. Maintenance Immunosuppression with Steroid favorable (p=0.0066)

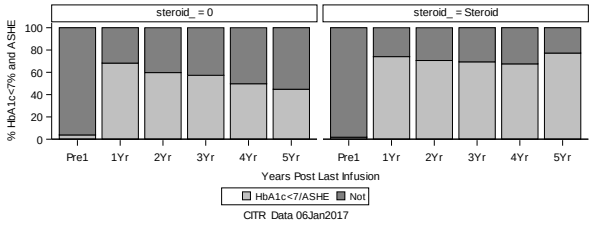
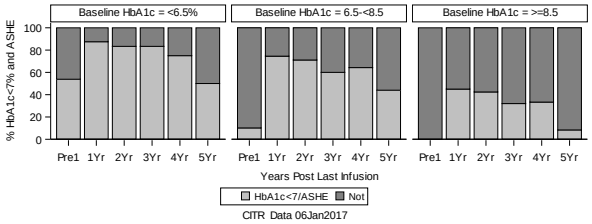
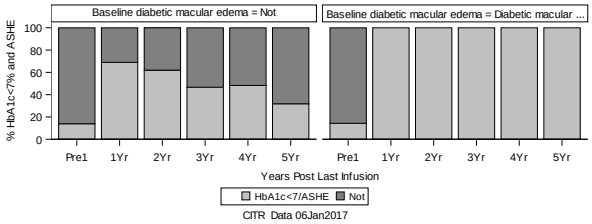


Exhibit 5-8C
Univariate Effects of Individual Variables (p<0.05) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

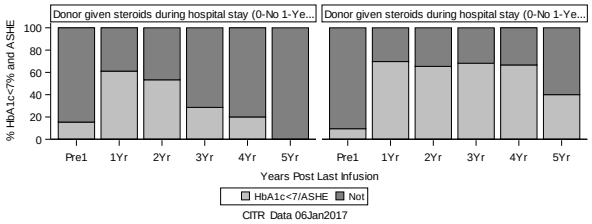
A. Baseline HbA1c <6.5% favorable (p=0.0026)



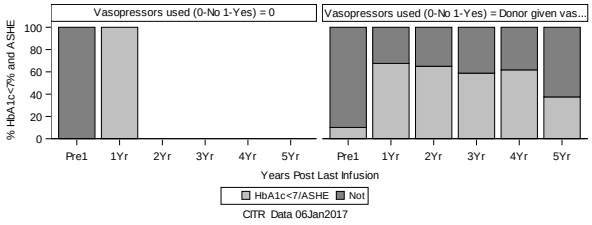
B. Baseline diabetic macular edema favorable (p<0.0001)



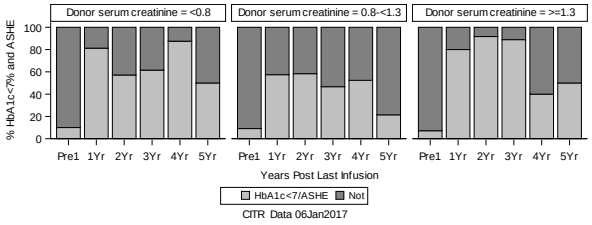
C. Donor given steroids during hospital stay favorable (p=0.0391)



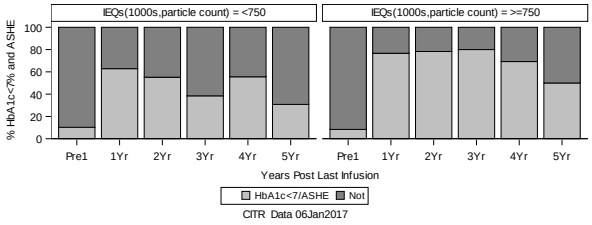
D. Vasopressors used favorable (p<0.0001)



E. Donor serum creatinine 0.8-<1.3 unfavorable (p=0.0413)



F. IEQs (1000s,particle count) ≥ 750 favorable (p=0.0275)



G. Induction Immunosuppression with IL2R antagonist favorable (p=0.0318)

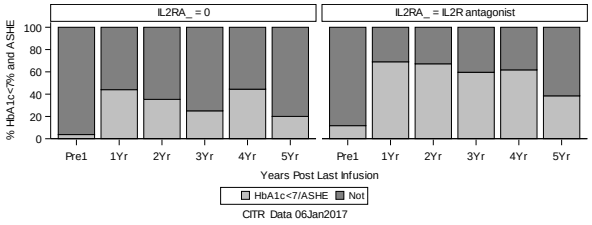
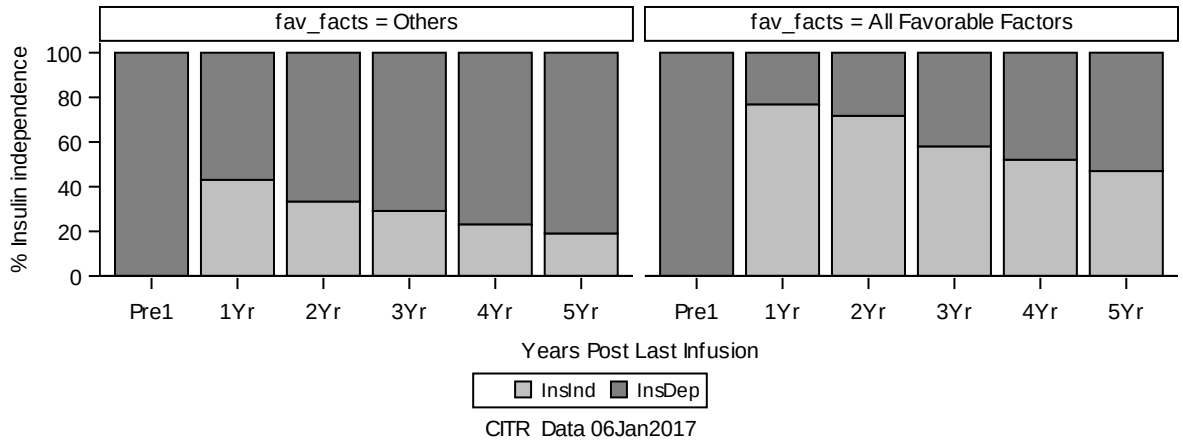


Exhibit 5 – 9
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

Favorable Factors for all Outcomes:

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

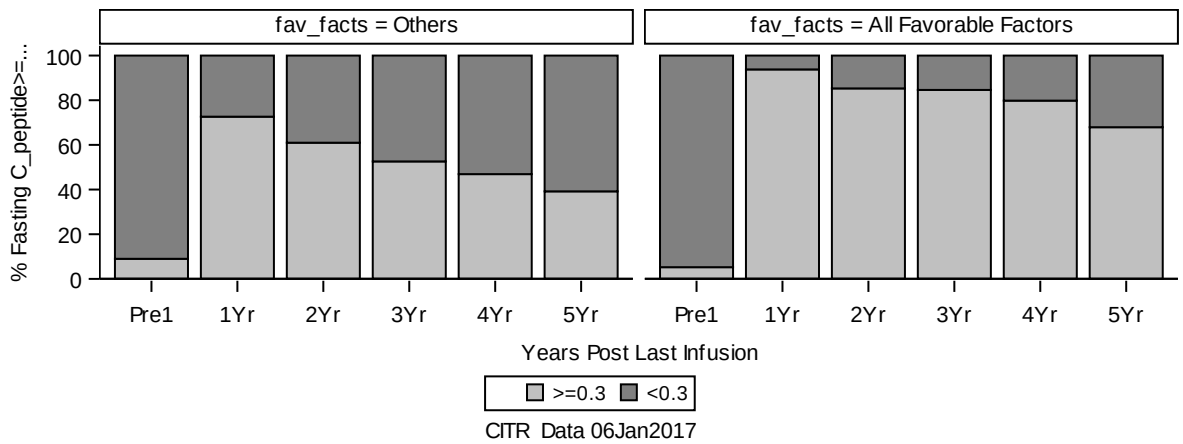
Insulin Independence (Prevalence, p<0.0001)



	Others												*All Favorable Factors*											
	Years Post Last Infusion												*Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Insulin Dependent	485	100.0	209	56.9	222	66.7	207	70.9	203	76.9	183	81.0	161	100.0	28	23.1	28	28.3	34	42.0	35	47.9	35	53.0
Insulin Independent	0	0	158	43.1	111	33.3	85	29.1	61	23.1	43	19.0	0	0	93	76.9	71	71.7	47	58.0	38	52.1	31	47.0
Total	485	100.0	367	100.0	333	100.0	292	100.0	264	100.0	226	100.0	161	100.0	121	100.0	99	100.0	81	100.0	73	100.0	66	100.0

Exhibit 5 – 9 (continued)
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

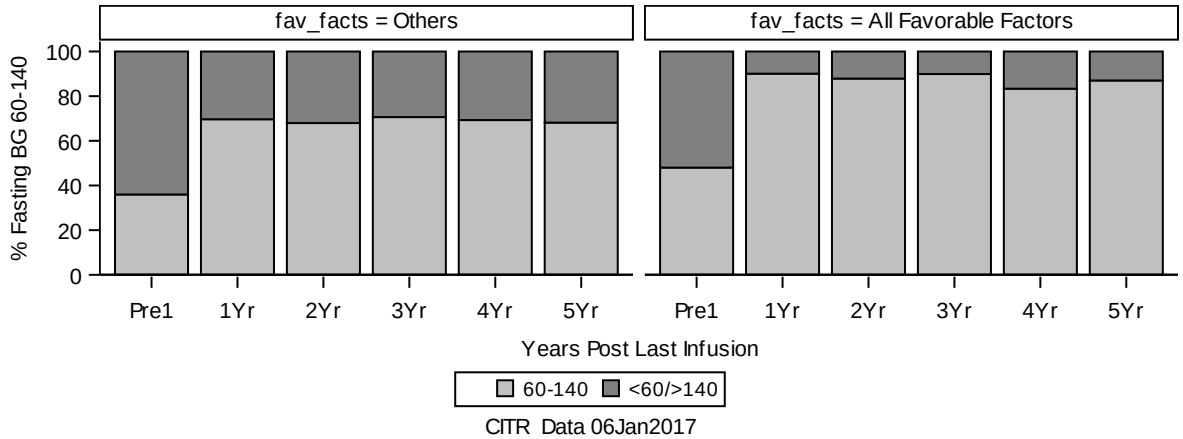
C-peptide ≥0.3 ng/mL (Prevalence, p<0.0001)



	Others												*All Favorable Factors*											
	Years Post Last Infusion												*Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
<0.3 ng/mL	366	91.0	98	27.4	121	39.0	129	47.4	128	53.1	132	60.8	146	94.8	9	6.2	20	14.7	18	15.4	22	20.2	26	32.1
>=0.3 ng/mL	36	9.0	260	72.6	189	61.0	143	52.6	113	46.9	85	39.2	8	5.2	136	93.8	116	85.3	99	84.6	87	79.8	55	67.9
Total	402	100.0	358	100.0	310	100.0	272	100.0	241	100.0	217	100.0	154	100.0	145	100.0	136	100.0	117	100.0	109	100.0	81	100.0

Exhibit 5 – 9 (continued)
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

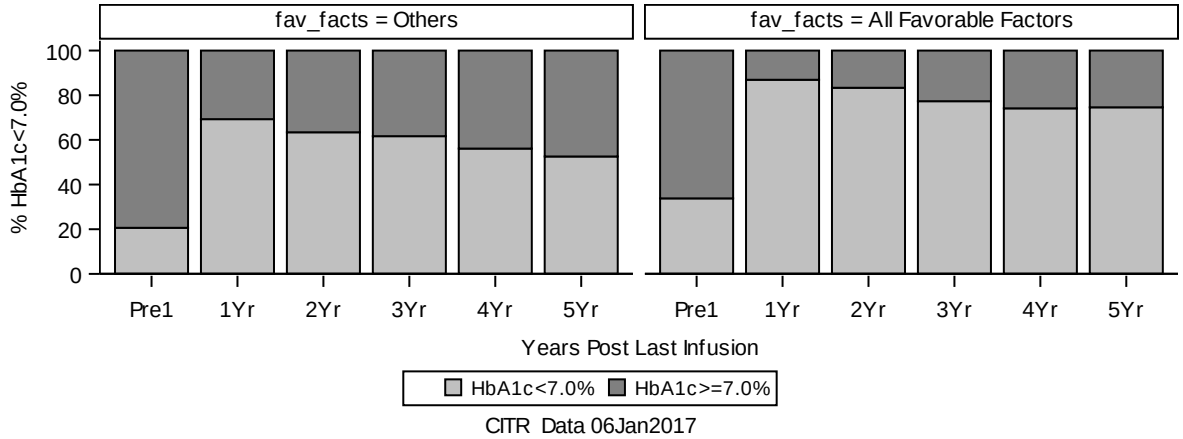
Fasting Blood Glucose 60-140 mg/mL (Prevalence, p<0.0001)



	Others *Years Post Last Infusion*												*All Favorable Factors* *Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
Fasting BG < 60 or > 140 mg/mL	253	64.1	98	30.3	75	32.1	52	29.4	43	30.7	36	31.9	78	52.0	14	9.9	16	12.1	11	10.1	17	16.7	10	13.0
Fasting BG 60-140 mg/mL	142	35.9	225	69.7	159	67.9	125	70.6	97	69.3	77	68.1	72	48.0	127	90.1	116	87.9	98	89.9	85	83.3	67	87.0
Total	395	100.0	323	100.0	234	100.0	177	100.0	140	100.0	113	100.0	150	100.0	141	100.0	132	100.0	109	100.0	102	100.0	77	100.0

Exhibit 5 – 9 (continued)
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

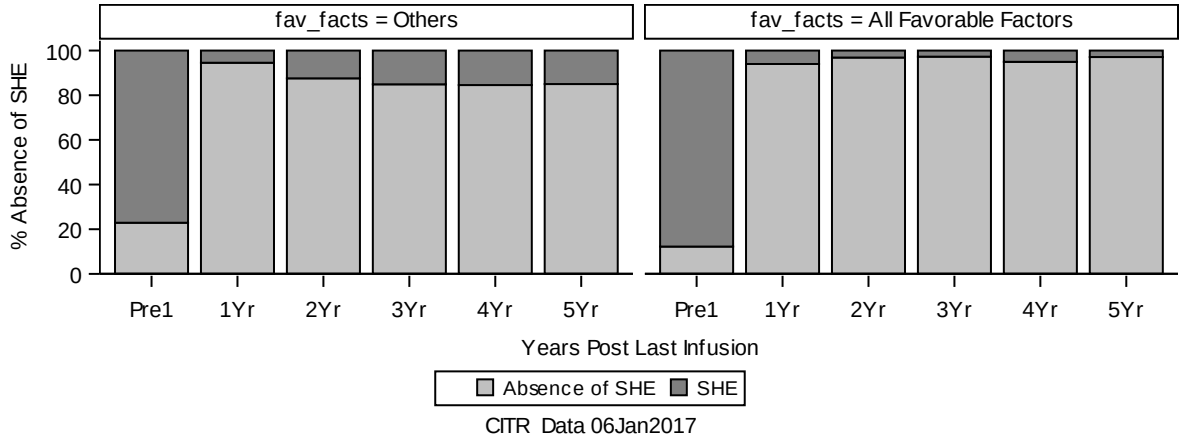
HbA1c<7.0% (Prevalence, p<0.0001)



	Others *Years Post Last Infusion*												*All Favorable Factors* *Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
HbA1c ≥ 7.0%	370	79.4	102	30.7	97	36.6	79	38.3	72	43.9	65	47.4	98	66.2	17	13.1	20	16.7	22	22.7	22	25.9	15	25.4
HbA1c < 7.0%	96	20.6	230	69.3	168	63.4	127	61.7	92	56.1	72	52.6	50	33.8	113	86.9	100	83.3	75	77.3	63	74.1	44	74.6
Total	466	100.0	332	100.0	265	100.0	206	100.0	164	100.0	137	100.0	148	100.0	130	100.0	120	100.0	97	100.0	85	100.0	59	100.0

Exhibit 5 – 9 (continued)
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

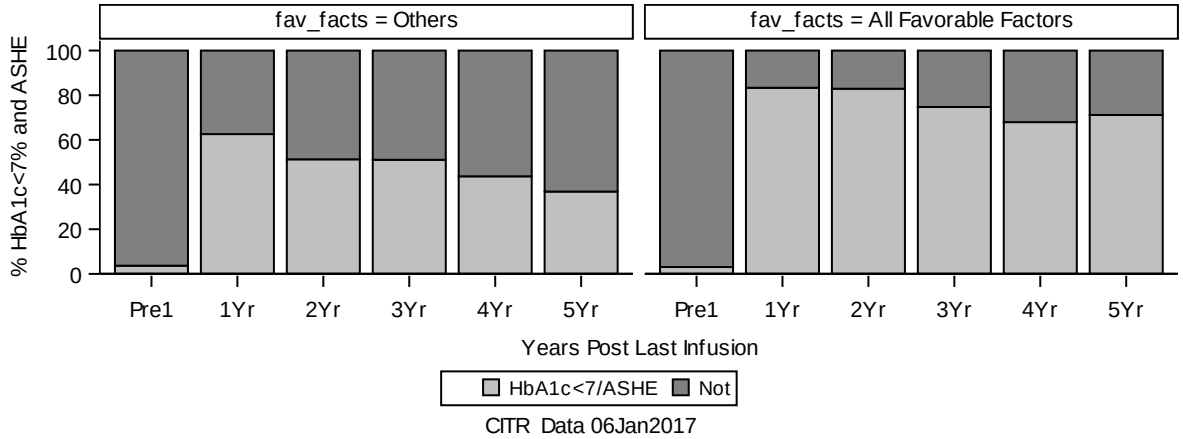
Absence of Severe Hypoglycemic Events (Prevalence, p=0.0004)



	Others												*All Favorable Factors*											
	Years Post Last Infusion												*Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
SHE	344	77.1	15	5.5	26	12.4	26	15.1	19	15.4	12	15.0	144	87.8	8	6.0	4	3.1	3	2.7	5	5.1	2	2.9
Absence of SHE	102	22.9	260	94.5	183	87.6	146	84.9	104	84.6	68	85.0	20	12.2	125	94.0	124	96.9	107	97.3	94	94.9	67	97.1
Total	446	100.0	275	100.0	209	100.0	172	100.0	123	100.0	80	100.0	164	100.0	133	100.0	128	100.0	110	100.0	99	100.0	69	100.0

Exhibit 5 – 9 (continued)
Combined Effect of the Common Favorable Factors on Outcomes Post Last Infusion for ITA Recipients

HbA1c<7.0% & Absence of Severe Hypoglycemic Events (Prevalence, p<0.0001)



	Others *Years Post Last Infusion*												*All Favorable Factors* *Years Post Last Infusion*											
	0		*1*		*2*		*3*		*4*		*5*		*0*		*1*		*2*		*3*		*4*		*5*	
	N	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*	*N*	*%*
HbA1c≥7.0 or SHE	478	96.4	107	37.4	114	48.7	92	48.9	80	56.3	72	63.2	160	97.0	21	16.7	20	17.1	23	25.3	25	32.1	15	28.8
HbA1c<7.0 and ASHE	18	3.6	179	62.6	120	51.3	96	51.1	62	43.7	42	36.8	5	3.0	105	83.3	97	82.9	68	74.7	53	67.9	37	71.2
Total	496	100.0	286	100.0	234	100.0	188	100.0	142	100.0	114	100.0	165	100.0	126	100.0	117	100.0	91	100.0	78	100.0	52	100.0

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

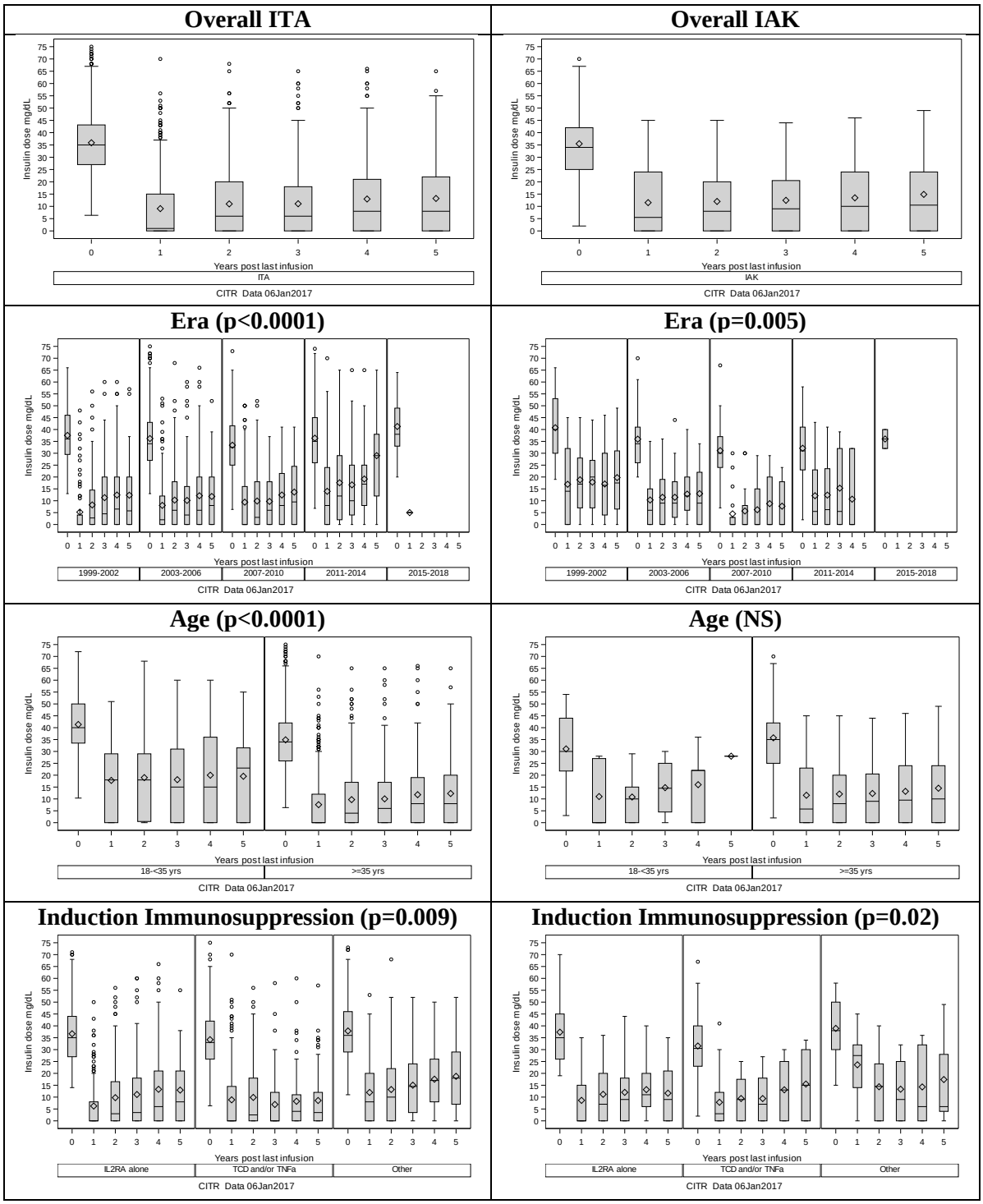


Exhibit 5-10 (continued)
Insulin Dose (U/day) Post Last Infusion

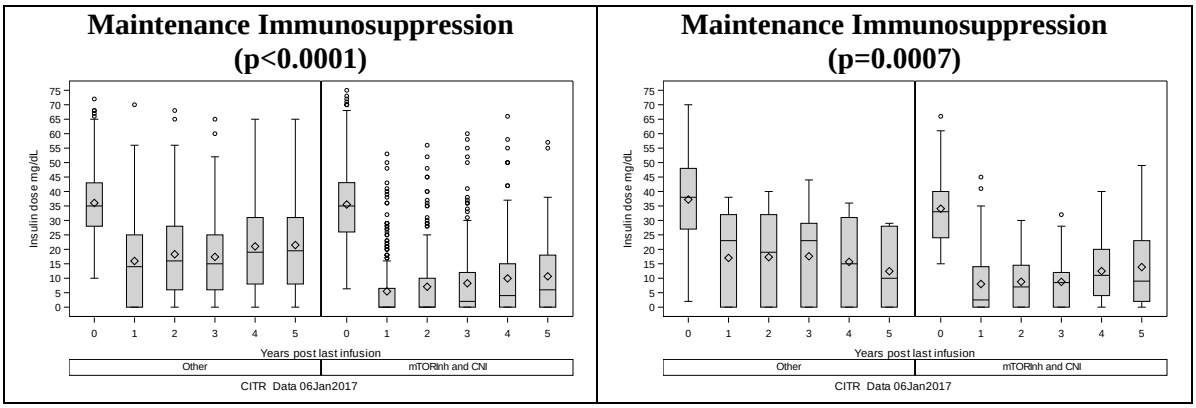


Exhibit 5-11
Fasting C-peptide (ng/mL) Post Last Infusion

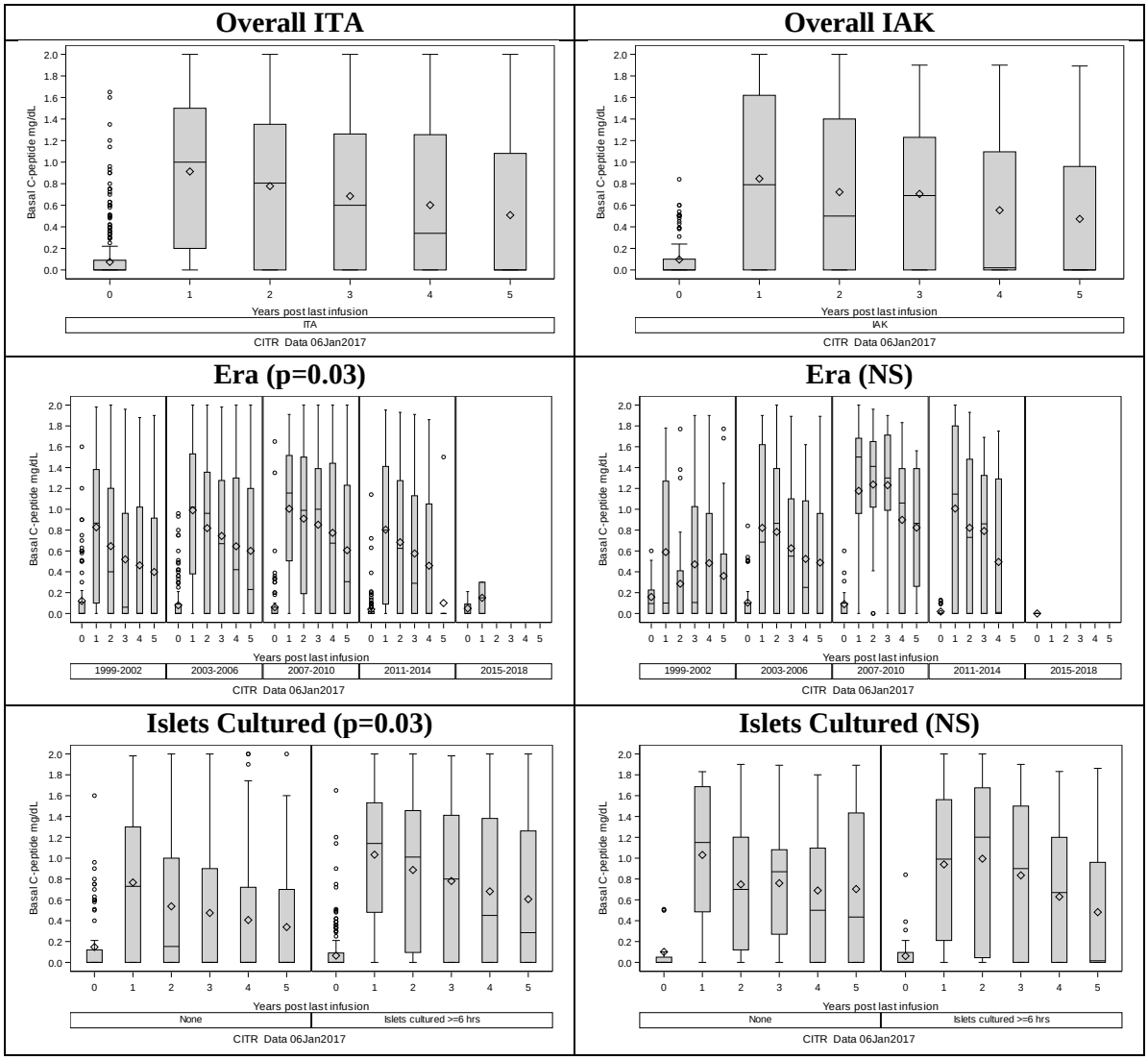


Exhibit 5-11 (continued)
Fasting C-peptide (ng/mL) Post Last Infusion

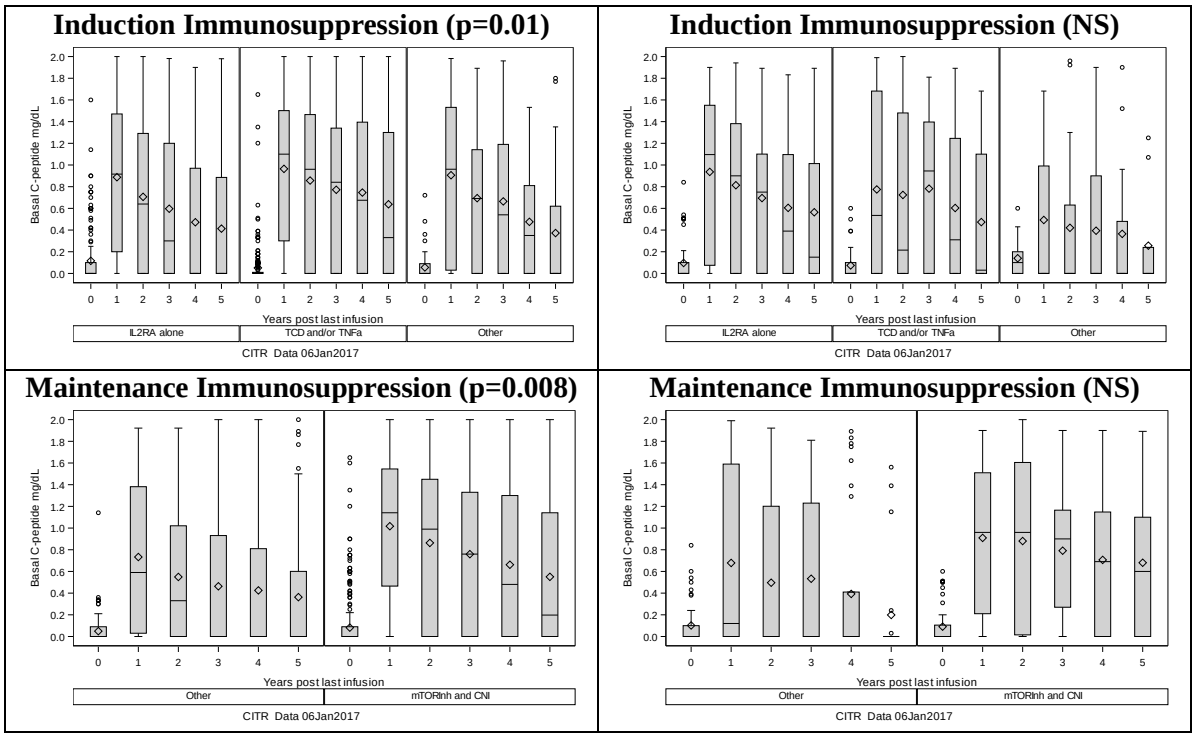


Exhibit 5-12
HbA1c (%) Post Last Infusion

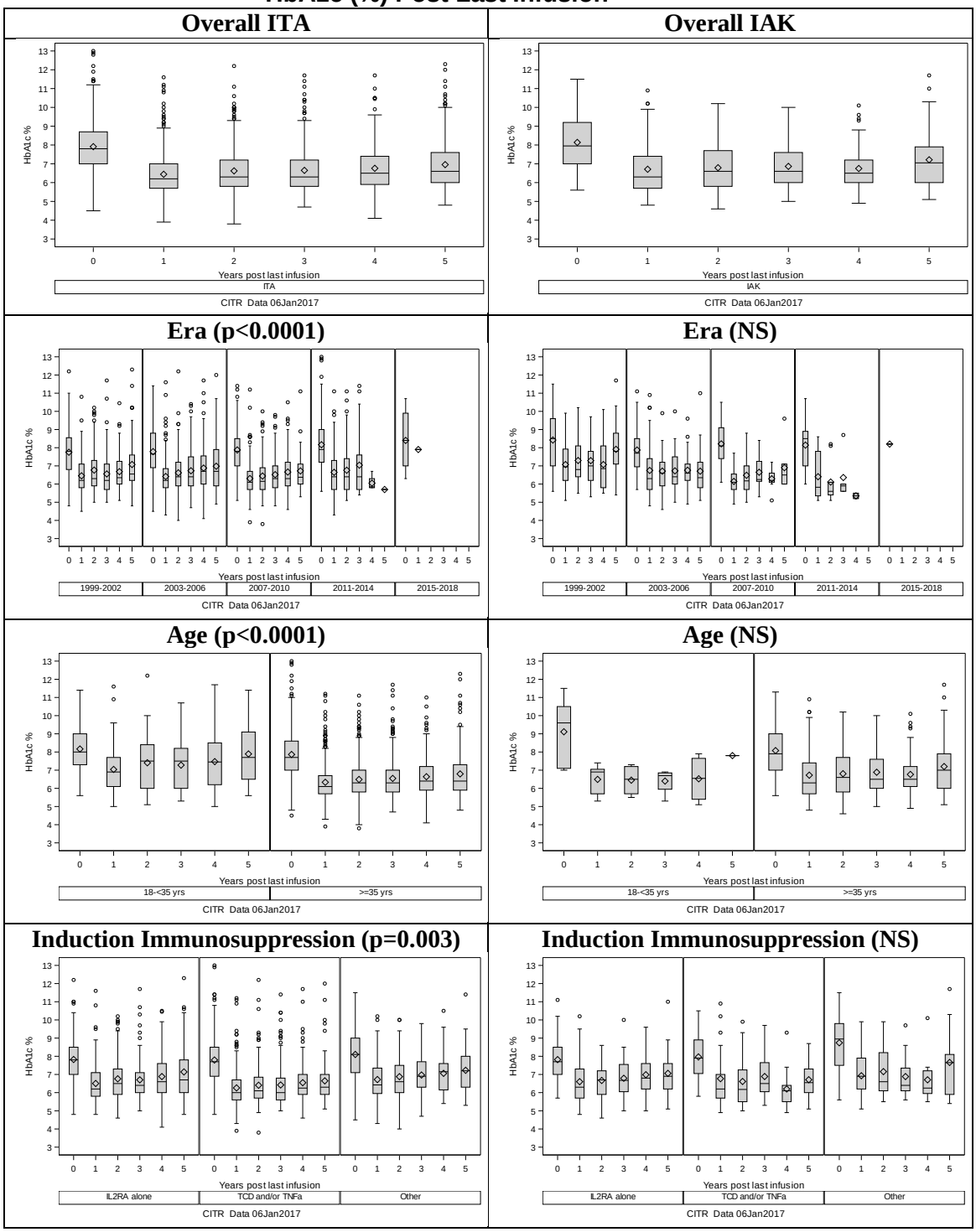


Exhibit 5-12 (continued)
HbA1c (%) Post Last Infusion

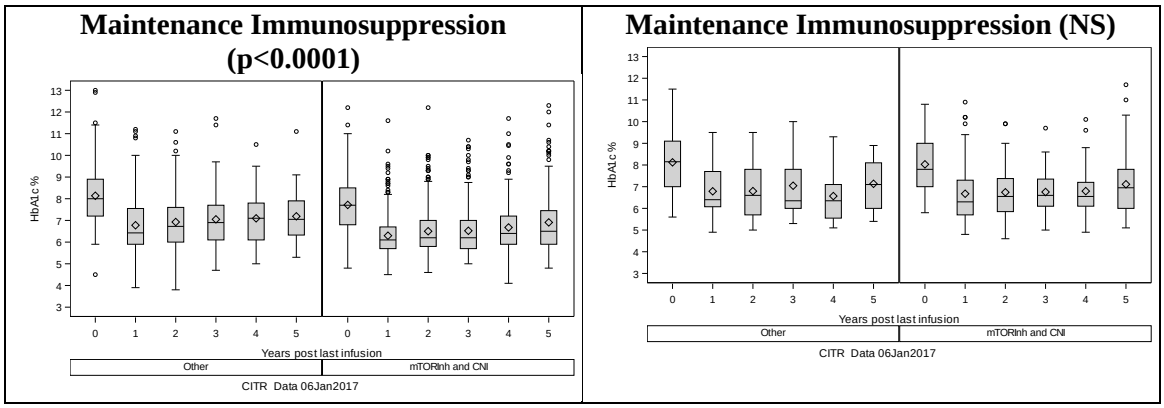


Exhibit 5-13
Fasting Blood Glucose (mg/dL) Post Last Infusion

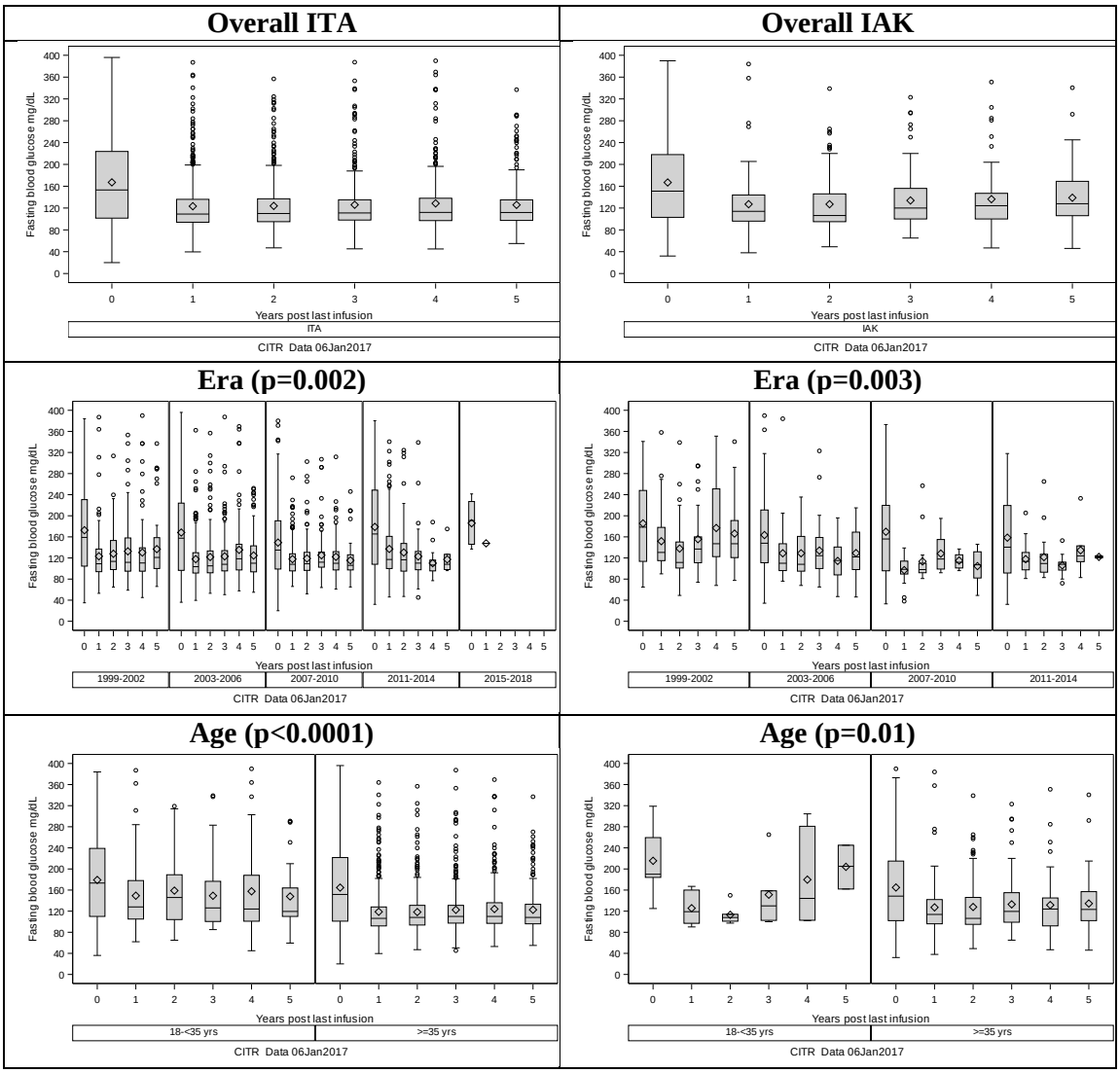


Exhibit 5-13 (continued)
Fasting Blood Glucose (mg/dL) Post Last Infusion

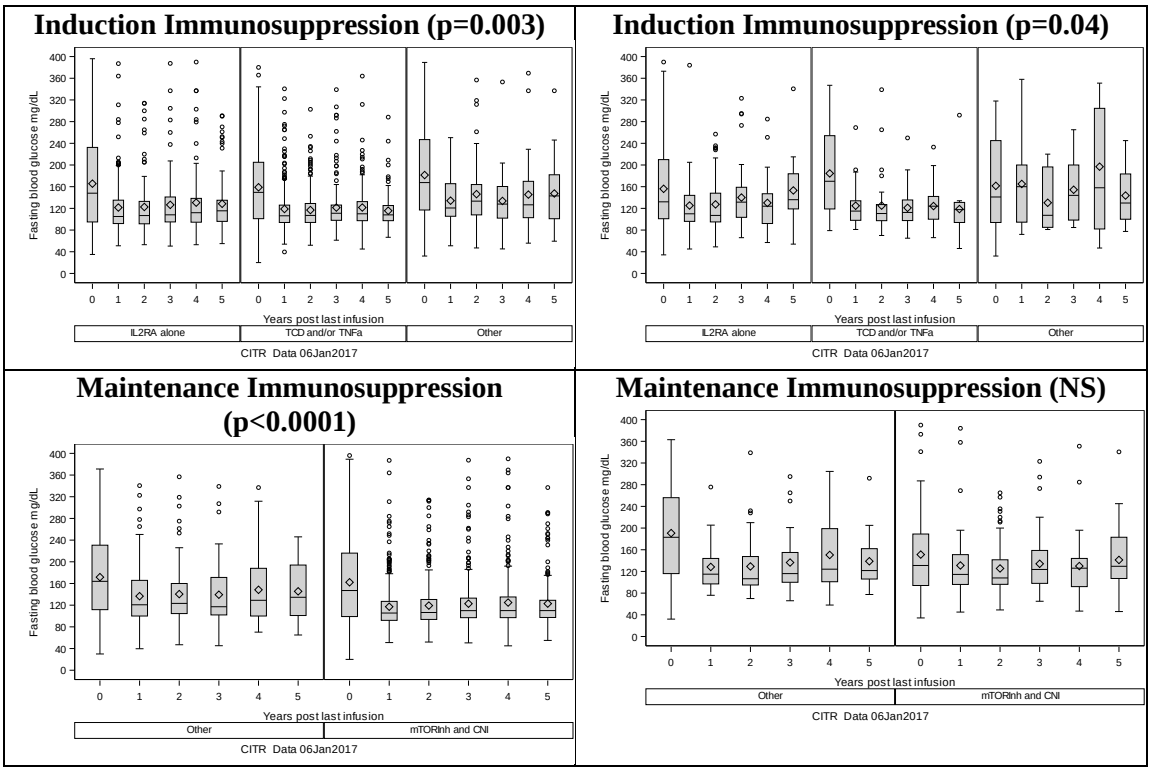
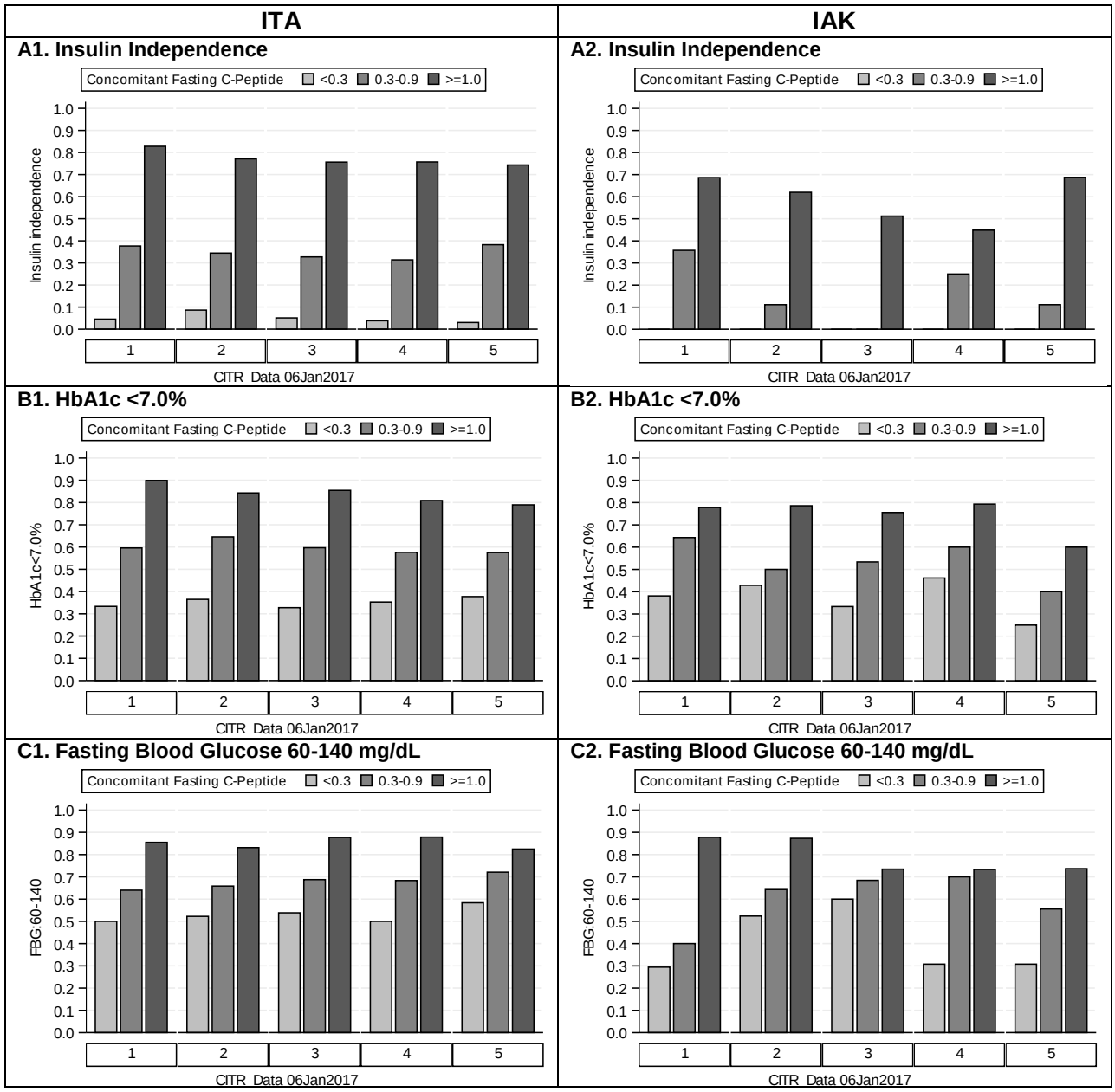


Exhibit 5-14
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years1-5 Post Last Infusion



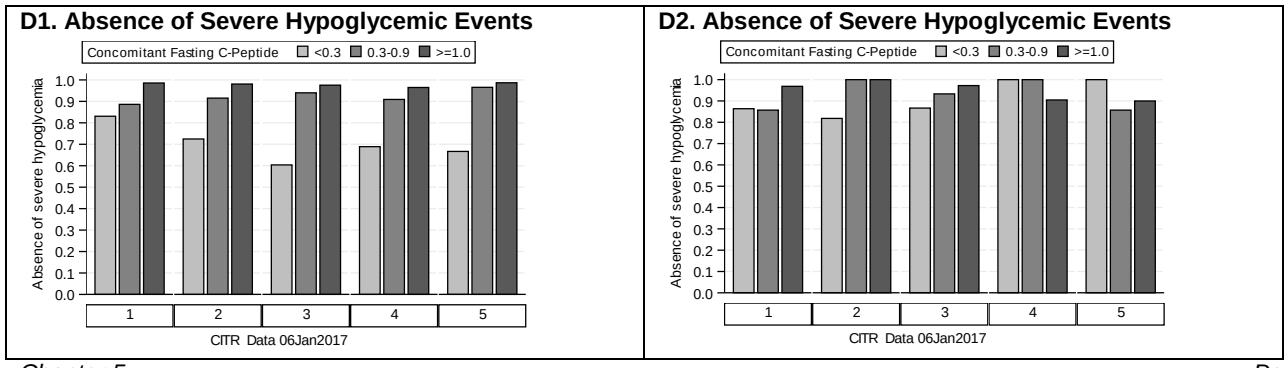
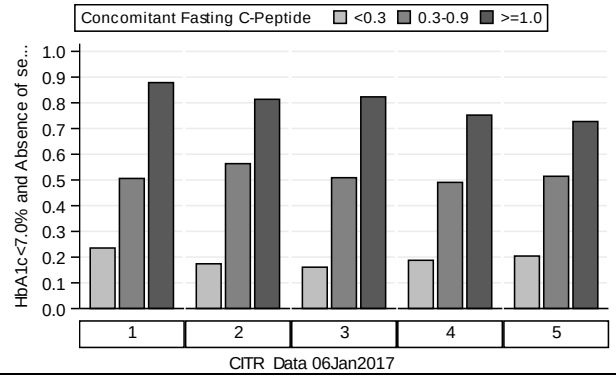


Exhibit 5-14 (continued)
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years1-5 Post Last Infusion

E1. HbA1c <7.0% & Absence of Severe Hypoglycemic Events



E2. HbA1c <7.0% & Absence of Severe Hypoglycemic Events

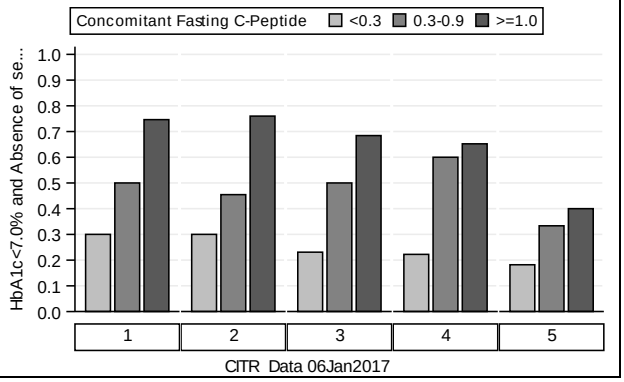
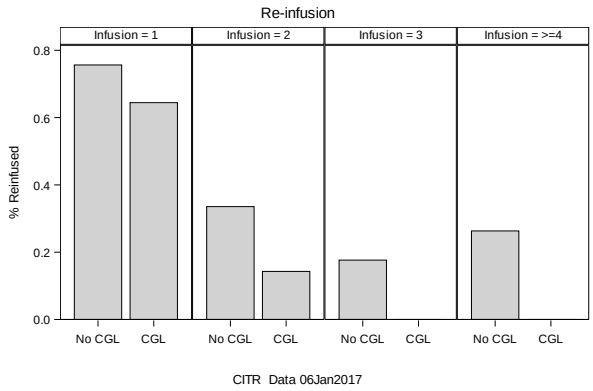
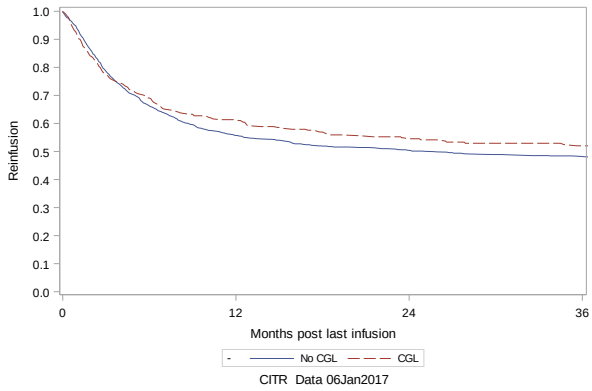


Exhibit 5-15
Re-Infusion
(after each infusion sequence)

A. By previous complete graft loss (CGL) (p=0.1)

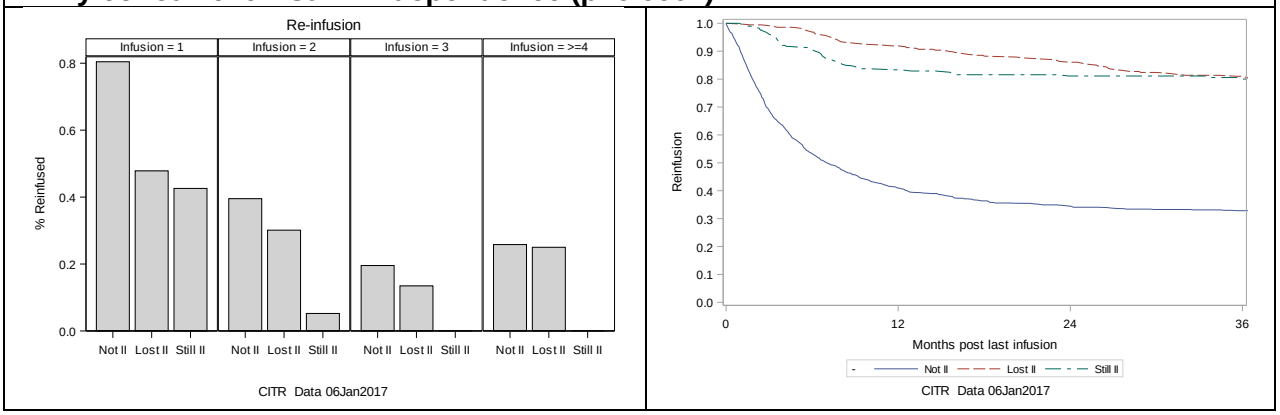




	Reinfusion		
	No	*Yes*	*Total*
	N	*N*	*N*
Infusion 1	275	730	1005
Infusion 2	504	226	730
Infusion 3	193	33	226
Infusion ≥ 4	33	10	43
All	1005	999	2004

Exhibit 5-15
Re-Infusion
(after each infusion sequence)

B. By concurrent insulin independence (p<0.0001)



C. By Era (p=0.04)

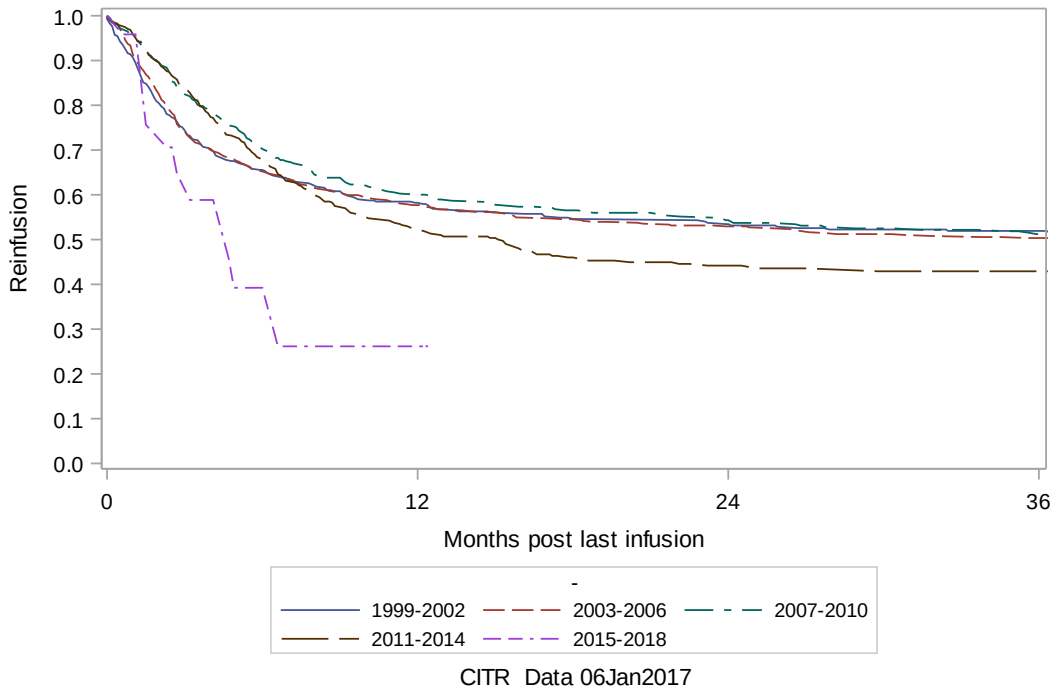
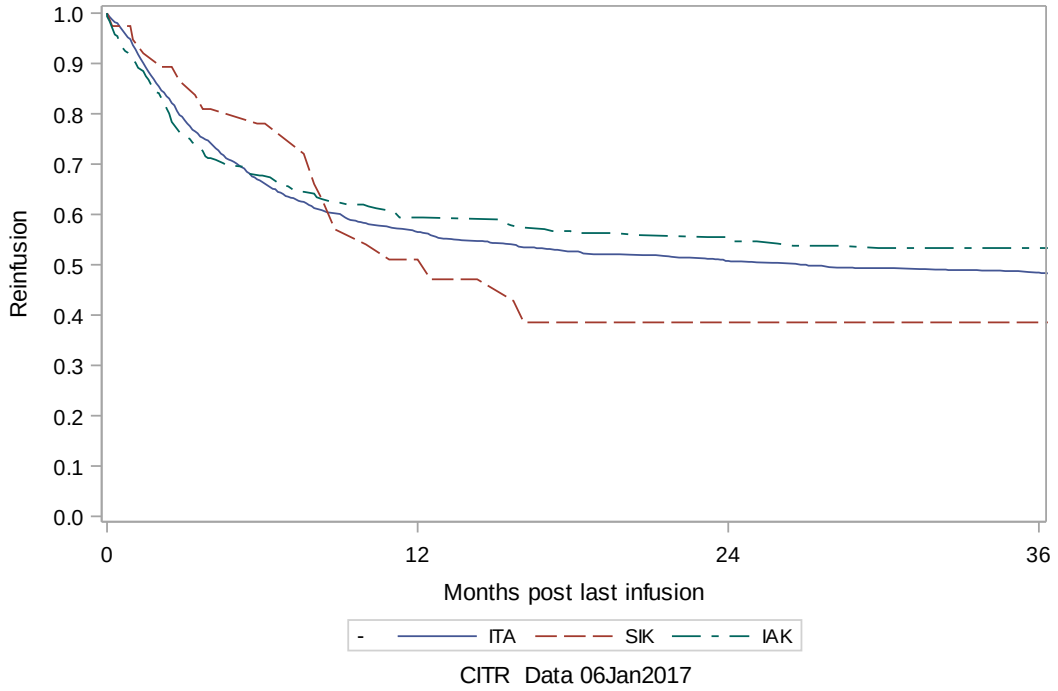


Exhibit 5-15 (continued)
Re-Infusion
(after each infusion sequence)

D. By Transplant Type (p=0.3)



Chapter 6
Liver, Kidney Lipid, and PRA Effects

Table of Contents

Introduction

Exhibits 6-1 to 6-9 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.

ALT typically rises after islet transplantation and then levels off (Exhibit 6-1A). Maintenance immunosuppression, while nominally significant at p=0.04, does not exhibit a clinically meaningful effect.

AST also rises after islet transplantation (Exhibit 6-1B). Long-term recovery appears to be better in recipients aged <35 years. Although statistically significant (p=0.004) the trend by maintenance immunosuppression does not reflect effects of concern.

There is very little change in alkaline phosphatase in follow-up after islet transplantation (Exhibit 6-2); however, across eras there has been a significant decline in initial – and hence follow-up -- levels. Initial levels are higher in IAK compared to ITA, and these levels persist relatively unchanged over follow-up. Recipients given induction with TCD+TNFa inhibitor had lower initial levels which then persisted relatively unchanged over long-term follow-up. Recipients infused with ≥ 325 IEQs also had lower levels at baseline which then persisted.

Total bilirubin varied somewhat over years of follow-up after islet transplantation, but in no consistent upward or downward trend (Exhibit 6-3). The difference between ITA and IAK is not clinically meaningful. Maintenance immunosuppression with mTOR inhibitors and calcineurin inhibitors showed slightly lower initial, and hence follow-up, levels (0.1-0.2 mg/dL). The difference between induction immunosuppression is not clinically meaningful.

There is a mild, statistically significant (p=0.04) decline in HDL cholesterol over the years following islet transplantation in both ITA and IAK, which was consistent across the eras, though the decline over follow-up time was slightly more pronounced in IAK and for those under 35 (Exhibit 6-4). There were no differences by immunosuppression regimen.

In the early eras, a notable decline in LDL cholesterol in follow-up was noted, which did not differ by type of transplant (Exhibit 6-5). Initial LDL levels were higher in recipients aged<35 years, though the subsequent rate of decline was comparable. This occurred primarily in those receiving Il1RA, which may account for the differences by era.

Triglycerides rose somewhat following islet transplantation (Exhibit 6-6). Initial levels were lower in ITA than IAK, but rose such that levels were similar between transplant types post transplant. There were no net effects of age or IEQ infused, but levels were higher among recipients managed with both

mTOR inhibitors and calcineurin inhibitors compared to other maintenance immunosuppression regimens, and for induction with IL2RA alone or TCD+TNFa inhibition compared to other induction immunosuppression regimens.

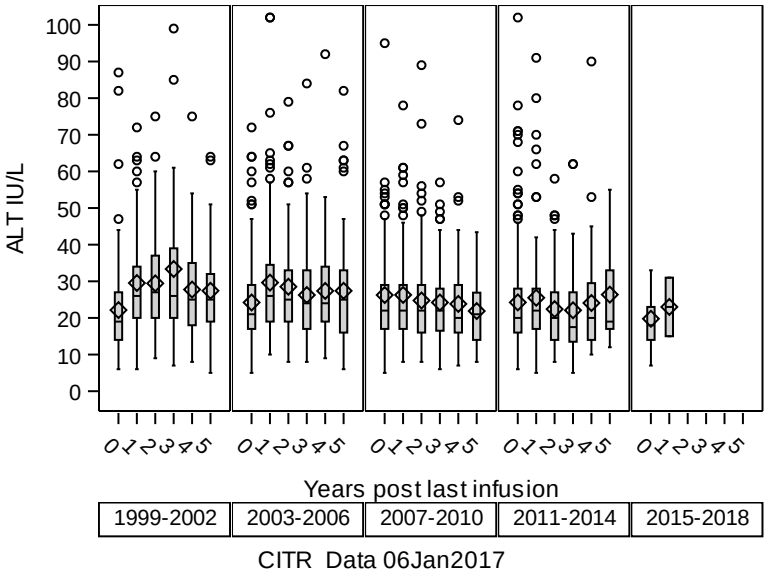
Total cholesterol generally declined in follow-up after islet transplantation, though with lower initial levels in the recent eras, though it remained level over follow-up (Exhibit 6-7). There was a notable difference by age, with those under 35 experiencing a greater decline. Induction with IL2RA alone or TCD+TNFa inhibition was associated with significantly less decline over follow-up time, though they started out higher. The differences by maintenance immunosupression are not clinically important.

Serum creatinine rose over years of follow-up after initial islet transplant, in both ITA and IAK, with the IAKs starting at higher levels (Exhibit 6-8). Those 35 and over also had higher initial levels. There were no significant differences by era, IEQ's infused, or immunosuppression.

The decline in CKD-Epi eGFR after islet transplantation is both statistically significant and clinically important (Exhibit 6-9). IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate. Initial levels were also lower in recipients age ≥ 35 and declined at slower rate compared to younger recipients. Levels were generally higher among recipients managed with both mTOR inhibitors and calcineurin inhibitors compared to other maintenance immunosuppression regimens.

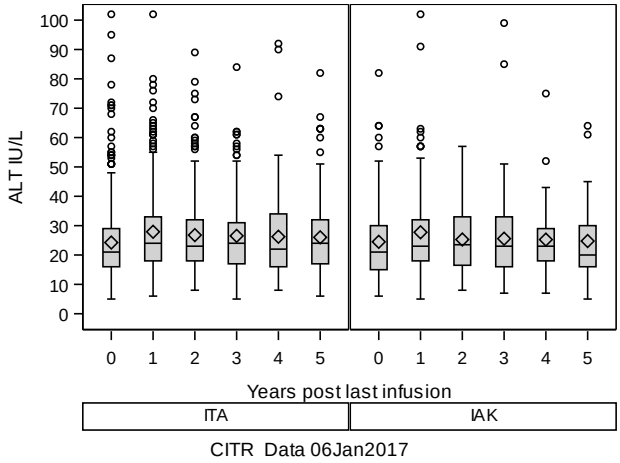
Exhibit 6 – 1A
ALT (IU/L)

A. Era (p=NS)

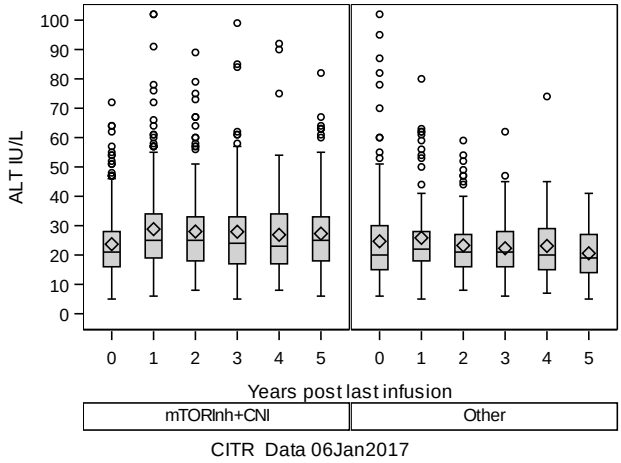


	1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean	22.1	29.5	29.4	33.4	27.8	27.4	24.2	29.6	28.5	26.3	27.4	27.4	26.3	26.3	24.8	24.2	23.8	21.9	24.2	25.5	22.4	22.1	24.1	26.4	19.8	23.0
S.E.	1.1	1.5	1.7	3.0	1.9	2.1	0.7	1.4	1.6	1.1	1.7	1.5	1.5	1.5	1.2	1.5	1.4	1.1	1.0	1.4	1.4	1.9	3.2	4.0	3.0	8.0

B. Type of Transplant (p=NS)



C. Maintenance IS (p=0.04)*

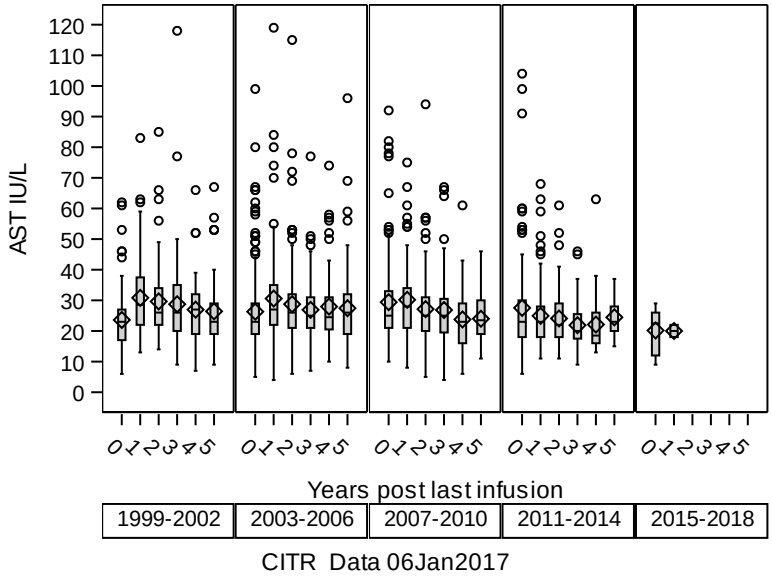


	ITA						IAK						mTORinh+CNI						Other					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean	24.2	27.9	26.8	26.5	26.2	26.0	24.5	27.7	25.3	25.6	25.2	24.8	23.7	28.8	28.0	27.9	26.9	27.3	24.7	25.8	23.3	22.3	23.1	20.6
S.E.	0.6	0.8	0.9	1.0	1.1	1.0	1.2	1.6	1.3	1.8	1.8	2.0	0.6	0.9	1.0	1.2	1.1	1.1	1.0	1.5	1.1	1.1	1.6	1.4

***Magnitude of difference was not clinically meaningful**

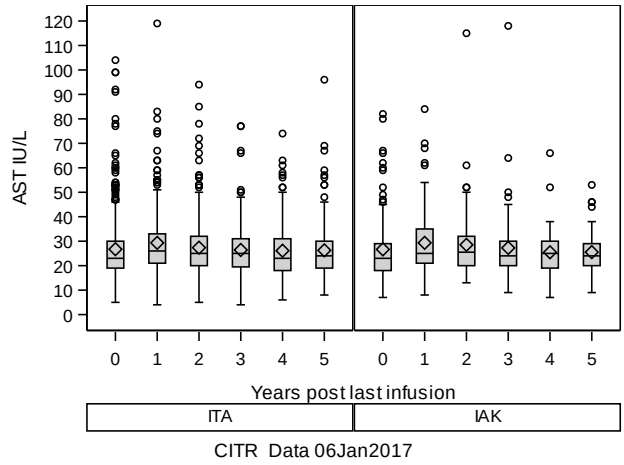
Exhibit 6 – 1B
AST (IU/L)

A. Era (p=NS)



1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
23.6	30.8	29.6	28.7	27.0	26.4	26.3	30.6	28.8	26.9	28.0	27.4	29.4	30.2	27.1	26.8	23.8	24.0	27.5	24.9	24.1	21.9	22.1	24.5	20.2	20.0
S.E.																									
0.7	1.2	1.5	1.9	1.4	1.9	0.7	1.4	1.1	0.9	1.7	1.4	1.4	1.7	1.1	1.1	1.1	1.0	1.5	1.0	1.1	1.2	2.1	2.2	3.3	2.0

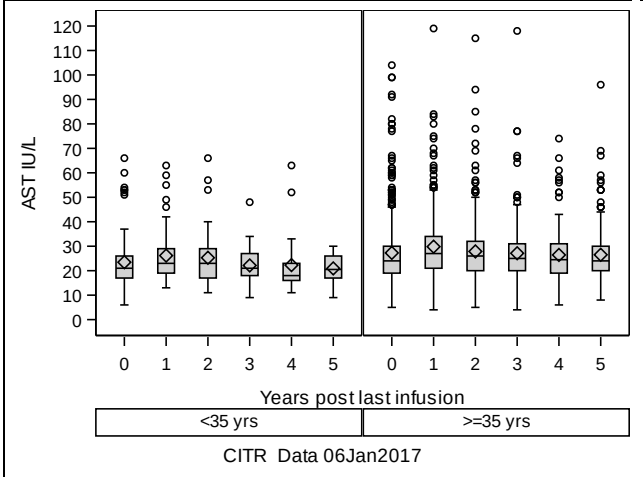
B. Type of Transplant (p=NS)



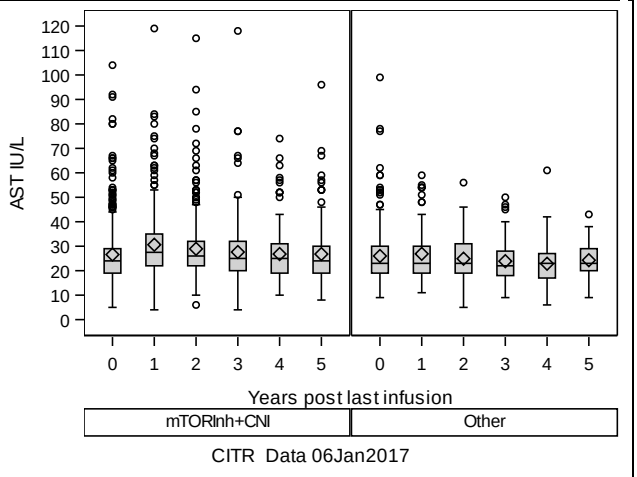
ITA						IAK					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
26.7	29.3	27.4	26.4	26.1	26.3	26.6	29.3	28.5	27.3	25.5	25.5
S.E.											
0.6	0.8	0.6	0.6	0.9	0.9	1.2	1.3	1.5	1.8	1.5	1.5

Exhibit 6 – 1B (Continued)
AST (IU/L)

C. Age (p=0.002)



D. Maintenance IS (p=0.004)*

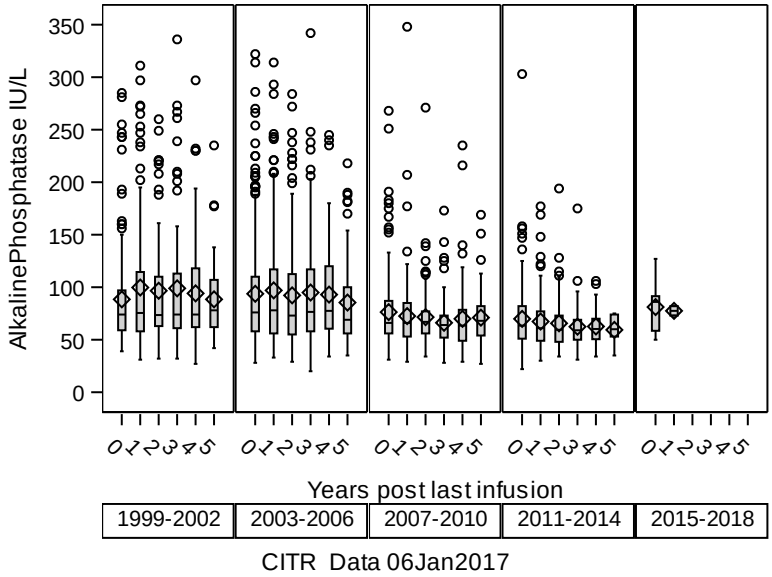


	<35 years						≥35 years						mTORInh+CNI						Other					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean	23.5	26.2	25.3	22.1	22.3	20.9	27.3	29.8	27.9	27.1	26.4	26.5	30.0	25.7	24.0	23.9	25.7	20.7	26.6	30.6	28.9	27.6	26.8	26.8
S.E.	1.0	1.2	1.8	1.3	2.3	1.6	0.6	0.8	0.6	0.7	0.9	0.8	3.8	1.6	1.9	2.3	1.9	2.3	0.7	0.9	0.8	0.8	1.0	1.0

***Magnitude of difference was not clinically meaningful**

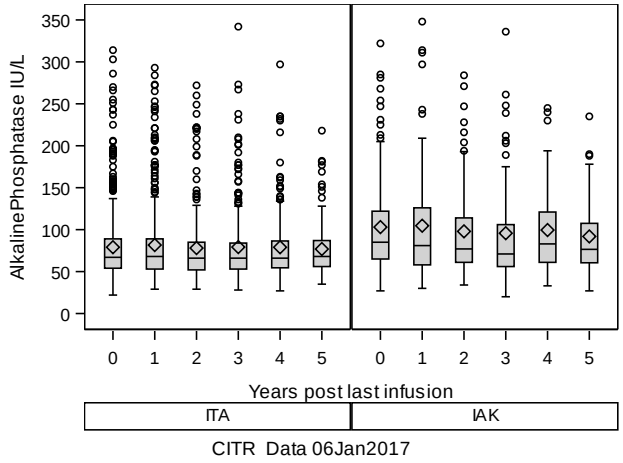
Exhibit 6 – 2
Alkaline Phosphatase (IU/L)

A. Era (p<0.0001)



1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
88.5	99.7	96.6	98.9	94.1	88.5	93.7	97.0	92.3	95.0	93.0	85.4	76.3	72.5	71.5	66.1	69.9	71.0	69.9	67.3	65.6	62.4	62.6	59.4	81.1	77.5
S.E.																									
4.1	6.3	6.9	8.2	7.5	6.0	3.6	4.4	4.9	5.4	5.3	5.3	3.0	3.4	2.9	2.5	4.3	3.8	2.4	2.9	3.4	3.4	3.2	3.9	8.9	4.5

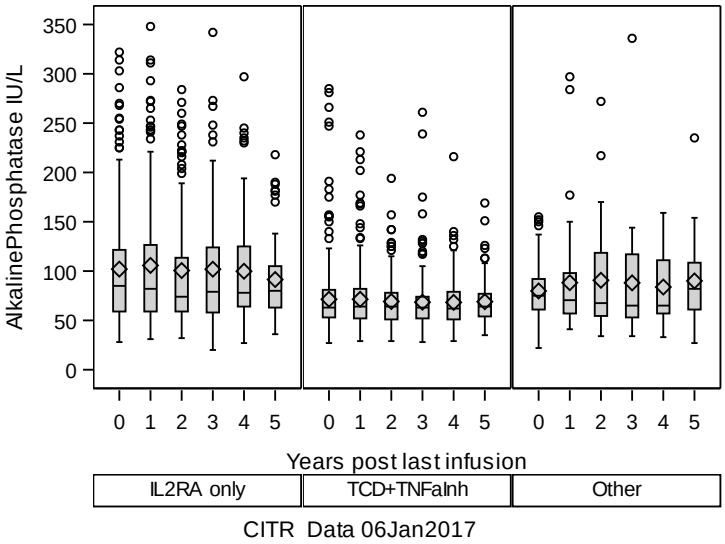
B. Type of Transplant (p<0.0001)



ITA						IAK					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
79.0	81.6	78.0	79.2	79.0	76.9	103	105	97.9	95.7	99.5	91.9
S.E.											
1.7	2.4	2.5	2.9	3.1	2.9	5.5	6.8	6.4	7.9	8.4	7.9

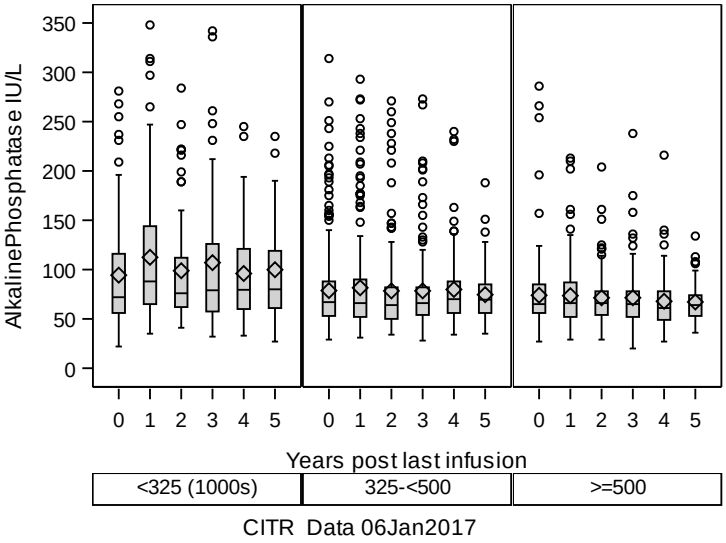
Exhibit 6 – 2 (Continued)
Alkaline Phosphatase (IU/L)

C. Induction IS (p<0.0001)



IL2RA only						TCD+TNFaInh						Other					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																	
102	106	101	102	99.8	91.4	71.4	71.4	69.1	68.4	68.3	69.0	79.8	88.2	90.7	88.0	83.8	90.0
S.E.																	
4.5	7.5	10.8	10.3	34.1	20.4	4.1	5.0	5.6	5.9	6.0	5.7	1.8	2.1	1.8	2.4	2.4	2.5

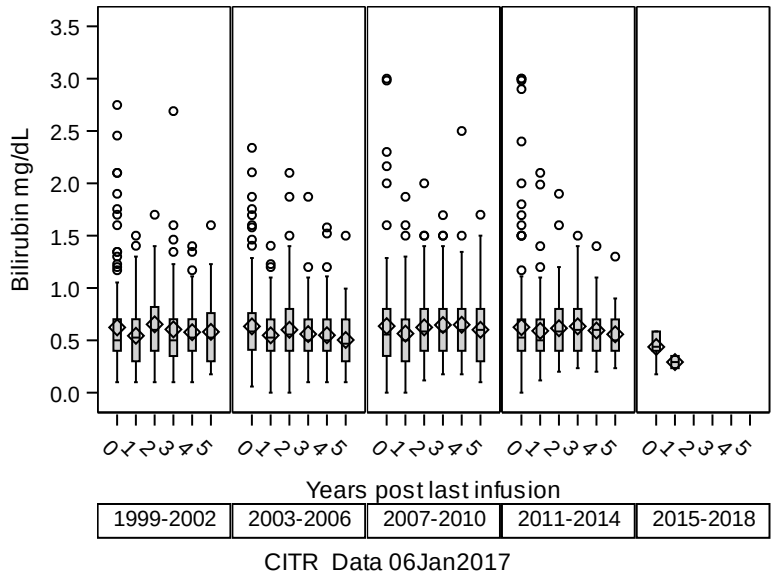
D. IEQ's Infused (p=0.008)



<325 (1000s)						325-<500						≥500					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																	
94.4	113	98.8	107	96.0	99.9	78.7	81.5	78.4	78.4	79.8	74.6	73.9	73.5	71.4	71.4	67.9	67.2
S.E.																	
4.8	7.1	7.4	9.9	7.5	8.8	2.4	3.5	3.8	3.8	4.0	3.4	2.5	2.8	2.7	3.5	3.7	3.1

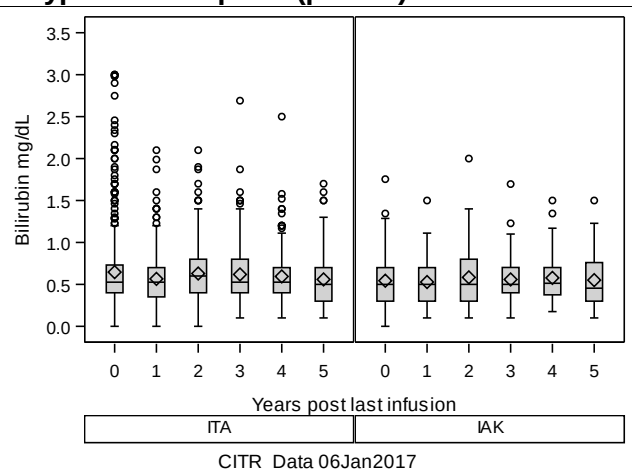
Exhibit 6 – 3
Total Bilirubin

A. Era (p=NS)



1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
0.6	0.5	0.7	0.6	0.6	0.6	0.6	0.5	0.6	0.6	0.5	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.4	0.3
S.E.																									
0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1

B. Type of Transplant (p=0.04)*

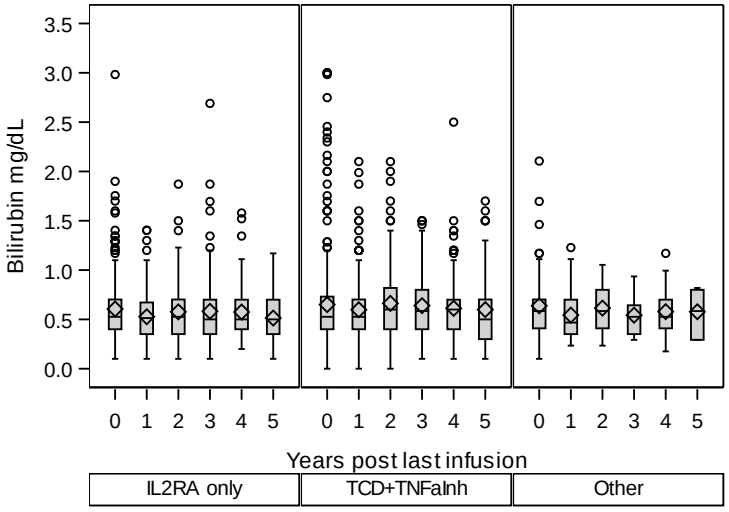


ITA						IAK					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.6	0.6	0.6	0.6
S.E.											
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1

***Magnitude of difference was not clinically meaningful**

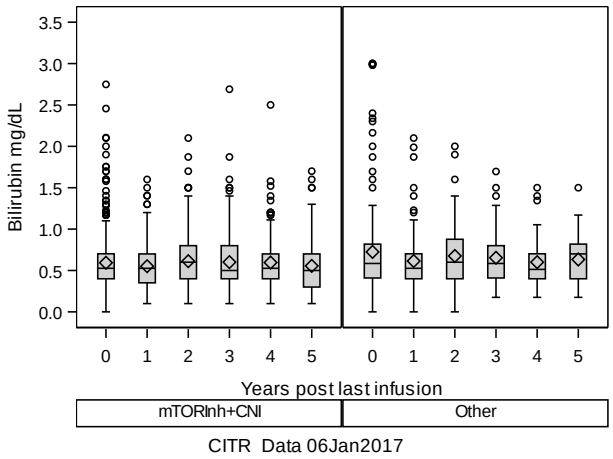
Exhibit 6 – 3 (Continued)
Total Bilirubin

C. Induction IS (p=0.006)*



IL2RA only						TCD+TNFaInh						Other					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																	
0.6	0.5	0.6	0.6	0.6	0.5	0.6	0.6	0.7	0.6	0.6	0.6	0.6	0.5	0.6	0.5	0.6	0.6
S.E.																	
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1

D. Maintenance IS (p=0.002)

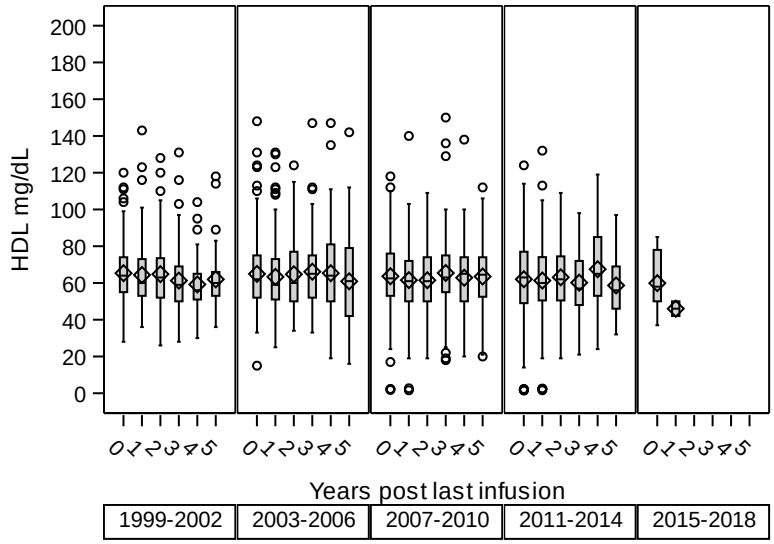


mTORInh+CNI						Other					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
0.6	0.6	0.6	0.6	0.6	0.6	0.7	0.6	0.7	0.7	0.6	0.6
S.E.											
0.1	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0

***Magnitude of difference was not clinically meaningful**

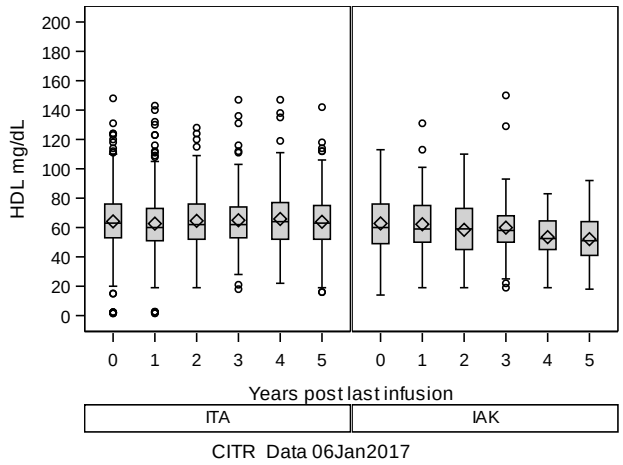
Exhibit 6 – 4
HDL Cholesterol (mg/dL)

A. Era (p=NS)

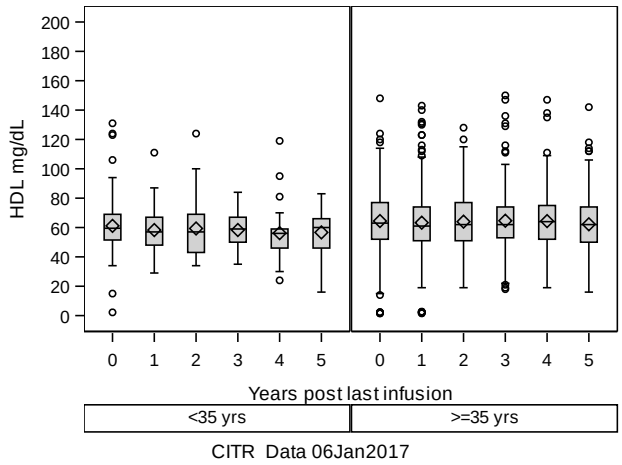


	1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean	65.3	64.4	64.8	61.3	59.2	62.0	64.9	63.3	64.7	66.1	65.3	60.9	63.6	61.5	61.5	65.4	62.8	63.5	62.0	61.3	63.1	60.2	67.5	58.7	59.9	46.0
S.E.	1.4	1.8	2.3	2.1	2.1	2.2	1.3	1.6	1.7	1.9	2.6	2.7	1.6	1.7	1.7	2.3	2.2	2.7	1.7	2.3	2.2	2.7	3.9	6.5	5.8	4.0

B. Type of Transplant (p=NS)



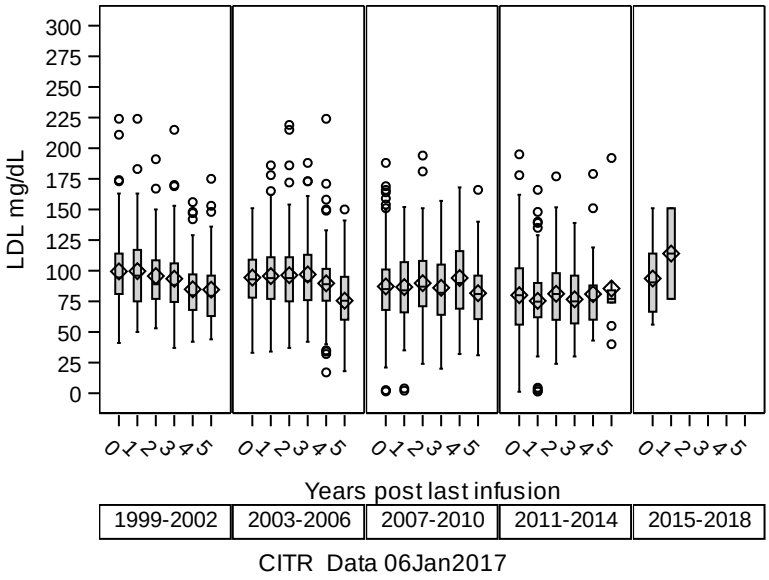
C. Age (p=0.04)



	ITA						IAK						<35 years						≥35 years					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean	64.2	62.7	64.5	65.0	65.8	63.9	62.8	62.2	58.4	59.9	53.5	52.1	61.1	58.3	59.3	58.3	56.2	56.7	64.4	63.3	64.0	64.6	64.4	62.2
S.E.	0.8	1.0	1.0	1.2	1.5	1.7	1.8	2.4	2.4	2.7	2.2	3.1	1.8	1.7	2.8	2.0	4.1	4.7	0.8	1.0	1.0	1.2	1.4	1.6

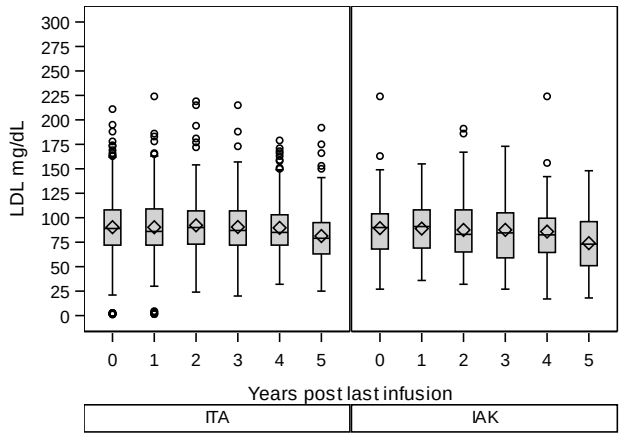
Exhibit 6 – 5
LDL Cholesterol (mg/dL)

A. Era (p<0.0001)

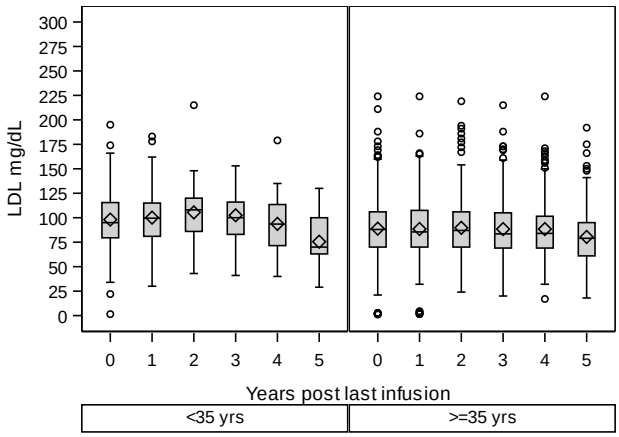


	1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean	99.4	99.6	95.7	93.5	84.8	84.5	94.4	95.6	96.3	97.0	89.7	75.5	87.2	86.6	89.8	86.1	94.1	81.7	80.0	75.4	81.2	76.6	80.9	85.4	93.6	114.0
S.E.	2.5	3.0	3.1	3.6	3.8	4.2	1.7	2.2	2.8	3.0	3.3	3.0	2.5	2.5	2.9	3.2	3.8	4.0	2.6	3.0	3.4	4.3	6.0	14.3	11.7	37.0

B. Type of Transplant (p=NS)



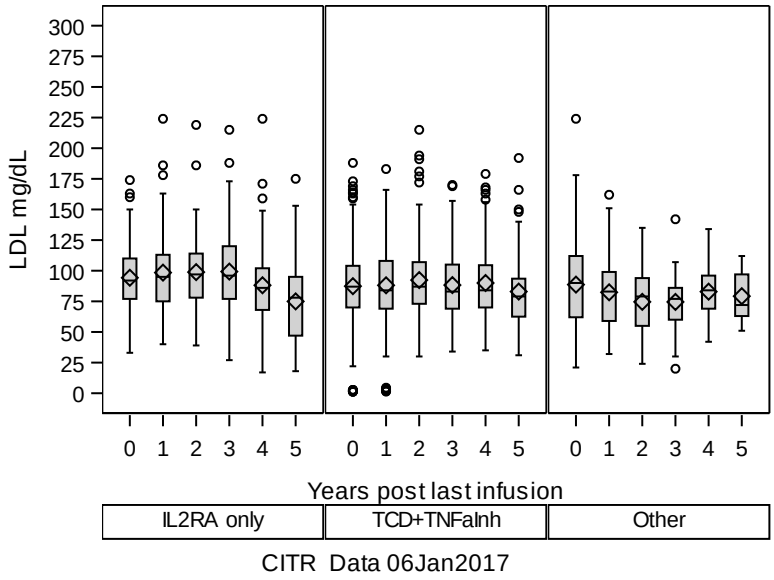
C. Age (p=0.0002)



	ITA						IAK						<35 years						≥35 years					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean	90.3	90.3	92.2	90.5	89.7	81.3	89.3	88.9	87.5	87.6	85.8	74.0	98.1	100.1	105.4	102.5	93.7	75.5	88.9	88.5	89.7	88.4	88.4	80.4
S.E.	1.3	1.5	1.7	1.9	2.1	2.3	3.1	3.4	4.2	4.6	5.6	5.4	3.3	3.6	4.7	4.9	6.2	7.8	1.2	1.5	1.6	1.9	2.1	2.2

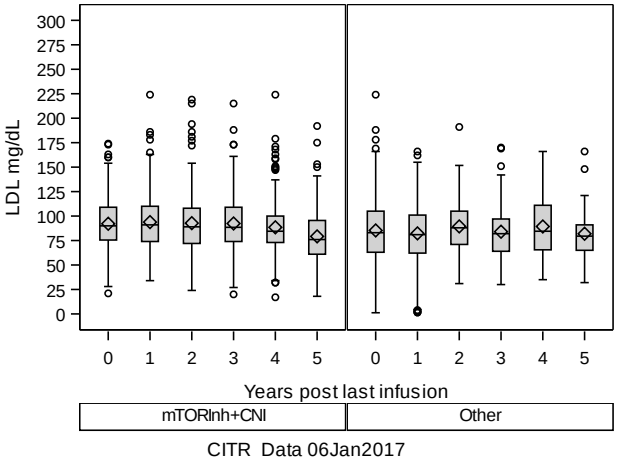
Exhibit 6 – 5
LDL Cholesterol (mg/dL)

D. Induction IS (p=0.0008)



IL2RA only						TCD+TNFaInh						Other					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																	
94.3	98.5	98.9	99.3	88.1	75.0	87.4	88.1	92.4	88.3	90.0	83.0	88.7	82.4	74.6	74.5	82.9	79.2
S.E.																	
1.9	2.3	2.7	3.3	3.9	3.9	1.7	2.0	2.2	2.3	2.6	2.9	3.3	3.7	3.8	4.3	4.6	4.2

E. Maintenance IS (p=0.0009)*

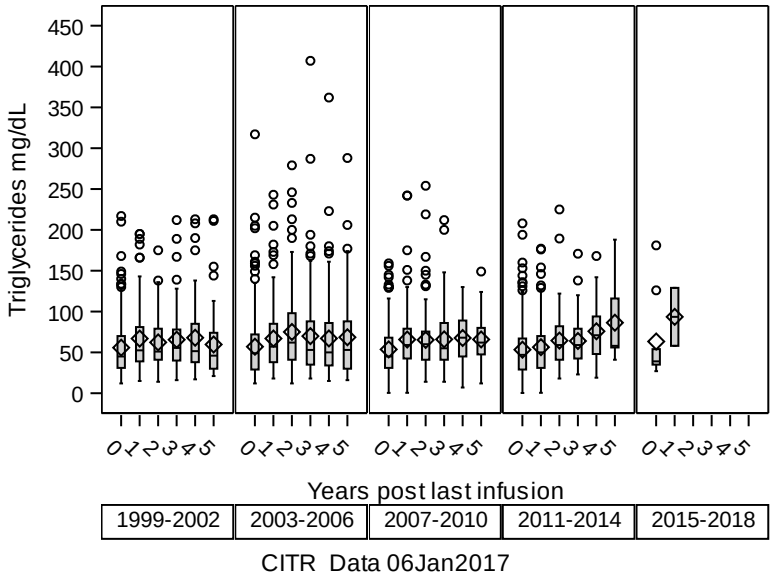


mTORInh+CNI						Other					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
92.1	93.8	92.7	92.4	88.5	79.2	85.3	82.3	89.4	84.0	89.3	81.9
S.E.											
4.6	3.7	5.7	6.6	13.6	26.1	1.3	1.5	1.9	2.0	2.2	2.3

***Magnitude of difference was not clinically meaningful**

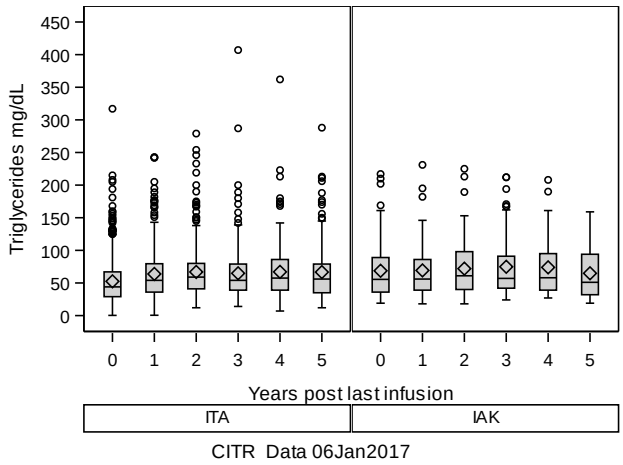
Exhibit 6 – 6
Triglycerides (mg/dL)

A. Era (p=NS)



1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
55.8	66.9	62.3	65.5	67.9	59.7	57.0	67.0	75.0	69.9	67.1	68.5	53.7	65.8	65.3	66.0	67.6	65.8	53.3	56.4	64.4	63.9	75.9	86.3	63.3	93.5
S.E.																									
3.0	4.1	3.7	4.6	6.2	6.0	2.6	3.0	4.3	5.2	5.4	5.5	2.3	3.3	3.5	3.9	3.5	4.0	2.6	3.6	4.2	4.4	6.6	16.6	17.8	35.5

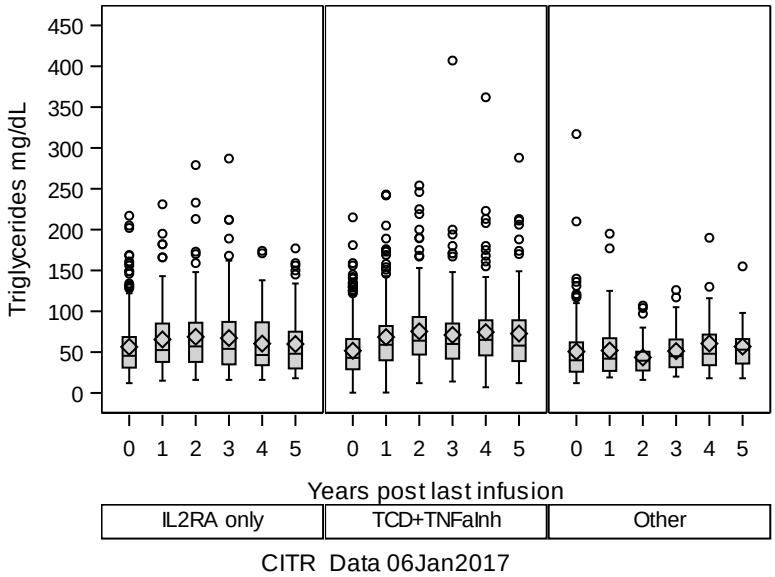
B. Type of Transplant (p<0.0001)



ITA						IAK					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
52.5	63.8	66.9	64.8	67.0	66.7	68.7	69.2	71.9	74.8	73.9	64.8
S.E.											
1.4	1.9	2.3	2.6	3.1	3.5	3.8	4.4	4.8	5.8	6.3	6.7

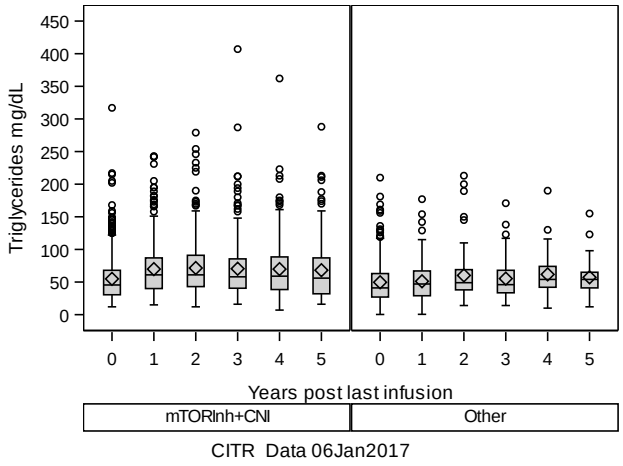
Exhibit 6 – 6 (Continued)
Triglycerides (mg/dL)

C. Induction IS (p=0.03)



IL2RA only						TCD+TNFaInh						Other					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																	
56.5	65.5	68.7	67.2	60.4	59.9	51.7	68.4	75.4	71.0	74.4	72.7	50.7	52.0	43.5	51.3	60.5	56.8
S.E.																	
2.4	2.9	3.8	4.2	4.0	4.6	1.8	2.8	3.1	3.7	4.1	4.9	3.4	4.2	3.0	4.5	8.3	6.0

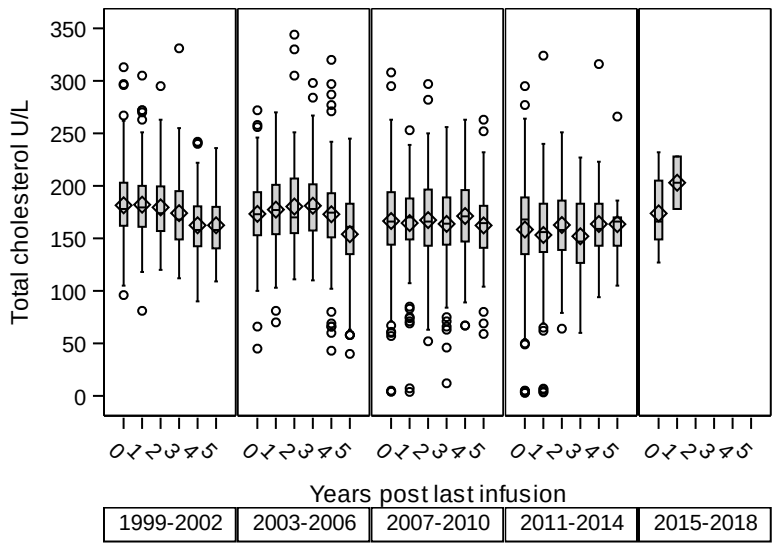
D. Maintenance IS (p=0.003)



mTORInh+CNI						Other					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
54.9	69.8	71.5	70.4	69.8	68.1	49.7	51.1	60.2	55.3	61.7	57.2
S.E.											
4.8	4.2	4.4	3.9	14.8	14.4	1.7	2.2	2.6	3.0	3.3	3.7

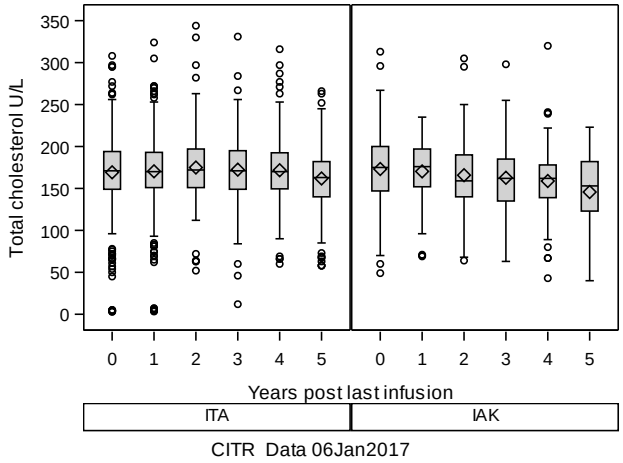
Exhibit 6 – 7
Total Cholesterol (mg/dL)

A. Era (p<0.0001)

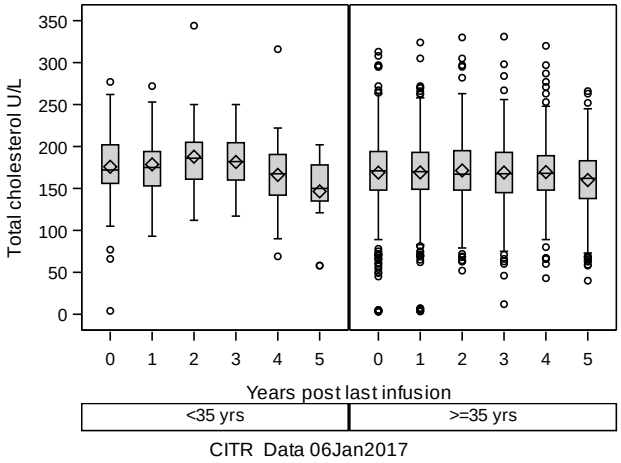


1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
182	182	180	174	163	163	173	177	180	181	173	154	167	165	167	164	171	162	158	153	163	152	164	164	174	203
S.E.																									
2.8	3.5	3.7	4.5	4.6	4.2	2.1	2.6	3.4	3.4	4.8	5.2	3.5	3.5	4.1	4.8	4.7	5.6	3.8	4.8	4.0	5.7	8.0	15.7	12.2	25.0

B. Type of Transplant (p=NS)



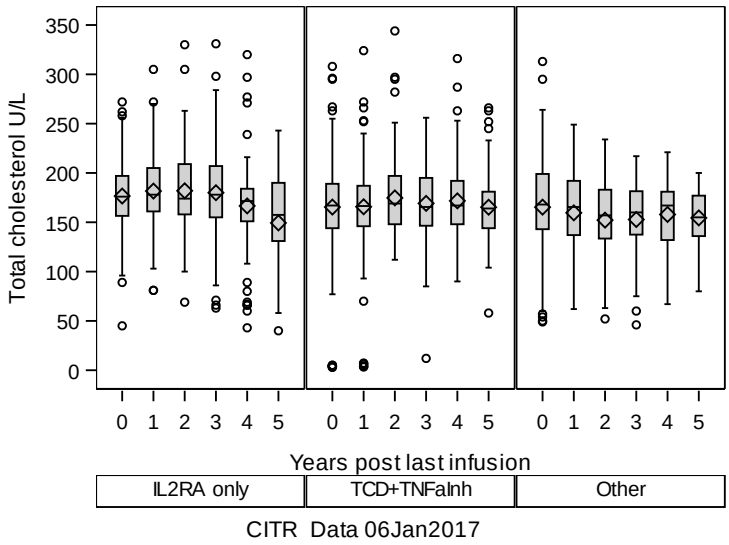
C. Age (p=0.048)



ITA						IAK						<35 years						≥35 years					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																							
169	170	175	172	172	162	173	170	166	163	159	146	176	179	188	182	166	147	169	169	171	169	170	160
S.E.																							
1.7	2.0	2.1	2.4	2.8	3.1	3.8	4.0	5.3	5.7	6.9	7.8	3.9	4.2	6.0	5.2	8.8	9.9	1.7	2.0	2.1	2.5	2.8	3.1

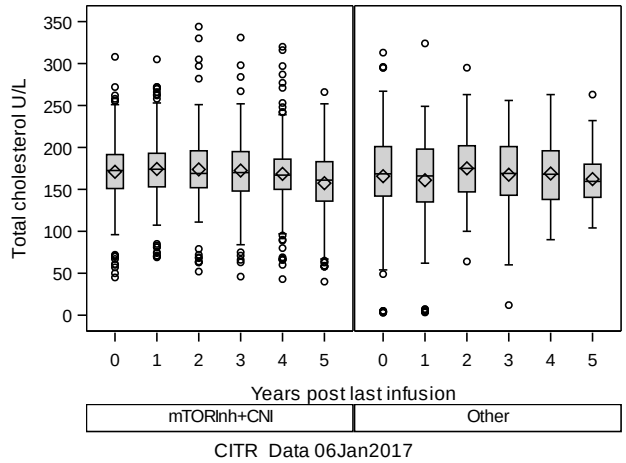
Exhibit 6 – 7 (Continued)
Total Cholesterol (mg/dL)

D. Induction IS (p=0.0006)



IL2RA only						TCD+TNFaInh						Other					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																	
177	182	182	180	167	149	165	166	175	169	172	165	165	160	152	153	158	154
S.E.																	
2.2	2.7	3.4	4.0	5.2	6.1	2.4	2.8	2.7	3.0	3.4	3.6	4.4	5.5	6.4	6.8	7.2	5.5

E. Maintenance IS (p=0.02)*

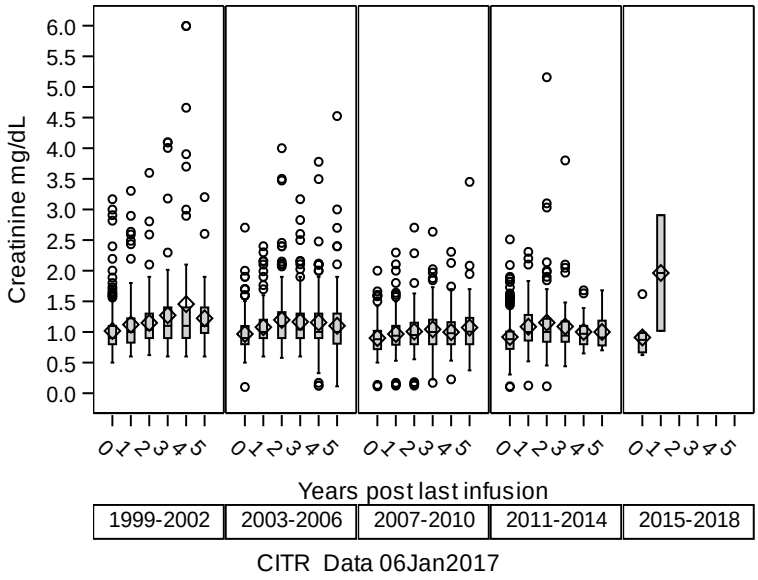


mTORInh+CNI						Other					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
171	174	174	172	168	157	166	161	175	168	169	162
S.E.											
1.6	1.9	2.4	2.6	3.0	3.4	3.5	4.8	4.1	5.4	5.6	5.7

***Magnitude of difference was not clinically meaningful**

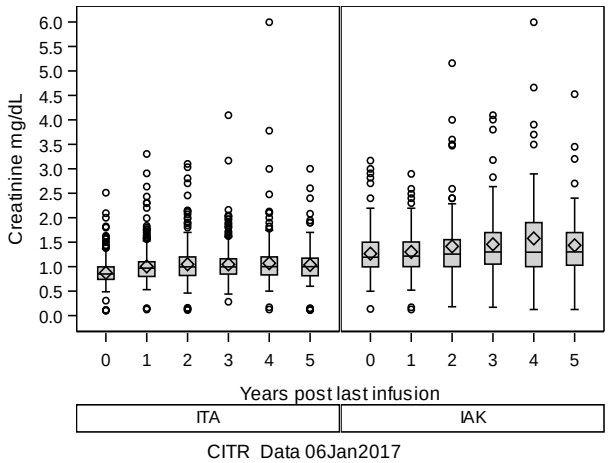
Exhibit 6 – 8
Serum Creatinine (mg/dL)

A. Era (p=0.0007)

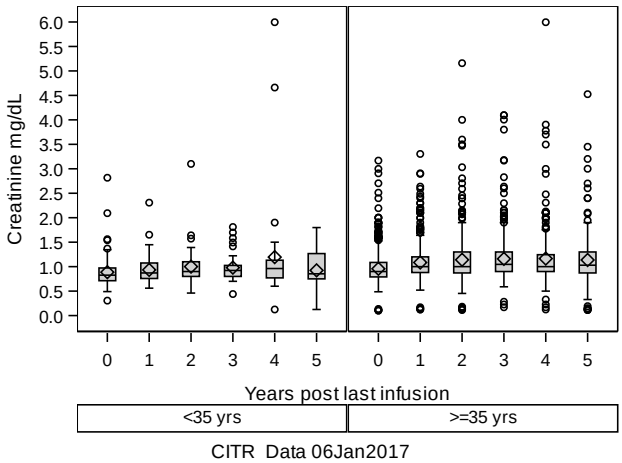


1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
1.0	1.1	1.1	1.3	1.5	1.2	1.0	1.1	1.2	1.2	1.2	1.1	0.9	1.0	1.0	1.0	1.0	1.1	0.9	1.1	1.2	1.1	1.0	1.0	0.9	2.0
S.E.																									
0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.1	0.1	0.0	0.1	0.1	0.9

B. Type of Transplant (p<0.0001)



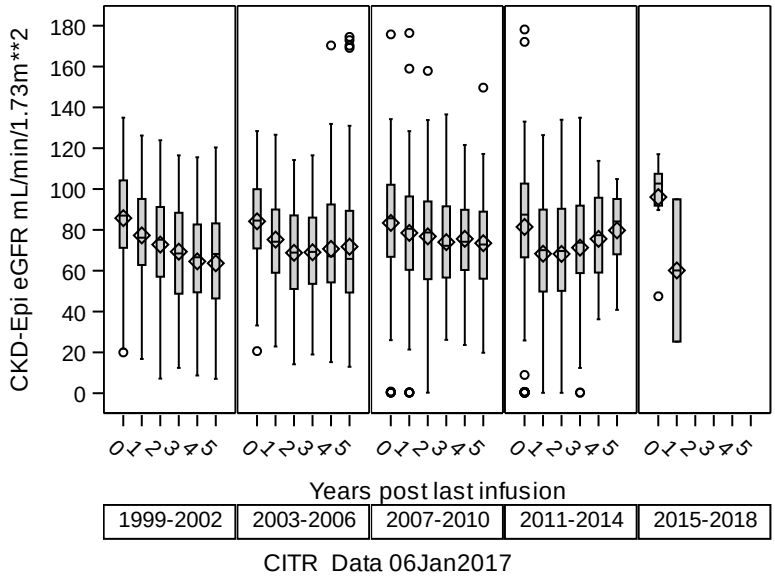
C. Age (p=0.003)



ITA						IAK						<35 years						≥35 years					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																							
0.9	1.0	1.0	1.0	1.1	1.0	1.3	1.3	1.4	1.5	1.6	1.4	0.9	0.9	1.0	1.0	1.2	0.9	1.0	1.1	1.1	1.2	1.2	1.1
S.E.																							
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.2	0.1	0.0	0.0	0.0	0.0	0.0	0.0

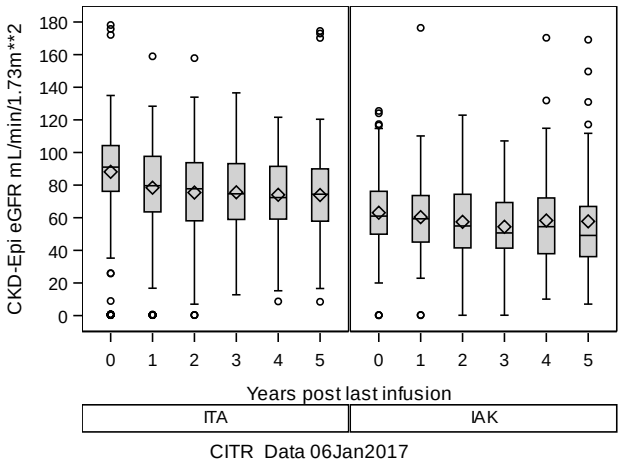
Exhibit 6 – 9
CKD-EPI eGFR

A. Era (p=NS)

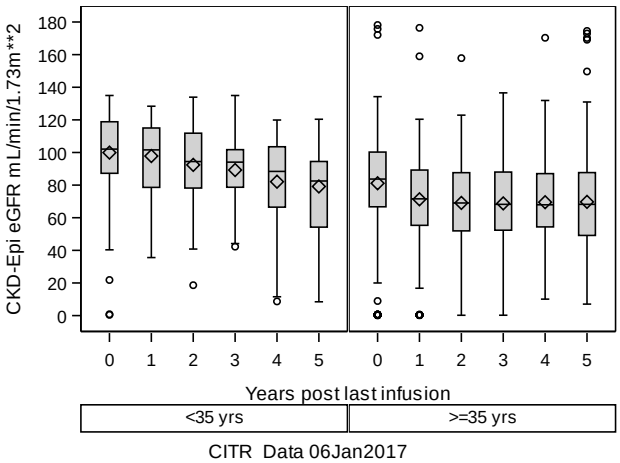


1999-2002						2003-2006						2007-2010						2011-2014						2015-2018	
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1
Mean																									
85.7	77.3	72.8	69.3	64.6	63.6	84.2	75.3	68.8	69.0	70.7	71.8	83.4	78.5	76.8	74.0	75.6	73.5	81.4	68.3	68.2	71.3	75.6	79.8	96.1	60.1
S.E.																									
1.9	2.3	2.7	2.9	3.1	3.3	1.4	1.7	1.9	2.0	2.6	3.3	2.0	2.3	2.1	2.2	2.4	3.1	1.9	2.5	3.1	3.8	4.0	6.1	7.6	34.9

B. Type of Transplant (p<0.0001)



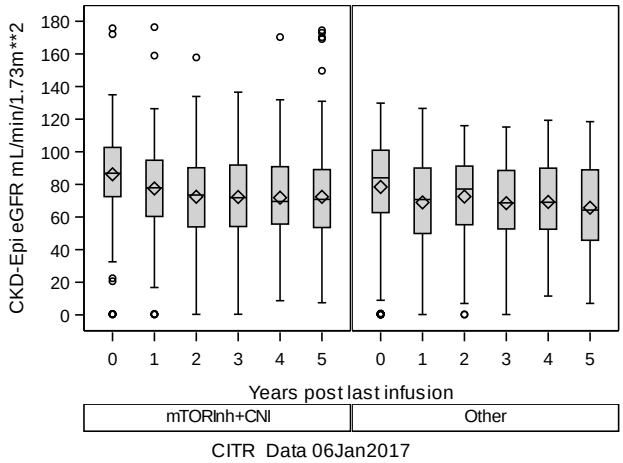
C. Age (p<0.0001)



ITA						IAK						<35 years						≥35 years					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Mean																							
88.1	78.4	75.4	75.6	74.0	73.9	63.1	60.4	57.5	54.5	58.3	57.8	99.9	97.8	92.4	89.2	82.1	79.2	81.1	71.3	69.1	68.8	69.5	69.7
S.E.																							
0.9	1.2	1.3	1.3	1.5	1.9	1.8	2.1	2.5	2.6	4.1	4.9	2.3	2.4	3.2	3.5	4.8	6.5	0.9	1.1	1.2	1.3	1.5	1.9

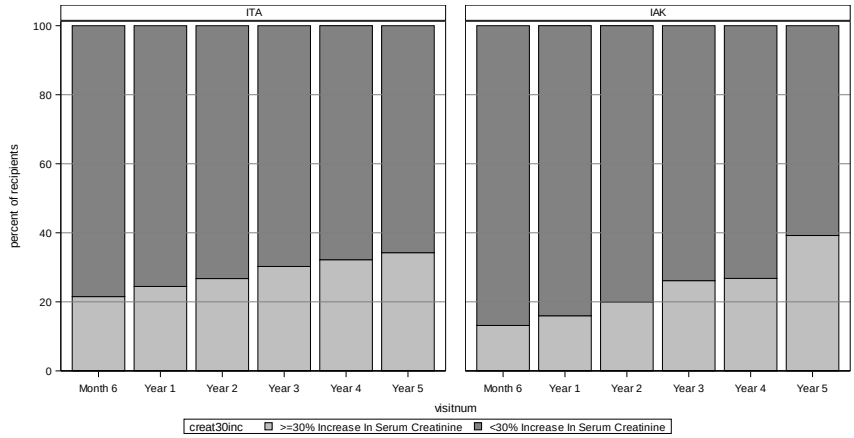
Exhibit 6 – 9 (Continued)
CKD-EPI eGFR

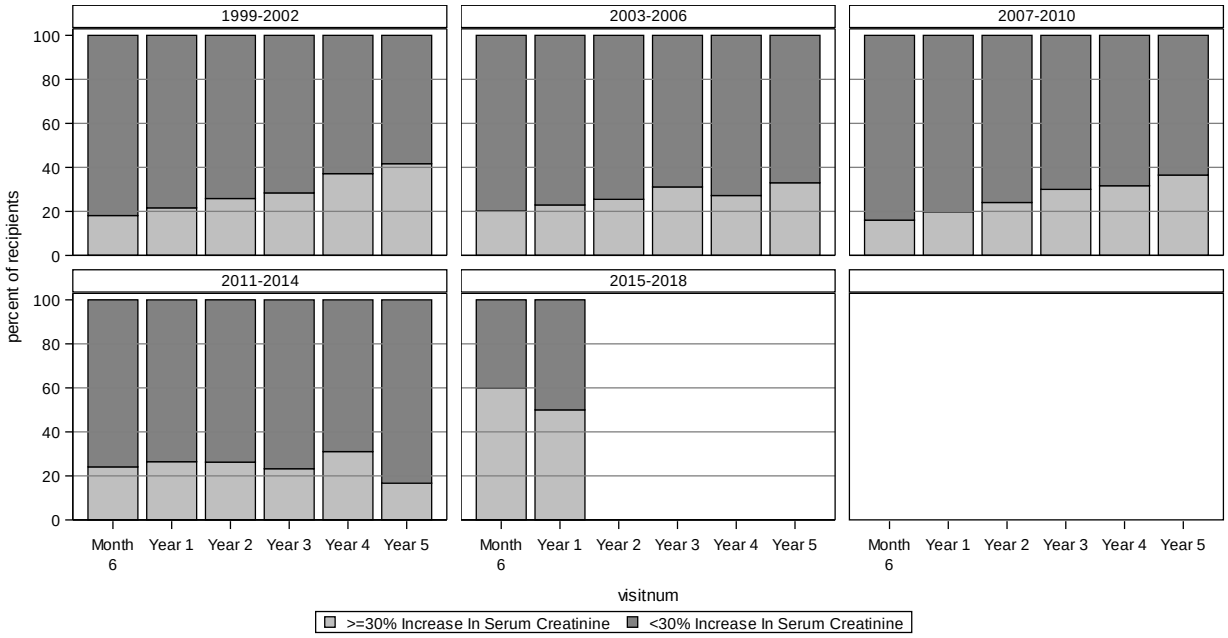
D. Maintenance IS (p<0.0001)



mTORInh+CNI						Other					
0	1	2	3	4	5	0	1	2	3	4	5
Mean											
86.2	77.5	72.4	72.3	71.9	72.4	78.4	68.9	72.5	68.5	69.2	65.7
S.E.											
3.1	3.4	4.6	5.7	7.5	10.3	1.1	1.3	1.4	1.5	1.7	2.1

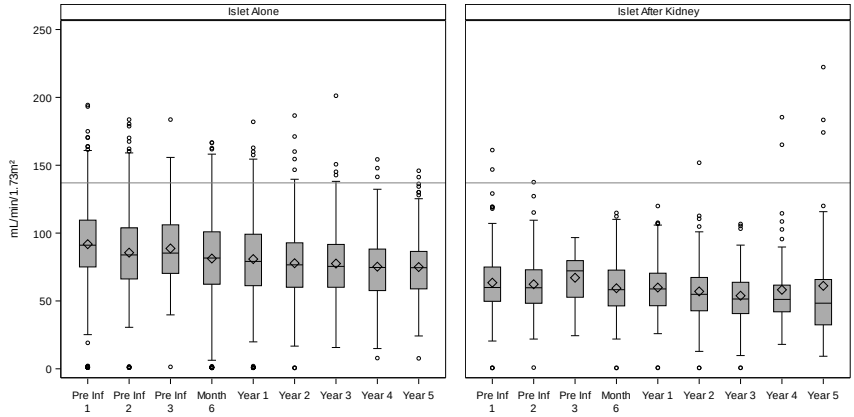
Exhibit 6 – 10
Percent of Recipients with a 30% increase in Serum Creatinine at each Follow-up Time Point by Infusion Type and Era

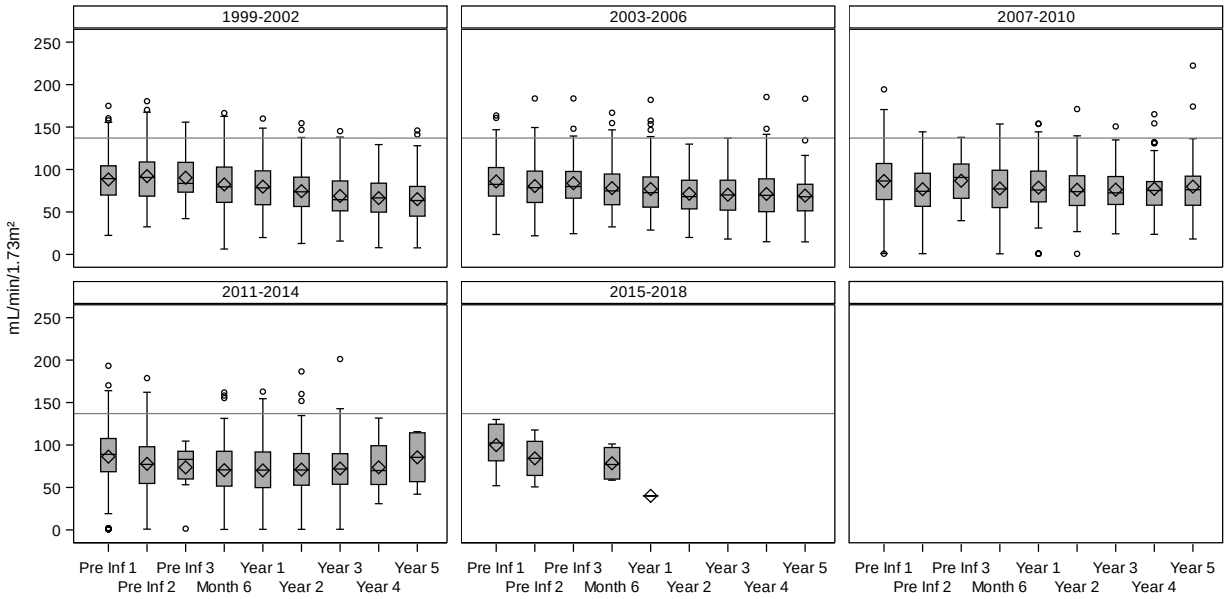




	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	488	462	359	281	236	184
Islet After Kidney	114	119	100	88	56	51
1999-2002	116	125	89	81	70	60
2003-2006	188	192	161	135	114	100
2007-2010	156	141	129	110	79	63
2011-2014	137	121	80	43	29	12
2015-2018	5	2	.	.	.	.

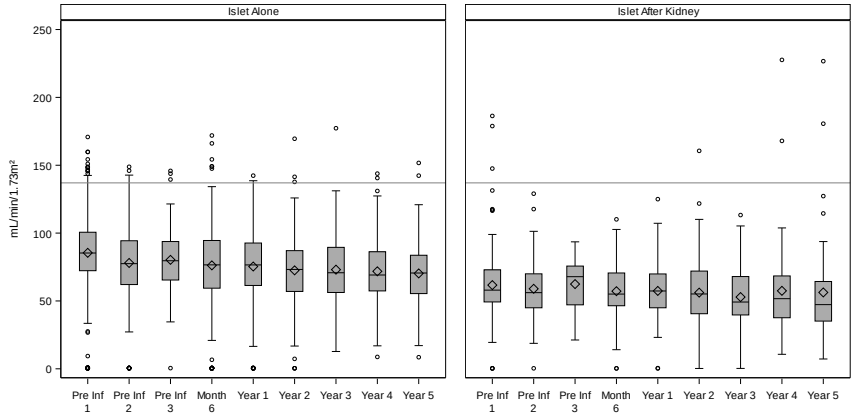
Exhibit 6 – 11
Cockgroft-Gault Calculated Clearance (mL/min/1.73m^2) by Infusion Type and Era

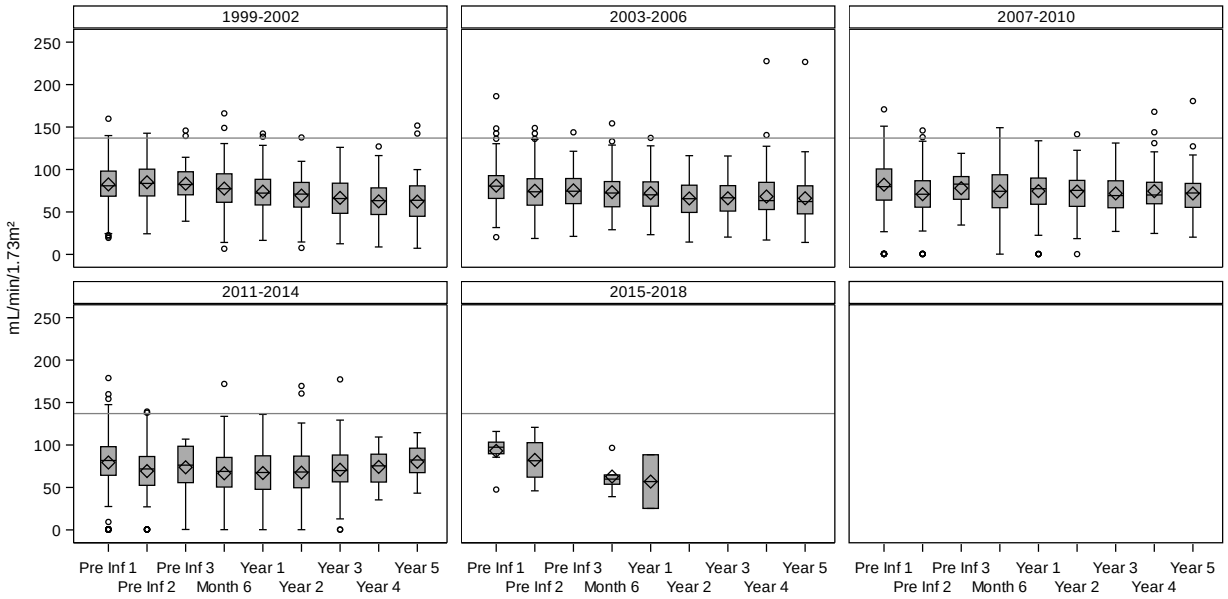




	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	711	435	122	467	436	334	257	203	140
Islet After Kidney	156	90	21	108	112	91	82	53	41
1999-2002	169	111	44	115	118	83	77	66	50
2003-2006	243	183	62	175	178	145	120	93	72
2007-2010	198	116	23	157	143	127	97	70	52
2011-2014	249	111	14	124	108	70	45	27	7
2015-2018	8	4	.	4	1	.	.	.	.

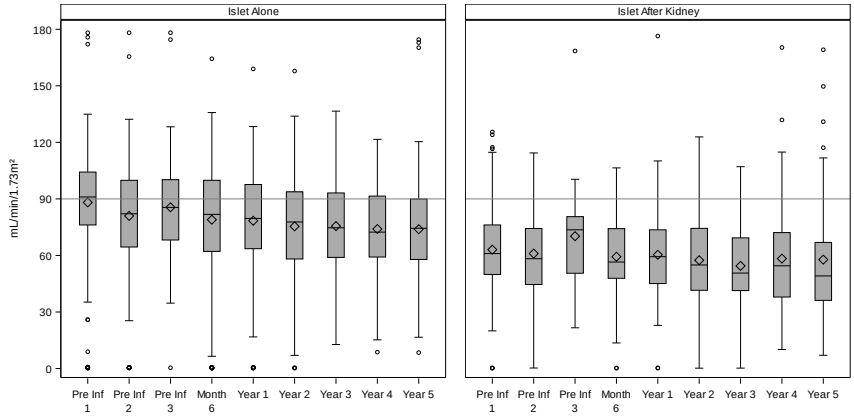
Exhibit 6 – 12
MDRD Estimated Cockgroft-Gault (mL/min/1.73m^2) by Infusion Type and Era

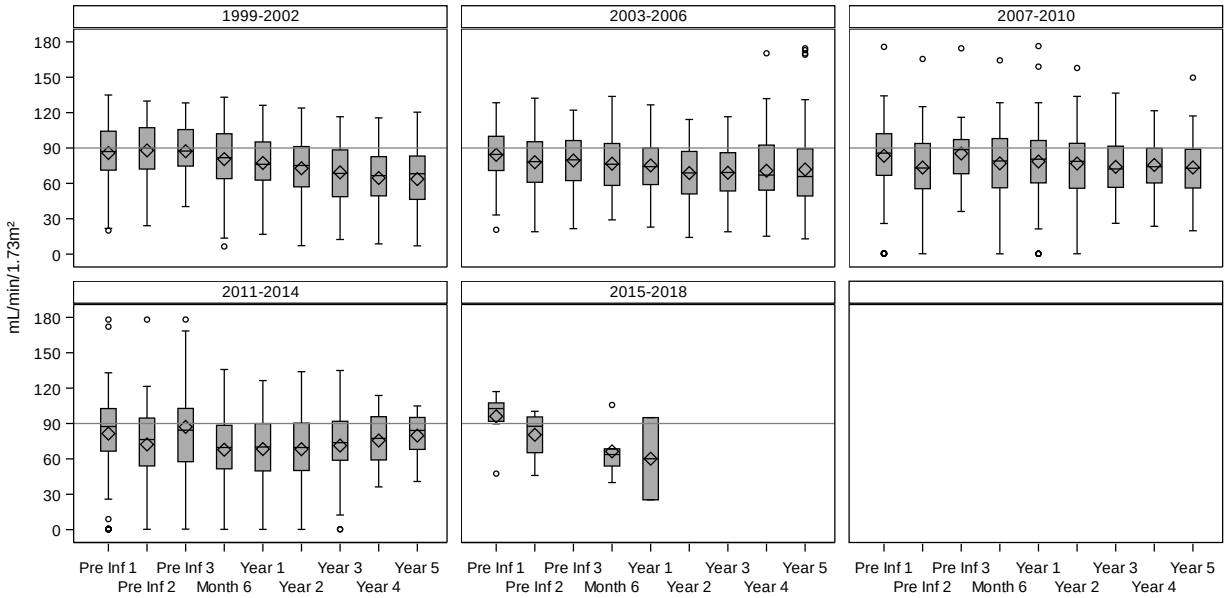




	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	728	467	138	501	488	382	301	240	189
Islet After Kidney	161	93	22	116	121	100	88	57	51
1999-2002	170	113	44	117	126	89	84	72	63
2003-2006	250	192	69	187	191	160	134	113	99
2007-2010	201	125	26	161	150	140	118	83	66
2011-2014	260	126	21	147	140	93	53	29	12
2015-2018	8	4	.	5	2	.	.	.	.

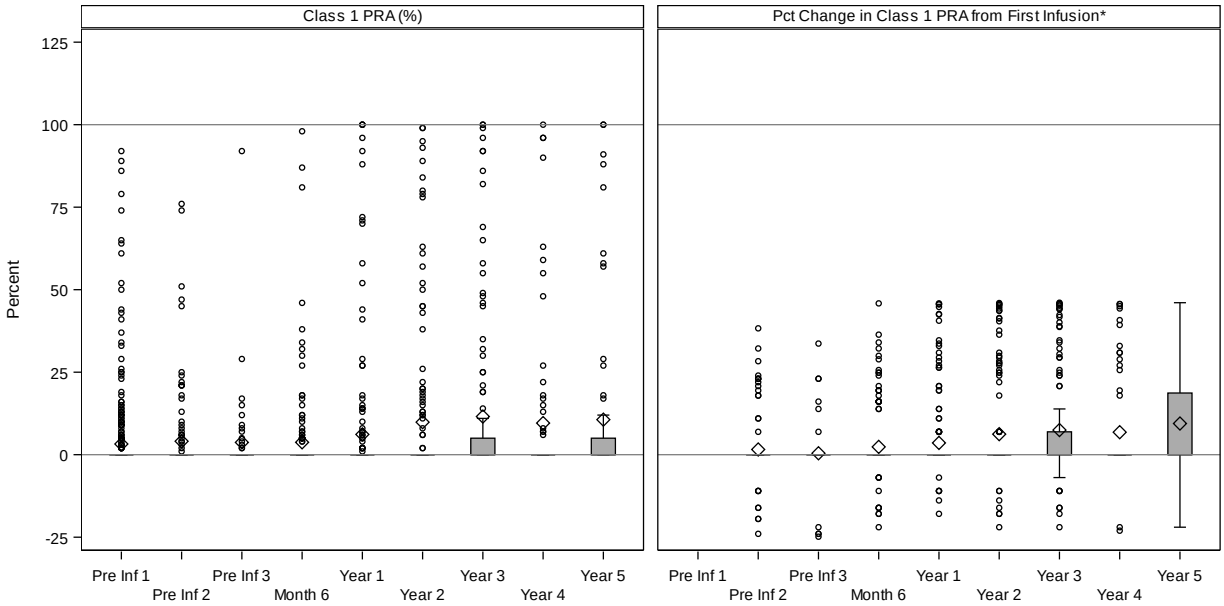
Exhibit 6 – 13
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m^2) by Infusion Type and Era





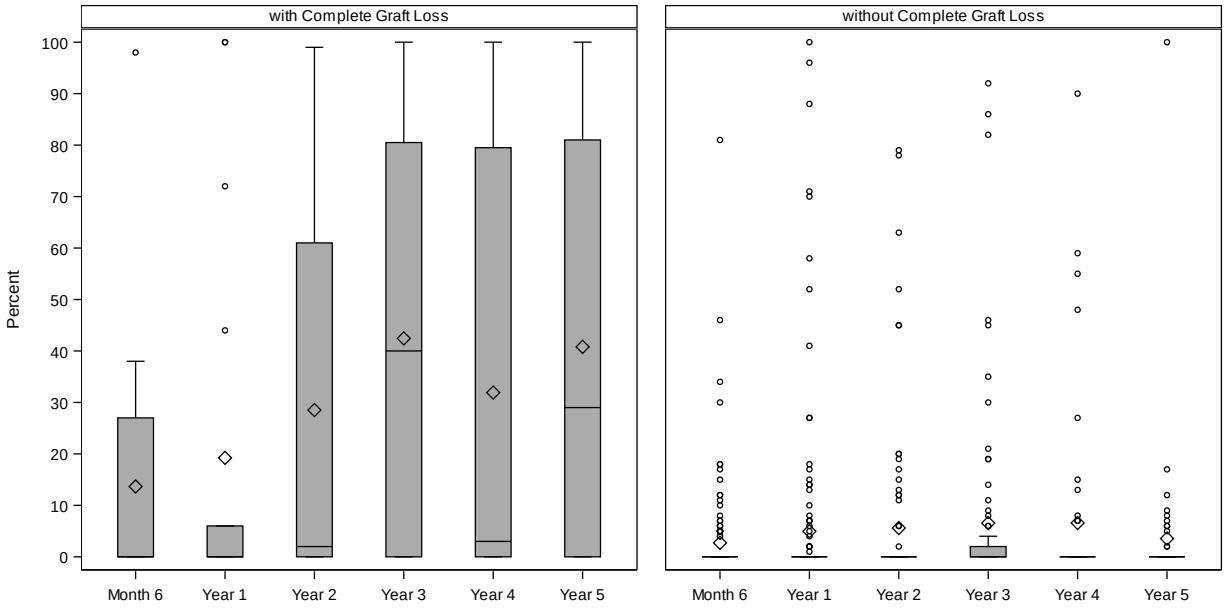
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	728	467	138	501	488	382	301	240	189
Islet After Kidney	161	93	22	116	121	100	88	57	51
1999-2002	170	113	44	117	126	89	84	72	63
2003-2006	250	192	69	187	191	160	134	113	99
2007-2010	201	125	26	161	150	140	118	83	66
2011-2014	260	126	21	147	140	93	53	29	12
2015-2018	8	4	.	5	2	.	.	.	.

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 (%)	481	134	55	178	203	153	128	78	74
*Pct Change in Class 1 PRA from First Infusion**	.	124	52	169	193	135	114	66	63

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	15	17	23	16	12	15
without Complete Graft Loss	138	158	92	83	50	49

Chapter 7
Adverse Events

Table of Contents

Introduction

All adverse events reported to the Registry on allo-islet recipients are tallied by relatedness to the infusion procedure or the immunosuppression regimen, as assessed by the local investigator (Exhibit 7-1). For islet-alone, the adverse events most frequently deemed "possibly or definitely related" to the infusion procedure included: peritoneal hemorrhage (n=33), hepatic hematoma, hepatic hemorrhage, or portal vein thrombosis (n=23), increased AST (n=7), blood alkaline phosphatase (n=19), gamma-glutamyl transferase (n=12), abnormal liver function tests (n=121), hematoma/hemorrhage (n=18), and GI/peritoneal hemorrhage (n=35), while those deemed "possibly or definitely related" to immunosuppression included leukopenia/lymphopenia/neutropenia/granulocytes (n=339), diarrhea/GI disorder (n=68), fatigue (n=13), mucosal inflammation (n=16), graft vs host disease (n=2), infection (n=65), pneumonia (n=10), increased blood creatinine (n=18), neoplasm (n=39), renal disorder/failure (n=14), lung disorder/infiltration (n=9), skin disorder/exfoliative rash (n=12), and hypertension (n=8). For IAK, the adverse events most frequently deemed "possibly or definitely related" to the infusion procedure included: blood disorder/leukopenia/lymphopenia/neutropenia (n=14), gastrointestinal/peritoneal hemorrhage (n=16), infection (n=36), and renal disorder/failure/pyelonephritis (n=15). For SIK, the adverse events most frequently deemed "possibly or definitely related" to immunosuppression included lymphopenia (n=4) and pneumonia (n=3). The adverse event most frequently deemed "possibly or definitely related" to the infusion procedure among SIK was peritoneal hemorrhage (n=3).

In the first 30 days following allo-islet transplantation, about 26% of recipients experienced a reportable adverse event (Exhibit 7-2A), which occurred less frequently in IAK (22%) than ITA (28%). The majority (70%) were adjudicated by the local investigator as possibly or definitely related to either the infusion procedure or the immunosuppression (IS). The majority were 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 14% of allo-islet recipients experienced a serious adverse event in the first 30 days (Exhibit 7-2B), which occurred about equally in IAK as in ITA, and have declined somewhat over the eras. There is likely some lag in reporting.

In the first year after islet transplantation, which includes a majority of the re-infusions that were performed, about 43% of all recipients experienced a reportable adverse event (Exhibit 7-3A), with a decline in the most recent eras. About one-third have experienced a serious adverse event within the first year (Exhibit 7-3B), 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 7-4).

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 7-5A). Again, there is likely some under-reporting in the most recent era. 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, 17% of all recipients failed to recover completely from an adverse event (Exhibit 7-5A). This is the worst outcome of all adverse events, including those not related to the islet infusion or immunosuppression. Among related adverse events only 11% failed to recover completely (Exhibit 7-5B). All adverse events and adverse events deemed related or possibly related to the islet infusion or immunosuppression are sorted by frequency and classified by outcome in Exhibit 7-6A and Exhibit 7-6B respectively.

Exhibit 7-8 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.

All adverse events reported to CITR since inception were updated for MedDRA coding in the analysis file for this report. All adverse events reported from the MedDRA classifications were reviewed and either confirmed, revised or left unclassified. Consequently, some adverse events have changed classification from previous Annual Reports.

The total cohort of 1086 allo-islet recipients were followed for a mean of 4.2±3.5 SD years, comprising 4,583 person-years of follow-up from first infusion (7-9A). A total of 51 events in 34 recipients were classified “Neoplasm”. Of the total 51 events, 73% were deemed possibly related to immunosuppression, and 6% definitely related. Of the total events, 65% recovered, 12% did not recover, and 6% recovered with sequelae. There were 35 instances in 22 patients of basal or squamous carcinoma of the skin (Exhibit 7-9B); 19 patients recovered from all instances (three with sequelae), one did not recover, and two had unknown outcome. There were 16 instances in 14 recipients of non-skin cancers, of whom 8 (57%) recovered completely, 1 was still recovering, 4 had not recovered, and 1 died (lung cancer). It is difficult with these few cases to determine if any of the reported neoplasms are related to islet transplantation.

There have been 33 or 3.0% deaths; cumulative mortality rates differed significantly both by era ($p=0.03$) and transplant type ($p<0.0001$) (Exhibit 7-10A). Mortality has declined steadily over the eras. SIK transplant recipients were disproportionately represented among fatalities comprising only 2% of the allo-islet recipient population, but 18% percent of deaths. Of the reported deaths, three were deemed possibly related and three were deemed definitely related to islet transplantation or immunosuppression (Exhibit 7-10B).

Life-threatening events have occurred in 13.5% of islet-alone, in 18.0% of IAK recipients, and in 29.2% of SIK recipients ($p<0.0001$, Exhibit 7-11B). Recent eras have seen a substantial decline in the incidence of life-threatening events ($p<0.0001$). Most involved neutropenia and abnormal liver function. The vast majority recovered, 3% died, 3% did not recover, and 8% recovered with sequelae.

Exhibit 7-1

All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
TOTAL		1854										
System/Organ Class	**Preferred term**											
Not yet coded	**Not yet coded**	74	43.2	20.3	24.3	4.1	8.1	43.2	12.2	16.2	23.0	5.4
Blood and lymphatic system disorders	**Afebrile neutropenia**	2	.	50.0	50.0	.	.	.	.	.	100	.
	Anaemia	32	12.5	34.4	25.0	18.8	9.4	6.3	6.3	12.5	68.8	6.3
	Blood disorder	3	33.3	66.7	.	.	.	33.3	.	.	33.3	33.3
	Febrile neutropenia	6	33.3	66.7	.	.	.	33.3	.	.	33.3	33.3
	Haemolysis	1	.	.	100	.	.	.	.	.	.	100
	Hypereosinophilia	1	.	100	.	.	.	.	.	100	.	.
	Leukocytosis	1	100	.	.	.	.	100	.	.	.	.
	Leukopenia	**6**	.	66.7	33.3	.	.	.	.	.	66.7	**33.3**
	Lymphatic disorder	1	.	100	.	.	.	.	.	100	.	.
	Lymphopenia	**57**	22.8	66.7	5.3	5.3	.	22.8	.	.	22.8	**54.4**
	Neutropenia	**35**	31.4	31.4	25.7	11.4	.	31.4	2.9	.	42.9	**22.9**
	Pancytopenia	1	100	.	.	.	.	.	.	.	100	.
	Platelet disorder	5	.	60.0	40.0	.	.	.	.	40.0	60.0	.
	Thrombocytopenia	5	40.0	60.0	.	.	.	.	.	.	100	.
Cardiac disorders	**Arrhythmia supraventricular**	3	.	33.3	.	33.3	33.3	.	66.7	.	33.3	.
	Atrioventricular block	1	.	100	.	.	.	.	100	.	.	.
	Cardiac disorder	2	.	50.0	50.0	.	.	.	50.0	50.0	.	.
	Myocardial ischaemia	9	.	88.9	.	11.1	.	.	55.6	33.3	11.1	.
	Myocarditis	2	.	100	.	.	.	.	.	100	.	.
	Pericardial effusion	2	.	50.0	50.0	.	.	.	.	50.0	50.0	.
	Pericarditis	1	.	.	100	.	.	.	.	.	100	.
Ear and labyrinth disorders	**Hearing impaired**	1	.	100	.	.	.	.	.	100	.	.
	Tinnitus	1	.	100	.	.	.	.	.	.	100	.
Endocrine disorders	**Endocrine disorder**	2	.	50.0	.	.	50.0	.	100	.	.	.
	Hypothyroidism	1	100	.	.	.	.	100	.	.	.	.
Eye disorders	**Eye disorder**	**10**	.	90.0	10.0	.	.	.	40.0	20.0	**30.0**	**10.0**
	Retinal detachment	3	.	100	.	.	.	.	33.3	66.7	.	.
	Retinal haemorrhage	1	.	.	.	100	.	.	.	100	.	.
	Vitreous haemorrhage	7	14.3	14.3	42.9	28.6	.	14.3	28.6	42.9	14.3	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Gastrointestinal disorders	Abdominal pain	1	100	.	.	.	.	100	.	.	.	.
	Ascites	5	20.0	20.0	20.0	40.0	.	.	20.0	40.0	.	40.0
	Barrett's oesophagus	1	.	.	100	.	.	.	.	.	100	.
	Colitis	5	.	80.0	20.0	.	.	.	20.0	.	80.0	.
	Constipation	2	.	100	.	.	.	.	.	50.0	50.0	.
	Diarrhoea	54	5.6	66.7	22.2	5.6	.	5.6	7.4	1.9	74.1	11.1
	Dysphagia	2	.	50.0	50.0	.	.	.	.	.	100	.
	Enteritis	1	.	.	100	.	.	.	.	100	.	.
	Gastritis	2	50.0	.	50.0	.	.	.	.	.	100	.
	Gastrointestinal disorder	14	7.1	50.0	14.3	28.6	.	.	35.7	14.3	42.9	7.1
	Gastrointestinal haemorrhage	2	.	.	.	.	100	.	100	.	.	.
	Gastrointestinal obstruction	7	.	71.4	.	14.3	14.3	.	14.3	28.6	57.1	.
	Gastrointestinal perforation	2	.	.	.	.	100	.	100	.	.	.
	Haemorrhoids	1	.	100	.	.	.	.	100	.	.	.
	Ileus	2	.	.	.	100	.	.	50.0	50.0	.	.
	Mouth ulceration	2	.	50.0	.	50.0	.	.	.	.	50.0	50.0
	Nausea	10	30.0	30.0	10.0	20.0	10.0	20.0	10.0	10.0	50.0	10.0
	Oral pain	1	.	100	.	.	.	.	.	.	100	.
	Pancreatitis	3	.	33.3	66.7	.	.	.	33.3	66.7	.	.
	Peritoneal haemorrhage	33	.	.	.	6.1	93.9	.	69.7	24.2	6.1	.
	Small intestinal obstruction	1	100	.	.	.	.	100	.	.	.	.
	Stomatitis	1	.	100	.	.	.	.	.	.	100	.
	Vomiting	39	48.7	43.6	.	5.1	2.6	35.9	10.3	10.3	28.2	15.4
General disorders and administration site conditions	Chest discomfort	2	.	.	100	.	.	.	.	100	.	.
	Chest pain	6	16.7	16.7	66.7	.	.	16.7	.	66.7	16.7	.
	Death	7	14.3	57.1	.	14.3	14.3	14.3	57.1	14.3	14.3	.
	Fatigue	13	.	61.5	15.4	15.4	7.7	.	7.7	.	92.3	.
	Influenza like illness	1	100	.	.	.	.	100	.	.	.	.
	Injection site reaction	2	.	100	.	.	.	.	50.0	.	50.0	.
	Mucosal inflammation	16	6.3	62.5	25.0	6.3	.	6.3	.	.	18.8	75.0
	Oedema peripheral	6	.	83.3	16.7	.	.	.	33.3	.	66.7	.
	Pain	60	1.7	46.7	21.7	15.0	15.0	1.7	31.7	20.0	43.3	3.3
	Pyrexia	6	16.7	66.7	16.7	.	.	16.7	.	.	83.3	.
	Ulcer	1	.	.	.	100	.	.	.	.	.	100

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Hepatobiliary disorders	Biliary tract disorder	1	.	.	.	.	100	.	100	.	.	.
	Cholecystitis	10	.	70.0	10.0	20.0	.	.	50.0	40.0	10.0	.
	Cholecystitis acute	1	100	.	.	.	.	100	.	.	.	.
	Hepatic haematoma	1	.	.	.	.	100	.	.	100	.	.
	Hepatic haemorrhage	10	80.0	.	.	.	20.0	80.0	20.0	.	.	.
	Portal vein thrombosis	12	8.3	.	.	.	91.7	8.3	66.7	25.0	.	.
Immune system disorders	Autoimmune disorder	1	.	100	.	.	.	.	.	.	100	.
	Cytokine release syndrome	1	100	.	.	.	.	100	.	.	.	.
	Graft versus host disease	2	.	.	.	.	100	.	.	.	.	100
	Hypersensitivity	22	22.7	36.4	22.7	4.5	13.6	13.6	36.4	9.1	18.2	22.7
	Sensitisation	1	.	100	.	.	.	.	100	.	.	.
	Serum sickness	3	66.7	33.3	.	.	.	33.3	.	.	.	66.7

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Infections and infestations	Appendicitis	4	.	.	100	.	.	.	.	100	.	.
	Appendicitis perforated	2	100	.	.	.	.	100	.	.	.	.
	Arthritis bacterial	1	.	100	.	.	.	.	.	.	100	.
	Bacillus infection	2	.	100	.	.	.	.	100	.	.	.
	Clostridium difficile colitis	1	100	.	.	.	.	100	.	.	.	.
	Cystitis	2	.	100	.	.	.	.	.	50.0	50.0	.
	Cytomegalovirus infection	2	.	.	50.0	50.0	.	.	50.0	.	.	50.0
	Ear infection	1	.	100	.	.	.	.	.	100	.	.
	Enterocolitis infectious	1	.	100	.	.	.	.	.	100	.	.
	Gastroenteritis viral	2	.	.	50.0	.	50.0	50.0	.	50.0	.	.
	Gastrointestinal infection	1	.	100	.	.	.	.	.	.	100	.
	H1N1 influenza	1	100	.	.	.	.	100	.	.	.	.
	Herpes simplex	1	100	.	.	.	.	100	.	.	.	.
	Infection	65	4.6	64.6	16.9	7.7	6.2	4.6	16.9	7.7	67.7	3.1
	Influenza	1	.	.	.	100	.	.	.	.	100	.
	Laryngitis	1	.	100	.	.	.	.	100	.	.	.
	Metapneumovirus infection	1	.	100	.	.	.	.	100	.	.	.
	Opportunistic infection	1	.	100	.	.	.	.	.	.	.	100
	Periorbital cellulitis	1	.	100	.	.	.	.	.	.	100	.
	Pneumococcal infection	1	100	.	.	.	.	100	.	.	.	.
	Pneumonia	10	30.0	10.0	50.0	10.0	.	30.0	.	.	60.0	10.0
	Pulmonary tuberculosis	1	.	100	.	.	.	.	100	.	.	.
	Pyelonephritis	1	.	100	.	.	.	.	.	.	100	.
	Respiratory tract infection	1	.	.	.	100	.	.	.	.	100	.
	Urinary tract infection	1	100	.	.	.	.	100	.	.	.	.
	Vestibular neuronitis	1	.	100	.	.	.	.	.	.	100	.
	Viral encephalitis	1	.	100	.	.	.	.	.	.	100	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Injury, poisoning and procedural complications	Fracture	9	.	77.8	11.1	11.1	.	.	77.8	.	22.2	.
	Hepatic haematoma	2	50.0	.	50.0	.	.	50.0	50.0	.	.	.
	Hip fracture	4	50.0	50.0	.	.	.	50.0	50.0	.	.	.
	Injury	1	100	.	.	.	.	.	100	.	.	.
	Laceration	1	100	.	.	.	.	100	.	.	.	.
	Limb injury	1	.	100	.	.	.	.	.	.	100	.
	Post procedural haemorrhage	1	.	.	.	.	100	.	100	.	.	.
	Toxicity to various agents	2	.	100	.	.	.	.	.	.	.	100
	Transplant failure	1	.	.	.	.	100	.	.	.	100	.
	Upper limb fracture	2	50.0	50.0	.	.	.	50.0	50.0	.	.	.
	Wound complication	**11**	9.1	54.5	9.1	**9.1**	**18.2**	9.1	27.3	36.4	**27.3**	.
	Wound dehiscence	1	100	.	.	.	.	100	.	.	.	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Investigations	Activated partial thromboplastin time	1	.	.	.	.	100	.	.	.	.	100
	Activated partial thromboplastin time prolonged	1	.	.	.	.	100	.	.	100	.	.
	Alanine aminotransferase increased	9	88.9	.	.	11.1	.	88.9	.	11.1	.	.
	Aspartate aminotransferase increased	7	57.1	.	.	14.3	28.6	57.1	14.3	28.6	.	.
	Bacillus test positive	1	.	100	.	.	.	.	100	.	.	.
	Blood albumin decreased	1	100	.	.	.	.	100	.	.	.	.
	Blood alkaline phosphatase	19	.	.	.	89.5	10.5	.	5.3	78.9	10.5	5.3
	Blood amylase	1	.	.	.	.	100	.	.	100	.	.
	Blood bilirubin	1	.	.	.	.	100	.	100	.	.	.
	Blood creatine phosphokinase	1	.	100	.	.	.	.	.	.	.	100
	Blood creatine phosphokinase increased	2	100	.	.	.	.	100	.	.	.	.
	Blood creatinine increased	18	22.2	50.0	16.7	11.1	.	22.2	.	.	66.7	11.1
	Blood phosphorus decreased	2	100	.	.	.	.	50.0	50.0	.	.	.
	Blood potassium increased	2	100	.	.	.	.	100	.	.	.	.
	Gamma-glutamyltransferase	12	25.0	.	.	66.7	8.3	25.0	16.7	8.3	50.0	.
	Gamma-glutamyltransferase increased	3	66.7	.	.	.	33.3	66.7	33.3	.	.	.
	Glomerular filtration rate	1	.	.	.	100	.	.	.	.	100	.
	Granulocytes abnormal	241	4.1	63.5	25.7	5.4	1.2	3.7	0.8	1.7	62.2	31.5
	Haemoglobin decreased	2	50.0	50.0	.	.	.	50.0	.	.	50.0	.
	Hepatic enzyme increased	4	.	.	.	50.0	50.0	.	.	100	.	.
	International normalised ratio increased	1	100	.	.	.	.	100	.	.	.	.
	Lipase	1	.	.	.	100	.	.	100	.	.	.
	Liver function test abnormal	121	9.9	2.5	1.7	60.3	25.6	9.1	20.7	44.6	22.3	3.3
	Low density lipoprotein abnormal	6	66.7	16.7	16.7	.	.	66.7	.	16.7	16.7	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

		Total	Related to Infusion?					Related to Immunosuppression?				
				Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
	Low density lipoprotein increased	13	46.2	38.5	7.7	7.7	.	46.2	.	7.7	46.2	.
	Neutrophil count	6	66.7	33.3	.	.	.	66.7	.	.	33.3	.
	Neutrophil count decreased	18	83.3	11.1	5.6	.	.	83.3	.	.	11.1	5.6
	Transaminases	4	100	.	.	.	.	100	.	.	.	.
	Transaminases increased	3	66.7	.	.	.	33.3	66.7	.	33.3	.	.
	Troponin T	1	.	100	.	.	.	.	100	.	.	.
	Weight decreased	3	33.3	33.3	33.3	.	.	33.3	.	.	66.7	.
Metabolism and nutrition disorders	Decreased appetite	2	.	100	.	.	.	.	.	50.0	50.0	.
	Dehydration	9	11.1	66.7	11.1	11.1	.	11.1	11.1	33.3	44.4	.
	Hyperglycaemia	8	37.5	50.0	.	.	12.5	37.5	25.0	37.5	.	.
	Hyperkalaemia	13	15.4	76.9	7.7	.	.	15.4	.	7.7	76.9	.
	Hypernatraemia	1	100	.	.	.	.	100	.	.	.	.
	Hypoalbuminaemia	4	25.0	.	50.0	.	25.0	25.0	25.0	50.0	.	.
	Hypocalcaemia	2	100	.	.	.	.	100	.	.	.	.
	Hypoglycaemia	116	39.7	48.3	6.9	3.4	1.7	37.1	48.3	8.6	6.0	.
	Hypokalaemia	14	21.4	28.6	42.9	7.1	.	21.4	7.1	21.4	42.9	7.1
	Hypomagnesaemia	1	.	100	.	.	.	.	.	.	100	.
	Hyponatraemia	23	4.3	43.5	47.8	4.3	.	4.3	26.1	65.2	4.3	.
	Hypophosphataemia	13	46.2	23.1	30.8	.	.	46.2	.	15.4	38.5	.
	Ketoacidosis	91	2.2	91.2	3.3	3.3	.	2.2	82.4	14.3	1.1	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	.	.	.	100	.	.	.	.	100	.
	Arthritis	3	.	100	.	.	.	.	33.3	.	66.7	.
	Arthropathy	1	.	100	.	.	.	.	.	100	.	.
	Back pain	1	100	.	.	.	.	100	.	.	.	.
	Muscle necrosis	1	.	100	.	.	.	.	.	.	100	.
	Muscular weakness	6	.	66.7	33.3	.	.	.	.	.	100	.
	Musculoskeletal disorder	5	.	100	.	.	.	.	40.0	.	60.0	.
	Musculoskeletal pain	2	.	.	.	100	.	.	100	.	.	.
	Myositis	1	.	.	100	.	.	.	.	.	100	.
	Rheumatoid arthritis	1	100	.	.	.	.	100	.	.	.	.
	Trigger finger	1	.	100	.	.	.	.	100	.	.	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	7	57.1	42.9	.	.	.	28.6	.	.	42.9	28.6
	Lobular breast carcinoma in situ	1	.	100	.	.	.	.	.	.	100	.
	Lymphoma	1	100	.	.	.	.	100	.	.	.	.
	Metastases	1	.	100	.	.	.	.	.	.	100	.
	Mucinous adenocarcinoma of appendix	1	100	.	.	.	.	100	.	.	.	.
	Neoplasm malignant	18	.	61.1	33.3	5.6	.	.	5.6	.	94.4	.
	Papillary thyroid cancer	1	.	100	.	.	.	.	.	.	100	.
	Post transplant lymphoproliferative disorder	1	100	.	.	.	.	100	.	.	.	.
	Skin cancer	1	100	.	.	.	.	100	.	.	.	.
	Squamous cell carcinoma	6	66.7	33.3	.	.	.	50.0	.	.	33.3	16.7
	Treatment related secondary malignancy	1	.	100	.	.	.	.	.	.	100	.
Nervous system disorders	Ataxia	2	.	50.0	50.0	.	.	.	.	100	.	.
	Cerebellar ischaemia	1	.	100	.	.	.	.	100	.	.	.
	Cerebral ischaemia	1	.	100	.	.	.	.	100	.	.	.
	Cognitive disorder	2	50.0	50.0	.	.	.	50.0	.	.	50.0	.
	Convulsion	1	.	100	.	.	.	.	.	.	100	.
	Dizziness	5	.	60.0	40.0	.	.	.	20.0	40.0	40.0	.
	Dyskinesia	1	.	.	.	100	.	.	.	100	.	.
	Frontotemporal dementia	1	.	100	.	.	.	.	100	.	.	.
	Headache	4	75.0	25.0	.	.	.	50.0	.	.	25.0	25.0
	Migraine	4	.	.	50.0	50.0	.	.	50.0	.	50.0	.
	Neuroleptic malignant syndrome	1	.	.	.	.	100	.	.	.	.	100
	Presyncope	1	100	.	.	.	.	100	.	.	.	.
	Serotonin syndrome	1	.	.	100	.	.	.	.	100	.	.
	Spinal cord compression	2	100	.	.	.	.	100	.	.	.	.
	Syncope	11	27.3	18.2	45.5	.	9.1	27.3	.	63.6	9.1	.
	Tremor	5	20.0	60.0	20.0	.	.	.	.	20.0	40.0	40.0

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Psychiatric disorders	Alcoholism	1	100	.	.	.	.	100	.	.	.	.
	Anxiety	1	.	.	100	.	.	.	.	100	.	.
	Cognitive disorder	2	50.0	50.0	.	.	.	50.0	50.0	.	.	.
	Confusional state	4	50.0	25.0	25.0	.	.	50.0	25.0	.	25.0	.
	Insomnia	2	.	50.0	50.0	.	.	.	.	.	50.0	50.0
	Mood altered	4	25.0	25.0	50.0	.	.	.	25.0	25.0	50.0	.
	Psychogenic seizure	2	.	100	.	.	.	.	50.0	50.0	.	.
	Psychotic disorder	1	.	100	.	.	.	.	.	.	100	.
Renal and urinary disorders	Albuminuria	3	.	.	100	.	.	.	.	100	.	.
	Haemoglobinuria	1	.	100	.	.	.	.	100	.	.	.
	Micturition urgency	1	.	100	.	.	.	.	.	.	100	.
	Peylonepr hitis	1	.	100	.	.	.	.	.	.	100	.
	Proteinuria	4	.	75.0	.	25.0	.	.	.	.	75.0	25.0
	Renal disorder	4	25.0	50.0	25.0	.	.	25.0	.	25.0	50.0	.
	Renal failure	10	.	50.0	40.0	10.0	.	.	.	10.0	70.0	20.0
	Tubulointerstitial nephritis	1	.	100	.	.	.	.	.	.	100	.
	Urinary bladder haemorrhage	3	.	33.3	33.3	.	33.3	.	33.3	.	33.3	33.3
Reproductive system and breast disorders	Lactation disorder	1	.	.	100	.	.	.	.	.	100	.
	Sexual dysfunction	7	.	85.7	14.3	.	.	.	14.3	28.6	57.1	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	.	100	.	.	.	.	.	100	.	.
	Aspiration	2	.	50.0	.	50.0	.	.	.	50.0	50.0	.
	Cough	1	.	.	100	.	.	.	.	.	100	.
	Dyspnoea	5	.	80.0	20.0	.	.	.	20.0	40.0	40.0	.
	Haemothorax	1	.	.	.	.	100	.	.	.	100	.
	Hypoxia	4	.	50.0	50.0	.	.	.	75.0	.	25.0	.
	Lung disorder	5	.	60.0	20.0	20.0	.	.	20.0	.	60.0	20.0
	Lung infiltration	4	.	100	.	.	.	.	.	.	50.0	50.0
	Pleural effusion	3	33.3	33.3	33.3	.	.	33.3	.	33.3	33.3	.
	Pneumonitis	4	25.0	75.0	.	.	.	25.0	.	.	75.0	.
	Pulmonary hypertension	1	.	100	.	.	.	.	100	.	.	.
	Pulmonary oedema	1	100	.	.	.	.	100	.	.	.	.
Skin and subcutaneous tissue disorders	Actinic keratosis	1	100	.	.	.	.	.	.	.	.	100
	Acute febrile neutrophilic dermatosis	1	.	100	.	.	.	.	.	.	.	100
	Dermatitis	1	100	.	.	.	.	100	.	.	.	.
	Exfoliative rash	7	.	100	.	.	.	.	.	14.3	85.7	.
	Pruritus	1	.	100	.	.	.	.	.	.	100	.
	Rash	1	.	100	.	.	.	.	.	.	100	.
	Skin disorder	5	.	40.0	60.0	.	.	.	.	20.0	80.0	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type ITA

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Surgical and medical procedures	Abdominal hernia repair	2	.	100	.	.	.	.	.	100	.	.
	Breast reconstruction	1	100	.	.	.	.	100	.	.	.	.
	Ileostomy	1	100	.	.	.	.	100	.	.	.	.
	Incisional hernia repair	2	50.0	.	.	.	50.0	50.0	50.0	.	.	.
	Laser therapy	1	.	.	100	.	.	.	.	100	.	.
	Surgery	4	.	100	.	.	.	.	100	.	.	.
	Toe operation	1	100	.	.	.	.	100	.	.	.	.
Vascular disorders	Haematoma	11	.	9.1	9.1	.	81.8	9.1	36.4	36.4	18.2	.
	Haemorrhage	7	.	.	.	14.3	85.7	.	85.7	14.3	.	.
	Hypertension	8	.	75.0	25.0	.	.	.	25.0	25.0	50.0	.
	Hypotension	3	.	33.3	.	.	66.7	.	66.7	33.3	.	.
	Peripheral arterial occlusive disease	1	.	100	.	.	.	.	100	.	.	.
	Thrombosis	2	.	100	.	.	.	.	50.0	.	50.0	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type SIK

			Related to Infusion?					Related to Immunosuppression?			
		Total		Not related	Unlikely related	Possibly related	Related	Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%
TOTAL		53									
System/Organ Class	**Preferred term**										
Not yet coded	**Not yet coded**	4	.	75.0	.	.	25.0	.	50.0	50.0	.
Blood and lymphatic system disorders	**Agranulocytosis**	1	.	100	.	.	.	.	.	.	100
	Leukopenia	1	.	100	.	.	.	.	.	100	.
	Lymphopenia	4	.	50.0	50.0	.	.	.	.	100	.
Cardiac disorders	**Myocardial ischaemia**	2	.	100	.	.	.	50.0	50.0	.	.
Eye disorders	**Eye disorder**	2	.	100	.	.	.	100	.	.	.
Gastrointestinal disorders	**Diarrhoea**	1	.	100	.	.	.	.	100	.	.
	Gastrointestinal disorder	2	.	.	.	100	.	.	.	100	.
	Peritoneal haemorrhage	3	.	.	.	.	100	100	.	.	.
General disorders and administration site conditions	**Death**	4	.	100	.	.	.	25.0	75.0	.	.
Hepatobiliary disorders	**Cholecystitis**	1	.	100	.	.	.	.	100	.	.
	Hepatic artery stenosis	1	.	100	.	.	.	100	.	.	.
Immune system disorders	**Hypersensitivity**	2	.	100	.	.	.	.	100	.	.
Infections and infestations	**Infection**	10	.	60.0	40.0	.	.	.	90.0	10.0	.
	Pneumonia	3	.	33.3	66.7	.	.	.	.	33.3	66.7
	Renal graft infection	1	.	100	.	.	.	.	.	100	.
	Urosepsis	1	100	.	.	.	.	.	.	100	.
Injury, poisoning and procedural complications	**Wound complication**	1	.	100	.	.	.	.	.	100	.
Metabolism and nutrition disorders	**Dehydration**	1	.	.	100	.	.	.	.	100	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	1	.	100	.	.	.	.	.	100	.
	Papillary thyroid cancer	1	.	100	.	.	.	.	.	100	.
Nervous system disorders	**Cerebral ischaemia**	1	.	.	100	.	.	.	100	.	.
Renal and urinary disorders	**Renal failure**	1	.	100	.	.	.	.	.	100	.
Respiratory, thoracic and mediastinal disorders	**Acute respiratory distress syndrome**	1	.	100	.	.	.	.	.	.	100

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type SIK

		Total	Related to Infusion?					Related to Immunosuppression?			
				Not related	Unlikely related	Possibly related	Related	Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%
Vascular disorders	**Peripheral ischaemia**	2	.	100	.	.	.	50.0	50.0	.	.
	Thrombosis	1	.	100	.	.	.	100	.	.	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type IAK

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
TOTAL		364										
System/Organ Class	**Preferred term**											
Not yet coded	**Not yet coded**	15	46.7	26.7	13.3	13.3	.	46.7	20.0	13.3	13.3	6.7
Blood and lymphatic system disorders	**Anaemia**	8	12.5	50.0	.	37.5	.	12.5	12.5	37.5	37.5	.
	Blood disorder	3	.	33.3	.	66.7	.	.	.	33.3	66.7	.
	Leukopenia	5	.	80.0	20.0	.	.	.	.	.	100	.
	Lymphopenia	3	.	66.7	.	33.3	.	.	.	.	33.3	66.7
	Neutropenia	3	33.3	33.3	33.3	.	.	33.3	.	.	66.7	.
Cardiac disorders	**Acute myocardial infarction**	1	.	100	.	.	.	.	100	.	.	.
	Cardio-respiratory arrest	2	.	50.0	50.0	.	.	.	50.0	50.0	.	.
	Myocardial ischaemia	7	14.3	57.1	28.6	.	.	28.6	42.9	28.6	.	.
	Pericardial effusion	2	.	100	.	.	.	.	50.0	50.0	.	.
Endocrine disorders	**Endocrine disorder**	2	100	.	.	.	.	100	.	.	.	.
Eye disorders	**Eye disorder**	2	.	100	.	.	.	.	50.0	.	50.0	.
	Ocular surface disease	1	.	100	.	.	.	.	.	.	100	.
	Retinal detachment	1	.	100	.	.	.	.	100	.	.	.
	Uveitis	1	.	100	.	.	.	.	.	.	100	.
	Vitreous haemorrhage	1	.	.	100	.	.	.	.	100	.	.
Gastrointestinal disorders	**Colitis**	3	.	66.7	33.3	.	.	.	33.3	33.3	33.3	.
	Diarrhoea	6	16.7	83.3	.	.	.	.	16.7	16.7	50.0	16.7
	Gastrointestinal disorder	7	.	71.4	28.6	.	.	.	.	14.3	85.7	.
	Gastrointestinal haemorrhage	3	.	.	.	33.3	66.7	.	33.3	66.7	.	.
	Gastrointestinal obstruction	4	.	50.0	50.0	.	.	.	.	.	100	.
	Mouth ulceration	1	.	.	100	.	.	.	.	.	100	.
	Nausea	2	.	50.0	.	50.0	.	.	.	.	100	.
	Peritoneal haemorrhage	13	.	7.7	.	.	92.3	.	61.5	15.4	23.1	.
	Vomiting	7	.	57.1	42.9	.	.	.	42.9	28.6	28.6	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type IAK

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
General disorders and administration site conditions	Death	3	33.3	33.3	33.3	.	.	.	33.3	33.3	.	33.3
	Fatigue	2	.	100	.	.	.	.	50.0	.	50.0	.
	Mucosal inflammation	3	.	66.7	33.3	.	.	.	.	.	66.7	33.3
	Oedema peripheral	2	50.0	50.0	.	.	.	50.0	.	.	50.0	.
	Pain	12	8.3	41.7	41.7	.	8.3	8.3	8.3	58.3	25.0	.
	Pyrexia	1	100	.	.	.	.	.	.	.	100	.
	Systemic inflammatory response syndrome	3	.	100	.	.	.	.	.	.	66.7	33.3
Hepatobiliary disorders	Cholecystitis	2	.	50.0	.	50.0	.	.	100	.	.	.
	Portal vein thrombosis	1	.	.	.	.	100	.	100	.	.	.
Immune system disorders	Hypersensitivity	2	.	.	100	.	.	.	.	.	100	.
	Sensitisation	1	.	.	.	100	.	.	100	.	.	.
Infections and infestations	Infection	28	7.1	64.3	25.0	3.6	.	10.7	21.4	21.4	39.3	7.1
	Opportunistic infection	1	.	100	.	.	.	.	.	.	100	.
	Pneumonia	4	25.0	25.0	50.0	.	.	.	.	25.0	75.0	.
	Pyelonephritis	1	.	.	100	.	.	.	.	.	100	.
	Salmonellosis	1	100	.	.	.	.	100	.	.	.	.
	Urinary tract infection	1	100	.	.	.	.	.	.	.	100	.
Injury, poisoning and procedural complications	Fracture	2	.	100	.	.	.	.	100	.	.	.
	Injury	1	.	100	.	.	.	.	.	.	100	.
Investigations	Activated partial thromboplastin time	1	.	.	.	100	.	.	100	.	.	.
	Blood alkaline phosphatase	2	.	.	.	.	100	.	.	.	100	.
	Blood amylase	1	.	100	.	.	.	.	100	.	.	.
	Blood creatinine increased	16	12.5	68.8	.	18.8	.	12.5	37.5	12.5	37.5	.
	Gamma-glutamyl transferase	1	.	.	.	.	100	.	.	100	.	.
	Glomerular filtration rate	1	.	100	.	.	.	.	100	.	.	.
	Granulocytes abnormal	13	.	84.6	15.4	.	.	.	.	.	92.3	7.7
	Lipase	4	.	.	25.0	75.0	.	.	100	.	.	.
	Lipase increased	1	.	100	.	.	.	.	.	.	.	100
	Liver function test abnormal	5	.	20.0	20.0	40.0	20.0	.	40.0	.	60.0	.
	Troponin I	1	.	100	.	.	.	.	100	.	.	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type IAK

			Related to Infusion?					Related to Immunosuppression?				
		Total		Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Metabolism and nutrition disorders	Dehydration	2	.	100	.	.	.	.	50.0	.	50.0	.
	Hyperglycaemia	7	.	14.3	.	85.7	.	.	14.3	.	85.7	.
	Hyperkalaemia	2	50.0	50.0	.	.	.	50.0	50.0	.	.	.
	Hypoglycaemia	20	50.0	30.0	10.0	5.0	5.0	30.0	40.0	30.0	.	.
	Hypokalaemia	3	66.7	.	33.3	.	.	66.7	.	.	33.3	.
	Hyponatraemia	2	.	50.0	.	50.0	.	.	100	.	.	.
	Hypophosphataemia	4	.	75.0	25.0	.	.	.	25.0	50.0	25.0	.
	Ketoacidosis	9	.	77.8	22.2	.	.	.	77.8	11.1	11.1	.
Musculoskeletal and connective tissue disorders	Joint range of motion decreased	1	.	100	.	.	.	.	.	100	.	.
	Muscular weakness	2	.	100	.	.	.	.	50.0	50.0	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	10	10.0	70.0	20.0	.	.	10.0	.	.	90.0	.
	Post transplant lymphoproliferative disorder	3	.	100	.	.	.	.	100	.	.	.
	Squamous cell carcinoma	4	.	100	.	.	.	.	.	.	100	.
Nervous system disorders	Cerebral ischaemia	5	.	60.0	40.0	.	.	.	60.0	40.0	.	.
	Hypoglycaemic seizure	1	.	100	.	.	.	.	100	.	.	.
Psychiatric disorders	Anxiety	2	.	.	100	.	.	.	.	100	.	.
Renal and urinary disorders	Acute kidney injury	1	.	.	.	.	100	.	100	.	.	.
	Proteinuria	1	.	100	.	.	.	.	.	.	100	.
	Pyelonephritis	1	.	.	100	.	.	.	.	.	100	.
	Renal disorder	4	.	50.0	25.0	25.0	.	.	50.0	25.0	.	25.0
	Renal failure	10	10.0	60.0	30.0	.	.	10.0	10.0	10.0	60.0	10.0
	Renal failure acute	1	.	100	.	.	.	.	100	.	.	.
	Urinary bladder haemorrhage	2	.	50.0	50.0	.	.	.	.	50.0	50.0	.
Reproductive system and breast disorders	Sexual dysfunction	1	.	100	.	.	.	.	.	100	.	.
Respiratory, thoracic and mediastinal disorders	Cough	2	.	100	.	.	.	.	.	.	100	.
	Dyspnoea	1	.	.	100	.	.	.	.	100	.	.
	Haemothorax	1	.	.	.	100	.	.	.	100	.	.
	Lung disorder	4	.	50.0	50.0	.	.	.	25.0	25.0	50.0	.
	Pleural effusion	1	.	.	.	100	.	.	.	100	.	.
	Pneumonitis	5	.	100	.	.	.	.	40.0	20.0	20.0	20.0
	Pulmonary hypertension	2	.	100	.	.	.	.	.	100	.	.

Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

Transplant type IAK

		Total	Related to Infusion?					Related to Immunosuppression?				
				Not related	Unlikely related	Possibly related	Related		Not related	Unlikely related	Possibly related	Related
		N	%	%	%	%	%	%	%	%	%	%
Skin and subcutaneous tissue disorders	Acne	1	100	.	.	.	.	100	.	.	.	.
	Decubitus ulcer	2	.	100	.	.	.	.	.	100	.	.
Surgical and medical procedures	Nephrectomy	1	100	.	.	.	.	100	.	.	.	.
	Surgery	5	20.0	80.0	.	.	.	20.0	.	60.0	20.0	.
Vascular disorders	Haematoma	4	.	25.0	.	.	75.0	.	75.0	25.0	.	.
	Haemorrhage	8	.	37.5	.	.	62.5	.	50.0	50.0	.	.
	Hypertension	5	.	80.0	20.0	.	.	.	40.0	20.0	40.0	.
	Hypotension	1	100	.	.	.	.	100	.	.	.	.
	Peripheral ischaemia	2	.	100	.	.	.	.	.	50.0	50.0	.
	Thrombosis	1	.	.	.	.	100	.	100	.	.	.

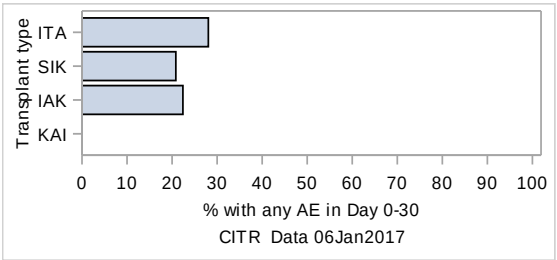
Exhibit 7-1 (continued)
All AEs Classified and by relatedness to infusion or IS

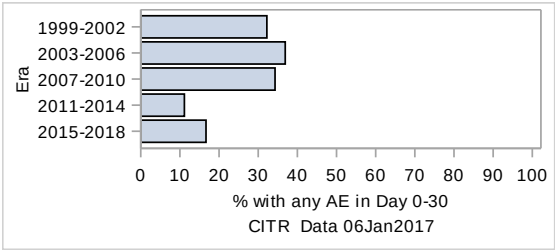
Transplant type KAI

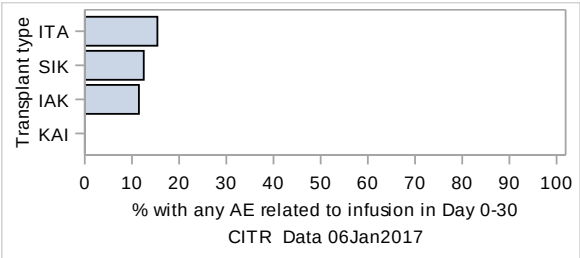
			Related to Infusion?			Related to Immunosuppression?	
		Total	Not related	Unlikely related	Related	Not related	Possibly related
		N	%	%	%	%	%
TOTAL		8					
System/Organ Class	**Preferred term**						
Not yet coded	**Not yet coded**	1	.	100	.	.	100
Blood and lymphatic system disorders	**Anaemia**	1	.	.	100	100	.
General disorders and administration site conditions	**Mucosal inflammation**	1	100	.	.	.	100
Infections and infestations	**Infection**	1	100	.	.	.	100
Injury, poisoning and procedural complications	**Fracture**	1	100	.	.	.	100
Renal and urinary disorders	**Renal failure**	1	100	.	.	.	100
Reproductive system and breast disorders	**Ovarian cyst ruptured**	1	.	100	.	.	100
Surgical and medical procedures	**Hysterectomy**	1	100	.	.	.	100

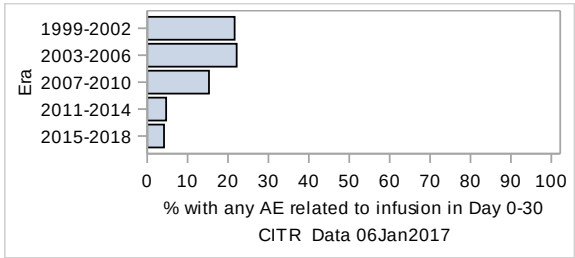
Exhibit 7-2A1
Adverse Events (AEs) in Days 0-30 Post First Infusion

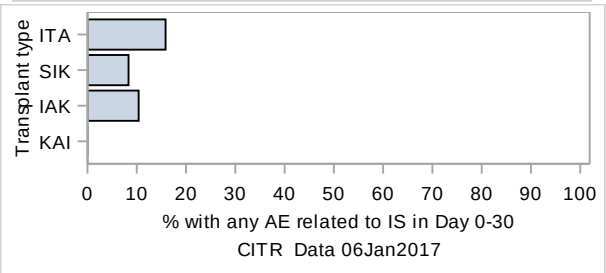
Percent of Recipients with:	Type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any AE in Day 0-30	246	28.1	5	20.8	41	22.4	.	.	67	32.2	100	36.9	83	34.3	38	11.1	4	16.7
Any AE related to infusion in Day 0-30	135	15.4	3	12.5	21	11.5	.	.	45	21.6	60	22.1	37	15.3	16	4.7	1	4.2
Any AE related to IS in Day 0-30	139	15.8	2	8.3	19	10.4	.	.	36	17.3	58	21.4	49	20.2	15	4.4	2	8.3
Any AE related to both in Day 0-30	40	4.6	1	4.2	6	3.3	.	.	15	7.2	13	4.8	12	5.0	7	2.1	.	.
Any AE related to neither in Day 0-30	70	8.0	3	12.5	13	7.1	.	.	9	4.3	14	5.2	39	16.1	23	6.7	1	4.2











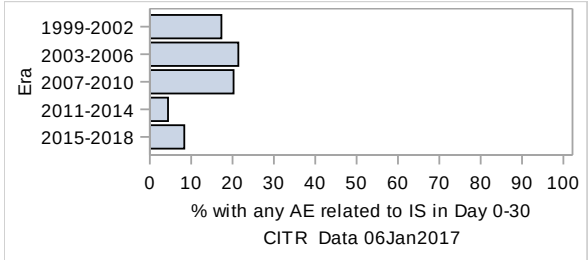
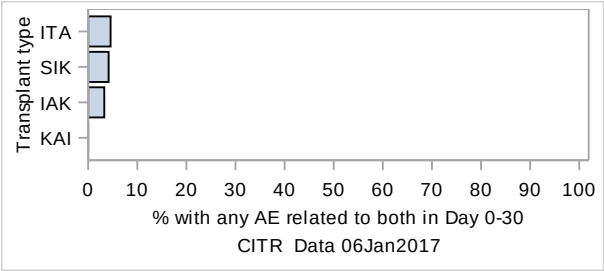
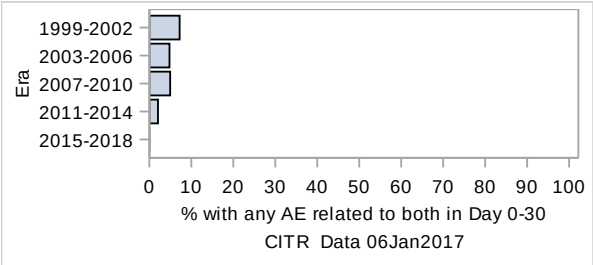
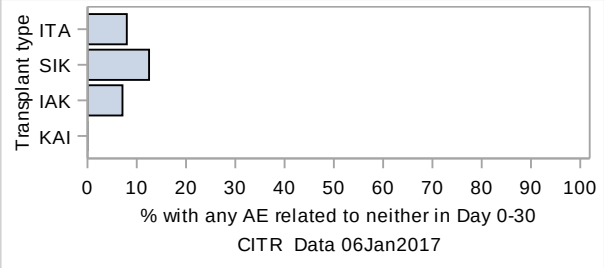


Exhibit 7-2A1 (continued)
Adverse Events (AEs) in Days 0-30 Post First Infusion







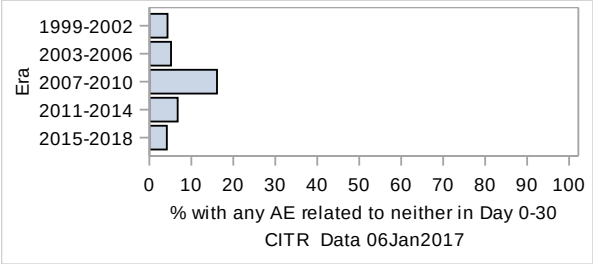


Exhibit 7-2A2
Adverse Events (AEs) RELATED TO PROCEDURE in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term									
Not yet coded	Not yet coded	4	4	.	.	.	1	2	1	.
Blood and lymphatic system disorders	Anaemia	4	3	.	1	.	2	1	1	.
	Lymphopenia	1	1	.	.	.	1	.	.	.
	Neutropenia	1	1	.	.	.	.	.	1	.
Cardiac disorders	Arrhythmia supraventricular	2	2	.	.	.	.	2	.	.
	Myocardial ischaemia	1	1	.	.	.	1	.	.	.
Eye disorders	Retinal haemorrhage	1	1	.	.	.	.	.	1	.
Gastrointestinal disorders	Diarrhoea	1	1	.	.	.	.	.	1	.
	Gastrointestinal disorder	2	.	2	.	.	.	.	2	.
	Gastrointestinal haemorrhage	3	1	.	2	1	2	.	.	.
	Gastrointestinal perforation	1	1	.	.	.	.	1	.	.
	Ileus	1	1	.	.	1	.	.	.	.
	Nausea	4	3	.	1	.	3	1	.	.
	Peritoneal haemorrhage	18	12	2	4	8	5	5	.	.
	Vomiting	2	2	.	.	.	.	2	.	.
General disorders and administration site conditions	Pain	6	6	.	.	2	1	2	1	.
Hepatobiliary disorders	Cholecystitis	2	1	.	1	.	1	1	.	.
	Portal vein thrombosis	7	7	.	.	2	3	1	1	.

Exhibit 7-2A3
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term									
Not yet coded	Not yet coded	7	7	.	.	.	.	6	1	.
Blood and lymphatic system disorders	Afebrile neutropenia	1	1	.	.	.	.	1	.	.
	Anaemia	6	5	.	1	1	2	2	1	.
	Blood disorder	1	1	.	.	.	.	1	.	.
	Febrile neutropenia	1	1	.	.	.	.	1	.	.
	Leukopenia	2	1	.	1	.	.	2	.	.
	Lymphopenia	27	24	1	2	.	10	14	3	.
	Neutropenia	8	7	.	1	.	.	7	1	.
	Pancytopenia	1	1	.	.	.	.	.	1	.
	Platelet disorder	1	1	.	.	.	1	.	.	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	1	.	.	.
Gastrointestinal disorders	Diarrhoea	6	5	.	1	.	4	1	1	.
	Gastrointestinal disorder	3	1	2	.	.	1	.	2	.
	Nausea	6	4	.	2	.	3	1	1	1
	Peritoneal haemorrhage	2	.	.	2	2	.	.	.	.
	Vomiting	9	8	.	1	2	.	4	.	3
General disorders and administration site conditions	Mucosal inflammation	1	1	.	.	.	1	.	.	.
	Pain	4	4	.	.	.	2	1	1	.
	Pyrexia	1	1	.	.	.	1	.	.	.
Immune system disorders	Hypersensitivity	1	1	.	.	.	1	.	.	.
	Serum sickness	1	1	.	.	.	.	.	.	1
Infections and infestations	Infection	5	3	.	2	.	4	1	.	.
Injury, poisoning and procedural complications	Toxicity to various agents	2	2	.	.	.	.	1	1	.

Exhibit 7-2A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
Investigations	Activated partial thromboplastin time	1	1	.	.	1	.	.	.	.
	Blood alkaline phosphatase	3	2	.	1	1	1	1	.	.
	Blood creatinine increased	1	.	.	1	.	.	1	.	.
	Gamma-glutamyltransferase	1	1	.	.	1	.	.	.	.
	Granulocytes abnormal	98	96	.	2	28	48	21	1	.
	Liver function test abnormal	23	21	.	2	12	6	5	.	.
	Neutrophil count	1	1	.	.	.	.	1	.	.
	Neutrophil count decreased	2	2	.	.	.	.	2	.	.
Metabolism and nutrition disorders	Hyperglycaemia	6	.	.	6	.	.	.	6	.
	Hyperkalaemia	1	1	.	.	1	.	.	.	.
	Hypoglycaemia	2	2	.	.	2	.	.	.	.
	Hypokalaemia	2	2	.	.	.	1	1	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	1	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	2	1	.	1	.	2	.	.	.
Nervous system disorders	Headache	1	1	.	.	.	.	1	.	.
	Migraine	2	2	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	1	.
Respiratory, thoracic and mediastinal disorders	Aspiration	1	1	.	.	.	.	1	.	.
	Hypoxia	1	1	.	.	.	.	1	.	.
	Pleural effusion	1	1	.	.	.	.	1	.	.
	Pneumonitis	1	.	.	1	1	.	.	.	.
Skin and subcutaneous tissue disorders	Exfoliative rash	1	1	.	.	.	.	1	.	.
Vascular disorders	Haematoma	1	1	.	.	.	.	1	.	.
	Hypertension	1	.	.	1	.	1	.	.	.

Exhibit 7-2B1
Serious Adverse Events (SAEs) in Days 0-30 Post 1st Infusion

Percent of Recipients with:	Type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE in Day 0-30	122	13.9	4	16.7	26	14.2	.	.	32	15.4	54	19.9	38	15.7	24	7.0	4	16.7
Any SAE related to infusion in Day 0-30	72	8.2	2	8.3	17	9.3	.	.	23	11.1	35	12.9	18	7.4	14	4.1	1	4.2
Any SAE related to IS in Day 0-30	60	6.8	2	8.3	10	5.5	.	.	6	2.9	26	9.6	26	10.7	12	3.5	2	8.3
Any SAE related to both in Day 0-30	15	1.7	1	4.2	3	1.6	.	.	1	0.5	5	1.8	7	2.9	6	1.8	.	.
Any SAE related to neither in Day 0-30	15	1.7	3	12.5	4	2.2	.	.	5	2.4	5	1.8	5	2.1	6	1.8	1	4.2

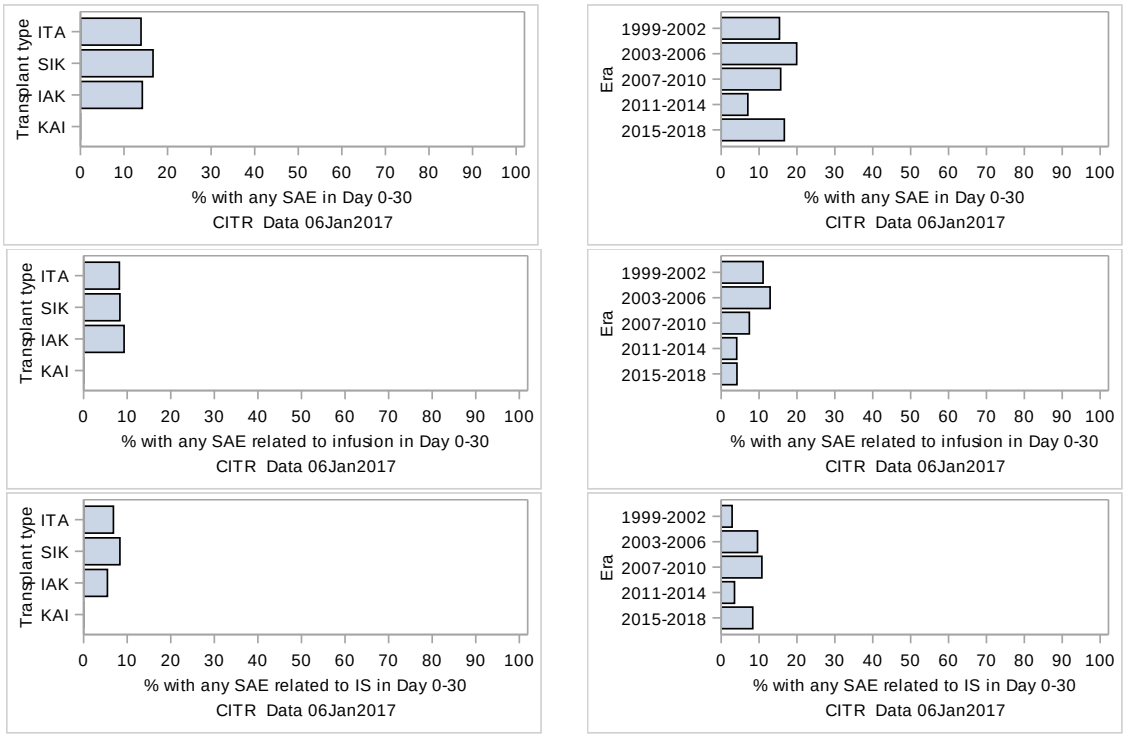
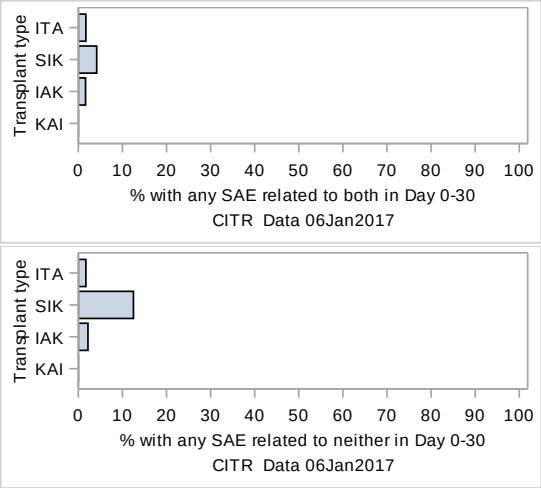


Exhibit 7-2B1(continued)
Serious Adverse Events (SAEs) in Days 0-30 Post 1st Infusion



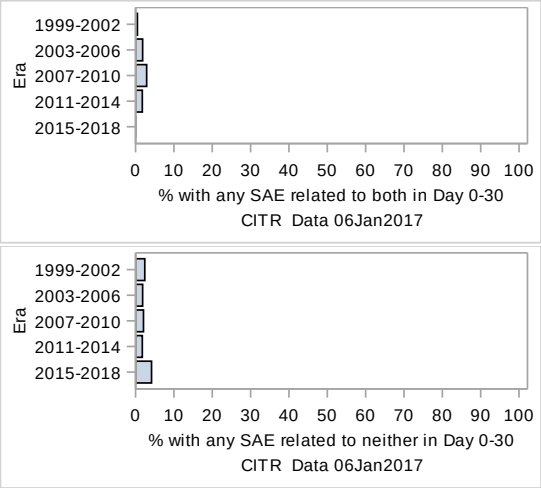


Exhibit 7-2B2
Serious Adverse Events (SAEs) RELATED TO PROCEDURE
in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
System/Organ Class	**Preferred term**									
Not yet coded	**Not yet coded**	3	3	.	.	.	1	1	1	.
Blood and lymphatic system disorders	**Anaemia**	2	1	.	1	.	2	.	.	.
	Neutropenia	1	1	.	.	.	.	.	1	.
Cardiac disorders	**Arrhythmia supraventricular**	1	1	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	1	.	.	.
Eye disorders	**Retinal haemorrhage**	1	1	.	.	.	.	.	1	.
Gastrointestinal disorders	**Diarrhoea**	1	1	.	.	.	.	.	1	.
	Gastrointestinal disorder	2	.	2	.	.	.	.	2	.
	Gastrointestinal haemorrhage	3	1	.	2	1	2	.	.	.
	Gastrointestinal perforation	1	1	.	.	.	.	1	.	.
	Ileus	1	1	.	.	1	.	.	.	.
	Nausea	2	2	.	.	.	1	1	.	.
	Peritoneal haemorrhage	13	9	1	3	6	4	3	.	.
	Vomiting	2	2	.	.	.	.	2	.	.
General disorders and administration site conditions	**Pain**	5	5	.	.	2	1	1	1	.
Hepatobiliary disorders	**Cholecystitis**	2	1	.	1	.	1	1	.	.
	Portal vein thrombosis	6	6	.	.	2	3	1	.	.
Infections and infestations	**Infection**	2	2	.	.	1	1	.	.	.

Exhibit 7-2B3
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION
in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
Investigations	**Blood alkaline phosphatase**	8	8	.	.	2	6	.	.	.
	Blood creatinine increased	1	.	.	1	.	.	1	.	.
	Granulocytes abnormal	1	1	.	.	.	1	.	.	.
	Hepatic enzyme increased	1	1	.	.	.	.	.	1	.
	Liver function test abnormal	27	27	.	.	12	15	.	.	.
Metabolism and nutrition disorders	**Hyperglycaemia**	6	.	.	6	.	.	.	6	.
	Hypoglycaemia	2	1	.	1	1	.	1	.	.
Musculoskeletal and connective tissue disorders	**Arthralgia**	1	1	.	.	.	.	.	1	.
Nervous system disorders	**Migraine**	2	2	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	1	.
Respiratory, thoracic and mediastinal disorders	**Aspiration**	1	1	.	.	.	.	1	.	.
	Haemothorax	1	.	.	1	.	1	.	.	.
Vascular disorders	**Haematoma**	7	5	.	2	1	3	.	3	.
	Haemorrhage	8	4	.	4	1	2	1	3	1
	Hypotension	1	1	.	.	.	.	1	.	.
	Thrombosis	1	.	.	1	1	.	.	.	.
Syst em/Organ Class	**Preferred term**									
Not yet coded	**Not yet coded**	5	5	.	.	.	.	4	1	.
Blood and lymphatic system disorders	**Afebrile neutropenia**	1	1	.	.	.	.	1	.	.
	Anaemia	1	.	.	1	.	.	1	.	.
	Blood disorder	1	1	.	.	.	.	1	.	.
	Febrile neutropenia	1	1	.	.	.	.	1	.	.
	Lymphopenia	6	5	1	.	.	4	2	.	.
	Neutropenia	3	3	.	.	.	.	2	1	.

Exhibit 7-2B3 (continued)
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION
in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
	Pancytopenia	1	1	.	.	.	.	.	1	.
	Platelet disorder	1	1	.	.	.	1	.	.	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	1	.	.	.
Gastrointestinal disorders	Diarrhoea	4	3	.	1	.	2	1	1	.
	Gastrointestinal disorder	3	1	2	.	.	1	.	2	.
	Nausea	4	3	.	1	.	1	1	1	1
	Peritoneal haemorrhage	1	.	.	1	1	.	.	.	.
	Vomiting	8	7	.	1	1	.	4	.	3
General disorders and administration site conditions	Mucosal inflammation	1	1	.	.	.	1	.	.	.
	Pain	1	1	.	.	.	.	.	1	.
	Pyrexia	1	1	.	.	.	1	.	.	.
Immune system disorders	Serum sickness	1	1	.	.	.	.	.	.	1
Infections and infestations	Infection	5	3	.	2	.	4	1	.	.
Injury, poisoning and procedural complications	Toxicity to various agents	2	2	.	.	.	.	1	1	.
Investigations	Blood creatinine increased	1	.	.	1	.	.	1	.	.
	Granulocytes abnormal	20	20	.	.	4	9	6	1	.
	Liver function test abnormal	2	2	.	.	.	2	.	.	.
	Neutrophil count	1	1	.	.	.	.	1	.	.
	Neutrophil count decreased	1	1	.	.	.	.	1	.	.
Metabolism and nutrition disorders	Hyperglycaemia	6	.	.	6	.	.	.	6	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	1	.

Exhibit 7-2B3 (continued)
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION
in Days 0-30 post First Infusion

			Transplant type			Era				
		Overall	ITA	SIK	IAK	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Neoplasm malignant**	1	1	.	.	.	1	.	.	.
Nervous system disorders	**Headache**	1	1	.	.	.	.	1	.	.
	Migraine	2	2	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	1	.
Respiratory, thoracic and mediastinal disorders	**Aspiration**	1	1	.	.	.	.	1	.	.
	Pleural effusion	1	1	.	.	.	.	1	.	.
	Pneumonitis	1	.	.	1	1	.	.	.	.

Exhibit 7-3A1
Adverse Events (AEs) in Year 1 Post 1st Infusion

Percent of Recipients with:	Type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any AE in 1-year	372	42.4	11	45.8	79	43.2	2	100.0	114	54.8	163	60.1	118	48.8	63	18.5	6	25.0
Any AE related to infusion in 1-year	187	21.3	4	16.7	37	20.2	1	50.0	64	30.8	87	32.1	54	22.3	22	6.5	2	8.3
Any AE related to IS in 1-year	244	27.8	7	29.2	45	24.6	2	100.0	74	35.6	121	44.6	75	31.0	25	7.3	3	12.5
Any AE related to both in 1-year	63	7.2	2	8.3	9	4.9	.	.	25	12.0	23	8.5	18	7.4	8	2.3	.	.
Any AE related to neither in 1-year	159	18.1	6	25.0	35	19.1	.	.	37	17.8	47	17.3	68	28.1	45	13.2	3	12.5

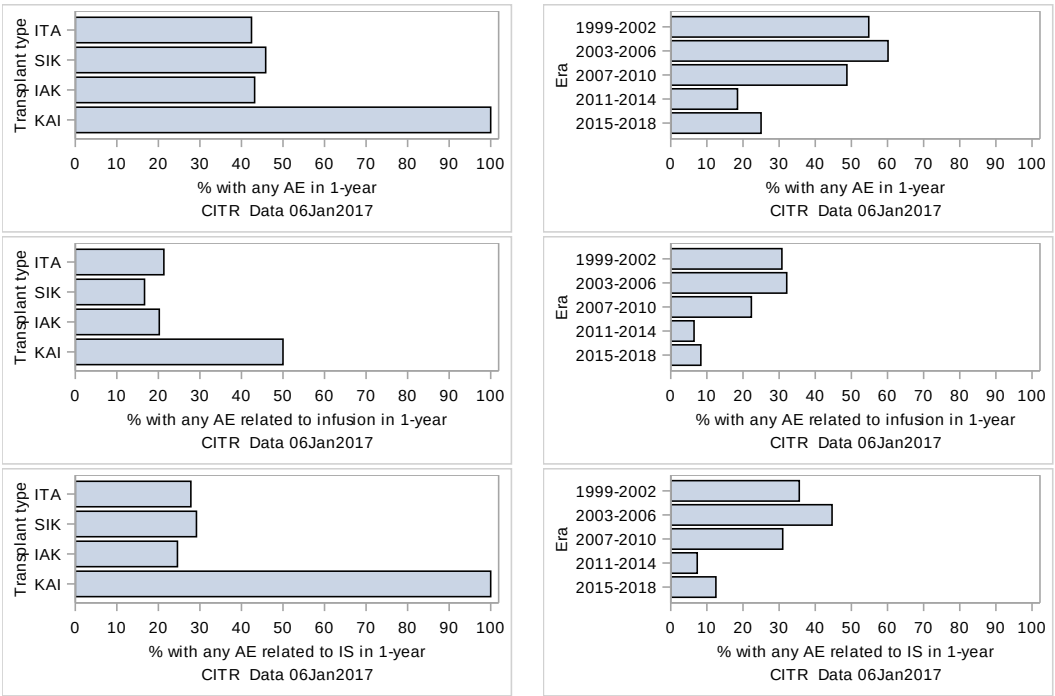
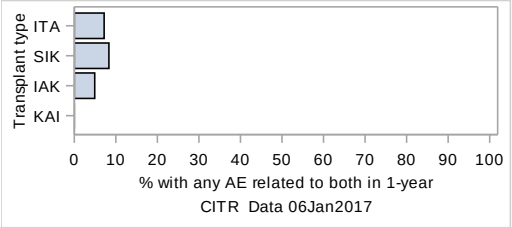
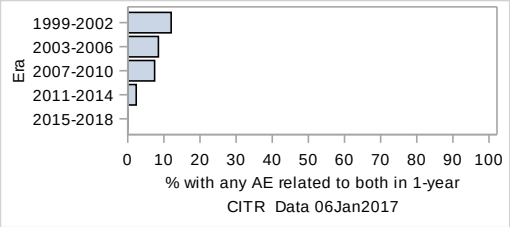
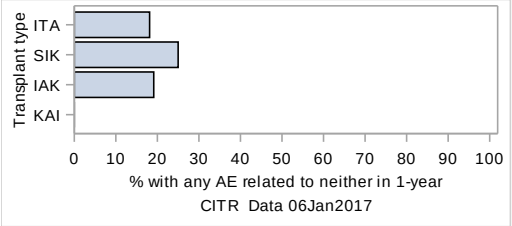


Exhibit 7-3A1 (continued)
Adverse Events (AEs) in Year 1 Post 1st Infusion







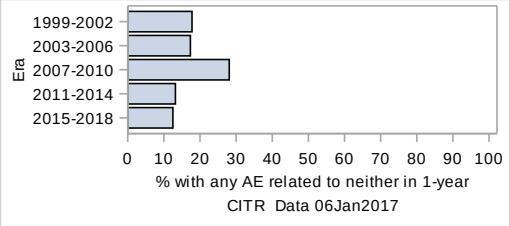


Exhibit 7-3A2
Adverse Events (AEs) RELATED TO PROCEDURE
in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term										
Not yet coded	Not yet coded	10	8	1	1	.	1	1	6	2	.
Blood and lymphatic system disorders	Anaemia	12	8	.	3	1	3	4	3	2	.
	Blood disorder	2	.	.	2	.	1	1	.	.	.
	Lymphopenia	3	2	.	1	.	1	2	.	.	.
	Neutropenia	4	4	.	.	.	.	.	.	4	.
Cardiac disorders	Arrhythmia supraventricular	2	2	.	.	.	.	.	2	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
Eye disorders	Retinal haemorrhage	1	1	.	.	.	.	.	.	1	.
	Vitreous haemorrhage	1	1	.	.	.	.	.	.	1	.
Gastrointestinal disorders	Ascites	2	2	.	.	.	1	1	.	.	.
	Diarrhoea	2	2	.	.	.	.	.	1	1	.
	Gastrointestinal disorder	4	2	2	.	.	.	1	.	2	1
	Gastrointestinal haemorrhage	5	2	.	3	.	2	3	.	.	.
	Gastrointestinal obstruction	1	1	.	.	.	.	1	.	.	.
	Gastrointestinal perforation	2	2	.	.	.	1	.	1	.	.
	Ileus	1	1	.	.	.	1	.	.	.	.
	Mouth ulceration	1	1	.	.	.	.	1	.	.	.
	Nausea	4	3	.	1	.	.	3	1	.	.
	Peritoneal haemorrhage	41	31	2	8	.	13	14	11	3	.
	Vomiting	2	2	.	.	.	.	.	2	.	.
General disorders and administration site conditions	Fatigue	3	3	.	.	.	.	3	.	.	.
	Mucosal inflammation	1	1	.	.	.	.	1	.	.	.
	Pain	16	15	.	1	.	4	7	4	1	.
	Ulcer	1	1	.	.	.	.	.	1	.	.
Hepatobiliary disorders	Biliary tract disorder	1	1	.	.	.	.	1	.	.	.

Exhibit 7-3A2 (continued)
Adverse Events (AEs) RELATED TO PROCEDURE
in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Cholecystitis	2	1	.	1	.	.	1	1	.	.
	Hepatic haematoma	1	1	.	.	.	.	1	.	.	.
	Hepatic haemorrhage	2	2	.	.	.	.	.	.	2	.
	Portal vein thrombosis	10	9	.	1	.	3	5	1	1	.
Immune system disorders	Hypersensitivity	1	1	.	.	.	.	1	.	.	.
Infections and infestations	Infection	6	5	.	1	.	2	4	.	.	.
Injury, poisoning and procedural complications	Post procedural haemorrhage	1	1	.	.	.	.	.	1	.	.
Investigations	Activated partial thromboplastin time	1	1	.	.	.	1	.	.	.	.
	Activated partial thromboplastin time prolonged	1	1	.	.	.	.	.	.	1	.
	Alanine aminotransferase increased	1	1	.	.	.	.	.	1	.	.
	Aspartate aminotransferase increased	3	3	.	.	.	.	.	3	.	.
	Blood alkaline phosphatase	18	16	.	2	.	4	12	2	.	.
	Blood bilirubin	1	1	.	.	.	1	.	.	.	.
	Blood creatinine increased	1	.	.	1	.	.	.	1	.	.
	Gamma-glutamyltransferase	5	4	.	1	.	1	3	1	.	.
	Gamma-glutamyltransferase increased	1	1	.	.	.	.	.	1	.	.
	Glomerular filtration rate	1	1	.	.	.	1	.	.	.	.
	Granulocytes abnormal	16	16	.	.	.	8	7	1	.	.

Exhibit 7-3A2 (continued)
Adverse Events (AEs) RELATED TO PROCEDURE
in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Hepatic enzyme increased	4	4	.	.	.	.	.	2	2	.
	Lipase	3	1	.	2	.	1	2	.	.	.
	Liver function test abnormal	99	96	.	3	.	41	47	11	.	.
	Low density lipoprotein increased	1	1	.	.	.	.	.	.	1	.
	Transaminases increased	1	1	.	.	.	.	.	.	1	.
Metabolism and nutrition disorders	Dehydration	1	1	.	.	.	.	1	.	.	.
	Hyperglycaemia	6	.	.	6	.	.	.	.	6	.
	Hypoalbuminaemia	1	1	.	.	.	.	.	1	.	.
	Hypoglycaemia	6	4	.	2	.	3	1	2	.	.
	Hypokalaemia	1	1	.	.	.	.	1	.	.	.
	Hyponatraemia	1	1	.	.	.	1	.	.	.	.
	Ketoacidosis	2	2	.	.	.	.	.	2	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Musculoskeletal pain	2	2	.	.	.	.	.	.	2	.
Nervous system disorders	Dyskinesia	1	1	.	.	.	.	.	1	.	.
	Migraine	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
Renal and urinary disorders	Acute kidney injury	1	.	.	1	.	.	.	.	.	1
	Proteinuria	1	1	.	.	.	1	.	.	.	.
	Urinary bladder haemorrhage	1	1	.	.	.	.	.	1	.	.
Respiratory, thoracic and mediastinal disorders	Aspiration	1	1	.	.	.	.	.	1	.	.
	Haemothorax	2	1	.	1	.	1	1	.	.	.
	Lung disorder	1	1	.	.	.	.	.	1	.	.
	Pleural effusion	1	.	.	1	.	.	1	.	.	.
Vascular disorders	Haematoma	10	7	.	3	.	2	5	.	3	.
	Haemorrhage	11	6	.	5	.	1	4	2	3	1

Exhibit 7-3A2 (continued)
Adverse Events (AEs) RELATED TO PROCEDURE
in Year 1 post First Infusion

		Transplant type				Era				
	Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
	N	N	N	N	N	N	N	N	N	N
Hypotension	2	2	.	.	.	.	.	2	.	.
Thrombosis	1	.	.	1	.	1	.	.	.	.

Exhibit 7-3A3
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term										
Not yet coded	Not yet coded	20	17	2	.	1	1	2	14	3	.
Blood and lymphatic system disorders	Afebrile neutropenia	2	2	.	.	.	.	.	1	1	.
	Anaemia	22	20	.	2	.	4	11	5	2	.
	Blood disorder	3	1	.	2	.	1	1	1	.	.
	Febrile neutropenia	4	4	.	.	.	.	.	4	.	.
	Leukopenia	6	2	.	4	.	.	.	3	3	.
	Lymphopenia	41	36	2	3	.	3	16	18	4	.
	Neutropenia	23	22	.	1	.	.	.	10	13	.
	Pancytopenia	1	1	.	.	.	.	.	.	1	.
	Platelet disorder	2	2	.	.	.	1	1	.	.	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
Eye disorders	Eye disorder	2	2	.	.	.	.	1	1	.	.
	Vitreous haemorrhage	1	1	.	.	.	1	.	.	.	.
Gastrointestinal disorders	Ascites	1	1	.	.	.	1	.	.	.	.
	Colitis	3	2	.	1	.	.	2	1	.	.
	Constipation	1	1	.	.	.	.	.	1	.	.
	Diarrhoea	27	23	.	4	.	2	15	8	2	.
	Dysphagia	2	2	.	.	.	.	2	.	.	.
	Gastritis	1	1	.	.	.	.	1	.	.	.
	Gastrointestinal disorder	9	4	2	3	.	.	7	.	2	.

Exhibit 7-3A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Gastrointestinal obstruction	2	2	.	.	.	.	2	.	.	.
	Mouth ulceration	2	2	.	.	.	.	1	1	.	.
	Nausea	8	6	.	2	.	1	4	1	1	1
	Oral pain	1	1	.	.	.	.	.	1	.	.
	Peritoneal haemorrhage	5	2	.	3	.	5	.	.	.	.
	Stomatitis	1	1	.	.	.	.	.	1	.	.
	Vomiting	13	12	.	1	.	2	3	5	.	3
General disorders and administration site conditions	Chest pain	1	1	.	.	.	.	.	1	.	.
	Death	1	.	.	1	.	1	.	.	.	.
	Fatigue	8	8	.	.	.	.	8	.	.	.
	Injection site reaction	1	1	.	.	.	.	1	.	.	.
	Mucosal inflammation	17	13	.	3	1	3	10	3	.	1
	Oedema peripheral	3	2	.	1	.	2	1	.	.	.
	Pain	20	19	.	1	.	4	12	3	1	.
	Pyrexia	1	1	.	.	.	.	1	.	.	.
	Ulcer	1	1	.	.	.	.	.	1	.	.
Hepatobiliary disorders	Cholecystitis	1	1	.	.	.	1	.	.	.	.
Immune system disorders	Autoimmune disorder	1	1	.	.	.	.	.	1	.	.
	Hypersensitivity	5	4	.	1	.	1	2	1	1	.
	Serum sickness	1	1	.	.	.	.	.	.	.	1
Infections and infestations	Cystitis	1	1	.	.	.	.	.	1	.	.
	Infection	30	20	1	8	1	10	16	4	.	.

Exhibit 7-3A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Periorbital cellulitis	1	1	.	.	.	.	.	1	.	.
	Pneumonia	5	3	.	2	.	1	3	1	.	.
	Renal graft infection	1	.	1	.	.	.	.	.	1	.
Injury, poisoning and procedural complications	Toxicity to various agents	2	2	.	.	.	.	.	1	1	.
Investigations	Activated partial thromboplastin time	1	1	.	.	.	1	.	.	.	.
	Blood alkaline phosphatase	5	3	.	2	.	2	2	1	.	.
	Blood creatine phosphokinase	1	1	.	.	.	.	1	.	.	.
	Blood creatinine increased	10	8	.	2	.	.	4	5	1	.
	Gamma-glutamyltransferase	1	1	.	.	.	1	.	.	.	.
	Glomerular filtration rate	1	1	.	.	.	1	.	.	.	.
	Granulocytes abnormal	203	193	.	10	.	65	100	35	3	.
	Lipase increased	1	.	.	1	.	.	.	.	1	.
	Liver function test abnormal	26	24	.	2	.	14	7	5	.	.
	Low density lipoprotein abnormal	1	1	.	.	.	.	1	.	.	.
	Low density lipoprotein increased	3	3	.	.	.	.	.	.	3	.
	Neutrophil count	2	2	.	.	.	.	.	2	.	.
	Neutrophil count decreased	3	3	.	.	.	.	.	3	.	.

Exhibit 7-3A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Year 1 post First Infusion

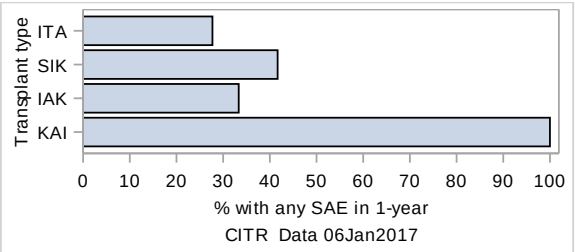
			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Metabolism and nutrition disorders	Decreased appetite	1	1	.	.	.	.	.	1	.	.
	Dehydration	4	3	1	.	.	.	.	3	1	.
	Hyperglycaemia	6	.	.	6	.	.	.	.	6	.
	Hyperkalaemia	4	4	.	.	.	2	1	.	1	.
	Hypoglycaemia	3	3	.	.	.	2	1	.	.	.
	Hypokalaemia	3	3	.	.	.	.	2	1	.	.
	Hypomagnesaemia	1	1	.	.	.	.	1	.	.	.
	Hyponatraemia	1	1	.	.	.	1	.	.	.	.
	Hypophosphataemia	5	4	.	1	.	1	4	.	.	.
	Ketoacidosis	1	.	.	1	.	.	1	.	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Arthritis	1	1	.	.	.	.	.	1	.	.
	Muscle necrosis	1	1	.	.	.	.	1	.	.	.
	Muscular weakness	4	4	.	.	.	.	4	.	.	.
	Musculoskeletal disorder	2	2	.	.	.	1	1	.	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	4	2	.	2	.	1	2	1	.	.
	Papillary thyroid cancer	1	1	.	.	.	.	1	.	.	.
	Treatment related secondary malignancy	1	1	.	.	.	.	1	.	.	.
Nervous system disorders	Cognitive disorder	1	1	.	.	.	1	.	.	.	.
	Convulsion	1	1	.	.	.	.	.	.	1	.
	Dizziness	1	1	.	.	.	.	1	.	.	.
	Headache	2	2	.	.	.	.	.	1	1	.
	Migraine	2	2	.	.	.	.	.	2	.	.

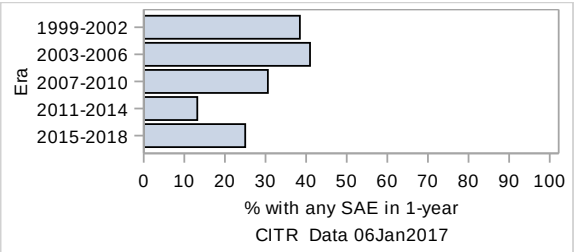
Exhibit 7-3A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
in Year 1 post First Infusion

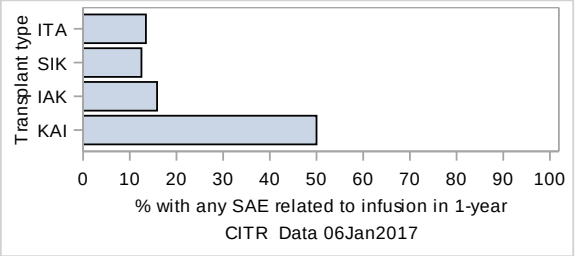
			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
	Tremor	3	3	.	.	.	1	.	2	.	.
Psychiatric disorders	Insomnia	1	1	.	.	.	.	1	.	.	.
	Mood altered	1	1	.	.	.	.	1	.	.	.
Renal and urinary disorders	Micturition urgency	1	1	.	.	.	.	1	.	.	.
	Proteinuria	1	1	.	.	.	1	.	.	.	.
	Renal disorder	2	2	.	.	.	2	.	.	.	.
	Renal failure	10	6	1	3	.	5	3	2	.	.
	Urinary bladder haemorrhage	2	1	.	1	.	.	1	1	.	.
Reproductive system and breast disorders	Ovarian cyst ruptured	1	.	.	.	1	.	1	.	.	.
	Sexual dysfunction	1	1	.	.	.	.	1	.	.	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	.	1	.	.	1	.	.	.	.
	Aspiration	1	1	.	.	.	.	.	1	.	.
	Cough	2	1	.	1	.	1	.	1	.	.
	Dyspnoea	1	1	.	.	.	.	1	.	.	.
	Haemothorax	1	1	.	.	.	1	.	.	.	.
	Hypoxia	1	1	.	.	.	.	.	1	.	.
	Lung disorder	2	2	.	.	.	.	1	1	.	.
	Pleural effusion	1	1	.	.	.	.	.	1	.	.
	Pneumonitis	3	2	.	1	.	2	1	.	.	.
Skin and subcutaneous tissue disorders	Exfoliative rash	4	4	.	.	.	1	1	2	.	.
	Pruritus	1	1	.	.	.	.	.	1	.	.
	Rash	1	1	.	.	.	.	.	1	.	.
Surgical and medical procedures	Hysterectomy	1	.	.	.	1	.	1	.	.	.
Vascular disorders	Haematoma	2	2	.	.	.	1	.	1	.	.
	Hypertension	2	.	.	2	.	.	2	.	.	.

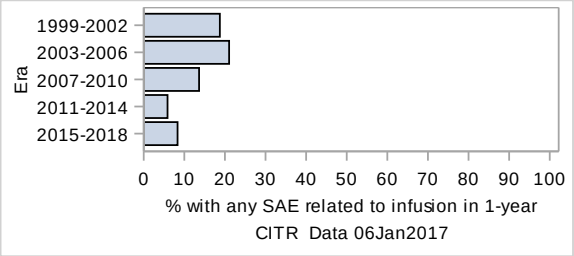
Exhibit 7-3B1
Serious Adverse Events (SAEs) in Year 1 Post 1st Infusion

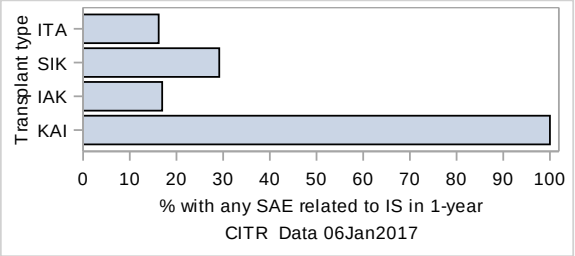
Percent of Recipients with:	Type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE in 1-year	243	27.7	10	41.7	61	33.3	2	100.0	80	38.5	111	41.0	74	30.6	45	13.2	6	25.0
Any SAE related to infusion in 1-year	118	13.5	3	12.5	29	15.8	1	50.0	39	18.8	57	21.0	33	13.6	20	5.9	2	8.3
Any SAE related to IS in 1-year	142	16.2	7	29.2	31	16.9	2	100.0	41	19.7	68	25.1	49	20.2	21	6.2	3	12.5
Any SAE related to both in 1-year	29	3.3	2	8.3	4	2.2	.	.	7	3.4	9	3.3	12	5.0	7	2.1	.	.
Any SAE related to neither in 1-year	75	8.6	6	25.0	24	13.1	.	.	26	12.5	27	10.0	30	12.4	19	5.6	3	12.5

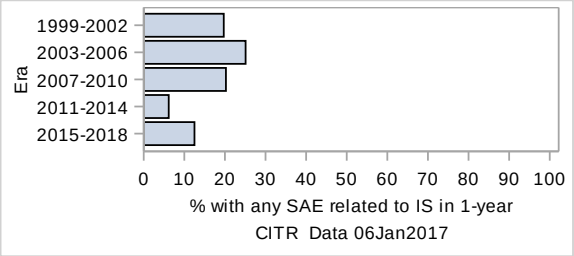


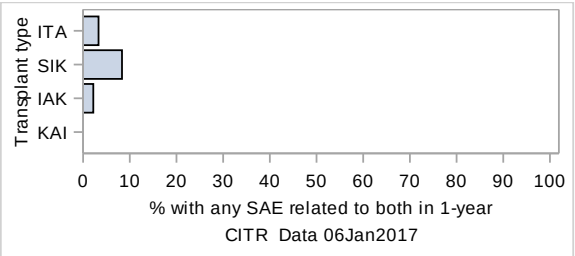












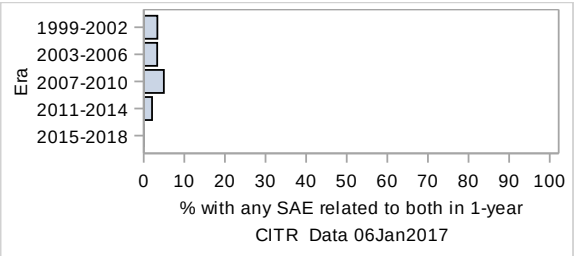
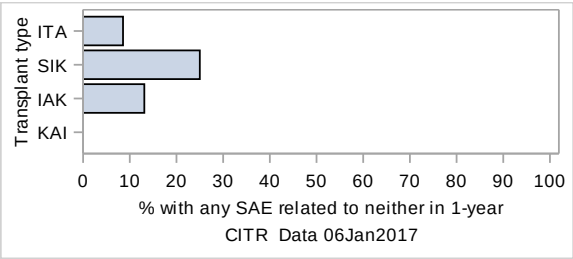


Exhibit 7-3B1 (continued)
Serious Adverse Events (SAEs) in Year 1 Post 1st Infusion



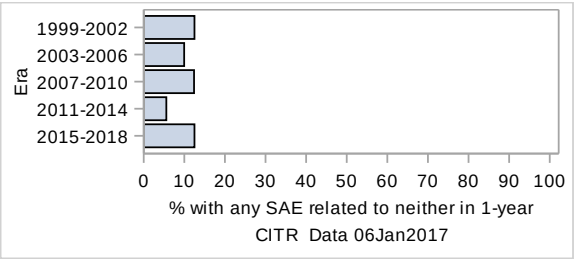


Exhibit 7-3B2
Serious Adverse Events (SAEs) RELATED TO PROCEDURE in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	**Preferred term**										
Not yet coded	**Not yet coded**	8	6	1	1	.	1	1	4	2	.
Blood and lymphatic system disorders	**Anaemia**	7	4	.	2	1	1	4	1	1	.
	Lymphopenia	2	1	.	1	.	1	1	.	.	.
	Neutropenia	4	4	.	.	.	.	.	.	4	.
Cardiac disorders	**Arrhythmia supraventricular**	1	1	.	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
Eye disorders	**Retinal haemorrhage**	1	1	.	.	.	.	.	.	1	.
	Vitreous haemorrhage	1	1	.	.	.	.	.	.	1	.
Gastrointestinal disorders	**Ascites**	2	2	.	.	.	1	1	.	.	.
	Diarrhoea	2	2	.	.	.	.	.	1	1	.
	Gastrointestinal disorder	3	1	2	.	.	.	.	.	2	1
	Gastrointestinal haemorrhage	5	2	.	3	.	2	3	.	.	.
	Gastrointestinal obstruction	1	1	.	.	.	.	1	.	.	.
	Gastrointestinal perforation	2	2	.	.	.	1	.	1	.	.
	Ileus	1	1	.	.	.	1	.	.	.	.
	Nausea	2	2	.	.	.	.	1	1	.	.
	Peritoneal haemorrhage	36	28	1	7	.	11	13	9	3	.
	Vomiting	2	2	.	.	.	.	.	2	.	.
General disorders and administration site conditions	**Pain**	12	12	.	.	.	4	4	3	1	.
Hepatobiliary disorders	**Biliary tract disorder**	1	1	.	.	.	.	1	.	.	.
	Cholecystitis	2	1	.	1	.	.	1	1	.	.
	Hepatic haematoma	1	1	.	.	.	.	1	.	.	.
	Hepatic haemorrhage	2	2	.	.	.	.	.	.	2	.
	Portal vein thrombosis	9	8	.	1	.	3	5	1	.	.
Immune system disorders	**Hypersensitivity**	1	1	.	.	.	.	1	.	.	.

Exhibit 7-3B2 (continued)
Serious Adverse Events (SAEs) RELATED TO PROCEDURE in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Infections and infestations	**Infection**	5	4	.	1	.	2	3	.	.	.
Injury, poisoning and procedural complications	**Post procedural haemorrhage**	1	1	.	.	.	.	.	1	.	.
Investigations	**Blood alkaline phosphatase**	11	11	.	.	.	3	8	.	.	.
	Blood creatinine increased	1	.	.	1	.	.	.	1	.	.
	Granulocytes abnormal	2	2	.	.	.	.	2	.	.	.
	Hepatic enzyme increased	2	2	.	.	.	.	.	.	2	.
	Liver function test abnormal	33	33	.	.	.	18	15	.	.	.
	Low density lipoprotein increased	1	1	.	.	.	.	.	.	1	.
Metabolism and nutrition disorders	**Dehydration**	1	1	.	.	.	.	1	.	.	.
	Hyperglycaemia	6	.	.	6	.	.	.	.	6	.
	Hypoglycaemia	4	2	.	2	.	1	1	2	.	.
	Ketoacidosis	2	2	.	.	.	.	.	2	.	.
Musculoskeletal and connective tissue disorders	**Arthralgia**	1	1	.	.	.	.	.	.	1	.
	Musculoskeletal pain	2	2	.	.	.	.	.	.	2	.
Nervous system disorders	**Migraine**	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
Renal and urinary disorders	**Urinary bladder haemorrhage**	1	1	.	.	.	.	.	1	.	.
Respiratory, thoracic and mediastinal disorders	**Aspiration**	1	1	.	.	.	.	.	1	.	.
	Haemothorax	2	1	.	1	.	1	1	.	.	.
	Lung disorder	1	1	.	.	.	.	.	1	.	.
	Pleural effusion	1	.	.	1	.	.	1	.	.	.
Vascular disorders	**Haematoma**	10	7	.	3	.	2	5	.	3	.
	Haemorrhage	11	6	.	5	.	1	4	2	3	1
	Hypotension	1	1	.	.	.	.	.	1	.	.
	Thrombosis	1	.	.	1	.	1	.	.	.	.

Exhibit 7-3B3
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term										
Not yet coded	Not yet coded	16	13	2	.	1	1	1	11	3	.
Blood and lymphatic system disorders	Afebrile neutropenia	2	2	.	.	.	.	.	1	1	.
	Anaemia	12	10	.	2	.	3	5	3	1	.
	Blood disorder	1	1	.	.	.	.	.	1	.	.
	Febrile neutropenia	4	4	.	.	.	.	.	4	.	.
	Leukopenia	3	.	.	3	.	.	.	.	3	.
	Lymphopenia	8	6	1	1	.	1	5	2	.	.
	Neutropenia	15	15	.	.	.	.	.	3	12	.
	Pancytopenia	1	1	.	.	.	.	.	.	1	.
	Platelet disorder	1	1	.	.	.	.	1	.	.	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
Eye disorders	Eye disorder	1	1	.	.	.	.	1	.	.	.
Gastrointestinal disorders	Ascites	1	1	.	.	.	1	.	.	.	.
	Colitis	3	2	.	1	.	.	2	1	.	.
	Constipation	1	1	.	.	.	.	.	1	.	.
	Diarrhoea	11	8	.	3	.	1	3	5	2	.
	Dysphagia	1	1	.	.	.	.	1	.	.	.
	Gastrointestinal disorder	7	3	2	2	.	.	5	.	2	.
	Gastrointestinal obstruction	1	1	.	.	.	.	1	.	.	.
	Nausea	6	5	.	1	.	1	2	1	1	1
	Peritoneal haemorrhage	3	2	.	1	.	3	.	.	.	.
	Vomiting	11	10	.	1	.	1	2	5	.	3
General disorders and administration site conditions	Chest pain	1	1	.	.	.	.	.	1	.	.
	Death	1	.	.	1	.	1	.	.	.	.
	Mucosal inflammation	8	5	.	2	1	2	4	1	.	1
	Oedema peripheral	1	.	.	1	.	.	1	.	.	.
	Pain	5	5	.	.	.	.	4	.	1	.
	Pyrexia	1	1	.	.	.	.	1	.	.	.

Exhibit 7-3B3 (continued)
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Hepatobiliary disorders	Cholecystitis	1	1	.	.	.	1	.	.	.	.
Immune system disorders	Autoimmune disorder	1	1	.	.	.	.	.	1	.	.
	Hypersensitivity	4	3	.	1	.	1	1	1	1	.
	Serum sickness	1	1	.	.	.	.	.	.	.	1
Infections and infestations	Infection	28	19	1	7	1	10	14	4	.	.
	Pneumonia	5	3	.	2	.	1	3	1	.	.
	Renal graft infection	1	.	1	.	.	.	.	.	1	.
Injury, poisoning and procedural complications	Toxicity to various agents	2	2	.	.	.	.	.	1	1	.
Investigations	Blood alkaline phosphatase	1	1	.	.	.	1	.	.	.	.
	Blood creatine phosphokinase	1	1	.	.	.	.	1	.	.	.
	Blood creatinine increased	10	8	.	2	.	.	4	5	1	.
	Granulocytes abnormal	51	45	.	6	.	17	19	12	3	.
	Liver function test abnormal	3	3	.	.	.	1	2	.	.	.
	Low density lipoprotein increased	1	1	.	.	.	.	.	.	1	.
	Neutrophil count	1	1	.	.	.	.	.	1	.	.
	Neutrophil count decreased	1	1	.	.	.	.	.	1	.	.
Metabolism and nutrition disorders	Dehydration	4	3	1	.	.	.	.	3	1	.
	Hyperglycaemia	6	.	.	6	.	.	.	.	6	.
	Hypoglycaemia	1	1	.	.	.	.	1	.	.	.
	Hypomagnesaemia	1	1	.	.	.	.	1	.	.	.
	Hypophosphataemia	1	1	.	.	.	.	1	.	.	.
	Ketoacidosis	1	.	.	1	.	.	1	.	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Arthritis	1	1	.	.	.	.	.	1	.	.
	Muscle necrosis	1	1	.	.	.	.	1	.	.	.
	Musculoskeletal disorder	2	2	.	.	.	1	1	.	.	.
	Neoplasm malignant	2	2	.	.	.	1	1	.	.	.

Exhibit 7-3B3 (continued)
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION in Year 1 post First Infusion

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Papillary thyroid cancer	1	1	.	.	.	.	1	.	.	.
	Treatment related secondary malignancy	1	1	.	.	.	.	1	.	.	.
Nervous system disorders	Cognitive disorder	1	1	.	.	.	1	.	.	.	.
	Convulsion	1	1	.	.	.	.	.	.	1	.
	Headache	2	2	.	.	.	.	.	1	1	.
	Migraine	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
Psychiatric disorders	Mood altered	1	1	.	.	.	.	1	.	.	.
Renal and urinary disorders	Renal disorder	2	2	.	.	.	2	.	.	.	.
	Renal failure	10	6	1	3	.	5	3	2	.	.
	Urinary bladder haemorrhage	2	1	.	1	.	.	1	1	.	.
Reproductive system and breast disorders	Ovarian cyst ruptured	1	.	.	.	1	.	1	.	.	.
	Sexual dysfunction	1	1	.	.	.	.	1	.	.	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	.	1	.	.	1	.	.	.	.
	Aspiration	1	1	.	.	.	.	.	1	.	.
	Cough	1	.	.	1	.	1	.	.	.	.
	Dyspnoea	1	1	.	.	.	.	1	.	.	.
	Haemothorax	1	1	.	.	.	1	.	.	.	.
	Lung disorder	2	2	.	.	.	.	1	1	.	.
	Pleural effusion	1	1	.	.	.	.	.	1	.	.
	Pneumonitis	2	1	.	1	.	2	.	.	.	.
Skin and subcutaneous tissue disorders	Exfoliative rash	1	1	.	.	.	.	.	1	.	.
	Rash	1	1	.	.	.	.	.	1	.	.
Surgical and medical procedures	Hysterectomy	1	.	.	.	1	.	1	.	.	.
Vascular disorders	Haematoma	1	1	.	.	.	1	.	.	.	.

Exhibit 7-4A1
Recipients with an Adverse Event (AE) Any Time Post Islet Transplant

Percent of Recipients with:	Type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any AE ever	438	49.9	13	54.2	105	57.4	2	100.0	137	65.9	193	71.2	144	59.5	77	22.6	7	29.2
Any AE related to infusion ever	216	24.6	5	20.8	45	24.6	1	50.0	72	34.6	106	39.1	60	24.8	27	7.9	2	8.3
Any AE related to IS ever	298	34.0	10	41.7	57	31.1	2	100.0	93	44.7	148	54.6	93	38.4	29	8.5	4	16.7
Any AE related to both ever	83	9.5	2	8.3	10	5.5	.	.	26	12.5	34	12.5	25	10.3	10	2.9	.	.
Any AE related to neither ever	255	29.1	8	33.3	68	37.2	.	.	74	35.6	94	34.7	102	42.1	58	17.0	3	12.5

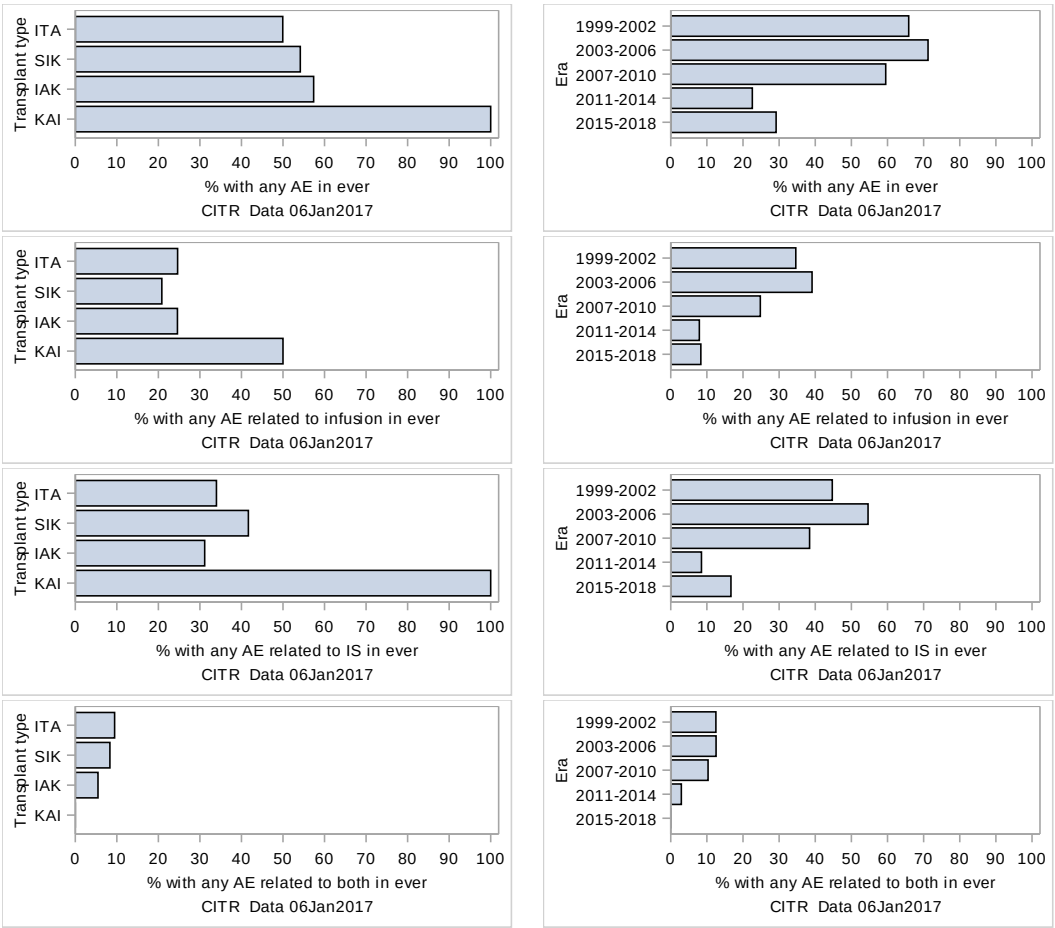
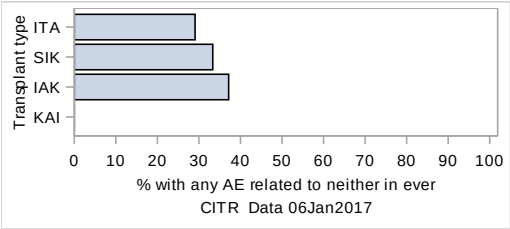


Exhibit 7-4A1(continued)
Recipients with an Adverse Event (AE) Any Time Post Islet Transplant



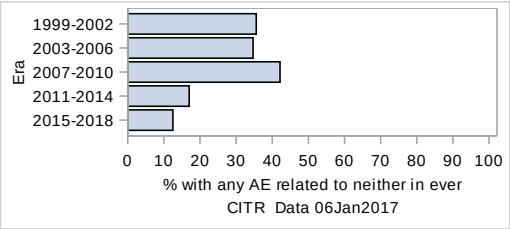


Exhibit 7-4A2
Adverse Events (AEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	**Preferred term**										
Not yet coded	**Not yet coded**	12	9	1	2	.	1	3	6	2	.
Blood and lymphatic system disorders	**Anaemia**	13	9	.	3	1	3	4	4	2	.
	Blood disorder	2	.	.	2	.	1	1	.	.	.
	Lymphopenia	4	3	.	1	.	1	3	.	.	.
	Neutropenia	4	4	.	.	.	.	.	.	4	.
Cardiac disorders	**Arrhythmia supraventricular**	2	2	.	.	.	.	.	2	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
Endocrine disorders	**Endocrine disorder**	1	1	.	.	.	.	.	1	.	.
Eye disorders	**Retinal haemorrhage**	1	1	.	.	.	.	.	.	1	.
	Vitreous haemorrhage	2	2	.	.	.	.	.	1	1	.
Gastrointestinal disorders	**Ascites**	2	2	.	.	.	1	1	.	.	.
	Diarrhoea	3	3	.	.	.	.	1	1	1	.
	Gastrointestinal disorder	6	4	2	.	.	.	3	.	2	1
	Gastrointestinal haemorrhage	5	2	.	3	.	2	3	.	.	.
	Gastrointestinal obstruction	2	2	.	.	.	1	1	.	.	.

Exhibit 7-4A2(continued)
Adverse Events (AEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Gastrointestinal perforation	2	2	.	.	.	1	.	1	.	.
	Ileus	2	2	.	.	.	1	1	.	.	.
	Mouth ulceration	1	1	.	.	.	.	1	.	.	.
	Nausea	4	3	.	1	.	.	3	1	.	.
	Peritoneal haemorrhage	48	33	3	12	.	16	16	12	4	.
	Vomiting	3	3	.	.	.	.	.	3	.	.
General disorders and administration site conditions	Death	1	1	.	.	.	.	.	1	.	.
	Fatigue	3	3	.	.	.	.	3	.	.	.
	Mucosal inflammation	1	1	.	.	.	.	1	.	.	.
	Pain	19	18	.	1	.	7	7	4	1	.
	Ulcer	1	1	.	.	.	.	.	1	.	.
Hepatobiliary disorders	Biliary tract disorder	1	1	.	.	.	.	1	.	.	.
	Cholecystitis	3	2	.	1	.	1	1	1	.	.
	Hepatic haematoma	1	1	.	.	.	.	1	.	.	.
	Hepatic haemorrhage	2	2	.	.	.	.	.	.	2	.
	Portal vein thrombosis	12	11	.	1	.	4	5	2	1	.
Immune system disorders	Graft versus host disease	2	2	.	.	.	.	.	.	2	.
	Hypersensitivity	4	4	.	.	.	.	2	2	.	.
	Sensitisation	1	.	.	1	.	.	.	.	1	.
Infections and infestations	Cytomegalovirus infection	1	1	.	.	.	.	.	.	1	.
	Gastroenteritis viral	1	1	.	.	.	1	.	.	.	.
	Infection	10	9	.	1	.	2	6	2	.	.
	Influenza	1	1	.	.	.	.	.	1	.	.

Exhibit 7-4A2(continued)
Adverse Events (AEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Pneumonia	1	1	.	.	.	.	.	1	.	.
	Respiratory tract infection	1	1	.	.	.	.	.	1	.	.
Injury, poisoning and procedural complications	Fracture	1	1	.	.	.	.	.	1	.	.
	Post procedural haemorrhage	1	1	.	.	.	.	.	1	.	.
	Transplant failure	1	1	.	.	.	.	.	.	1	.
	Wound complication	3	3	.	.	.	.	1	2	.	.
Investigations	Activated partial thromboplastin time	2	1	.	1	.	1	1	.	.	.
	Activated partial thromboplastin time prolonged	1	1	.	.	.	.	.	.	1	.
	Alanine aminotransferase increased	1	1	.	.	.	.	.	1	.	.
	Aspartate aminotransferase increased	3	3	.	.	.	.	.	3	.	.
	Blood alkaline phosphatase	21	19	.	2	.	5	14	2	.	.
	Blood amylase	1	1	.	.	.	.	1	.	.	.
	Blood bilirubin	1	1	.	.	.	1	.	.	.	.
	Blood creatinine increased	5	2	.	3	.	.	4	1	.	.
	Gamma-glutamyltransferase	10	9	.	1	.	6	3	1	.	.
	Gamma-glutamyltransferase increased	1	1	.	.	.	.	.	1	.	.
	Glomerular filtration rate	1	1	.	.	.	1	.	.	.	.
	Granulocytes abnormal	16	16	.	.	.	8	7	1	.	.

Exhibit 7-4A2(continued)
Adverse Events (AEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Hepatic enzyme increased	4	4	.	.	.	.	.	2	2	.
	Lipase	4	1	.	3	.	1	3	.	.	.
	Liver function test abnormal	107	104	.	3	.	46	50	11	.	.
	Low density lipoprotein increased	1	1	.	.	.	.	.	.	1	.
	Transaminases increased	1	1	.	.	.	.	.	.	1	.
Metabolism and nutrition disorders	Dehydration	1	1	.	.	.	.	1	.	.	.
	Hyperglycaemia	7	1	.	6	.	.	.	.	7	.
	Hypoalbuminaemia	1	1	.	.	.	.	.	1	.	.
	Hypoglycaemia	8	6	.	2	.	3	2	3	.	.
	Hypokalaemia	1	1	.	.	.	.	1	.	.	.
	Hyponatraemia	2	1	.	1	.	1	1	.	.	.
	Ketoacidosis	3	3	.	.	.	1	.	2	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Musculoskeletal pain	2	2	.	.	.	.	.	.	2	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1	1	.	.	.	.	1	.	.	.
Nervous system disorders	Dyskinesia	1	1	.	.	.	.	.	1	.	.
	Migraine	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
	Syncope	1	1	.	.	.	.	.	1	.	.
	Acute kidney injury	1	.	.	1	.	.	.	.	.	1

Exhibit 7-4A2(continued)
Adverse Events (AEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Renal and urinary disorders	Proteinuria	1	1	.	.	.	1	.	.	.	.
	Renal disorder	1	.	.	1	.	.	1	.	.	.
	Renal failure	1	1	.	.	.	.	1	.	.	.
	Urinary bladder haemorrhage	1	1	.	.	.	.	.	1	.	.
Respiratory, thoracic and mediastinal disorders	Aspiration	1	1	.	.	.	.	.	1	.	.
	Haemothorax	2	1	.	1	.	1	1	.	.	.
	Lung disorder	1	1	.	.	.	.	.	1	.	.
	Pleural effusion	1	.	.	1	.	.	1	.	.	.
Surgical and medical procedures	Incisional hernia repair	1	1	.	.	.	.	.	1	.	.
Vascular disorders	Haematoma	12	9	.	3	.	3	6	.	3	.
	Haemorrhage	12	7	.	5	.	1	4	3	3	1
	Hypotension	2	2	.	.	.	.	.	2	.	.
	Thrombosis	1	.	.	1	.	1	.	.	.	.

Exhibit 7-4A3
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term										
Not yet coded	Not yet coded	27	21	2	3	1	2	3	17	3	2
Blood and lymphatic system disorders	Afebrile neutropenia	2	2	.	.	.	.	.	1	1	.
	Agranulocytosis	1	.	1	.	.	.	1	.	.	.
	Anaemia	27	24	.	3	.	5	14	6	2	.
	Blood disorder	4	2	.	2	.	1	1	2	.	.
	Febrile neutropenia	4	4	.	.	.	.	.	4	.	.
	Haemolysis	1	1	.	.	.	.	1	.	.	.
	Leukopenia	12	6	1	5	.	.	.	3	9	.
	Lymphopenia	51	44	4	3	.	3	21	21	6	.
	Neutropenia	25	23	.	2	.	.	.	10	15	.
	Pancytopenia	1	1	.	.	.	.	.	.	1	.
	Platelet disorder	3	3	.	.	.	1	2	.	.	.
	Thrombocytopenia	5	5	.	.	.	.	.	5	.	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
	Pericardial effusion	1	1	.	.	.	.	1	.	.	.
	Pericarditis	1	1	.	.	.	.	1	.	.	.
Ear and labyrinth disorders	Tinnitus	1	1	.	.	.	1	.	.	.	.
Eye disorders	Eye disorder	5	4	.	1	.	1	3	1	.	.
	Ocular surface disease	1	.	.	1	.	.	1	.	.	.
	Uveitis	1	.	.	1	.	.	.	1	.	.

Exhibit 7-4A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Vitreous haemorrhage	1	1	.	.	.	1	.	.	.	.
Gastrointestinal disorders	Ascites	2	2	.	.	.	1	1	.	.	.
	Barrett's oesophagus	1	1	.	.	.	.	1	.	.	.
	Colitis	5	4	.	1	.	.	4	1	.	.
	Constipation	1	1	.	.	.	.	.	1	.	.
	Diarrhoea	50	46	.	4	.	6	26	16	2	.
	Dysphagia	2	2	.	.	.	.	2	.	.	.
	Gastritis	2	2	.	.	.	1	1	.	.	.
	Gastrointestinal disorder	15	7	2	6	.	.	13	.	2	.
	Gastrointestinal obstruction	8	4	.	4	.	.	8	.	.	.
	Mouth ulceration	3	2	.	1	.	.	2	1	.	.
	Nausea	8	6	.	2	.	1	4	1	1	1
	Oral pain	1	1	.	.	.	.	.	1	.	.
	Peritoneal haemorrhage	5	2	.	3	.	5	.	.	.	.
	Stomatitis	1	1	.	.	.	.	.	1	.	.
	Vomiting	19	17	.	2	.	4	4	7	1	3
General disorders and administration site conditions	Chest pain	1	1	.	.	.	.	.	1	.	.
	Death	3	2	.	1	.	1	1	1	.	.
	Fatigue	13	12	.	1	.	1	10	2	.	.
	Injection site reaction	1	1	.	.	.	.	1	.	.	.
	Mucosal inflammation	19	15	.	3	1	3	12	3	.	1
	Oedema peripheral	5	4	.	1	.	2	1	2	.	.
	Pain	31	28	.	3	.	7	19	4	1	.
	Pyrexia	6	5	.	1	.	3	2	1	.	.

Exhibit 7-4A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Systemic inflammatory response syndrome	3	.	.	3	.	.	1	2	.	.
	Ulcer	1	1	.	.	.	.	.	1	.	.
Hepatobiliary disorders	Cholecystitis	1	1	.	.	.	1	.	.	.	.
Immune system disorders	Autoimmune disorder	1	1	.	.	.	.	.	1	.	.
	Graft versus host disease	2	2	.	.	.	.	.	.	2	.
	Hypersensitivity	11	9	.	2	.	1	5	4	1	.
	Serum sickness	2	2	.	.	.	.	.	1	.	1
Infections and infestations	Arthritis bacterial	1	1	.	.	.	.	1	.	.	.
	Cystitis	1	1	.	.	.	.	.	1	.	.
	Cytomegalovirus infection	1	1	.	.	.	.	1	.	.	.
	Gastrointestinal infection	1	1	.	.	.	.	.	.	1	.
	Infection	61	46	1	13	1	20	28	12	1	.
	Influenza	1	1	.	.	.	.	.	1	.	.
	Opportunistic infection	2	1	.	1	.	.	.	2	.	.
	Periorbital cellulitis	1	1	.	.	.	.	.	1	.	.
	Pneumonia	13	7	3	3	.	1	7	5	.	.
	Pyelonephritis	2	1	.	1	.	.	1	.	1	.
	Renal graft infection	1	.	1	.	.	.	.	.	1	.
	Respiratory tract infection	1	1	.	.	.	.	.	1	.	.
	Urinary tract infection	1	.	.	1	.	.	.	.	1	.
	Urosepsis	1	.	1	.	.	.	.	.	1	.
	Vestibular neuronitis	1	1	.	.	.	.	.	1	.	.

Exhibit 7-4A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Viral encephalitis	1	1	.	.	.	1	.	.	.	.
Injury, poisoning and procedural complications	Fracture	3	2	.	.	1	2	.	1	.	.
	Injury	1	.	.	1	.	.	1	.	.	.
	Limb injury	1	1	.	.	.	.	.	1	.	.
	Toxicity to various agents	2	2	.	.	.	.	.	1	1	.
	Transplant failure	1	1	.	.	.	.	.	.	1	.
	Wound complication	4	3	1	.	.	3	1	.	.	.
Investigations	Activated partial thromboplastin time	1	1	.	.	.	1	.	.	.	.
	Blood alkaline phosphatase	5	3	.	2	.	2	2	1	.	.
	Blood creatine phosphokinase	1	1	.	.	.	.	1	.	.	.
	Blood creatinine increased	20	14	.	6	.	4	10	5	1	.
	Gamma-glutamyltransferase	6	6	.	.	.	6	.	.	.	.
	Glomerular filtration rate	1	1	.	.	.	1	.	.	.	.
	Granulocytes abnormal	239	226	.	13	.	82	118	36	3	.
	Haemoglobin decreased	1	1	.	.	.	.	1	.	.	.
	Lipase increased	1	.	.	1	.	.	.	.	1	.
	Liver function test abnormal	34	31	.	3	.	19	10	5	.	.
	Low density lipoprotein abnormal	1	1	.	.	.	.	1	.	.	.
	Low density lipoprotein increased	6	6	.	.	.	.	1	.	5	.
	Neutrophil count	2	2	.	.	.	.	.	2	.	.

Exhibit 7-4A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Neutrophil count decreased	3	3	.	.	.	.	.	3	.	.
	Weight decreased	2	2	.	.	.	.	1	1	.	.
Metabolism and nutrition disorders	Decreased appetite	1	1	.	.	.	.	.	1	.	.
	Dehydration	6	4	1	1	.	1	1	3	1	.
	Hyperglycaemia	6	.	.	6	.	.	.	.	6	.
	Hyperkalaemia	10	10	.	.	.	6	3	.	1	.
	Hypoglycaemia	7	7	.	.	.	3	4	.	.	.
	Hypokalaemia	8	7	.	1	.	.	6	2	.	.
	Hypomagnesaemia	1	1	.	.	.	.	1	.	.	.
	Hyponatraemia	1	1	.	.	.	1	.	.	.	.
	Hypophosphataemia	6	5	.	1	.	1	5	.	.	.
	Ketoacidosis	2	1	.	1	.	1	1	.	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Arthritis	2	2	.	.	.	.	1	1	.	.
	Muscle necrosis	1	1	.	.	.	.	1	.	.	.
	Muscular weakness	6	6	.	.	.	.	6	.	.	.
	Musculoskeletal disorder	3	3	.	.	.	1	2	.	.	.
	Myositis	1	1	.	.	.	.	1	.	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	5	5	.	.	.	.	2	2	1	.
	Lobular breast carcinoma in situ	1	1	.	.	.	.	1	.	.	.
	Metastases	1	1	.	.	.	.	1	.	.	.
	Neoplasm malignant	28	17	1	10	.	15	11	2	.	.
	Papillary thyroid cancer	2	1	1	.	.	.	2	.	.	.
	Squamous cell carcinoma	7	3	.	4	.	.	6	1	.	.

Exhibit 7-4A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

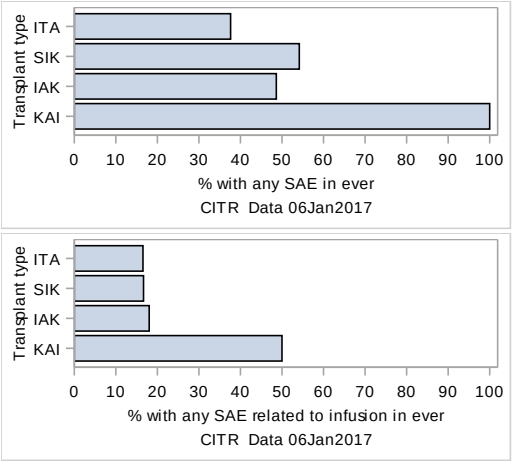
			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Treatment related secondary malignancy	1	1	.	.	.	.	1	.	.	.
Nervous system disorders	Cognitive disorder	1	1	.	.	.	1	.	.	.	.
	Convulsion	1	1	.	.	.	.	.	.	1	.
	Dizziness	2	2	.	.	.	.	2	.	.	.
	Headache	2	2	.	.	.	.	.	1	1	.
	Migraine	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
	Syncope	1	1	.	.	.	.	.	1	.	.
	Tremor	4	4	.	.	.	2	.	2	.	.
Psychiatric disorders	Confusional state	1	1	.	.	.	.	.	1	.	.
	Insomnia	2	2	.	.	.	1	1	.	.	.
	Mood altered	2	2	.	.	.	1	1	.	.	.
	Psychotic disorder	1	1	.	.	.	1	.	.	.	.
Renal and urinary disorders	Micturition urgency	1	1	.	.	.	.	1	.	.	.
	Peylonepr hitis	1	1	.	.	.	.	.	.	1	.
	Proteinuria	5	4	.	1	.	1	4	.	.	.
	Pyelonephritis	1	.	.	1	.	.	1	.	.	.
	Renal disorder	3	2	.	1	.	2	1	.	.	.
	Renal failure	18	9	1	7	1	11	5	2	.	.
	Tubulointerstitial nephritis	1	1	.	.	.	.	.	1	.	.
	Urinary bladder haemorrhage	3	2	.	1	.	.	2	1	.	.
Reproductive system and breast disorders	Lactation disorder	1	1	.	.	.	.	1	.	.	.
	Ovarian cyst ruptured	1	.	.	.	1	.	1	.	.	.
	Sexual dysfunction	4	4	.	.	.	2	2	.	.	.

Exhibit 7-4A3 (continued)
Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	.	1	.	.	1	.	.	.	.
	Aspiration	1	1	.	.	.	.	.	1	.	.
	Cough	3	1	.	2	.	1	1	1	.	.
	Dyspnoea	2	2	.	.	.	.	2	.	.	.
	Haemothorax	1	1	.	.	.	1	.	.	.	.
	Hypoxia	1	1	.	.	.	.	.	1	.	.
	Lung disorder	6	4	.	2	.	1	3	2	.	.
	Lung infiltration	4	4	.	.	.	.	.	4	.	.
	Pleural effusion	1	1	.	.	.	.	.	1	.	.
	Pneumonitis	5	3	.	2	.	3	2	.	.	.
Skin and subcutaneous tissue disorders	Actinic keratosis	1	1	.	.	.	.	1	.	.	.
	Acute febrile neutrophilic dermatosis	1	1	.	.	.	.	.	1	.	.
	Exfoliative rash	6	6	.	.	.	2	2	2	.	.
	Pruritus	1	1	.	.	.	.	.	1	.	.
	Rash	1	1	.	.	.	.	.	1	.	.
	Skin disorder	4	4	.	.	.	2	2	.	.	.
Surgical and medical procedures	Hysterectomy	1	.	.	.	1	.	1	.	.	.
	Surgery	1	.	.	1	.	.	.	1	.	.
Vascular disorders	Haematoma	2	2	.	.	.	1	.	1	.	.
	Hypertension	6	4	.	2	.	1	5	.	.	.
	Peripheral ischaemia	1	.	.	1	.	.	1	.	.	.
	Thrombosis	1	1	.	.	.	1	.	.	.	.

Exhibit 7-4B1
Recipients with a Serious Adverse Event (SAE) Any Time Post Islet Transplant

Percent of Recipients with:	Type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE ever	330	37.6	13	54.2	89	48.6	2	100.0	110	52.9	153	56.5	103	42.6	61	17.9	7	29.2
Any SAE related to infusion ever	145	16.5	4	16.7	33	18.0	1	50.0	46	22.1	69	25.5	41	16.9	25	7.3	2	8.3
Any SAE related to IS ever	202	23.0	10	41.7	47	25.7	2	100.0	62	29.8	103	38.0	67	27.7	25	7.3	4	16.7
Any SAE related to both ever	46	5.2	2	8.3	5	2.7	.	.	8	3.8	17	6.3	19	7.9	9	2.6	.	.
Any SAE related to neither ever	169	19.3	8	33.3	57	31.1	.	.	58	27.9	75	27.7	63	26.0	35	10.3	3	12.5



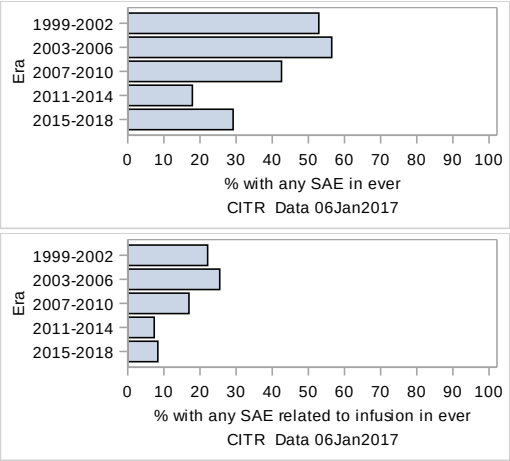


Exhibit 7-4B1 (continued)
Recipients with a Serious Adverse Event (SAE) Any Time Post Islet Transplant

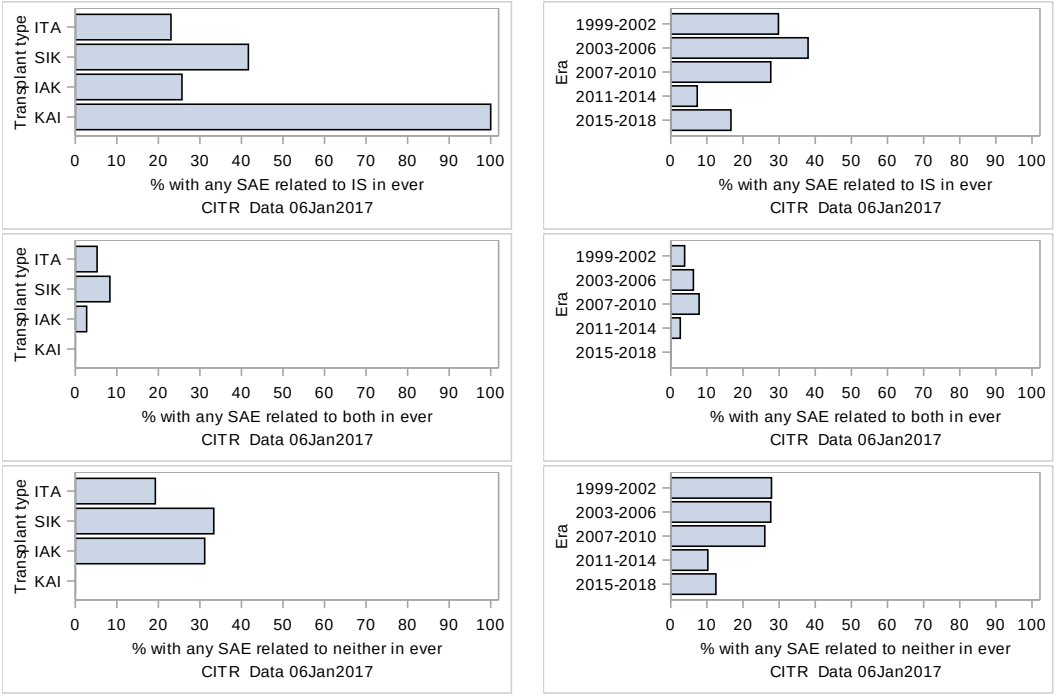


Exhibit 7-4B2
Serious Adverse Events (SAEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term										
Not yet coded	Not yet coded	9	6	1	2	.	1	2	4	2	.
Blood and lymphatic system disorders	Anaemia	8	5	.	2	1	1	4	2	1	.
	Lymphopenia	2	1	.	1	.	1	1	.	.	.
	Neutropenia	4	4	.	.	.	.	.	.	4	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
Endocrine disorders	Endocrine disorder	1	1	.	.	.	.	.	1	.	.
Eye disorders	Retinal haemorrhage	1	1	.	.	.	.	.	.	1	.
	Vitreous haemorrhage	2	2	.	.	.	.	.	1	1	.
Gastrointestinal disorders	Ascites	2	2	.	.	.	1	1	.	.	.
	Diarrhoea	3	3	.	.	.	.	1	1	1	.
	Gastrointestinal disorder	5	3	2	.	.	.	2	.	2	1
	Gastrointestinal haemorrhage	5	2	.	3	.	2	3	.	.	.
	Gastrointestinal obstruction	2	2	.	.	.	1	1	.	.	.
	Gastrointestinal perforation	2	2	.	.	.	1	.	1	.	.
	Ileus	2	2	.	.	.	1	1	.	.	.
	Nausea	2	2	.	.	.	.	1	1	.	.
	Peritoneal haemorrhage	41	30	2	9	.	13	14	10	4	.
	Vomiting	3	3	.	.	.	.	.	3	.	.

Exhibit 7-4B2 (continued)
Serious Adverse Events (SAEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
General disorders and administration site conditions	Death	1	1	.	.	.	.	.	1	.	.
	Pain	14	14	.	.	.	6	4	3	1	.
Hepatobiliary disorders	Biliary tract disorder	1	1	.	.	.	.	1	.	.	.
	Cholecystitis	3	2	.	1	.	1	1	1	.	.
	Hepatic haematoma	1	1	.	.	.	.	1	.	.	.
	Hepatic haemorrhage	2	2	.	.	.	.	.	.	2	.
	Portal vein thrombosis	11	10	.	1	.	4	5	2	.	.
Immune system disorders	Graft versus host disease	2	2	.	.	.	.	.	.	2	.
	Hypersensitivity	3	3	.	.	.	.	1	2	.	.
	Sensitisation	1	.	.	1	.	.	.	.	1	.
Infections and infestations	Cytomegalovirus infection	1	1	.	.	.	.	.	.	1	.
	Infection	9	8	.	1	.	2	5	2	.	.
	Influenza	1	1	.	.	.	.	.	1	.	.
	Pneumonia	1	1	.	.	.	.	.	1	.	.
	Respiratory tract infection	1	1	.	.	.	.	.	1	.	.
Injury, poisoning and procedural complications	Fracture	1	1	.	.	.	.	.	1	.	.
	Post procedural haemorrhage	1	1	.	.	.	.	.	1	.	.
	Transplant failure	1	1	.	.	.	.	.	.	1	.
	Wound complication	3	3	.	.	.	.	1	2	.	.
Investigations	Blood alkaline phosphatase	14	14	.	.	.	4	10	.	.	.

Exhibit 7-4B2 (continued)
Serious Adverse Events (SAEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Blood creatinine increased	5	2	.	3	.	.	4	1	.	.
	Granulocytes abnormal	2	2	.	.	.	.	2	.	.	.
	Hepatic enzyme increased	2	2	.	.	.	.	.	.	2	.
	Liver function test abnormal	36	36	.	.	.	19	17	.	.	.
	Low density lipoprotein increased	1	1	.	.	.	.	.	.	1	.
Metabolism and nutrition disorders	Dehydration	1	1	.	.	.	.	1	.	.	.
	Hyperglycaemia	7	1	.	6	.	.	.	.	7	.
	Hypoglycaemia	5	3	.	2	.	1	1	3	.	.
	Ketoacidosis	3	3	.	.	.	1	.	2	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Musculoskeletal pain	2	2	.	.	.	.	.	.	2	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1	1	.	.	.	.	1	.	.	.
Nervous system disorders	Migraine	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
	Syncope	1	1	.	.	.	.	.	1	.	.
Renal and urinary disorders	Renal disorder	1	.	.	1	.	.	1	.	.	.
	Renal failure	1	1	.	.	.	.	1	.	.	.
	Urinary bladder haemorrhage	1	1	.	.	.	.	.	1	.	.
	Aspiration	1	1	.	.	.	.	.	1	.	.

Exhibit 7-4B2 (continued)
Serious Adverse Events (SAEs) RELATED TO PROCEDURE
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Respiratory, thoracic and mediastinal disorders	Haemothorax	2	1	.	1	.	1	1	.	.	.
	Lung disorder	1	1	.	.	.	.	.	1	.	.
	Pleural effusion	1	.	.	1	.	.	1	.	.	.
Surgical and medical procedures	Incisional hernia repair	1	1	.	.	.	.	.	1	.	.
Vascular disorders	Haematoma	12	9	.	3	.	3	6	.	3	.
	Haemorrhage	12	7	.	5	.	1	4	3	3	1
	Hypotension	1	1	.	.	.	.	.	1	.	.
	Thrombosis	1	.	.	1	.	1	.	.	.	.

Exhibit 7-4B3
Serious Adverse Events (SAEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
System/Organ Class	Preferred term										
Not yet coded	Not yet coded	20	14	2	3	1	1	2	13	3	1
Blood and lymphatic system disorders	Afebrile neutropenia	2	2	.	.	.	.	.	1	1	.
	Agranulocytosis	1	.	1	.	.	.	1	.	.	.
	Anaemia	16	13	.	3	.	4	7	4	1	.
	Blood disorder	1	1	.	.	.	.	.	1	.	.
	Febrile neutropenia	4	4	.	.	.	.	.	4	.	.
	Haemolysis	1	1	.	.	.	.	1	.	.	.
	Leukopenia	4	.	1	3	.	.	.	.	4	.
	Lymphopenia	11	8	2	1	.	1	7	2	1	.
	Neutropenia	16	16	.	.	.	.	.	3	13	.
	Pancytopenia	1	1	.	.	.	.	.	.	1	.
	Platelet disorder	1	1	.	.	.	.	1	.	.	.
	Thrombocytopenia	5	5	.	.	.	.	.	5	.	.
Cardiac disorders	Arrhythmia supraventricular	1	1	.	.	.	.	.	1	.	.
	Myocardial ischaemia	1	1	.	.	.	.	1	.	.	.
	Pericardial effusion	1	1	.	.	.	.	1	.	.	.
	Pericarditis	1	1	.	.	.	.	1	.	.	.
Eye disorders	Eye disorder	2	2	.	.	.	.	2	.	.	.
	Ocular surface disease	1	.	.	1	.	.	1	.	.	.
	Uveitis	1	.	.	1	.	.	.	1	.	.

Exhibit 7-4B3 (continued)
Serious Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Gastrointestinal disorders	Ascites	2	2	.	.	.	1	1	.	.	.
	Barrett's oesophagus	1	1	.	.	.	.	1	.	.	.
	Colitis	5	4	.	1	.	.	4	1	.	.
	Constipation	1	1	.	.	.	.	.	1	.	.
	Diarrhoea	31	28	.	3	.	5	12	12	2	.
	Dysphagia	1	1	.	.	.	.	1	.	.	.
	Gastritis	1	1	.	.	.	1	.	.	.	.
	Gastrointestinal disorder	13	6	2	5	.	.	11	.	2	.
	Gastrointestinal obstruction	5	1	.	4	.	.	5	.	.	.
	Mouth ulceration	1	.	.	1	.	.	1	.	.	.
	Nausea	6	5	.	1	.	1	2	1	1	1
	Peritoneal haemorrhage	3	2	.	1	.	3	.	.	.	.
	Vomiting	17	15	.	2	.	3	3	7	1	3
General disorders and administration site conditions	Chest pain	1	1	.	.	.	.	.	1	.	.
	Death	3	2	.	1	.	1	1	1	.	.
	Fatigue	2	2	.	.	.	1	.	1	.	.
	Mucosal inflammation	10	7	.	2	1	2	6	1	.	1
	Oedema peripheral	2	1	.	1	.	.	1	1	.	.
	Pain	12	10	.	2	.	3	8	.	1	.
	Pyrexia	5	4	.	1	.	3	1	1	.	.
	Systemic inflammatory response syndrome	3	.	.	3	.	.	1	2	.	.
Hepatobiliary disorders	Cholecystitis	1	1	.	.	.	1	.	.	.	.

Exhibit 7-4B3 (continued)
Serious Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Immune system disorders	Autoimmune disorder	1	1	.	.	.	.	.	1	.	.
	Graft versus host disease	2	2	.	.	.	.	.	.	2	.
	Hypersensitivity	9	7	.	2	.	1	3	4	1	.
	Serum sickness	2	2	.	.	.	.	.	1	.	1
Infections and infestations	Arthritis bacterial	1	1	.	.	.	.	1	.	.	.
	Cytomegalovirus infection	1	1	.	.	.	.	1	.	.	.
	Gastrointestinal infection	1	1	.	.	.	.	.	.	1	.
	Infection	53	40	1	11	1	19	24	9	1	.
	Influenza	1	1	.	.	.	.	.	1	.	.
	Opportunistic infection	2	1	.	1	.	.	.	2	.	.
	Pneumonia	13	7	3	3	.	1	7	5	.	.
	Pyelonephritis	2	1	.	1	.	.	1	.	1	.
	Renal graft infection	1	.	1	.	.	.	.	.	1	.
	Respiratory tract infection	1	1	.	.	.	.	.	1	.	.
	Urinary tract infection	1	.	.	1	.	.	.	.	1	.
	Urosepsis	1	.	1	.	.	.	.	.	1	.
	Vestibular neuronitis	1	1	.	.	.	.	.	1	.	.
	Viral encephalitis	1	1	.	.	.	1	.	.	.	.
Injury, poisoning and procedural complications	Fracture	3	2	.	.	1	2	.	1	.	.
	Injury	1	.	.	1	.	.	1	.	.	.
	Limb injury	1	1	.	.	.	.	.	1	.	.
	Toxicity to various agents	2	2	.	.	.	.	.	1	1	.
	Transplant failure	1	1	.	.	.	.	.	.	1	.

Exhibit 7-4B3 (continued)
Serious Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Wound complication	4	3	1	.	.	3	1	.	.	.
Investigations	Blood alkaline phosphatase	1	1	.	.	.	1	.	.	.	.
	Blood creatine phosphokinase	1	1	.	.	.	.	1	.	.	.
	Blood creatinine increased	20	14	.	6	.	4	10	5	1	.
	Granulocytes abnormal	64	56	.	8	.	22	26	13	3	.
	Haemoglobin decreased	1	1	.	.	.	.	1	.	.	.
	Liver function test abnormal	3	3	.	.	.	1	2	.	.	.
	Low density lipoprotein increased	1	1	.	.	.	.	.	.	1	.
	Neutrophil count	1	1	.	.	.	.	.	1	.	.
	Neutrophil count decreased	1	1	.	.	.	.	.	1	.	.
	Weight decreased	1	1	.	.	.	.	1	.	.	.
Metabolism and nutrition disorders	Dehydration	5	4	1	.	.	1	.	3	1	.
	Hyperglycaemia	6	.	.	6	.	.	.	.	6	.
	Hypoglycaemia	3	3	.	.	.	1	2	.	.	.
	Hypokalaemia	1	1	.	.	.	.	1	.	.	.
	Hypomagnesaemia	1	1	.	.	.	.	1	.	.	.
	Hypophosphataemia	1	1	.	.	.	.	1	.	.	.
	Ketoacidosis	2	1	.	1	.	1	1	.	.	.
Musculoskeletal and connective tissue disorders	Arthralgia	1	1	.	.	.	.	.	.	1	.
	Arthritis	2	2	.	.	.	.	1	1	.	.
	Muscle necrosis	1	1	.	.	.	.	1	.	.	.
	Musculoskeletal disorder	3	3	.	.	.	1	2	.	.	.

Exhibit 7-4B3 (continued)
Serious Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

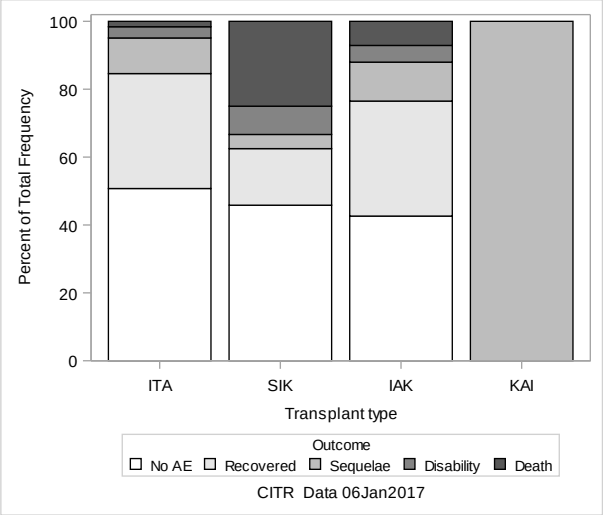
			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lobular breast carcinoma in situ	1	1	.	.	.	.	1	.	.	.
	Metastases	1	1	.	.	.	.	1	.	.	.
	Neoplasm malignant	17	12	1	4	.	8	8	1	.	.
	Papillary thyroid cancer	2	1	1	.	.	.	2	.	.	.
	Squamous cell carcinoma	2	.	.	2	.	.	2	.	.	.
	Treatment related secondary malignancy	1	1	.	.	.	.	1	.	.	.
Nervous system disorders	Cognitive disorder	1	1	.	.	.	1	.	.	.	.
	Convulsion	1	1	.	.	.	.	.	.	1	.
	Headache	2	2	.	.	.	.	.	1	1	.
	Migraine	2	2	.	.	.	.	.	2	.	.
	Neuroleptic malignant syndrome	1	1	.	.	.	.	.	.	1	.
	Syncope	1	1	.	.	.	.	.	1	.	.
	Tremor	1	1	.	.	.	1	.	.	.	.
Psychiatric disorders	Confusional state	1	1	.	.	.	.	.	1	.	.
	Insomnia	1	1	.	.	.	1	.	.	.	.
	Mood altered	2	2	.	.	.	1	1	.	.	.
	Psychotic disorder	1	1	.	.	.	1	.	.	.	.
Renal and urinary disorders	Peylonepr hitis	1	1	.	.	.	.	.	.	1	.
	Proteinuria	2	1	.	1	.	.	2	.	.	.
	Pyelonephritis	1	.	.	1	.	.	1	.	.	.
	Renal disorder	3	2	.	1	.	2	1	.	.	.
	Renal failure	17	9	1	7	.	10	5	2	.	.
	Tubulointerstitial nephritis	1	1	.	.	.	.	.	1	.	.

Exhibit 7-4B3 (continued)
Serious Adverse Events (AEs) RELATED TO IMMUNOSUPPRESSION
Any Time Post Islet Transplantation

			Transplant type				Era				
		Overall	ITA	SIK	IAK	KAI	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
		N	N	N	N	N	N	N	N	N	N
	Urinary bladder haemorrhage	2	1	.	1	.	.	1	1	.	.
Reproductive system and breast disorders	Lactation disorder	1	1	.	.	.	.	1	.	.	.
	Ovarian cyst ruptured	1	.	.	.	1	.	1	.	.	.
	Sexual dysfunction	4	4	.	.	.	2	2	.	.	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	.	1	.	.	1	.	.	.	.
	Aspiration	1	1	.	.	.	.	.	1	.	.
	Cough	2	.	.	2	.	1	1	.	.	.
	Dyspnoea	1	1	.	.	.	.	1	.	.	.
	Haemothorax	1	1	.	.	.	1	.	.	.	.
	Lung disorder	6	4	.	2	.	1	3	2	.	.
	Lung infiltration	4	4	.	.	.	.	.	4	.	.
	Pleural effusion	1	1	.	.	.	.	.	1	.	.
	Pneumonitis	3	1	.	2	.	3	.	.	.	.
Skin and subcutaneous tissue disorders	Acute febrile neutrophilic dermatosis	1	1	.	.	.	.	.	1	.	.
	Exfoliative rash	1	1	.	.	.	.	.	1	.	.
	Rash	1	1	.	.	.	.	.	1	.	.
Surgical and medical procedures	Hysterectomy	1	.	.	.	1	.	1	.	.	.
	Surgery	1	.	.	1	.	.	.	1	.	.
Vascular disorders	Haematoma	1	1	.	.	.	1	.	.	.	.
	Hypertension	1	1	.	.	.	1	.	.	.	.
	Peripheral ischaemia	1	.	.	1	.	.	1	.	.	.

Exhibit 7-5A
Worst Outcome of Adverse Events (per Recipient)

	Total		Transplant type								Era									
			ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	1086	100.0	877	100.0	24	100.0	183	100.0	2	100.0	208	100.0	271	100.0	242	100.0	341	100.0	24	100.0
No AE	534	49.2	445	50.7	11	45.8	78	42.6	.	.	71	34.1	78	28.8	101	41.7	267	78.3	17	70.8
Recovered	363	33.4	297	33.9	4	16.7	62	33.9	.	.	89	42.8	129	47.6	87	36.0	52	15.2	6	25.0
Sequelae	116	10.7	92	10.5	1	4.2	21	11.5	2	100.0	22	10.6	43	15.9	34	14.0	16	4.7	1	4.2
Disability	40	3.7	29	3.3	2	8.3	9	4.9	.	.	7	3.4	13	4.8	15	6.2	5	1.5	.	.
Death	33	3.0	14	1.6	6	25.0	13	7.1	.	.	19	9.1	8	3.0	5	2.1	1	0.3	.	.



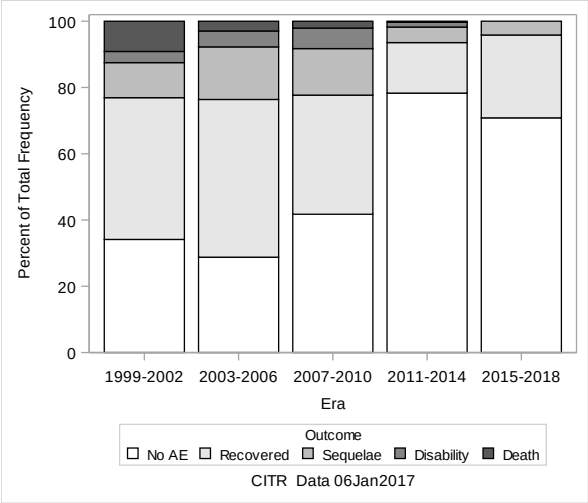
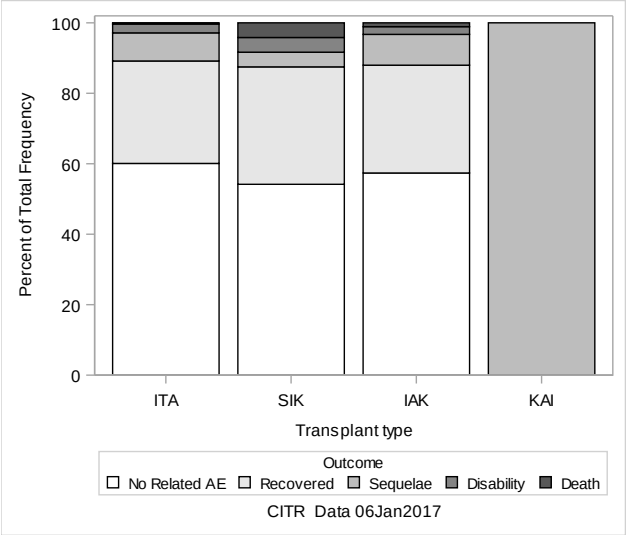


Exhibit 7-5B
Worst Outcome of Infusion or Immunosuppression Related Adverse Events (per Recipient)

	Total		Transplant type								Era									
			ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total	1086	100.0	877	100.0	24	100.0	183	100.0	2	100.0	208	100.0	271	100.0	242	100.0	341	100.0	24	100.0
No Related AE	645	59.4	527	60.1	13	54.2	105	57.4	.	.	94	45.2	95	35.1	138	57.0	299	87.7	19	79.2
Recovered	319	29.4	255	29.1	8	33.3	56	30.6	.	.	89	42.8	131	48.3	65	26.9	29	8.5	5	20.8
Sequelae	89	8.2	70	8.0	1	4.2	16	8.7	2	100.0	16	7.7	38	14.0	26	10.7	9	2.6	.	.
Disability	27	2.5	22	2.5	1	4.2	4	2.2	.	.	6	2.9	6	2.2	11	4.5	4	1.2	.	.
Death	6	0.6	3	0.3	1	4.2	2	1.1	.	.	3	1.4	1	0.4	2	0.8	.	.	.	.



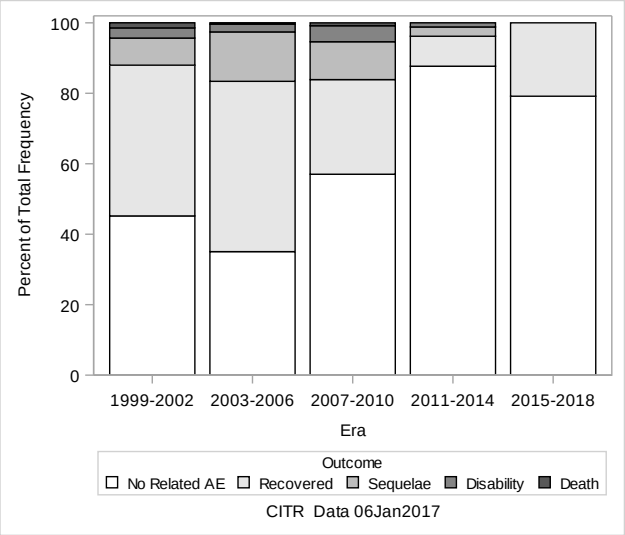


Exhibit 7-6A
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

	Total	Outcome				
		0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
	N	%	%	%	%	%
Total adverse events following islet transplantation	2189	1.7	82.6	11.6	2.5	1.5

		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**	254	.	94.1	5.5	0.4	.
2	**Hypoglycaemia**	136	2.9	94.1	2.2	0.7	.
3	**Liver function test abnormal**	126	0.8	96.0	3.2	.	.
4	**Infection**	104	.	78.8	15.4	3.8	1.9
5	**Ketoacidosis**	100	.	98.0	2.0	.	.
6	**Pain**	72	.	80.6	19.4	.	.
7	**Lymphopenia**	64	1.6	90.6	7.8	.	.
8	**Diarrhoea**	61	.	78.7	18.0	3.3	.
9	**Peritoneal haemorrhage**	49	.	91.8	8.2	.	.
10	**Vomiting**	46	.	87.0	13.0	.	.
11	**Anaemia**	41	.	97.6	.	2.4	.
12	**Neutropenia**	38	.	73.7	26.3	.	.
13	**Blood creatinine increased**	34	.	70.6	29.4	.	.
14	**Neoplasm malignant**	29	3.4	72.4	20.7	3.4	.
15	**Hypersensitivity**	26	3.8	50.0	42.3	.	3.8
16	**Hyponatraemia**	25	.	92.0	8.0	.	.
17	**Gastrointestinal disorder**	23	.	95.7	4.3	.	.
18	**Death**	22	.	.	.	.	100.0
19	**Renal failure**	22	.	63.6	22.7	13.6	.
20	**Blood alkaline phosphatase**	21	.	90.5	9.5	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
21	Mucosal inflammation	20	.	85.0	10.0	5.0	.
22	Myocardial ischaemia	18	5.6	61.1	22.2	11.1	.
23	Neutrophil count decreased	18	.	100.0	.	.	.
24	Hypokalaemia	17	.	94.1	.	5.9	.
25	Hypophosphataemia	17	.	100.0	.	.	.
26	Pneumonia	17	5.9	70.6	17.6	5.9	.
27	Fatigue	15	.	93.3	.	6.7	.
28	Haematoma	15	.	86.7	13.3	.	.
29	Haemorrhage	15	.	86.7	6.7	.	6.7
30	Hyperglycaemia	15	.	60.0	26.7	13.3	.
31	Hyperkalaemia	15	.	86.7	13.3	.	.
32	Eye disorder	14	.	64.3	7.1	28.6	.
33	Cholecystitis	13	.	92.3	.	7.7	.
34	Gamma-glutamyltransferase	13	.	84.6	15.4	.	.
35	Hypertension	13	.	69.2	30.8	.	.
36	Low density lipoprotein increased	13	7.7	69.2	23.1	.	.
37	Portal vein thrombosis	13	.	84.6	7.7	7.7	.
38	Dehydration	12	.	91.7	8.3	.	.
39	Fracture	12	.	58.3	41.7	.	.
40	Leukopenia	12	.	83.3	16.7	.	.
41	Nausea	12	.	91.7	8.3	.	.
42	Wound complication	12	.	100.0	.	.	.
43	Gastrointestinal obstruction	11	9.1	54.5	36.4	.	.
44	Syncope	11	.	90.9	.	9.1	.
45	Hepatic haemorrhage	10	70.0	30.0	.	.	.
46	Squamous cell carcinoma	10	30.0	70.0	.	.	.
47	Alanine aminotransferase increased	9	.	100.0	.	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
48	**Lung disorder**	9	.	77.8	22.2	.	.
49	**Pneumonitis**	9	.	88.9	.	.	11.1
50	**Surgery**	9	.	66.7	11.1	22.2	.
51	**Colitis**	8	.	75.0	25.0	.	.
52	**Muscular weakness**	8	.	62.5	37.5	.	.
53	**Oedema peripheral**	8	.	100.0	.	.	.
54	**Renal disorder**	8	.	87.5	.	12.5	.
55	**Sexual dysfunction**	8	.	100.0	.	.	.
56	**Vitreous haemorrhage**	8	.	37.5	25.0	37.5	.
57	**Aspartate aminotransferase increased**	7	.	100.0	.	.	.
58	**Basal cell carcinoma**	7	28.6	57.1	14.3	.	.
59	**Cerebral ischaemia**	7	14.3	14.3	42.9	14.3	14.3
60	**Exfoliative rash**	7	.	85.7	14.3	.	.
61	**Pyrexia**	7	.	100.0	.	.	.
62	**Blood disorder**	6	.	100.0	.	.	.
63	**Chest pain**	6	.	66.7	33.3	.	.
64	**Dyspnoea**	6	.	83.3	.	16.7	.
65	**Febrile neutropenia**	6	.	83.3	16.7	.	.
66	**Low density lipoprotein abnormal**	6	.	66.7	33.3	.	.
67	**Neutrophil count**	6	.	100.0	.	.	.
68	**Ascites**	5	.	100.0	.	.	.
69	**Dizziness**	5	.	100.0	.	.	.
70	**Gastrointestinal haemorrhage**	5	.	100.0	.	.	.
71	**Lipase**	5	.	100.0	.	.	.
72	**Musculoskeletal disorder**	5	.	60.0	20.0	20.0	.
73	**Platelet disorder**	5	.	100.0	.	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
74	Proteinuria	5	.	20.0	80.0	.	.
75	Skin disorder	5	20.0	80.0	.	.	.
76	Thrombocytopenia	5	.	20.0	80.0	.	.
77	Tremor	5	20.0	80.0	.	.	.
78	Urinary bladder haemorrhage	5	.	80.0	20.0	.	.
79	Appendicitis	4	.	50.0	50.0	.	.
80	Cognitive disorder	4	.	75.0	.	25.0	.
81	Confusional state	4	25.0	50.0	25.0	.	.
82	Endocrine disorder	4	.	100.0	.	.	.
83	Headache	4	.	100.0	.	.	.
84	Hepatic enzyme increased	4	.	100.0	.	.	.
85	Hip fracture	4	.	75.0	25.0	.	.
86	Hypoalbuminaemia	4	.	100.0	.	.	.
87	Hypotension	4	.	75.0	25.0	.	.
88	Hypoxia	4	.	100.0	.	.	.
89	Lung infiltration	4	.	25.0	75.0	.	.
90	Migraine	4	.	100.0	.	.	.
91	Mood altered	4	.	25.0	75.0	.	.
92	Pericardial effusion	4	.	100.0	.	.	.
93	Peripheral ischaemia	4	.	50.0	50.0	.	.
94	Pleural effusion	4	.	75.0	25.0	.	.
95	Post transplant lymphoproliferative disorder	4	.	25.0	75.0	.	.
96	Retinal detachment	4	.	50.0	25.0	25.0	.
97	Thrombosis	4	.	75.0	25.0	.	.
98	Transaminases	4	.	100.0	.	.	.
99	Albuminuria	3	.	33.3	66.7	.	.
100	Anxiety	3	.	33.3	33.3	33.3	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
101	Arrhythmia supraventricular	3	.	100.0	.	.	.
102	Arthritis	3	.	.	.	100.0	.
103	Cough	3	.	100.0	.	.	.
104	Gamma-glutamyltransferase increased	3	.	100.0	.	.	.
105	Hepatic haematoma	3	.	66.7	33.3	.	.
106	Mouth ulceration	3	.	100.0	.	.	.
107	Pancreatitis	3	.	66.7	33.3	.	.
108	Pulmonary hypertension	3	33.3	33.3	33.3	.	.
109	Pyelonephritis	3	.	33.3	66.7	.	.
110	Serum sickness	3	.	66.7	33.3	.	.
111	Systemic inflammatory response syndrome	3	.	100.0	.	.	.
112	Transaminases increased	3	.	100.0	.	.	.
113	Weight decreased	3	.	100.0	.	.	.
114	Abdominal hernia repair	2	.	50.0	50.0	.	.
115	Activated partial thromboplastin time	2	.	100.0	.	.	.
116	Acute respiratory distress syndrome	2	.	.	.	.	100.0
117	Afebrile neutropenia	2	.	.	100.0	.	.
118	Appendicitis perforated	2	.	100.0	.	.	.
119	Aspiration	2	.	100.0	.	.	.
120	Ataxia	2	.	100.0	.	.	.
121	Bacillus infection	2	.	100.0	.	.	.
122	Blood amylase	2	.	100.0	.	.	.
123	Blood creatine phosphokinase increased	2	.	50.0	50.0	.	.
124	Blood phosphorus decreased	2	.	100.0	.	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
125	Blood potassium increased	2	.	100.0	.	.	.
126	Cardiac disorder	2	.	100.0	.	.	.
127	Cardio-respiratory arrest	2	.	50.0	.	.	50.0
128	Chest discomfort	2	.	50.0	50.0	.	.
129	Constipation	2	.	50.0	.	50.0	.
130	Cystitis	2	.	100.0	.	.	.
131	Cytomegalovirus infection	2	.	100.0	.	.	.
132	Decreased appetite	2	.	100.0	.	.	.
133	Decubitus ulcer	2	.	.	100.0	.	.
134	Dysphagia	2	.	50.0	50.0	.	.
135	Gastritis	2	.	100.0	.	.	.
136	Gastroenteritis viral	2	50.0	50.0	.	.	.
137	Gastrointestinal perforation	2	.	100.0	.	.	.
138	Glomerular filtration rate	2	.	50.0	50.0	.	.
139	Graft versus host disease	2	.	.	100.0	.	.
140	Haemoglobin decreased	2	.	100.0	.	.	.
141	Haemothorax	2	.	100.0	.	.	.
142	Hypocalcaemia	2	.	100.0	.	.	.
143	Ileus	2	.	100.0	.	.	.
144	Incisional hernia repair	2	50.0	50.0	.	.	.
145	Injection site reaction	2	.	100.0	.	.	.
146	Injury	2	.	50.0	50.0	.	.
147	Insomnia	2	.	50.0	50.0	.	.
148	Musculoskeletal pain	2	.	50.0	50.0	.	.
149	Myocarditis	2	.	100.0	.	.	.
150	Opportunistic infection	2	.	100.0	.	.	.
151	Papillary thyroid cancer	2	.	50.0	.	50.0	.
152	Psychogenic seizure	2	.	50.0	50.0	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
153	Sensitisation	2	.	.	50.0	50.0	.
154	Spinal cord compression	2	50.0	50.0	.	.	.
155	Toxicity to various agents	2	.	100.0	.	.	.
156	Upper limb fracture	2	.	100.0	.	.	.
157	Urinary tract infection	2	.	50.0	50.0	.	.
158	Abdominal pain	1	.	100.0	.	.	.
159	Acne	1	.	100.0	.	.	.
160	Actinic keratosis	1	.	100.0	.	.	.
161	Activated partial thromboplastin time prolonged	1	.	100.0	.	.	.
162	Acute febrile neutrophilic dermatosis	1	.	.	.	100.0	.
163	Acute kidney injury	1	.	100.0	.	.	.
164	Acute myocardial infarction	1	.	.	.	.	100.0
165	Agranulocytosis	1	.	100.0	.	.	.
166	Alcoholism	1	.	100.0	.	.	.
167	Arthralgia	1	.	100.0	.	.	.
168	Arthritis bacterial	1	.	.	.	100.0	.
169	Arthropathy	1	.	100.0	.	.	.
170	Atrioventricular block	1	.	.	100.0	.	.
171	Autoimmune disorder	1	.	100.0	.	.	.
172	Bacillus test positive	1	.	100.0	.	.	.
173	Back pain	1	.	100.0	.	.	.
174	Barrett's oesophagus	1	.	100.0	.	.	.
175	Biliary tract disorder	1	.	100.0	.	.	.
176	Blood albumin decreased	1	.	100.0	.	.	.
177	Blood bilirubin	1	.	100.0	.	.	.
178	Blood creatine phosphokinase	1	.	100.0	.	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
179	Breast reconstruction	1	.	100.0	.	.	.
180	Cerebellar ischaemia	1	.	.	100.0	.	.
181	Cholecystitis acute	1	.	100.0	.	.	.
182	Clostridium difficile colitis	1	.	100.0	.	.	.
183	Convulsion	1	.	.	100.0	.	.
184	Cytokine release syndrome	1	.	100.0	.	.	.
185	Dermatitis	1	.	100.0	.	.	.
186	Dyskinesia	1	.	100.0	.	.	.
187	Ear infection	1	.	.	100.0	.	.
188	Enteritis	1	.	100.0	.	.	.
189	Enterocolitis infectious	1	.	100.0	.	.	.
190	Frontotemporal dementia	1	.	100.0	.	.	.
191	Gastrointestinal infection	1	.	100.0	.	.	.
192	H1N1 influenza	1	100.0	.	.	.	.
193	Haemoglobinuria	1	.	100.0	.	.	.
194	Haemolysis	1	.	100.0	.	.	.
195	Haemorrhoids	1	.	100.0	.	.	.
196	Hearing impaired	1	.	.	100.0	.	.
197	Hepatic artery stenosis	1	.	.	.	100.0	.
198	Herpes simplex	1	.	100.0	.	.	.
199	Hypereosinophilia	1	.	100.0	.	.	.
200	Hypernatraemia	1	.	100.0	.	.	.
201	Hypoglycaemic seizure	1	.	100.0	.	.	.
202	Hypomagnesaemia	1	.	100.0	.	.	.
203	Hypothyroidism	1	100.0	.	.	.	.
204	Hysterectomy	1	.	100.0	.	.	.
205	Ileostomy	1	.	100.0	.	.	.
206	Influenza	1	.	.	.	100.0	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
207	Influenza like illness	1	.	100.0	.	.	.
208	International normalised ratio increased	1	.	100.0	.	.	.
209	Joint range of motion decreased	1	.	100.0	.	.	.
210	Laceration	1	.	100.0	.	.	.
211	Lactation disorder	1	.	100.0	.	.	.
212	Laryngitis	1	.	100.0	.	.	.
213	Laser therapy	1	.	100.0	.	.	.
214	Leukocytosis	1	.	100.0	.	.	.
215	Limb injury	1	.	.	.	100.0	.
216	Lipase increased	1	.	100.0	.	.	.
217	Lobular breast carcinoma in situ	1	.	100.0	.	.	.
218	Lymphatic disorder	1	.	100.0	.	.	.
219	Lymphoma	1	.	100.0	.	.	.
220	Metapneumovirus infection	1	.	.	.	100.0	.
221	Metastases	1	.	100.0	.	.	.
222	Micturition urgency	1	.	100.0	.	.	.
223	Mucinous adenocarcinoma of appendix	1	.	.	100.0	.	.
224	Muscle necrosis	1	.	100.0	.	.	.
225	Myositis	1	.	100.0	.	.	.
226	Nephrectomy	1	.	100.0	.	.	.
227	Neuroleptic malignant syndrome	1	.	100.0	.	.	.
228	Ocular surface disease	1	.	100.0	.	.	.
229	Oral pain	1	.	100.0	.	.	.
230	Ovarian cyst ruptured	1	.	.	100.0	.	.
231	Pancytopenia	1	.	100.0	.	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
232	Pericarditis	1	.	100.0	.	.	.
233	Periorbital cellulitis	1	.	100.0	.	.	.
234	Peripheral arterial occlusive disease	1	.	100.0	.	.	.
235	Peylonepr hitis	1	.	.	100.0	.	.
236	Pneumococcal infection	1	100.0	.	.	.	.
237	Post procedural haemorrhage	1	.	.	100.0	.	.
238	Presyncope	1	.	100.0	.	.	.
239	Pruritus	1	.	.	100.0	.	.
240	Psychotic disorder	1	.	100.0	.	.	.
241	Pulmonary oedema	1	100.0	.	.	.	.
242	Pulmonary tuberculosis	1	.	100.0	.	.	.
243	Rash	1	.	100.0	.	.	.
244	Renal failure acute	1	.	.	.	.	100.0
245	Renal graft infection	1	.	100.0	.	.	.
246	Respiratory tract infection	1	.	100.0	.	.	.
247	Retinal haemorrhage	1	.	.	.	100.0	.
248	Rheumatoid arthritis	1	.	100.0	.	.	.
249	Salmonellosis	1	.	100.0	.	.	.
250	Serotonin syndrome	1	.	.	.	100.0	.
251	Skin cancer	1	100.0	.	.	.	.
252	Small intestinal obstruction	1	.	100.0	.	.	.
253	Stomatitis	1	.	100.0	.	.	.
254	Tinnitus	1	.	.	100.0	.	.
255	Toe operation	1	.	100.0	.	.	.
256	Transplant failure	1	.	100.0	.	.	.
257	Treatment related secondary malignancy	1	.	100.0	.	.	.

Exhibit 7-6A (continued)
ALL Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
258	**Trigger finger**	1	.	.	100.0	.	.
259	**Troponin I**	1	.	100.0	.	.	.
260	**Troponin T**	1	.	100.0	.	.	.
261	**Tubulointerstitial nephritis**	1	.	100.0	.	.	.
262	**Ulcer**	1	.	100.0	.	.	.
263	**Urosepsis**	1	.	100.0	.	.	.
264	**Uveitis**	1	.	100.0	.	.	.
265	**Vestibular neuronitis**	1	.	.	.	100.0	.
266	**Viral encephalitis**	1	.	100.0	.	.	.
267	**Wound dehiscence**	1	.	100.0	.	.	.

Exhibit 7-6B
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

	Total	Outcome				
		0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
	N	%	%	%	%	%
Total adverse events following islet transplantation	1304	0.7	83.7	12.6	2.5	0.5

		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**	242	.	94.6	5.0	0.4	.
2	**Liver function test abnormal**	114	0.9	95.6	3.5	.	.
3	**Infection**	66	.	78.8	15.2	4.5	1.5
4	**Lymphopenia**	51	2.0	88.2	9.8	.	.
5	**Diarrhoea**	50	.	74.0	22.0	4.0	.
6	**Pain**	49	.	83.7	16.3	.	.
7	**Peritoneal haemorrhage**	49	.	91.8	8.2	.	.
8	**Anaemia**	34	.	97.1	.	2.9	.
9	**Neoplasm malignant**	28	3.6	75.0	17.9	3.6	.
10	**Neutropenia**	25	.	60.0	40.0	.	.
11	**Blood creatinine increased**	22	.	86.4	13.6	.	.
12	**Blood alkaline phosphatase**	21	.	90.5	9.5	.	.
13	**Mucosal inflammation**	19	.	84.2	10.5	5.3	.
14	**Vomiting**	19	.	84.2	15.8	.	.
15	**Renal failure**	18	.	61.1	27.8	11.1	.
16	**Gastrointestinal disorder**	16	.	93.8	6.3	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
17	Fatigue	14	.	92.9	.	7.1	.
18	Haematoma	13	.	84.6	15.4	.	.
19	Pneumonia	13	.	76.9	15.4	7.7	.
20	Haemorrhage	12	.	100.0	.	.	.
21	Hypersensitivity	12	.	58.3	41.7	.	.
22	Hypoglycaemia	12	8.3	75.0	16.7	.	.
23	Leukopenia	12	.	83.3	16.7	.	.
24	Portal vein thrombosis	12	.	83.3	8.3	8.3	.
25	Gamma-glutamyltransferase	10	.	80.0	20.0	.	.
26	Gastrointestinal obstruction	10	10.0	50.0	40.0	.	.
27	Hyperkalaemia	10	.	90.0	10.0	.	.
28	Hypokalaemia	8	.	87.5	.	12.5	.
29	Nausea	8	.	100.0	.	.	.
30	Dehydration	7	.	85.7	14.3	.	.
31	Hyperglycaemia	7	.	57.1	42.9	.	.
32	Squamous cell carcinoma	7	.	100.0	.	.	.
33	Wound complication	7	.	100.0	.	.	.
34	Exfoliative rash	6	.	83.3	16.7	.	.
35	Hypertension	6	.	50.0	50.0	.	.
36	Hypophosphataemia	6	.	100.0	.	.	.
37	Low density lipoprotein increased	6	16.7	50.0	33.3	.	.
38	Lung disorder	6	.	83.3	16.7	.	.
39	Muscular weakness	6	.	66.7	33.3	.	.
40	Pyrexia	6	.	100.0	.	.	.
41	Basal cell carcinoma	5	.	80.0	20.0	.	.
42	Colitis	5	.	60.0	40.0	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
43	Eye disorder	5	.	60.0	20.0	20.0	.
44	Gastrointestinal haemorrhage	5	.	100.0	.	.	.
45	Ketoacidosis	5	.	60.0	40.0	.	.
46	Oedema peripheral	5	.	100.0	.	.	.
47	Pneumonitis	5	.	80.0	.	.	20.0
48	Proteinuria	5	.	20.0	80.0	.	.
49	Thrombocytopenia	5	.	20.0	80.0	.	.
50	Ascites	4	.	100.0	.	.	.
51	Blood disorder	4	.	100.0	.	.	.
52	Cholecystitis	4	.	75.0	.	25.0	.
53	Febrile neutropenia	4	.	75.0	25.0	.	.
54	Hepatic enzyme increased	4	.	100.0	.	.	.
55	Lipase	4	.	100.0	.	.	.
56	Lung infiltration	4	.	25.0	75.0	.	.
57	Sexual dysfunction	4	.	100.0	.	.	.
58	Skin disorder	4	25.0	75.0	.	.	.
59	Tremor	4	25.0	75.0	.	.	.
60	Urinary bladder haemorrhage	4	.	75.0	25.0	.	.
61	Aspartate aminotransferase increased	3	.	100.0	.	.	.
62	Cough	3	.	100.0	.	.	.
63	Death	3	.	.	.	.	100.0
64	Fracture	3	.	66.7	33.3	.	.
65	Mouth ulceration	3	.	100.0	.	.	.
66	Musculoskeletal disorder	3	.	33.3	33.3	33.3	.
67	Neutrophil count decreased	3	.	100.0	.	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
68	Platelet disorder	3	.	100.0	.	.	.
69	Pyelonephritis	3	.	33.3	66.7	.	.
70	Renal disorder	3	.	100.0	.	.	.
71	Systemic inflammatory response syndrome	3	.	100.0	.	.	.
72	Vitreous haemorrhage	3	.	33.3	.	66.7	.
73	Activated partial thromboplastin time	2	.	100.0	.	.	.
74	Afebrile neutropenia	2	.	.	100.0	.	.
75	Arrhythmia supraventricular	2	.	100.0	.	.	.
76	Arthritis	2	.	.	.	100.0	.
77	Cytomegalovirus infection	2	.	100.0	.	.	.
78	Dizziness	2	.	100.0	.	.	.
79	Dysphagia	2	.	50.0	50.0	.	.
80	Dyspnoea	2	.	100.0	.	.	.
81	Gastritis	2	.	100.0	.	.	.
82	Gastrointestinal perforation	2	.	100.0	.	.	.
83	Graft versus host disease	2	.	.	100.0	.	.
84	Haemothorax	2	.	100.0	.	.	.
85	Headache	2	.	100.0	.	.	.
86	Hepatic haemorrhage	2	.	100.0	.	.	.
87	Hyponatraemia	2	.	100.0	.	.	.
88	Hypotension	2	.	100.0	.	.	.
89	Ileus	2	.	100.0	.	.	.
90	Insomnia	2	.	50.0	50.0	.	.
91	Migraine	2	.	100.0	.	.	.
92	Mood altered	2	.	50.0	50.0	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
93	Musculoskeletal pain	2	.	50.0	50.0	.	.
94	Neutrophil count	2	.	100.0	.	.	.
95	Opportunistic infection	2	.	100.0	.	.	.
96	Papillary thyroid cancer	2	.	50.0	.	50.0	.
97	Pleural effusion	2	.	50.0	50.0	.	.
98	Serum sickness	2	.	50.0	50.0	.	.
99	Thrombosis	2	.	100.0	.	.	.
100	Toxicity to various agents	2	.	100.0	.	.	.
101	Weight decreased	2	.	100.0	.	.	.
102	Actinic keratosis	1	.	100.0	.	.	.
103	Activated partial thromboplastin time prolonged	1	.	100.0	.	.	.
104	Acute febrile neutrophilic dermatosis	1	.	.	.	100.0	.
105	Acute kidney injury	1	.	100.0	.	.	.
106	Acute respiratory distress syndrome	1	.	.	.	.	100.0
107	Agranulocytosis	1	.	100.0	.	.	.
108	Alanine aminotransferase increased	1	.	100.0	.	.	.
109	Arthralgia	1	.	100.0	.	.	.
110	Arthritis bacterial	1	.	.	.	100.0	.
111	Aspiration	1	.	100.0	.	.	.
112	Autoimmune disorder	1	.	100.0	.	.	.
113	Barrett's oesophagus	1	.	100.0	.	.	.
114	Biliary tract disorder	1	.	100.0	.	.	.
115	Blood amylase	1	.	100.0	.	.	.
116	Blood bilirubin	1	.	100.0	.	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
117	Blood creatine phosphokinase	1	.	100.0	.	.	.
118	Chest pain	1	.	.	100.0	.	.
119	Cognitive disorder	1	.	.	.	100.0	.
120	Confusional state	1	.	.	100.0	.	.
121	Constipation	1	.	.	.	100.0	.
122	Convulsion	1	.	.	100.0	.	.
123	Cystitis	1	.	100.0	.	.	.
124	Decreased appetite	1	.	100.0	.	.	.
125	Dyskinesia	1	.	100.0	.	.	.
126	Endocrine disorder	1	.	100.0	.	.	.
127	Gamma-glutamyltransferase increased	1	.	100.0	.	.	.
128	Gastroenteritis viral	1	100.0	.	.	.	.
129	Gastrointestinal infection	1	.	100.0	.	.	.
130	Glomerular filtration rate	1	.	100.0	.	.	.
131	Haemoglobin decreased	1	.	100.0	.	.	.
132	Haemolysis	1	.	100.0	.	.	.
133	Hepatic haematoma	1	.	100.0	.	.	.
134	Hypoalbuminaemia	1	.	100.0	.	.	.
135	Hypomagnesaemia	1	.	100.0	.	.	.
136	Hypoxia	1	.	100.0	.	.	.
137	Hysterectomy	1	.	100.0	.	.	.
138	Incisional hernia repair	1	.	100.0	.	.	.
139	Influenza	1	.	.	.	100.0	.
140	Injection site reaction	1	.	100.0	.	.	.
141	Injury	1	.	.	100.0	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
142	Lactation disorder	1	.	100.0	.	.	.
143	Limb injury	1	.	.	.	100.0	.
144	Lipase increased	1	.	100.0	.	.	.
145	Lobular breast carcinoma in situ	1	.	100.0	.	.	.
146	Low density lipoprotein abnormal	1	.	100.0	.	.	.
147	Metastases	1	.	100.0	.	.	.
148	Micturition urgency	1	.	100.0	.	.	.
149	Muscle necrosis	1	.	100.0	.	.	.
150	Myocardial ischaemia	1	.	.	100.0	.	.
151	Myositis	1	.	100.0	.	.	.
152	Neuroleptic malignant syndrome	1	.	100.0	.	.	.
153	Ocular surface disease	1	.	100.0	.	.	.
154	Oral pain	1	.	100.0	.	.	.
155	Ovarian cyst ruptured	1	.	.	100.0	.	.
156	Pancytopenia	1	.	100.0	.	.	.
157	Pericardial effusion	1	.	100.0	.	.	.
158	Pericarditis	1	.	100.0	.	.	.
159	Periorbital cellulitis	1	.	100.0	.	.	.
160	Peripheral ischaemia	1	.	.	100.0	.	.
161	Peylonepr hitis	1	.	.	100.0	.	.
162	Post procedural haemorrhage	1	.	.	100.0	.	.
163	Pruritus	1	.	.	100.0	.	.

Exhibit 7-6B (continued)
Infusion or Immunosuppression Related Adverse Events Following Islet Transplant
In order by frequency, with final outcome

		Total events	Outcome				
			0-Unknown	1-Recovered	2-Sequelae	3-Disability	4-Death
		N	Row %	Row %	Row %	Row %	Row %
164	Psychotic disorder	1	.	100.0	.	.	.
165	Rash	1	.	100.0	.	.	.
166	Renal graft infection	1	.	100.0	.	.	.
167	Respiratory tract infection	1	.	100.0	.	.	.
168	Retinal haemorrhage	1	.	.	.	100.0	.
169	Sensitisation	1	.	.	.	100.0	.
170	Stomatitis	1	.	100.0	.	.	.
171	Surgery	1	.	100.0	.	.	.
172	Syncope	1	.	.	.	100.0	.
173	Tinnitus	1	.	.	100.0	.	.
174	Transaminases increased	1	.	100.0	.	.	.
175	Transplant failure	1	.	100.0	.	.	.
176	Treatment related secondary malignancy	1	.	100.0	.	.	.
177	Tubulointerstitial nephritis	1	.	100.0	.	.	.
178	Ulcer	1	.	100.0	.	.	.
179	Urinary tract infection	1	.	.	100.0	.	.
180	Urosepsis	1	.	100.0	.	.	.
181	Uveitis	1	.	100.0	.	.	.
182	Vestibular neuronitis	1	.	.	.	100.0	.
183	Viral encephalitis	1	.	100.0	.	.	.

Exhibit 7-7
SAE Criteria

	Transplant type								Era									
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Total recipients (N)	877	100.0	24	100.0	183	100.0	2	100.0	208	100.0	271	100.0	242	100.0	341	100.0	24	100.0
Death	9	1.0	5	20.8	10	5.5	.	.	15	7.2	6	2.2	3	1.2	.	.	.	.
Life Threatening	118	13.5	7	29.2	33	18.0	1	50.0	50	24.0	76	28.0	19	7.9	12	3.5	2	8.3
Hospitalization	253	28.8	12	50.0	75	41.0	2	100.0	96	46.2	133	49.1	74	30.6	33	9.7	6	25.0
Congenital abnormality	2	0.2	1	4.2	.	.	.	.	1	0.5	1	0.4	.	.	1	0.3	.	.
Long term disability	29	3.3	2	8.3	12	6.6	.	.	9	4.3	13	4.8	16	6.6	5	1.5	.	.
PI Indicated Serious	76	8.7	2	8.3	20	10.9	1	50.0	19	9.1	42	15.5	29	12.0	8	2.3	1	4.2

Exhibit 7-8
Incidence of AEs and SAEs per Recipient by Type of Transplant and Era

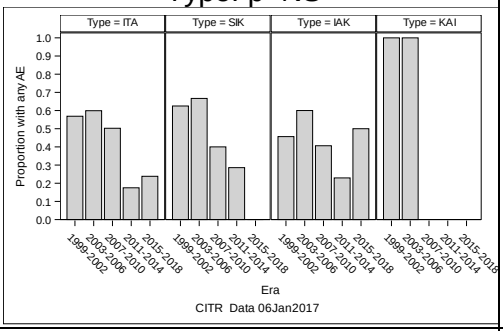
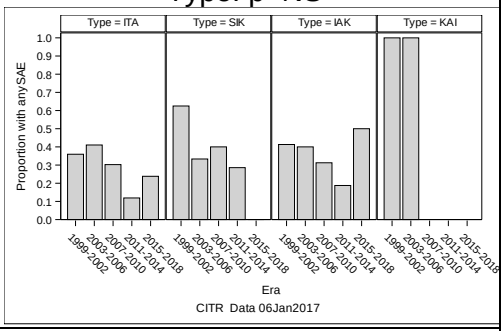
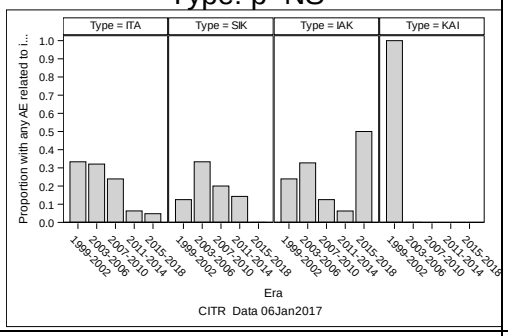
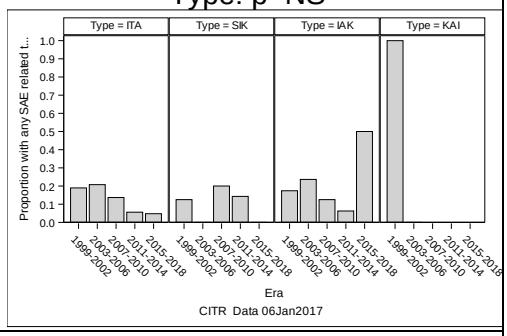
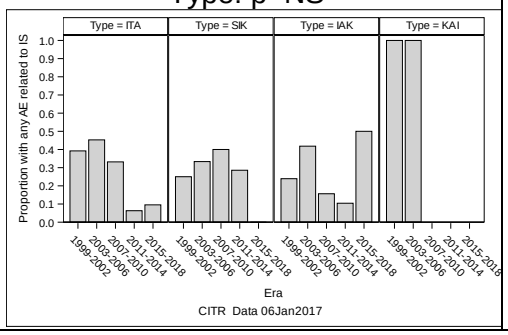
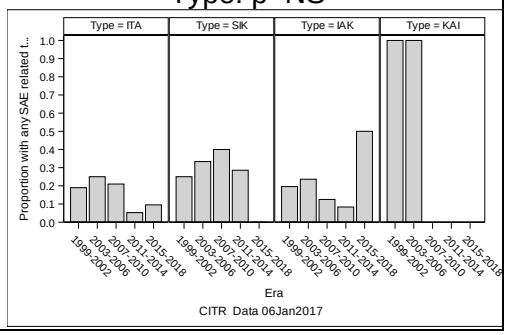
	Any AE	Any SAE
Any AE in First Year Post Transplant	Era: p<0.0001 Type: p=NS 	Era: p<0.0001 Type: p=NS 
Any AE in First Year Post Transplant Related to Infusion	Era: p<0.0001 Type: p=NS 	Era: p<0.0001 Type: p=NS 
Any AE in First Year Post Transplant Related to Immuno-suppression	Era: p<0.0001 Type: p=NS 	Era: p<0.0001 Type: p=NS 

Exhibit 7-9A
Total years of follow-up

	N	Mean	Std
Total years of follow-up	1086	4.2	3.5

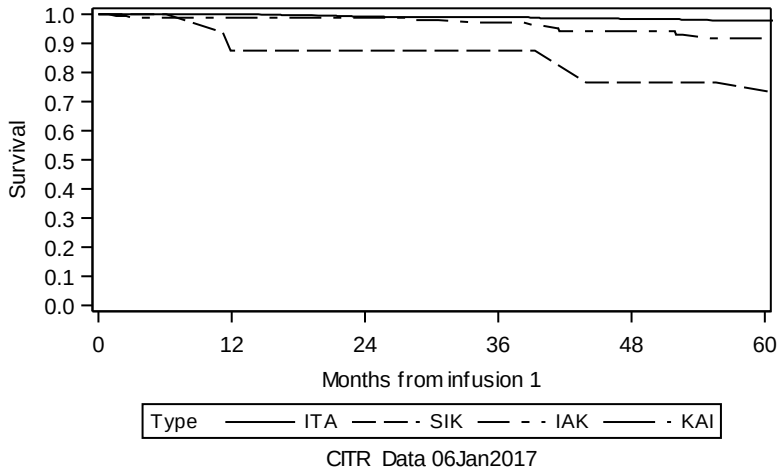
Exhibit 7-9B
All Neoplasms

		Relatedness to Immunosuppression				Outcome				
	Total	Unk.	Not related	Possibly related	Related	Unk.	Not recovered	Recovered	Recovered with seq	Recovering
	N	%	%	%	%	%	%	%	%	%
Total Events	**51**	**15.7**	**5.9**	**72.5**	**5.9**	**13.7**	**11.8**	**64.7**	**5.9**	**3.9**
Other	**5**	20.0	20.0	60.0	.	.	20.0	80.0	.	.
Basal cell carcinoma	**13**	15.4	.	69.2	15.4	23.1	.	69.2	7.7	.
Ductal carcinoma	**2**	.	50.0	50.0	.	.	50.0	50.0	.	.
Lung carcinoma	**1**	.	.	100	.	.	100	.	.	.
Metastasis	**1**	.	.	100	.	.	.	100	.	.
Papillary	**4**	.	.	100	.	.	.	75.0	.	25.0
Post-transplant lymphoproliferative	**2**	50.0	50.0	.	.	.	50.0	50.0	.	.
Pulmonary nodules	**1**	.	.	100	.	.	100	.	.	.
Skin, type not reported	**4**	25.0	.	75.0	.	25.0	25.0	.	25.0	25.0
Squamous cell	**18**	16.7	.	77.8	5.6	16.7	.	77.8	5.6	.

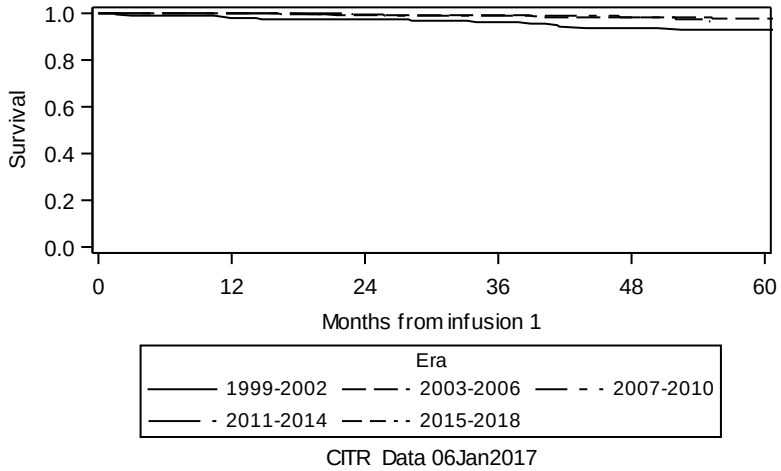
Exhibit 7-9C
First Neoplasm in Patient

		Relatedness to Immunosuppression			Outcome				
	Total	Unk.	Not related	Possibly related	Unk.	Not recovered	Recovered	Recovered with seq	Recovering
	N	%	%	%	%	%	%	%	%
Total First Events	**34**	**8.8**	**8.8**	**82.4**	**8.8**	**14.7**	**70.6**	**2.9**	**2.9**
Other	**4**	.	25.0	75.0	.	25.0	75.0	.	.
Basal cell carcinoma	**10**	10.0	.	90.0	20.0	.	80.0	.	.
Ductal carcinoma	**2**	.	50.0	50.0	.	50.0	50.0	.	.
Lung carcinoma	**1**	.	.	100	.	100	.	.	.
Papillary	**3**	.	.	100	.	.	66.7	.	33.3
Post-transplant lymphoproliferative	**2**	50.0	50.0	.	.	50.0	50.0	.	.
Pulmonary nodules	**1**	.	.	100	.	100	.	.	.
Squamous cell	**11**	9.1	.	90.9	9.1	.	81.8	9.1	.

Exhibit 7-10A
Deaths



	ITA	SIK	IAK	KAI
Deaths/N	14/877 (1.6%)	6/24 (25%)	13/183 (7.1%)	0/2 (0%)

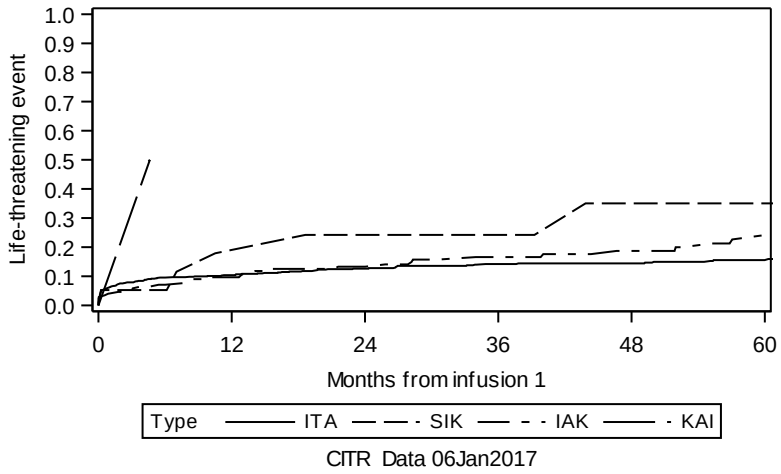


	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
Deaths/N	19/208 (5.3%)	8/271 (3.0%)	5/242 (2.1%)	1/341 (0.3%)	0/24 (0%)

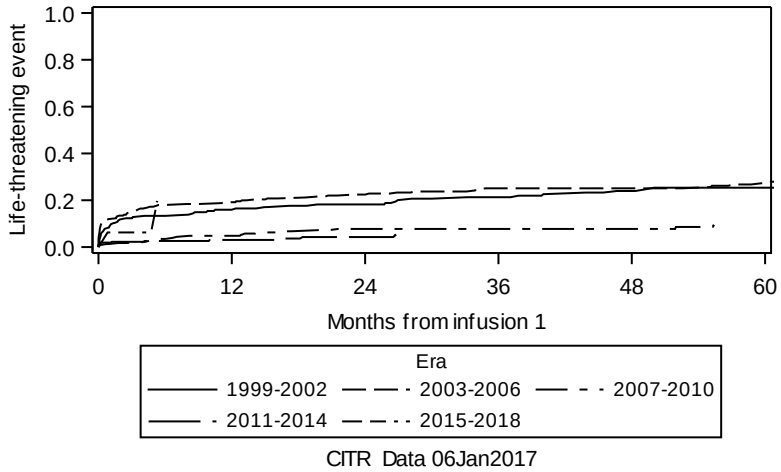
Exhibit 7-10B
Deaths by Cause and Relatedness to Procedure or Immunosuppression

	Type of Transplant	Years post infusion 1	Year of Transplant	Age at Death	Primary Cause of Death	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immuno-supression
1	ITA	1.2	2002	44		Missing Information	Missing Information	.	
2	ITA	1.4	2005	46	Atherosclerotic Coronary Artery Disease	Not related	Not related	.	Yes
3	ITA	1.7	2008	63	Multiorgan failure of unknown etiology	Possibly related	Possibly related	.	Yes
4	ITA	1.8	2003	43	Acute Methadone and Diphenhydramine Toxicity	Not related	Not related	>0	Yes
5	ITA	1.9	2012	59	myocardial infarction	Not related	Not related	.	
6	ITA	2.1	2009	45		Missing Information	Missing Information	.	Yes
7	ITA	3.2	2002	45	viral meningitis	Not related	Possibly related	.	Yes
8	ITA	3.3	2006	58		Missing Information	Missing Information	.	Yes
9	ITA	3.9	2010	66		Missing Information	Missing Information	.	
10	ITA	4.4	2001	40	Unknown	Not related	Unlikely related	.	Yes
11	ITA	4.6	2006	71	Renal failure	Not related	Related	>0	No
12	ITA	5.3	2003	30	infection	Not related	Unlikely related	>0	
13	ITA	6.5	2000	46	Diabetic Ketoacidosis due to Diabetes Mellitus	Not related	Not related	.	Yes
14	ITA	8.2	2000	40	Pneumonia	Not related	Not related	>0	Yes
1	SIK	0.9	2001	51	respiratory arrest after therapy withdrawal	Not related	Related	.	Yes
2	SIK	1	2000	34	Unknown	Not related	Unlikely related	.	Yes
3	SIK	3.7	2002	62	Subarachnoid hemorrhage mesencephalic	Not related	Not related	.	Yes
4	SIK	6.2	2000	56	Unknown	Not related	Unlikely related	.	Yes
5	SIK	8.8	1999	63	Lung Carcinoma Non-small cell poorly differentiate	Not related	Unlikely related	>0	Yes
6	SIK	15.8	2000	70	necrosis of the foot surinfected	Not related	Missing Information	.	Yes
1	IAK	0.1	2002	52	Infectious pneumopathy	Not related	Related	.	Yes
2	IAK	0.3	2001	35	CARDIO RESPIRATORY ARREST	Unlikely related	Unlikely related	.	Yes
3	IAK	2.3	1999	53	Congestive heart failure	Not related	Not related	.	
4	IAK	2.8	2000	36	Respiratory arrest	Not related	Not related	.	
5	IAK	3.3	2004	46	Brain hemorrhage	Not related	Not related	>0	Yes
6	IAK	3.4	2000	52	Cerebrovascular event	Not related	Not related	>0	Yes
7	IAK	3.5	2001	52	massive Hemorrhagic Infarct	Not related	Not related	.	Yes
8	IAK	4.3	2008	51	Squamous cell	Unlikely related	Possibly related	>0	Yes
9	IAK	4.6	2007	56	Acute renal failure	Not related	Not related	>0	Yes
10	IAK	5.7	2000	40	Acute myocardial infarction	Not related	Not related	.	
11	IAK	6.3	2003	62	pneumonia	Not related	Not related	.	Yes
12	IAK	10.2	2003	55	Cardiac decomposition	Missing Information	Missing Information	.	Yes
13	IAK	11	1999	60	Acute myocardial infarction	Not related	Missing Information	.	Yes

Exhibit 7-11A
Life-Threatening Events



	ITA	SIK	IAK	KAI
Life-threatening events	118/877	7/24	33/183	1/2



	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018
Life-threatening events	50/208	76/271	19/242	12/341	2/24

Exhibit 7-11B
Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
ITA	Not related	Not related	Cardiac disorders	Myocardial ischaemia	2003-2006	87.5
					2007-2010	0.7
			Infections and infestations	Infection	1999-2002	106.8
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	26.9
					1999-2002	8.7
					1999-2002	14.9
					2003-2006	11.1
					2003-2006	34.9
					2003-2006	12.4
					2003-2006	-8.1
					2011-2014	1.2
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	2003-2006	4.4
			Nervous system disorders	Cerebellar ischaemia	2007-2010	55.4
		Possibly related	Infections and infestations	Infection	2003-2006	20.7
					2003-2006	33.9
			Investigations	Granulocytes abnormal	1999-2002	1.9
					1999-2002	2.5
					1999-2002	26.7
					1999-2002	1.4
					1999-2002	4.1
					1999-2002	1.7
					1999-2002	49.2
					1999-2002	0.5
					2003-2006	3.4
					2007-2010	1.8
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	11.3
				Hypophosphataemia	2003-2006	2.3
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lobular breast carcinoma in situ	2003-2006	23.0
				Neoplasm malignant	1999-2002	26.9
			Vascular disorders	Hypertension	1999-2002	50.0

Exhibit 7-11B (continued)
Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
ITA		Related	Blood and lymphatic system disorders	Lymphopenia	2003-2006	0.0
					2003-2006	0.0
					2003-2006	-1.2
					2003-2006	0.0
					2011-2014	18.4
			Investigations	Granulocytes abnormal	1999-2002	37.8
					1999-2002	9.8
					2003-2006	0.2
					2003-2006	0.7
					2003-2006	5.2
					2003-2006	3.6
			Psychiatric disorders	Insomnia	1999-2002	19.7
			Renal and urinary disorders	Proteinuria	2003-2006	24.3
		Unlikely related	Cardiac disorders	Myocardial ischaemia	2007-2010	4.1
			Gastrointestinal disorders	Vomiting	2007-2010	5.6
	Possibly related	Not related	Gastrointestinal disorders	Gastrointestinal disorder	2015-2018	5.3
		Possibly related	Cardiac disorders	Myocardial ischaemia	2003-2006	0.0
			General disorders and administration site conditions	Death	2007-2010	19.8
	Possibly related		Infections and infestations	Infection	2003-2006	-6.0
		Possibly related	Investigations	Liver function test abnormal	2003-2006	0.2
					2003-2006	0.1
			Respiratory, thoracic and mediastinal disorders	Aspiration	2007-2010	0.1
		Related	Blood and lymphatic system disorders	Neutropenia	2011-2014	0.1
		Unlikely related	Hepatobiliary disorders	Cholecystitis	1999-2002	12.4
			Investigations	Blood alkaline phosphatase	1999-2002	0.2
					2003-2006	0.1
					2003-2006	0.1
				Liver function test abnormal	1999-2002	0.3
					1999-2002	0.2
					1999-2002	0.2
					2003-2006	0.0
					2003-2006	0.3
					1999-2002	0.2
					1999-2002	0.1
					1999-2002	0.0

Exhibit 7-11B (continued)
Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

					1999-2002	0.1
					1999-2002	0.1
					2003-2006	12.9
					2003-2006	0.1
					2003-2006	0.1
					2003-2006	0.1
					2003-2006	0.3
					2003-2006	0.3
					2003-2006	0.2
					2003-2006	0.0
					2003-2006	0.0
			Metabolism and nutrition disorders	Ketoacidosis	2007-2010	4.5
	Related	Not related			2011-2014	0.1
			Gastrointestinal disorders	Gastrointestinal obstruction	2003-2006	1.6
				Peritoneal haemorrhage	2003-2006	0.0
					1999-2002	17.2
					2007-2010	8.2
					2011-2014	16.2
			General disorders and administration site conditions	Death	2003-2006	55.1
			Hepatobiliary disorders	Portal vein thrombosis	2003-2006	3.3
					2003-2006	0.0
			Infections and infestations	Infection	2003-2006	1.6
			Investigations	Liver function test abnormal	1999-2002	0.1
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	2.6
			Vascular disorders	Haematoma	2003-2006	0.0
		Possibly related	Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	1.1
		Related	Investigations	Granulocytes abnormal	2003-2006	0.1
			Investigations	Liver function test abnormal	1999-2002	1.1
			Nervous system disorders	Neuroleptic malignant syndrome	2011-2014	0.0
ITA		Unlikely related	Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	1.0
					2007-2010	6.7
			Hepatobiliary disorders	Hepatic haematoma	2003-2006	1.6
	Unlikely related	Possibly related			2011-2014	0.2
			Infections and infestations	Infection	1999-2002	33.2
			Investigations	Granulocytes abnormal	1999-2002	0.9
					2003-2006	19.7
					2003-2006	0.1
					2003-2006	0.7
					2003-2006	0.3
					2007-2010	0.1
			Renal and urinary disorders	Renal failure	2003-2006	3.3

Exhibit 7-11B (continued)
Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

ITA		**Related**	Infections and infestations	Cytomegalovirus infection	2003-2006	60.3
			Investigations	Granulocytes abnormal	2003-2006	0.1
					2007-2010	4.8
					2011-2014	0.1
		Unlikely related			2007-2010	14.3
			Blood and lymphatic system disorders	Anaemia	2003-2006	1.9
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	0.0
					2007-2010	16.5
IAK	**Not related**	**Not related**	Cardiac disorders	Cardio-respiratory arrest	1999-2002	28.2
				Myocardial ischaemia	2003-2006	59.8
			Investigations	Troponin I	2003-2006	57.1
			Nervous system disorders	Cerebral ischaemia	2007-2010	13.2
			Vascular disorders	Haematoma	1999-2002	25.8
		Possibly related	Blood and lymphatic system disorders	Anaemia	1999-2002	46.6
			Infections and infestations	Opportunistic infection	2007-2010	12.8
			Investigations	Granulocytes abnormal	1999-2002	3.1
					2003-2006	3.8
					2003-2006	2.5
					2003-2006	7.9
			Renal and urinary disorders	Proteinuria	2003-2006	28.3
		Related	Respiratory, thoracic and mediastinal disorders	Pneumonitis	1999-2002	0.6
		Unlikely related			2007-2010	21.6
			Blood and lymphatic system disorders	Blood disorder	1999-2002	8.5
	Possibly related	**Unlikely related**	Blood and lymphatic system disorders	Anaemia	2003-2006	0.9
	Related	**Not related**	Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	0.0
					2003-2006	15.2
					1999-2002	1.8
			Vascular disorders	Haematoma	2003-2006	0.0
				Haemorrhage	2011-2014	0.0
		Unlikely related	Gastrointestinal disorders	Gastrointestinal haemorrhage	2003-2006	0.0
			Vascular disorders	Haemorrhage	2003-2006	5.4
					1999-2002	0.0
	Unlikely related	**Not related**	Nervous system disorders	Cerebral ischaemia	1999-2002	66.6
		Possibly related			2007-2010	52.0
			Immune system disorders	Hypersensitivity	2003-2006	34.0
			Infections and infestations	Pyelonephritis	2003-2006	14.1
			Investigations	Granulocytes abnormal	2011-2014	10.0
			Renal and urinary disorders	Renal failure	1999-2002	8.1
		Unlikely related	Cardiac disorders	Cardio-respiratory arrest	2003-2006	55.2
				Myocardial ischaemia	1999-2002	40.0

Exhibit 7-11B (continued)
Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

SIK	**Not related**	**Not related**	General disorders and administration site conditions	Death	1999-2002	43.9
		Possibly related	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1999-2002	105.0
				Papillary thyroid cancer	2003-2006	79.0
		Unlikely related	Immune system disorders	Hypersensitivity	1999-2002	10.5
	Related	**Possibly related**			2007-2010	7.0
	Unlikely related	**Possibly related**	Blood and lymphatic system disorders	Lymphopenia	2003-2006	18.6
		Unlikely related	Nervous system disorders	Cerebral ischaemia	1999-2002	0.2
KAI	**Unlikely related**	**Possibly related**	Reproductive system and breast disorders	Ovarian cyst ruptured	2003-2006	4.6

Exhibit 7-11C
Life-Threatening Events (Outcome by System/Organ Class)

			AE Outcome					
		Total	Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	Row %	Row%	Row%	Row%	Row%	Row%
Total		**153**	**3.3**	**3.3**	**84.3**	**7.8**	**0.7**	**0.7**
System/Organ Class	**Preferred Term**							
Blood and lymphatic system disorders	**Anaemia**	3	.	.	100.0	.	.	.
	Blood disorder	1	.	.	100.0	.	.	.
	Lymphopenia	6	.	.	100.0	.	.	.
	Neutropenia	1	.	.	100.0	.	.	.
Cardiac disorders	**Cardio-respiratory arrest**	2	50.0	.	50.0	.	.	.
	Myocardial ischaemia	7	.	.	85.7	14.3	.	.
Gastrointestinal disorders	**Gastrointestinal disorder**	1	.	.	100.0	.	.	.
	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	.	.	.
	Cholecystitis acute	1	.	.	100.0	.	.	.
	Hepatic haematoma	1	.	.	100.0	.	.	.
	Portal vein thrombosis	2	.	.	100.0	.	.	.
	Hypersensitivity	**3**	.	.	33.3	33.3	.	33.3
	Cytomegalovirus infection	**1**	.	.	100.0	.	.	.
	Infection	**6**	.	.	50.0	50.0	.	.
	Opportunistic infection	**1**	.	.	100.0	.	.	.
	Pyelonephritis	**1**	.	.	.	100.0	.	.

Exhibit 7-11C (continued)
Life-Threatening Events (Outcome by System/Organ Class)

			AE Outcome					
		Total	Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	Row %	Row%	Row%	Row%	Row%	Row%
Infections and infestations	Cytomegalovirus infection	1	.	.	100.0	.	.	.
	Infection	6	.	.	50.0	50.0	.	.
	Opportunistic infection	1	.	.	100.0	.	.	.
	Pyelonephritis	1	.	.	.	100.0	.	.
Investigations	Blood alkaline phosphatase	3	.	.	100.0	.	.	.
	Granulocytes abnormal	31	.	3.2	96.8	.	.	.
	Liver function test abnormal	23	.	.	95.7	4.3	.	.
	Troponin I	1	.	.	100.0	.	.	.
Metabolism and nutrition disorders	Hypoglycaemia	14	.	.	100.0	.	.	.
	Hypophosphataemia	1	.	.	100.0	.	.	.
	Ketoacidosis	1	.	.	100.0	.	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lobular breast carcinoma in situ	1	.	.	100.0	.	.	.
	Neoplasm malignant	3	.	66.7	33.3	.	.	.
	Papillary thyroid cancer	1	.	.	.	.	100.0	.
Nervous system disorders	Cerebellar ischaemia	1	.	.	.	100.0	.	.
	Cerebral ischaemia	3	.	33.3	.	66.7	.	.
	Neuroleptic malignant syndrome	1	.	.	100.0	.	.	.
Psychiatric disorders	Insomnia	1	.	.	100.0	.	.	.
Renal and urinary disorders	Proteinuria	2	.	50.0	50.0	.	.	.
	Renal failure	2	.	.	50.0	50.0	.	.
Reproductive system and breast disorders	Ovarian cyst ruptured	1	.	.	.	100.0	.	.
Respiratory, thoracic and mediastinal disorders	Aspiration	1	.	.	100.0	.	.	.
	Pneumonitis	1	100.0	.	.	.	.	.

Exhibit 7-11C (continued)
Life-Threatening Events (Outcome by System/Organ Class)

			AE Outcome					
		Total	Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	Row %	Row%	Row%	Row%	Row%	Row%
Vascular disorders	Haematoma	3	.	.	100.0	.	.	.
	Haemorrhage	3	.	.	100.0	.	.	.
	Hypertension	1	.	.	100.0	.	.	.

Chapter 8
Registry Data Quality Review

Table of Contents

Introduction

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

Ns	Overall						EurAusAsia						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	208	202	201	197	191	190	85	79	79	77	75	75	123	123	122	120	116	115
2003 - 2006	271	270	266	262	258	249	105	105	104	104	104	100	166	165	162	158	154	149
2007 - 2010	242	242	237	230	226	216	107	107	107	105	105	103	135	135	130	125	121	113
2011 - 2014	341	340	317	255	171	69	188	187	176	143	86	35	153	153	141	112	85	34
2015 - 2018	24	21	.	.	.	.	15	12	.	.	.	.	9	9	.	.	.	.

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

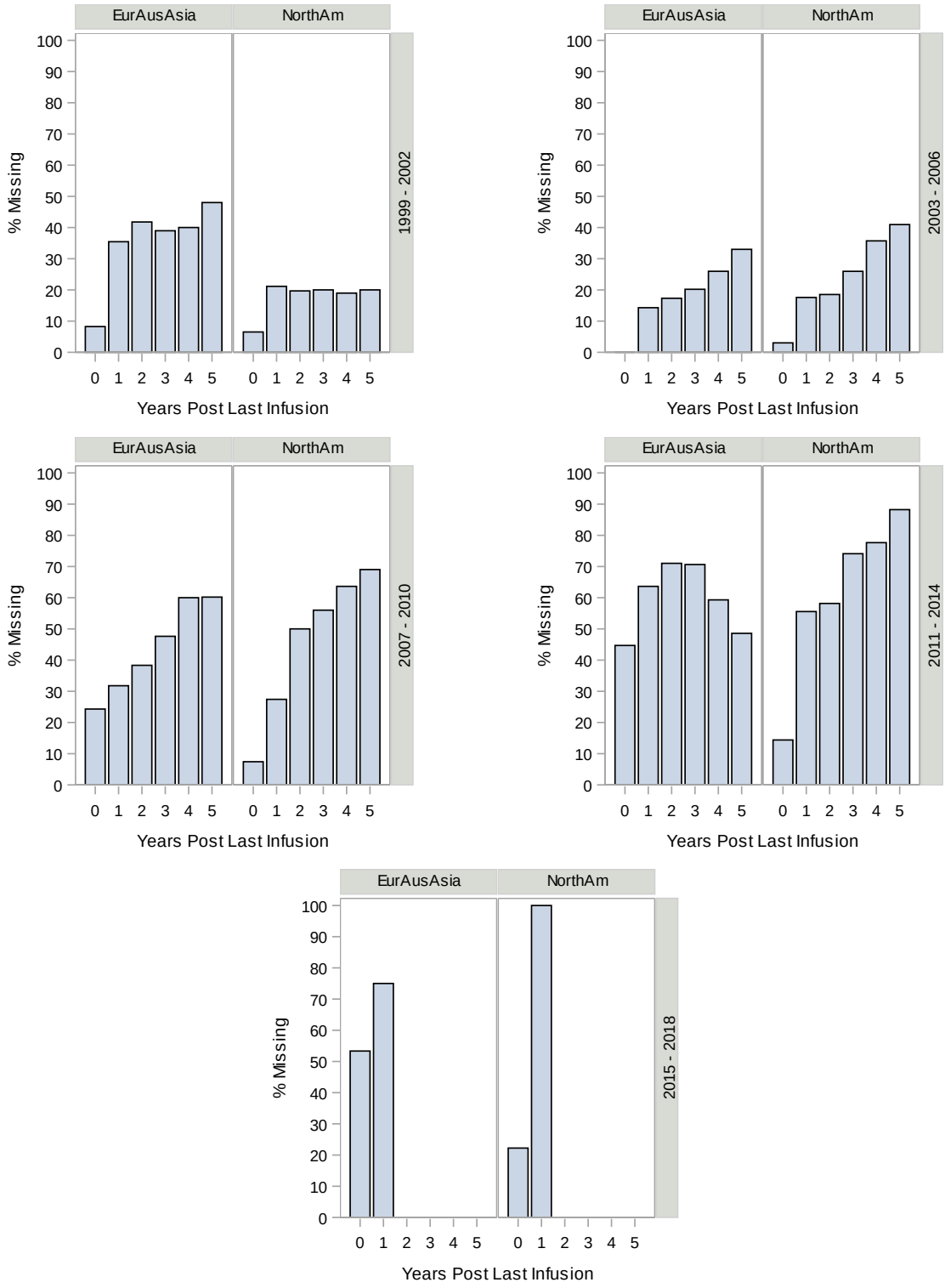


Exhibit 8 – 2
Missing Data for Fasting C-Peptide by Era and Continent

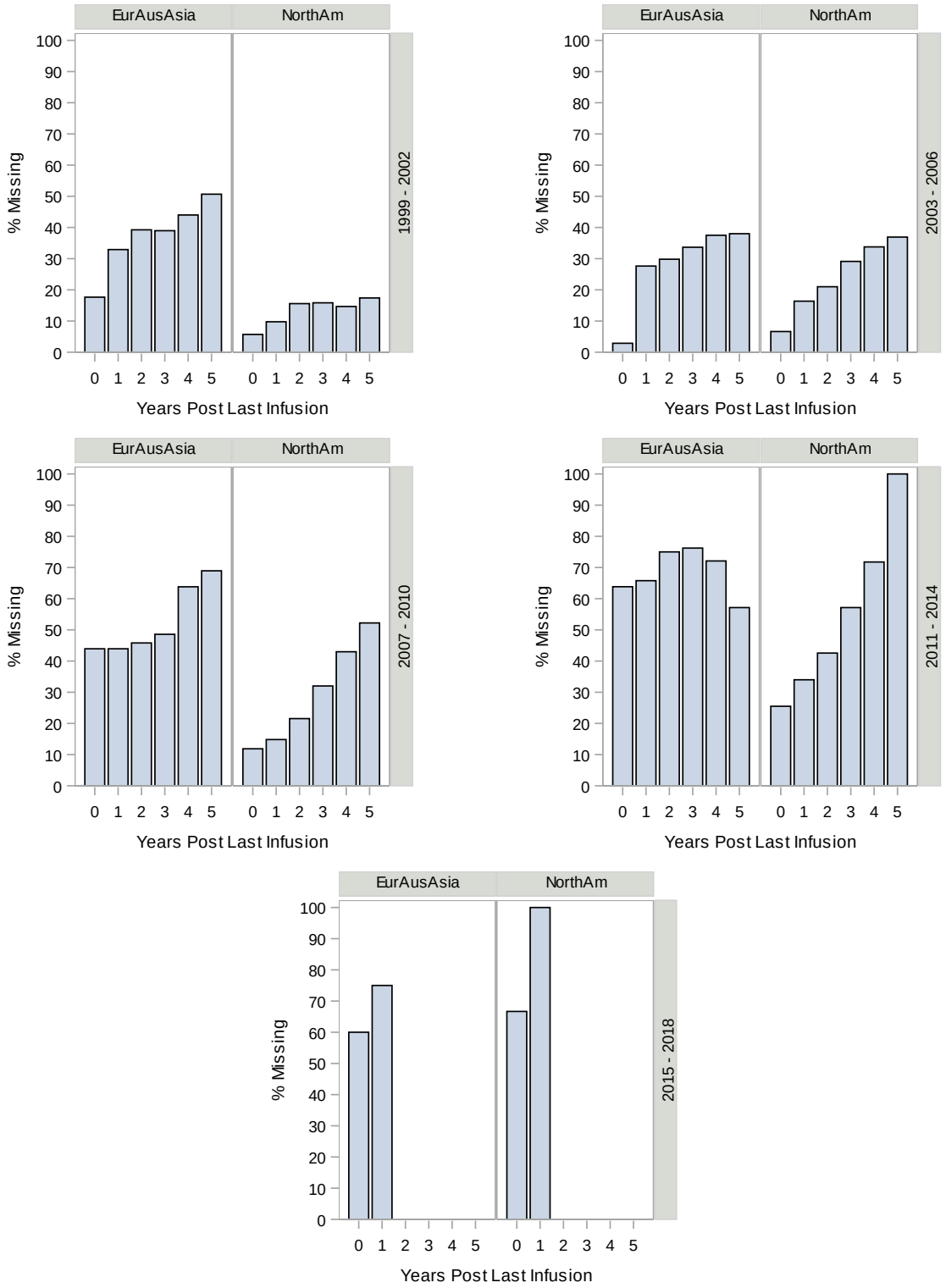


Exhibit 8 – 3
Missing Data for Hemoglobin A1c by Era and Continent

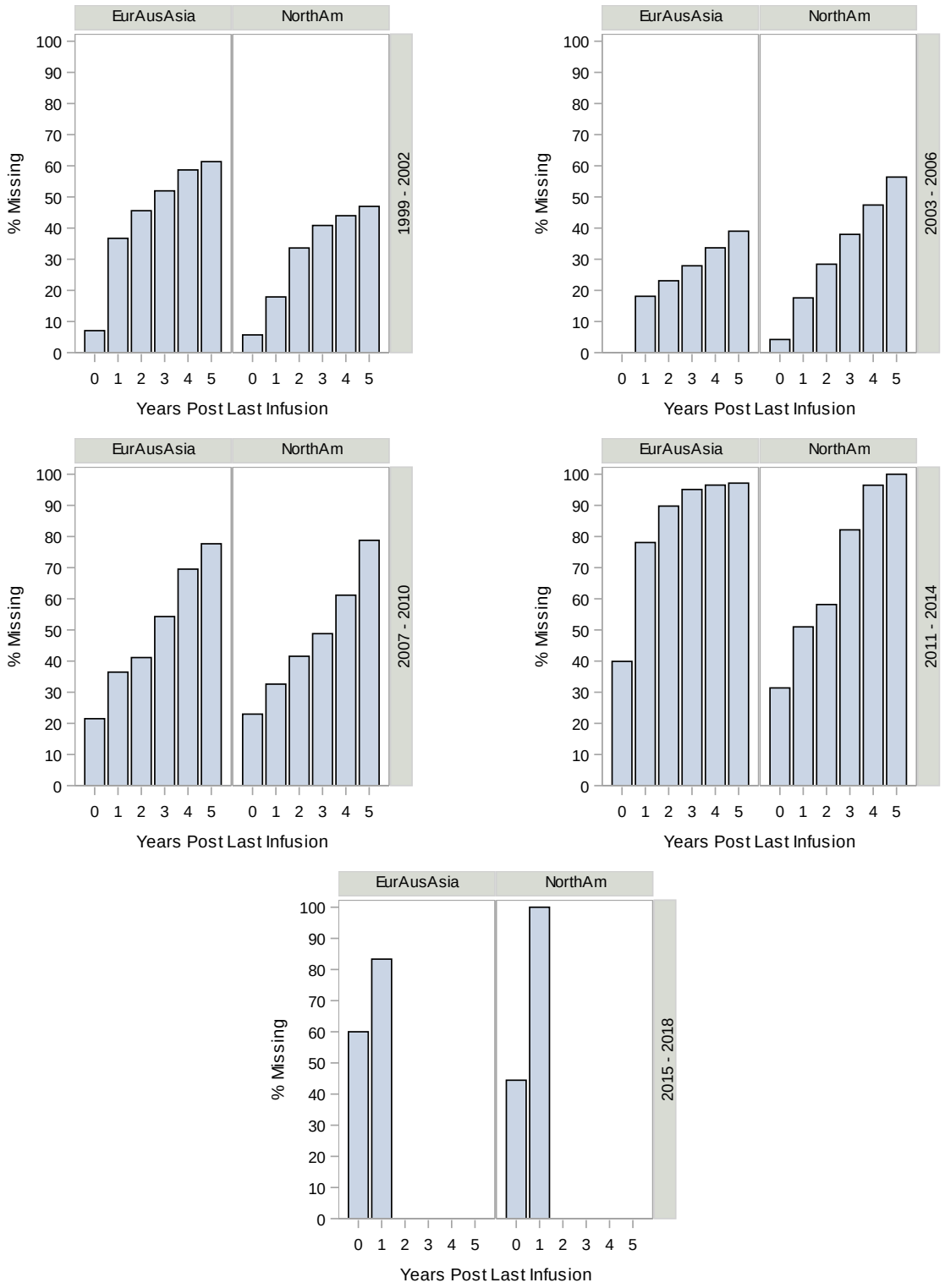


Exhibit 8 – 4
Missing Data for Fasting Blood Glucose by Era and Continent

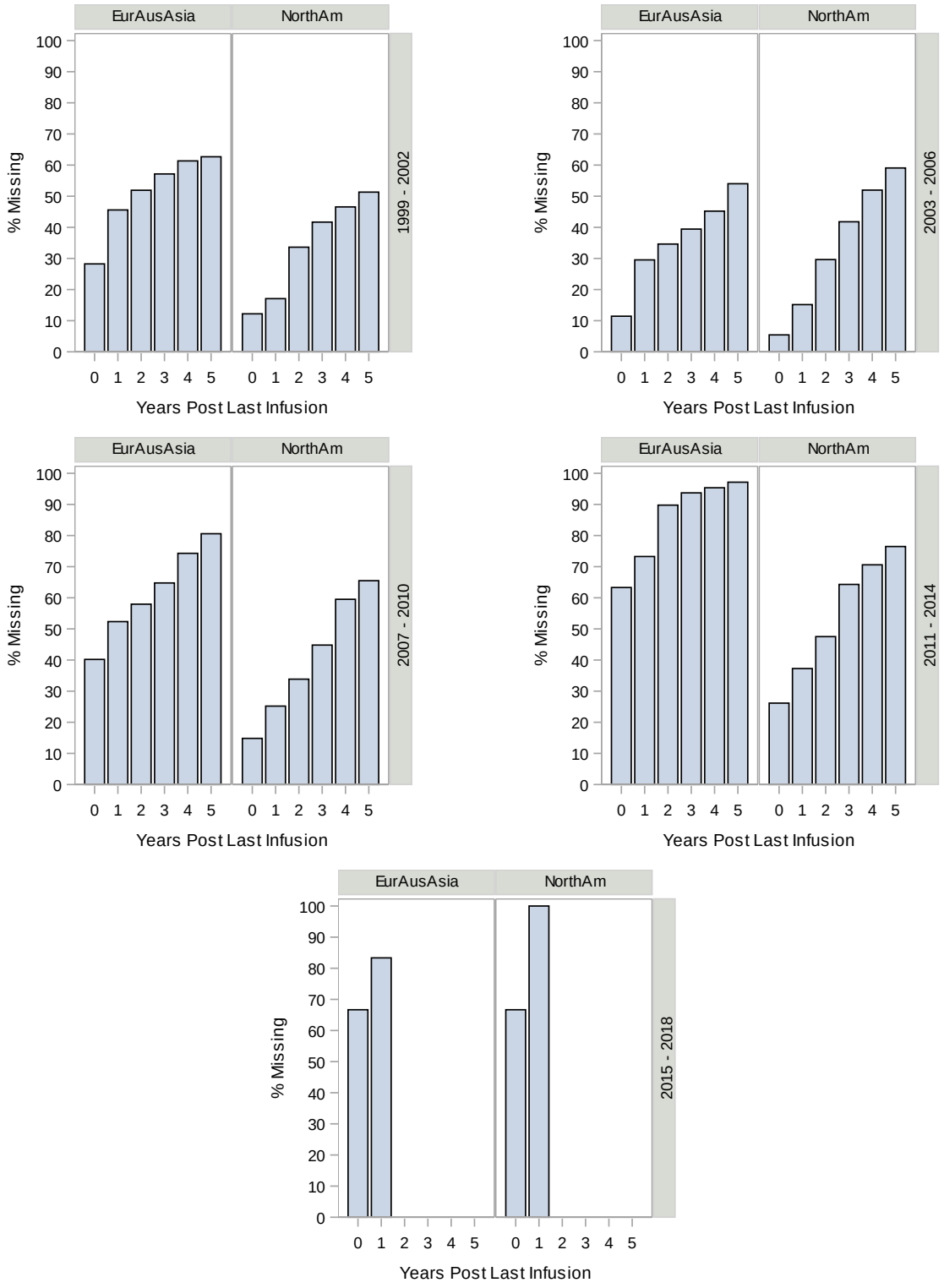


Exhibit 8 – 5
Missing Data for Severe HypoGlycemia by Era and Continent

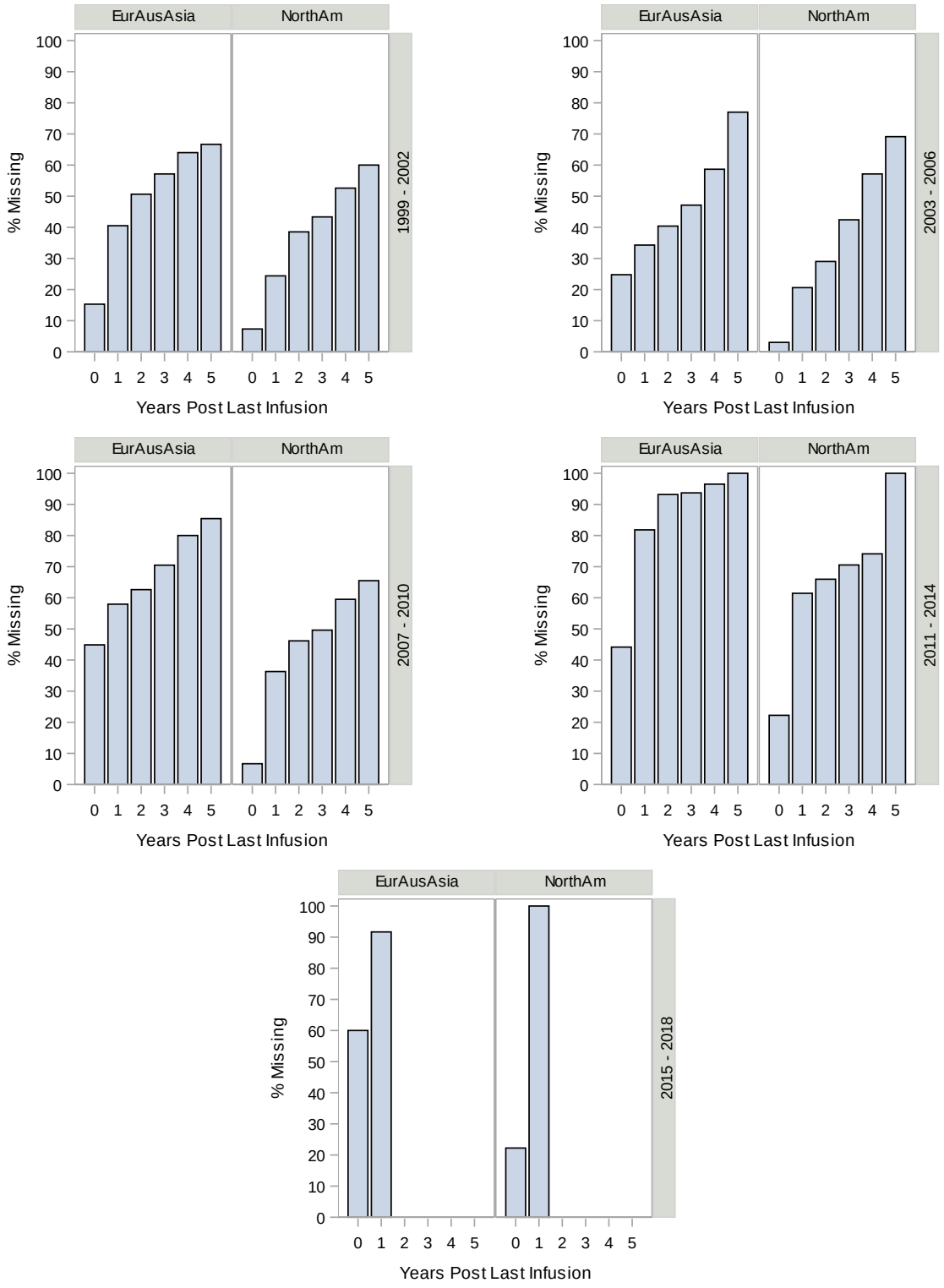


Exhibit 8 – 6
Missing Data for BMI by Era and Continent

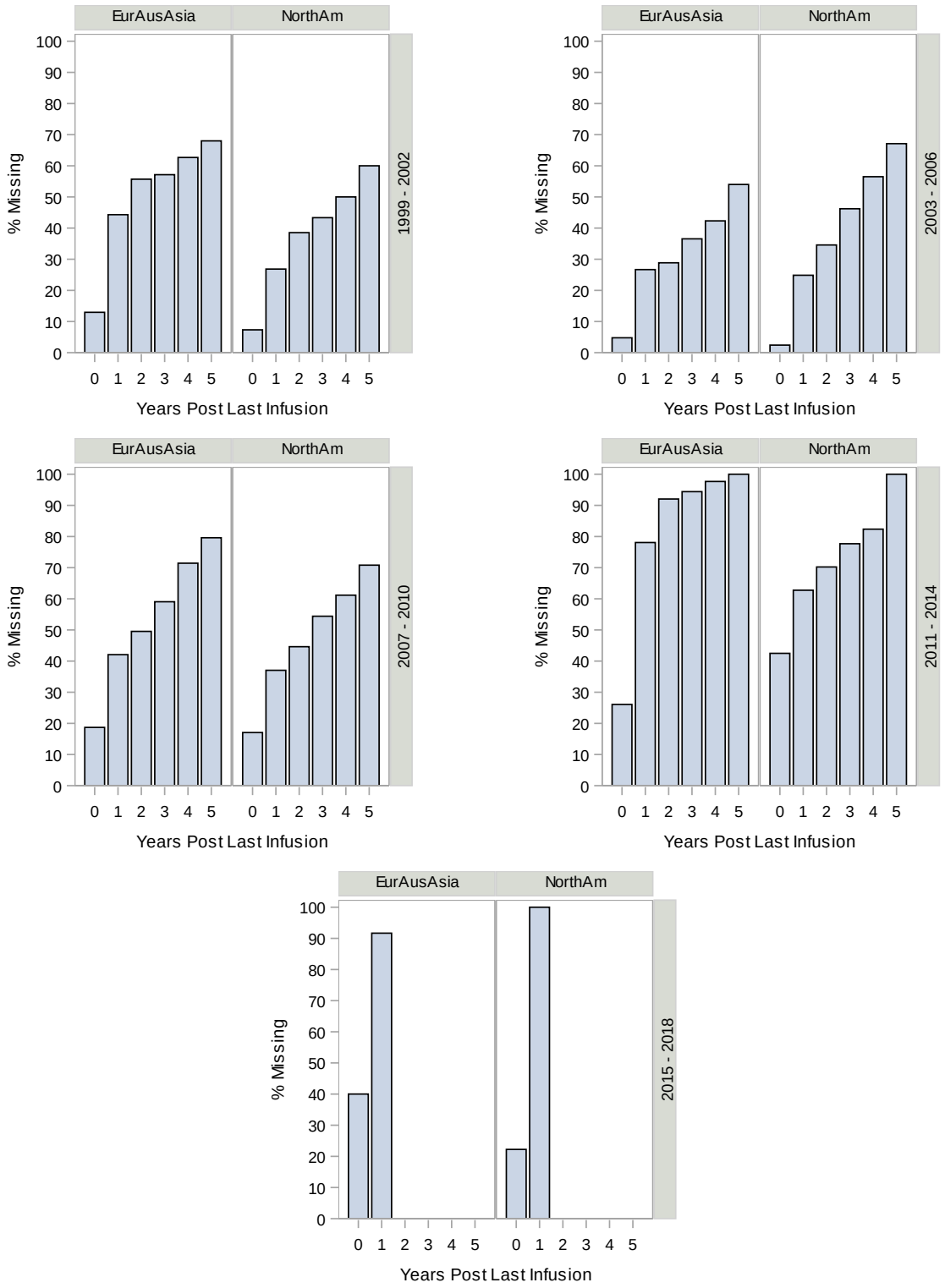


Exhibit 8 – 7
Missing Data for Clarke Score by Era and Continent

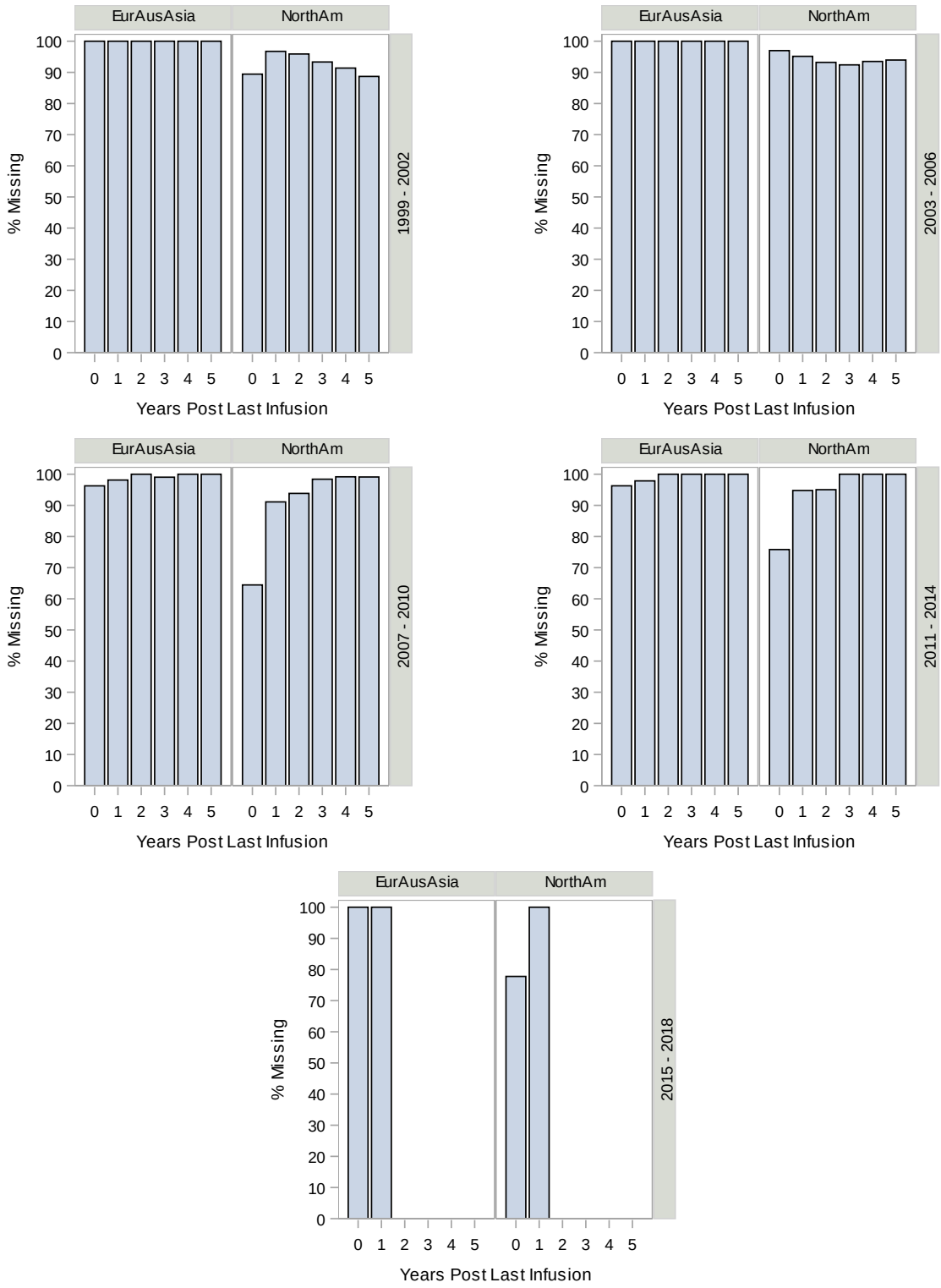


Exhibit 8 – 8
Missing Data for Ryan Hypo by Era and Continent

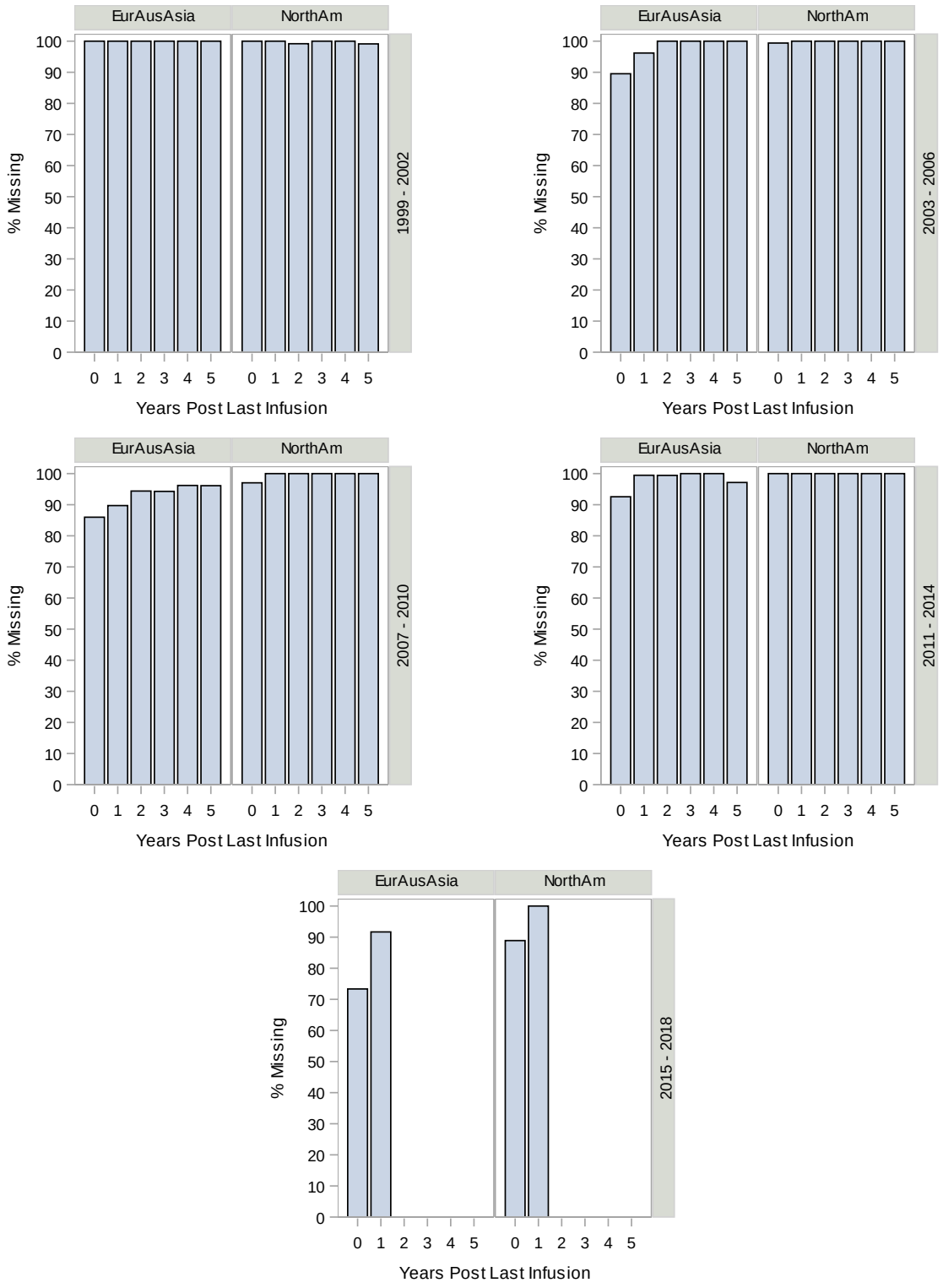


Exhibit 8 – 9
Missing Data for C-Peptide AUC by Era and Continent

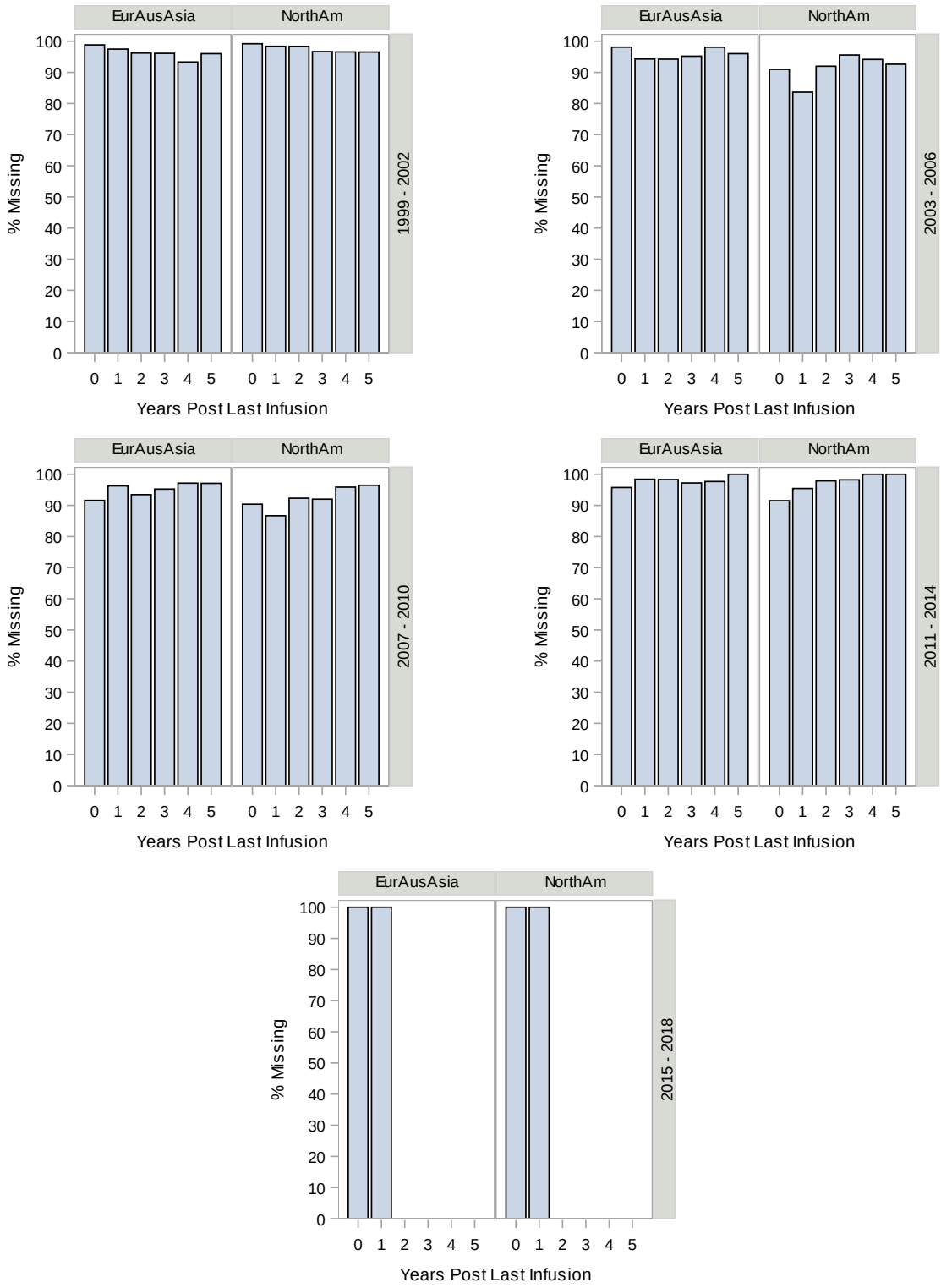


Exhibit 8 – 10
Missing Data for Cockcroft-Gaullt by Era and Continent

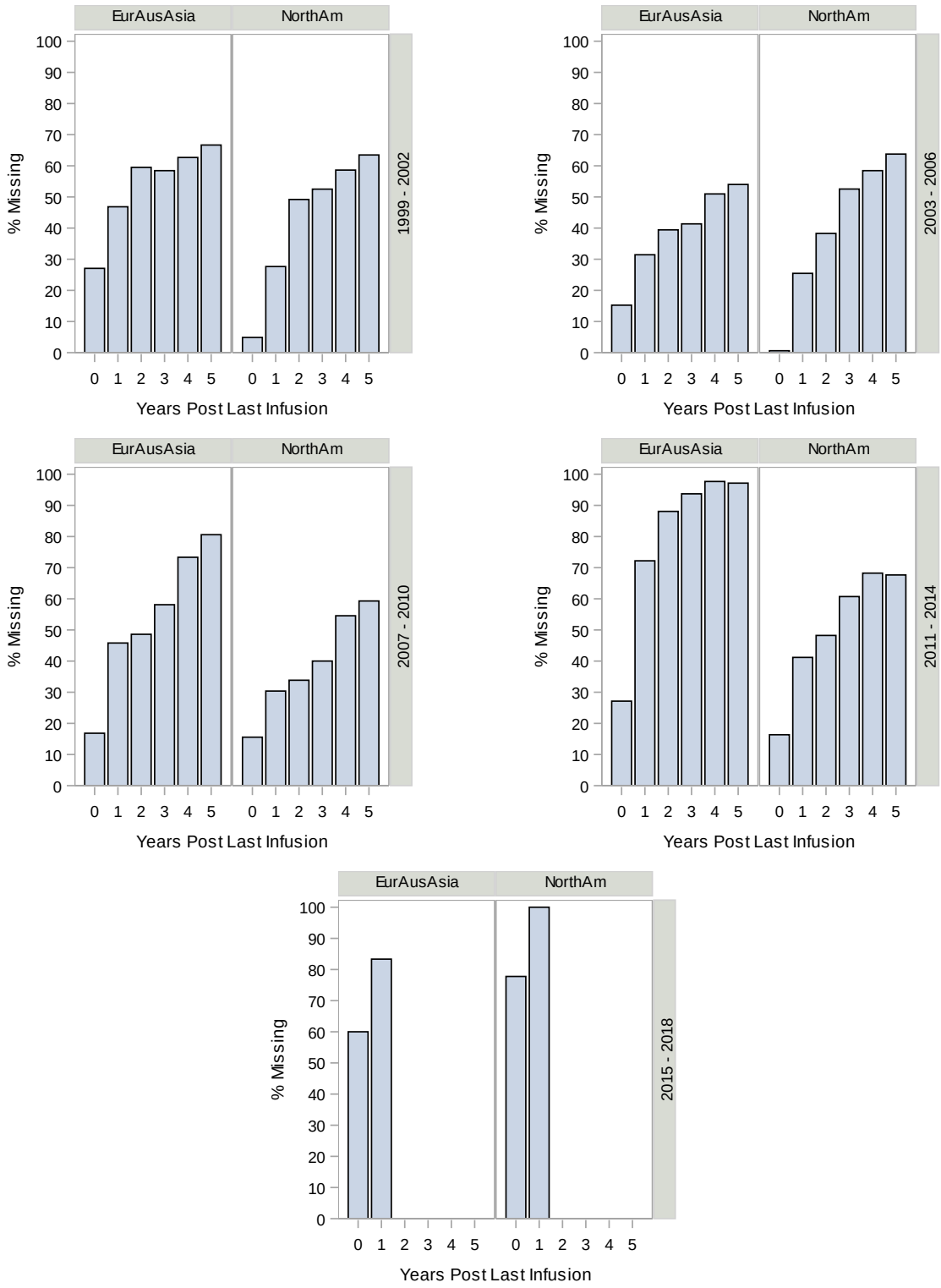


Exhibit 8 – 11
Missing Data for Creatinine by Era and Continent

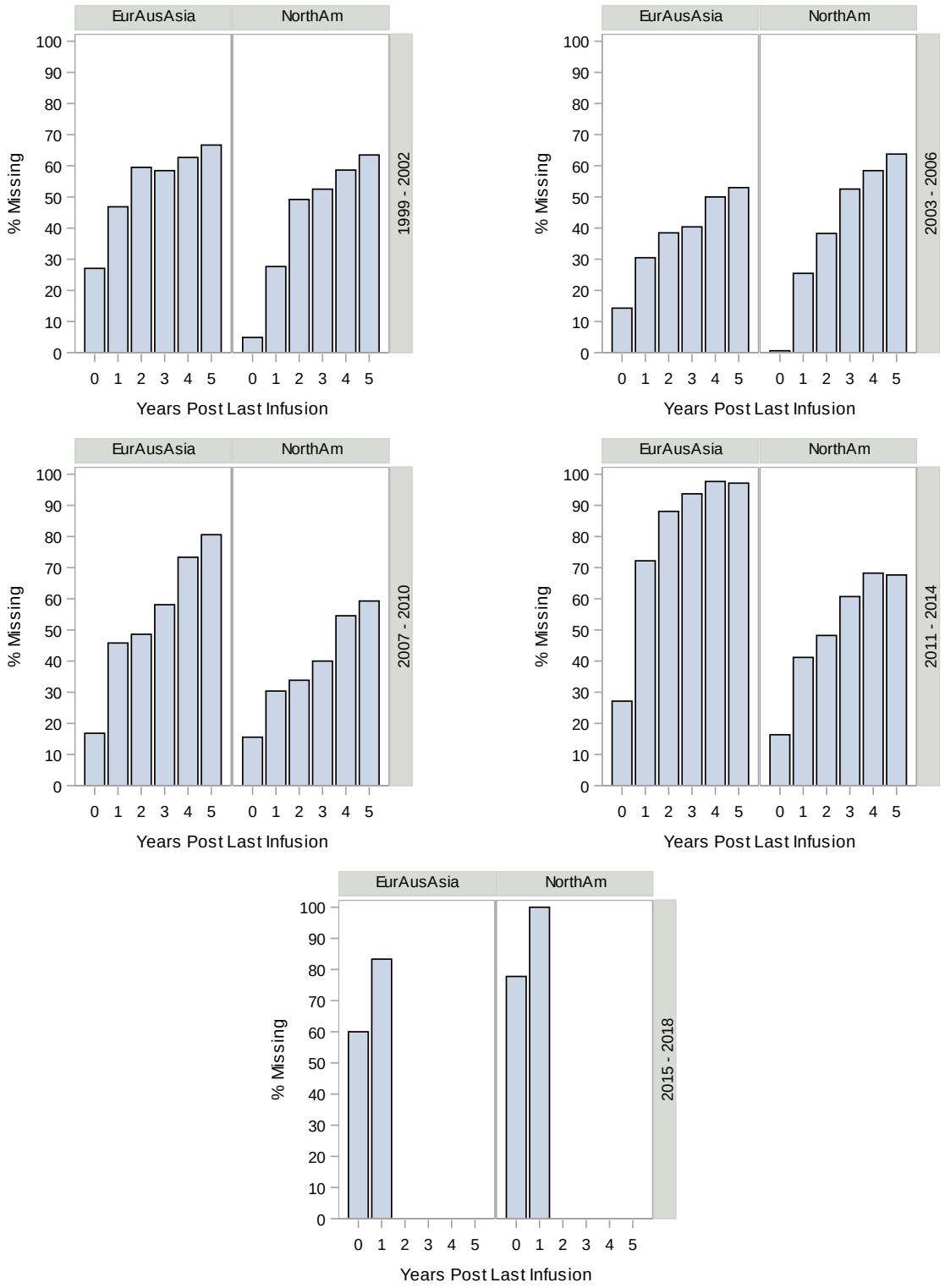


Exhibit 8 – 12
Missing Data for Cholesterol by Era and Continent

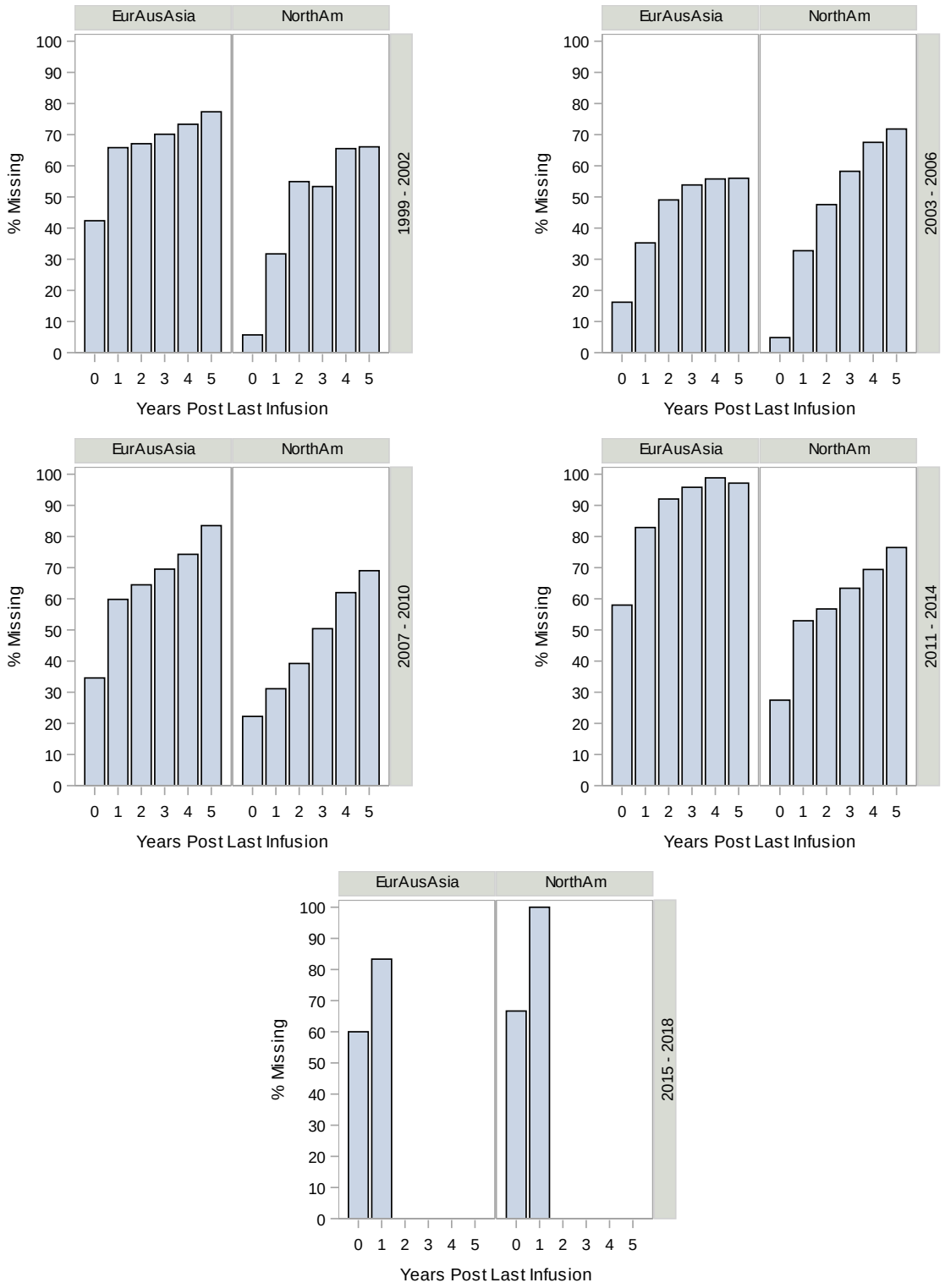


Exhibit 8 – 13
Missing Data for HDL by Era and Continent

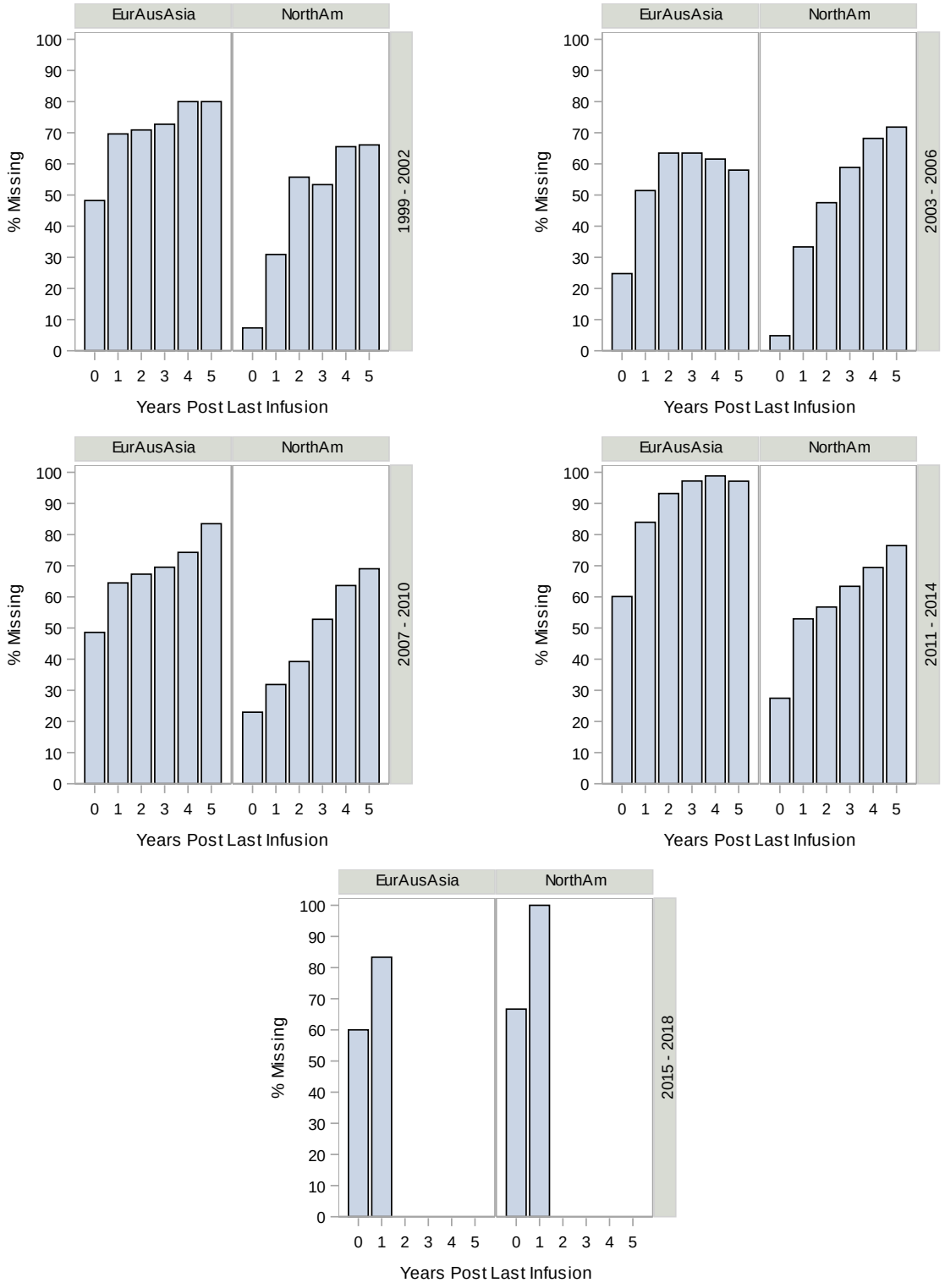


Exhibit 8 – 14
Missing Data for LDL by Era and Continent

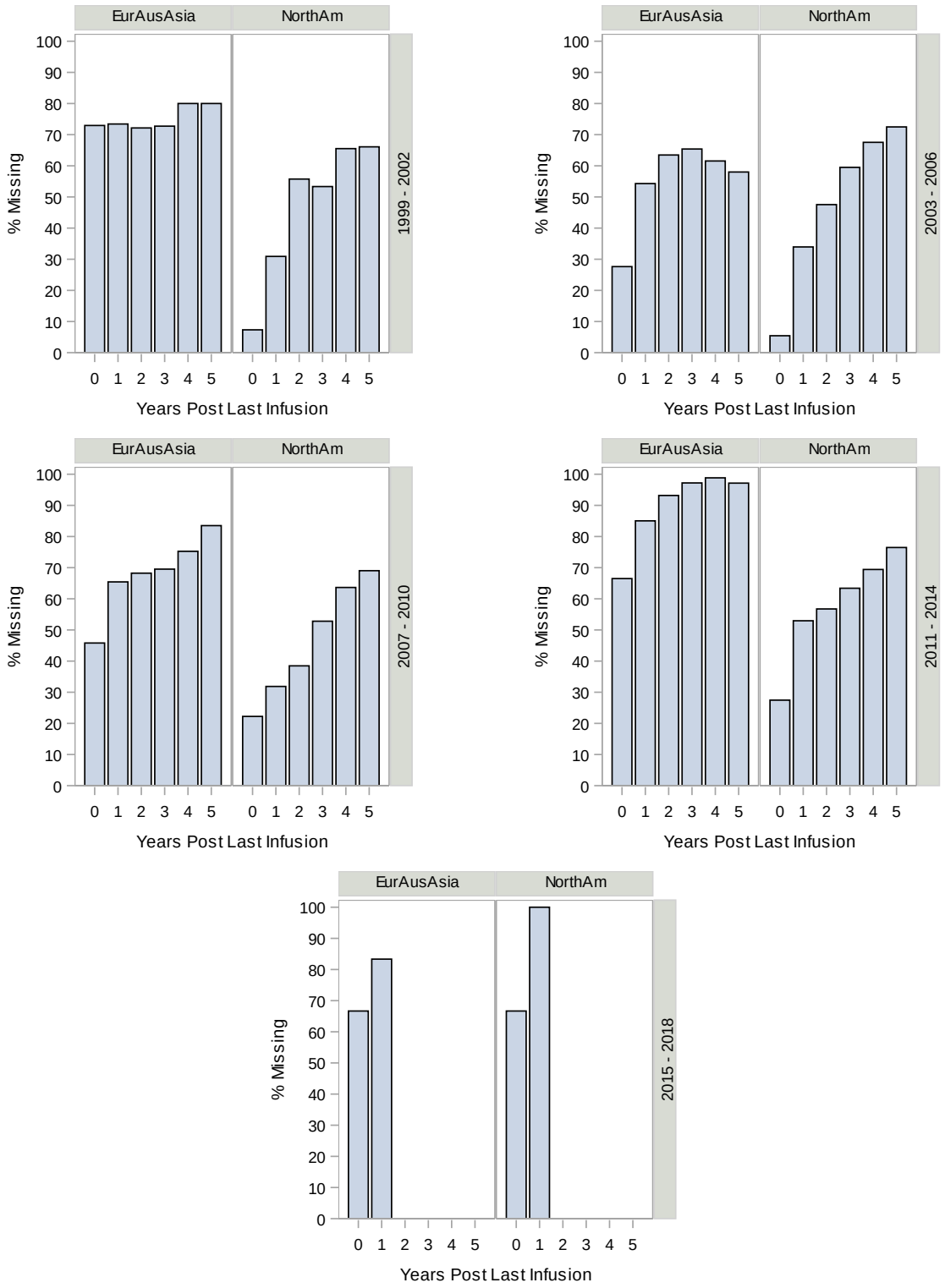


Exhibit 8 – 15
Missing Data for Triglycerides by Era and Continent

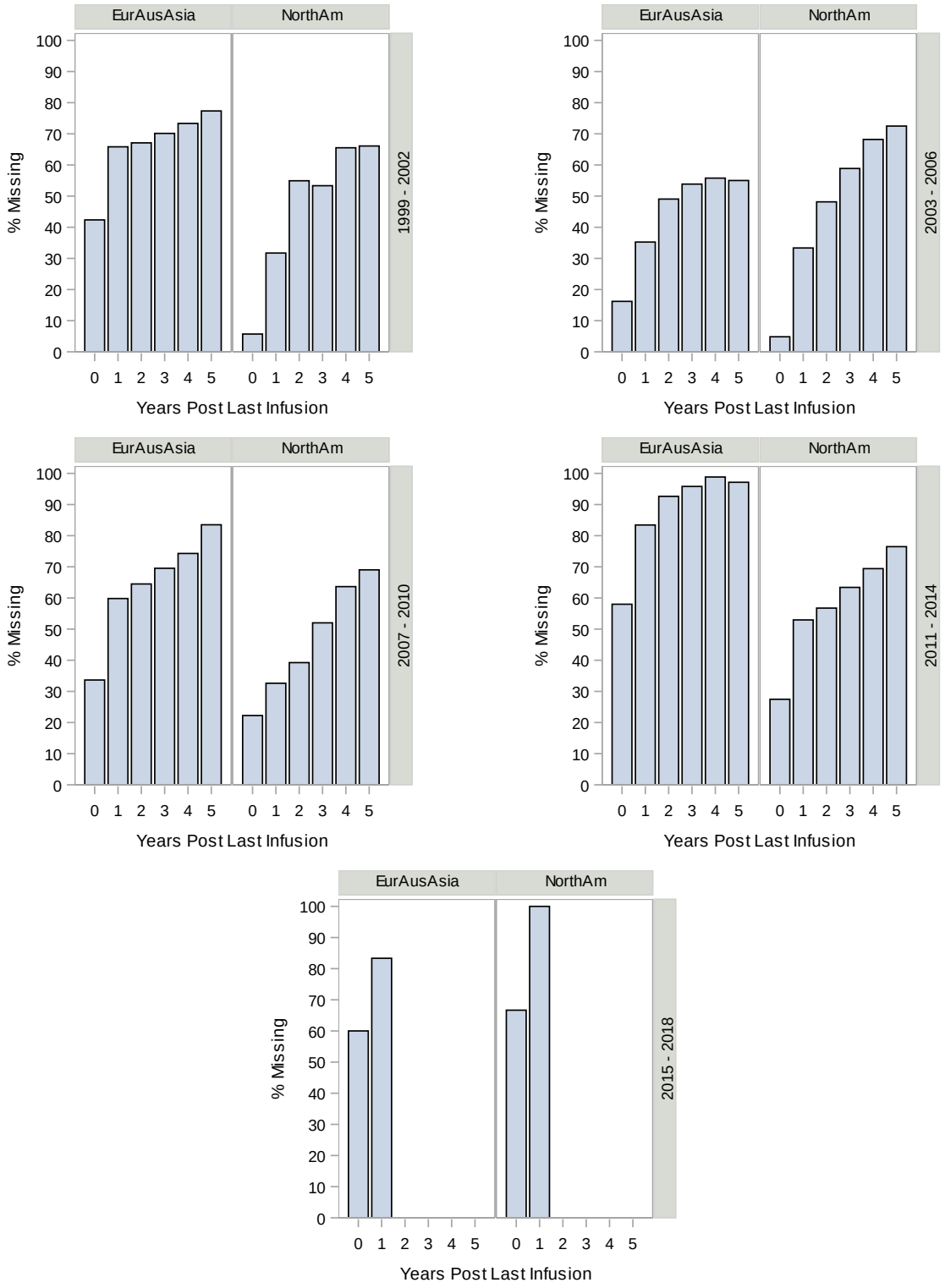


Exhibit 8 – 16
Missing Data for Bilirubin by Era and Continent

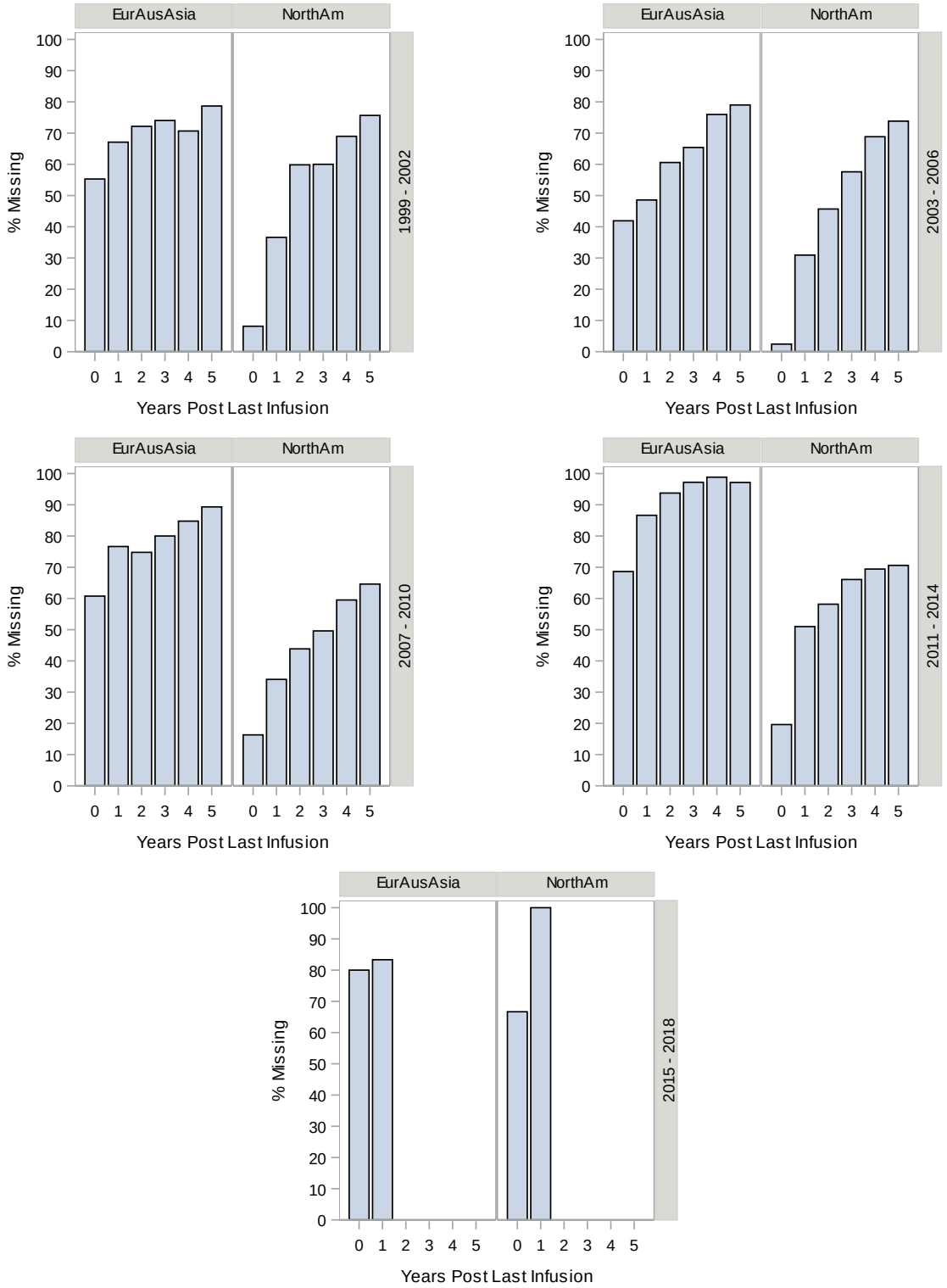


Exhibit 8 – 17
Missing Data for ALT by Era and Continent

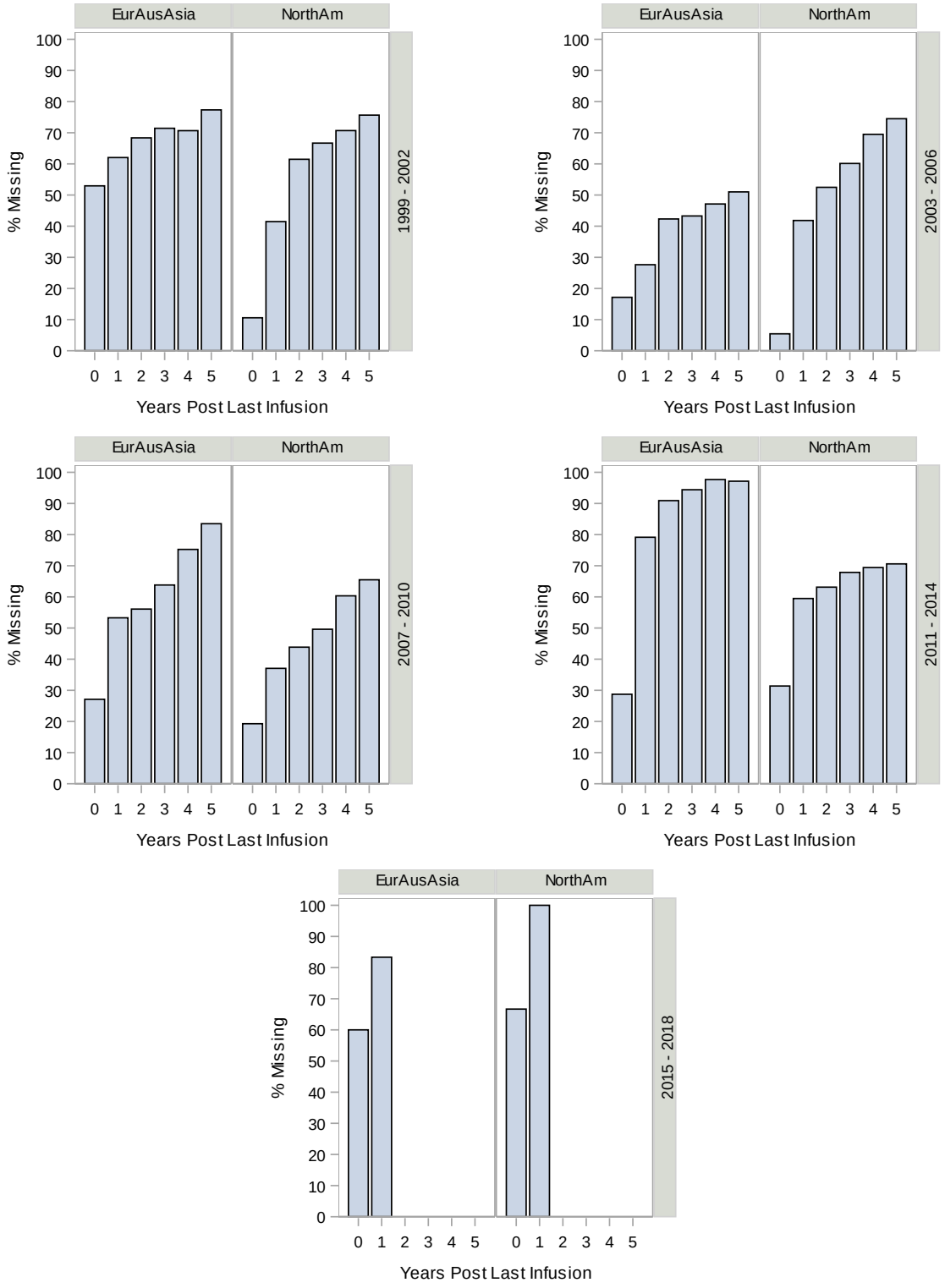


Exhibit 8 – 18
Missing Data for AST by Era and Continent

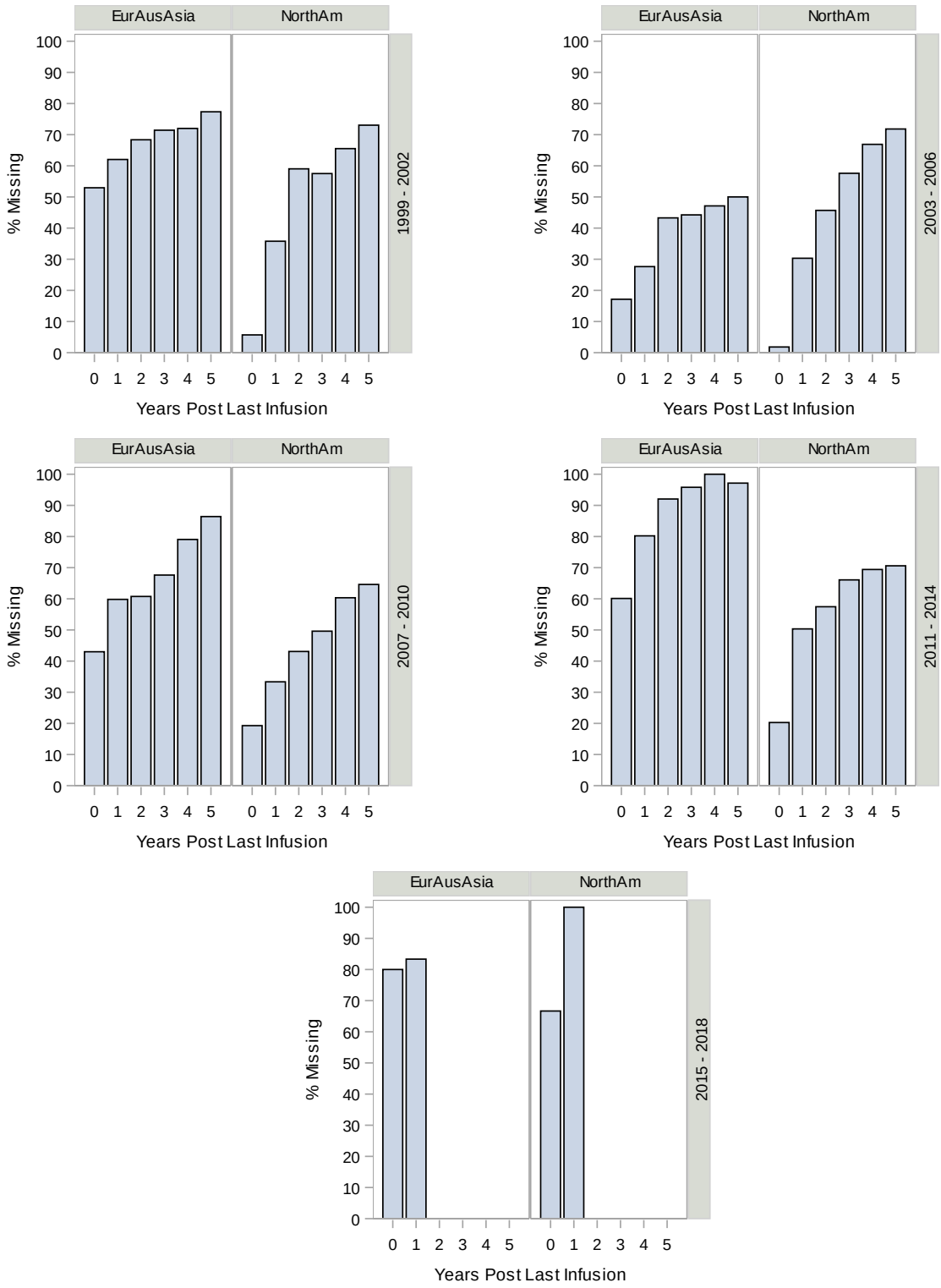
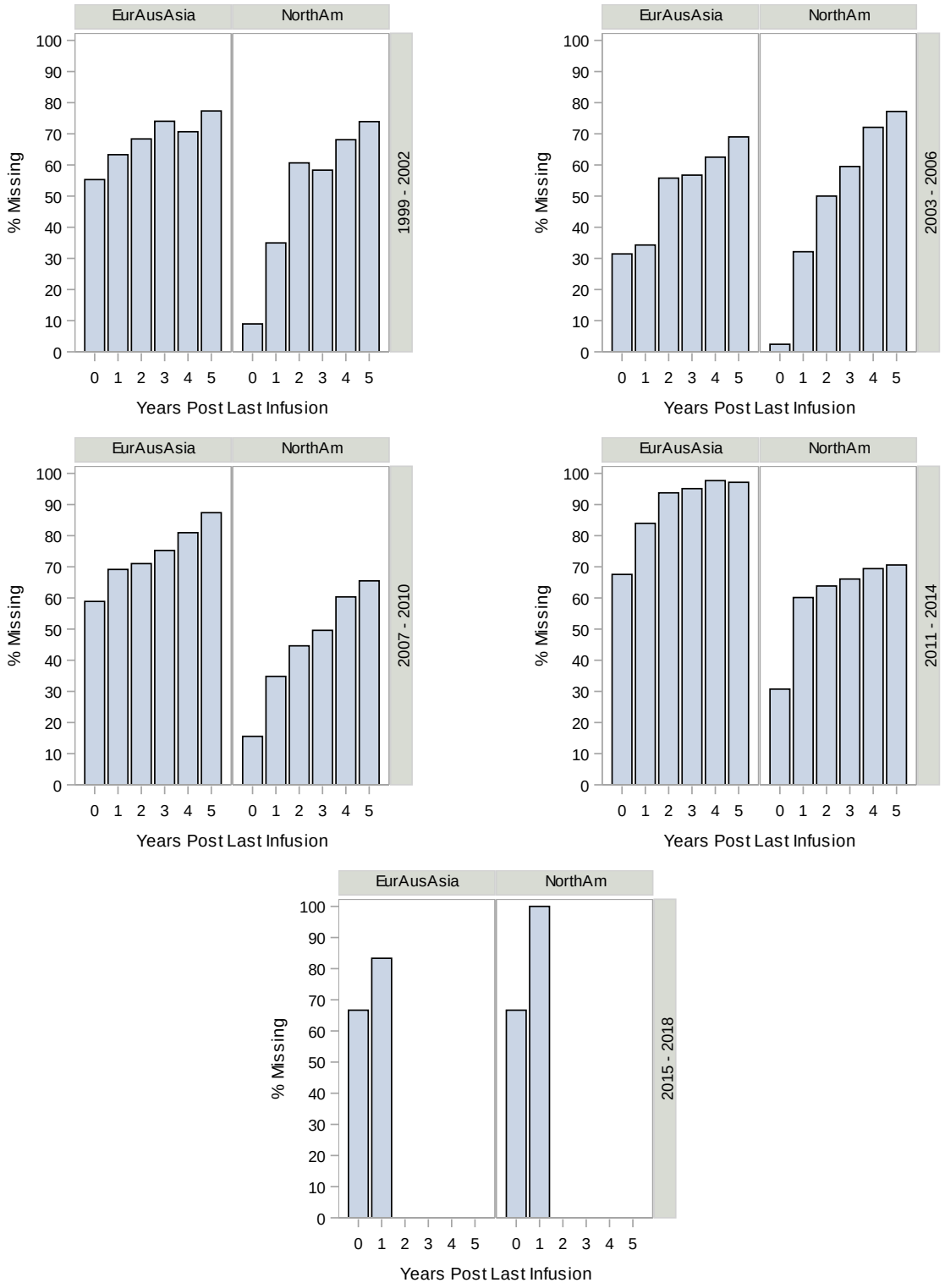


Exhibit 8 – 19
Missing Data for Alkaline Phosphate by Era and Continent



Appendix A: Islet Transplant Center Contributors

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CITR Coordinating Center

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Fouad Kandeel
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