Twelfth Allograft Report

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

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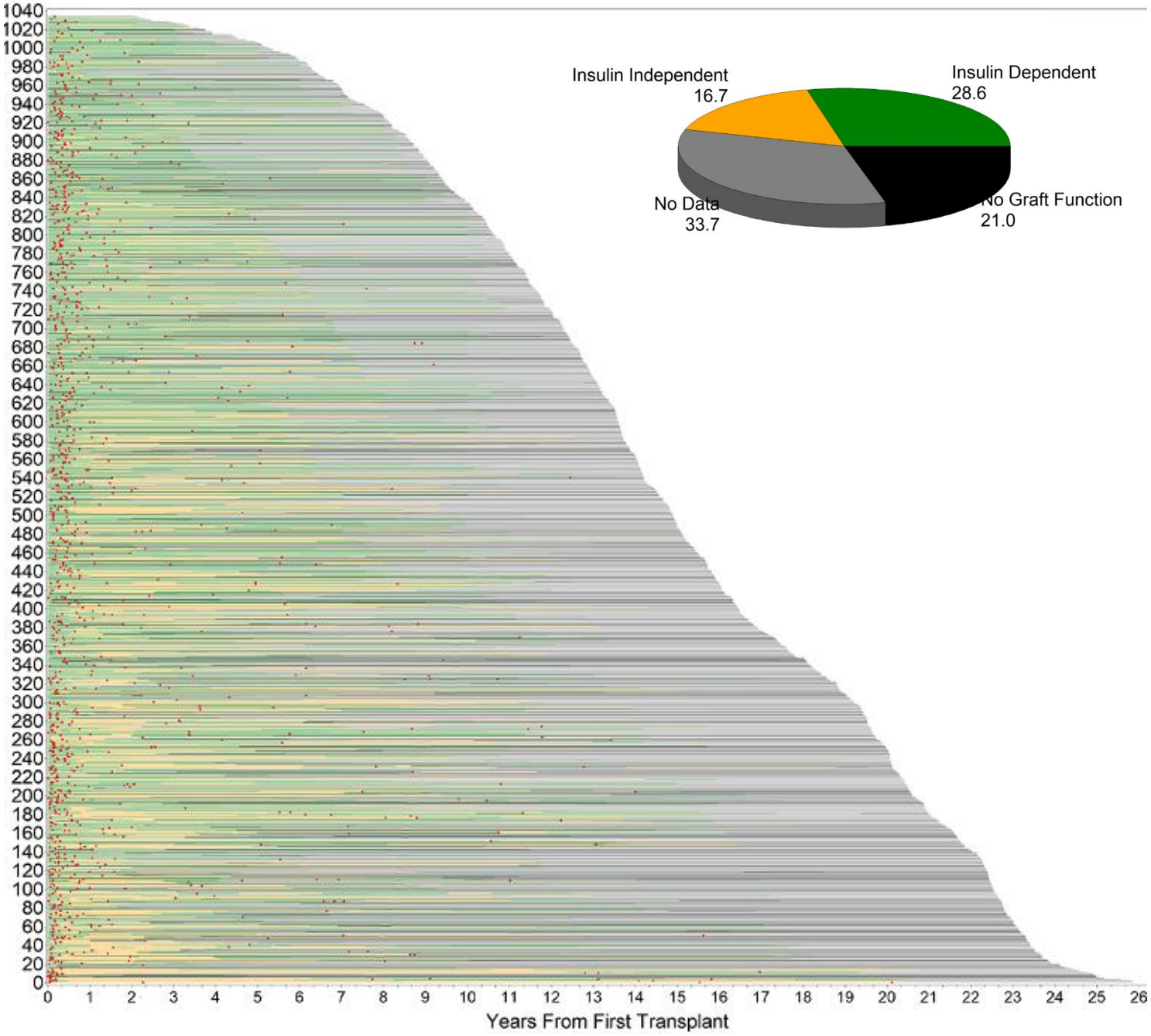
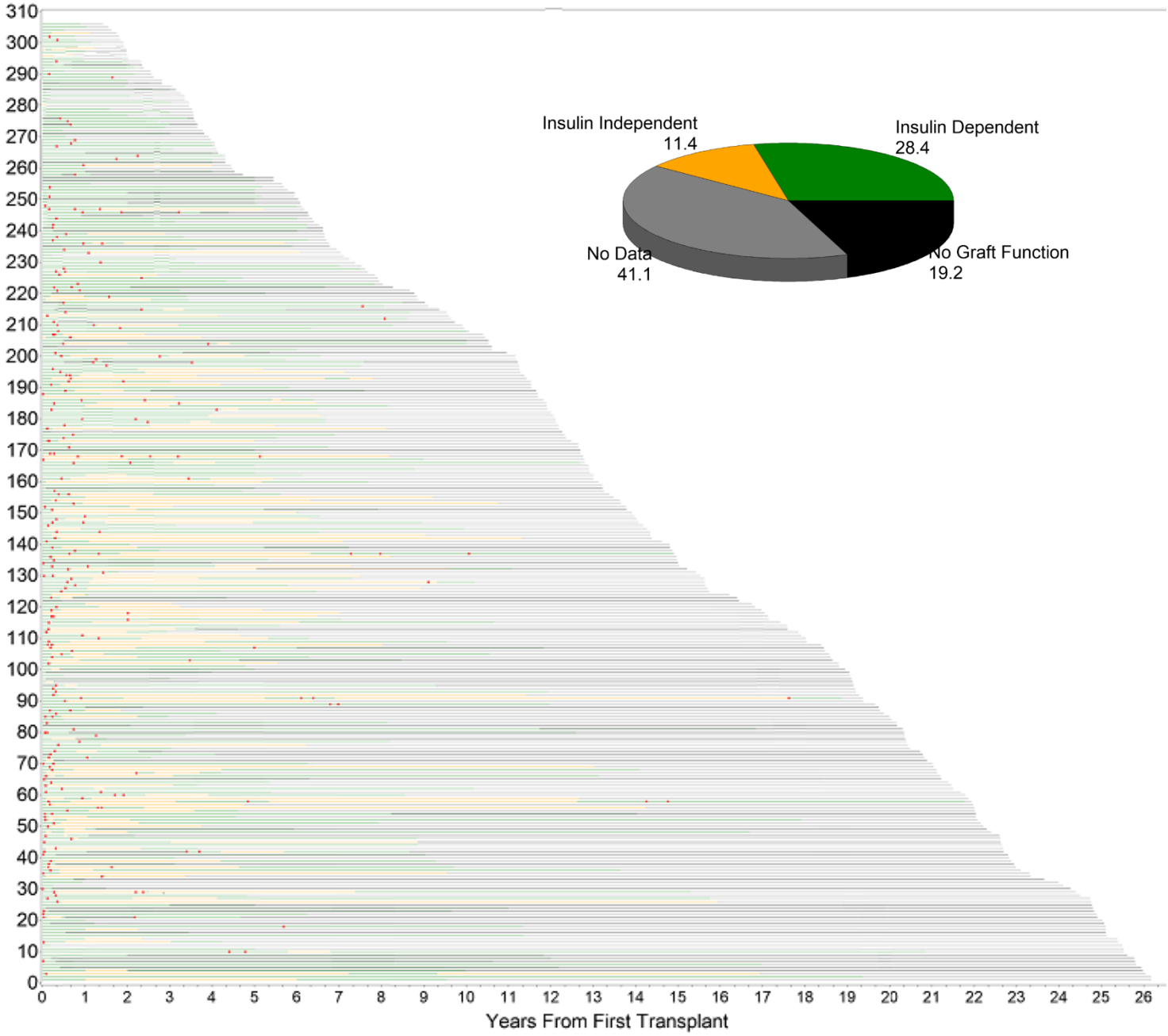


Collaborative Islet Transplant Registry 2025

Islet transplant alone (ITA, N=1,134)
Yellow: insulin independent; Green: insulin-using with graft function; Black: no islet function (C-peptide<0.3 ng/ml); Gray: missing data; Red: re-infusions.
Pie chart shows percent of all follow-up time



Collaborative Islet Transplant Registry 2025

Islet after kidney, simultaneous islet-kidney, or kidney after islet (IAK/SIK/KAI, N=343)
Yellow: insulin independent; Green: insulin-using with graft function; Black: no islet function (C-peptide<0.3 ng/ml); Gray: missing data; Red: re-infusions.
Pie chart shows percent of all follow-up time

COLLABORATIVE ISLET TRANSPLANT REGISTRY

COORDINATING CENTER

June 30, 2025

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
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SUBJECT: CITR Twelfth Allograft Report (2025)

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 Twelfth Allograft Report (infusions as of Dec 2023, follow-up as of March 2025) including data from the great majority of the islet transplant programs active in 1999-2025. We are privileged to have the 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 Company, LLC under the leadership of the CITR Publications and Presentations Committee chaired by Dr. Michael Rickels, and CITR Coordinating Center Principal Investigator, Dr. Elizabeth H. Payne.

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

NOTICE:

The CITR Allograft Report details data received as of March 26, 2025 for all islet transplant recipients transplanted by December 31, 2023.

The Scientific Summary of the CITR Twelfth Allograft Report may be downloaded at www.CITRegistry.org.

Scientific Summary of the Collaborative Islet Transplant Registry (CITR) 2023 Twelfth Allograft Data Report

BACKGROUND AND PURPOSE

Pancreatic islets of Langerhans contain insulin producing beta cells that regulate the utilization of dietary sugars by all cells in the body. In persons with Type 1 diabetes mellitus (T1DM), most of the beta cells are destroyed by an autoimmune attack, resulting in the need for pharmaceutical insulin delivered by injection or pump to avoid diabetes-related illness and death. About 2 million people in the US have Type 1 diabetes mellitus, with this number expected to rise to 5 million by the year 2050. The only alternatives to daily insulin injections or pump currently available are solid organ pancreas transplant or transplantation of islets of Langerhans isolated from a donated pancreas.

Islet transplantation was recently approved by the US Food and Drug Administration (in 2023) for adults with type 1 diabetes complicated by recurrent severe hypoglycemia events. From 2005 through 2017 the Clinical Islet Transplant Consortium (www.CITIsletStudy.org) conducted studies designed to advance the field of islet transplantation. At the Canadian, European and Australian sites, both research and standard of care protocols have been available. Research investigators in clinical islet transplantation and islet science from all such programs have contributed data and collaborated on the data analysis to advance knowledge about the risks and benefits of islet transplantation. Each center may publish the results of their local protocols or aggregate experience, and disseminate information regarding their open and recruiting protocols through their own means and/or at the National Library of Medicine's developed website www.clinicaltrials.gov. In addition, CITR maintains interactive maps of North American and JDRF European and Australian islet transplant programs at www.citregistry.org.

In 2001, the National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) to compile data from all islet transplant programs in North America from 1999 to the present. The Juvenile Diabetes Research Foundation (JDRF) granted additional funding to include the participation of JDRF-funded European and Australian centers from 2006 through 2015. The cumulated North American, European and Australian data are pooled for analyses included in the annual report. CITR Data Reports are publicly available as open access and can be downloaded at www.citregistry.org. **This Scientific Summary highlights results from the CITR 2023 (12th) Allograft Data Report, either by direct inclusion or by reference.**

PATIENTS AND METHODS

From 1999 through 2023 – the cut-off for the 12th Data Report – CITR has collected data on the following groups of study subjects:

- Allogeneic islet transplantation (typically cadaveric donor), performed as either islet-transplant alone (ITA) or islet-after-kidney (IAK). A small number of cases have been performed as islet simultaneous with kidney (SIK) or kidney-after-islet (KAI). SIK and KAI are included in summaries of islet transplant activity presented in Chapter 1 and missing data in Chapter 8 of this report, but were otherwise excluded from analyses to reduce

heterogeneity in the transplant groups (SIK and KAI are more similar to ITA than IAK in terms of immunosuppression, but also similar to IAK in terms of kidney transplant).

- Autologous islet transplantation, performed after total pancreatectomy are also reported to CITR. They are summarized in a separate report.

The 12th Annual Report and this Summary focus on the allogeneic islet transplant recipients. The autologous islet transplant recipients are the subject of a separate report.

The database for the 12th Annual Report was closed for analysis on March 26, 2025 for data on recipients that were first transplanted as of December 31, 2023.

At the time of their first islet transplant (from Chapter 2),

- ITA recipients were, on average, 47±0.3 standard error (STE) years of age, had diabetes 30±0.4 years, and 73% had very poor diabetes control including hypoglycemia unawareness. Poor glycemic control can manifest as frequent episodes of critically low blood sugar levels (which often result as a reaction to injected insulin, requiring the assistance of another person to avert a possibly life-threatening loss of consciousness), wide swings in blood sugar levels (blood glucose lability), or consistently high HbA_{1C} levels (>8% of total hemoglobin).

- IAK recipients were 49±0.6 years of age, had diabetes for 35±0.7 years, and 44% had very poor diabetes control including hypoglycemia unawareness.

Data reported to the Registry are abstracted from medical information that is routinely collected by investigators in the course of their research protocols or clinical practice, and for reports to the multiple agencies and entities required by US-FDA regulated trials or according to the requirements of the respective nation.

Detailed baseline and follow-up data are abstracted pre-infusion (baseline) and at Days 28, 75, Month 6, and annually post infusion. At each new infusion, a new follow-up schedule is established.

As of 2021, by decision of the Executive Committee, only serious adverse events (regardless of grade) are mandatorily reportable to CITR. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center (citr@emmes.com), or viewed at the CITR website (www.citregistry.org).

CITR utilizes the Coordinating Center's (The Emmes Company, LLC, Rockville, MD; www.emmes.com) web-based data entry and management systems to capture data on recipients, donors and pancreata. Additional data are obtained through data sharing agreements with the United Network for Organ Sharing (UNOS) for US donor data, the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers for the islet data, and the Data Coordinating Center of the Clinical Islet Transplant Consortium (CIT, 2005-2017).

The Registry data exists because of the voluntary participation of the transplanting centers, with written informed consent for participation in the Registry by the islet recipients. While the Registry represents the most comprehensive collection of the human islet transplantation experience since 1999, there may exist uncontrollable biases and imbalances including selective reporting and differences in clinical care and decision-making.

Statistical Analysis

In addition to updating information on total islet transplant procedures and descriptions of the recipient, donor, islet and immunosuppression data, a major focus of the present analyses is to continue identifying and corroborating factors of patient selection, islet processing and islet transplantation management that result in the best possible clinical outcomes of islet transplantation. Reduced data reporting, particularly in long-term follow-up, has posed a challenge for the present analyses. The primary endpoints of insulin use, hence independence or not, and fasting C-peptide levels are the most completely available outcomes data. Monitoring site visits have been performed and included data audits for key recipient baseline, primary outcome, and safety data. Additionally, since 2008, site-by-site reviews have been conducted by teleconference as needed to maximize reporting of primary endpoints.

Descriptive analyses include tabular or graphical displays of sample means and their standard deviations (SD) or standard errors (STE), median, interquartile range (IQR) and extremes.

First achievement of insulin independence, as well as complete graft failure, were analyzed by Kaplan-Meier time-to-event analysis with proportional hazards investigation of predictive factors, employing multivariate models to adjust for correlated or confounding factors. Factors identified as meeting significance criteria in modeling are considered predictive based also on significant log-rank test results.

Primary outcomes, analyzed as prevalence (percent) at annual study time points post last infusion, include:

- Insulin independence (≥14 consecutive days)
- C-peptide ≥ 0.3 ng/mL
- HbA1c <7.0%
- Fasting blood glucose of 60-140 mg/dL, and
- Absence of severe hypoglycemic events requiring the assistance of another person to diagnose symptoms or administer treatment
- Combined HbA1c <7.0% and absence of severe hypoglycemic events

An “all-factors-on-all-outcomes” analytical approach was undertaken to uncover the most predictive recipient, donor, islet and medical management practices associated with the greatest success rates in the primary outcomes, within each of ITA and IAK. Analysis of IAK is the subject of a forthcoming publication. Every variable available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome with significance determined at $p<0.01$.

Secondary outcomes include description of laboratory measurements, metabolic test results, liver and kidney function measures, and complications of diabetes.

Safety is monitored by incidence rates of serious adverse events classified by CIT-TCAE criteria and related to either infusion procedure or immunosuppression as determined by the local investigator.

Statistical comparisons are observational in nature: reported p-values are not based on controlled, experimental design but on the available data as a sample of convenience. The results should be used to direct future research and may guide current clinical practice.

Statistical analyses were conducted using SAS 9.4.

RESULTS

Islet Allograft Transplantation Activity 1999-2023. As of December 31, 2023, the CITR Registry included data on 1,477 allogeneic islet transplant recipients (1,134 islet transplant alone, ITA, and 260 islet after kidney, IAK, 77 simultaneous islet kidney, SIK, and 6 kidney after islet, KAI), who received 2,947 infusions from 3,442 donors (Exhibit 1). The North American sites contributed 46% of recipients, while the Eurasian and Australian sites contributed 54%. Combining the ITA and IAK recipients, 28% received a single islet infusion, 48% received two, 20% received three, and 4% received 4-6 infusions.

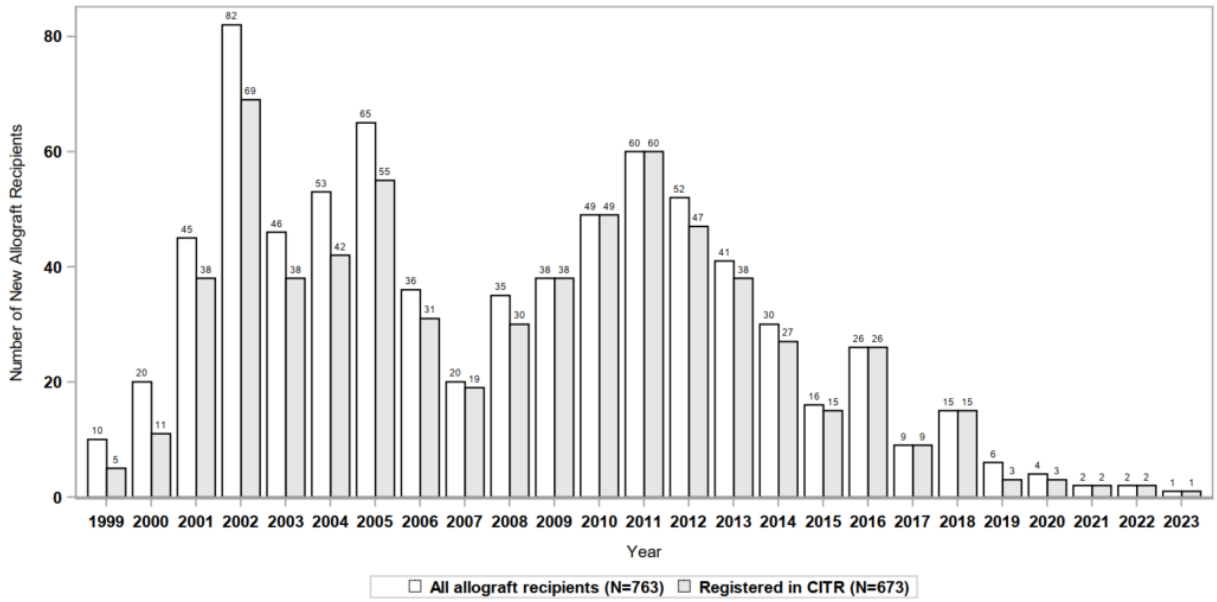
Exhibit 1
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK/KAI
Consented, Registered and First Infused in 1999-2023

	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	**1,134**	583	551	**260**	86	174	**77**	1	76	**6**	3	3	**1,477**
Infusions	**2,329**	1,211	1,118	**471**	157	314	**134**	1	133	**13**	7	6	**2,947**
Donors	**2,764**	1,274	1,490	**528**	167	361	**137**	1	136	**13**	7	6	**3,442**

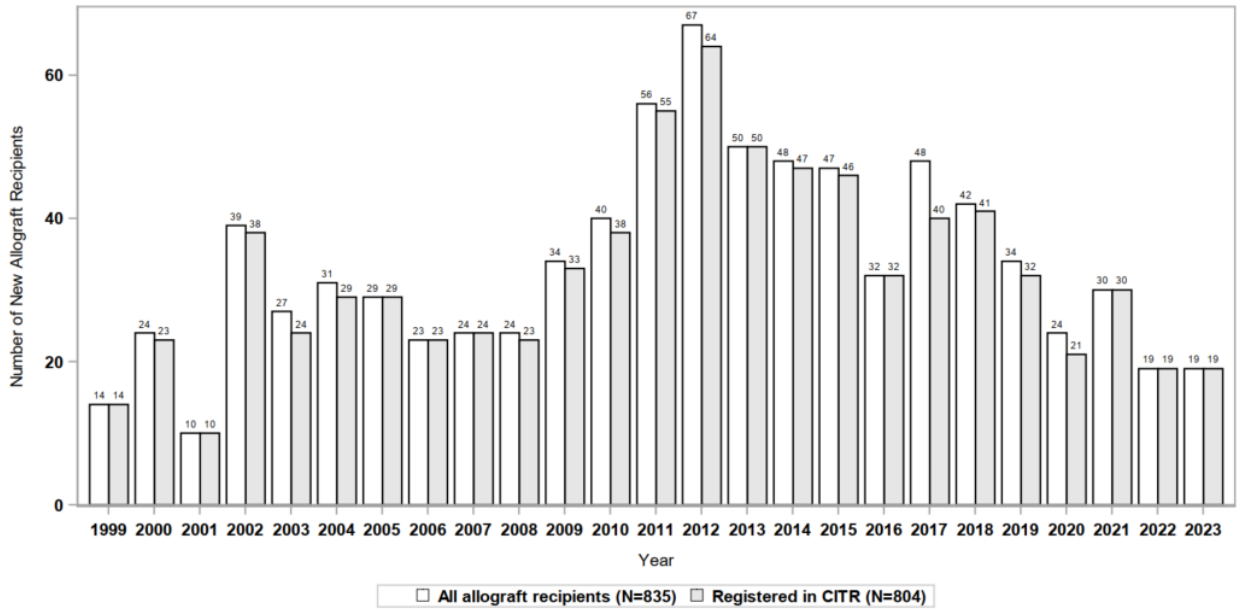
The below Exhibits 2A and 2B display the data collected from the islet transplant programs in North America and the Eurasian and Australian sites by year. Of the 763 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2023, 673 (88%) consented to and were registered in CITR. Of the 835 total reported Eurasian and Australian recipients, 96% (804) were consented and registered in CITR. All sites saw a decline in new recipients around 2007, followed by an increase in following years which peaked in 2011 for North American sites and in 2012 for Eurasian and Australian sites. All sites again saw a decline in the number of new recipients over the 2013 to 2023 period.

Exhibit 2
Total Number of Islet Allograft Recipients, Recipients at CITR-Participating Centers, and Recipients with Detailed Data Reported to CITR by Year of First Islet Allograft Infusion

A. Allograft recipients at CITR North American Centers 1999-2023



B. Allograft recipients at CITR Eurasian and Australian Centers 1999-2023



Islet Transplant Recipient Characteristics. Over the eras of the Registry, the following trends are observed for recipients of allogeneic islets from eras 1999-2006 to 2015-2022, respectively (refer to Chapter 2):

- Recipients have been selected at older age (43±0.4* to 51±0.7) and longer wait time (286±16 days to 423±31days) at initial transplant
- Recipients have been selected with increased use of insulin pump (35% to 50%)
- A lesser proportion had positive GAD65 autoantibody in the earliest era compared to a greater proportion in later years (36% to 55%)
- Recipients had lower levels of total cholesterol (177±1.7 to 168±4.4) and LDL cholesterol (96±1.4 to 85±3.2) in recent years

*Mean±STE

There were also notable differences in medical characteristics between ITA and IAK recipients, most notably, a much lower prevalence of hypoglycemia unawareness (73% vs. 44% for ITA and IAK, respectively), and much lower initial eGFR in the IAK (62±1.5 vs. 91±0.7) recipients.

Donor Information. All allograft donors were deceased. Donor weight and BMI have increased over the eras, from 28.6±0.2 BMI in 1999-2006 to 29.9±0.4 in 2015-2022. Infusions (an "infusion" is defined as all islet products from one, two or three (maximum) donors given to a single recipient on a single day) were comprised of about 57% all male donors, 39% all female donors, and 4% mixed male and female donors. About 18% of infusions derived from Hispanic donors (with the remaining non-Hispanic), while about 10% derived from non-white donors. About 61% of the donors had cerebrovascular accident/stroke as their cause of death while 23% experienced trauma.

About 28% of the donors received a transfusion, while only 6% received a transfusion intraoperatively, during their terminal hospitalization. Sixty-seven percent (67%) of the donors received steroids and 80% received at least one vasopressor during the terminal hospitalization. Fewer donors received a vasopressor in recent eras ($p<0.001$), declining from 97% in 1999-2006 to 47% in 2015-2022. Insulin was administered during hospitalization to 48%. A total of 13 donors tested positive for anti-HBc, three tested positive for RPR-VDRL and two for HCV. Mean serum creatinine of the donors has decreased slightly from 1.2±0 SE to 0.9±0 mg/dL over the prior eras of the registry. Mean maximum stimulated blood glucose decreased from 233±3 SE to 199±6 mg/dL over the prior eras.

Islet product characteristics per infusion (refer to Chapter 3). Total cell volume infused has declined over the eras (3.9±0.1 mL SE in 1999-2006 to 3.4±0.1 mL in 2015-2022). Total IEQs increased from 1999-2006 to 2007-2014 and declined again in the most recent era, but IEQ/Kg recipient have remained fairly stable. Endotoxin (both total and /kg) has declined since the initial era (25.1±2.3 SE to 15.7±4.3 for total). Islet viability has declined over the eras (90.8±0.2 SE to 87.1±0.4).

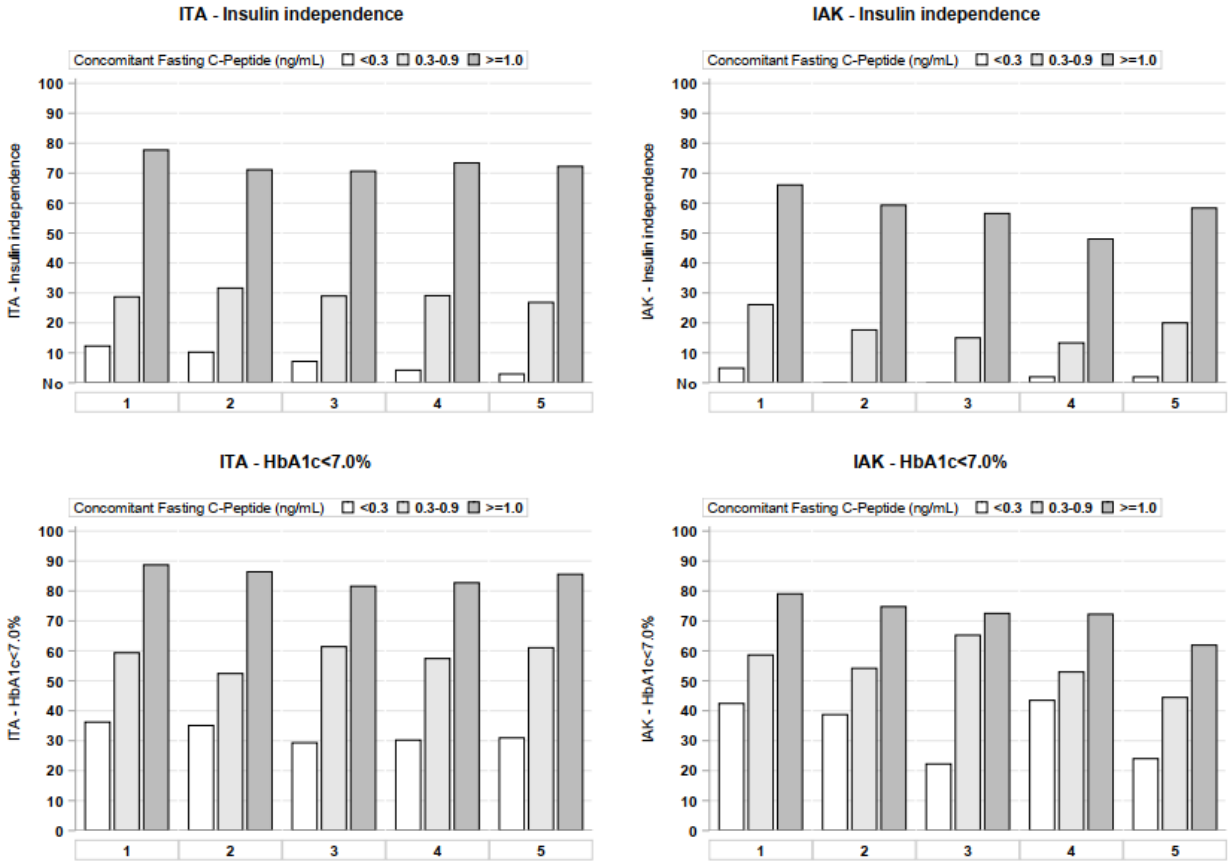
Immunosuppression therapy (refer to Chapter 4). Induction with IL2R antagonists only, which comprised about 53% of all initial infusions in 1999-2006, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in about 46% of the new infusions performed since 2015. In 1999-2006, maintenance immunosuppression was predominantly (61%) calcineurin (CNI)+mTOR inhibitors. It was increasingly replaced or supplemented throughout the eras by a CNI and IMPDH-inhibitor combination; in 2015-2022, CNI+mTOR inhibitors were used in 10% of new infusions while CNI+IMPDH inhibitors were used in about 78%.

Graft Function. First achievement of insulin independence measured from initial islet infusion, with or without subsequent infusion, is an indicator of the rate of engraftment under real-time conditions that include early graft loss, islet resource availability, patient/doctor decisions and myriad other factors, some of which are characterized in the CITR data and others not. It is notable that the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions.

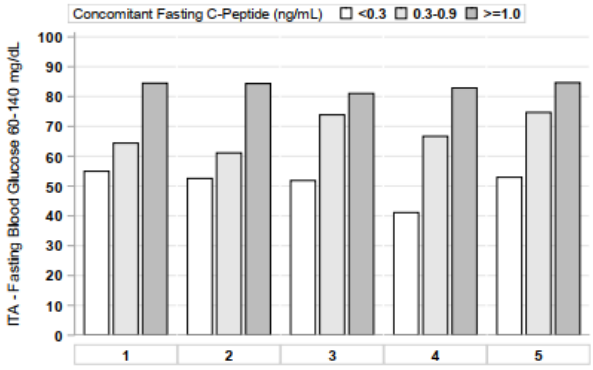
The primary endpoints are analyzed as prevalence at annual time points post last infusion to isolate the factors that optimized the outcomes. Refer to Chapter 5 for detailed outputs.

In both transplant groups, the higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<7.0%, FBG of 60-140 mg/dL, and the lower the likelihood of severe hypoglycemia (Exhibit 3). Even partial graft function, i.e., fasting C-peptide of 0.3-0.9 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced from pre-infusion (baseline) over all follow-up even with C-peptide<0.3 ng/mL.

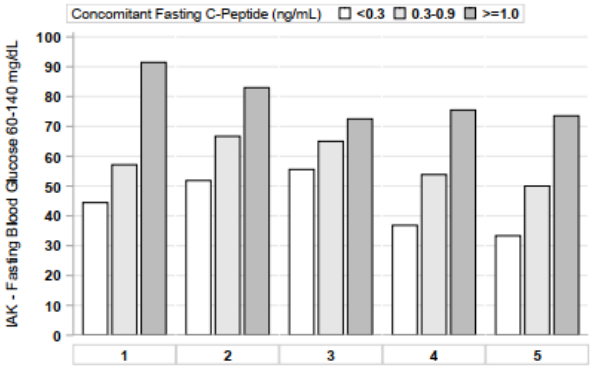
Exhibit 3
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years1-5 Post Last Infusion



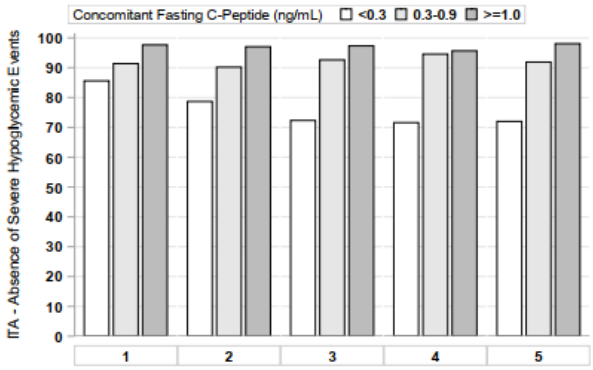
ITA - Fasting Blood Glucose 60-140 mg/dL



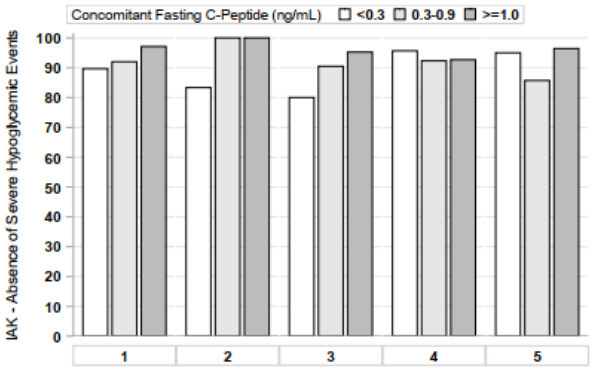
IAK - Fasting Blood Glucose 60-140 mg/dL



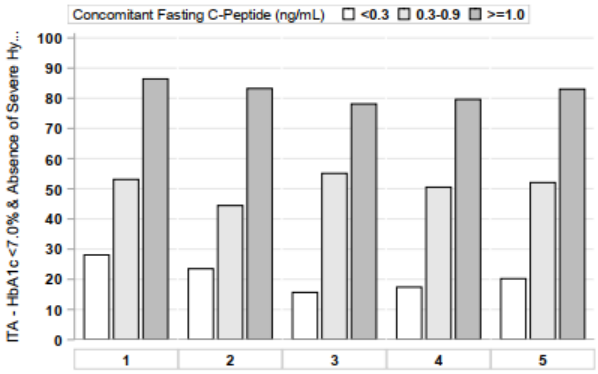
ITA - Absence of Severe Hypoglycemic Events



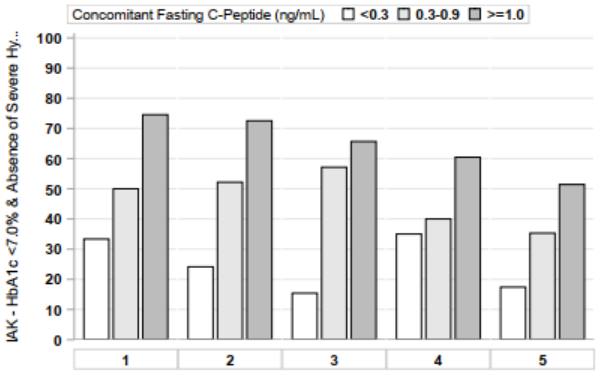
IAK - Absence of Severe Hypoglycemic Events



ITA - HbA1c <7.0% & Absence of Severe Hypoglycemic Events



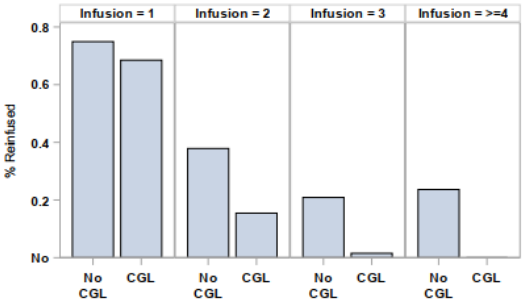
IAK - HbA1c <7.0% & Absence of Severe Hypoglycemic Events

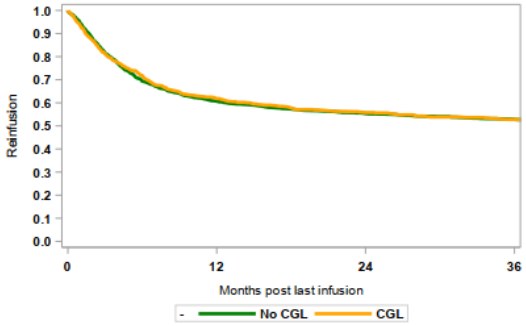


Over the years of the CITR data, re-infusion (Exhibit 4) has been performed in 73% of allograft recipients. It may have been performed after complete graft failure (no detectable C-peptide), or while the recipient still had at least some graft function (C-peptide≥0.3 ng/mL), or even while the patient was fully insulin independent. The group most likely to be re-infused were those who were not insulin independent (Exhibit 4B). This Kaplan-Meier also shows that time to re-infusion varied substantially from days to years. Re-infusions also appear to have occurred sooner in the earliest era (Exhibit 4C) and did not differ significantly by transplant type (Exhibit 4D).

Exhibit 4
Re-infusion (Kaplan-Meier), over all infusions

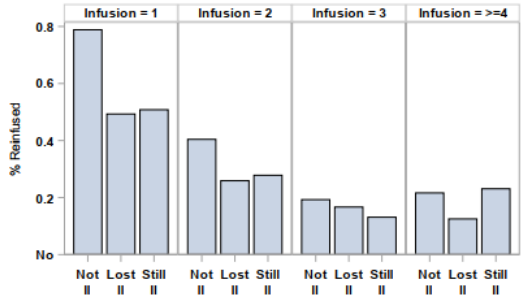
A. By previous complete graft loss (CGL) (p=0.606)

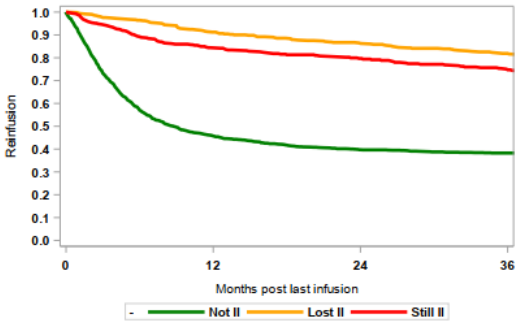




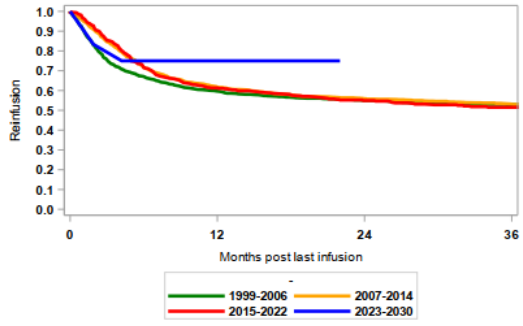
	Reinfusion		
	No	Yes	Total
	N	N	N
Infusion 1	347	928	1275
Infusion 2	613	315	928
Infusion 3	262	53	315
Infusion >=4	53	13	66
All	1275	1309	2584

B. By concurrent insulin independence (II) (p=<0.001)

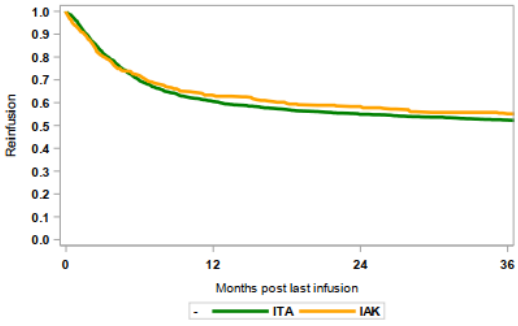




C. By Era (p=0.011)



D. By Transplant Type (p=0.193)



Adverse Effects (laboratory determinations and reported adverse events). Data collection on serious adverse events and other effects of islet transplantation continues for all islet transplant recipients. Confirmation via regularly scheduled site visits that include 100% data audit for adverse events has occurred as needed. The reported data are coded for system/organ class and preferred term for tabulation and summary reporting, using the Medical Dictionary for Regulatory Activities, a part of the overall data quality and assurance process integral to The Emmes Corporation's Advantage EDC system. The coding is conducted by trained Emmes medical coders. Over the years of the Registry, both the MedDRA lexicon and coding processes, as well as the data structures for reporting adverse events have evolved. As of the 11th Allograft Data Report, the entire history of serious adverse events was re-coded to the current MedDRA lexicon (Version 19.0 or above), using a uniform process and the most complete descriptions of all the reported adverse events.

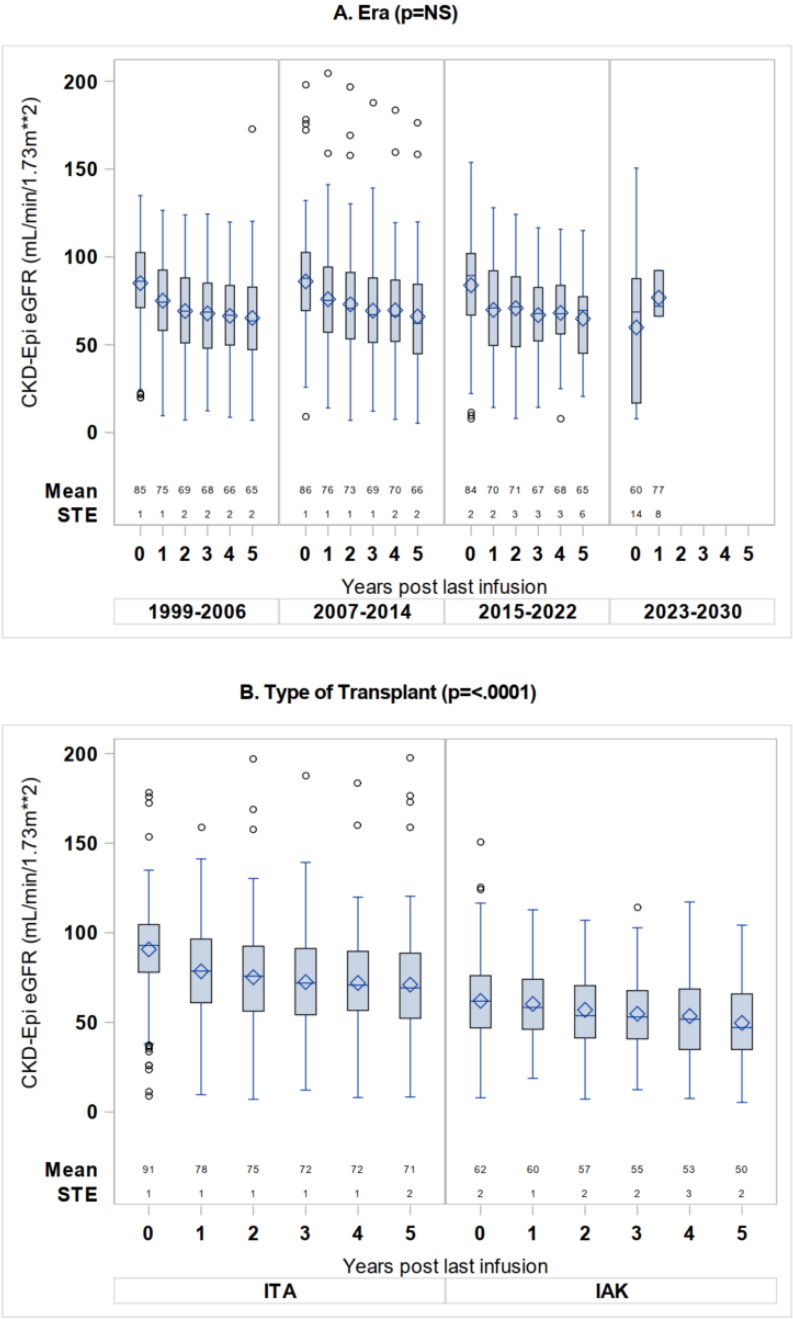
From the laboratory determinations (refer to Chapter 6), ALT and AST levels typically rise after islet transplantation then level off, although mean values consistently remained <30 IU/L. ALT levels decreased after the first year post-last infusion among recipients who received maintenance immunosuppression with CNI+IMPDH, but ALT remained elevated among those who received other regimens (p=0.0057). A similar trend (p=0.0013) with respect to rise after islet transplantation and maintenance immunosuppression regimen is observed for AST. AST levels over 5 years post-last infusion were highest in those who received IL2RA only for induction immunosuppression (p=0.0006), while those receiving other regimens gradually returned to baseline levels after an increase in Year 1.

Serum creatinine rose over years of follow-up after initial islet transplant, in both ITA and IAK, but started higher in IAK. Those aged 35 and over also had higher initial levels.

The decline in eGFR (CKD-EPI) after islet transplantation differing by transplant type is both statistically significant and clinically important (p<0.0001). IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate. Refer to Exhibit 5 below. Initial levels were also lower in recipients age 35 and older and declined at a slower rate compared to younger recipients. Levels were generally lower among recipients managed with CNI+IMPDH compared to other maintenance immunosuppression regimens (p=0.0002).

Compared with an age-unadjusted cohort of 1,141 T1D followed by the Diabetes Control and Complications Trial and then by the Epidemiology of Diabetes Interventions and Complications (EDIC) (The DCCT/EDIC Research Group, 2011) who started with mean eGFR (also CKD-EPI) levels of 126 ml/min/1.73m^3, CITR allograft recipients had much lower mean eGFR (91±1SE for ITA and 62±2 for IAK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 20 ml/min/1.73m3 and IAK experienced a mean decline of 12 ml/min/1.73m^3 at 5 years from last infusion, compared to a mean decline of about 9 ml/min/1.73m^3 over the first 5 years in the DCCT.

Exhibit 5
Chronic Kidney Disease Collaboration (CKD-EPI) Estimated GFR (mL/min/1.73m2)



Malignancies. A total of 188 instances of malignancy have been diagnosed in 100 of the 1,394 ITA/IAK islet recipients who collectively represent a total of 10,472 person-years of observed follow-up. This equates to about 0.02 neoplasms per person-year. Of all malignancies reported, 60% were deemed possibly related to immunosuppression, and 12% definitely related. The outcomes of 72% of events were complete recovery with an additional 5% recovered with sequelae. There were 41 instances in 28 patients of basal carcinoma of the skin and 84 instances in 43 patients of squamous carcinoma of the skin. Refer to Chapter 7 for details.

Deaths. There have been 70 reports of death to the Registry for ITA/IAK recipients, for 5.0% crude mortality. A listing of causes of death is provided in Chapter 7. Ten deaths due to cancer occurred. Twenty-four deaths did not have a cause specified.

CONCLUSIONS

The number of North American centers performing allogeneic islet transplantation, as well as the number allogeneic islet transplant recipients have fluctuated substantially over the life of the CITR, with the number of centers peaking in 2005 and then declining in 2006/2007. With the addition of Clinical Islet Transplantation (CIT) Consortium protocols from 2008 to 2015, the number of new islet cell recipients rebounded somewhat in North America from 2008 through 2012, but activity has since declined again. New allograft recipient activity at the Eurasian and Australian sites has paralleled the North American experience.

The safety-risk profile indicates that over 1999-2025, recipients of allogeneic islet transplantation were much more impacted by their disease than either of the DCCT-EDIC T1D cohorts, being substantially older, having diabetes for many more years, exhibiting much more impaired kidney function at initial transplant, and suffering from very poor glycemic control marked by frequent episodes of severe hypoglycemia. Despite the burden of immunosuppression, CITR allograft recipients exhibited substantial benefit with acceptable risk as evidenced by low levels of infusion-related complications, and relatively few events of immunosuppression-related cancer and death. Increased cancer risk is associated with both diabetes (Hemkens, et al., 2009; Suh, 2011; Noto, Osame, Sasazuki, and Noda 2010) and solid organ transplantation (Engels, et al., 2011), making it difficult to predict expected rates of neoplasm in diabetic islet transplant recipients. Declining kidney function, while of concern, is not comparable to the full DCCT-EDIC cohorts: in CITR allograft recipients, eGFR started much lower relative to the DCCT-EDIC cohorts, declined at higher rates in the ITA group and declined at similar rates in the IAK group, which were very low to start.

The most remarkable clinical effect of islet transplantation are the very high levels of resolution of severe hypoglycemic events which are sustained long-term, even after complete loss of graft function (Exhibit 3 – while the event rates for absence of severe hypoglycemic events (ASHE) are lower when C-peptide is <0.3 ng/mL, they are still at least 70%). The predictor of clinical benefit appears to be maintenance of C-peptide≥0.3 ng/mL: the higher, the better (Exhibit 3, all panels).

Acknowledgments and Disclaimers

The Collaborative Islet Transplant Registry is funded by the National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, USA, and by a supplemental grant from the Juvenile Diabetes Foundation International. Additional data is made available through cooperative agreements with the US United Network for Organ Sharing, Alexandria, VA, and the Administrative and Bioinformatics Coordinating Center of the City of Hope, Duarte, CA (1999-2009). The CITR investigators (roster available at www.citregistry.org) have contributed data used in this report. The principal investigator and biostatisticians of the CITR Coordinating Center (roster available at www.citregistry.org), had full access to all the study data and assume responsibility for the integrity of the data, the accuracy of the data analysis, and the overall results and conclusions presented. Members of the CITR Publications and Presentations Committee over the life of the Registry (roster available at www.citregistry.org) contributed substantially to the analysis of the data and interpretation of the results. No collaborator discloses any conflict of interest in reporting the results presented in the CITR Annual Reports or the Scientific Summary. The voluntary participation of the islet transplant recipients is gratefully acknowledged.

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Table of Contents

Detailed Methods and Definitions

Background and Purpose

Funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) 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 Network Data Reports. This twelfth allograft report summarizing Registry progress summarizes information on patients who received one or more islet cell transplants between 1999 and 2023. All CITR Network Data Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Status and History

This report focuses on 1,477 islet allograft recipients (1,134 islet alone, 260 islet after kidney, 77 simultaneous islet kidney, and 6 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 December 31, 2023, a total of 1,320 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 Network Data Reports to date.

CITR Allograft Reports (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
Eleventh (2020)	1,399	2,832	3,326
Twelfth (2023)	1,477	2,947	3,442

The current report represents a 5.6% increase in the number of recipients, a 4.1% increase in the

number of infusion procedures, and 3.5% increase in donors, compared to the 11th 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.

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 have been sent regular questionnaires 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 ≥0.3 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
- Serious 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 cumulative incidence curves, Kaplan-Meier time-to-event curves or hazard estimates 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 cumulative incidence curves, Kaplan-Meier curves, 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. Nominal statistical significance of analyses presented in other CITR Network Data Reports may be based on different sample sizes and therefore vary by 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, mixed effects models were used to estimate effects at a population level and allow analysis of individual trajectories of outcomes over longitudinal follow-up. Mixed effects models are robust to missing data -- common in registry studies. They assume data missing at random (MAR). Univariate models were used to identify possible associations with the outcomes. 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.

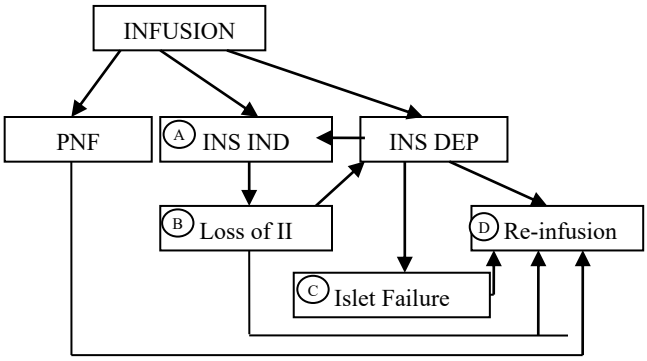


Figure 1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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 complements the independent state, it is not modeled separately. Because of low event numbers, primary non-function is not analyzed. The final state of death has occurred too infrequently in the registry data 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 Network Data 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. Therefore, analysis of this outcome state is done by logistic regression in addition to considering time to event.

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.

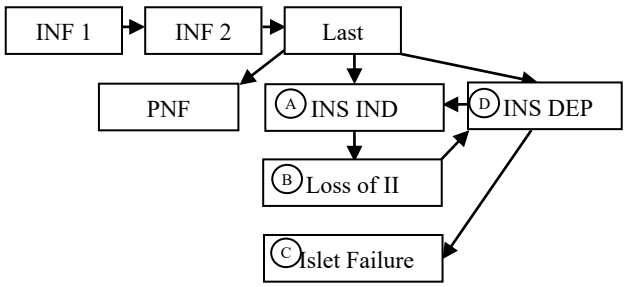


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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.

Limitations and Disclaimers

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

No center-specific information is presented in this report.

Data Quality Assurance and Closure

CITR adheres to strict quality control and assurance procedures. All data submitted are reviewed through several quality review processes. Islet transplant recipient data for this report reflect data entered by the islet transplant centers on participants receiving their first infusion from **January 1, 1999 through December 31, 2023**. These data were reviewed by the Coordinating Center for quality assurance, errors and data outliers. Missing follow-up information on these participants were identified and conveyed back to the center for verification and correction. 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 March 26, 2025 based on the recipients that had been registered for CITR at the December 31, 2023 participant registration closure date for purposes of this report.**

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 Allograft Report exhibits are listed below with their respective CITR definitions:

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

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

Total cholesterol:	*240 mg/dL*
Triglycerides:	*150 mg/dL*

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Islet graft dysfunction:

In insulin independent recipients (after completion of induction immunotherapy), islet graft dysfunction is defined as when the recipient displays, with no evidence of infection or drug toxicity, 3 blood glucose readings 2 hours or longer post prandial over 180 mg/dL in any 1-week period OR 3 pre-prandial blood glucose readings over 140 mg/dL in any 1-week period.

In insulin dependent recipients (after completion of induction immunotherapy), islet graft dysfunction will be suspected if the recipient displays, with no evidence of infection or drug toxicity, a 50% increase in insulin requirements (with a minimum increase of 5 units per day) OR an increase of 10 units per day over a 1-2 week period.

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

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

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

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

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

Partial recovery: Recovery achieved but not to the functional level (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

Full recovery: Recipient was able to obtain the same level of functioning (as assessed by glycemic control, C-peptide level, and/or insulin requirements) prior to the change in islet graft function.

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

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

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

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

Chapter 1
Islet Transplant Activity

Introduction

From 1999 through 2023, 28 National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) sponsored North American and 12 international Eurasian and Australian islet transplant centers (40 total) contributed data to the Collaborative Islet Transplant Registry (CITR). These sites registered 1,134 islet transplant alone (ITA) and 337 islet after kidney or simultaneous islet-kidney (IAK/SIK), and six kidney-after-islet allograft recipients consenting to have their data reported to the Registry, for a total of 1,477 allogeneic, human-to-human islet transplant recipients. In 2023, one North American site reported performing allogeneic islet transplantation and participated in CITR (Exhibit 1-3). 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, 673 (88.2%) of 763 islet allograft recipients and 1,376 (89.5%) of all islet allograft infusion procedures performed in North America from 1999-2023 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, followed by a decline over the last decade.

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 **Eurasian and Australian** sites by year.

Infusions

A summary of the total 2,947 North American and international islet allograft infusions by year of infusion is included in Exhibit 1-5A and B. These infusions derived from 3,442 total donors: 2,654 (90.1%) were single donor preparations and 293 (9.9%) were multiple (2 or more) donor preparations.

Four hundred and thirty (430) recipients (29.1%) have received a single islet infusion at the time of this report, 700 (47.4%) received a total of two infusions, 289 (19.6%) received three infusions, and 58 recipients (3.9%) received a total of four to six islet infusions (Exhibit 1-7).

Of the 1,477 islet allograft recipients presented in this report, 1,134 (76.8%) are islet alone recipients, 260 (17.6%) are islet after kidney recipients, 77 (5.2%) were islet simultaneous with kidney, and 6 (0.4%) were kidney after islet.

CITR Allografts Overall

There has been a 5.6% increase in the number of allograft recipients reported to the Registry since the last Network Data Report, as well as a 4.1% increase in the total number of islet allograft infusion procedures reported.

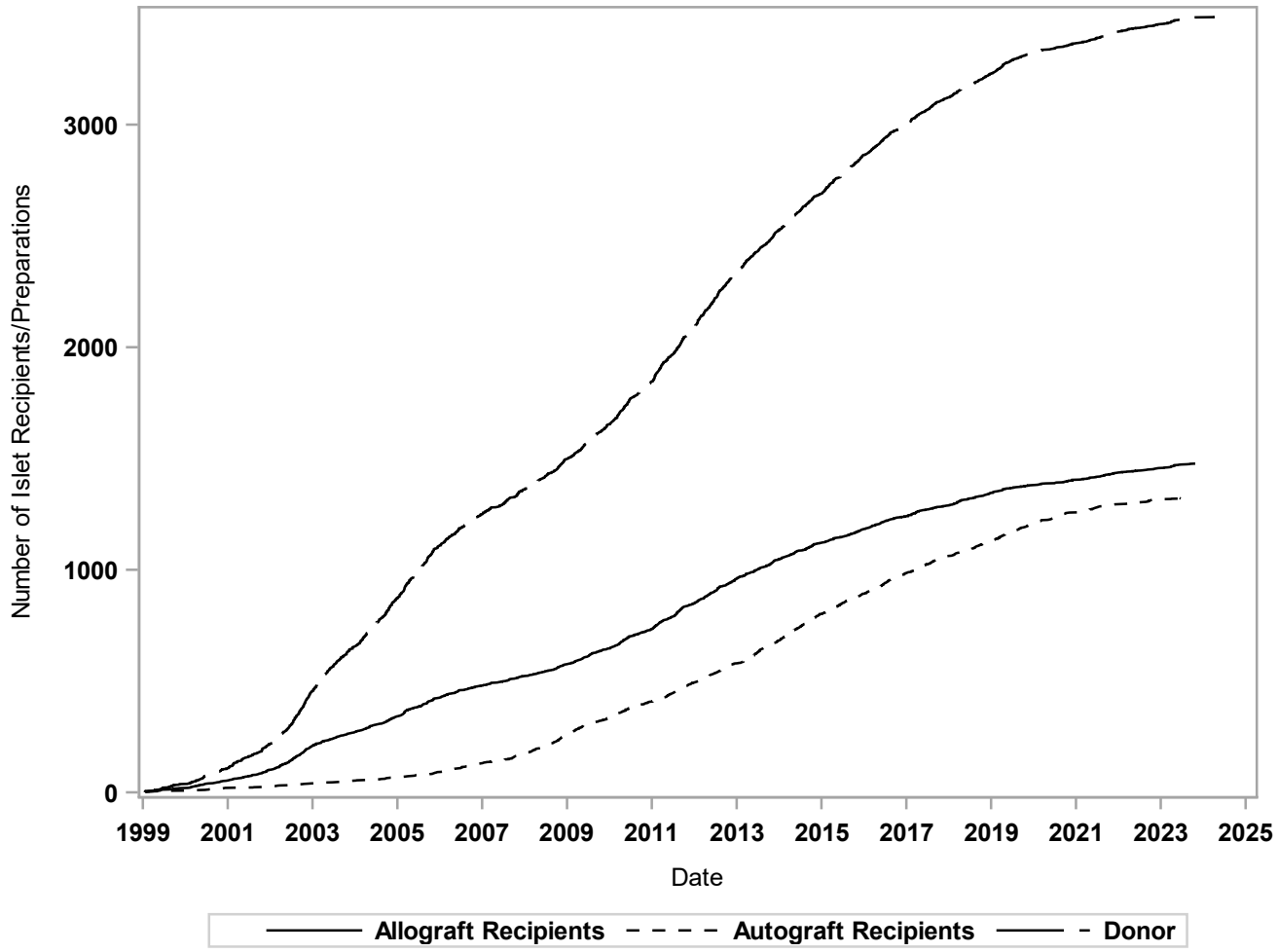
Autografts

There have been 1,205 North American and 115 international autograft consenting recipients registered in the Registry. A brief supplemental Report will present analyses for autologous islet transplants.

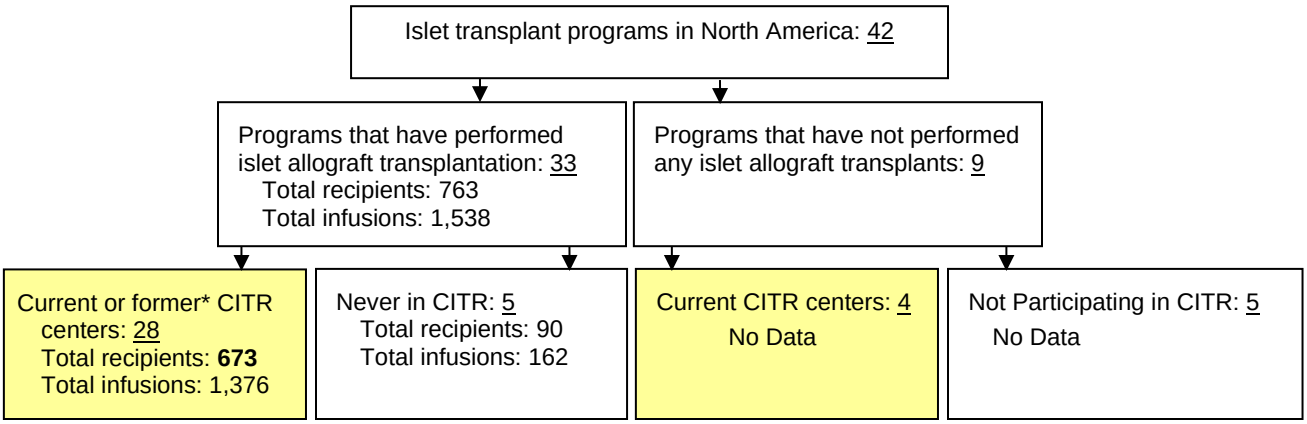
Exhibit 1-1A
CITR Allograft Recipients, Infusions and Donors by International Sites and by ITA/IAK/SIK/KAI Consented, Registered and First Infused in 1999-2023

	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	**1134**	583	551	**260**	86	174	**77**	1	76	**6**	3	3	**1477**
Infusions	**2329**	1211	1118	**471**	157	314	**134**	1	133	**13**	7	6	**2947**
Donors	**2764**	1274	1490	**528**	167	361	**137**	1	136	**13**	7	6	**3442**

Exhibit 1-1B
Cumulative Enrollment in CITR by Module



NORTH AMERICAN CENTERS
Total Performed and Total Reported to CITR 1999-2023



One North American center reported performing at least one islet allograft infusion procedure in 2023. This center participated in and reported the information to CITR.

* Former CITR centers 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 1999-2023

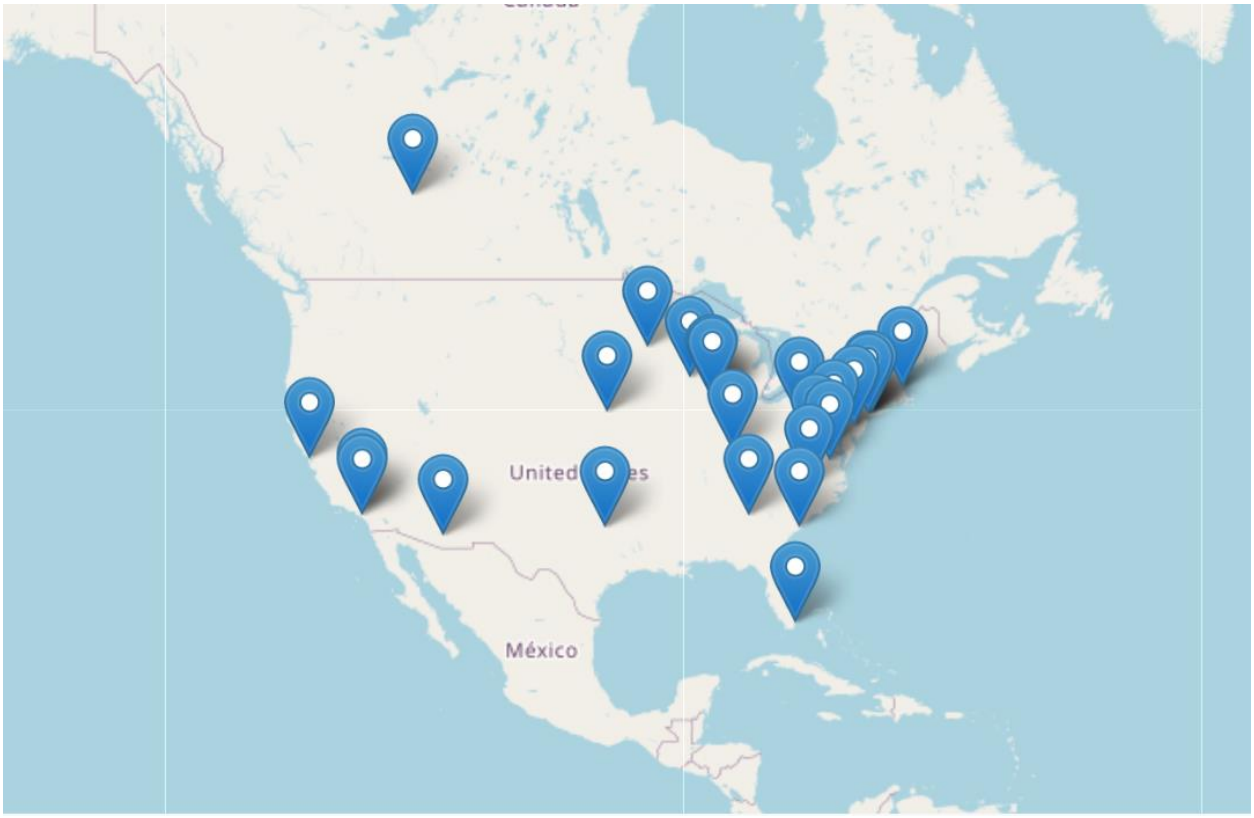


Exhibit 1 – 2B
Islet Transplant Centers Reporting Data to CITR
Participating European Centers 1999-2023

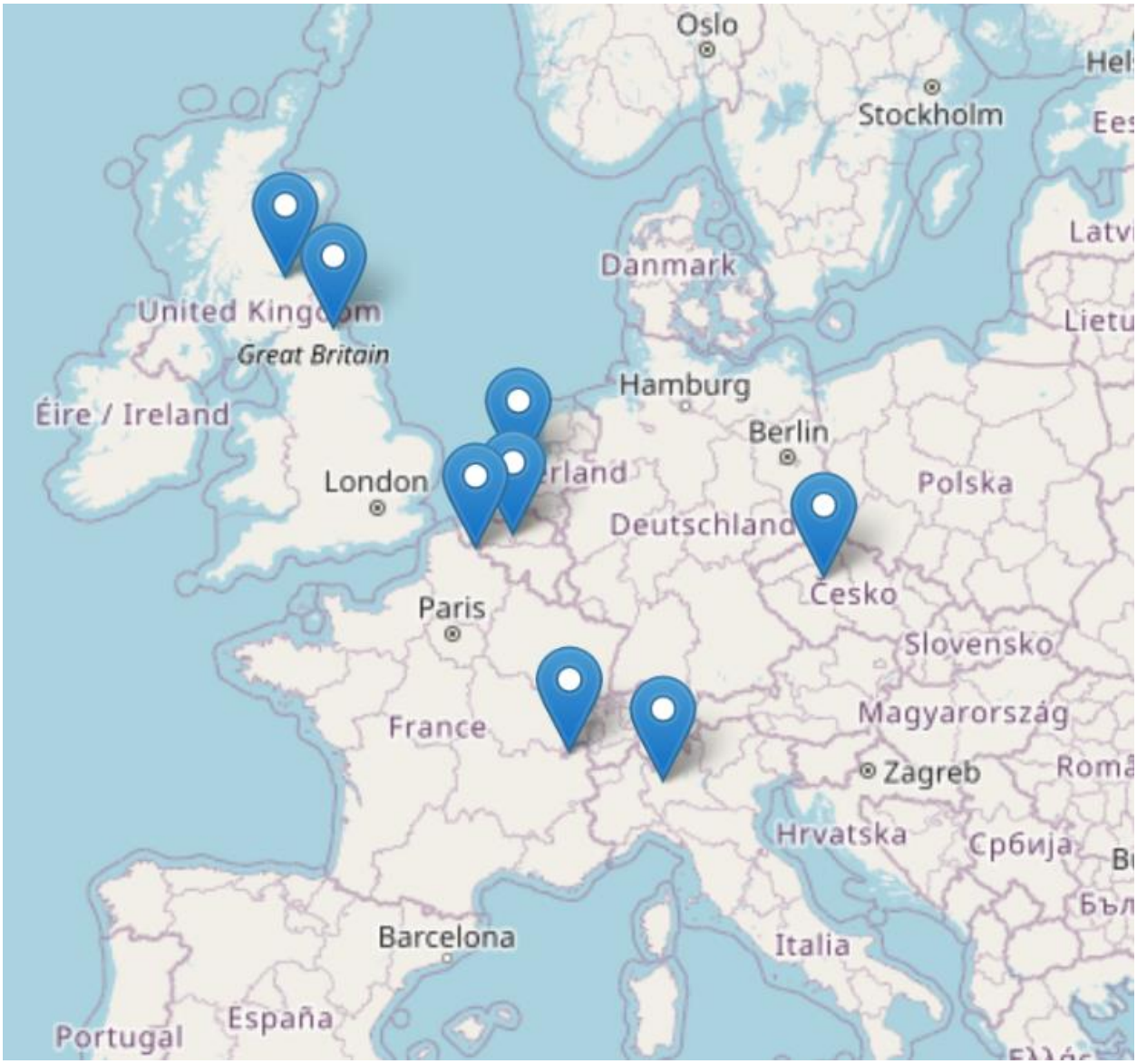
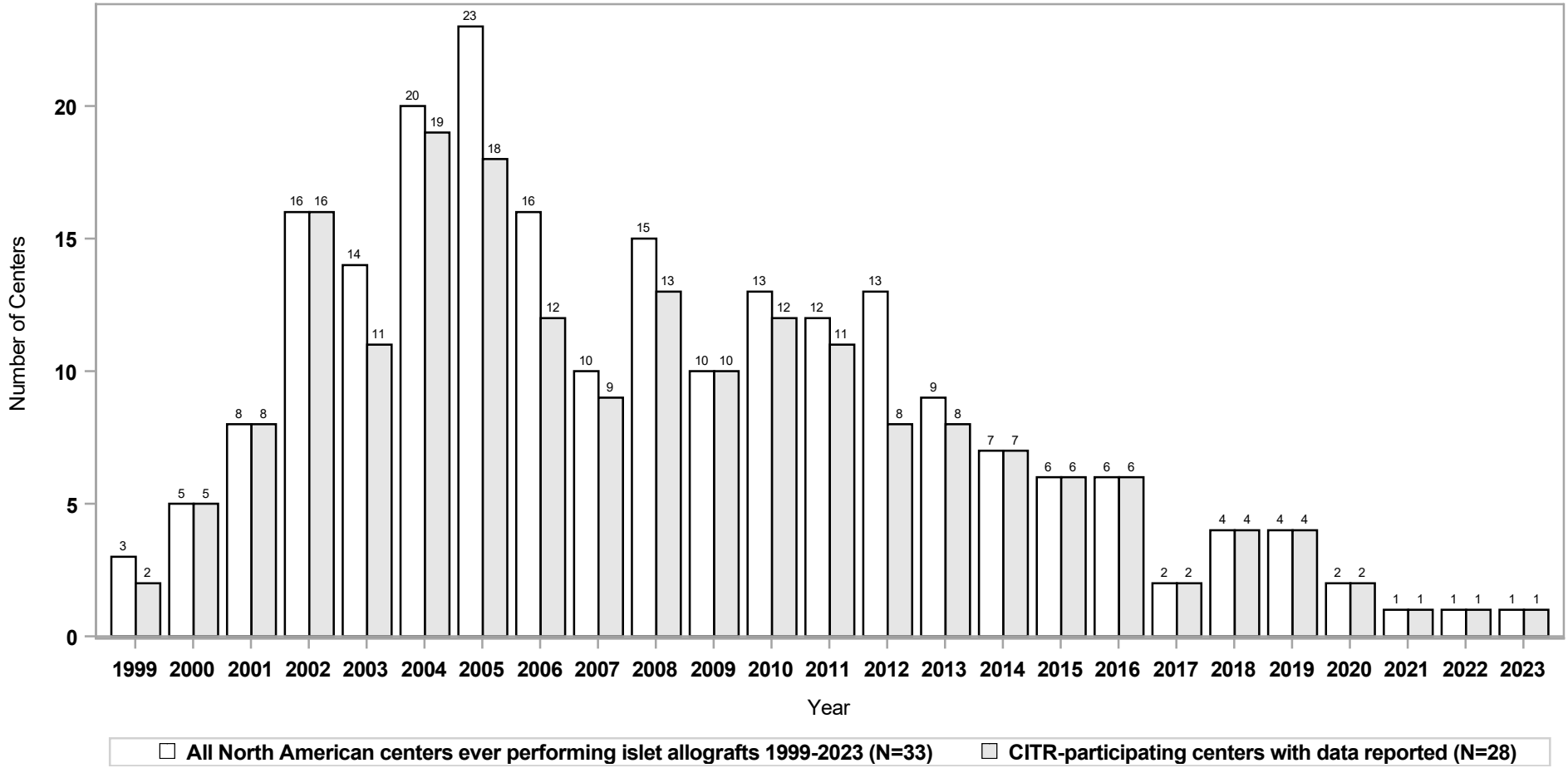


Exhibit 1 – 2C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2023

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 1999-2023



"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 by Year: Allograft recipients at CITR-Participating North American Islet Transplant Centers 1999-2023

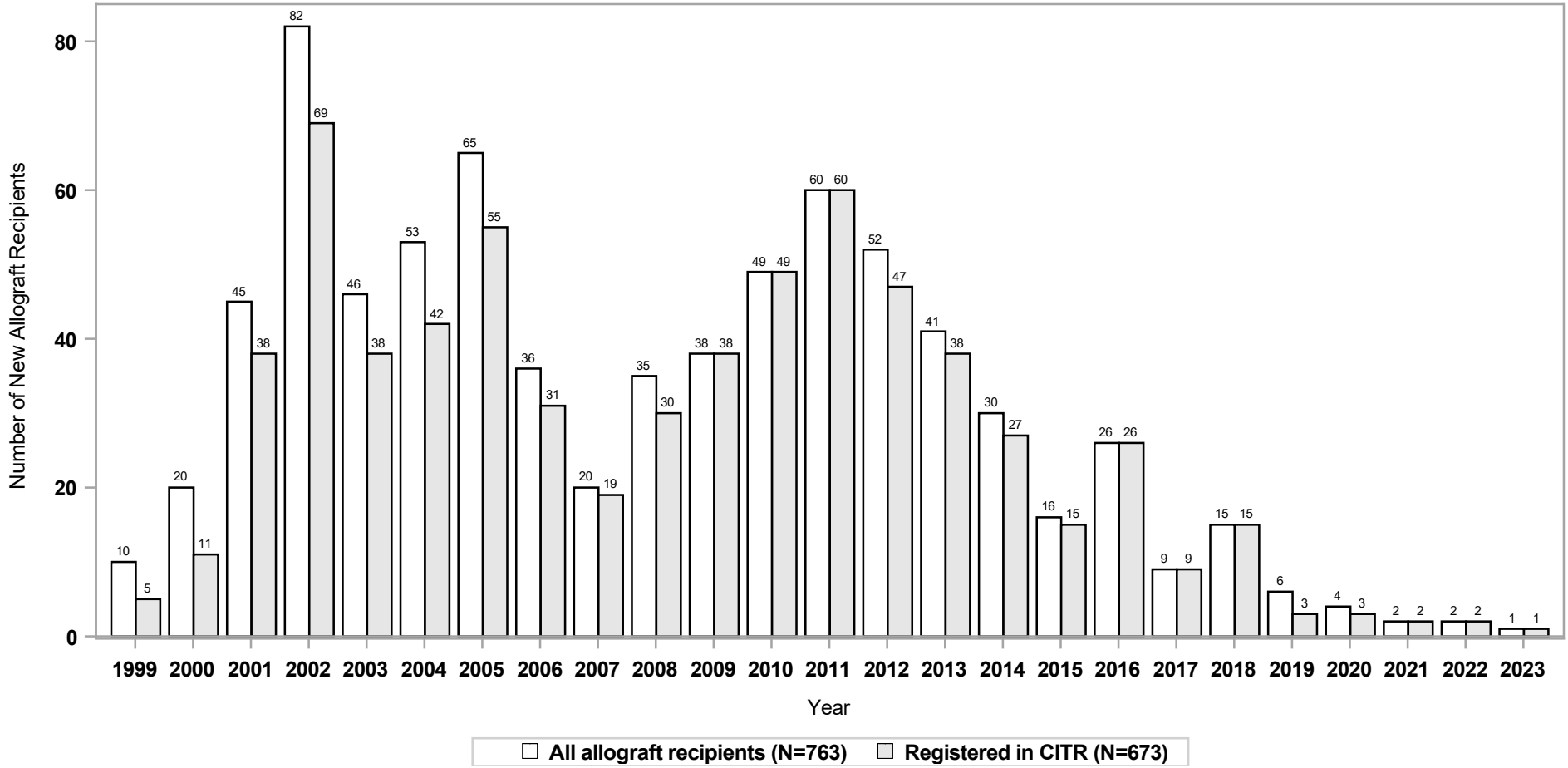


Exhibit 1 – 4B
Total Number of Islet Allograft Recipients Receiving Their First Islet Allograft Infusion and Number with Data Reported to CITR by Year: Allograft recipients at CITR-Participating European, Australian, and Asian Islet Transplant Centers 1999-2023

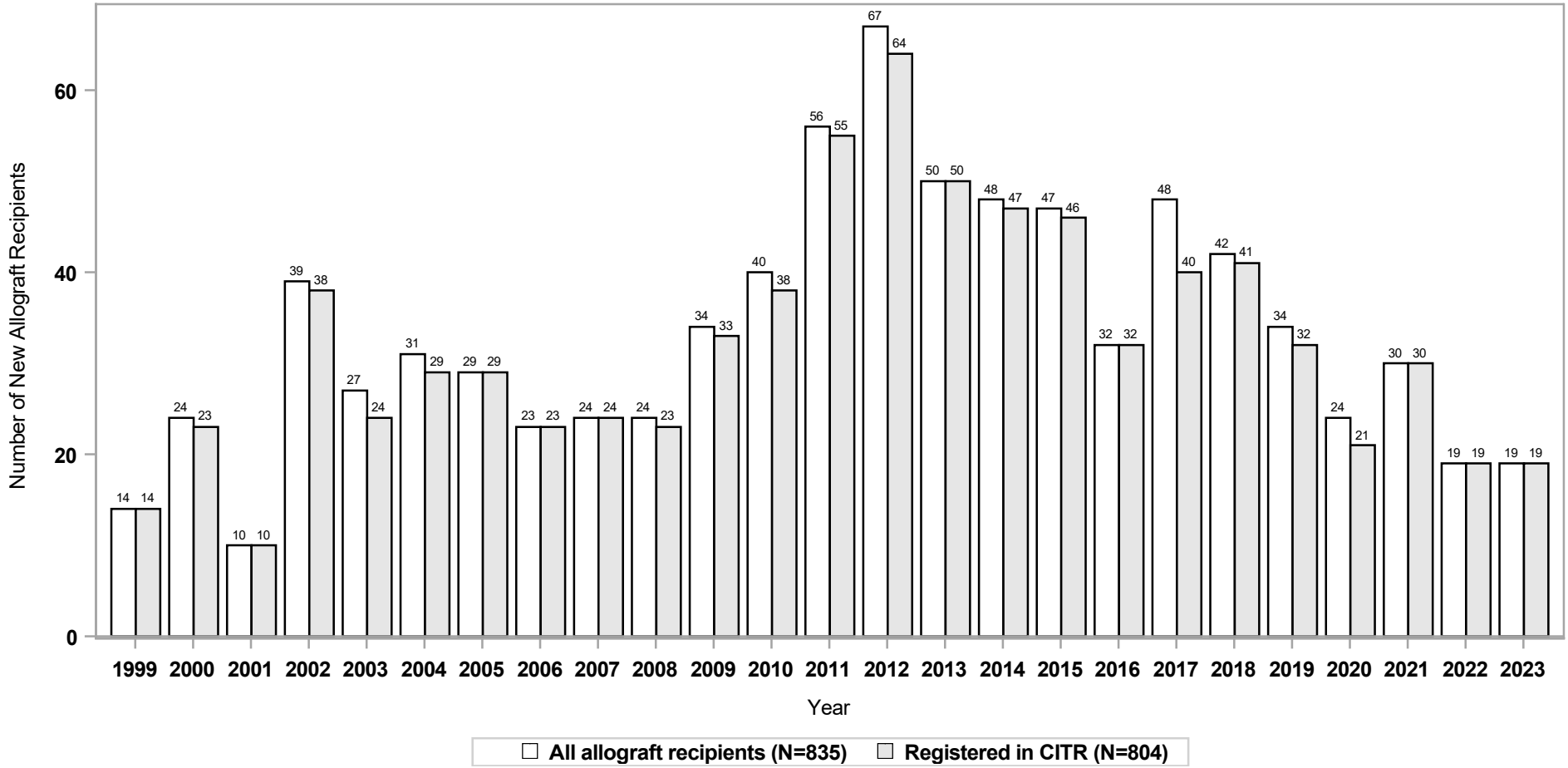


Exhibit 1 – 5A
Total Number of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database by Year:
CITR-Participating North American Islet Transplant Centers, 1999-2025

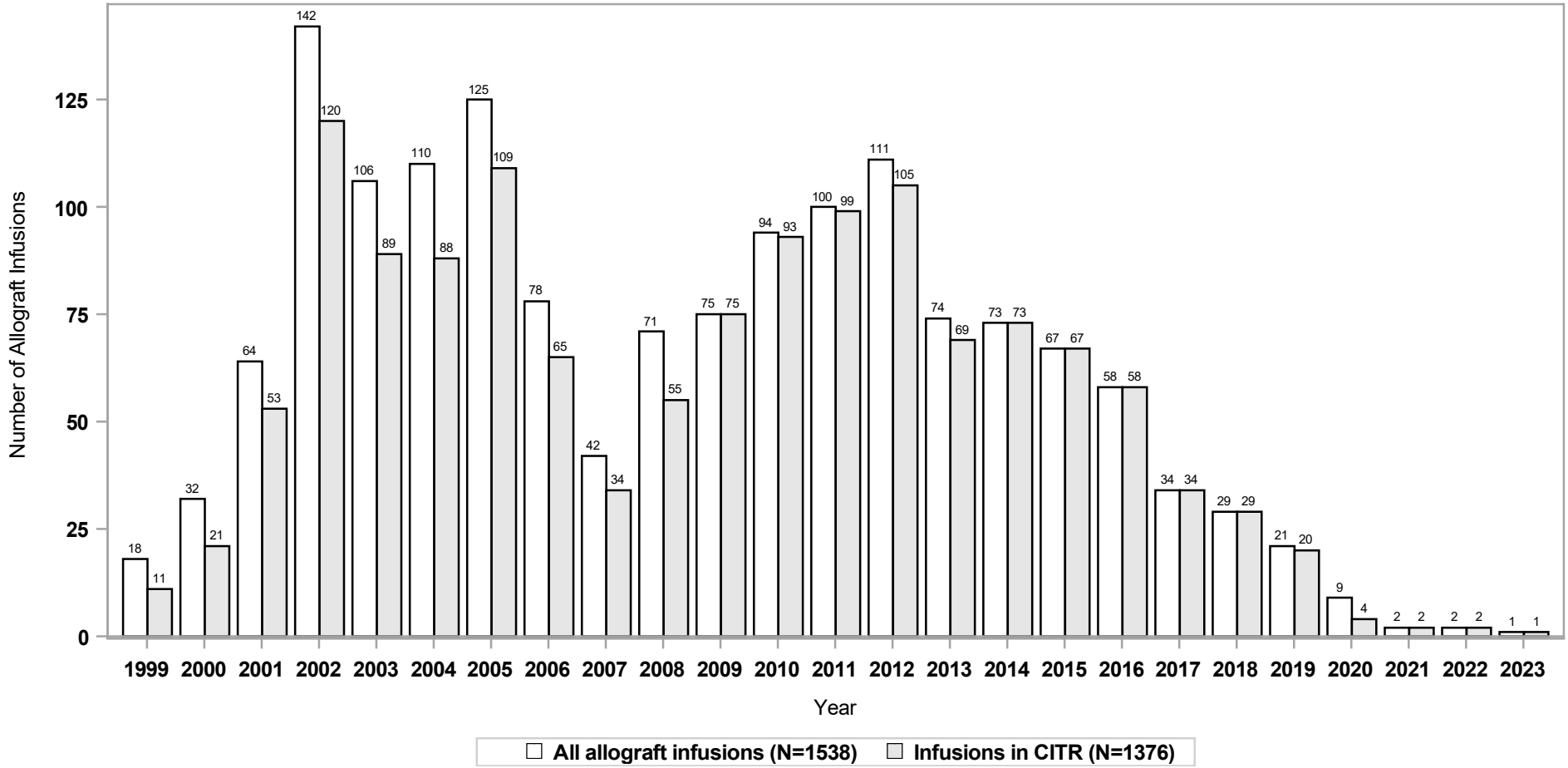


Exhibit 1 – 5B
Total Number of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database by Year:
CITR-Participating European, Australian, and Asian Islet Transplant Centers, 1999-2025

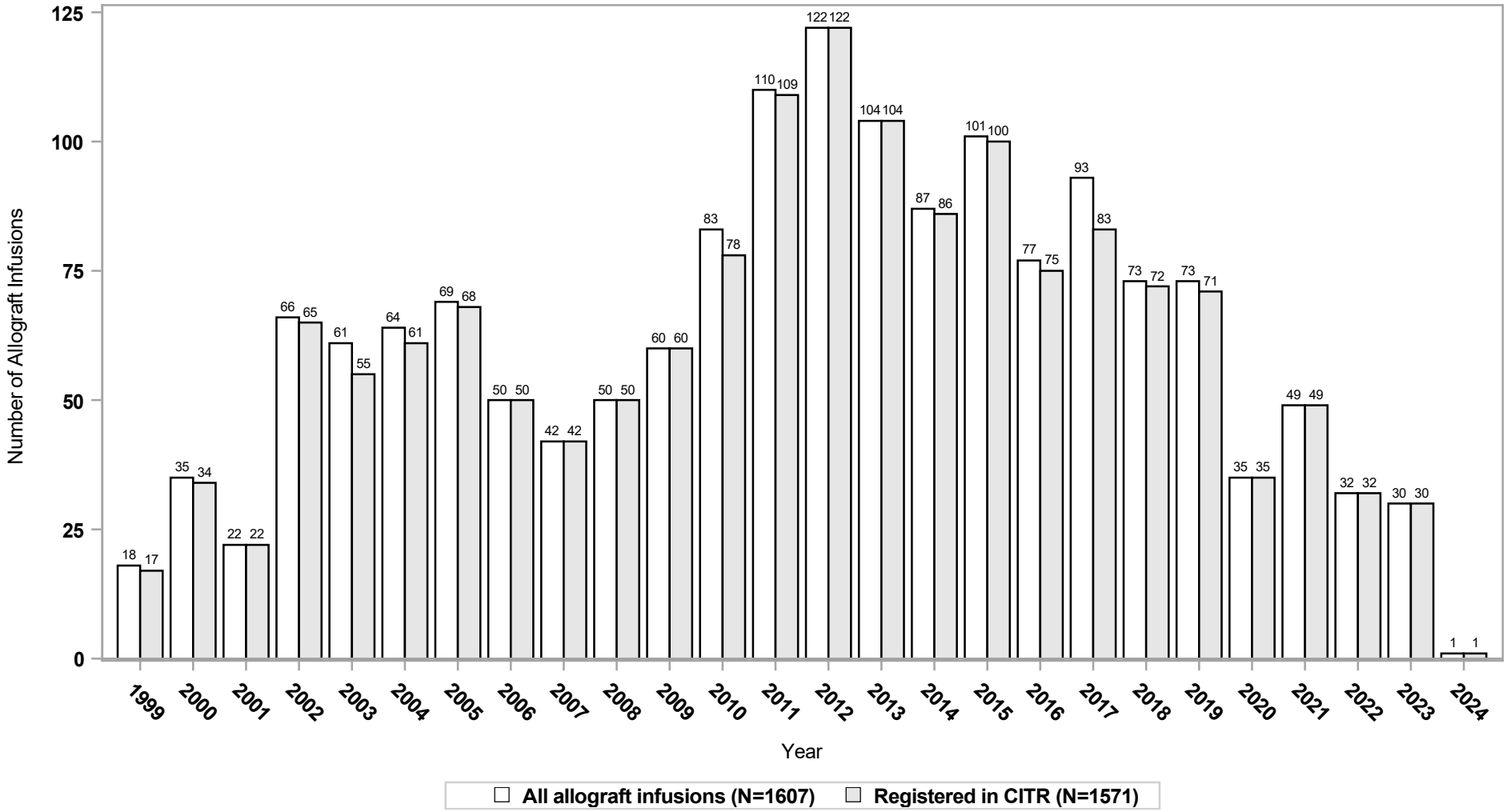


Exhibit 1 – 6A
Islet Allograft Infusions by Infusion Sequence Number and Year:
CITR-Participating North American and International Centers, 1999-2025

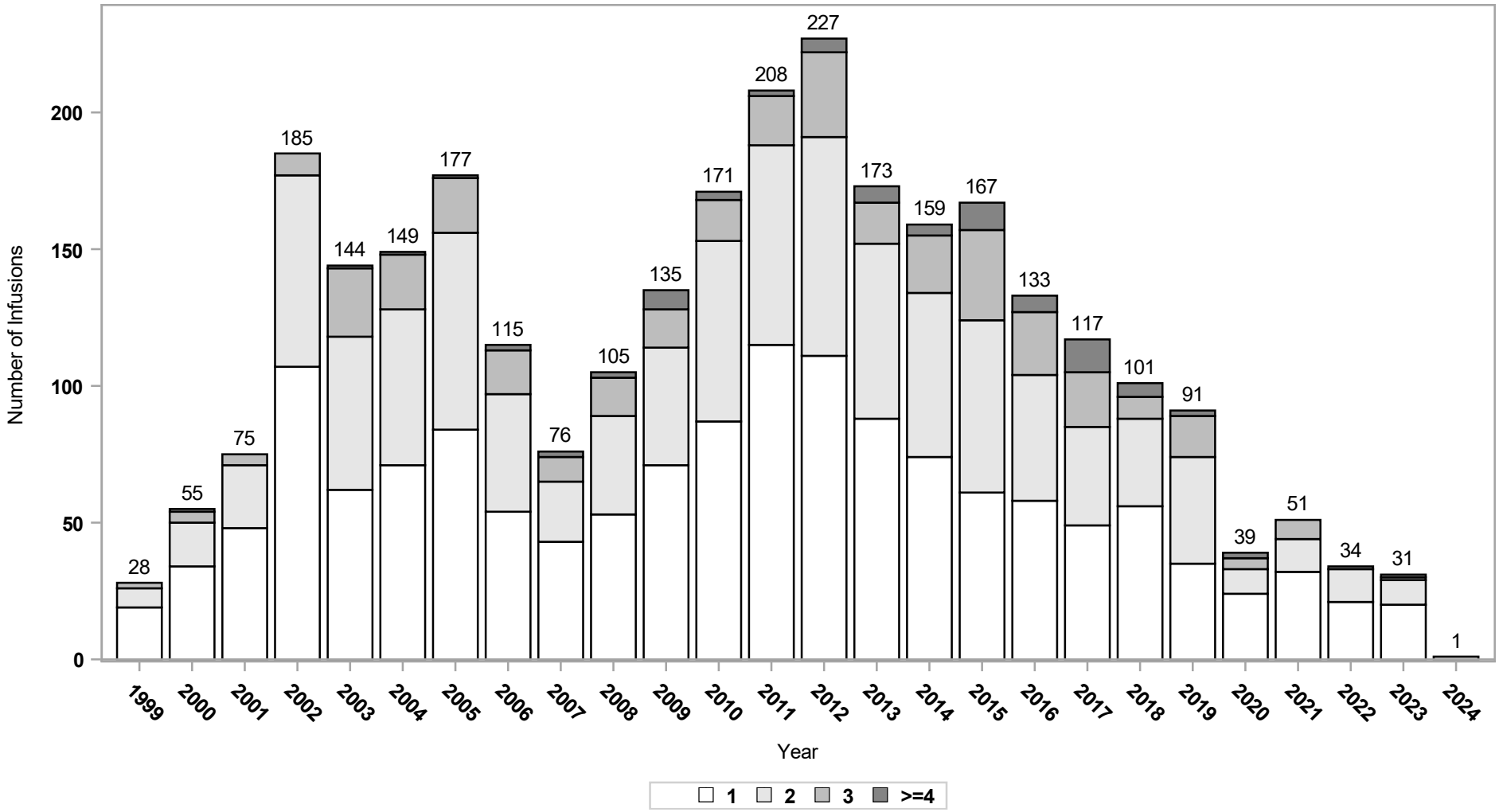


Exhibit 1 – 6B
Islet Allograft Recipients by Total Infusions to Date and Year:
CITR-Participating North American and International Centers, 1999-2025

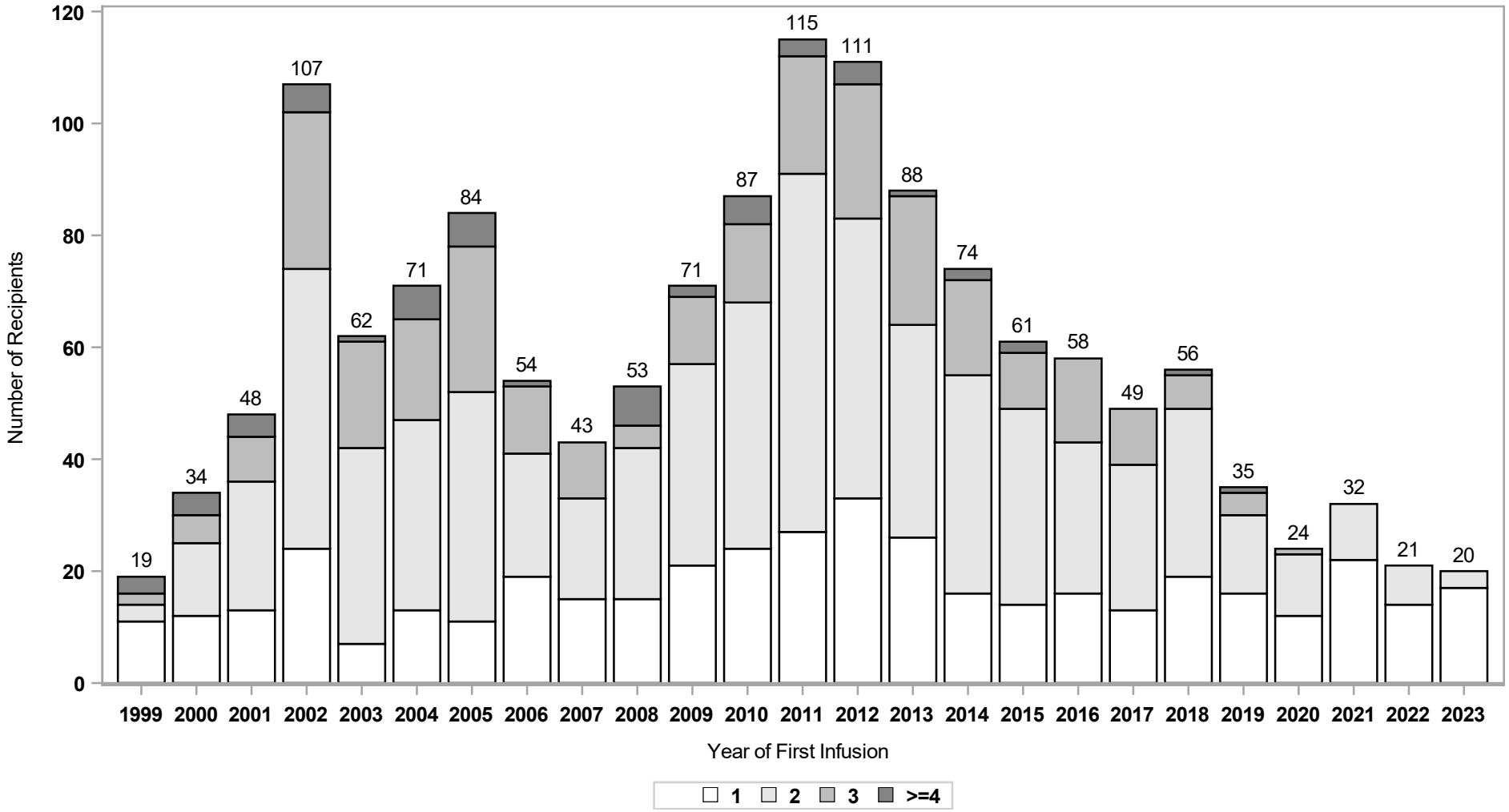


Exhibit 1 – 7
Total Number of Islet Allograft Infusion Procedures Per Recipient:
CITR-Participating North American and International Centers, 1999-2025

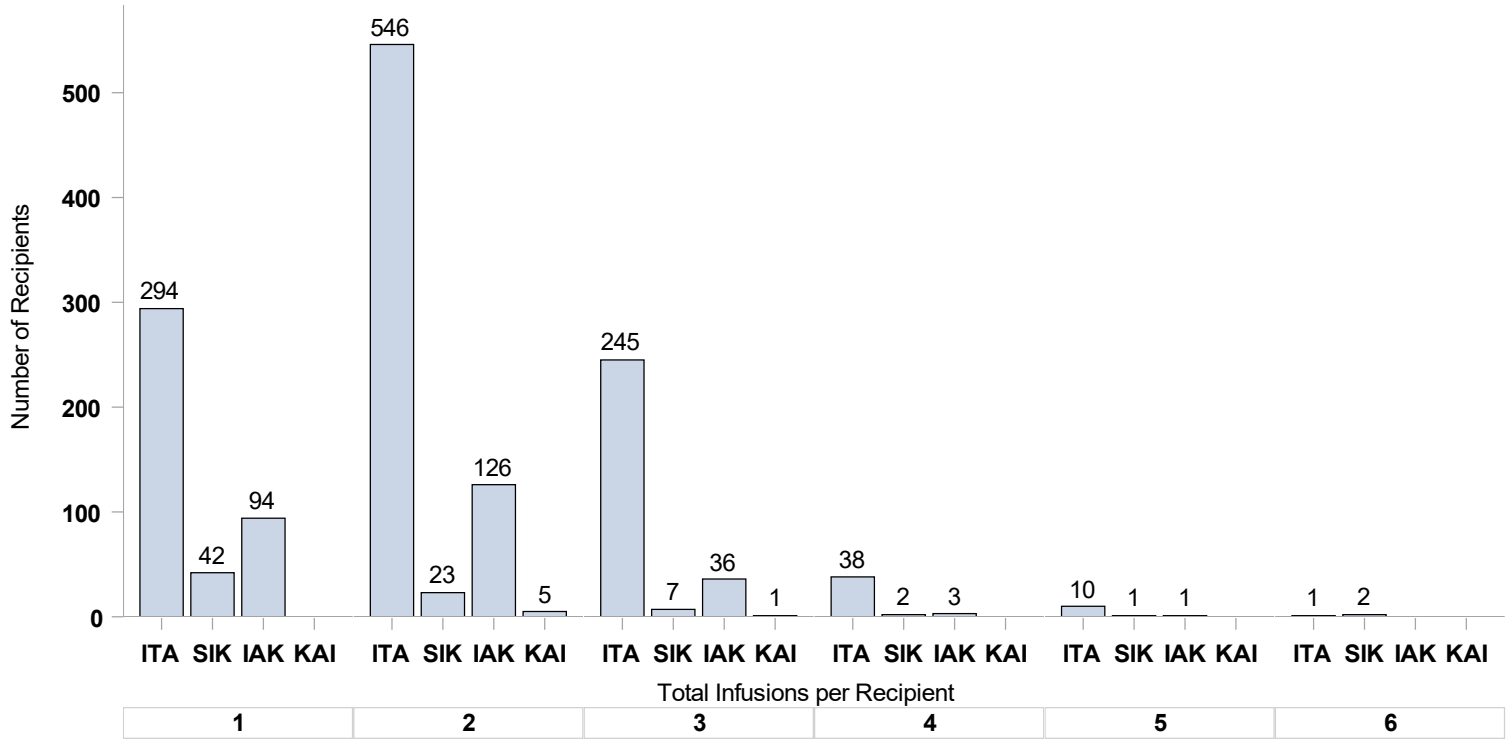
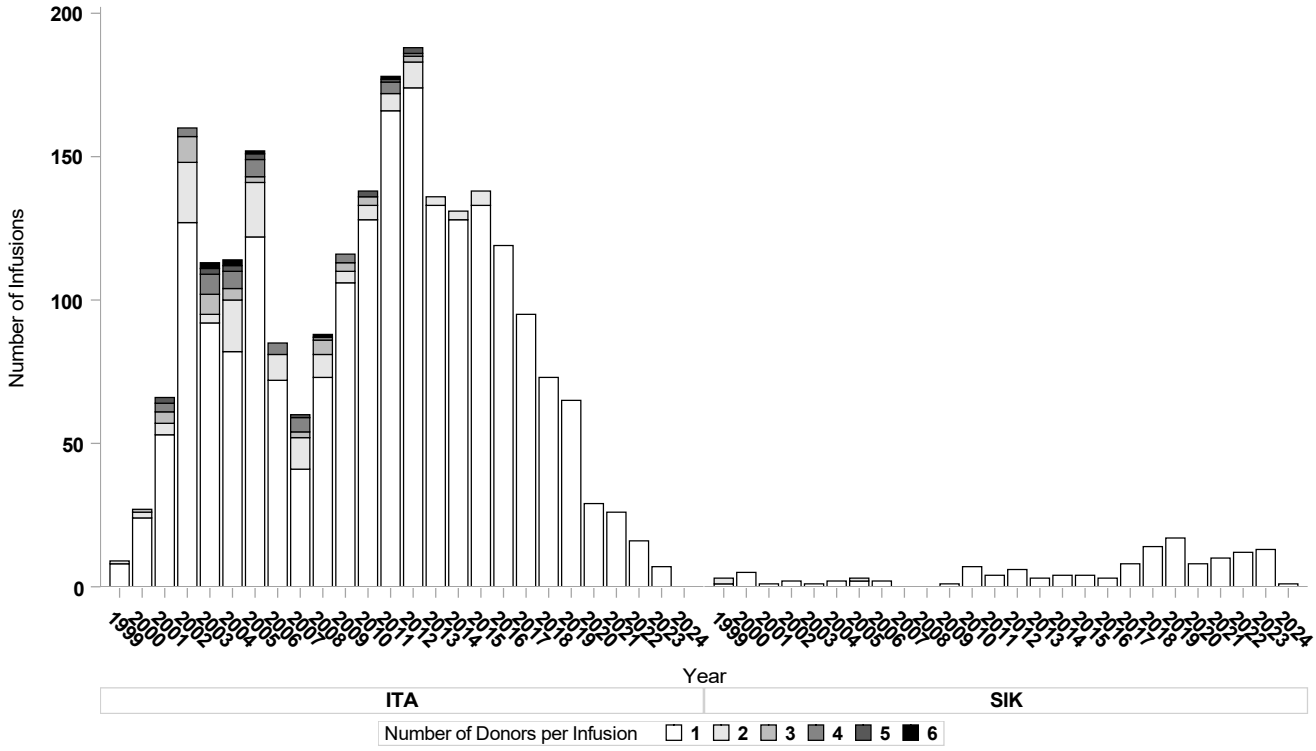
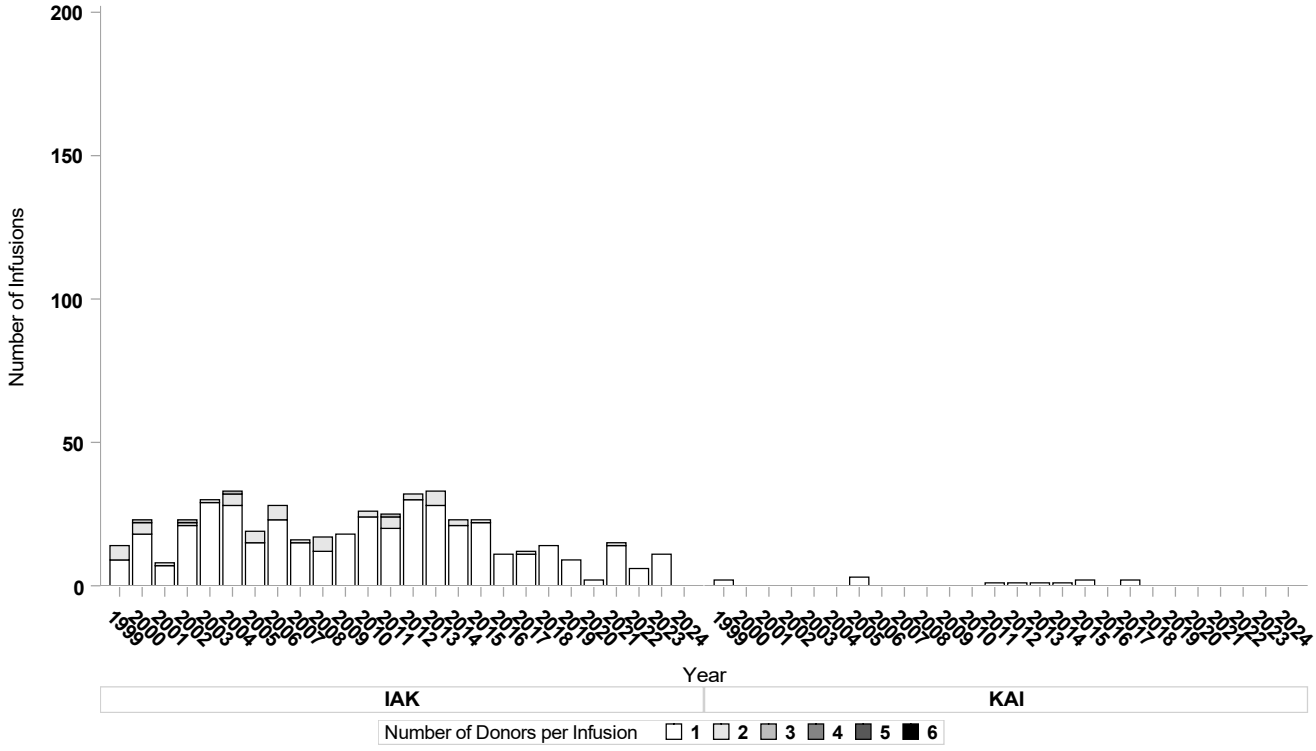


Exhibit 1 – 8
Total Number of Deceased Donors per Islet Allograft Infusion Procedure:
CITR-Participating North American and International Centers, 1999-2025





Chapter 2
Recipient and Donor Demographics

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 (1999-2006, 2007-2014, 2015-2022, and 2023-2030). In each table per variable, the distribution of available data is shown and tested for differences by transplant type and era. Data missingness is also provided. Nominal p-values are calculated but are not based on experimental design.

In Exhibits 2-10 to 2-15, multiple donor information has been summarized over one to several donors/pancreata per islet infusion. There were 2,654 single-donor, 183 two-donor, 46 three-donor, 43 four-donor, 14 five-donor, and 7 six-donor, for a total of 3,442 donors and 2,947 infusions.

Recipient demographics are summarized in Exhibit 2-1, and indication for receiving islet transplantation is summarized in Exhibit 2-2. Recipient characteristics at first infusion are summarized in Exhibits 2-3 (by transplant type and era) and 2-7 (by total number of infusions received). Diabetes characteristics and medical history are presented for recipients in Exhibit 2-4. Exhibits 2-5 and 2-8 summarize measures of recipient autoantibody and sensitization at first infusion, by transplant type and era and by total number of infusions received, respectively. Recipient infectious disease testing results are summarized in Exhibit 2-6, and laboratory values at first infusion are summarized in Exhibit 2-9.

Donor demographics and characteristics are summarized in Exhibits 2-10 and 2-11, respectively. Characteristics of hospitalization and organ procurement are presented in Exhibit 2-12. Measures of donor serology, laboratory data, and organ cross match results are presented, respectively, in Exhibits 2-13, 2-14, and 2-15.

Exhibit 2-1
Recipient Demographics

	Transplant Type (p=<0.01)						Era (p=0.50)											
	ITA (N[1]=1133, Total [2]=1134)			IAK (N=257, Total=260)			Era 1 1999-2006 (N=465, Total=466)			Era 2 2007-2014 (N=626, Total=628)			Era 3 2015-2022 (N=288, Total=289)			Era 4 2023-2030 (N=11, Total=11)		
Gender	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Female	691	61.0	60.9	129	50.2	49.6	270	58.1	57.9	371	59.3	59.1	171	59.4	59.2	8	72.7	72.7
Male	442	39.0	39.0	128	49.8	49.2	195	41.9	41.8	255	40.7	40.6	117	40.6	40.5	3	27.3	27.3
Missing	1	N/A	0.1	3	N/A	1.2	1	N/A	0.2	2	N/A	0.3	1	N/A	0.3	0	N/A	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 2-1 (continued)
Recipient Demographics

	Transplant Type (p=0.86)						Era (p=<0.001)											
	ITA (N[1]=1134, Total [2]=1134)			IAK (N=258, Total=260)			Era 1 1999-2006 (N=466, Total=466)			Era 2 2007-2014 (N=627, Total=628)			Era 3 2015-2022 (N=288, Total=289)			Era 4 2023-2030 (N=11, Total=11)		
Race	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
American Indian/Alaska Native	2	0.2	0.2	0	0.0	0.0	1	0.2	0.2	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
Asian	3	0.3	0.3	0	0.0	0.0	0	0.0	0.0	2	0.3	0.3	1	0.3	0.3	0	0.0	0.0
Black or African American	7	0.6	0.6	3	1.2	1.2	1	0.2	0.2	8	1.3	1.3	1	0.3	0.3	0	0.0	0.0
Multiple	3	0.3	0.3	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	2	0.7	0.7	0	0.0	0.0
Other	4	0.4	0.4	1	0.4	0.4	0	0.0	0.0	1	0.2	0.2	3	1.0	1.0	1	9.1	9.1
Unknown	322	28.4	28.4	63	24.4	24.2	129	27.7	27.7	180	28.7	28.7	74	25.7	25.6	2	18.2	18.2
White	793	69.9	69.9	191	74.0	73.5	334	71.7	71.7	435	69.4	69.3	207	71.9	71.6	8	72.7	72.7
Missing	0	N/A	0.0	2	N/A	0.8	0	N/A	0.0	1	N/A	0.2	1	N/A	0.3	0	N/A	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 2-1 (continued)
Recipient Demographics

	Transplant Type (p=0.86)						Era (p=0.25)											
	ITA (N[1]=1134, Total [2]=1134)			IAK (N=258, Total=260)			Era 1 1999-2006 (N=466, Total=466)			Era 2 2007-2014 (N=627, Total=628)			Era 3 2015-2022 (N=288, Total=289)			Era 4 2023-2030 (N=11, Total=11)		
Ethnicity	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Hispanic or Latino	7	0.6	0.6	6	2.3	2.3	8	1.7	1.7	4	0.6	0.6	0	0.0	0.0	1	9.1	9.1
Not Hispanic or Latino	641	56.5	56.5	179	69.4	68.8	328	70.4	70.4	354	56.5	56.4	131	45.5	45.3	7	63.6	63.6
Not reported	133	11.7	11.7	33	12.8	12.7	18	3.9	3.9	52	8.3	8.3	94	32.6	32.5	2	18.2	18.2
Unknown	353	31.1	31.1	40	15.5	15.4	112	24.0	24.0	217	34.6	34.6	63	21.9	21.8	1	9.1	9.1
Missing	0	N/A	0.0	2	N/A	0.8	0	N/A	0.0	1	N/A	0.2	1	N/A	0.3	0	N/A	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 2-1 (continued)
Recipient Demographics

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=909, Total [2]=1134)			IAK (N=205, Total=260)			Era 1 1999-2006 (N=413, Total=466)			Era 2 2007-2014 (N=495, Total=628)			Era 3 2015-2022 (N=199, Total=289)			Era 4 2023-2030 (N=7, Total=11)		
Employment	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Employment status unknown	211	23.2	18.6	78	38.0	30.0	73	17.7	15.7	170	34.3	27.1	45	22.6	15.6	1	14.3	9.1
Not applicable, less than 5 years old	0	0.0	0.0	1	0.5	0.4	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Not working by choice	37	4.1	3.3	4	2.0	1.5	18	4.4	3.9	21	4.2	3.3	2	1.0	0.7	0	0.0	0.0
Not working due to disease	142	15.6	12.5	47	22.9	18.1	60	14.5	12.9	72	14.5	11.5	53	26.6	18.3	4	57.1	36.4
Not working, reason unknown	7	0.8	0.6	8	3.9	3.1	5	1.2	1.1	9	1.8	1.4	1	0.5	0.3	0	0.0	0.0
Not working, unable to find employment	5	0.6	0.4	0	0.0	0.0	1	0.2	0.2	4	0.8	0.6	0	0.0	0.0	0	0.0	0.0
Retired	48	5.3	4.2	10	4.9	3.8	16	3.9	3.4	28	5.7	4.5	14	7.0	4.8	0	0.0	0.0
Student	11	1.2	1.0	2	1.0	0.8	4	1.0	0.9	8	1.6	1.3	1	0.5	0.3	0	0.0	0.0
Working full time	364	40.0	32.1	38	18.5	14.6	196	47.5	42.1	146	29.5	23.2	60	30.2	20.8	0	0.0	0.0
Working part time by choice	40	4.4	3.5	10	4.9	3.8	17	4.1	3.6	23	4.6	3.7	9	4.5	3.1	1	14.3	9.1
Working part time due to disease	36	4.0	3.2	7	3.4	2.7	20	4.8	4.3	9	1.8	1.4	14	7.0	4.8	0	0.0	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 2-1 (continued)
Recipient Demographics

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=909, Total [2]=1134)			IAK (N=205, Total=260)			Era 1 1999-2006 (N=413, Total=466)			Era 2 2007-2014 (N=495, Total=628)			Era 3 2015-2022 (N=199, Total=289)			Era 4 2023-2030 (N=7, Total=11)		
Employment	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Working part time, reason unknown	8	0.9	0.7	0	0.0	0.0	2	0.5	0.4	5	1.0	0.8	0	0.0	0.0	1	14.3	9.1
Missing	225	N/A	19.8	55	N/A	21.2	53	N/A	11.4	133	N/A	21.2	90	N/A	31.1	4	N/A	36.4

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

Indication				ITA													
				Total (N[1]=1089, Total[2]=1134)			Era 1 1999-2006 (N=365, Total=365)			Era 2 2007-2014 (N=508, Total=523)			Era 3 2015-2022 (N=214, Total=243)			Era 4 2023-2030 (N=2, Total=3)		
Diabetes History	Severe Hypo-glycemia	Fasting C-peptide	Insulin Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Cystic fibrosis related	ASHE	<0.3	On	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
		0.3-0.4	Missing	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
		>=0.5	On	5	0.5	0.4	1	0.3	0.3	3	0.6	0.6	1	0.5	0.4	0	0.0	0.0
			Missing	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
		Missing	On	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
	Missing	0.3-0.4	On	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
		Missing	Missing	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
Other	ASHE	<0.3	Missing	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0	1	0.5	0.4	0	0.0	0.0
Pancreatectomy induced	ASHE	<0.3	On	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
	SHE	<0.3	On	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0	1	0.5	0.4	0	0.0	0.0
		0.3-0.4	On	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
Type 1	ASHE	<0.3	On	136	12.5	12.0	50	13.7	13.7	54	10.6	10.3	32	15.0	13.2	0	0.0	0.0
			Missing	5	0.5	0.4	3	0.8	0.8	1	0.2	0.2	1	0.5	0.4	0	0.0	0.0
		0.3-0.4	On	2	0.2	0.2	1	0.3	0.3	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

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

Indication				ITA															
				Total (N[1]=1089, Total[2]=1134)			Era 1 1999-2006 (N=365, Total=365)			Era 2 2007-2014 (N=508, Total=523)			Era 3 2015-2022 (N=214, Total=243)			Era 4 2023-2030 (N=2, Total=3)		
Diabetes History	Severe Hypo-glycemia	Fasting C-peptide	Insulin Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Type 1	ASHE	>=0.5	On	4	0.4	0.4	2	0.5	0.5	2	0.4	0.4	0	0.0	0.0	0	0.0	0.0
			Missing	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
		Missing	Off	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
			On	61	5.6	5.4	2	0.5	0.5	35	6.9	6.7	23	10.7	9.5	1	50.0	33.3
			Missing	9	0.8	0.8	0	0.0	0.0	2	0.4	0.4	7	3.3	2.9	0	0.0	0.0
	SHE	<0.3	On	416	38.2	36.7	216	59.2	59.2	166	32.7	31.7	34	15.9	14.0	0	0.0	0.0
			Missing	43	3.9	3.8	6	1.6	1.6	37	7.3	7.1	0	0.0	0.0	0	0.0	0.0
		0.3-0.4	On	17	1.6	1.5	10	2.7	2.7	5	1.0	1.0	2	0.9	0.8	0	0.0	0.0
		>=0.5	On	20	1.8	1.8	18	4.9	4.9	2	0.4	0.4	0	0.0	0.0	0	0.0	0.0
			Missing	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
		Missing	On	148	13.6	13.1	10	2.7	2.7	77	15.2	14.7	60	28.0	24.7	1	50.0	33.3
			Missing	9	0.8	0.8	0	0.0	0.0	7	1.4	1.3	2	0.9	0.8	0	0.0	0.0
	Missing	<0.3	On	37	3.4	3.3	15	4.1	4.1	21	4.1	4.0	1	0.5	0.4	0	0.0	0.0
			Missing	30	2.8	2.6	3	0.8	0.8	10	2.0	1.9	17	7.9	7.0	0	0.0	0.0
		0.3-0.4	On	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
		>=0.5	Missing	1	0.1	0.1	1	0.3	0.3	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

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

Indication				ITA															
				Total (N[1]=1089, Total[2]=1134)			Era 1 1999-2006 (N=365, Total=365)			Era 2 2007-2014 (N=508, Total=523)			Era 3 2015-2022 (N=214, Total=243)			Era 4 2023-2030 (N=2, Total=3)		
Diabetes History	Severe Hypo-glycemia	Fasting C-peptide	Insulin Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Type 1	Missing	Missing	On	24	2.2	2.1	9	2.5	2.5	10	2.0	1.9	5	2.3	2.1	0	0.0	0.0
			Missing	29	2.7	2.6	4	1.1	1.1	13	2.6	2.5	12	5.6	4.9	0	0.0	0.0
Type 2	ASHE	<0.3	On	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
	SHE	Missing	On	1	0.1	0.1	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
Missing	ASHE	<0.3	On	6	0.6	0.5	0	0.0	0.0	4	0.8	0.8	2	0.9	0.8	0	0.0	0.0
		0.3-0.4	On	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0	1	0.5	0.4	0	0.0	0.0
		>=0.5	On	4	0.4	0.4	0	0.0	0.0	2	0.4	0.4	2	0.9	0.8	0	0.0	0.0
		Missing	On	2	0.2	0.2	0	0.0	0.0	0	0.0	0.0	2	0.9	0.8	0	0.0	0.0
	SHE	<0.3	On	14	1.3	1.2	0	0.0	0.0	10	2.0	1.9	4	1.9	1.6	0	0.0	0.0
			Missing	4	0.4	0.4	0	0.0	0.0	3	0.6	0.6	1	0.5	0.4	0	0.0	0.0
		Missing	On	4	0.4	0.4	0	0.0	0.0	4	0.8	0.8	0	0.0	0.0	0	0.0	0.0
			Missing	6	0.6	0.5	0	0.0	0.0	6	1.2	1.1	0	0.0	0.0	0	0.0	0.0
	Missing	<0.3	On	25	2.3	2.2	14	3.8	3.8	10	2.0	1.9	1	0.5	0.4	0	0.0	0.0
			Missing	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0	1	0.5	0.4	0	0.0	0.0
		Missing	On	14	1.3	1.2	0	0.0	0.0	13	2.6	2.5	1	0.5	0.4	0	0.0	0.0
			Missing	45	N/A	4.0	0	N/A	0.0	15	N/A	2.9	29	N/A	11.9	1	N/A	33.3

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

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

Indication				IAK															
				Total (N[1]=248, Total [2]=260)			Era 1 1999-2006 (N=98, Total=101)			Era 2 2007-2014 (N=96, Total=105)			Era 3 2015-2022 (N=46, Total=46)			Era 4 2023-2030 (N=8, Total=8)		
Diabetes History	Severe Hypo-glycemia	Fasting C-peptide	Insulin Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Cystic fibrosis related	ASHE	<0.3	On	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
		0.3-0.4	Missing	1	0.4	0.4	0	0.0	0.0	0	0.0	0.0	1	2.2	2.2	0	0.0	0.0
		>=0.5	On	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
			Missing	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
		Missing	On	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
	Missing	0.3-0.4	On	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
		Missing	Missing	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
Other	ASHE	<0.3	Missing	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
Pancreatectomy induced	ASHE	<0.3	On	1	0.4	0.4	0	0.0	0.0	0	0.0	0.0	1	2.2	2.2	0	0.0	0.0
	SHE	<0.3	On	1	0.4	0.4	0	0.0	0.0	0	0.0	0.0	1	2.2	2.2	0	0.0	0.0
		0.3-0.4	On	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
Type 1	ASHE	<0.3	On	59	23.8	22.7	38	38.8	37.6	14	14.6	13.3	4	8.7	8.7	3	37.5	37.5
			Missing	4	1.6	1.5	1	1.0	1.0	0	0.0	0.0	3	6.5	6.5	0	0.0	0.0
		0.3-0.4	On	6	2.4	2.3	4	4.1	4.0	2	2.1	1.9	0	0.0	0.0	0	0.0	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

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

Indication				IAK															
				Total (N[1]=248, Total [2]=260)			Era 1 1999-2006 (N=98, Total=101)			Era 2 2007-2014 (N=96, Total=105)			Era 3 2015-2022 (N=46, Total=46)			Era 4 2023-2030 (N=8, Total=8)		
Diabetes History	Severe Hypo-glycemia	Fasting C-peptide	Insulin Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Type 1	ASHE	>=0.5	On	9	3.6	3.5	7	7.1	6.9	1	1.0	1.0	0	0.0	0.0	1	12.5	12.5
			Missing	1	0.4	0.4	0	0.0	0.0	0	0.0	0.0	1	2.2	2.2	0	0.0	0.0
		Missing	Off	3	1.2	1.2	0	0.0	0.0	1	1.0	1.0	1	2.2	2.2	1	12.5	12.5
			On	24	9.7	9.2	5	5.1	5.0	3	3.1	2.9	15	32.6	32.6	1	12.5	12.5
			Missing	6	2.4	2.3	0	0.0	0.0	1	1.0	1.0	4	8.7	8.7	1	12.5	12.5
	SHE	<0.3	On	59	23.8	22.7	35	35.7	34.7	21	21.9	20.0	3	6.5	6.5	0	0.0	0.0
			Missing	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
		0.3-0.4	On	1	0.4	0.4	1	1.0	1.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
		>=0.5	On	3	1.2	1.2	2	2.0	2.0	1	1.0	1.0	0	0.0	0.0	0	0.0	0.0
			Missing	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
		Missing	On	13	5.2	5.0	0	0.0	0.0	6	6.3	5.7	6	13.0	13.0	1	12.5	12.5
			Missing	2	0.8	0.8	1	1.0	1.0	0	0.0	0.0	1	2.2	2.2	0	0.0	0.0
	Missing	<0.3	On	7	2.8	2.7	1	1.0	1.0	6	6.3	5.7	0	0.0	0.0	0	0.0	0.0
			Missing	1	0.4	0.4	0	0.0	0.0	0	0.0	0.0	1	2.2	2.2	0	0.0	0.0
		0.3-0.4	On	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
		>=0.5	Missing	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] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

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

Indication				IAK															
				Total (N[1]=248, Total [2]=260)			Era 1 1999-2006 (N=98, Total=101)			Era 2 2007-2014 (N=96, Total=105)			Era 3 2015-2022 (N=46, Total=46)			Era 4 2023-2030 (N=8, Total=8)		
Diabetes History	Severe Hypo-glycemia	Fasting C-peptide	Insulin Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Type 1	Missing	Missing	On	3	1.2	1.2	1	1.0	1.0	2	2.1	1.9	0	0.0	0.0	0	0.0	0.0
			Missing	23	9.3	8.8	1	1.0	1.0	20	20.8	19.0	2	4.3	4.3	0	0.0	0.0
Type 2	ASHE	<0.3	On	1	0.4	0.4	0	0.0	0.0	1	1.0	1.0	0	0.0	0.0	0	0.0	0.0
	SHE	Missing	On	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
Missing	ASHE	<0.3	On	2	0.8	0.8	0	0.0	0.0	2	2.1	1.9	0	0.0	0.0	0	0.0	0.0
		0.3-0.4	On	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
		>=0.5	On	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
		Missing	On	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
	SHE	<0.3	On	12	4.8	4.6	0	0.0	0.0	11	11.5	10.5	1	2.2	2.2	0	0.0	0.0
			Missing	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
		Missing	On	3	1.2	1.2	0	0.0	0.0	2	2.1	1.9	1	2.2	2.2	0	0.0	0.0
			Missing	1	0.4	0.4	0	0.0	0.0	1	1.0	1.0	0	0.0	0.0	0	0.0	0.0
	Missing	<0.3	On	1	0.4	0.4	0	0.0	0.0	1	1.0	1.0	0	0.0	0.0	0	0.0	0.0
			Missing	1	0.4	0.4	1	1.0	1.0	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
		Missing	On	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
			Missing	12	N/A	4.6	3	N/A	3.0	9	N/A	8.6	0	N/A	0.0	0	N/A	0.0

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

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

	Transplant Type						Era											
	ITA (N[1]=1008, Total[2]=1134)			IAK (N=228, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=535, Total=628)			Era 3 2015-2022 (N=243, Total=289)			Era 4 2023-2030 (N=10, Total=11)		
Indication for ITx	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Cystic fibrosis related	10	1.0	0.9	1	0.4	0.4	1	0.2	0.2	8	1.5	1.3	2	0.8	0.7	0	0.0	0.0
Other	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0	1	0.4	0.3	0	0.0	0.0
Pancreatectomy induced	2	0.2	0.2	2	0.9	0.8	0	0.0	0.0	1	0.2	0.2	3	1.2	1.0	0	0.0	0.0
Type 1	994	98.6	87.7	224	98.2	86.2	447	99.8	95.9	524	97.9	83.4	237	97.5	82.0	10	100.0	90.9
Type 2	1	0.1	0.1	1	0.4	0.4	0	0.0	0.0	2	0.4	0.3	0	0.0	0.0	0	0.0	0.0
Missing	126	N/A	11.1	32	N/A	12.3	18	N/A	3.9	93	N/A	14.8	46	N/A	15.9	1	N/A	9.1

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type receiving first transplant in the given era

Exhibit 2-3
Recipient Characteristics at First Infusion

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Age at Transplant	1134	47.1	0.3	258	48.7	0.6	0.022
Days Listed	735	334.1	13.5	183	416.3	37.1	0.012
Duration of Diabetes (yrs)	903	29.7	0.4	214	34.9	0.7	<0.001
Weight (kg)	990	68.1	0.4	227	66	0.7	0.013
Body Mass Index (kg/m ^{2})	700	23.8	0.1	189	23.2	0.2	0.019
Daily Insulin Requirement Prior to Transplant (units)	948	37.2	0.5	208	36.4	1	0.459
Duration of intensive therapy (yrs)	423	20.5	0.7	39	27.9	2.1	0.001
Avg daily insulin/kg recipient body weight	909	0.5	0	198	0.6	0	0.068
Fasting plasma glucose (mg/dL)	739	170.4	3.2	149	164.2	6.9	0.425
Basal C-Peptide (ng/mL)	779	0.1	0	170	0.2	0.1	<0.001
HbA1C (%)	885	7.9	0	225	8.1	0.1	0.050
Class I PRA (%)	561	3.2	0.5	117	1	0.6	0.053
Class II PRA (%)	446	2.4	0.5	84	0.8	0.7	0.192

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

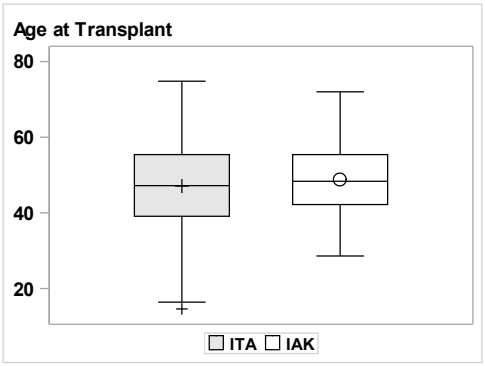
Exhibit 2-3
Recipient Characteristics at First Infusion

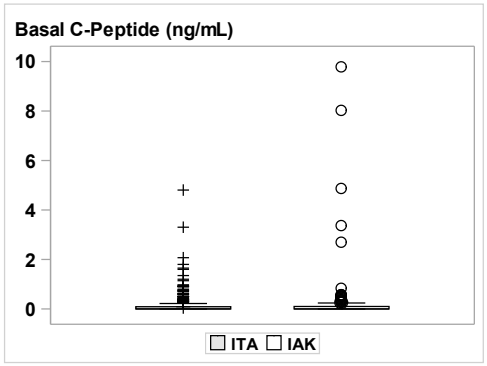
	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Age at Transplant	466	43.3	0.4	627	48.9	0.4	288	50.5	0.7	11	52.1	3	<0.001
Days Listed	389	286	16.2	337	388.4	24.6	186	422.6	31.1	6	167.2	86.9	<0.001
Duration of Diabetes (yrs)	438	28.6	0.5	477	30.9	0.5	192	34.4	0.9	10	38.1	3.5	<0.001
Weight (kg)	445	65.5	0.5	543	68.5	0.5	219	70.2	0.8	10	70.5	3.5	<0.001
Body Mass Index (kg/m ^{2})	437	23.4	0.1	310	23.7	0.2	134	24.5	0.3	8	25	1	0.002
Daily Insulin Requirement Prior to Transplant (units)	442	38.3	0.7	500	36.5	0.7	205	36.7	1.2	9	21.3	4.4	0.004
Duration of intensive therapy (yrs)	251	21.3	0.9	149	21.3	1.2	61	20.2	1.6	1	5	.	0.638
Avg daily insulin/kg recipient body weight	434	0.6	0	469	0.5	0	195	0.5	0	9	0.3	0.1	<0.001
Fasting plasma glucose (mg/dL)	410	174	4.6	392	164	4.2	85	173	8.1	1	85	.	0.292
Basal C-Peptide (ng/mL)	430	0.1	0	397	0.1	0	118	0.2	0.1	4	2.1	2	<0.001
HbA1C (%)	447	7.8	0.1	518	8	0.1	137	8.1	0.1	8	7	0.3	0.002
Class I PRA (%)	324	3	0.6	280	2.8	0.6	73	2.2	1	1	0	.	0.947
Class II PRA (%)	199	2.1	0.7	256	2.4	0.7	74	1.6	1.1	1	0	.	0.941

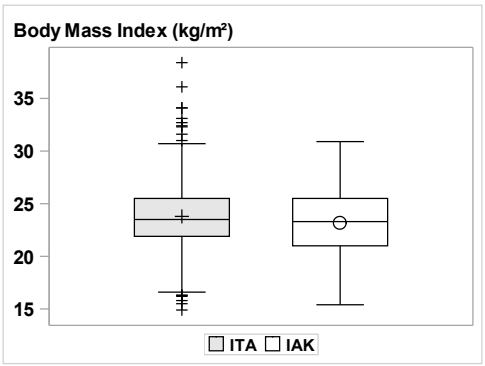
Significant differences by type and era are displayed in the following box-and-whisker plots.

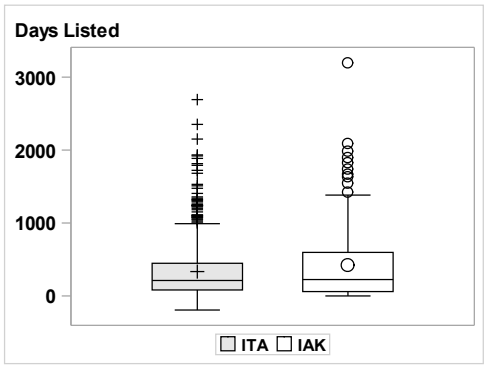
Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

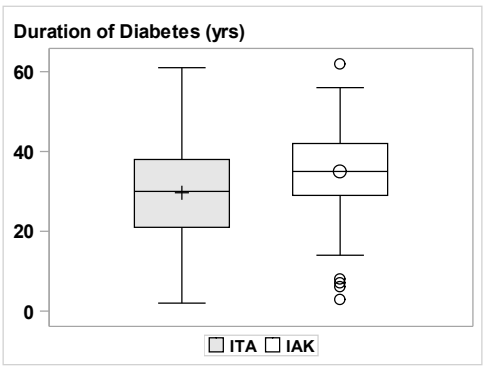
Significant trends in patient characteristics from table above by ITA or IAK

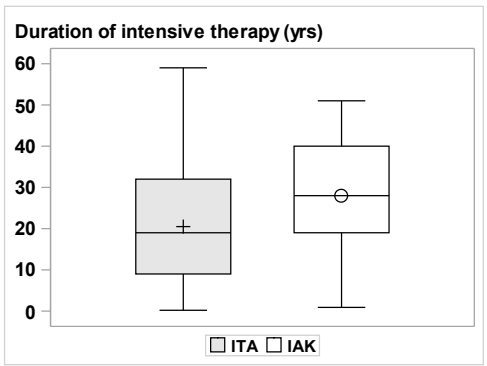


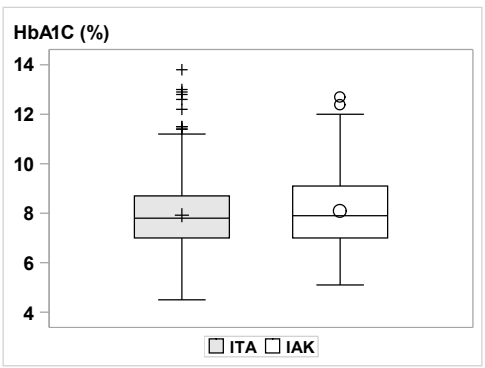












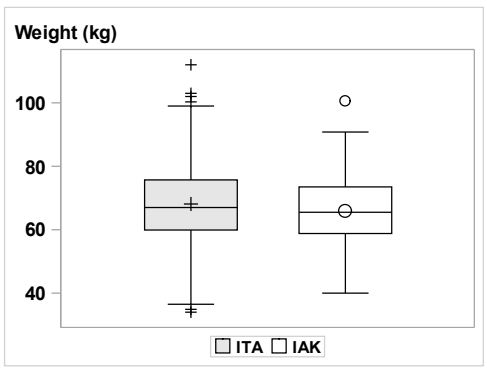
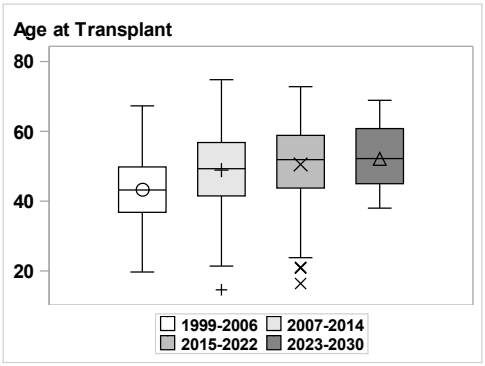
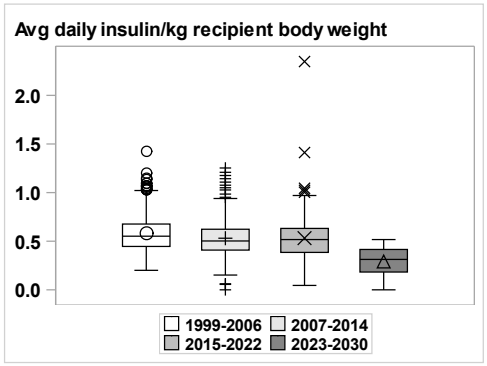
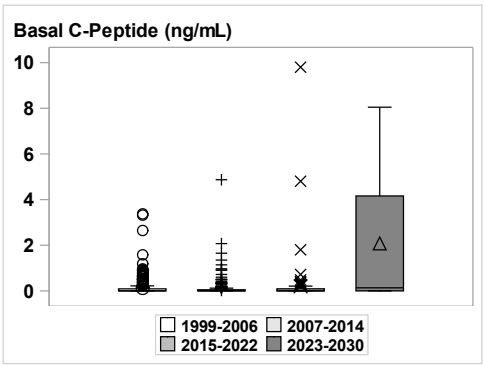


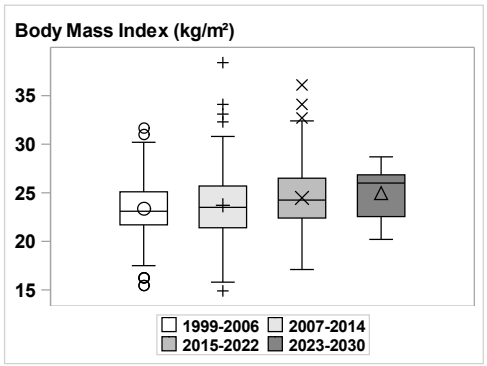
Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

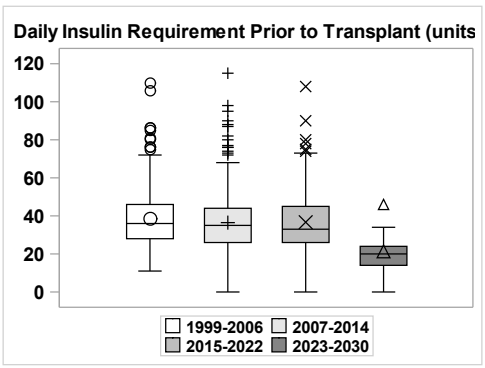
Significant trends in patient characteristics from table above by Era

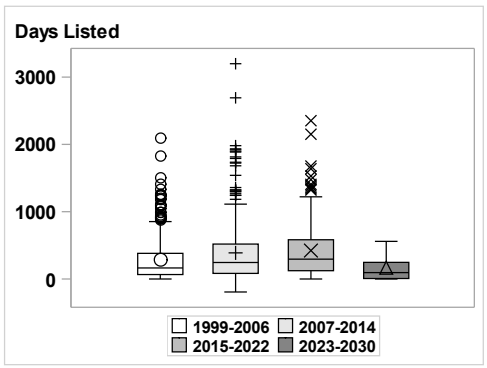


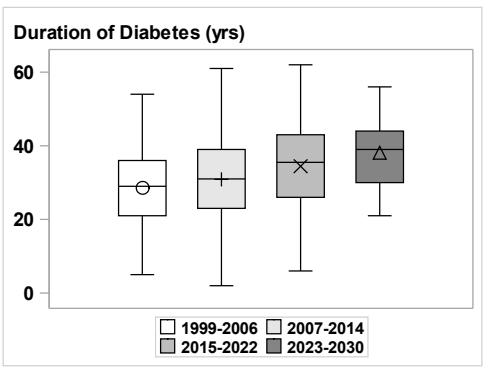












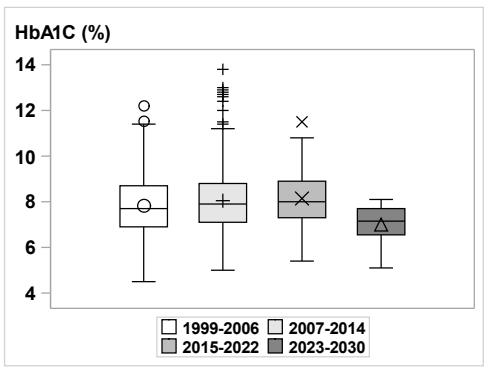


Exhibit 2-3 (continued)
Recipient Characteristics at First Infusion

Significant trends in patient characteristics from table above by Era

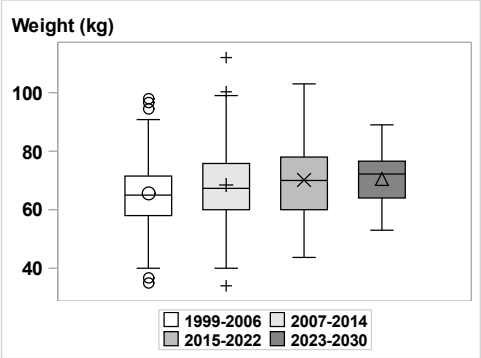
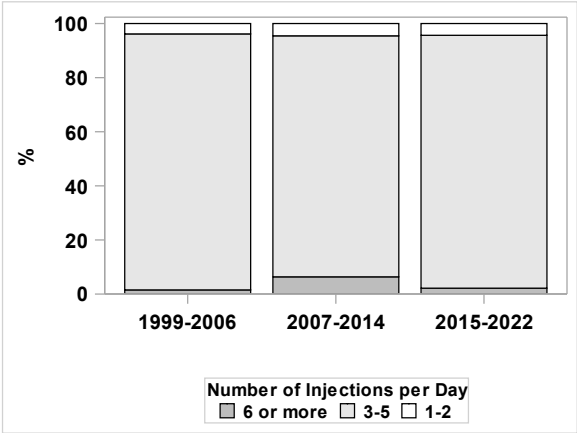


Exhibit 2-4
Recipient Diabetes Characteristics and Medical History

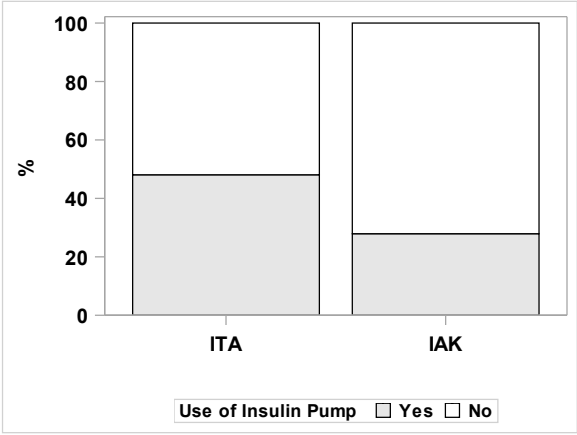
	Transplant Type (p=0.06)						Era (p=<0.001)											
	ITA (N[1]=318, Total [2]=1134)			IAK (N=99, Total=260)			Era 1 1999-2006 (N=261, Total=466)			Era 2 2007-2014 (N=110, Total=628)			Era 3 2015-2022 (N=46, Total=289)			Era 4 2023-2030 (N=0, Total=11)		
Number of Injections per Day	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
1-2	10	3.1	0.9	7	7.1	2.7	10	3.8	2.1	5	4.5	0.8	2	4.3	0.7	0	.	0.0
3-5	299	94.0	26.4	89	89.9	34.2	247	94.6	53.0	98	89.1	15.6	43	93.5	14.9	0	.	0.0
6 or more	9	2.8	0.8	3	3.0	1.2	4	1.5	0.9	7	6.4	1.1	1	2.2	0.3	0	.	0.0
Missing	816	N/A	72.0	161	N/A	61.9	205	N/A	44.0	518	N/A	82.5	243	N/A	84.1	11	N/A	100.0



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

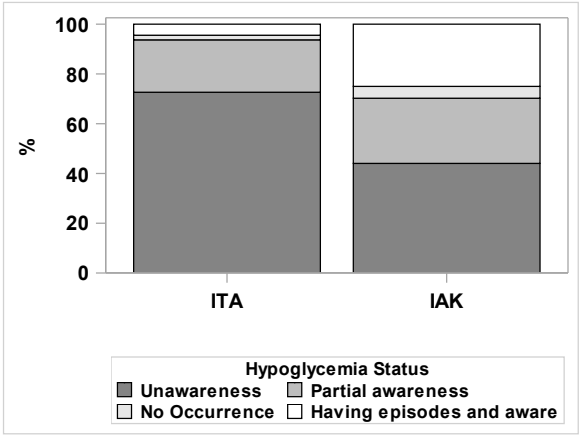
	Transplant Type (p=<0.001)						Era (p=0.05)											
	ITA (N[1]=726, Total [2]=1134)			IAK (N=172, Total=260)			Era 1 1999-2006 (N=445, Total=466)			Era 2 2007-2014 (N=319, Total=628)			Era 3 2015-2022 (N=128, Total=289)			Era 4 2023-2030 (N=6, Total=11)		
Use of Insulin Pump	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	377	51.9	33.2	124	72.1	47.7	290	65.2	62.2	145	45.5	23.1	64	50.0	22.1	2	33.3	18.2
Yes	349	48.1	30.8	48	27.9	18.5	155	34.8	33.3	174	54.5	27.7	64	50.0	22.1	4	66.7	36.4
Missing	408	N/A	36.0	88	N/A	33.8	21	N/A	4.5	309	N/A	49.2	161	N/A	55.7	5	N/A	45.5

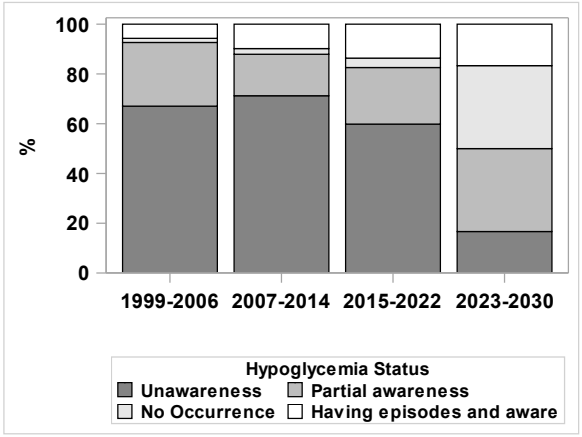


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=698, Total [2]=1134)			IAK (N=168, Total=260)			Era 1 1999-2006 (N=422, Total=466)			Era 2 2007-2014 (N=306, Total=628)			Era 3 2015-2022 (N=132, Total=289)			Era 4 2023-2030 (N=6, Total=11)		
Hypoglycemia Status	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Having episodes and aware	31	4.4	2.7	42	25.0	16.2	24	5.7	5.2	30	9.8	4.8	18	13.6	6.2	1	16.7	9.1
No Occurrence	13	1.9	1.1	8	4.8	3.1	7	1.7	1.5	7	2.3	1.1	5	3.8	1.7	2	33.3	18.2
Partial awareness	147	21.1	13.0	44	26.2	16.9	108	25.6	23.2	51	16.7	8.1	30	22.7	10.4	2	33.3	18.2
Unawareness	507	72.6	44.7	74	44.0	28.5	283	67.1	60.7	218	71.2	34.7	79	59.8	27.3	1	16.7	9.1
Missing	436	N/A	38.4	92	N/A	35.4	44	N/A	9.4	322	N/A	51.3	157	N/A	54.3	5	N/A	45.5

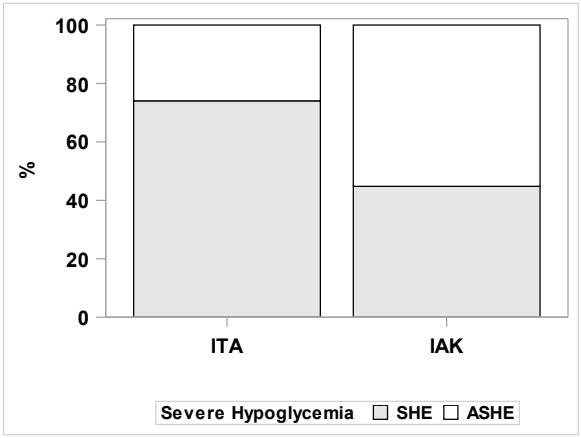


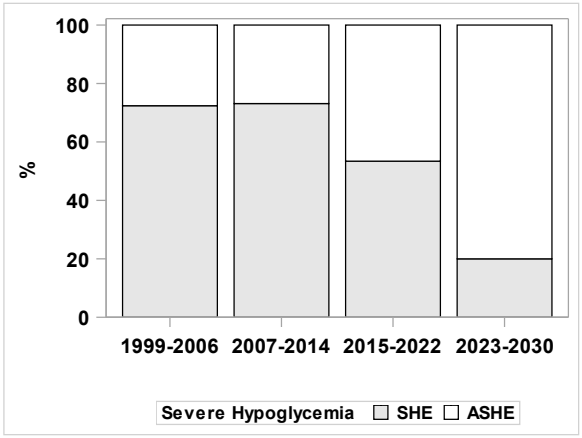


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=925, Total [2]=1134)			IAK (N=212, Total=260)			Era 1 1999-2006 (N=413, Total=466)			Era 2 2007-2014 (N=495, Total=628)			Era 3 2015-2022 (N=219, Total=289)			Era 4 2023-2030 (N=10, Total=11)		
Severe Hypoglycemia	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
ASHE	240	25.9	21.2	117	55.2	45.0	114	27.6	24.5	133	26.9	21.2	102	46.6	35.3	8	80.0	72.7
SHE	685	74.1	60.4	95	44.8	36.5	299	72.4	64.2	362	73.1	57.6	117	53.4	40.5	2	20.0	18.2
Missing	209	N/A	18.4	48	N/A	18.5	53	N/A	11.4	133	N/A	21.2	70	N/A	24.2	1	N/A	9.1

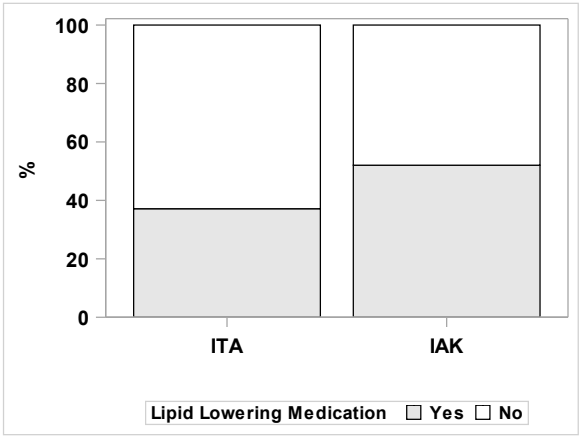


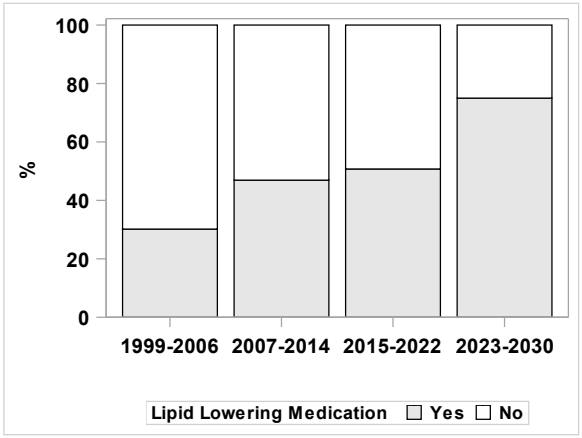


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.01)											
	ITA (N[1]=770, Total [2]=1134)			IAK (N=196, Total=260)			Era 1 1999-2006 (N=434, Total=466)			Era 2 2007-2014 (N=390, Total=628)			Era 3 2015-2022 (N=134, Total=289)			Era 4 2023-2030 (N=8, Total=11)		
Lipid Lowering Medication	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	484	62.9	42.7	94	48.0	36.2	303	69.8	65.0	207	53.1	33.0	66	49.3	22.8	2	25.0	18.2
Yes	286	37.1	25.2	102	52.0	39.2	131	30.2	28.1	183	46.9	29.1	68	50.7	23.5	6	75.0	54.5
Missing	364	N/A	32.1	64	N/A	24.6	32	N/A	6.9	238	N/A	37.9	155	N/A	53.6	3	N/A	27.3

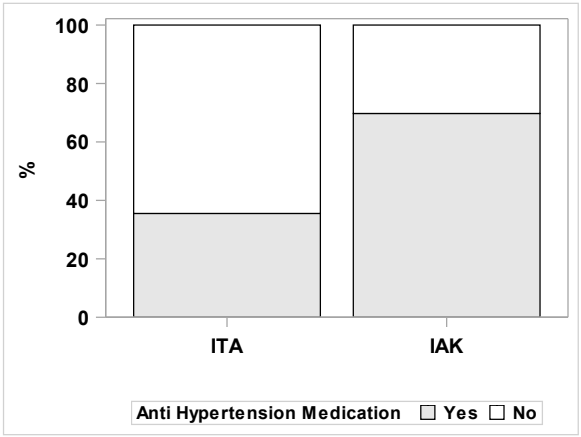


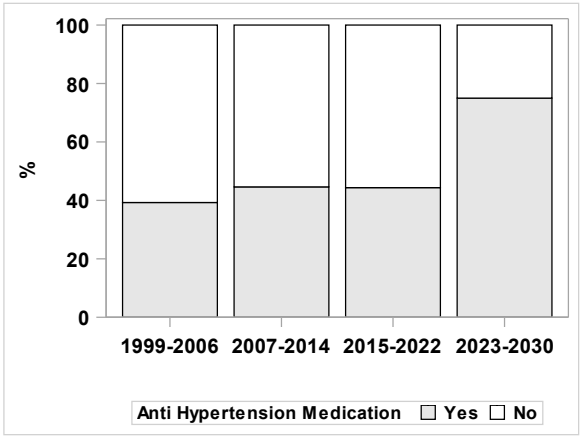


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.01)											
	ITA (N[1]=774, Total [2]=1134)			IAK (N=195, Total=260)			Era 1 1999-2006 (N=438, Total=466)			Era 2 2007-2014 (N=390, Total=628)			Era 3 2015-2022 (N=133, Total=289)			Era 4 2023-2030 (N=8, Total=11)		
Anti Hypertension Medication	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	499	64.5	44.0	59	30.3	22.7	266	60.7	57.1	216	55.4	34.4	74	55.6	25.6	2	25.0	18.2
Yes	275	35.5	24.3	136	69.7	52.3	172	39.3	36.9	174	44.6	27.7	59	44.4	20.4	6	75.0	54.5
Missing	360	N/A	31.7	65	N/A	25.0	28	N/A	6.0	238	N/A	37.9	156	N/A	54.0	3	N/A	27.3

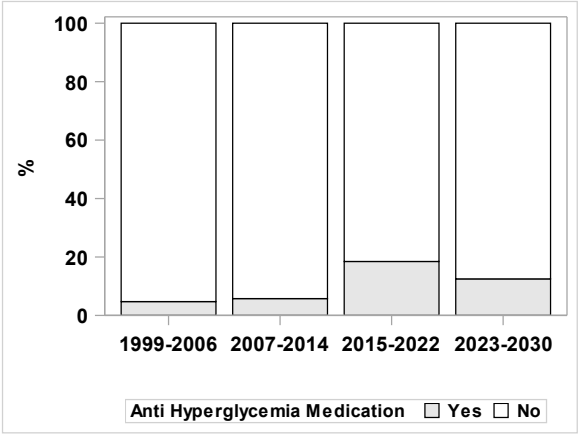




[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

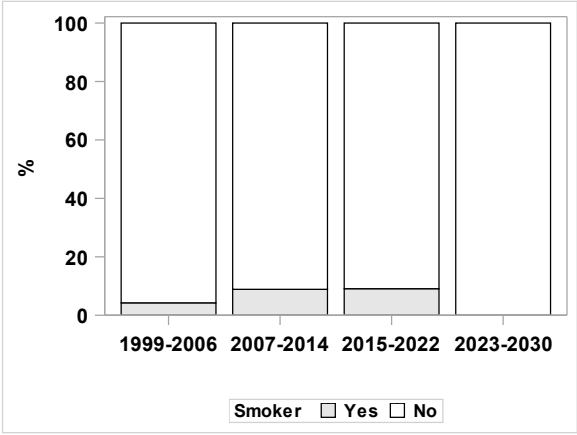
	Transplant Type (p=0.89)						Era (p=<0.01)											
	ITA (N[1]=507, Total [2]=1134)			IAK (N=130, Total=260)			Era 1 1999-2006 (N=169, Total=466)			Era 2 2007-2014 (N=330, Total=628)			Era 3 2015-2022 (N=130, Total=289)			Era 4 2023-2030 (N=8, Total=11)		
Anti Hyperglycemia Medication	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	466	91.9	41.1	119	91.5	45.8	161	95.3	34.5	311	94.2	49.5	106	81.5	36.7	7	87.5	63.6
Yes	41	8.1	3.6	11	8.5	4.2	8	4.7	1.7	19	5.8	3.0	24	18.5	8.3	1	12.5	9.1
Missing	627	N/A	55.3	130	N/A	50.0	297	N/A	63.7	298	N/A	47.5	159	N/A	55.0	3	N/A	27.3



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

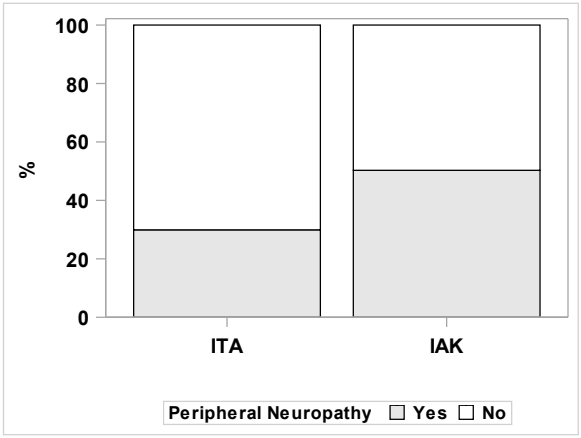
	Transplant Type (p=0.72)						Era (p=<0.001)											
	ITA (N[1]=900, Total [2]=1134)			IAK (N=153, Total=260)			Era 1 1999-2006 (N=376, Total=466)			Era 2 2007-2014 (N=484, Total=628)			Era 3 2015-2022 (N=187, Total=289)			Era 4 2023-2030 (N=6, Total=11)		
Smoker	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	834	92.7	73.5	143	93.5	55.0	360	95.7	77.3	441	91.1	70.2	170	90.9	58.8	6	100.0	54.5
Yes	66	7.3	5.8	10	6.5	3.8	16	4.3	3.4	43	8.9	6.8	17	9.1	5.9	0	0.0	0.0
Missing	234	N/A	20.6	107	N/A	41.2	90	N/A	19.3	144	N/A	22.9	102	N/A	35.3	5	N/A	45.5

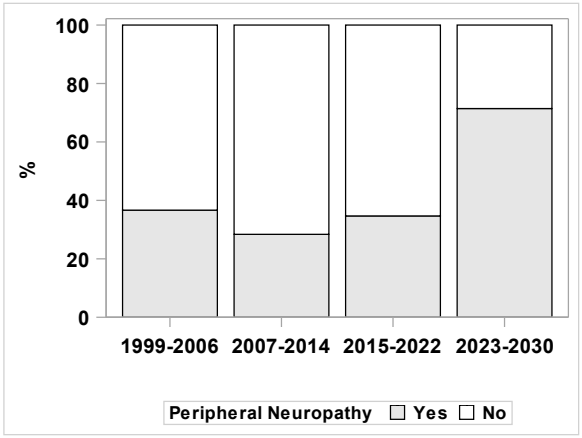


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=819, Total [2]=1134)			IAK (N=169, Total=260)			Era 1 1999-2006 (N=431, Total=466)			Era 2 2007-2014 (N=377, Total=628)			Era 3 2015-2022 (N=173, Total=289)			Era 4 2023-2030 (N=7, Total=11)		
Peripheral Neuropathy	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	574	70.1	50.6	84	49.7	32.3	273	63.3	58.6	270	71.6	43.0	113	65.3	39.1	2	28.6	18.2
Yes	245	29.9	21.6	85	50.3	32.7	158	36.7	33.9	107	28.4	17.0	60	34.7	20.8	5	71.4	45.5
Missing	315	N/A	27.8	91	N/A	35.0	35	N/A	7.5	251	N/A	40.0	116	N/A	40.1	4	N/A	36.4

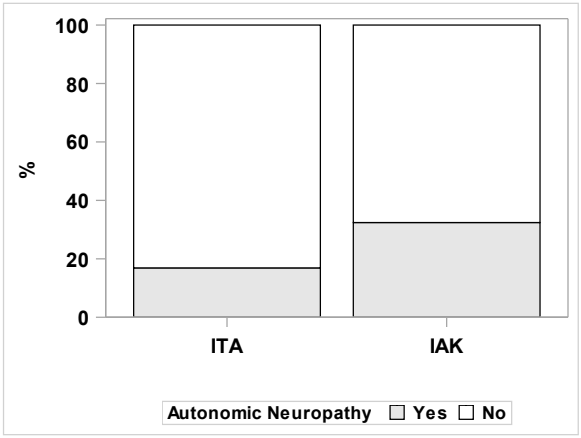


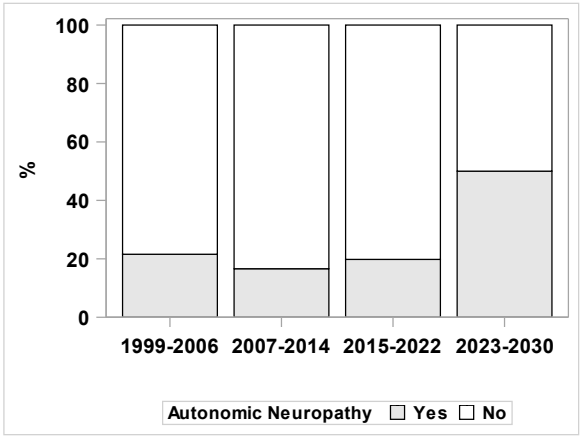


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=657, Total [2]=1134)			IAK (N=145, Total=260)			Era 1 1999-2006 (N=408, Total=466)			Era 2 2007-2014 (N=289, Total=628)			Era 3 2015-2022 (N=101, Total=289)			Era 4 2023-2030 (N=4, Total=11)		
Autonomic Neuropathy	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	546	83.1	48.1	98	67.6	37.7	320	78.4	68.7	241	83.4	38.4	81	80.2	28.0	2	50.0	18.2
Yes	111	16.9	9.8	47	32.4	18.1	88	21.6	18.9	48	16.6	7.6	20	19.8	6.9	2	50.0	18.2
Missing	477	N/A	42.1	115	N/A	44.2	58	N/A	12.4	339	N/A	54.0	188	N/A	65.1	7	N/A	63.6

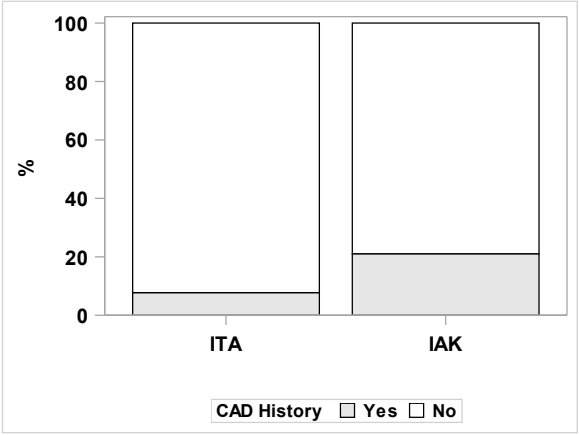




[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

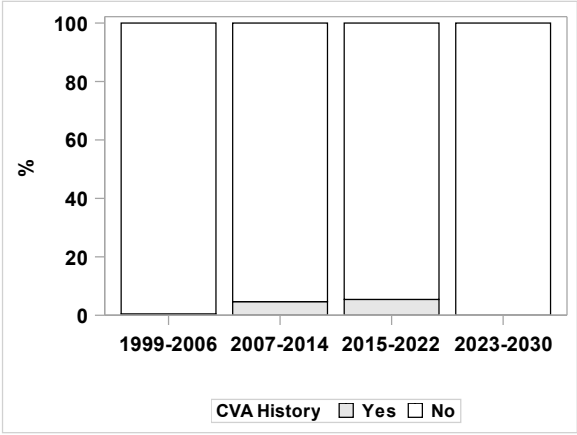
	Transplant Type (p=<0.001)						Era (p=0.35)											
	ITA (N[1]=813, Total [2]=1134)			IAK (N=171, Total=260)			Era 1 1999-2006 (N=437, Total=466)			Era 2 2007-2014 (N=373, Total=628)			Era 3 2015-2022 (N=168, Total=289)			Era 4 2023-2030 (N=6, Total=11)		
CAD History	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	750	92.3	66.1	135	78.9	51.9	398	91.1	85.4	333	89.3	53.0	149	88.7	51.6	5	83.3	45.5
Yes	63	7.7	5.6	36	21.1	13.8	39	8.9	8.4	40	10.7	6.4	19	11.3	6.6	1	16.7	9.1
Missing	321	N/A	28.3	89	N/A	34.2	29	N/A	6.2	255	N/A	40.6	121	N/A	41.9	5	N/A	45.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

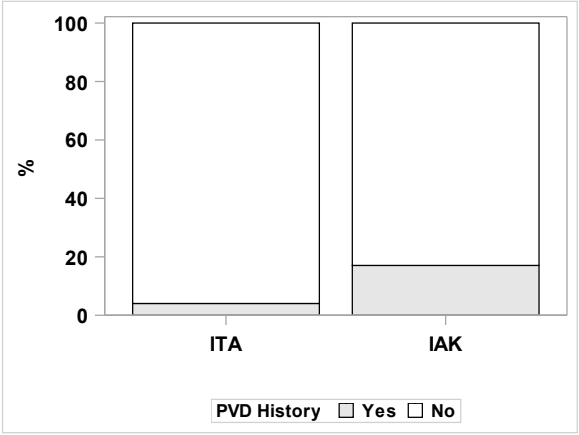
	Transplant Type (p=0.12)						Era (p=<0.05)											
	ITA (N[1]=800, Total [2]=1134)			IAK (N=163, Total=260)			Era 1 1999-2006 (N=426, Total=466)			Era 2 2007-2014 (N=365, Total=628)			Era 3 2015-2022 (N=166, Total=289)			Era 4 2023-2030 (N=6, Total=11)		
CVA History	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	780	97.5	68.8	155	95.1	59.6	424	99.5	91.0	348	95.3	55.4	157	94.6	54.3	6	100.0	54.5
Yes	20	2.5	1.8	8	4.9	3.1	2	0.5	0.4	17	4.7	2.7	9	5.4	3.1	0	0.0	0.0
Missing	334	N/A	29.5	97	N/A	37.3	40	N/A	8.6	263	N/A	41.9	123	N/A	42.6	5	N/A	45.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

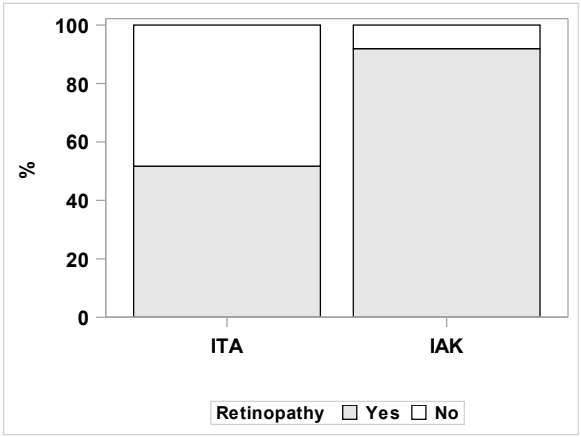
	Transplant Type (p=<0.001)						Era (p=0.30)											
	ITA (N[1]=644, Total [2]=1134)			IAK (N=129, Total=260)			Era 1 1999-2006 (N=407, Total=466)			Era 2 2007-2014 (N=265, Total=628)			Era 3 2015-2022 (N=97, Total=289)			Era 4 2023-2030 (N=4, Total=11)		
PVD History	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	618	96.0	54.5	107	82.9	41.2	387	95.1	83.0	244	92.1	38.9	91	93.8	31.5	3	75.0	27.3
Yes	26	4.0	2.3	22	17.1	8.5	20	4.9	4.3	21	7.9	3.3	6	6.2	2.1	1	25.0	9.1
Missing	490	N/A	43.2	131	N/A	50.4	59	N/A	12.7	363	N/A	57.8	192	N/A	66.4	7	N/A	63.6

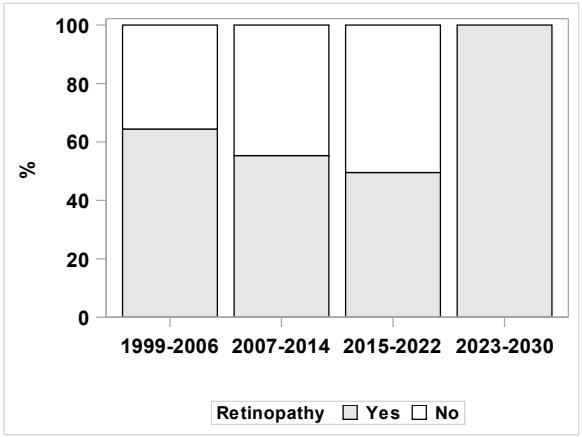


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=671, Total [2]=1134)			IAK (N=161, Total=260)			Era 1 1999-2006 (N=430, Total=466)			Era 2 2007-2014 (N=291, Total=628)			Era 3 2015-2022 (N=107, Total=289)			Era 4 2023-2030 (N=4, Total=11)		
Retinopathy	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	324	48.3	28.6	13	8.1	5.0	153	35.6	32.8	130	44.7	20.7	54	50.5	18.7	0	0.0	0.0
Yes	347	51.7	30.6	148	91.9	56.9	277	64.4	59.4	161	55.3	25.6	53	49.5	18.3	4	100.0	36.4
Missing	463	N/A	40.8	99	N/A	38.1	36	N/A	7.7	337	N/A	53.7	182	N/A	63.0	7	N/A	63.6

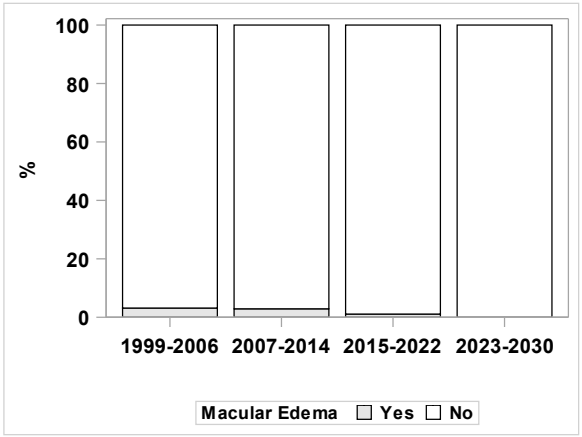




[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

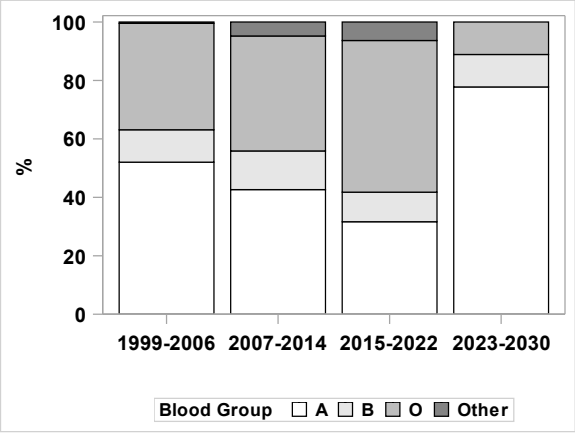
	Transplant Type (p=<0.05)						Era (p=<0.05)											
	ITA (N[1]=576, Total [2]=1134)			IAK (N=109, Total=260)			Era 1 1999-2006 (N=348, Total=466)			Era 2 2007-2014 (N=242, Total=628)			Era 3 2015-2022 (N=91, Total=289)			Era 4 2023-2030 (N=4, Total=11)		
Macular Edema	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	564	97.9	49.7	102	93.6	39.2	337	96.8	72.3	235	97.1	37.4	90	98.9	31.1	4	100.0	36.4
Yes	12	2.1	1.1	7	6.4	2.7	11	3.2	2.4	7	2.9	1.1	1	1.1	0.3	0	0.0	0.0
Missing	558	N/A	49.2	151	N/A	58.1	118	N/A	25.3	386	N/A	61.5	198	N/A	68.5	7	N/A	63.6



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

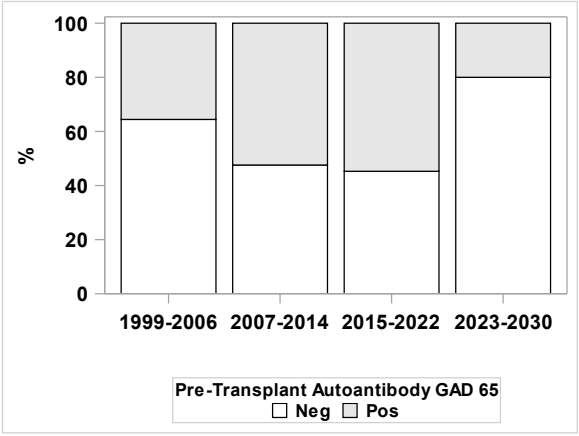
	Transplant Type (p=0.76)						Era (p=<0.001)											
	ITA (N[1]=999, Total [2]=1134)			IAK (N=233, Total=260)			Era 1 1999-2006 (N=442, Total=466)			Era 2 2007-2014 (N=544, Total=628)			Era 3 2015-2022 (N=237, Total=289)			Era 4 2023-2030 (N=9, Total=11)		
Blood Group	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
A	434	43.4	38.3	110	47.2	42.3	230	52.0	49.4	232	42.6	36.9	75	31.6	26.0	7	77.8	63.6
B	119	11.9	10.5	27	11.6	10.4	49	11.1	10.5	72	13.2	11.5	24	10.1	8.3	1	11.1	9.1
O	411	41.1	36.2	88	37.8	33.8	161	36.4	34.5	214	39.3	34.1	123	51.9	42.6	1	11.1	9.1
Other	35	3.5	3.1	8	3.4	3.1	2	0.5	0.4	26	4.8	4.1	15	6.3	5.2	0	0.0	0.0
Missing	135	N/A	11.9	27	N/A	10.4	24	N/A	5.2	84	N/A	13.4	52	N/A	18.0	2	N/A	18.2



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 2-5
Recipient Autoantibody and Sensitization at First Infusion

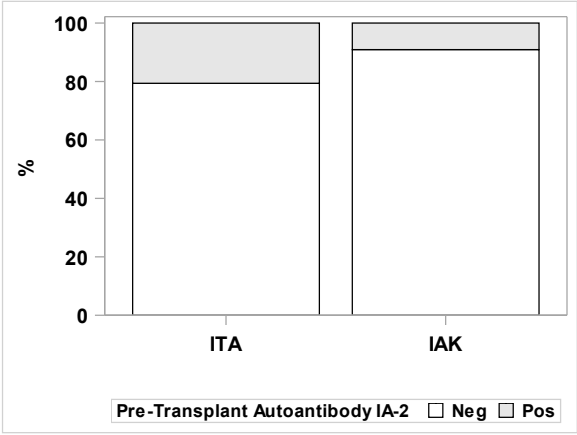
	Transplant Type (p=0.06)						Era (p=<0.001)											
	ITA (N[1]=516, Total [2]=1134)			IAK (N=140, Total=260)			Era 1 1999-2006 (N=329, Total=466)			Era 2 2007-2014 (N=227, Total=628)			Era 3 2015-2022 (N=95, Total=289)			Era 4 2023-2030 (N=5, Total=11)		
Pre-Transplant Autoantibody GAD 65	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Neg	279	54.1	24.6	88	62.9	33.8	212	64.4	45.5	108	47.6	17.2	43	45.3	14.9	4	80.0	36.4
Pos	237	45.9	20.9	52	37.1	20.0	117	35.6	25.1	119	52.4	18.9	52	54.7	18.0	1	20.0	9.1
Missing	618	N/A	54.5	120	N/A	46.2	137	N/A	29.4	401	N/A	63.9	194	N/A	67.1	6	N/A	54.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

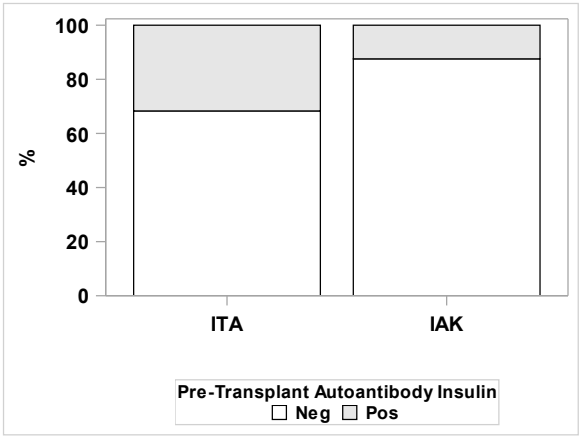
	Transplant Type (p=<0.001)						Era (p=0.95)											
	ITA (N[1]=810, Total [2]=1134)			IAK (N=209, Total=260)			Era 1 1999-2006 (N=456, Total=466)			Era 2 2007-2014 (N=441, Total=628)			Era 3 2015-2022 (N=114, Total=289)			Era 4 2023-2030 (N=8, Total=11)		
Pre-Transplant Autoantibody IA-2	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Neg	643	79.4	56.7	190	90.9	73.1	375	82.2	80.5	358	81.2	57.0	93	81.6	32.2	7	87.5	63.6
Pos	167	20.6	14.7	19	9.1	7.3	81	17.8	17.4	83	18.8	13.2	21	18.4	7.3	1	12.5	9.1
Missing	324	N/A	28.6	51	N/A	19.6	10	N/A	2.1	187	N/A	29.8	175	N/A	60.6	3	N/A	27.3

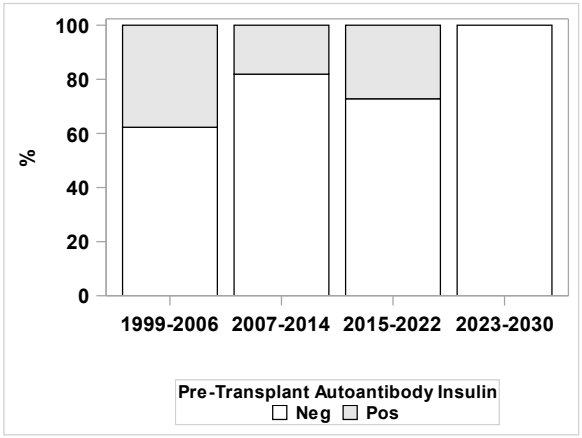


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=811, Total [2]=1134)			IAK (N=209, Total=260)			Era 1 1999-2006 (N=456, Total=466)			Era 2 2007-2014 (N=442, Total=628)			Era 3 2015-2022 (N=114, Total=289)			Era 4 2023-2030 (N=8, Total=11)		
Pre-Transplant Autoantibody Insulin	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Neg	554	68.3	48.9	183	87.6	70.4	284	62.3	60.9	362	81.9	57.6	83	72.8	28.7	8	100.0	72.7
Pos	257	31.7	22.7	26	12.4	10.0	172	37.7	36.9	80	18.1	12.7	31	27.2	10.7	0	0.0	0.0
Missing	323	N/A	28.5	51	N/A	19.6	10	N/A	2.1	186	N/A	29.6	175	N/A	60.6	3	N/A	27.3

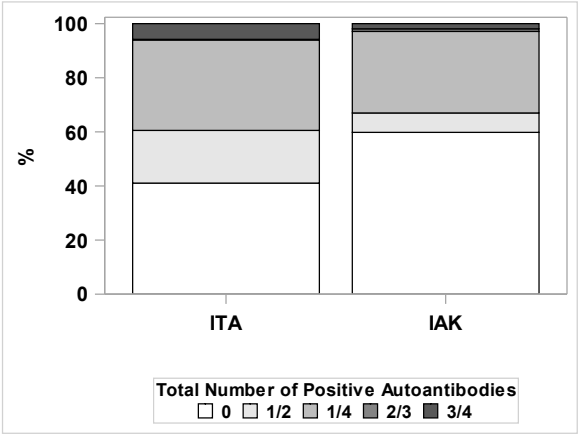




[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

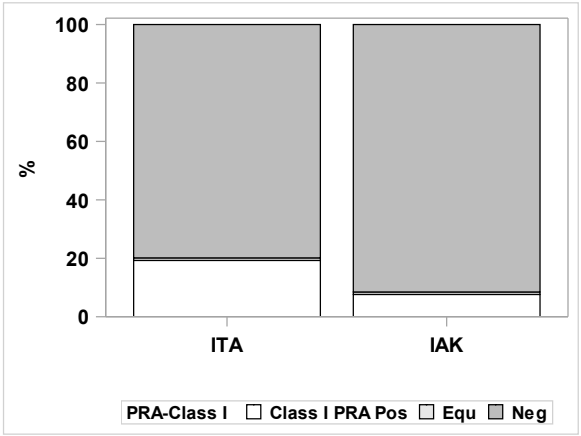
	Transplant Type (p=<0.001)						Era (p=0.20)											
	ITA (N[1]=811, Total [2]=1134)			IAK (N=209, Total=260)			Era 1 1999-2006 (N=456, Total=466)			Era 2 2007-2014 (N=442, Total=628)			Era 3 2015-2022 (N=114, Total=289)			Era 4 2023-2030 (N=8, Total=11)		
Total Number of Positive Autoantibodies	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
0	333	41.1	29.4	125	59.8	48.1	202	44.3	43.3	207	46.8	33.0	42	36.8	14.5	7	87.5	63.6
1/2	158	19.5	13.9	15	7.2	5.8	92	20.2	19.7	58	13.1	9.2	22	19.3	7.6	1	12.5	9.1
1/4	271	33.4	23.9	63	30.1	24.2	142	31.1	30.5	147	33.3	23.4	45	39.5	15.6	0	0.0	0.0
2/3	2	0.2	0.2	2	1.0	0.8	1	0.2	0.2	3	0.7	0.5	0	0.0	0.0	0	0.0	0.0
3/4	47	5.8	4.1	4	1.9	1.5	19	4.2	4.1	27	6.1	4.3	5	4.4	1.7	0	0.0	0.0
Missing	323	N/A	28.5	51	N/A	19.6	10	N/A	2.1	186	N/A	29.6	175	N/A	60.6	3	N/A	27.3

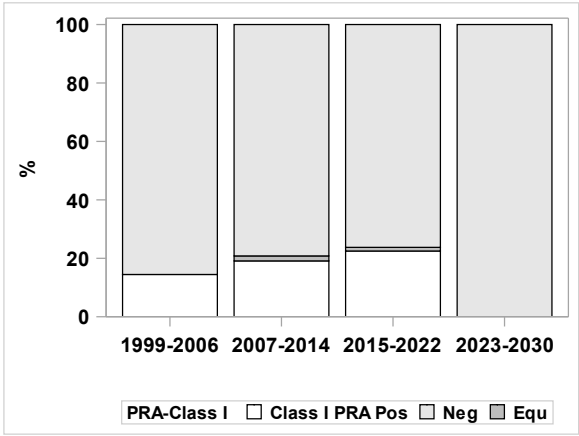


[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=<0.01)						Era (p=<0.05)											
	ITA (N[1]=581, Total [2]=1134)			IAK (N=118, Total=260)			Era 1 1999-2006 (N=325, Total=466)			Era 2 2007-2014 (N=293, Total=628)			Era 3 2015-2022 (N=80, Total=289)			Era 4 2023-2030 (N=1, Total=11)		
PRA-Class I	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Class I PRA Pos	112	19.3	9.9	9	7.6	3.5	47	14.5	10.1	56	19.1	8.9	18	22.5	6.2	0	0.0	0.0
Equ	5	0.9	0.4	1	0.8	0.4	0	0.0	0.0	5	1.7	0.8	1	1.3	0.3	0	0.0	0.0
Neg	464	79.9	40.9	108	91.5	41.5	278	85.5	59.7	232	79.2	36.9	61	76.3	21.1	1	100.0	9.1
Missing	553	N/A	48.8	142	N/A	54.6	141	N/A	30.3	335	N/A	53.3	209	N/A	72.3	10	N/A	90.9

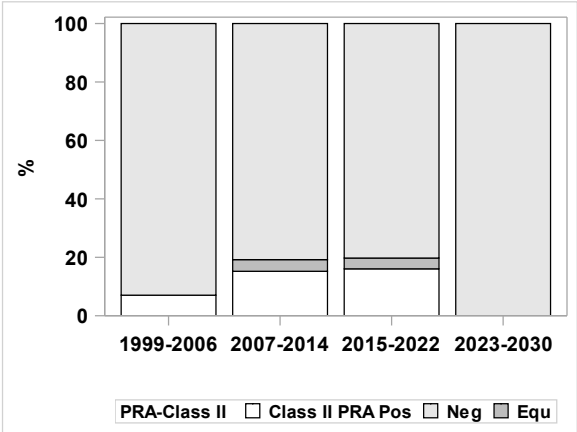




[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type (p=0.16)						Era (p=<0.001)											
	ITA (N[1]=471, Total [2]=1134)			IAK (N=86, Total=260)			Era 1 1999-2006 (N=199, Total=466)			Era 2 2007-2014 (N=276, Total=628)			Era 3 2015-2022 (N=81, Total=289)			Era 4 2023-2030 (N=1, Total=11)		
PRA-Class II	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Class II PRA Pos	63	13.4	5.6	6	7.0	2.3	14	7.0	3.0	42	15.2	6.7	13	16.0	4.5	0	0.0	0.0
Equ	13	2.8	1.1	1	1.2	0.4	0	0.0	0.0	11	4.0	1.8	3	3.7	1.0	0	0.0	0.0
Neg	395	83.9	34.8	79	91.9	30.4	185	93.0	39.7	223	80.8	35.5	65	80.2	22.5	1	100.0	9.1
Missing	663	N/A	58.5	174	N/A	66.9	267	N/A	57.3	352	N/A	56.1	208	N/A	72.0	10	N/A	90.9



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 2-6
Recipient Infectious Disease Testing at First Infusion

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
HIV	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Indeterminate	3	0.3	0.3	1	0.5	0.4	0	0.0	0.0	4	0.7	0.6	0	0.0	0.0	0	0.0	0.0
Negative	880	90.0	77.6	166	82.2	63.8	413	92.2	88.6	459	85.5	73.1	172	89.1	59.5	2	100.0	18.2
Not Done	31	3.2	2.7	13	6.4	5.0	6	1.3	1.3	24	4.5	3.8	14	7.3	4.8	0	0.0	0.0
Positive	0	0.0	0.0	1	0.5	0.4	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	0	0.0	0.0
Unknown	64	6.5	5.6	21	10.4	8.1	29	6.5	6.2	49	9.1	7.8	7	3.6	2.4	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
CMV-IgG	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Indeterminate	3	0.3	0.3	0	0.0	0.0	0	0.0	0.0	1	0.2	0.2	2	1.0	0.7	0	0.0	0.0
Negative	505	51.6	44.5	72	35.6	27.7	224	50.0	48.1	257	47.9	40.9	95	49.2	32.9	1	50.0	9.1
Not Done	25	2.6	2.2	11	5.4	4.2	12	2.7	2.6	22	4.1	3.5	2	1.0	0.7	0	0.0	0.0
Positive	413	42.2	36.4	100	49.5	38.5	193	43.1	41.4	228	42.5	36.3	91	47.2	31.5	1	50.0	9.1
Unknown	32	3.3	2.8	19	9.4	7.3	19	4.2	4.1	29	5.4	4.6	3	1.6	1.0	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
CMV-IgM	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Indeterminate	5	0.5	0.4	4	2.0	1.5	0	0.0	0.0	7	1.3	1.1	2	1.0	0.7	0	0.0	0.0
Negative	633	64.7	55.8	85	42.1	32.7	263	58.7	56.4	355	66.1	56.5	99	51.3	34.3	1	50.0	9.1
Not Done	200	20.4	17.6	63	31.2	24.2	128	28.6	27.5	93	17.3	14.8	42	21.8	14.5	0	0.0	0.0
Positive	74	7.6	6.5	17	8.4	6.5	9	2.0	1.9	44	8.2	7.0	37	19.2	12.8	1	50.0	9.1
Unknown	66	6.7	5.8	33	16.3	12.7	48	10.7	10.3	38	7.1	6.1	13	6.7	4.5	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
Hepatitis B Core	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Indeterminate	3	0.3	0.3	0	0.0	0.0	1	0.2	0.2	0	0.0	0.0	2	1.0	0.7	0	0.0	0.0
Negative	647	66.2	57.1	129	63.9	49.6	323	72.1	69.3	352	65.5	56.1	101	52.3	34.9	0	0.0	0.0
Not Done	239	24.4	21.1	37	18.3	14.2	68	15.2	14.6	120	22.3	19.1	86	44.6	29.8	2	100.0	18.2
Positive	20	2.0	1.8	5	2.5	1.9	6	1.3	1.3	15	2.8	2.4	4	2.1	1.4	0	0.0	0.0
Unknown	69	7.1	6.1	31	15.3	11.9	50	11.2	10.7	50	9.3	8.0	0	0.0	0.0	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
Hepatitis B Surface	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Indeterminate	2	0.2	0.2	0	0.0	0.0	0	0.0	0.0	1	0.2	0.2	1	0.5	0.3	0	0.0	0.0
Negative	299	30.6	26.4	43	21.3	16.5	88	19.6	18.9	191	35.6	30.4	63	32.6	21.8	0	0.0	0.0
Not Done	217	22.2	19.1	64	31.7	24.6	21	4.7	4.5	147	27.4	23.4	111	57.5	38.4	2	100.0	18.2
Positive	84	8.6	7.4	16	7.9	6.2	21	4.7	4.5	63	11.7	10.0	16	8.3	5.5	0	0.0	0.0
Unknown	376	38.4	33.2	79	39.1	30.4	318	71.0	68.2	135	25.1	21.5	2	1.0	0.7	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
HCV	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Negative	870	89.0	76.7	170	84.2	65.4	405	90.4	86.9	451	84.0	71.8	182	94.3	63.0	2	100.0	18.2
Not Done	19	1.9	1.7	8	4.0	3.1	8	1.8	1.7	18	3.4	2.9	1	0.5	0.3	0	0.0	0.0
Positive	9	0.9	0.8	6	3.0	2.3	5	1.1	1.1	7	1.3	1.1	3	1.6	1.0	0	0.0	0.0
Unknown	80	8.2	7.1	18	8.9	6.9	30	6.7	6.4	61	11.4	9.7	7	3.6	2.4	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
EBV-IgG	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	88	9.0	7.8	8	4.0	3.1	27	6.0	5.8	51	9.5	8.1	18	9.3	6.2	0	0.0	0.0
Not Done	96	9.8	8.5	16	7.9	6.2	39	8.7	8.4	71	13.2	11.3	2	1.0	0.7	0	0.0	0.0
Positive	748	76.5	66.0	159	78.7	61.2	362	80.8	77.7	378	70.4	60.2	165	85.5	57.1	2	100.0	18.2
Unknown	46	4.7	4.1	19	9.4	7.3	20	4.5	4.3	37	6.9	5.9	8	4.1	2.8	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

	Transplant Type						Era											
	ITA (N[1]=978, Total [2]=1134)			IAK (N=202, Total=260)			Era 1 1999-2006 (N=448, Total=466)			Era 2 2007-2014 (N=537, Total=628)			Era 3 2015-2022 (N=193, Total=289)			Era 4 2023-2030 (N=2, Total=11)		
EBV-IgM	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Indeterminate	3	0.3	0.3	2	1.0	0.8	1	0.2	0.2	0	0.0	0.0	4	2.1	1.4	0	0.0	0.0
Negative	468	47.9	41.3	83	41.1	31.9	228	50.9	48.9	254	47.3	40.4	69	35.8	23.9	0	0.0	0.0
Not Done	190	19.4	16.8	56	27.7	21.5	130	29.0	27.9	74	13.8	11.8	42	21.8	14.5	0	0.0	0.0
Positive	150	15.3	13.2	17	8.4	6.5	17	3.8	3.6	79	14.7	12.6	69	35.8	23.9	2	100.0	18.2
Unknown	167	17.1	14.7	44	21.8	16.9	72	16.1	15.5	130	24.2	20.7	9	4.7	3.1	0	0.0	0.0
Missing	156	N/A	13.8	58	N/A	22.3	18	N/A	3.9	91	N/A	14.5	96	N/A	33.2	9	N/A	81.8

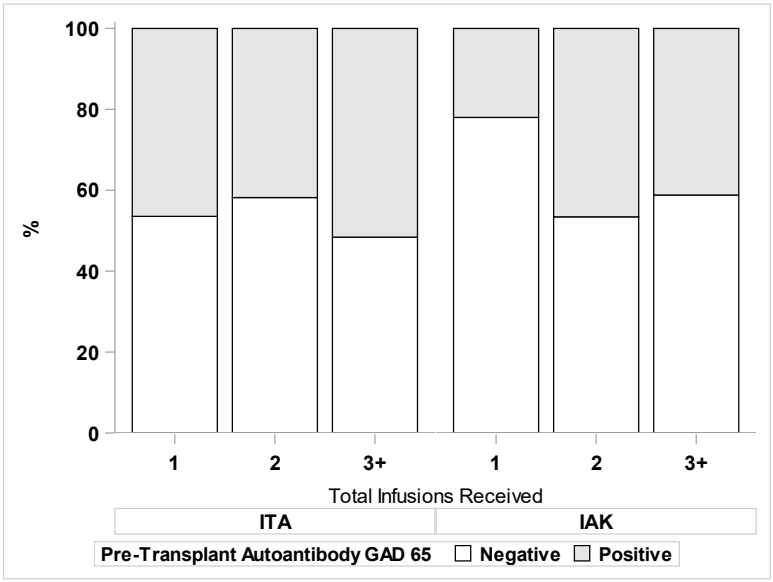
[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

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

	ITA Total Number of Infusions Received									IAK 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)	294	47.1	0.7	546	47.4	0.5	294	46.4	0.6	93	49.4	1.0	125	48.7	0.8	40	47.4	1.5
Duration of Diabetes (yrs)	232	29.9	0.8	455	30.3	0.6	216	28.0	0.7	82	36.1	1.2	107	34.2	1.0	25	34.1	1.5
Weight (kg)	242	66.1	0.8	487	67.9	0.5	261	70.2	0.7	82	66.4	1.4	112	65.0	1.0	33	68.4	1.6
BMI (kg/m^2)	168	23.3	0.2	311	23.7	0.2	221	24.3	0.2	70	23.5	0.4	90	22.8	0.3	29	23.7	0.5
Daily Insulin Requirement (units)	229	34.2	1.1	459	36.7	0.7	260	40.8	1.0	76	36.0	1.7	100	36.8	1.3	32	36.1	2.6
Average Daily Insulin/kg Recipient Body Weight	218	0.5	0.0	444	0.5	0.0	247	0.6	0.0	72	0.6	0.0	96	0.6	0.0	30	0.5	0.0
Duration of Intensive Insulin Therapy (yrs)	97	18.9	1.5	202	21.9	1.0	124	19.5	1.1	22	31.3	2.9	16	25.1	2.8	1	0.9	-
Fasting Glucose (mg/dL)	186	162.0	6.5	330	168.4	4.7	223	180.5	5.9	43	164.7	13.1	77	164.0	8.5	29	164.0	20.2
Basal C-Peptide (ng/mL)	201	0.1	0.0	343	0.1	0.0	235	0.1	0.0	58	0.3	0.2	84	0.3	0.1	28	0.1	0.0
HbA1c (%)	219	7.8	0.1	414	8.0	0.1	252	7.9	0.1	80	7.9	0.2	111	8.3	0.1	34	7.8	0.2

Exhibit 2-8
Recipient Baseline Autoantibodies by Total Infusions Received

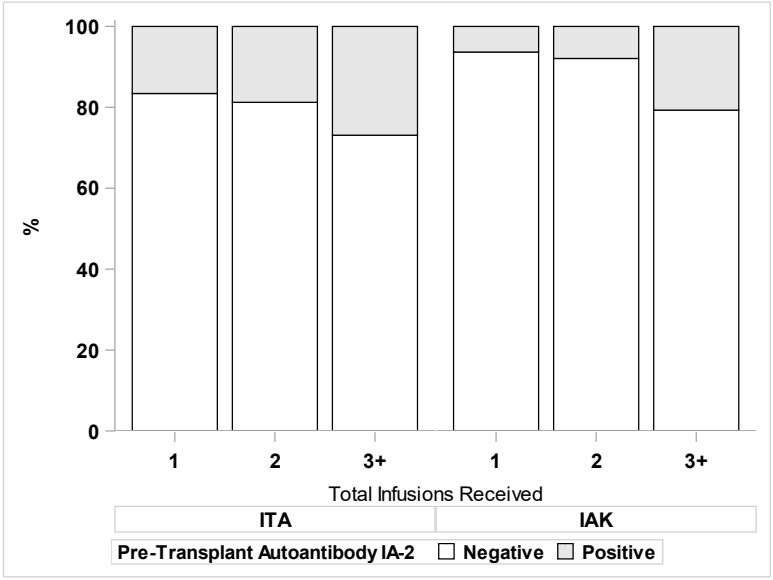
		ITA Total Number of Infusions Received									IAK Total Number of Infusions Received								
		One Infusion (N[1]=127, Total [2]=294)			Two Infusions (N[1]=232, Total [2]=546)			>=Three Infusions (N[1]=157, Total [2]=294)			One Infusion (N=50, Total=94)			Two Infusions (N=73, Total=126)			>=Three Infusions (N=17, Total=40)		
		n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Pre-Transplant Autoantibody GAD 65	Negative	68	53.5	23.1	135	58.2	24.7	76	48.4	25.9	39	78.0	41.5	39	53.4	31.0	10	58.8	25.0
	Positive	59	46.5	20.1	97	41.8	17.8	81	51.6	27.6	11	22.0	11.7	34	46.6	27.0	7	41.2	17.5
	Unknown/Missing	167	N/A	56.8	314	N/A	57.5	137	N/A	46.6	44	N/A	46.8	53	N/A	42.1	23	N/A	57.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type

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

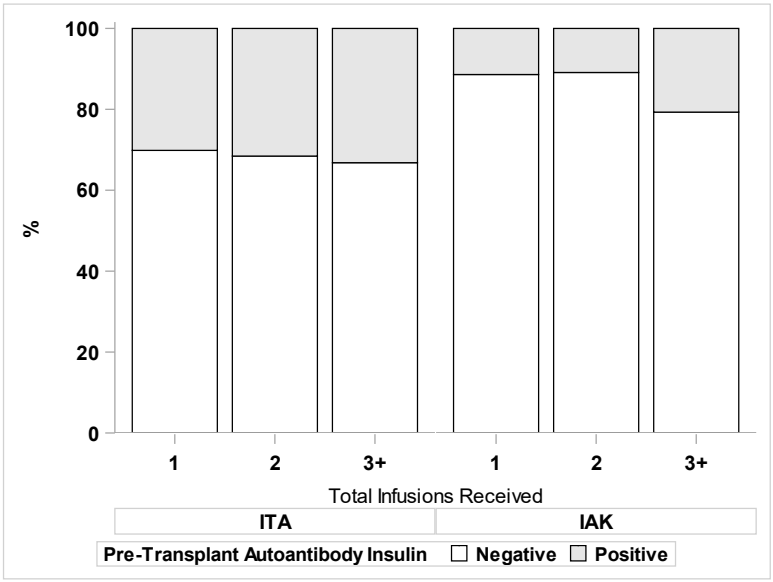
		ITA Total Number of Infusions Received									IAK Total Number of Infusions Received								
		One Infusion (N[1]=199, Total[2]=294)			Two Infusions (N[1]=373, Total[2]=546)			>=Three Infusions (N[1]=238, Total[2]=294)			One Infusion (N=79, Total=94)			Two Infusions (N=101, Total=126)			>=Three Infusions (N=29, Total=40)		
		n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Pre-Transplant Autoantibody IA-2	Negative	166	83.4	56.5	303	81.2	55.5	174	73.1	59.2	74	93.7	78.7	93	92.1	73.8	23	79.3	57.5
	Positive	33	16.6	11.2	70	18.8	12.8	64	26.9	21.8	5	6.3	5.3	8	7.9	6.3	6	20.7	15.0
	Unknown/Missing	95	N/A	32.3	173	N/A	31.7	56	N/A	19.0	15	N/A	16.0	25	N/A	19.8	11	N/A	27.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type

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

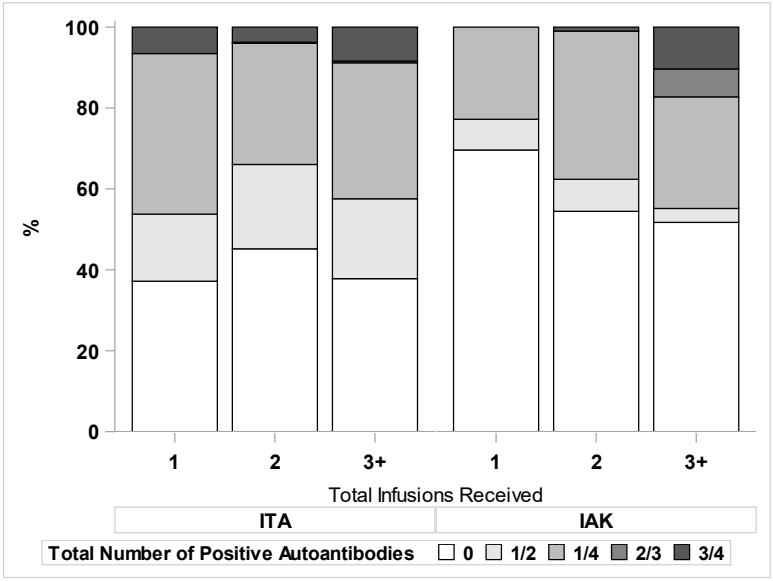
		ITA Total Number of Infusions Received									IAK Total Number of Infusions Received								
		One Infusion (N[1]=199, Total[2]=294)			Two Infusions (N[1]=374, Total[2]=546)			>=Three Infusions (N[1]=238, Total[2]=294)			One Infusion (N=79, Total=94)			Two Infusions (N=101, Total=126)			>=Three Infusions (N=29, Total=40)		
		n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Pre-Transplant Autoantibody Insulin	Negative	139	69.8	47.3	256	68.4	46.9	159	66.8	54.1	70	88.6	74.5	90	89.1	71.4	23	79.3	57.5
	Positive	60	30.2	20.4	118	31.6	21.6	79	33.2	26.9	9	11.4	9.6	11	10.9	8.7	6	20.7	15.0
	Unknown/Missing	95	N/A	32.3	172	N/A	31.5	56	N/A	19.0	15	N/A	16.0	25	N/A	19.8	11	N/A	27.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type

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

		ITA Total Number of Infusions Received									IAK Total Number of Infusions Received								
		One Infusion (N[1]=199, Total[2]=294)			Two Infusions (N[1]=374, Total[2]=546)			>=Three Infusions (N[1]=238, Total[2]=294)			One Infusion (N=79, Total=94)			Two Infusions (N=101, Total=126)			>=Three Infusions (N=29, Total=40)		
		n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Total Number of Positive Autoantibodies	0	74	37.2	25.2	169	45.2	31.0	90	37.8	30.6	55	69.6	58.5	55	54.5	43.7	15	51.7	37.5
	1/2	33	16.6	11.2	78	20.9	14.3	47	19.7	16.0	6	7.6	6.4	8	7.9	6.3	1	3.4	2.5
	1/4	79	39.7	26.9	112	29.9	20.5	80	33.6	27.2	18	22.8	19.1	37	36.6	29.4	8	27.6	20.0
	2/3	0	0.0	0.0	1	0.3	0.2	1	0.4	0.3	0	0.0	0.0	0	0.0	0.0	2	6.9	5.0
	3/4	13	6.5	4.4	14	3.7	2.6	20	8.4	6.8	0	0.0	0.0	1	1.0	0.8	3	10.3	7.5
	Unknown/Missing	95	N/A	32.3	172	N/A	31.5	56	N/A	19.0	15	N/A	16.0	25	N/A	19.8	11	N/A	27.5



[1] N = Recipients with data
[2] Total = Recipients of the given transplant type

Exhibit 2-9
Recipient Laboratory Values at First Infusion

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
HbA1C (%)	885	7.9	0	225	8.1	0.1	0.050
Basal C-Peptide (ng/mL)	779	0.1	0	170	0.2	0.1	<0.001
Fasting Blood Glucose (mg/dL)	739	170.4	3.2	149	164.2	6.9	0.425
ALT (U/L)	892	24.1	0.6	197	24.3	0.9	0.936
AST (U/L)	761	27	0.8	188	25.8	0.9	0.475
Alkaline Phosphatase (U/L)	678	80.1	1.6	173	108.5	5.3	<0.001
Total Bilirubin (mg/dL)	662	0.6	0	177	0.5	0	0.001
Total Cholesterol (mg/dL)	742	170.7	1.4	177	172.1	3.1	0.673
HDL (mg/dL)	717	65.2	0.7	166	63.2	1.6	0.245
LDL (mg/dL)	701	90.9	1.1	151	86.6	2.4	0.103
Triglycerides (mg/dL)	742	52.2	1.2	177	67.7	3	<0.001
Serum Creatinine (mg/dL)	946	0.9	0	238	1.4	0	<0.001
eGFR-CKD (mL/min/1.73m ^{2})	946	91	0.7	235	61.9	1.5	<0.001

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

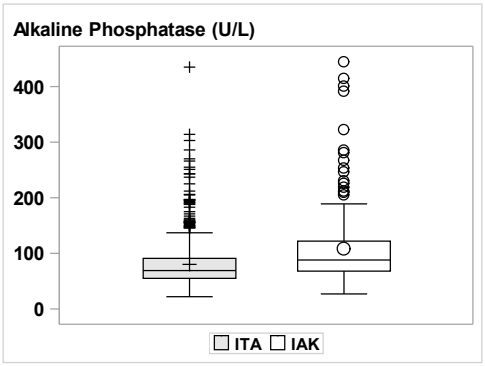
Exhibit 2-9
Recipient Laboratory Values at First Infusion

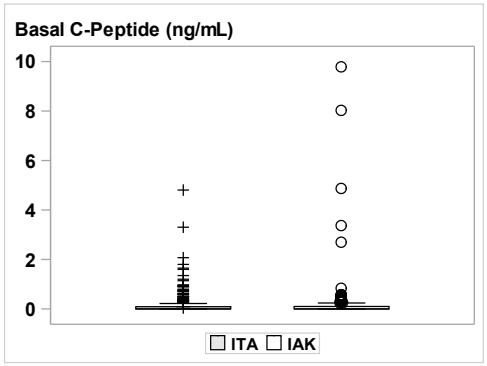
	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
HbA1C (%)	447	7.8	0.1	518	8	0.1	137	8.1	0.1	8	7	0.3	0.002
Basal C-Peptide (ng/mL)	430	0.1	0	397	0.1	0	118	0.2	0.1	4	2.1	2	<0.001
Fasting Blood Glucose (mg/dL)	410	174	4.6	392	164	4.2	85	173	8.1	1	85	-	0.292
ALT (U/L)	381	23.7	0.7	499	25.4	1	199	21.6	0.8	10	29.9	4	0.061
AST (U/L)	394	25.3	0.6	426	29.1	1.3	121	22.9	0.8	8	28.9	2.7	0.006
Alkaline Phosphatase (U/L)	372	96.2	3.3	364	74.4	1.8	111	87.5	3	4	131.5	10.5	<0.001
Total Bilirubin (mg/dL)	361	0.6	0	371	0.6	0	101	0.5	0	6	0.4	0	0.009
Total Cholesterol (mg/dL)	397	176.7	1.7	417	166.4	2	105	168	4.4	0	-	-	<0.001
HDL (mg/dL)	383	65.1	0.9	400	65.2	1	100	62.6	2.3	0	-	-	0.488
LDL (mg/dL)	363	96.3	1.4	394	85.6	1.5	95	85.4	3.2	0	-	-	<0.001
Triglycerides (mg/dL)	397	56.8	2	418	54.1	1.5	104	53.2	3.1	0	-	-	0.447
Serum Creatinine (mg/dL)	421	1	0	542	0.9	0	211	1	0	10	2.2	0.7	<0.001
eGFR-CKD (mL/min/1.73m ^{2})	420	85.4	1.2	541	86	1	210	83.9	1.8	10	59.8	14.3	0.008

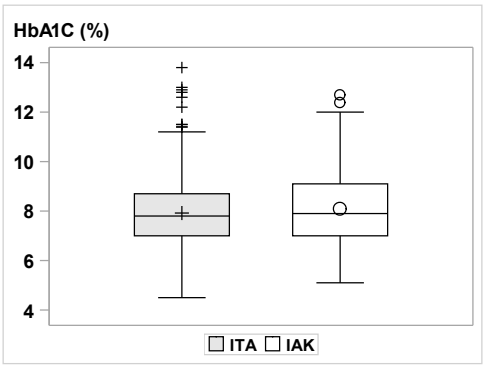
Significant differences by type and era are displayed in the following box-and-whisker plots.

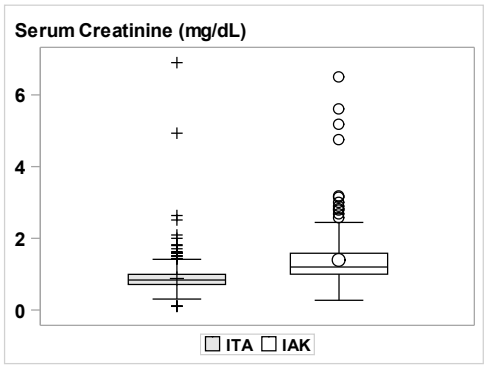
Exhibit 2-9 (continued)
Recipient Laboratory Values at First Infusion

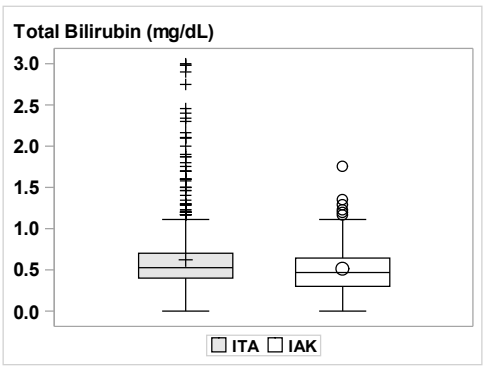
Significant trends in patient characteristics from table above by ITA or IAK

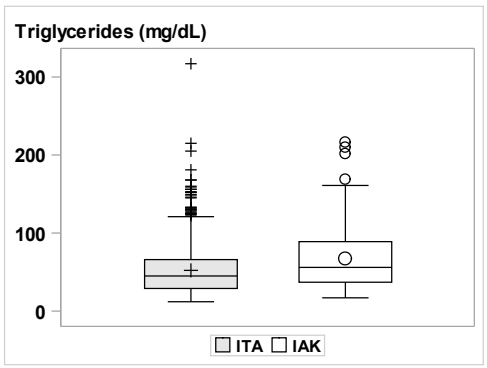












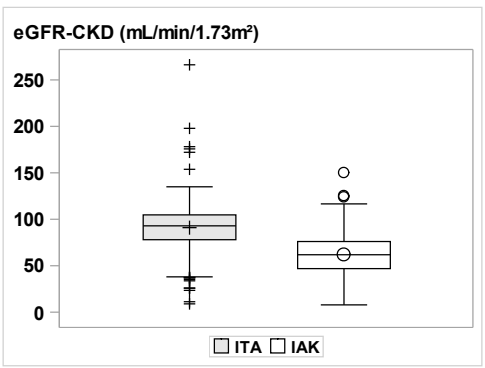
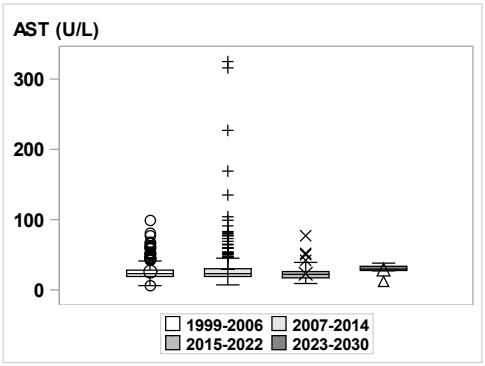
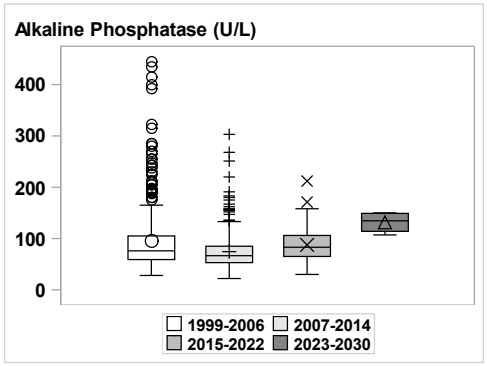
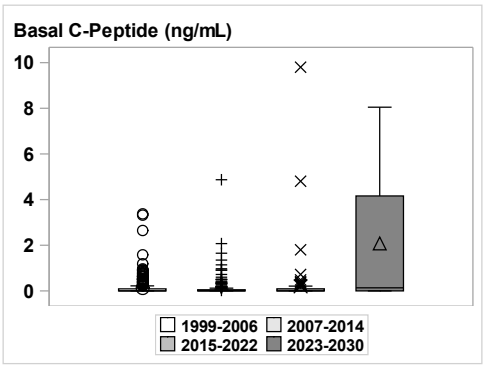


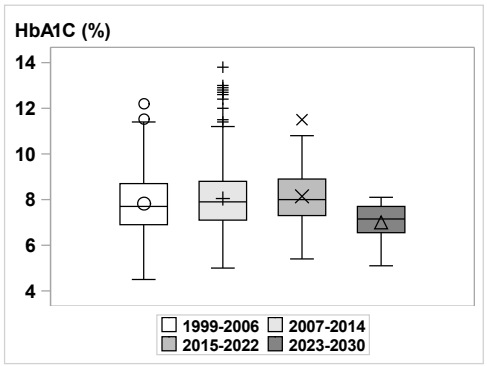
Exhibit 2-9 (continued)
Recipient Laboratory Values at First Infusion

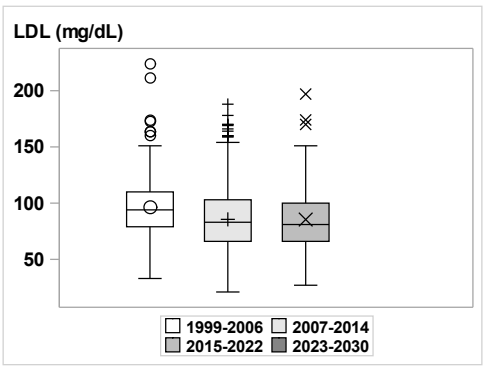
Significant trends in patient characteristics from table above by Era

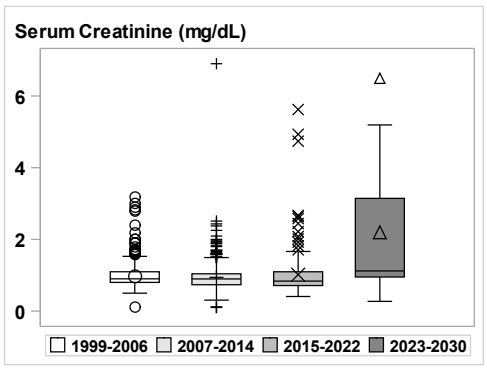


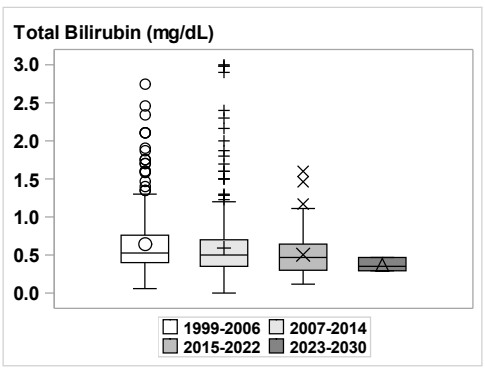












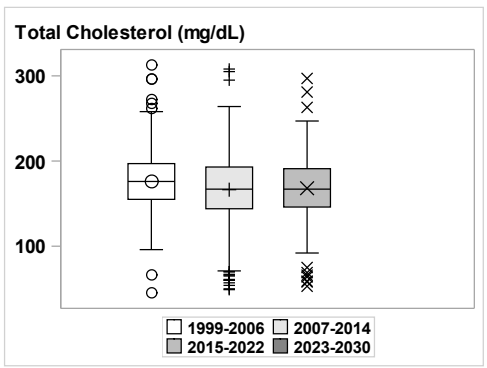


Exhibit 2-9 (continued)
Recipient Laboratory Values at First Infusion

Significant trends in patient characteristics from table above by Era

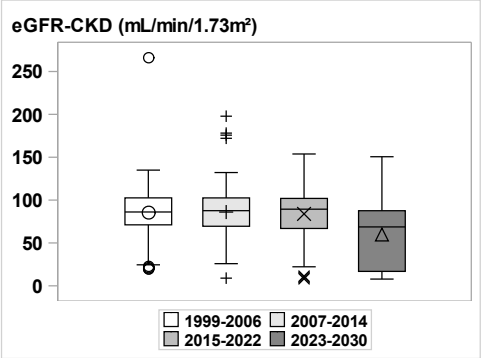


Exhibit 2-10
Donor Demographics per Infusion

	Transplant Type (p=<0.05)						Era (p=0.06)											
	ITA (N[1]=1892, Total [2]=2329)			IAK (N=383, Total=471)			Era 1 1999-2006 (N=851, Total=1009)			Era 2 2007-2014 (N=1071, Total=1254)			Era 3 2015-2022 (N=342, Total=523)			Era 4 2023-2030 (N=11, Total=14)		
Gender	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Female	755	39.9	32.4	135	35.2	28.7	326	38.3	32.3	415	38.7	33.1	147	43.0	28.1	2	18.2	14.3
Male	1073	56.7	46.1	225	58.7	47.8	487	57.2	48.3	611	57.0	48.7	191	55.8	36.5	9	81.8	64.3
Mixed	64	3.4	2.7	23	6.0	4.9	38	4.5	3.8	45	4.2	3.6	4	1.2	0.8	0	0.0	0.0
Missing	437	N/A	18.8	88	N/A	18.7	158	N/A	15.7	183	N/A	14.6	181	N/A	34.6	3	N/A	21.4

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-10 (continued)
Donor Demographics per Infusion

	Transplant Type (p=0.59)						Era (p=0.74)											
	ITA (N[1]=1223, Total [2]=2329)			IAK (N=171, Total=471)			Era 1 1999-2006 (N=529, Total=1009)			Era 2 2007-2014 (N=610, Total=1254)			Era 3 2015-2022 (N=248, Total=523)			Era 4 2023-2030 (N=7, Total=14)		
Race	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Mixed	7	0.6	0.3	0	0.0	0.0	3	0.6	0.3	4	0.7	0.3	0	0.0	0.0	0	0.0	0.0
Non-white	128	10.5	5.5	17	9.9	3.6	57	10.8	5.6	67	11.0	5.3	21	8.5	4.0	0	0.0	0.0
White	1088	89.0	46.7	154	90.1	32.7	469	88.7	46.5	539	88.4	43.0	227	91.5	43.4	7	100.0	50.0
Missing	1106	N/A	47.5	300	N/A	63.7	480	N/A	47.6	644	N/A	51.4	275	N/A	52.6	7	N/A	50.0

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-10 (continued)
Donor Demographics per Infusion

	Transplant Type (p=0.08)						Era (p=<0.001)											
	ITA (N[1]=331, Total [2]=2329)			IAK (N=48, Total=471)			Era 1 1999-2006 (N=152, Total=1009)			Era 2 2007-2014 (N=169, Total=1254)			Era 3 2015-2022 (N=54, Total=523)			Era 4 2023-2030 (N=4, Total=14)		
Ethnicity	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Hispanic	55	16.6	2.4	13	27.1	2.8	21	13.8	2.1	45	26.6	3.6	2	3.7	0.4	0	0.0	0.0
Non-Hispanic	276	83.4	11.9	35	72.9	7.4	131	86.2	13.0	124	73.4	9.9	52	96.3	9.9	4	100.0	28.6
Missing	1998	N/A	85.8	423	N/A	89.8	857	N/A	84.9	1085	N/A	86.5	469	N/A	89.7	10	N/A	71.4

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-11
Donor Characteristics (per Infusion)

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Donor Age (yrs)	1080	44.6	0.4	229	45.6	0.8	0.279
Donor Weight (kg)	1904	88.5	0.4	384	87	1	0.194
Donor Height (cm)	1903	172.9	0.2	384	174	0.5	0.052
Donor BMI (kg/m ^{2})	1902	29.6	0.1	384	28.7	0.3	0.011

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

Exhibit 2-11
Donor Characteristics (per Infusion)

	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Donor Age (yrs)	683	43.7	0.5	483	45.9	0.5	135	46.4	1.1	8	48.6	4.3	0.004
Donor Weight (kg)	861	85.9	0.7	1074	90	0.6	342	88.5	1	11	88.1	3.3	<0.001
Donor Height (cm)	859	173.2	0.3	1074	173.3	0.3	343	172.3	0.6	11	175.2	2.3	0.367
Donor BMI (kg/m ^{2})	859	28.6	0.2	1074	29.9	0.2	342	29.9	0.4	11	28.7	1	<0.001

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

Exhibit 2-11 (continued)
Donor Characteristics (per Infusion)

Significant trends in donor characteristics from table above by ITA or IAK

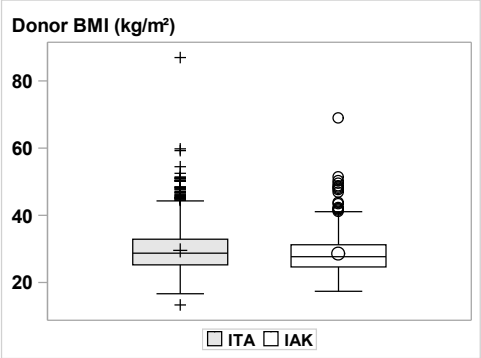
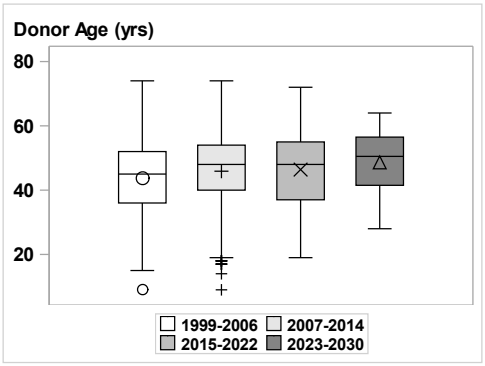
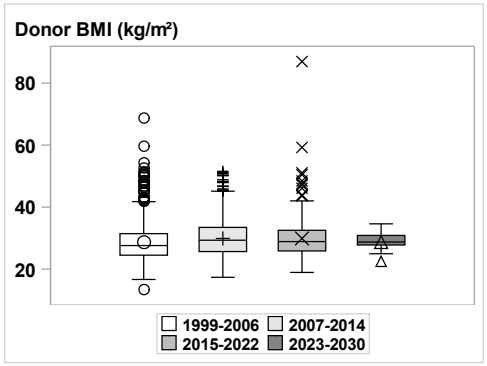


Exhibit 2-11 (continued)
Donor Characteristics (per Infusion)

Significant trends in donor characteristics from table above by Era





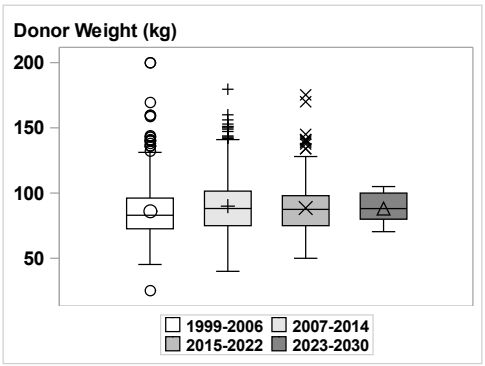
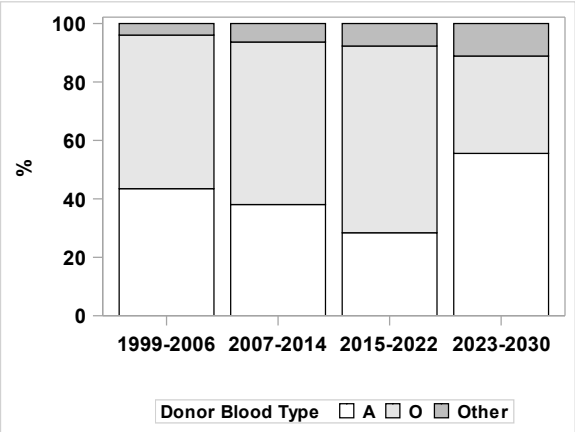


Exhibit 2-11 (continued)
Donor Characteristics (per Infusion)

	Transplant Type (p=0.58)						Era (p=<0.001)											
	ITA (N[1]=1886, Total [2]=2329)			IAK (N=380, Total=471)			Era 1 1999-2006 (N=860, Total=1009)			Era 2 2007-2014 (N=1059, Total=1254)			Era 3 2015-2022 (N=338, Total=523)			Era 4 2023-2030 (N=9, Total=14)		
Donor Blood Type	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
A	739	39.2	31.7	139	36.6	29.5	374	43.5	37.1	403	38.1	32.1	96	28.4	18.4	5	55.6	35.7
O	1043	55.3	44.8	217	57.1	46.1	452	52.6	44.8	589	55.6	47.0	216	63.9	41.3	3	33.3	21.4
Other	104	5.5	4.5	24	6.3	5.1	34	4.0	3.4	67	6.3	5.3	26	7.7	5.0	1	11.1	7.1
Missing	443	N/A	19.0	91	N/A	19.3	149	N/A	14.8	195	N/A	15.6	185	N/A	35.4	5	N/A	35.7



[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-11 (continued)
Donor Characteristics (per Infusion)

	Transplant Type (p=0.65)						Era (p=0.08)											
	ITA (N[1]=1574, Total [2]=2329)			IAK (N=302, Total=471)			Era 1 1999-2006 (N=716, Total=1009)			Era 2 2007-2014 (N=908, Total=1254)			Era 3 2015-2022 (N=242, Total=523)			Era 4 2023-2030 (N=10, Total=14)		
History of Hypertension	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	1053	66.9	45.2	198	65.6	42.0	470	65.6	46.6	595	65.5	47.4	179	74.0	34.2	7	70.0	50.0
Yes	521	33.1	22.4	104	34.4	22.1	246	34.4	24.4	313	34.5	25.0	63	26.0	12.0	3	30.0	21.4
Missing	755	N/A	32.4	169	N/A	35.9	293	N/A	29.0	346	N/A	27.6	281	N/A	53.7	4	N/A	28.6

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-11 (continued)
Donor Characteristics (per Infusion)

	Transplant Type (p=0.69)						Era (p=0.16)											
	ITA (N[1]=1414, Total [2]=2329)			IAK (N=284, Total=471)			Era 1 1999-2006 (N=697, Total=1009)			Era 2 2007-2014 (N=875, Total=1254)			Era 3 2015-2022 (N=119, Total=523)			Era 4 2023-2030 (N=7, Total=14)		
History of Alcohol Dependency	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	1217	86.1	52.3	247	87.0	52.4	588	84.4	58.3	765	87.4	61.0	106	89.1	20.3	5	71.4	35.7
Yes	197	13.9	8.5	37	13.0	7.9	109	15.6	10.8	110	12.6	8.8	13	10.9	2.5	2	28.6	14.3
Missing	915	N/A	39.3	187	N/A	39.7	312	N/A	30.9	379	N/A	30.2	404	N/A	77.2	7	N/A	50.0

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-11 (continued)
Donor Characteristics (per Infusion)

	Transplant Type (p=1.00)						Era (p=0.38)											
	ITA (N[1]=1625, Total [2]=2329)			IAK (N=306, Total=471)			Era 1 1999-2006 (N=778, Total=1009)			Era 2 2007-2014 (N=898, Total=1254)			Era 3 2015-2022 (N=244, Total=523)			Era 4 2023-2030 (N=11, Total=14)		
History of Diabetes	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	1617	99.5	69.4	305	99.7	64.8	776	99.7	76.9	893	99.4	71.2	242	99.2	46.3	11	100.0	78.6
Yes	8	0.5	0.3	1	0.3	0.2	2	0.3	0.2	5	0.6	0.4	2	0.8	0.4	0	0.0	0.0
Missing	704	N/A	30.2	165	N/A	35.0	231	N/A	22.9	356	N/A	28.4	279	N/A	53.3	3	N/A	21.4

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

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

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Time from Admission to Brain Death (hrs)	985	58.8	2.3	201	55	3.7	0.902
Time from Cross Clamp to Pancreas Recovery (hrs)	759	0.9	0	202	1	0.1	0.540
Cold Ischemia Time (hrs)	1087	8	0.2	305	7.6	0.4	0.568

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

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

	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Time from Admission to Brain Death (hrs)	532	51.4	2.7	495	63.9	3.2	245	61.1	4.4	11	66	7.9	0.024
Time from Cross Clamp to Pancreas Recovery (hrs)	559	0.8	0.1	368	1	0.1	94	0.9	0	3	0.5	0.3	0.118
Cold Ischemia Time (hrs)	851	7.3	0.1	496	8.6	0.3	117	9.4	0.8	5	4.5	1	<0.001

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

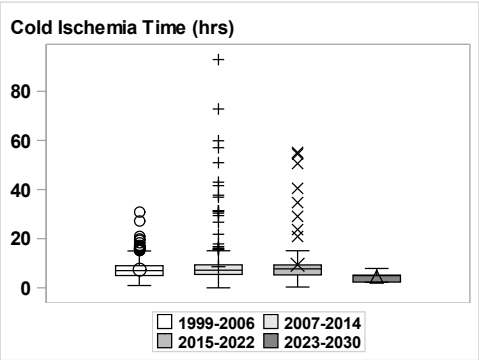
Exhibit 2-12 (continued)
Characteristics of Hospitalization and Organ Procurement (per Infusion)

Significant trends in patient characteristics from table above by ITA or IAK

There are no significant results.

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

Significant trends in patient characteristics from table above by Era



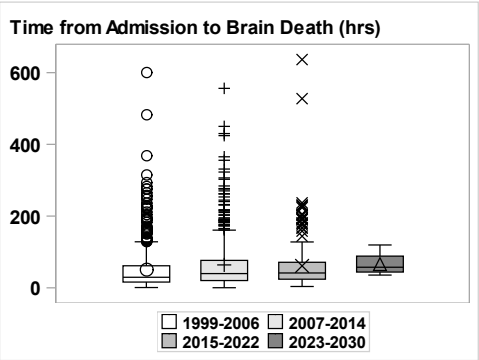
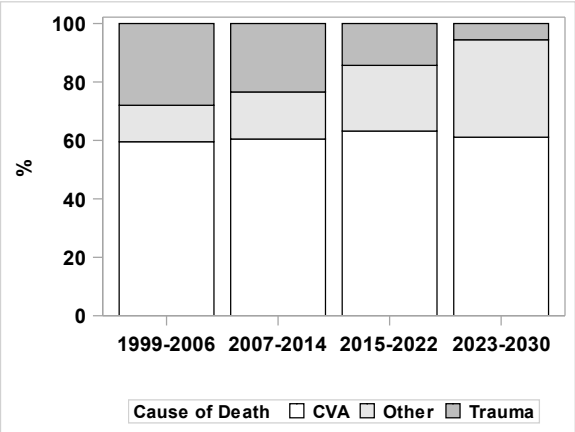


Exhibit 2-12 (continued)
Characteristics of Hospitalization and Organ Procurement (per Infusion)

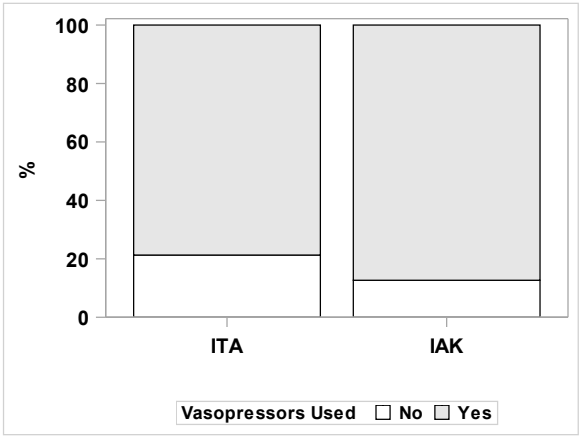
	Transplant Type (p=0.18)						Era (p=<0.001)											
	ITA (N[1]=1800, Total [2]=2329)			IAK (N=337, Total=471)			Era 1 1999-2006 (N=833, Total=1036)			Era 2 2007-2014 (N=1012, Total=1287)			Era 3 2015-2022 (N=405, Total=600)			Era 4 2023-2030 (N=18, Total=23)		
Cause of Death	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
CVA	1080	60.0	46.4	220	65.3	46.7	496	59.5	47.9	612	60.5	47.6	256	63.2	42.7	11	61.1	47.8
Other	287	15.9	12.3	49	14.5	10.4	104	12.5	10.0	163	16.1	12.7	91	22.5	15.2	6	33.3	26.1
Trauma	433	24.1	18.6	68	20.2	14.4	233	28.0	22.5	237	23.4	18.4	58	14.3	9.7	1	5.6	4.3
Missing	529	N/A	22.7	134	N/A	28.5	203	N/A	19.6	275	N/A	21.4	195	N/A	32.5	5	N/A	21.7

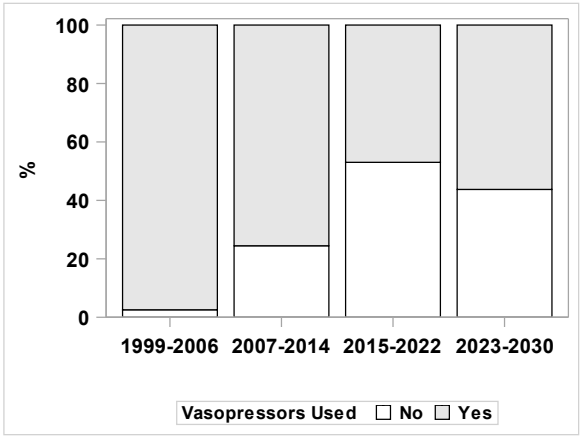


[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

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

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=1644, Total [2]=2329)			IAK (N=300, Total=471)			Era 1 1999-2006 (N=783, Total=1036)			Era 2 2007-2014 (N=899, Total=1287)			Era 3 2015-2022 (N=364, Total=600)			Era 4 2023-2030 (N=16, Total=23)		
Vasopressors Used	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	350	21.3	15.0	38	12.7	8.1	20	2.6	1.9	220	24.5	17.1	193	53.0	32.2	7	43.8	30.4
Yes	1294	78.7	55.6	262	87.3	55.6	763	97.4	73.6	679	75.5	52.8	171	47.0	28.5	9	56.3	39.1
Missing	685	N/A	29.4	171	N/A	36.3	253	N/A	24.4	388	N/A	30.1	236	N/A	39.3	7	N/A	30.4

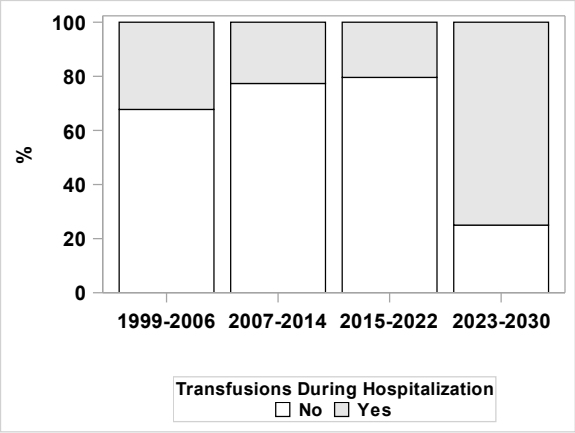




[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

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

	Transplant Type (p=0.38)						Era (p=<0.001)											
	ITA (N[1]=975, Total [2]=2329)			IAK (N=179, Total=471)			Era 1 1999-2006 (N=673, Total=1036)			Era 2 2007-2014 (N=437, Total=1287)			Era 3 2015-2022 (N=98, Total=600)			Era 4 2023-2030 (N=4, Total=23)		
Transfusions During Hospitalization	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	699	71.7	30.0	134	74.9	28.5	456	67.8	44.0	338	77.3	26.3	78	79.6	13.0	1	25.0	4.3
Yes	276	28.3	11.9	45	25.1	9.6	217	32.2	20.9	99	22.7	7.7	20	20.4	3.3	3	75.0	13.0
Missing	1354	N/A	58.1	292	N/A	62.0	363	N/A	35.0	850	N/A	66.0	502	N/A	83.7	19	N/A	82.6



[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

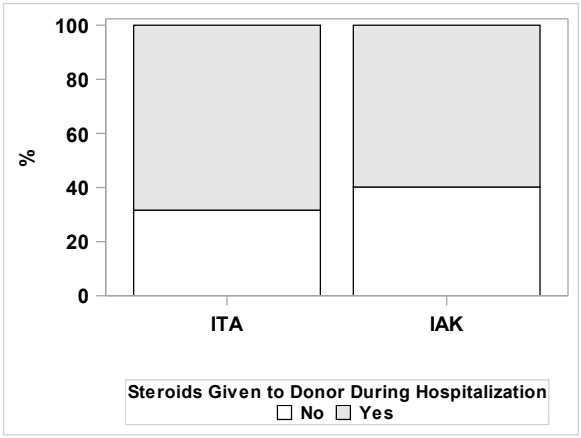
Exhibit 2-12 (continued)
Characteristics of Hospitalization and Organ Procurement (per Infusion)

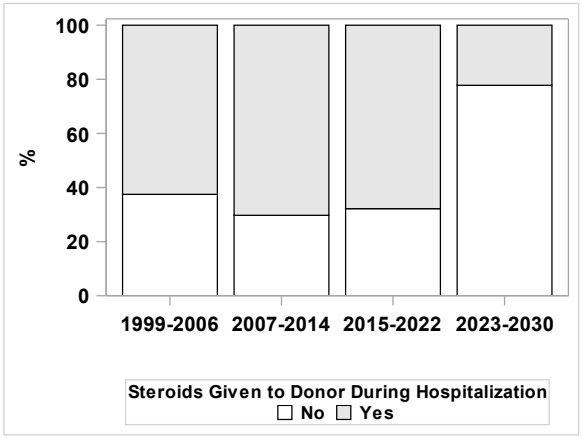
	Transplant Type (p=0.81)						Era (p=0.42)											
	ITA (N[1]=716, Total [2]=2329)			IAK (N=131, Total=471)			Era 1 1999-2006 (N=567, Total=1036)			Era 2 2007-2014 (N=254, Total=1287)			Era 3 2015-2022 (N=47, Total=600)			Era 4 2023-2030 (N=1, Total=23)		
Transfusions Intraoperatively	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	674	94.1	28.9	124	94.7	26.3	529	93.3	51.1	243	95.7	18.9	45	95.7	7.5	1	100.0	4.3
Yes	42	5.9	1.8	7	5.3	1.5	38	6.7	3.7	11	4.3	0.9	2	4.3	0.3	0	0.0	0.0
Missing	1613	N/A	69.3	340	N/A	72.2	469	N/A	45.3	1033	N/A	80.3	553	N/A	92.2	22	N/A	95.7

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

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

	Transplant Type (p=<0.05)						Era (p=<0.01)											
	ITA (N[1]=1005, Total [2]=2329)			IAK (N=209, Total=471)			Era 1 1999-2006 (N=499, Total=1036)			Era 2 2007-2014 (N=555, Total=1287)			Era 3 2015-2022 (N=202, Total=600)			Era 4 2023-2030 (N=9, Total=23)		
Steroids Given to Donor During Hospitalization	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
No	318	31.6	13.7	84	40.2	17.8	187	37.5	18.1	165	29.7	12.8	65	32.2	10.8	7	77.8	30.4
Yes	687	68.4	29.5	125	59.8	26.5	312	62.5	30.1	390	70.3	30.3	137	67.8	22.8	2	22.2	8.7
Missing	1324	N/A	56.8	262	N/A	55.6	537	N/A	51.8	732	N/A	56.9	398	N/A	66.3	14	N/A	60.9

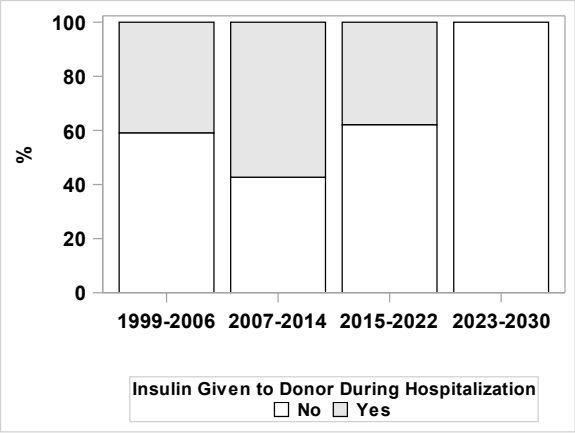




[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

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

	Transplant Type (p=0.28)						Era (p=<0.001)											
	ITA (N[1]=1287, Total [2]=2329)			IAK (N=254, Total=471)			Era 1 1999-2006 (N=697, Total=1036)			Era 2 2007-2014 (N=754, Total=1287)			Era 3 2015-2022 (N=132, Total=600)			Era 4 2023-2030 (N=10, Total=23)		
Insulin Given to Donor During Hospitalization	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	671	52.1	28.8	123	48.4	26.1	412	59.1	39.8	322	42.7	25.0	82	62.1	13.7	10	100.0	43.5
Yes	616	47.9	26.4	131	51.6	27.8	285	40.9	27.5	432	57.3	33.6	50	37.9	8.3	0	0.0	0.0
Missing	1042	N/A	44.7	217	N/A	46.1	339	N/A	32.7	533	N/A	41.4	468	N/A	78.0	13	N/A	56.5



[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-13
Donor Serology

	Transplant Type						Era											
	ITA (N[1]=1653, Total [2]=2329)			IAK (N=318, Total=471)			Era 1 1999-2006 (N=798, Total=1009)			Era 2 2007-2014 (N=925, Total=1254)			Era 3 2015-2022 (N=243, Total=523)			Era 4 2023-2030 (N=5, Total=14)		
HIV	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	1653	100.0	71.0	318	100.0	67.5	798	100.0	79.1	925	100.0	73.8	243	100.0	46.5	5	100.0	35.7
Missing	676	N/A	29.0	153	N/A	32.5	211	N/A	20.9	329	N/A	26.2	280	N/A	53.5	9	N/A	64.3

	Transplant Type						Era											
	ITA (N[1]=1120, Total [2]=2329)			IAK (N=203, Total=471)			Era 1 1999-2006 (N=707, Total=1009)			Era 2 2007-2014 (N=559, Total=1254)			Era 3 2015-2022 (N=57, Total=523)			Era 4 2023-2030 (N=-, Total=14)		
HTLV	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	1120	100.0	48.1	203	100.0	43.1	707	100.0	70.1	559	100.0	44.6	57	100.0	10.9	0	.	0.0
Missing	1209	N/A	51.9	268	N/A	56.9	302	N/A	29.9	695	N/A	55.4	466	N/A	89.1	14	N/A	100.0

	Transplant Type						Era											
	ITA (N[1]=1131, Total [2]=2329)			IAK (N=240, Total=471)			Era 1 1999-2006 (N=721, Total=1009)			Era 2 2007-2014 (N=615, Total=1254)			Era 3 2015-2022 (N=35, Total=523)			Era 4 2023-2030 (N=-, Total=14)		
VDRL	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	1128	99.7	48.4	240	100.0	51.0	720	99.9	71.4	613	99.7	48.9	35	100.0	6.7	0	.	0.0
Positive	3	0.3	0.1	0	0.0	0.0	1	0.1	0.1	2	0.3	0.2	0	0.0	0.0	0	.	0.0
Missing	1198	N/A	51.4	231	N/A	49.0	288	N/A	28.5	639	N/A	51.0	488	N/A	93.3	14	N/A	100.0

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-13 (continued)
Donor Serology

	Transplant Type						Era											
	ITA (N[1]=1591, Total [2]=2329)			IAK (N=314, Total=471)			Era 1 1999-2006 (N=763, Total=1009)			Era 2 2007-2014 (N=907, Total=1254)			Era 3 2015-2022 (N=230, Total=523)			Era 4 2023-2030 (N=5, Total=14)		
CMV	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	737	46.3	31.6	146	46.5	31.0	332	43.5	32.9	420	46.3	33.5	129	56.1	24.7	2	40.0	14.3
Positive	854	53.7	36.7	168	53.5	35.7	431	56.5	42.7	487	53.7	38.8	101	43.9	19.3	3	60.0	21.4
Missing	738	N/A	31.7	157	N/A	33.3	246	N/A	24.4	347	N/A	27.7	293	N/A	56.0	9	N/A	64.3

	Transplant Type						Era											
	ITA (N[1]=1639, Total [2]=2329)			IAK (N=314, Total=471)			Era 1 1999-2006 (N=792, Total=1009)			Era 2 2007-2014 (N=916, Total=1254)			Era 3 2015-2022 (N=240, Total=523)			Era 4 2023-2030 (N=5, Total=14)		
HBsAg	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	1637	99.9	70.3	314	100.0	66.7	791	99.9	78.4	915	99.9	73.0	240	100.0	45.9	5	100.0	35.7
Positive	2	0.1	0.1	0	0.0	0.0	1	0.1	0.1	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0
Missing	690	N/A	29.6	157	N/A	33.3	217	N/A	21.5	338	N/A	27.0	283	N/A	54.1	9	N/A	64.3

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-13 (continued)
Donor Serology

	Transplant Type						Era											
	ITA (N[1]=1564, Total [2]=2329)			IAK (N=295, Total=471)			Era 1 1999-2006 (N=768, Total=1009)			Era 2 2007-2014 (N=857, Total=1254)			Era 3 2015-2022 (N=229, Total=523)			Era 4 2023-2030 (N=5, Total=14)		
HBc	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	1552	99.2	66.6	294	99.7	62.4	762	99.2	75.5	852	99.4	67.9	227	99.1	43.4	5	100.0	35.7
Positive	12	0.8	0.5	1	0.3	0.2	6	0.8	0.6	5	0.6	0.4	2	0.9	0.4	0	0.0	0.0
Missing	765	N/A	32.8	176	N/A	37.4	241	N/A	23.9	397	N/A	31.7	294	N/A	56.2	9	N/A	64.3

	Transplant Type						Era											
	ITA (N[1]=1502, Total [2]=2329)			IAK (N=280, Total=471)			Era 1 1999-2006 (N=775, Total=1009)			Era 2 2007-2014 (N=791, Total=1254)			Era 3 2015-2022 (N=211, Total=523)			Era 4 2023-2030 (N=5, Total=14)		
HCV	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Negative	1501	99.9	64.4	279	99.6	59.2	774	99.9	76.7	790	99.9	63.0	211	100.0	40.3	5	100.0	35.7
Positive	1	0.1	0.0	1	0.4	0.2	1	0.1	0.1	1	0.1	0.1	0	0.0	0.0	0	0.0	0.0
Missing	827	N/A	35.5	191	N/A	40.6	234	N/A	23.2	463	N/A	36.9	312	N/A	59.7	9	N/A	64.3

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Exhibit 2-14
Donor Laboratory Data

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Serum creatinine (mg/dL)	1292	1.1	0	296	1	0	0.060
BUN (mg/dL)	871	15.5	0.3	264	15.6	0.5	0.923
Total bilirubin (mg/dL)	1085	0.9	0	268	0.8	0	0.177
AST (U/L)	1244	76.3	5.4	282	70.5	9.2	0.634
ALT (U/L)	1432	66.5	4	295	57.8	6.7	0.352
Serum lipase (mKat/L)	1131	1	0.1	228	0.9	0.1	0.528
Serum amylase (mKat/L)	1128	2.2	0.1	271	2.4	0.3	0.456
Minimum pre-insulin blood glucose (mg/dL)	990	131.5	1.3	240	137.3	2.9	0.060
Maximum blood glucose (mg/dL)	1081	219.7	2.4	252	228.4	5	0.113

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

Exhibit 2-14
Donor Laboratory Data

	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Serum creatinine (mg/dL)	694	1.2	0	750	1.1	0	140	0.9	0	4	0.7	0.1	0.025
BUN (mg/dL)	521	14.9	0.4	516	16.1	0.4	94	15.6	0.9	4	18.5	7.9	0.160
Total bilirubin (mg/dL)	568	0.9	0	683	0.8	0	98	0.8	0.1	4	1.1	0.4	0.132
AST (U/L)	593	75.5	8.2	750	73.6	6.1	179	81.6	15.7	4	69.5	11	0.965
ALT (U/L)	599	60.2	6.7	868	68.6	4.9	254	64.6	5.3	6	41.7	9.2	0.725
Serum lipase (mKat/L)	602	1	0.1	649	1	0.1	107	0.8	0.2	1	0.2	-	0.486
Serum amylase (mKat/L)	677	2.4	0.2	635	1.8	0.1	85	3.3	1	2	1	1	0.003
Minimum pre-insulin blood glucose (mg/dL)	666	127.5	1.5	478	137.2	2.1	83	148.1	5.6	3	102.7	9.4	<0.001
Maximum blood glucose (mg/dL)	656	232.8	3.4	579	212.6	2.8	91	199.3	6.1	7	158	10.4	<0.001

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

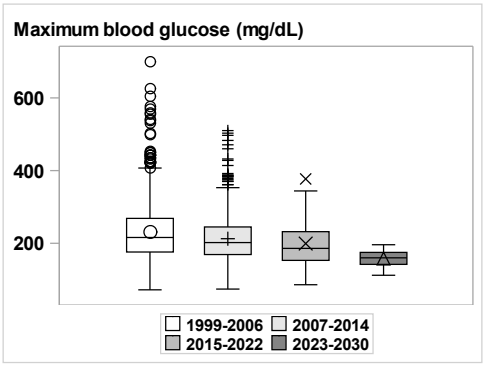
Exhibit 2-14 (continued)
Donor Laboratory Data

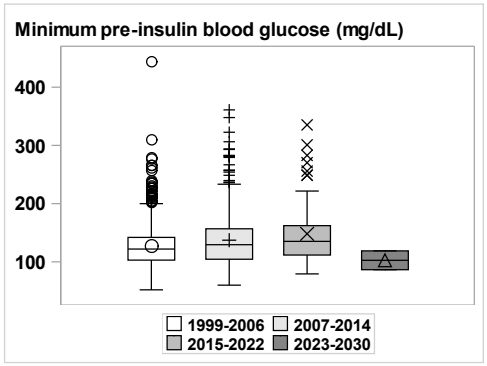
Significant trends in donor characteristics from table above by ITA or IAK

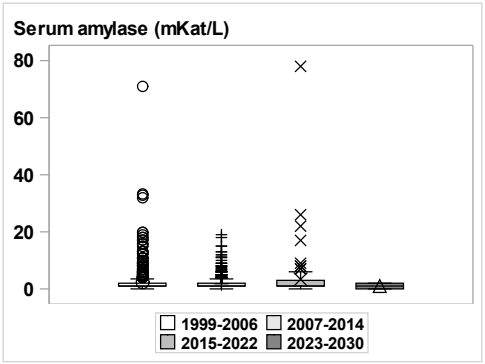
There are no significant results.

Exhibit 2-14 (continued)
Donor Laboratory Data

Significant trends in donor characteristics from table above by Era







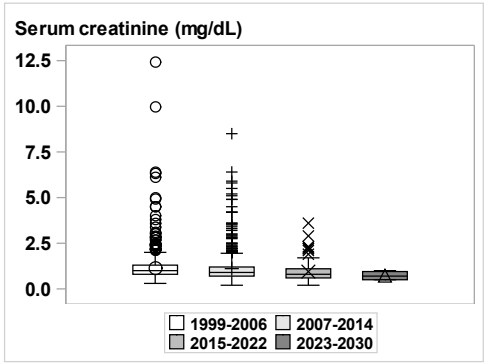


Exhibit 2-15
Organ Crossmatch Results

	Transplant Type (p=0.12)						Era (p=0.64)											
	ITA (N[1]=774, Total [2]=2329)			IAK (N=221, Total=471)			Era 1 1999-2006 (N=499, Total=1009)			Era 2 2007-2014 (N=401, Total=1254)			Era 3 2015-2022 (N=92, Total=523)			Era 4 2023-2030 (N=3, Total=14)		
Positive Cross Match	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
No	748	96.6	32.1	218	98.6	46.3	487	97.6	48.3	389	97.0	31.0	87	94.6	16.6	3	100.0	21.4
Yes	26	3.4	1.1	3	1.4	0.6	12	2.4	1.2	12	3.0	1.0	5	5.4	1.0	0	0.0	0.0
Missing	1555	N/A	66.8	250	N/A	53.1	510	N/A	50.5	853	N/A	68.0	431	N/A	82.4	11	N/A	78.6

[1] N = Infusions with data
[2] Total = Infusions of the given transplant type or recipient receiving first transplant in the given era

Chapter 3
Pancreas Procurement, Islet Processing, and Infusion Characteristics

Introduction

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

For the roughly 10% of infusions which were derived from more than one donor pancreas, the donor information was collapsed appropriately, either by logical combination (e.g., an infusion product derived from a female donor and a male donor is termed “Mixed”); averaging, (e.g., viability, stimulation index, etc.); or summation (e.g., total beta cells, islet particle count, total IEQs infused, etc.). Exhibits 3-1 to 3-4 describe all the variables according to ITA vs. IAK and by era (1999-2006, 2007-2014, 2015-2022, and 2023-2030).

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., sex, 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 1.2% in 1999-2006 to 28.6% in 2015-2022, while the proportion of procurement teams unrelated to the islet transplant center has declined steadily from 32.0% in 1999-2006 to 11.4% in 2015-2022 (Exhibit 3-1A).

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 recent years (97.2% in 2015-2022 vs. 59.1% in 1999-2006) and mean culture time has increased since the first era (Exhibit 3-2).

- Total cell volume infused has declined over the eras, with a possible current uptick, while IEQ/Kg recipient has remained fairly stable (Exhibit 3-4A).
- Endotoxin (both total and /kg) has declined since the initial era (Exhibit 3-4A).
- For both ITA and IAK, IEQs/kg recipient have decreased notably with subsequent infusions (Exhibit 3-4B).

Exhibit 3-1A
Islet Processing Summary

	Transplant Type (p=<0.001)						Era (p=<0.001)											
	ITA (N[1]=1279, Total [2]=2329)			IAK (N=323, Total=471)			Era 1 1999-2006 (N=841, Total=1009)			Era 2 2007-2014 (N=659, Total=1254)			Era 3 2015-2022 (N=98, Total=523)			Era 4 2023-2030 (N=4, Total=14)		
Islet processing center	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Mixed	4	0.3	0.2	1	0.3	0.2	0	0.0	0.0	4	0.6	0.3	1	1.0	0.2	0	0.0	0.0
Processing/ transplant centers related	1174	91.8	50.4	265	82.0	56.3	831	98.8	82.4	539	81.8	43.0	69	70.4	13.2	0	0.0	0.0
Unrelated	101	7.9	4.3	57	17.6	12.1	10	1.2	1.0	116	17.6	9.3	28	28.6	5.4	4	100.0	28.6
Missing	1050	N/A	45.1	148	N/A	31.4	168	N/A	16.7	595	N/A	47.4	425	N/A	81.3	10	N/A	71.4

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1A
Islet Processing Summary

	Transplant Type (p=0.07)						Era (p=<0.001)											
	ITA (N[1]=1375, Total [2]=2329)			IAK (N=299, Total=471)			Era 1 1999-2006 (N=794, Total=1009)			Era 2 2007-2014 (N=643, Total=1254)			Era 3 2015-2022 (N=229, Total=523)			Era 4 2023-2030 (N=8, Total=14)		
Procurement Team	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Mixed	27	2.0	1.2	4	1.3	0.8	22	2.8	2.2	9	1.4	0.7	0	0.0	0.0	0	0.0	0.0
Procurement/ transplant centers related	992	72.1	42.6	235	78.6	49.9	518	65.2	51.3	499	77.6	39.8	203	88.6	38.8	7	87.5	50.0
Unrelated	356	25.9	15.3	60	20.1	12.7	254	32.0	25.2	135	21.0	10.8	26	11.4	5.0	1	12.5	7.1
Missing	954	N/A	41.0	172	N/A	36.5	215	N/A	21.3	611	N/A	48.7	294	N/A	56.2	6	N/A	42.9

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1A
Islet Processing Summary

	Transplant Type (p=0.18)						Era (p=<0.001)											
	ITA (N[1]=1248, Total [2]=2329)			IAK (N=244, Total=471)			Era 1 1999-2006 (N=722, Total=1009)			Era 2 2007-2014 (N=588, Total=1254)			Era 3 2015-2022 (N=180, Total=523)			Era 4 2023-2030 (N=2, Total=14)		
Cultured	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Islets cultured >=6 hrs	964	77.2	41.4	198	81.1	42.0	427	59.1	42.3	560	95.2	44.7	175	97.2	33.5	0	0.0	0.0
None	284	22.8	12.2	46	18.9	9.8	295	40.9	29.2	28	4.8	2.2	5	2.8	1.0	2	100.0	14.3
Missing	1081	N/A	46.4	227	N/A	48.2	287	N/A	28.4	666	N/A	53.1	343	N/A	65.6	12	N/A	85.7

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1A
Islet Processing Summary

	Transplant Type (p=<0.05)						Era (p=<0.001)											
	ITA (N[1]=1184, Total [2]=2329)			IAK (N=262, Total=471)			Era 1 1999-2006 (N=760, Total=1009)			Era 2 2007-2014 (N=586, Total=1254)			Era 3 2015-2022 (N=96, Total=523)			Era 4 2023-2030 (N=4, Total=14)		
Gradient type	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
Both	66	5.6	2.8	6	2.3	1.3	63	8.3	6.2	7	1.2	0.6	2	2.1	0.4	0	0.0	0.0
Continuous	1068	90.2	45.9	236	90.1	50.1	634	83.4	62.8	574	98.0	45.8	92	95.8	17.6	4	100.0	28.6
Discontinuous	34	2.9	1.5	17	6.5	3.6	49	6.4	4.9	1	0.2	0.1	1	1.0	0.2	0	0.0	0.0
Mixed	14	1.2	0.6	3	1.1	0.6	13	1.7	1.3	4	0.7	0.3	0	0.0	0.0	0	0.0	0.0
None	2	0.2	0.1	0	0.0	0.0	1	0.1	0.1	0	0.0	0.0	1	1.0	0.2	0	0.0	0.0
Missing	1145	N/A	49.2	209	N/A	44.4	249	N/A	24.7	668	N/A	53.3	427	N/A	81.6	10	N/A	71.4

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1B
Final Islet Preparation Microbiology

	Transplant Type (p=0.80)						Era (p=0.61)											
	ITA (N[1]=1249, Total [2]=2329)			IAK (N=263, Total=471)			Era 1 1999-2006 (N=755, Total=1009)			Era 2 2007-2014 (N=619, Total=1254)			Era 3 2015-2022 (N=130, Total=523)			Era 4 2023-2030 (N=8, Total=14)		
Aerobic culture	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Negative	1227	98.2	52.7	258	98.1	54.8	744	98.5	73.7	605	97.7	48.2	128	98.5	24.5	8	100.0	57.1
Positive	22	1.8	0.9	5	1.9	1.1	11	1.5	1.1	14	2.3	1.1	2	1.5	0.4	0	0.0	0.0
Missing	1080	N/A	46.4	208	N/A	44.2	254	N/A	25.2	635	N/A	50.6	393	N/A	75.1	6	N/A	42.9

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1B
Final Islet Preparation Microbiology

	Transplant Type (p=0.24)						Era (p=0.92)											
	ITA (N[1]=1128, Total[2]=2329)			IAK (N=234, Total=471)			Era 1 1999-2006 (N=615, Total=1009)			Era 2 2007-2014 (N=612, Total=1254)			Era 3 2015-2022 (N=129, Total=523)			Era 4 2023-2030 (N=6, Total=14)		
Anaerobic culture	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Negative	1116	98.9	47.9	234	100.0	49.7	610	99.2	60.5	606	99.0	48.3	128	99.2	24.5	6	100.0	42.9
Positive	12	1.1	0.5	0	0.0	0.0	5	0.8	0.5	6	1.0	0.5	1	0.8	0.2	0	0.0	0.0
Missing	1201	N/A	51.6	237	N/A	50.3	394	N/A	39.0	642	N/A	51.2	394	N/A	75.3	8	N/A	57.1

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1B
Final Islet Preparation Microbiology

	Transplant Type (p=0.52)						Era (p=<0.05)											
	ITA (N[1]=1173, Total [2]=2329)			IAK (N=220, Total=471)			Era 1 1999-2006 (N=758, Total=1009)			Era 2 2007-2014 (N=542, Total=1254)			Era 3 2015-2022 (N=85, Total=523)			Era 4 2023-2030 (N=8, Total=14)		
Fungal Culture	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Negative	1158	98.7	49.7	216	98.2	45.9	753	99.3	74.6	531	98.0	42.3	83	97.6	15.9	7	87.5	50.0
Positive	15	1.3	0.6	4	1.8	0.8	5	0.7	0.5	11	2.0	0.9	2	2.4	0.4	1	12.5	7.1
Missing	1156	N/A	49.6	251	N/A	53.3	251	N/A	24.9	712	N/A	56.8	438	N/A	83.7	6	N/A	42.9

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-1B
Final Islet Preparation Microbiology

	Transplant Type (p=1.00)						Era (p=1.00)											
	ITA (N[1]=710, Total [2]=2329)			IAK (N=67, Total=471)			Era 1 1999-2006 (N=481, Total=1009)			Era 2 2007-2014 (N=256, Total=1254)			Era 3 2015-2022 (N=39, Total=523)			Era 4 2023-2030 (N=1, Total=14)		
Mycoplasma	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**	**n**	**% of N**	**% of Total**
Negative	709	99.9	30.4	67	100.0	14.2	480	99.8	47.6	256	100.0	20.4	39	100.0	7.5	1	100.0	7.1
Positive	1	0.1	0.0	0	0.0	0.0	1	0.2	0.1	0	0.0	0.0	0	0.0	0.0	0	0.0	0.0
Missing	1619	N/A	69.5	404	N/A	85.8	528	N/A	52.3	998	N/A	79.6	484	N/A	92.5	13	N/A	92.9

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 3-2
Cold Ischemia Information

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Time from cross clamp to pancreas recovery (hrs)	759	0.9	0	202	1	0.1	0.378
Duration of cold ischemia (hrs)	1087	8	0.2	305	7.6	0.4	0.244
Time from brain death to pancreas recovery (hrs)	704	20.1	0.3	188	17.3	0.7	<0.001
Culture time (hrs)	1247	20.9	0.5	244	25.7	1.2	<0.001

Exhibit 3-2
Cold Ischemia Information

	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Time from cross clamp to pancreas recovery (hrs)	537	0.8	0.1	344	1	0.1	78	0.8	0.1	2	0.3	0.1	0.107
Duration of cold ischemia (hrs)	826	7.3	0.1	471	8.5	0.3	93	9.7	1	2	2.3	0.1	<0.001
Time from brain death to pancreas recovery (hrs)	491	19.1	0.4	323	19.9	0.5	76	20.7	1.4	2	19.1	4.3	0.373
Culture time (hrs)	722	17.3	0.7	587	26.7	0.6	180	23.2	0.9	2	0	0	<0.001

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

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Total cell volume	703	7	0.2	140	6.9	0.4	0.703
Total islet particles (final preparation)	565	819.1	18.9	120	779.1	38.8	0.371
Embedded islets (%)	485	15.5	0.6	74	14.6	1.6	0.614
Islet equivalents (1000s)	783	853.9	15.1	170	894.6	37.5	0.269
Islet equivalents(1000s)/kg recipient	736	12.6	0.2	190	12.9	0.4	0.484
Beta cells (x10 ^{6})	207	417.3	22.3	22	426.5	76.9	0.899
Beta cells/kg recipient weight	168	6.3	0.4	15	8.5	1.8	0.116
Insulin content (1000s micrograms)	169	6.2	0.3	16	5.3	0.8	0.431
Total Endotoxin units	545	30.9	3.6	133	47.9	7.2	0.035
Endotoxin units/kg recipient weight	510	0.5	0.1	121	0.7	0.1	0.040
Islet potency: Stimulation index	596	3.1	0.1	154	3.7	0.3	0.006
Islet viability	773	89.3	0.2	147	91.5	0.5	<0.001
Purity	577	61.2	0.6	159	60.4	1.1	0.538
Total DNA	253	19.6	1.1	26	16.9	2.6	0.448

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

	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Total cell volume	342	8.3	0.2	357	6.2	0.2	137	5.9	0.3	7	8.2	2.3	<0.001
Total islet particles (final preparation)	312	890.1	25.1	274	774.9	26.1	93	678.7	46.2	6	518.8	99.7	<0.001
Embedded islets (%)	232	15.2	0.9	252	16.3	0.9	73	12.7	1.5	2	10.8	3.8	0.236
Islet equivalents (1000s)	325	887.5	23.4	457	900.3	21.5	163	714.6	28	8	541.1	130.5	<0.001
Islet equivalents(1000s)/kg recipient	382	13.7	0.3	422	12.2	0.3	115	11	0.5	7	7.1	1.9	<0.001
Beta cells (x10 ^{6})	142	440.6	27.7	87	381.6	33.3	0	.	.	0	.	.	0.181
Beta cells/kg recipient weight	132	6.7	0.5	51	5.8	0.6	0	.	.	0	.	.	0.302
Insulin content (1000s micrograms)	157	6.2	0.3	13	5.7	0.8	15	5.9	1.1	0	.	.	0.903
Total Endotoxin units	310	49.8	6.1	313	20.4	3	54	25.5	7.5	1	0.5	.	<0.001
Endotoxin units/kg recipient weight	295	0.8	0.1	286	0.3	0	49	0.4	0.1	1	0	.	<0.001
Islet potency: Stimulation index	337	3.4	0.1	311	3	0.1	99	3.5	0.3	3	6.3	2.7	0.014
Islet viability	353	91.1	0.3	395	89.6	0.3	169	87	0.5	3	87.7	3.8	<0.001
Purity	368	60.6	0.8	281	62.6	0.8	86	58.1	1.5	1	68	.	0.052
Total DNA	162	19.3	1.4	102	20.6	1.7	15	10.5	2.5	0	.	.	0.104

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

	ITA			IAK			
	N	Mean	STE	N	Mean	STE	p
Total cell volume	1374	3.6	0.1	246	3.9	0.2	0.022
Total islet particles (final preparation)	1180	391.8	4.9	225	415.5	12.3	0.056
Embedded islets (%)	993	15.2	0.5	119	14	1.3	0.474
Islet equivalents (1000s)	1524	438.3	4.2	305	498.7	14.5	<0.001
Islet equivalents(1000s)/kg recipient	1461	6.3	0.1	328	7.5	0.2	<0.001
Beta cells (x10 ^{6})	363	237.8	10.6	33	284.3	32.3	0.204
Beta cells/kg recipient weight	299	3.5	0.2	24	5.3	0.6	0.008
Insulin content (1000s micrograms)	303	3.4	0.1	29	2.9	0.4	0.257
Total Endotoxin units	1004	16.8	1.5	224	28.4	3.5	<0.001
Endotoxin units/kg recipient weight	944	0.3	0	204	0.4	0.1	0.001
Islet potency: Stimulation index	1167	3.1	0.1	247	3.5	0.2	0.019
Islet viability	1518	89.2	0.2	281	91.2	0.4	<0.001
Purity	1136	61	0.5	298	60.2	1	0.488
Total DNA	472	10.4	0.5	42	10.5	1.4	0.964

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

	Era 1 1999-2006			Era 2 2007-2014			Era 3 2015-2022			Era 4 2023-2030			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Total cell volume	729	3.9	0.1	645	3.4	0.1	237	3.4	0.1	9	6.4	1.9	<0.001
Total islet particles (final preparation)	682	406.5	6.4	543	391	7.4	172	367	13.6	8	389.1	39	0.045
Embedded islets (%)	497	15.7	0.8	475	15.4	0.7	136	11.5	1.2	4	10.8	5.2	0.062
Islet equivalents (1000s)	695	414	5.6	847	485.8	7.1	276	422	9.7	11	393.5	54.8	<0.001
Islet equivalents(1000s)/kg recipient	808	6.5	0.1	775	6.6	0.1	197	6.4	0.2	9	5.5	0.7	0.306
Beta cells (x10 ^{6})	267	234.1	12	129	257.3	18.5	0	.	.	0	.	.	0.282
Beta cells/kg recipient weight	247	3.6	0.2	76	3.9	0.4	0	.	.	0	.	.	0.413
Insulin content (1000s micrograms)	276	3.5	0.1	29	2.5	0.3	27	3.3	0.5	0	.	.	0.088
Total Endotoxin units	615	25.1	2.3	524	12.2	1.4	88	15.7	4.3	1	0.5	.	<0.001
Endotoxin units/kg recipient weight	587	0.4	0	479	0.2	0	81	0.3	0.1	1	0	.	<0.001
Islet potency: Stimulation index	699	3.3	0.1	551	2.9	0.1	161	3.2	0.2	3	6.3	2.7	0.023
Islet viability	747	90.8	0.2	745	89.2	0.2	303	87.1	0.4	4	86	4.8	<0.001
Purity	762	60.7	0.6	519	62.2	0.7	152	56.8	1.2	1	68	.	0.005
Total DNA	322	9.6	0.6	168	12.5	0.8	24	6.6	1.2	0	.	.	0.003

Exhibit 3-4B
Islet Product Characteristics by Infusion Sequence

	ITA Total Number of Infusions Received										IAK Total Number of Infusions Received									
	One Infusion			Two Infusions			>=Three Infusions				One Infusion			Two Infusions			>=Three Infusions			
	N	Mean	STE	N	Mean	STE	N	Mean	STE	p	N	Mean	STE	N	Mean	STE	N	Mean	STE	p
Total cell volume	659	3.7	0.1	498	3.5	0.1	217	3.4	0.1	0.107	131	4.3	0.3	95	3.4	0.2	20	4.1	0.4	0.068
Total islet particles (final preparation)	535	395.9	7.7	424	390.1	8	221	385.1	9.8	0.703	111	431.8	19.4	82	391.6	17.4	32	420.2	30.7	0.324
Embedded islets (%)	444	15.5	0.8	354	15.8	1	195	13.1	1.1	0.166	60	15.3	1.9	45	13	2	14	11.6	3.3	0.563
Islet equivalents (1000s)	732	444.6	6.4	574	436	6.7	218	423	9.5	0.218	161	535.5	21.4	110	472.2	21.9	34	409.6	34.2	0.011
Islet equivalents(1000s)/kg recipient	723	6.5	0.1	523	6.2	0.1	215	5.9	0.2	0.001	184	8.1	0.3	118	6.9	0.3	26	5.7	0.5	<0.001
Beta cells (x10 ^{6})	171	232.8	16	137	231.7	16.5	55	268.3	27.2	0.479	17	292.9	47.5	12	272.5	47.9	4	283.5	123.5	0.961
Beta cells/kg recipient weight	135	3.4	0.3	115	3.5	0.3	49	3.8	0.4	0.774	11	5	0.9	9	6	0.9	4	4.5	2	0.674
Insulin content (1000s micrograms)	154	3.6	0.2	116	3.1	0.2	33	3.8	0.4	0.142	11	3.1	0.5	12	3.1	0.7	6	2.2	0.5	0.613
Total Endotoxin units	503	14.3	1.5	359	19.4	2.9	142	18.7	4.8	0.234	124	30.6	4.8	81	28.9	6	19	12.6	9	0.382
Endotoxin units/kg recipient weight	471	0.2	0	340	0.3	0	133	0.3	0.1	0.373	113	0.5	0.1	73	0.4	0.1	18	0.2	0.1	0.348
Islet potency: Stimulation index	556	3.1	0.1	410	3.2	0.2	201	2.6	0.2	0.062	138	3.9	0.3	83	3.1	0.3	26	2.5	0.3	0.036
Islet viability	715	89.6	0.2	559	89	0.3	244	88.5	0.5	0.070	138	91.6	0.5	109	91	0.6	34	89.9	1	0.330
Purity	520	61.5	0.7	408	61.1	0.8	208	59.4	1.1	0.291	154	60.7	1.3	113	60.1	1.5	31	58.2	3.9	0.744
Total DNA	220	10.6	0.8	177	9.6	0.7	75	11.6	1.3	0.391	21	10.2	1.8	16	11.9	2.9	5	6.9	2.6	0.579

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

	Islet characteristics													
p>=0.05 or p<0.05 (regression coefficient)	**Total 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**
Donor CMV	0.1036	0.4802	**0.0138**	0.6042	0.5197	0.7964	0.7620	0.9291	0.1478	0.2186	0.5913	**0.0017**	0.7945	0.6666
	0.2017	-7.2083	2.9069	4.9507	0.0976	5.3281	-0.1073	-0.0226	4.1753	0.056	-0.0933	1.126	-0.2592	0.4145
Donor Hx ETOH	0.4258	0.1333	0.4406	0.8679	0.9085	0.8342	0.9295	0.7909	0.2800	0.5120	0.8718	0.5886	0.3290	0.3779
	0.1442	22.5538	1.3645	2.3487	0.0257	6.7462	0.0513	-0.1101	4.8784	0.0464	0.0406	-0.2873	-1.4668	1.3386
Donor Hx HPT	0.3619	**0.0056**	**0.0006**	0.0725	0.1348	0.7170	0.1912	0.8852	**0.0134**	**0.0181**	0.9437	0.5188	0.4111	0.9858
	0.1177	29.8094	-4.1698	17.8536	0.2345	-8.5345	-0.5395	-0.043	7.3084	0.1105	0.0127	-0.2478	-0.8564	0.0195
Donor blood type A	**0.0176**	0.3405	**0.0138**	0.3696	0.4050	0.3772	0.3397	**0.0175**	0.3945	0.4052	0.4721	0.3311	0.2481	0.8581
	-0.2736	8.9736	-2.5581	7.8614	0.1161	18.2582	0.3399	-0.5887	-2.3962	-0.037	0.1147	-0.3247	1.0592	0.1732
Donor gender	0.1735	**<.0001**	0.9364	**<.0001**	**0.0001**	0.8668	0.9856	0.5531	0.2133	0.1798	**0.0363**	0.4723	0.2580	0.2688
	0.16	37.0177	0.084	47.9512	0.5457	-3.5351	0.0066	0.1537	-3.5365	-0.0604	0.3393	0.2393	1.047	1.0962
Donor given insulin	0.5031	0.7207	0.4074	**0.0004**	**0.0097**	**0.0002**	**0.0067**	0.3153	**0.0332**	**0.0391**	0.3184	0.5090	**0.0336**	**0.0022**
	0.0872	3.709	0.974	35.1054	0.403	78.0197	1.0112	-0.273	6.5903	0.0991	-0.17	0.268	2.2036	3.0385
Donor given steroid	0.2322	0.2905	0.8221	**<.0001**	**<.0001**	**0.0059**	**0.0310**	0.2019	**0.0058**	**0.0133**	0.8685	0.4959	**<.0001**	0.3405
	-0.223	16.5216	-0.4637	78.7094	1.0688	111.8623	1.5296	-0.4334	11.9925	0.1676	0.0403	0.3141	7.3972	-1.4249
Donor hospital transfusion	0.0948	0.3961	0.0862	0.7291	0.6945	0.5678	0.7332	0.5243	0.0655	0.1583	0.7577	**0.0117**	0.0784	0.0724
	0.2498	10.7039	2.5592	-4.4579	-0.0805	-15.5406	-0.1489	-0.1768	7.1889	0.0867	-0.0669	1.2154	2.1514	-2.1967
Donor intra-op transfusion	0.9102	0.1030	0.1877	0.8207	0.8588	0.1504	0.1770	0.7325	0.4568	0.5747	0.5099	0.1249	0.8875	0.9381
	0.038	46.5751	5.0718	6.7816	-0.0829	108.0093	1.4871	-0.231	7.0347	0.0825	-0.3286	1.5292	0.3761	-0.2317
Gradient type	**0.0120**	0.2840	0.3539	**0.0187**	**0.0330**	**0.0038**	**0.0004**	0.2670	0.0656	0.0824	0.6063	0.1531	0.2962	**<.0001**
	-0.4359	-15.5755	-1.763	33.664	0.4765	-109.0472	-2.2671	-0.3307	-9.2386	-0.1357	-0.1493	0.8486	1.4486	-6.9563
Islet predictors ITA vs IAK	0.8915	0.4016	0.0798	**<.0001**	**0.0037**	0.8727	0.9376	0.6697	0.5078	0.5097	0.0895	**0.0009**	**0.0080**	0.0963
	-0.0141	7.6511	-1.7713	36.7276	0.3719	-3.3065	0.0293	0.1135	1.8074	0.0286	0.2628	-1.0794	-2.3473	1.6059
Procurement team related	**<.0001**	0.5009	0.9266	0.1228	**0.0178**	0.4631	0.7930	0.3472	0.0530	**0.0215**	**0.0463**	**<.0001**	0.7406	0.8923
	-0.6728	-8.0816	0.1285	-18.0293	-0.4338	17.3856	0.105	0.2462	-6.8433	-0.1253	-0.4144	-2.0498	-0.3721	0.1536
Year	**0.0001**	0.0736	**0.0037**	**0.0010**	0.4391	**0.0055**	**0.0056**	0.5204	**<.0001**	**<.0001**	0.0554	**<.0001**	**0.0232**	**<.0001**
	-0.0357	-1.4659	-0.2762	2.559	-0.0093	6.235	0.1086	-0.0162	-1.1755	-0.0198	-0.0275	-0.2945	-0.1935	0.3752

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									
	Total cell volume	**Total islet particles (final preparation)**	**Embedded islets (%)**	**Islet equivalents (1000s)**	**Islet equivalents (1000s)/kg recipient**	**Beta cells (x10⁶)**	**Beta cells/kg recipient weight**	**Insulin content (1000s micrograms)**	**Total Endotoxin units**	**Islet potency: Stimulation index**
Cold ischemic time (hrs)	-0.0689	0.0835	-0.1266	0.0465	0.0132	-0.0196	-0.0257	0.0599	-0.0046	-0.0486
	0.0232	0.0073	0.0005	0.1218	0.6508	0.7426	0.6843	0.2839	0.8821	0.1154
	1084	1029	755	1110	1180	282	253	322	1036	1049
Culture time (hrs)	-0.1219	0.0455	-0.0328	0.1878	0.0863	0.2384	0.2434	-0.0327	0.1617	0.0612
	0	0.1055	0.2923	0	0.003	0	0	0.5614	0	0.0315
	1211	1266	1031	1299	1181	382	309	317	979	1234
Donor ALT	0.0645	0.0219	0.0059	0.0795	0.0752	-0.0312	-0.042	0.0496	-0.0304	0.0467
	0.0347	0.4775	0.8681	0.0033	0.0094	0.6238	0.5683	0.4925	0.3181	0.1181
	1072	1054	799	1367	1193	249	187	194	1083	1121
Donor AST	0.0235	-0.004	0.0074	-0.0018	-0.0004	-0.0575	-0.0501	0.0705	-0.0374	0.0433
	0.445	0.8979	0.8356	0.95	0.9901	0.3721	0.5021	0.3365	0.2276	0.1499
	1057	1042	786	1203	1155	243	182	188	1044	1106
Donor BUN	0.1186	0.0043	-0.0353	0.1537	0.121	-0.0469	-0.0869	-0.0155	-0.011	0.1111
	0.0006	0.9031	0.4182	0	0.0001	0.5662	0.3714	0.8377	0.7348	0.0009
	844	791	527	942	981	152	108	178	953	885
Donor Body Mass Index (kg/m ²)	0.0645	0.0265	-0.001	0.2666	0.2182	0.068	0.0448	-0.0245	0.0524	0.0621
	0.015	0.3212	0.9728	0	0	0.1788	0.4241	0.6576	0.0669	0.02
	1420	1399	1106	1823	1569	393	320	329	1224	1403
Donor Height	0.0288	0.1103	0.0168	0.1885	0.1857	-0.0604	-0.0714	0.0925	-0.0203	0.0431
	0.2781	0	0.5757	0	0	0.2325	0.2029	0.0941	0.4779	0.1064
	1421	1400	1107	1823	1569	393	320	329	1224	1404
Donor Weight (kg)	0.0809	0.0764	0.0132	0.336	0.2885	0.0425	0.0113	0.0119	0.0377	0.0718
	0.0023	0.0042	0.6598	0	0	0.4003	0.8398	0.8289	0.1873	0.0071
	1422	1401	1108	1825	1571	394	321	330	1224	1404
Donor bilirubin	0.0716	0.0732	-0.0307	0.1112	0.1105	0.028	0.1108	0.0857	0.0143	0.0226
	0.0231	0.0241	0.4161	0.0002	0.0002	0.6662	0.1421	0.2555	0.6476	0.472
	1006	950	702	1120	1136	239	177	178	1023	1014
Donor creatinine	0.0977	0.0237	-0.0106	0.1381	0.1313	-0.0623	-0.0614	0.0385	-0.0276	0.0504
	0.0008	0.4167	0.7484	0	0	0.2691	0.3344	0.5535	0.3583	0.081
	1165	1176	922	1354	1296	317	249	239	1113	1201

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									
	Total cell volume	**Total islet particles (final preparation)**	**Embedded islets (%)**	**Islet equivalents (1000s)**	**Islet equivalents (1000s)/kg recipient**	**Beta cells (x10⁶)**	**Beta cells/kg recipient weight**	**Insulin content (1000s micrograms)**	**Total Endotoxin units**	**Islet potency: Stimulation index**
Donor lipase	0.0339	0.0213	-0.029	0.05	0.0507	-0.0547	-0.0495	0.008	-0.0164	0.0205
	0.2913	0.5045	0.4155	0.0913	0.0918	0.3548	0.4528	0.9033	0.6054	0.5037
	969	987	789	1140	1109	288	232	232	992	1063
Donor serum amylase	0.043	0.044	0.0277	-0.0242	-0.0173	-0.1006	-0.1228	0.1151	-0.0208	0.0345
	0.1681	0.1615	0.4393	0.4073	0.5534	0.0923	0.069	0.085	0.51	0.2634
	1029	1013	781	1173	1170	281	220	225	1010	1053
Max donor glucose	0.0287	-0.0392	-0.0007	0.0888	0.0855	0.1055	0.1389	-0.0625	0.0488	0.0206
	0.3541	0.2125	0.9847	0.0026	0.0035	0.0601	0.0248	0.3271	0.1195	0.5075
	1042	1012	754	1150	1165	318	261	248	1020	1040
Mean donor age (yrs)	-0.0895	0.0717	-0.172	-0.0655	-0.0706	-0.0224	-0.0522	0.0475	0.0135	-0.1181
	0.003	0.0246	0	0.0325	0.0201	0.7149	0.4179	0.4085	0.6765	0.0002
	1099	983	754	1065	1084	268	243	305	963	1016
Pre-ins donor glucose	-0.0352	-0.066	0.0723	0.013	0.0157	-0.0218	0.0001	0.0024	0.0911	0.0586
	0.2749	0.0436	0.0565	0.6713	0.6045	0.7069	0.9984	0.968	0.0047	0.0671
	964	934	697	1063	1092	299	256	286	960	979
Time from brain death to pancreas recovery (hrs)	-0.0012	-0.0414	0.0423	0.035	-0.0046	0.1294	0.0729	-0.0671	-0.0072	0.0433
	0.9733	0.2709	0.3336	0.3265	0.9001	0.0571	0.3419	0.3321	0.8462	0.2381
	762	709	525	787	755	217	172	211	735	743
Time from cross clamp to pancreas recovery (hrs)	-0.0797	0.0299	-0.0349	-0.0687	-0.0534	-0.0747	-0.0198	-0.0279	-0.2203	0.0075
	0.0222	0.4066	0.4056	0.0453	0.1275	0.2563	0.7901	0.6784	0	0.8353
	823	774	571	850	817	233	183	223	768	780

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

	ITA Total Number of Infusions Received									IAK Total Number of Infusions Received								
	One Infusion			Two Infusions			>=Three Infusions			One Infusion			Two Infusions			>=Three Infusions		
	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE	N	Mean	STE
Islet equivalents infused (1000s)	802	437.8	6.0	576	420.7	6.6	235	406.6	9.0	202	533.8	18.2	130	459.2	19.7	29	430.9	49.9
Islet equivalents infused(1000s)/donor kg	723	6.5	0.1	523	6.2	0.1	215	5.9	0.2	184	8.1	0.3	118	6.9	0.3	26	5.7	0.5
Embedded islets (%)	444	15.5	0.8	354	15.8	1.0	195	13.1	1.1	60	15.3	1.9	45	13.0	2.0	14	11.6	3.3
Cell volume (mL)	659	3.7	0.1	498	3.5	0.1	217	3.4	0.1	131	4.3	0.3	95	3.4	0.2	20	4.1	0.4
Time since first infusion (weeks)	840	32.8	1.8	840	32.8	1.8	355	23.0	2.1	166	37.3	4.7	166	37.3	4.7	45	28.3	9.2
Time since second infusion (weeks)	294	102.4	7.9	294	102.4	7.9	355	107.8	7.3	40	74.4	14.8	40	74.4	14.8	45	83.2	14.5
Time since third infusion (weeks)	49	195.9	31.3	49	195.9	31.3	110	201.3	21.5	4	129.1	120.7	4	129.1	120.7	9	169.3	80.5

Chapter 4
Immunosuppression and Other Medications

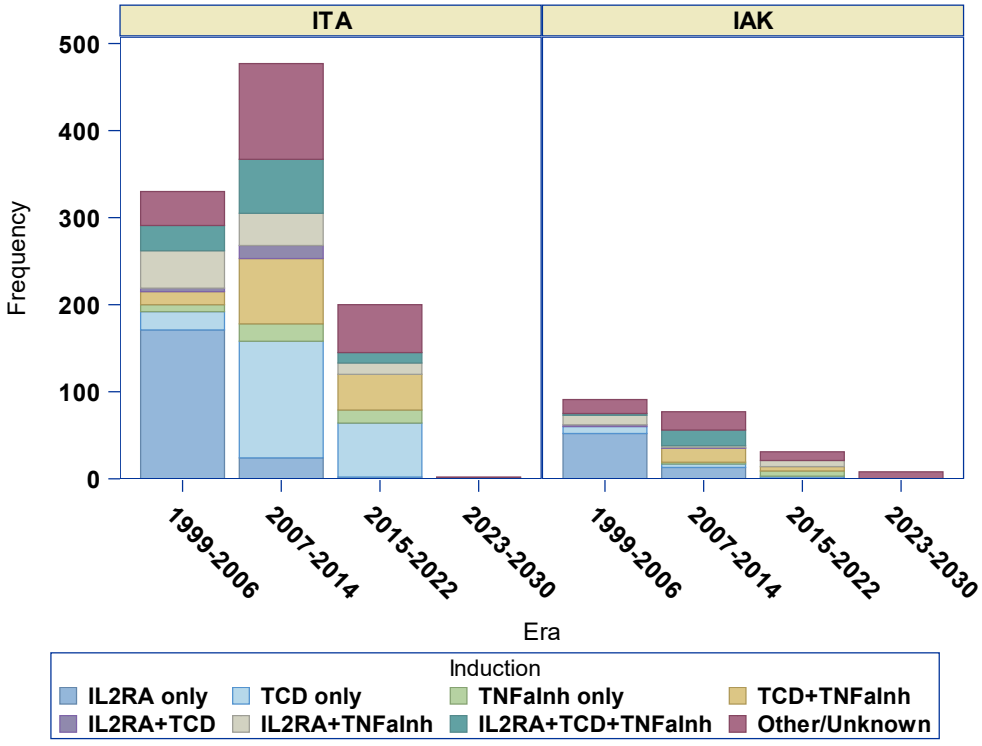
Introduction

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

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

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

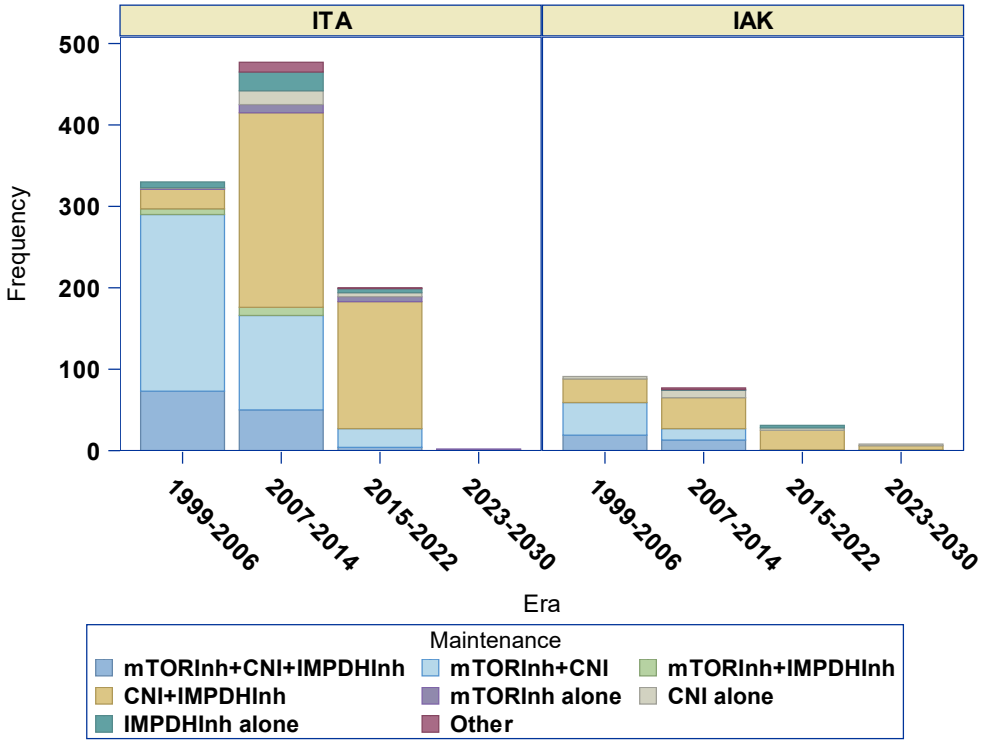
Exhibit 4-1
Induction Immunosuppression by Transplant Type and Era



	Transplant Type						Era											
	ITA (N[1]=1009, Total[2]=1134)			IAK (N=207, Total=260)			Era 1 1999-2006 (N=421, Total=466)			Era 2 2007-2014 (N=554, Total=628)			Era 3 2015-2022 (N=231, Total=289)			Era 4 2023-2030 (N=10, Total=11)		
Induction	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
IL2RA only	197	19.5	17.4	66	31.9	25.4	223	53.0	47.9	37	6.7	5.9	3	1.3	1.0	0	0.0	0.0
IL2RA+TCD	19	1.9	1.7	3	1.4	1.2	6	1.4	1.3	16	2.9	2.5	0	0.0	0.0	0	0.0	0.0
IL2RA+TCD+TNFaInh	103	10.2	9.1	20	9.7	7.7	31	7.4	6.7	80	14.4	12.7	12	5.2	4.2	0	0.0	0.0
IL2RA+TNFaInh	93	9.2	8.2	20	9.7	7.7	54	12.8	11.6	39	7.0	6.2	20	8.7	6.9	0	0.0	0.0
Other/ Unknown	205	20.3	18.1	55	26.6	21.2	55	13.1	11.8	131	23.6	20.9	65	28.1	22.5	9	90.0	81.8
TCD only	217	21.5	19.1	14	6.8	5.4	29	6.9	6.2	138	24.9	22.0	64	27.7	22.1	0	0.0	0.0
TCD+TNFaInh	132	13.1	11.6	21	10.1	8.1	15	3.6	3.2	91	16.4	14.5	46	19.9	15.9	1	10.0	9.1
TNFaInh only	43	4.3	3.8	8	3.9	3.1	8	1.9	1.7	22	4.0	3.5	21	9.1	7.3	0	0.0	0.0
Missing	125	N/A	11.0	53	N/A	20.4	45	N/A	9.7	74	N/A	11.8	58	N/A	20.1	1	N/A	9.1

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Exhibit 4-2
Maintenance Immunosuppression by Transplant Type and Era



	Transplant Type						Era											
	ITA (N[1]=1009, Total[2]=1134)			IAK (N=207, Total=260)			Era 1 1999-2006 (N=421, Total=466)			Era 2 2007-2014 (N=554, Total=628)			Era 3 2015-2022 (N=231, Total=289)			Era 4 2023-2030 (N=10, Total=11)		
Maintenance	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total	n	% of N	% of Total
CNI alone	23	2.3	2.0	17	8.2	6.5	4	1.0	0.9	26	4.7	4.1	8	3.5	2.8	2	20.0	18.2
CNI+IMPDHInh	420	41.6	37.0	96	46.4	36.9	53	12.6	11.4	277	50.0	44.1	180	77.9	62.3	6	60.0	54.5
IMPDHInh alone	35	3.5	3.1	4	1.9	1.5	7	1.7	1.5	24	4.3	3.8	8	3.5	2.8	0	0.0	0.0
Other	13	1.3	1.1	2	1.0	0.8	0	0.0	0.0	14	2.5	2.2	1	0.4	0.3	0	0.0	0.0
mTORInh alone	18	1.8	1.6	0	0.0	0.0	1	0.2	0.2	10	1.8	1.6	6	2.6	2.1	1	10.0	9.1
mTORInh+CNI	356	35.3	31.4	56	27.1	21.5	257	61.0	55.2	130	23.5	20.7	24	10.4	8.3	1	10.0	9.1
mTORInh+CNI+IMPDHInh	127	12.6	11.2	32	15.5	12.3	92	21.9	19.7	63	11.4	10.0	4	1.7	1.4	0	0.0	0.0
mTORInh+IMPDHInh	17	1.7	1.5	0	0.0	0.0	7	1.7	1.5	10	1.8	1.6	0	0.0	0.0	0	0.0	0.0
Missing	125	N/A	11.0	53	N/A	20.4	45	N/A	9.7	74	N/A	11.8	58	N/A	20.1	1	N/A	9.1

[1] N = Recipients with data
[2] Total = Recipients of the given transplant type or receiving first transplant in the given era

Chapter 5
Graft Function

Introduction

Summary

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

The analytical process was conducted for the ITA and IAK transplant groups separately. Every variable available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome with significance determined at $p<0.01$. Results are presented by outcome as outlined in the following tables:

Insulin Independence

First achievement of insulin independence (Exhibit 5-1) is an indicator of the rate of engraftment under the real-time conditions of competing events including early graft function or loss, islet resource availability for re-infusion, individual tolerance of immunosuppression, patient/doctor decisions, and myriad other factors, some of which are characterized in the CITR data and others not. Notably, the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope. Using all the information in the Registry over the eras, factors predictive of first achievement of insulin independence in ITA and IAK were identified in Exhibits 5-1A and 5-1B, respectively.

- 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. 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 ($p<0.01$) 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.

C-peptide≥0.3 ng/mL

The univariate effects of individual variables significantly ($p<0.01$) associated with retention of graft function (C-peptide ≥0.3 ng/mL) post last infusion in ITA and IAK, modeled as time to complete graft loss (CGL), are presented in Exhibits 5-3A and 5-3B, respectively.

The raw, unadjusted prevalence of C-peptide ≥0.3 ng/mL stratified by transplant type is shown in Exhibit 5-4A. Prevalence of C-peptide ≥0.3 ng/mL was ~80% at one year post last transplant and gradually declined to ~50-60% at 5 year post last infusion, with IAK patients showing somewhat less decline. Individual factors that were significantly ($p<0.01$) 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.

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 70% or higher 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 ($p<0.01$) 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.

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 ~50% of IAK patients over 5 years of follow-up time. Individual factors that were significantly ($p<0.01$) 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 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 ($p<0.01$) 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 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 nearly 40% at 5 years. Factors that were significantly ($p<0.01$) associated with maintaining ASHE at higher levels through 5 years are presented in Exhibit 5-8B for ITA and Exhibit 5-8C for IAK.

Levels of daily insulin requirement (U/day) declined dramatically in follow-up through 5-years after islet transplantation, with some return upwards over 5 years of follow-up for both ITA and IAK patients (Exhibit 5-9).

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 5-4 and 5-10). Factors associated with improved results for each group are shown in Exhibit 5-10.

HbA1c in both ITA and IAK groups declines sharply after islet transplantation, and does not return to pre-transplant levels (Exhibit 5-11). Factors associated with improved results in each group are shown in Exhibit 5-11.

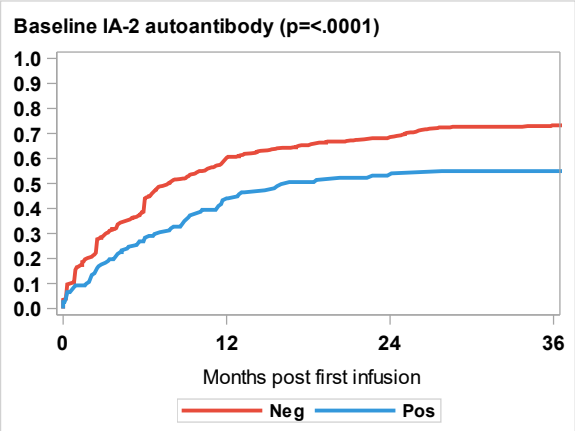
Fasting blood glucose also declines dramatically after islet transplantation and in over 70% of ITA patients and almost 60% of IAK patient remains at levels of 60-140 mg/dL (Exhibits 5-5 and 5-12). Factors associated with improved results in each group are shown in Exhibit 5-12.

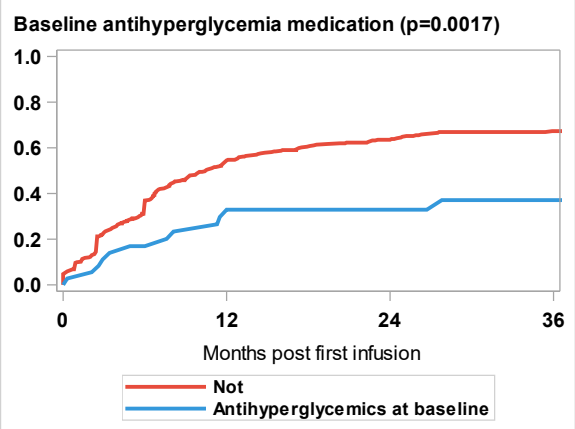
The higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c <7.0%, fasting blood glucose of 60-140 mg/dL, and the lower the likelihood of severe hypoglycemia (Exhibit 5-13). This holds true for both ITA and IAK patients. Even partial graft function, i.e., fasting C-peptide of 0.3-0.9 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced from pre-infusion (baseline) 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.

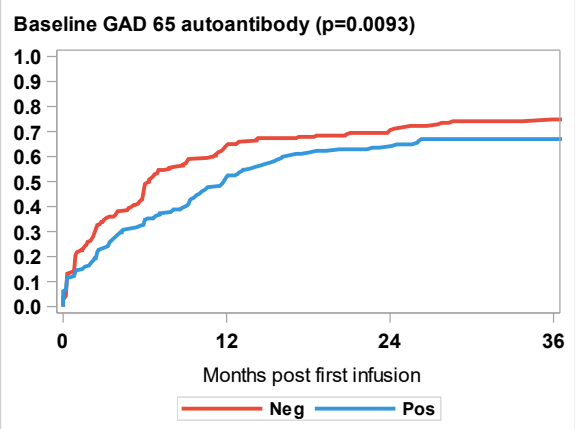
Re-infusion

Re-infusion has been performed in 73% of recipients, and may have been conducted without or after complete graft failure (fasting C-peptide<0.3 ng/mL without recovery, Exhibit 5-14A). Viewed as time-to-event, reinfusion was not significantly more likely with a functioning graft than with a lost graft (p=0.6). A number of re-infusions were conducted while the patient was not only C-peptide positive but also insulin independent (Exhibit 5-14B): re-infusion was much more likely when the patient had not yet achieved insulin independence (p<0.001, Exhibit 5-14B). Re-infusions also appear to have occurred sooner in the earliest era (p=0.01, Exhibit 5-14C) and do not differ significantly by transplant type (p=0.2, Exhibit 5-14D).

Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients







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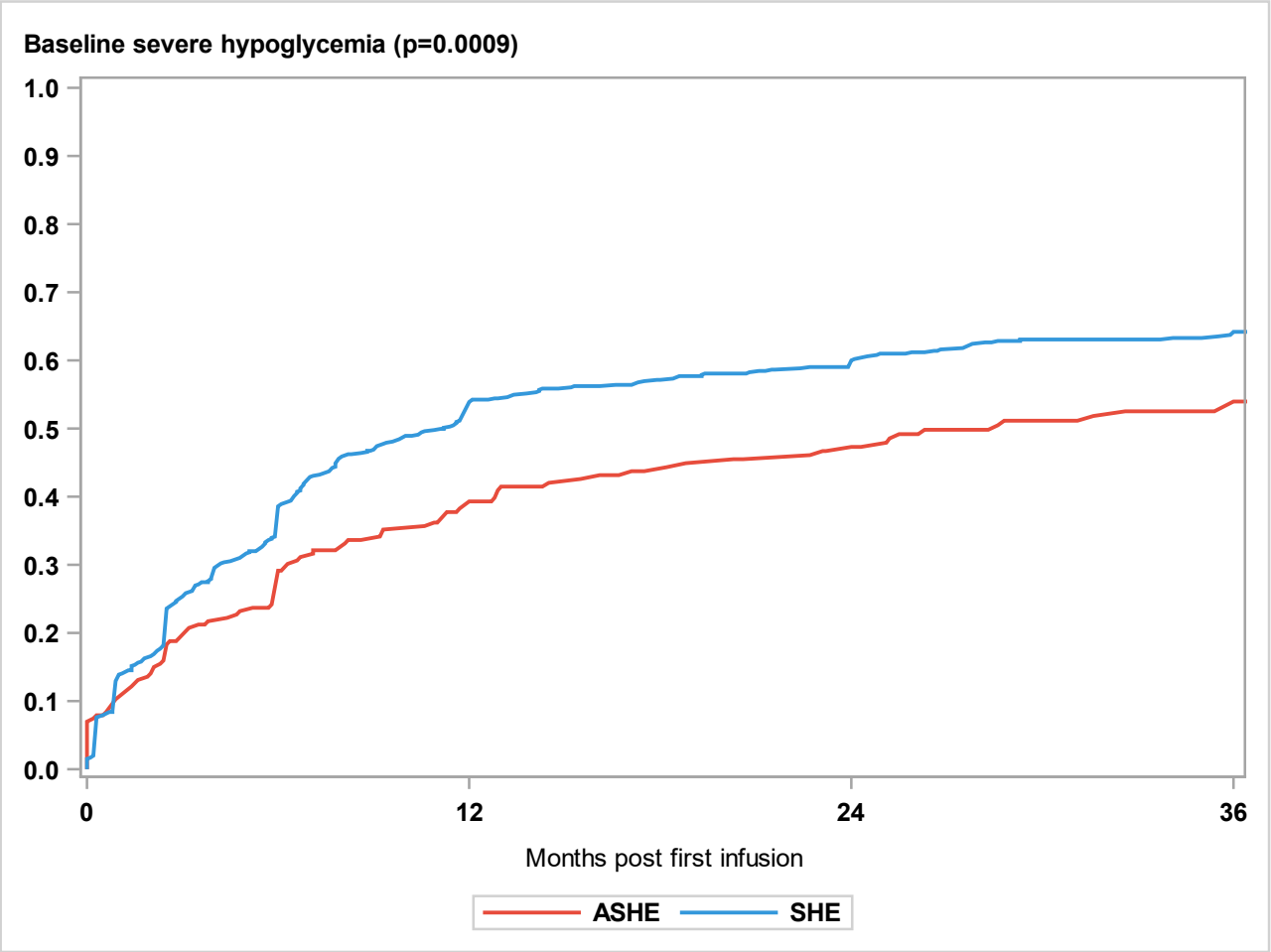
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients



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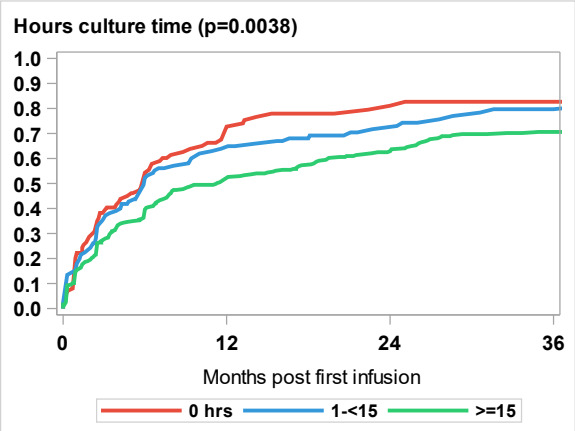
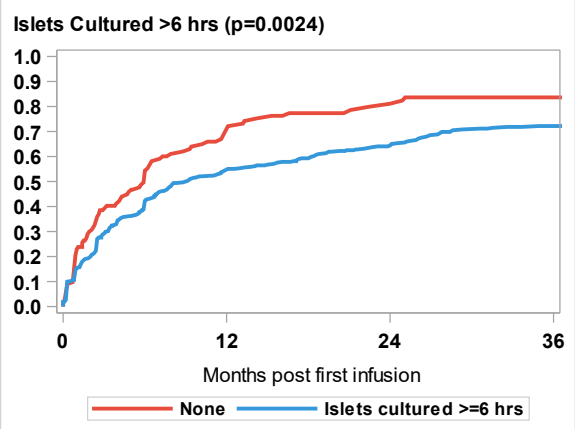




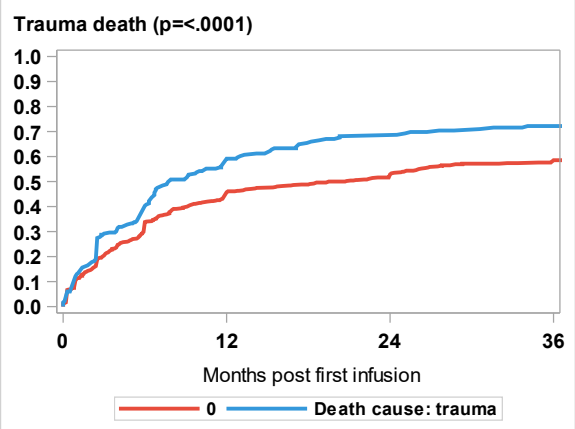


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

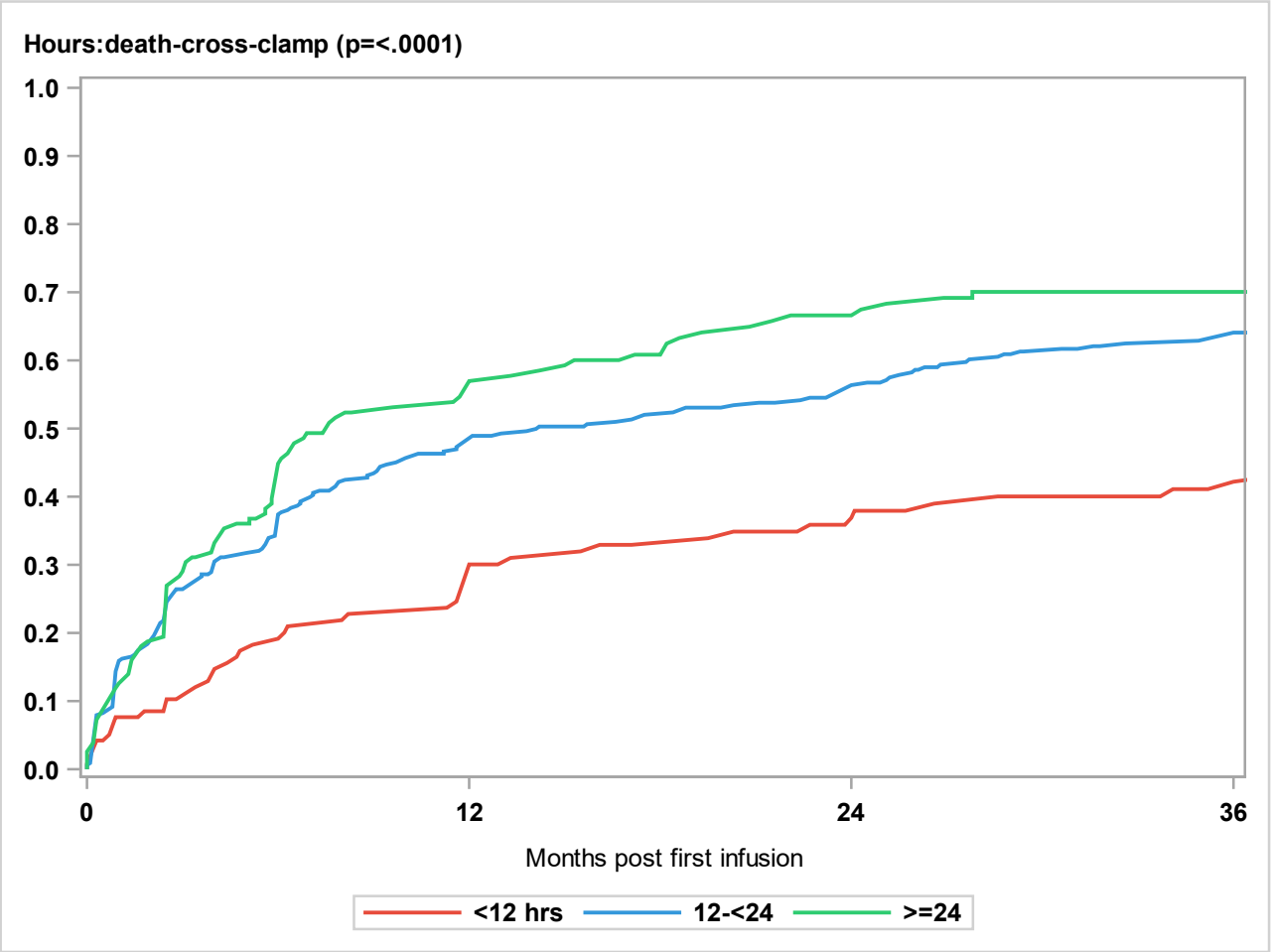


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

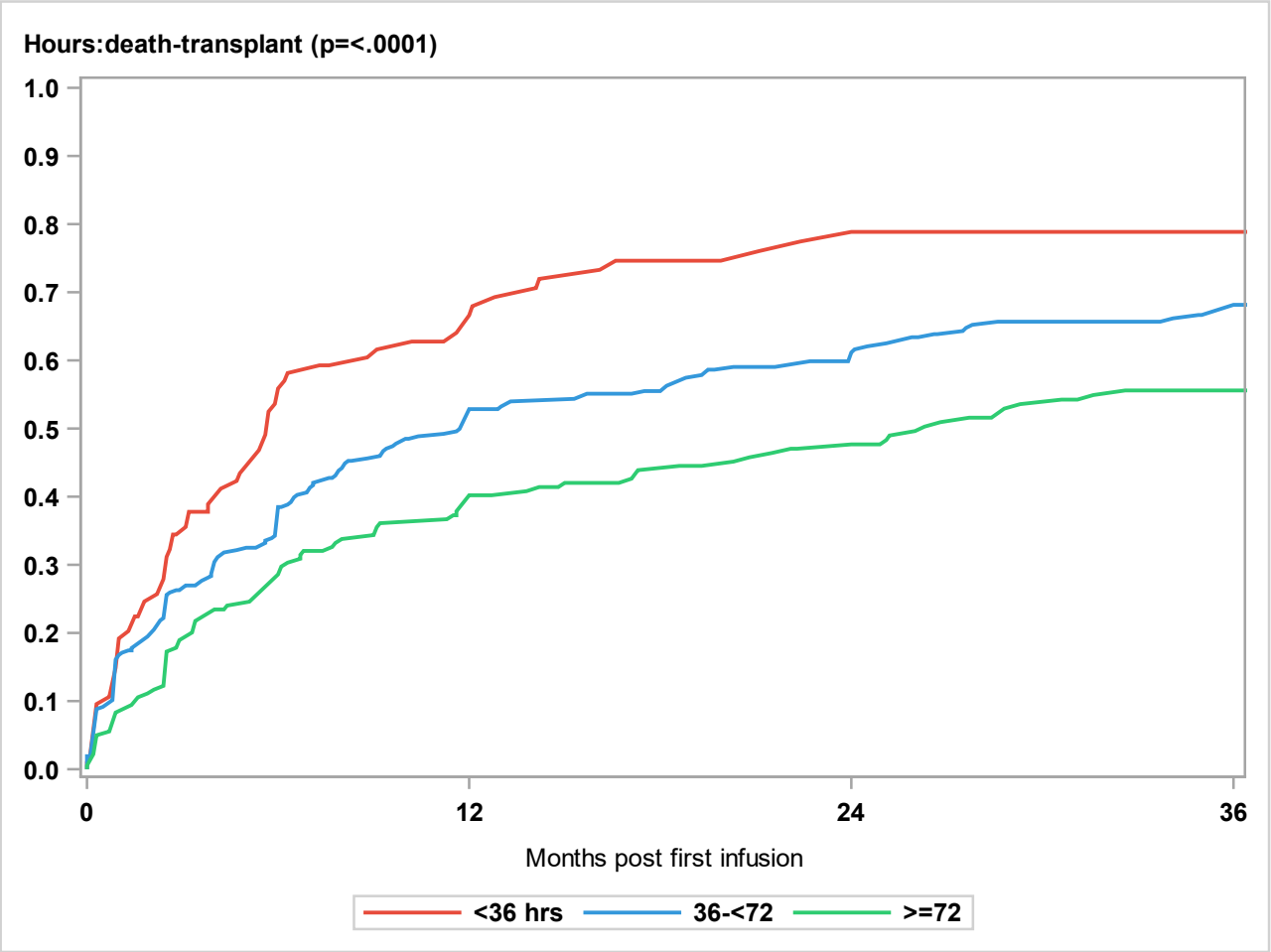
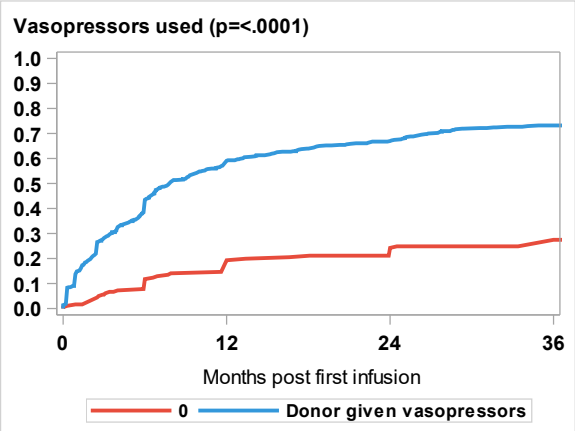
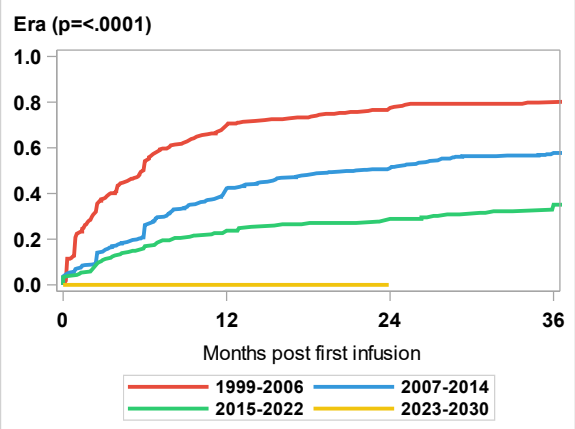


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients





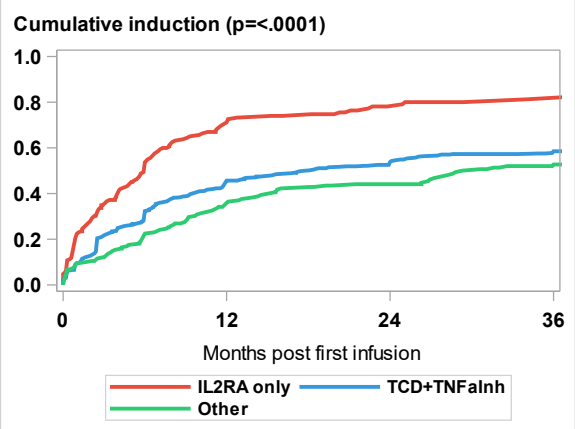


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

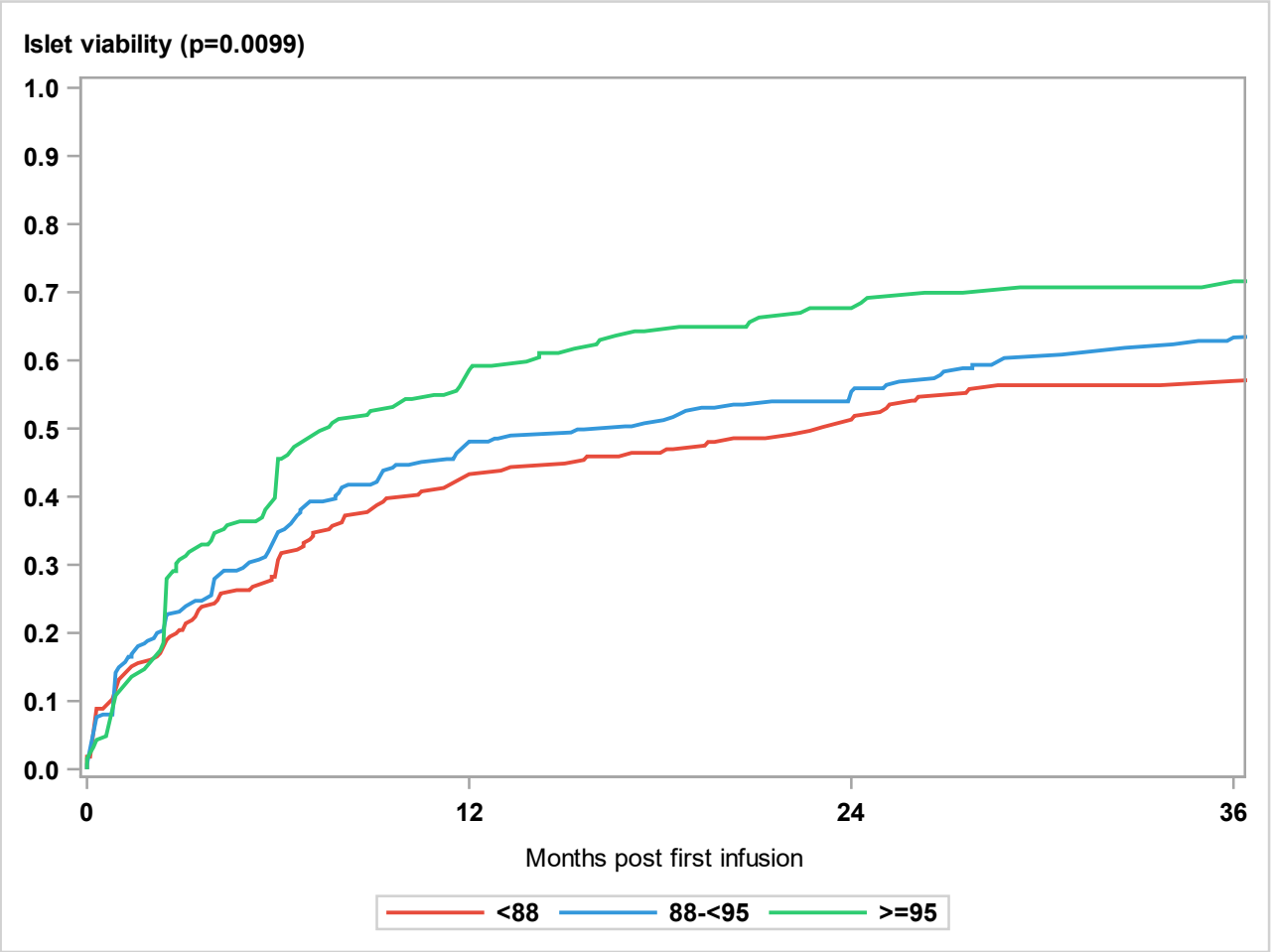


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

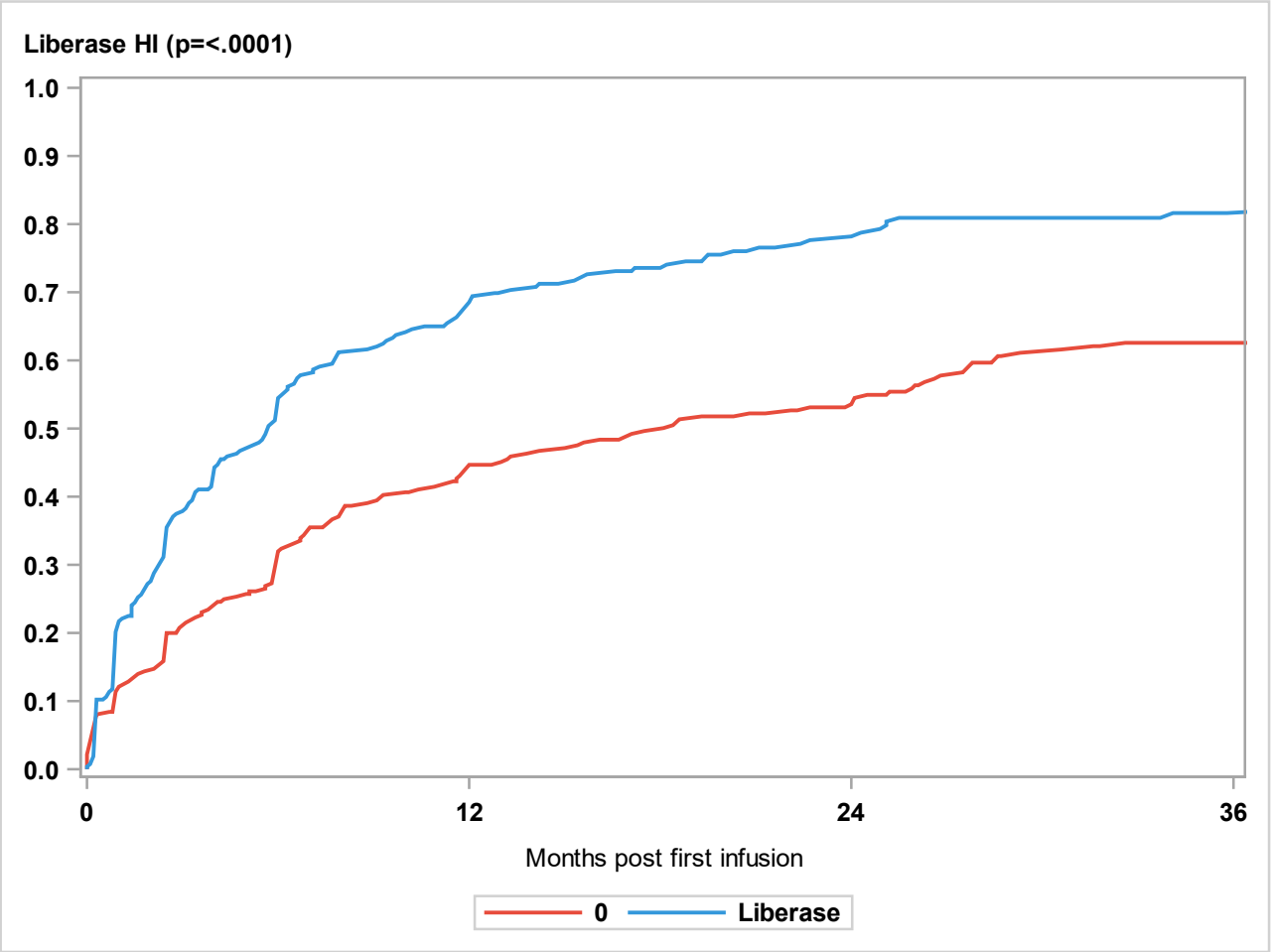


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

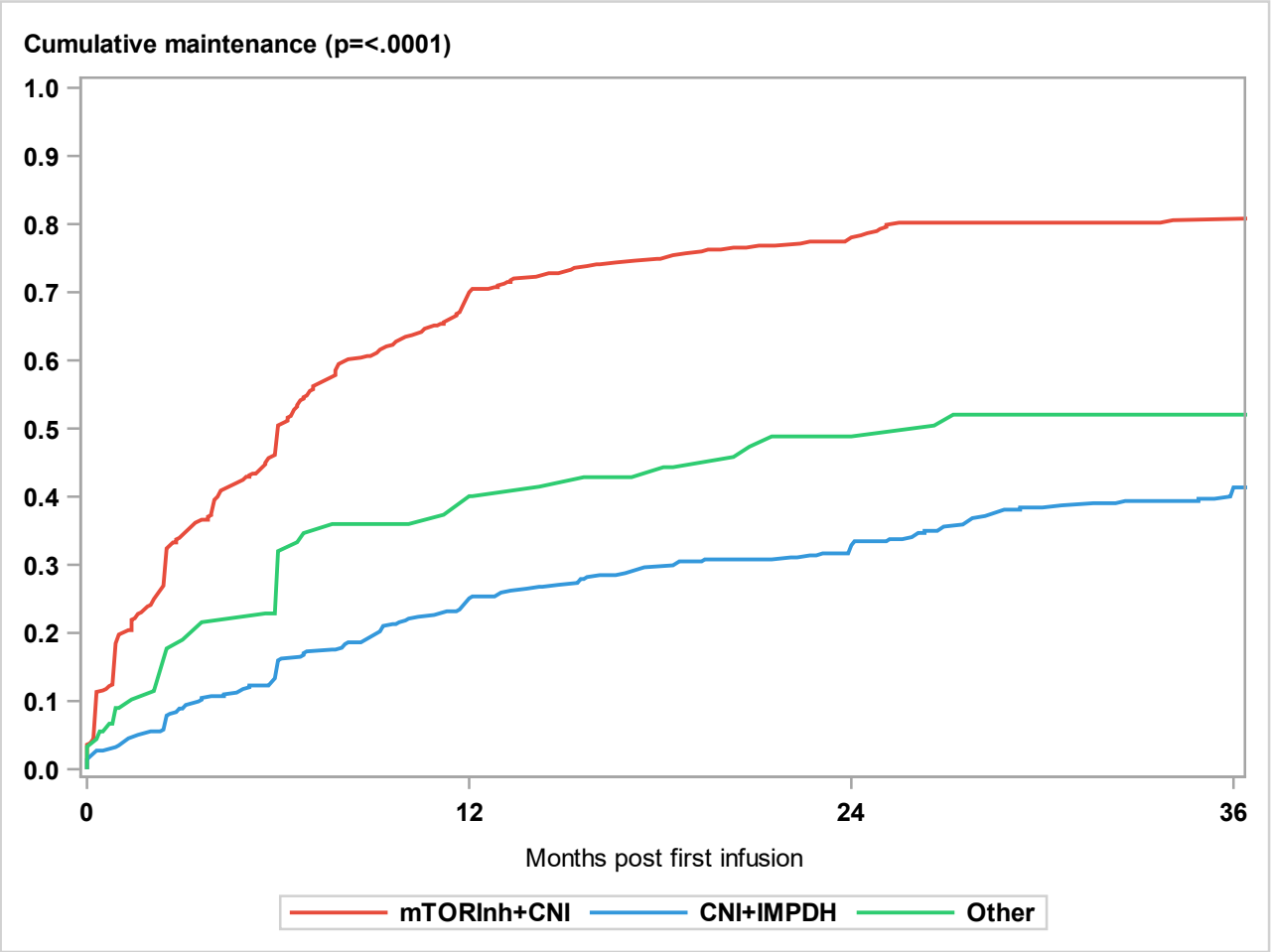
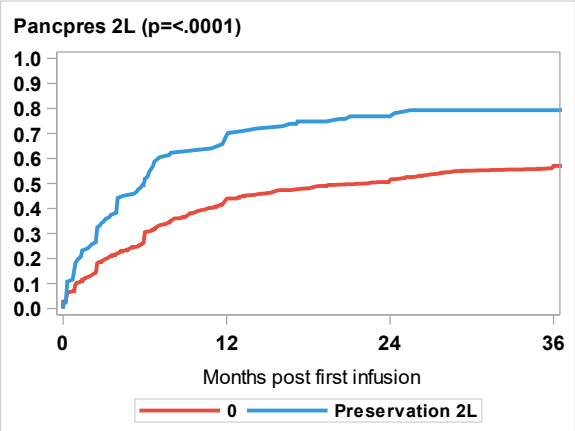
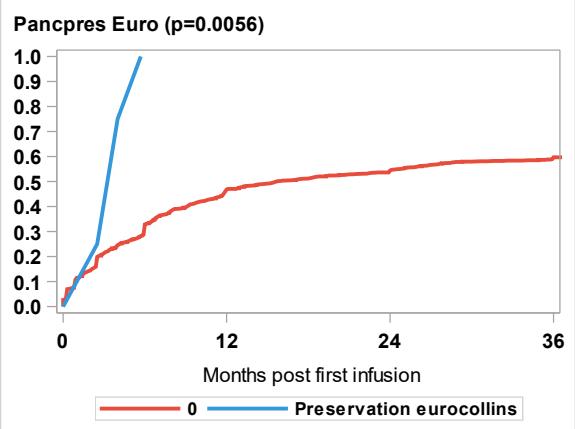


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients





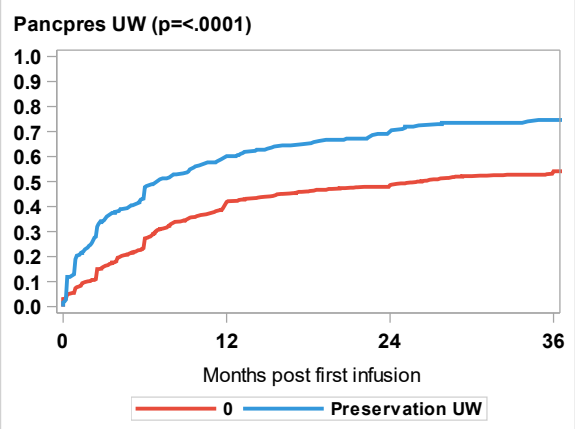


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

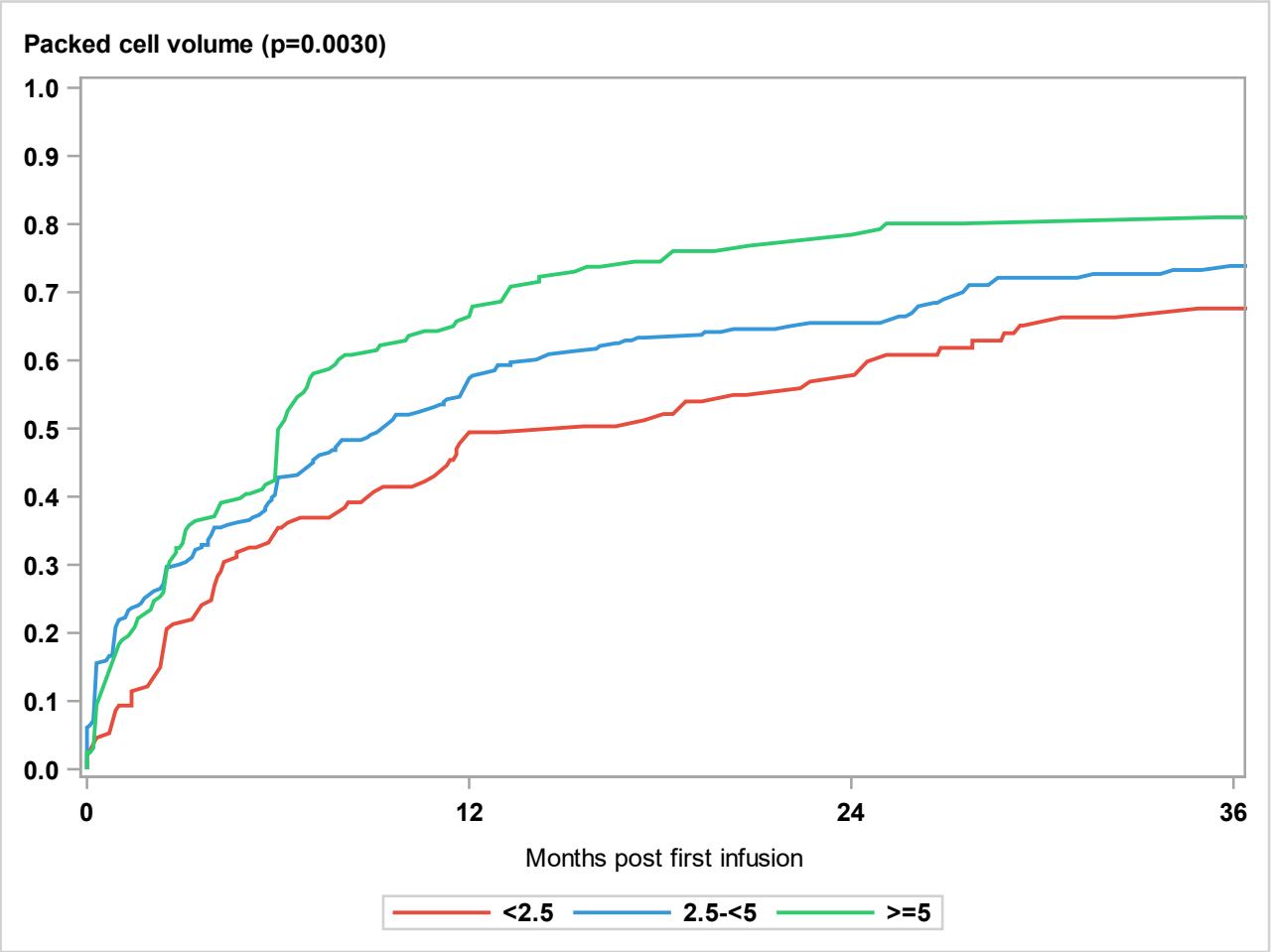


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

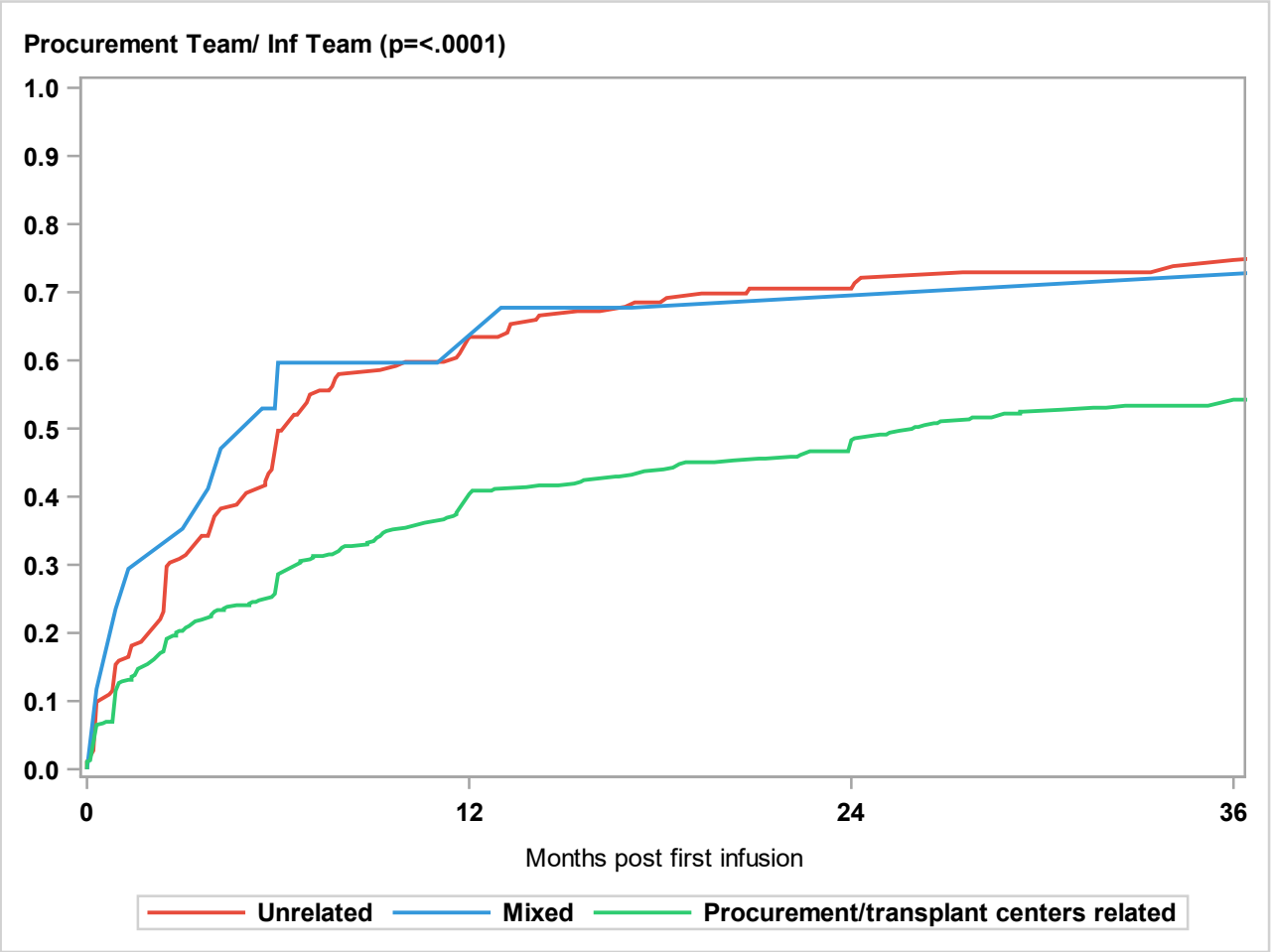


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

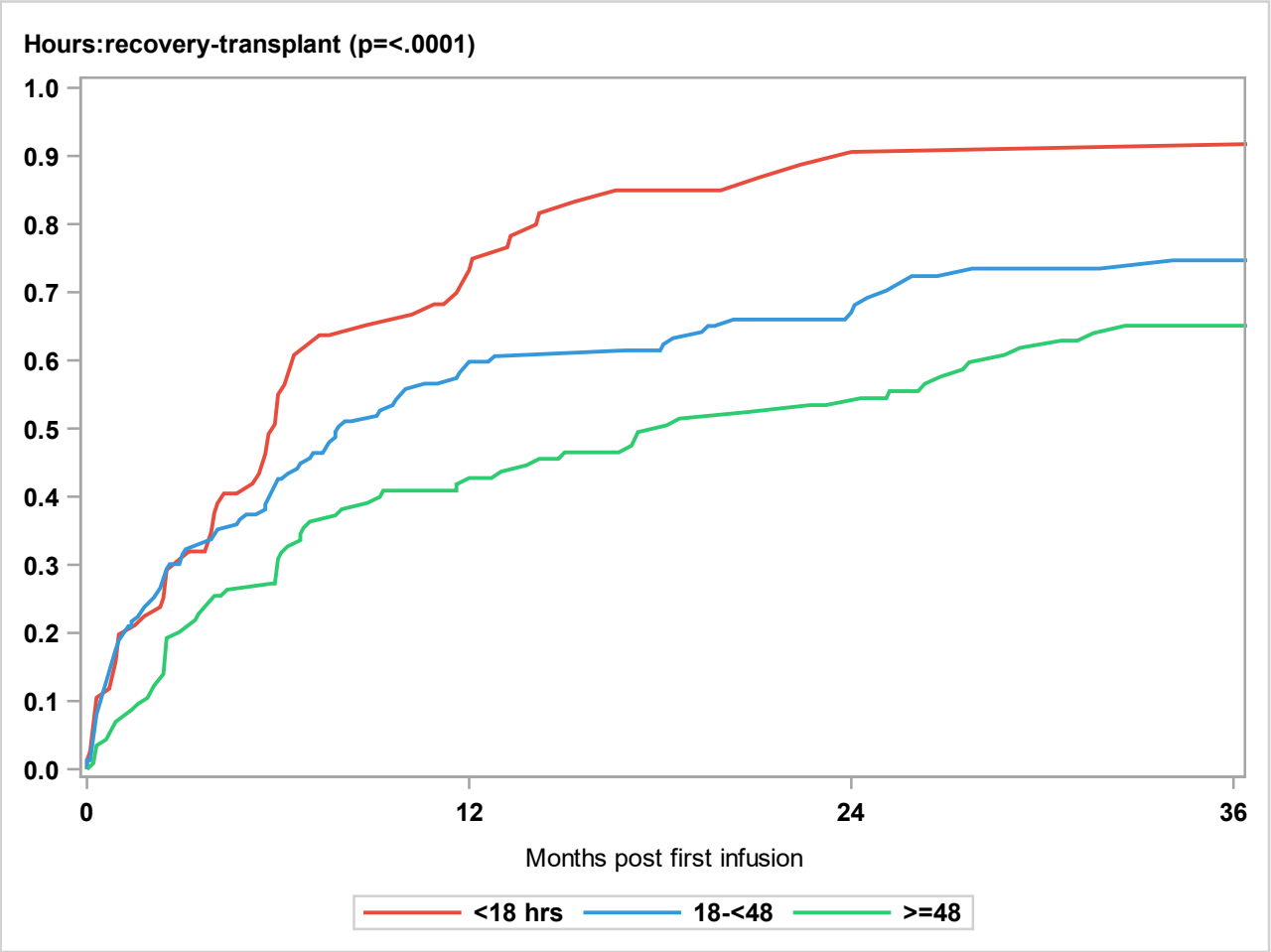
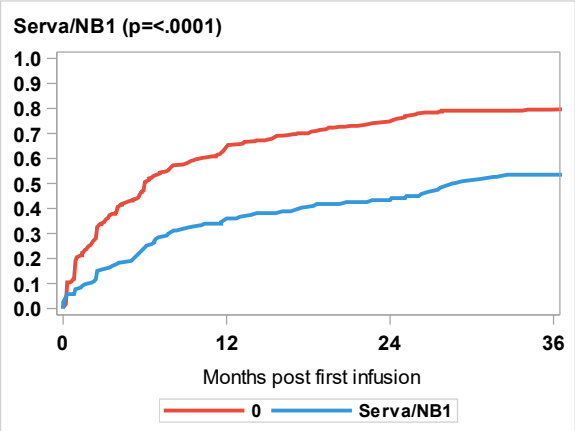
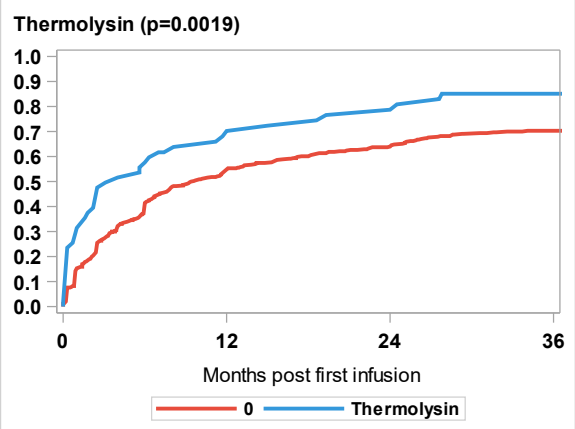


Exhibit 5-1A
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients





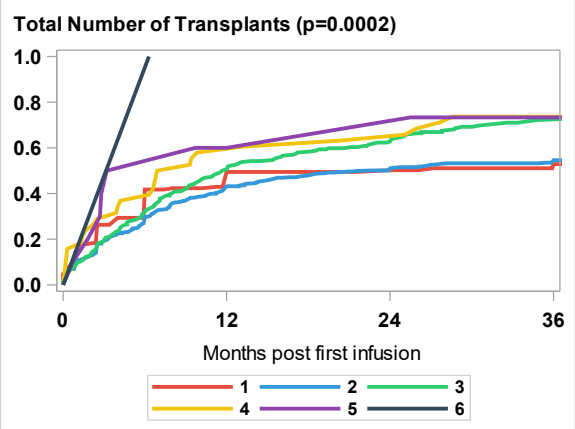


Exhibit 5-1B
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among IAK Recipients

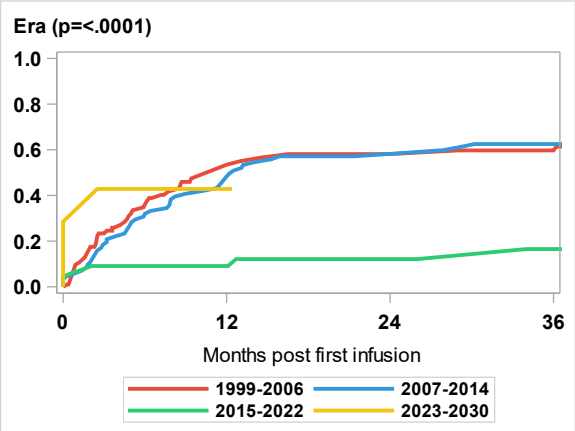
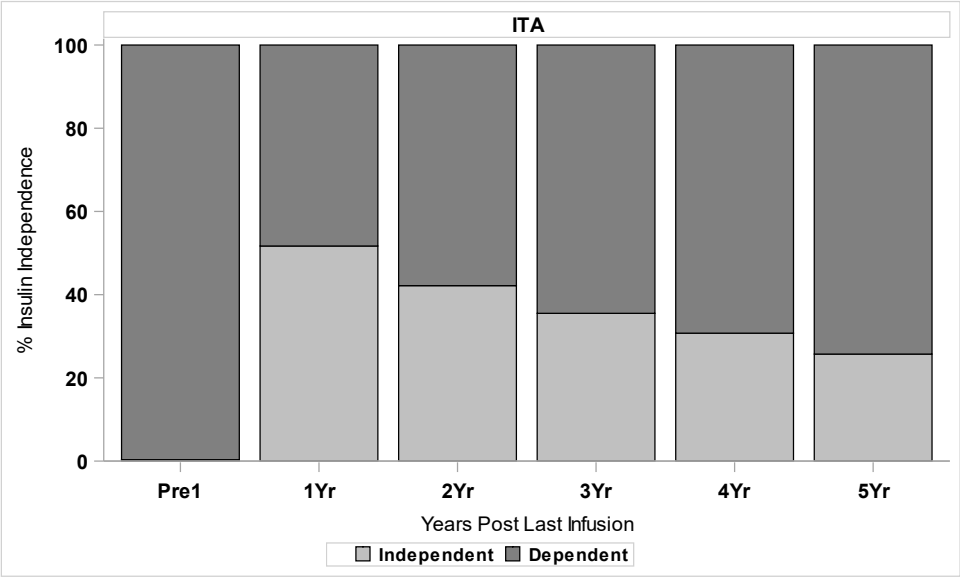


Exhibit 5-2A
Unadjusted Prevalence of Insulin Independence Post Last Infusion



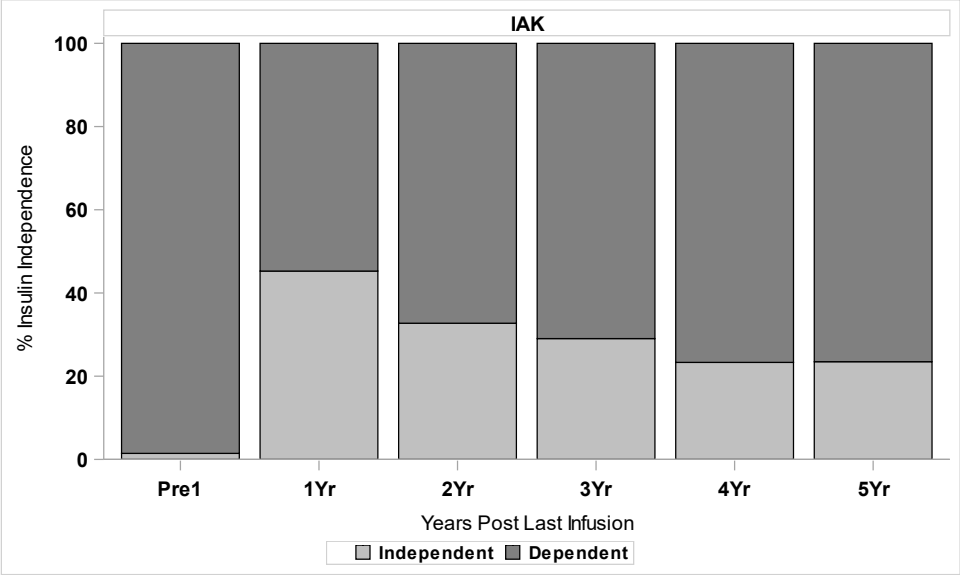
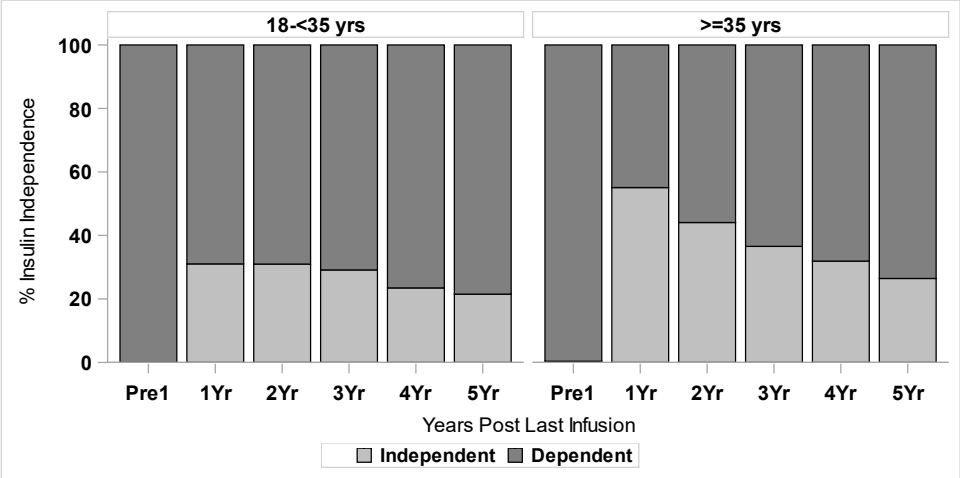
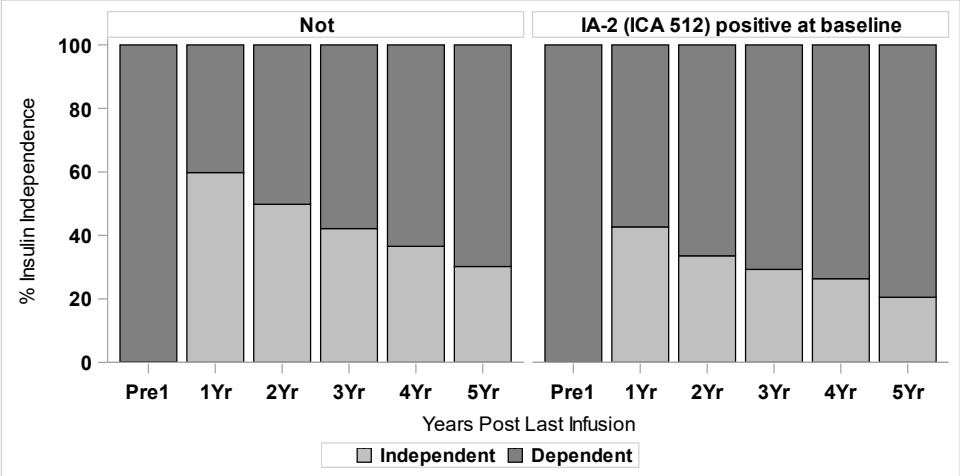


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Age (p=0.0029)



Baseline +IA2 (p=0.0008)



Baseline CAD (p=0.0092)

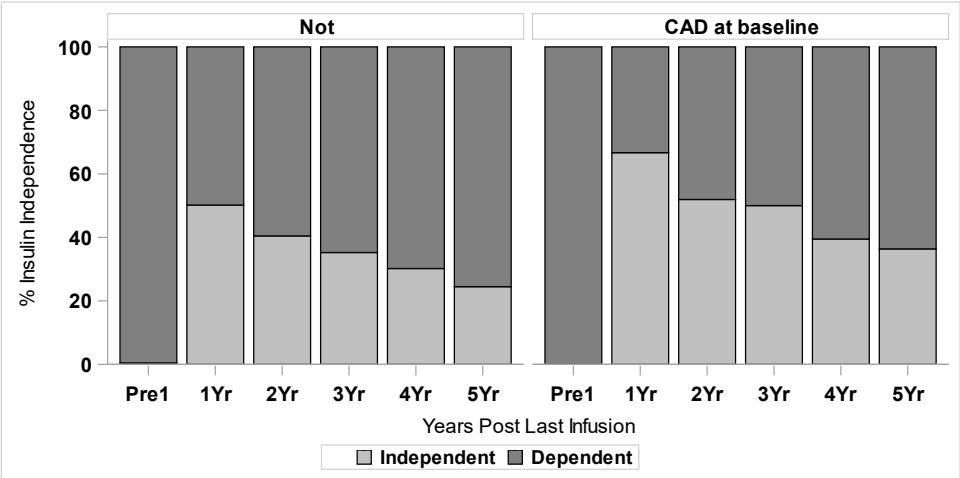
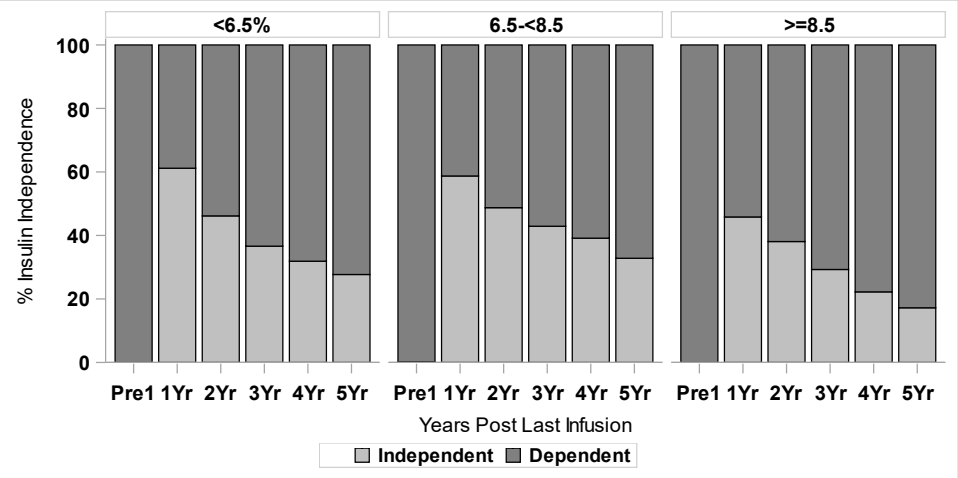
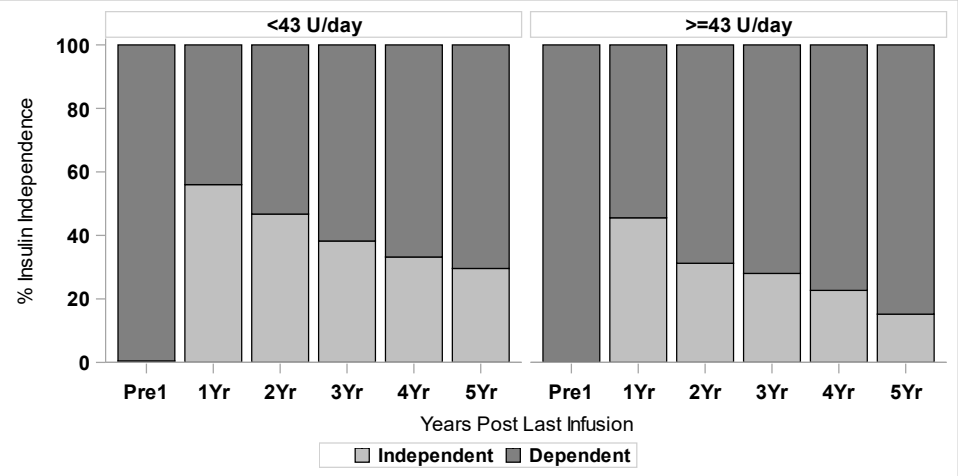


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Baseline HbA1c (p=0.0009)



Baseline insulin (U/day) (p=0.0005)



Baseline +microinsulin AAB (p=0.0005)

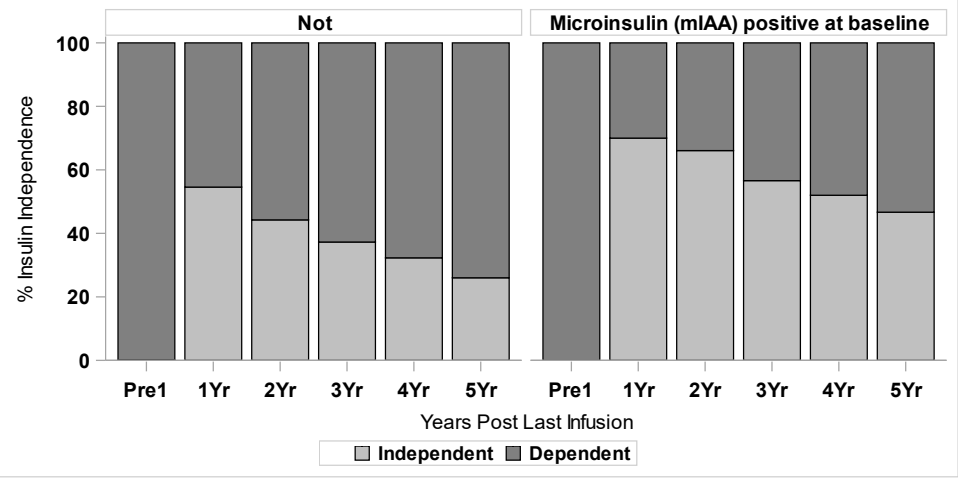
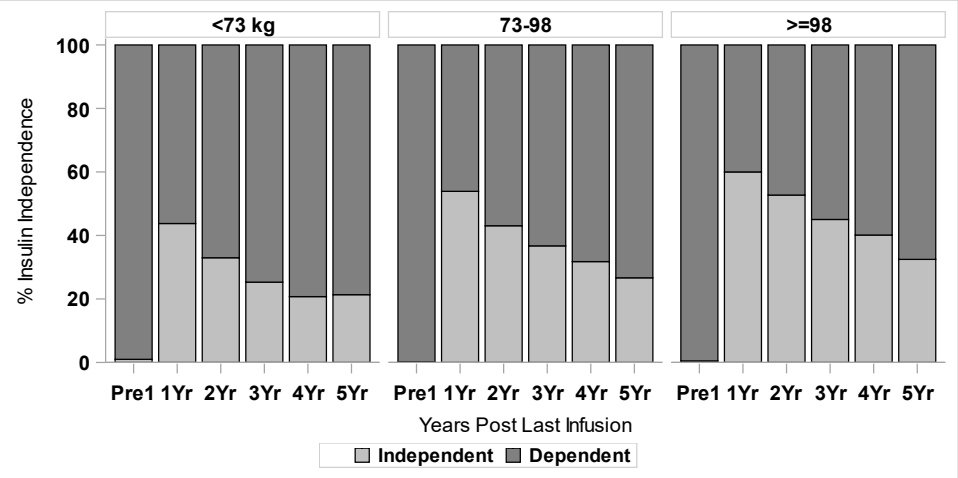
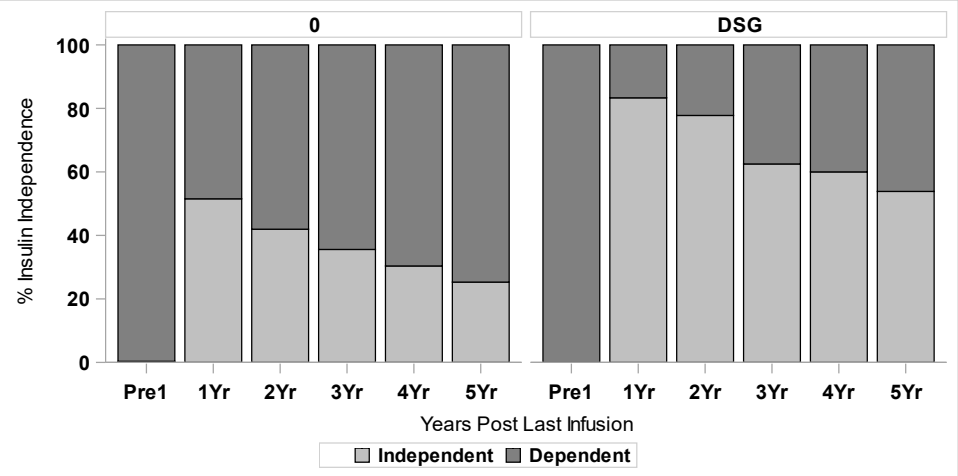


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Donor weight (kg) (p=0.0047)



DSG (p=<.0001)



Trauma death (p=0.0009)

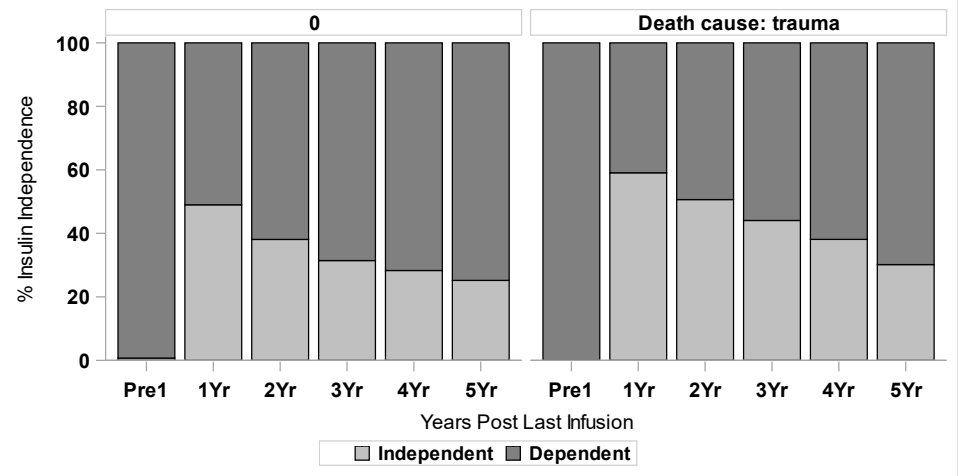
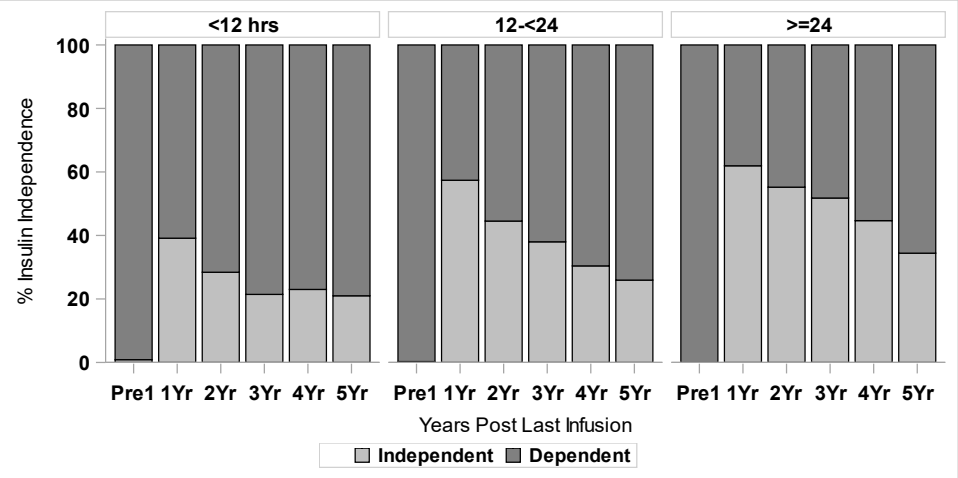
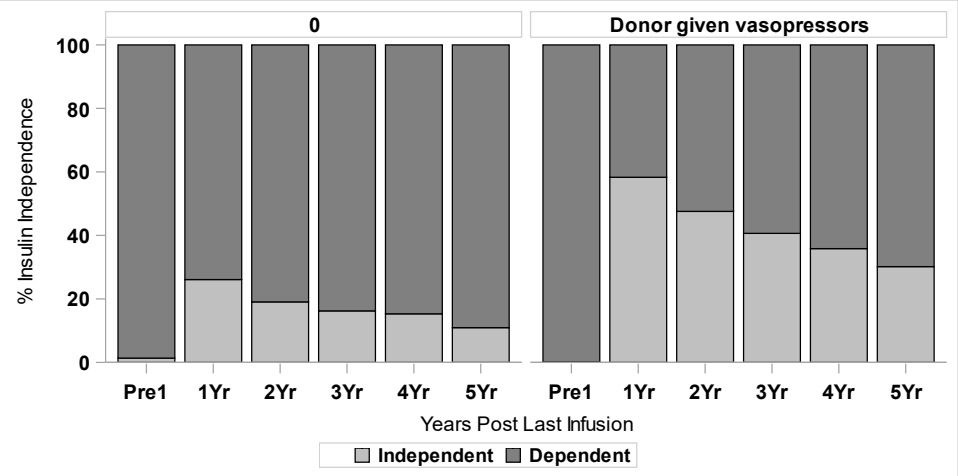


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Hours: Death to cross-clamp (p=0.0003)



Donor given vasopressors (p=<.0001)



Eflizumab (p=<.0001)

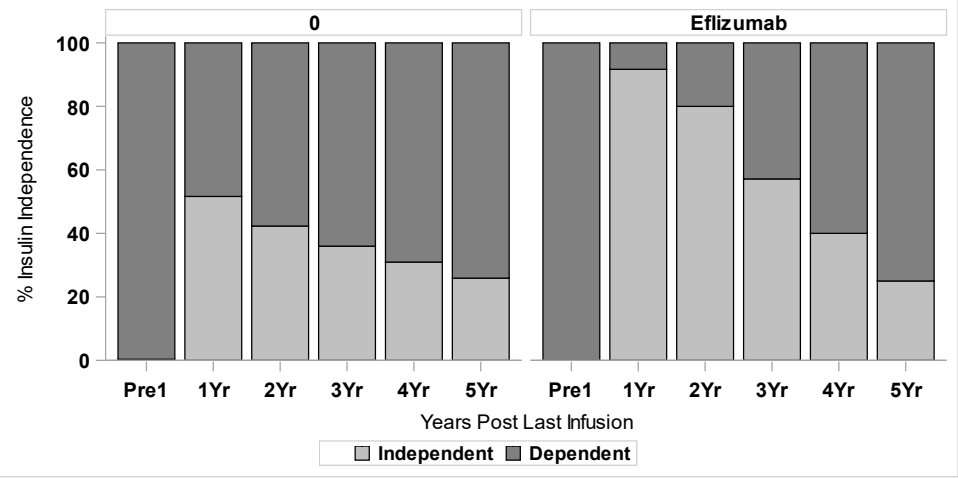
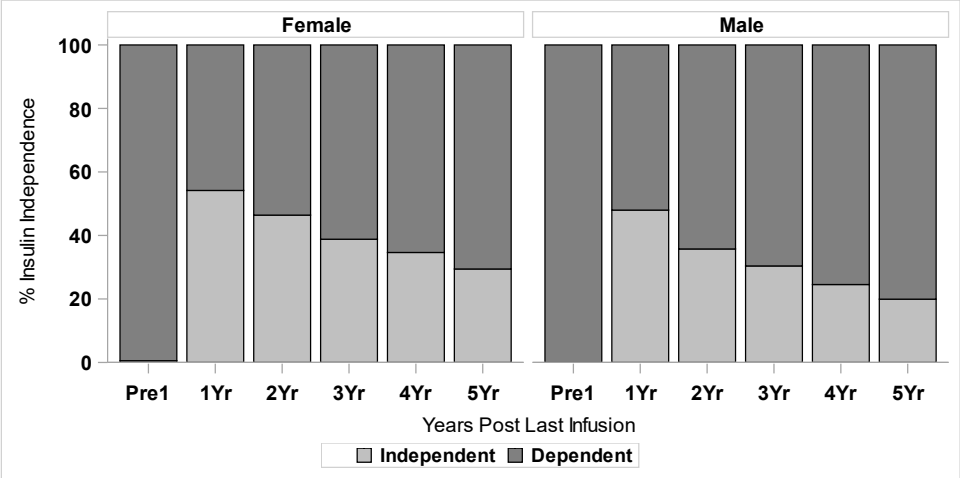
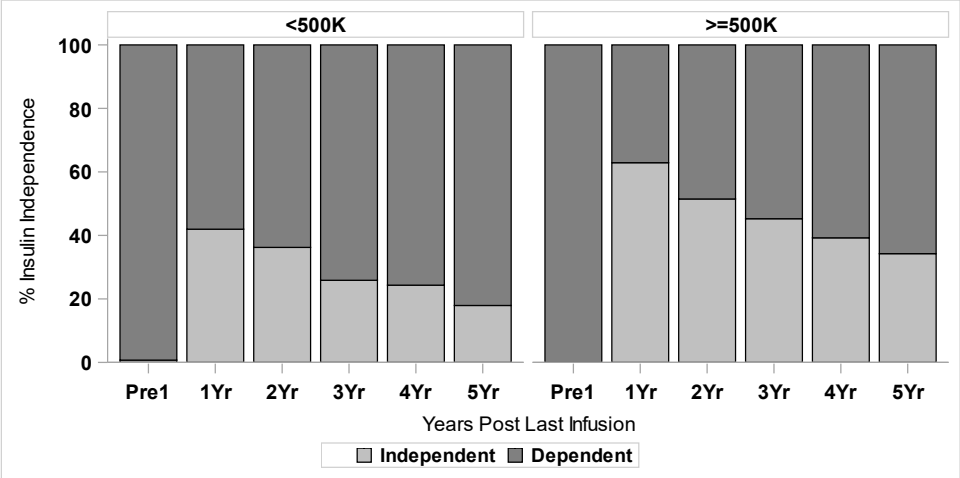


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Gender (p=0.0050)



Islets IEQs all infusions (p=0.0001)



Islets IEQs/kg recipient (p=0.0003)

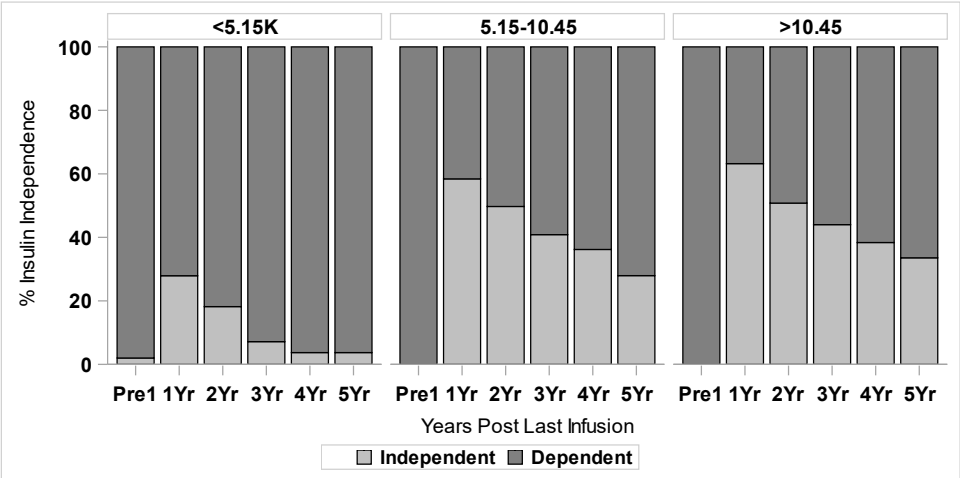
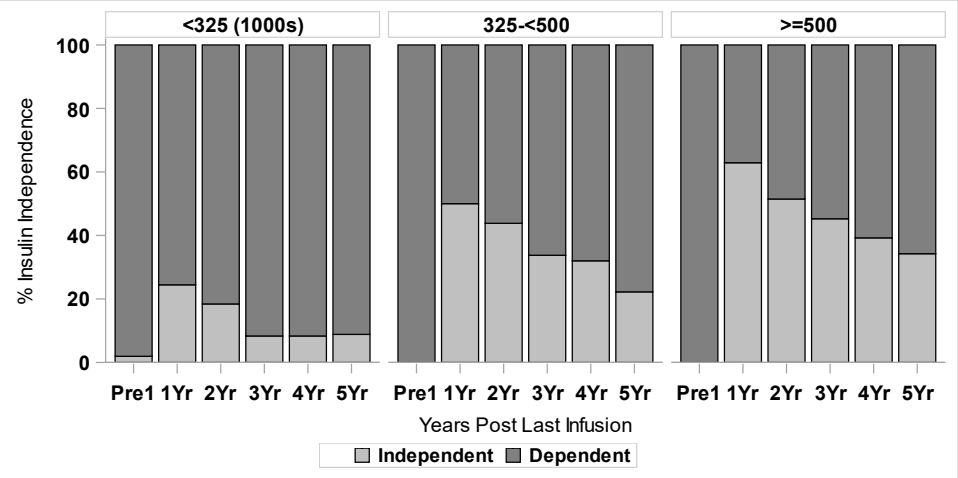
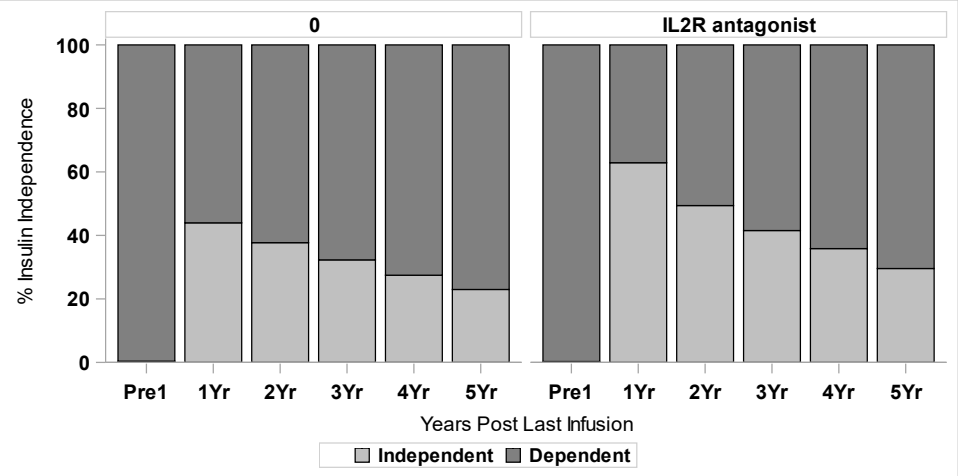


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Islets IEQs infused (p=<.0001)



IL2RA inhibition (p=0.0001)



LFA-1 inhibitor (Efalizumab) (p=<.0001)

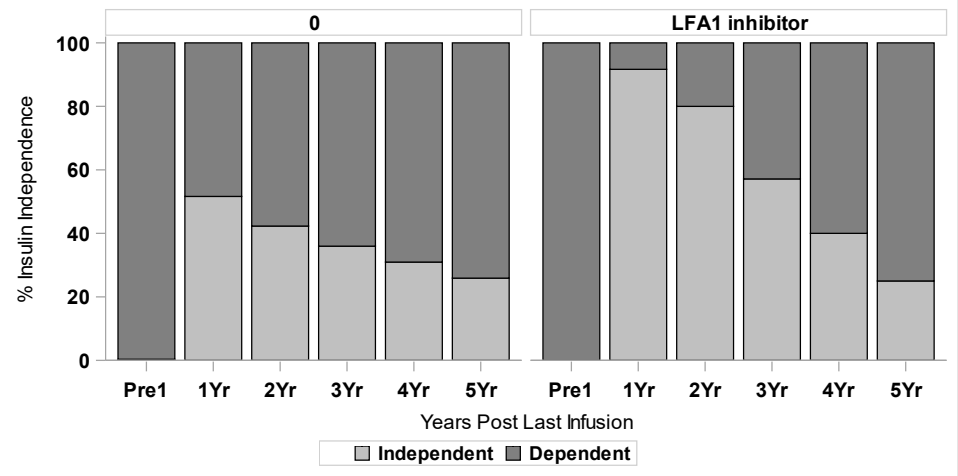
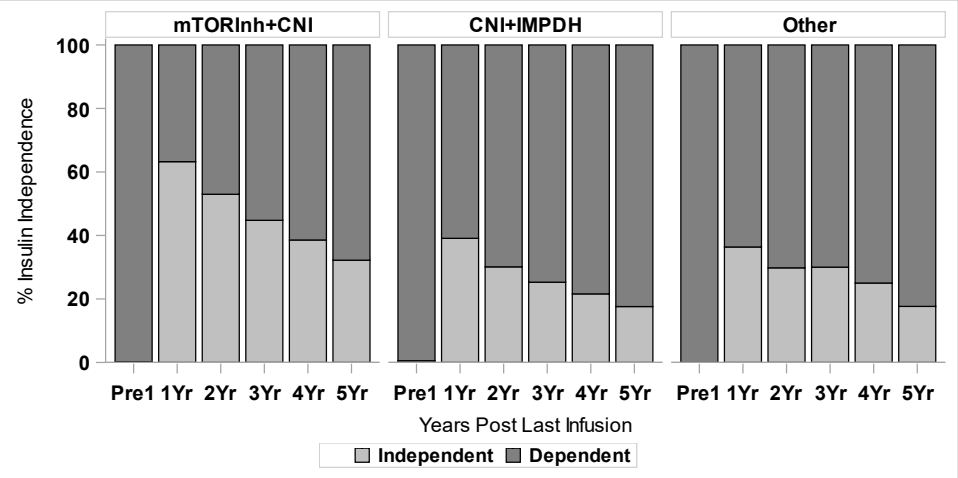
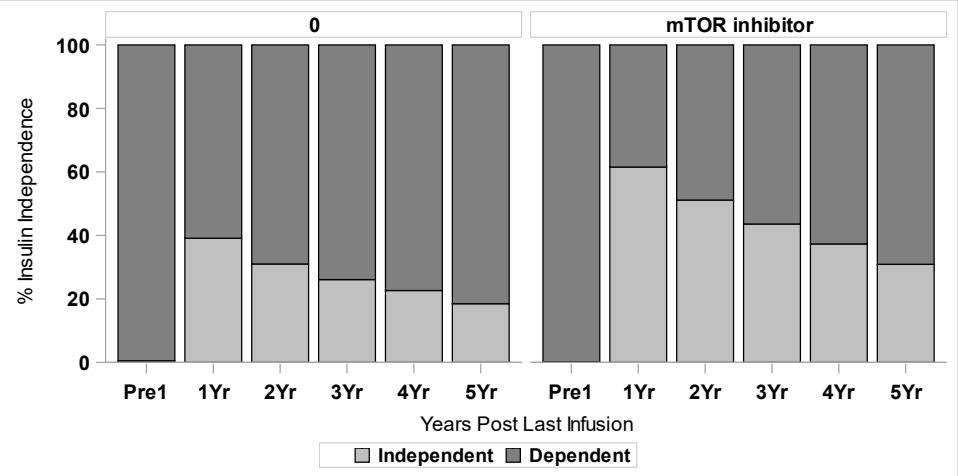


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Maintenance combination (p=<.0001)



mTOR inhibitor (p=<.0001)



2L preservation (p=0.0015)

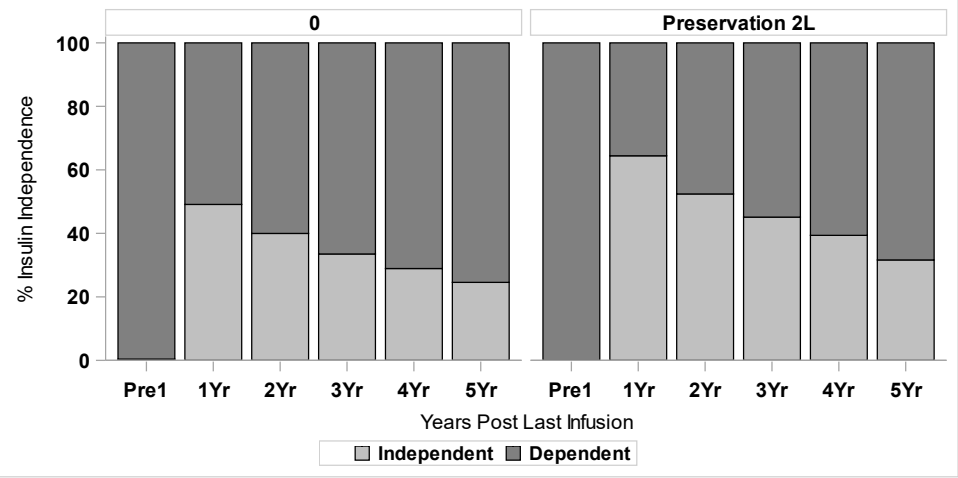
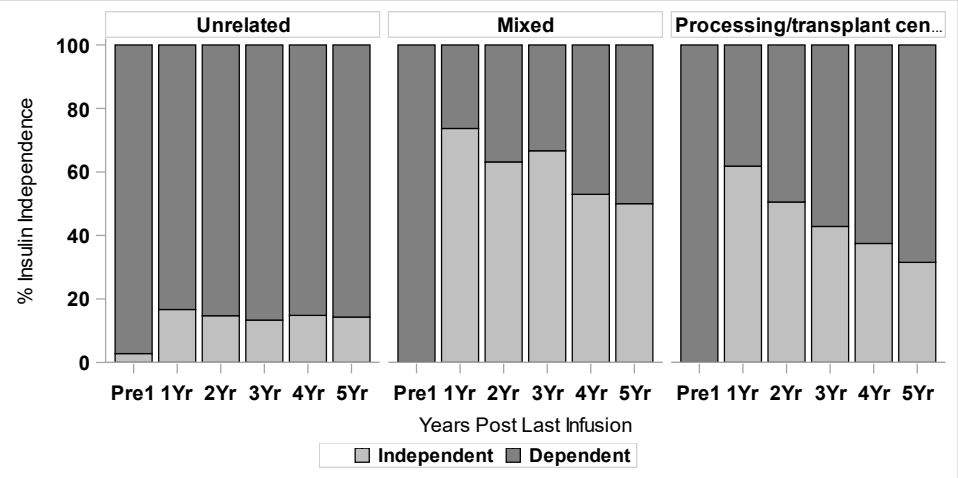
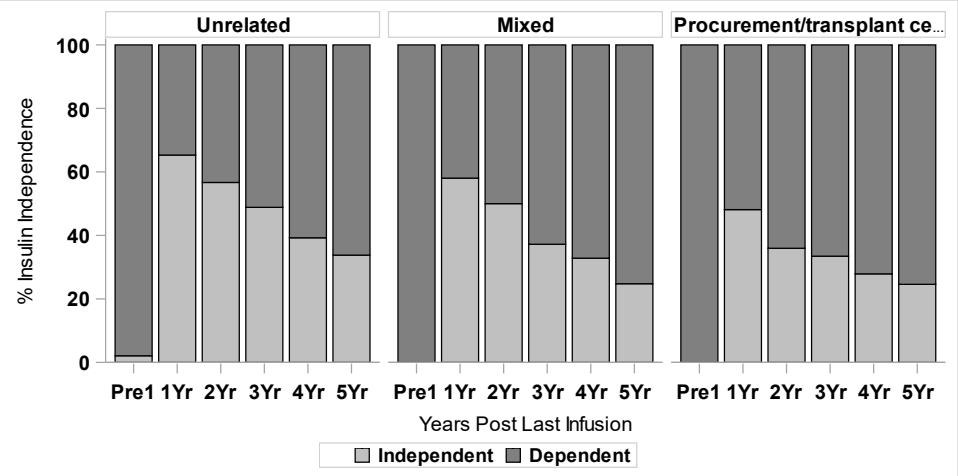


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

Processing center (p=0.0005)



Procurement center (p=0.0012)



Thermolysin (p=0.0089)

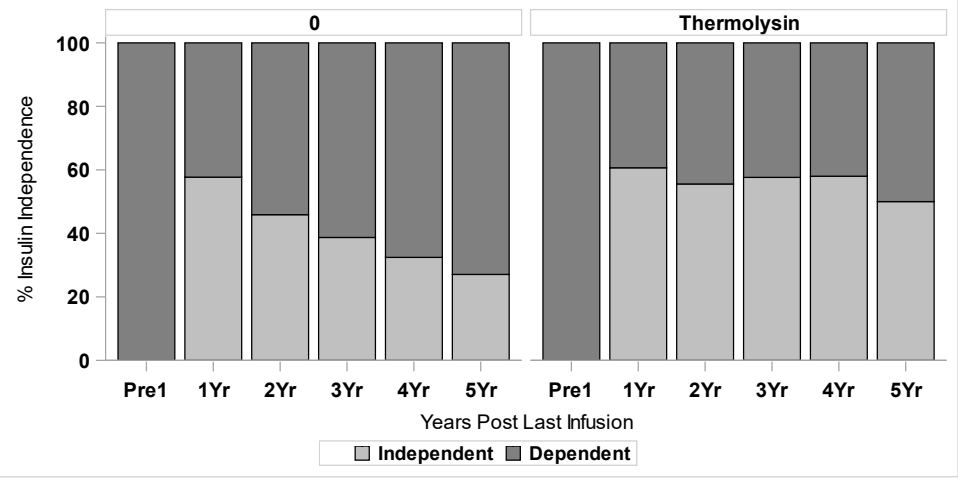
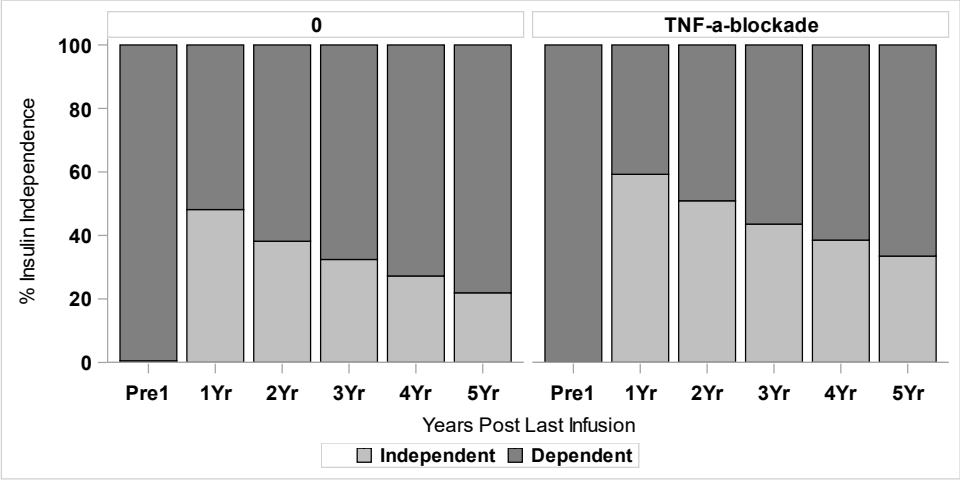
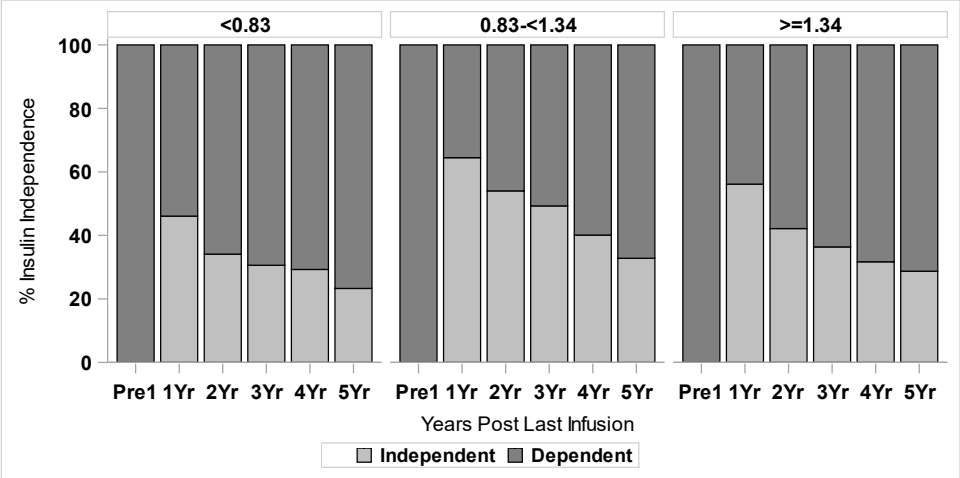


Exhibit 5-2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

TNFa inhibitor (p=0.0002)



Islets IEQs/particle ratio (p=0.0058)



Total infusions (p=0.0040)

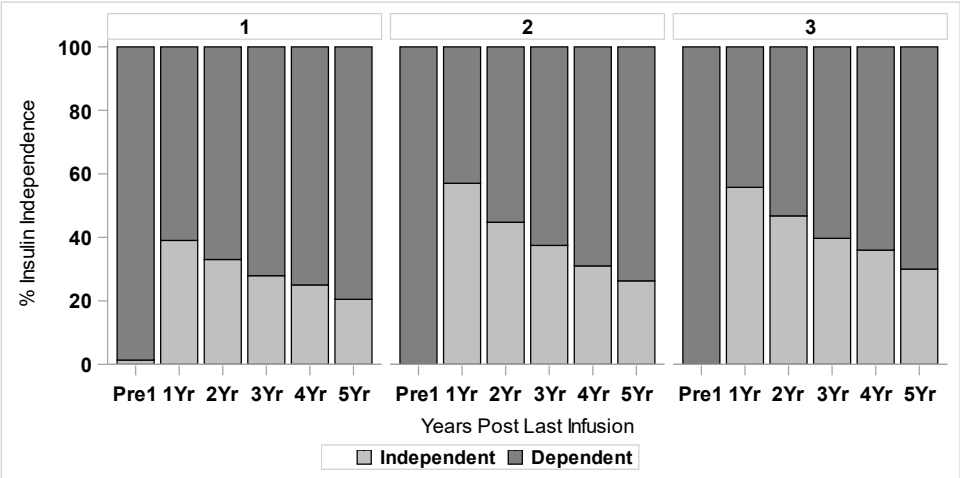
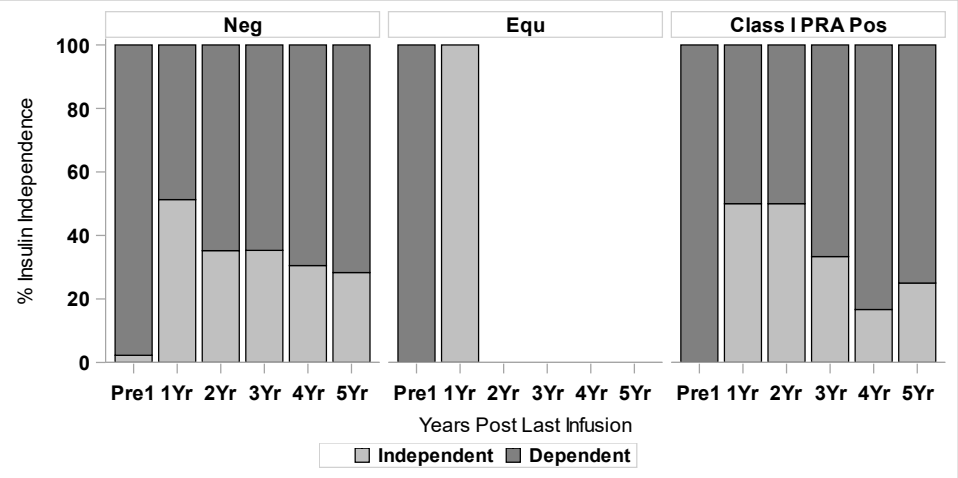
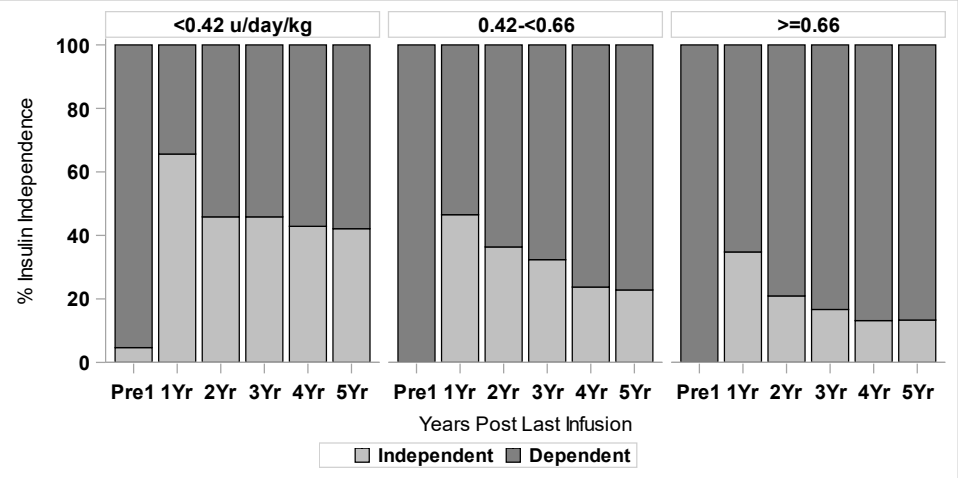


Exhibit 5-2C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

Baseline +Class I PRA (p=<.0001)



Baseline insulin (U/kg/day) (p=0.0099)



Donor gender (p=0.0088)

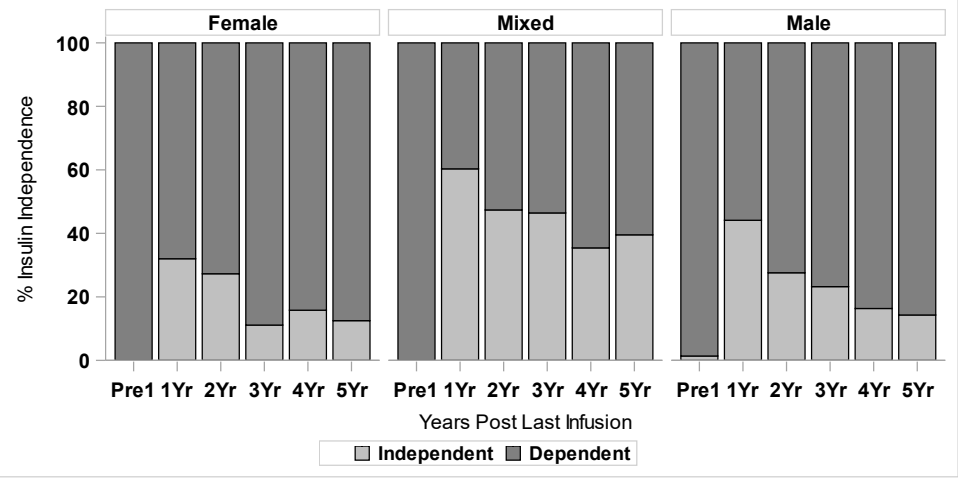
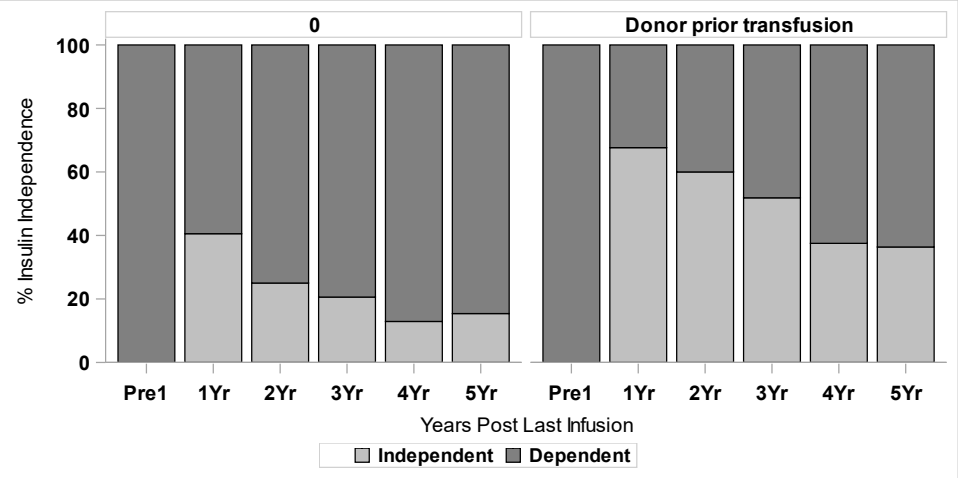
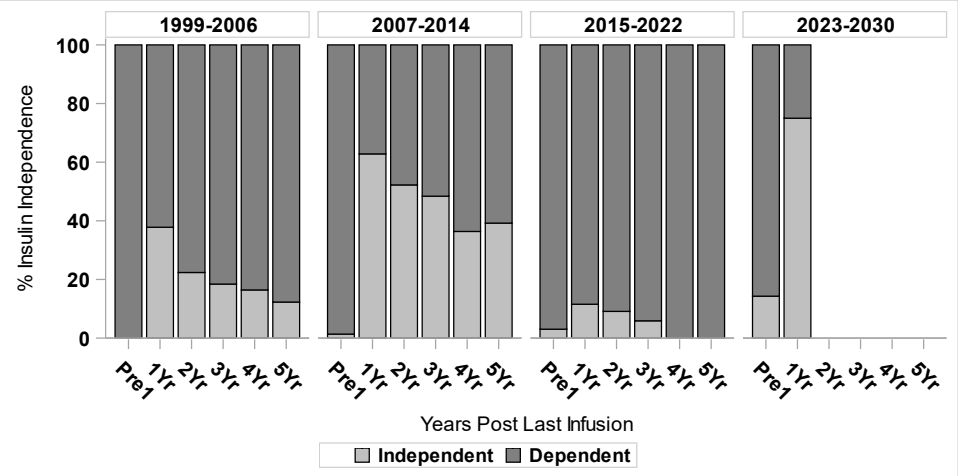


Exhibit 5-2C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

Donor transfused before hospital (p=0.0049)



Era (p=<.0001)



Total infusions (p=0.0022)

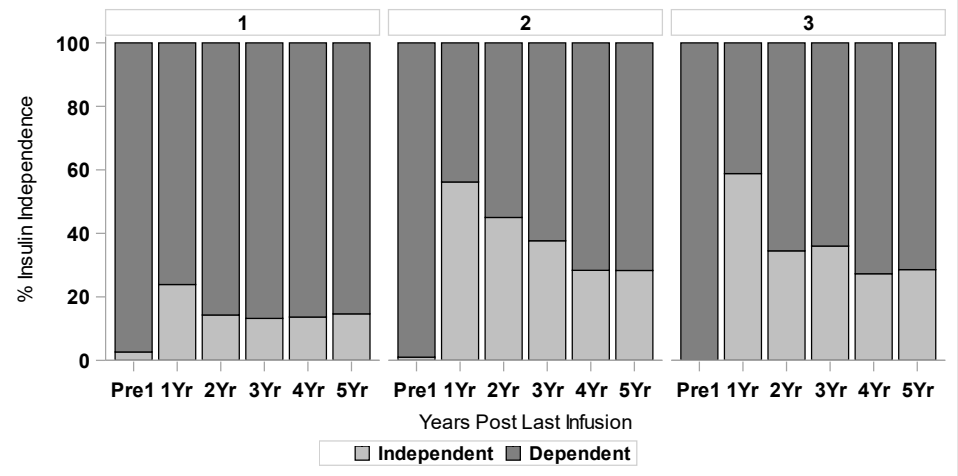
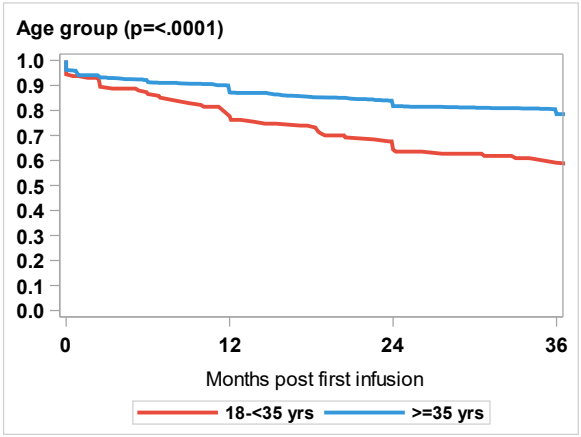
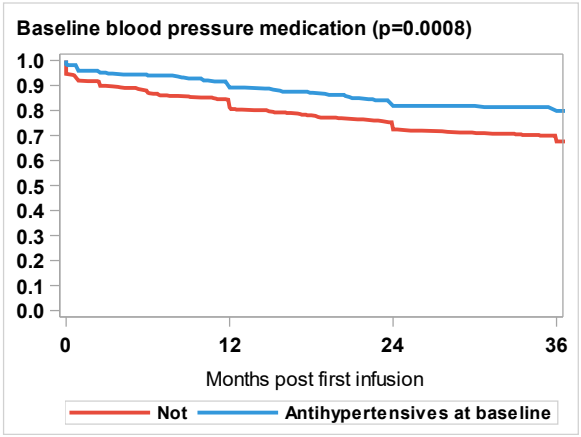


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients





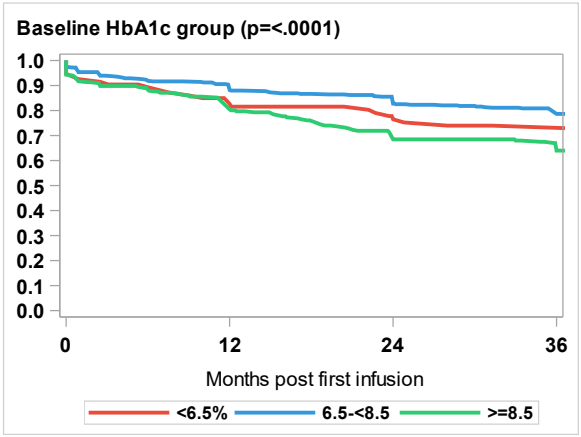


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

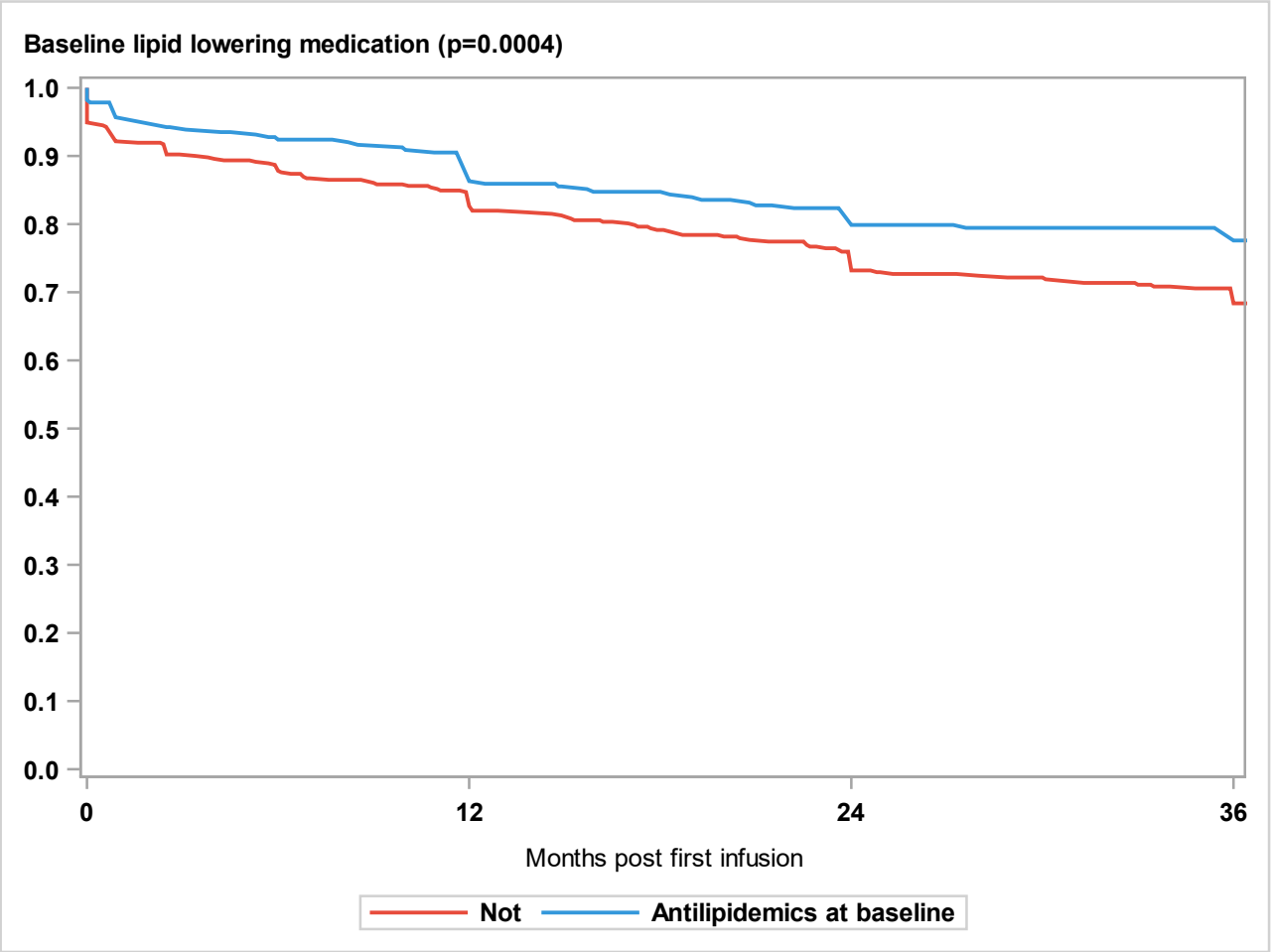


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

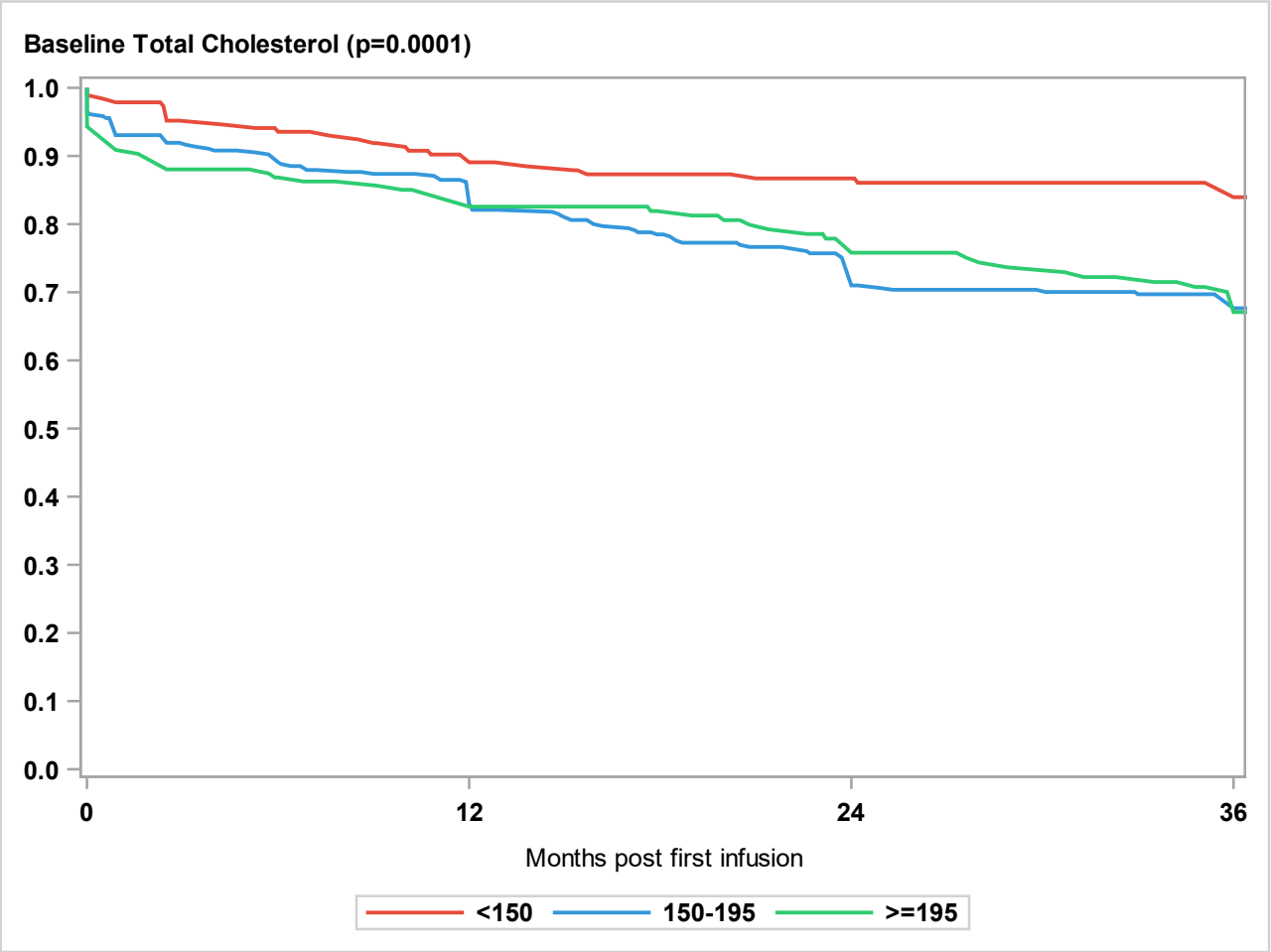
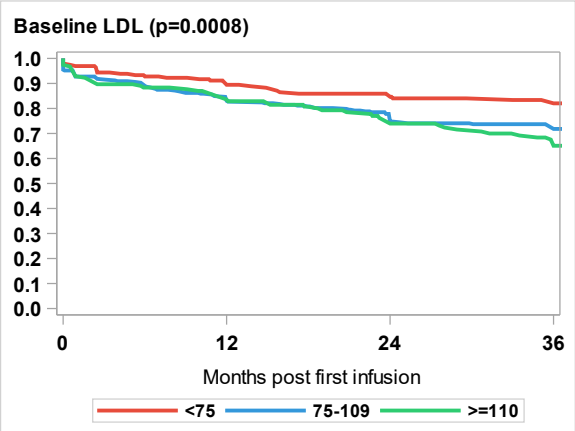
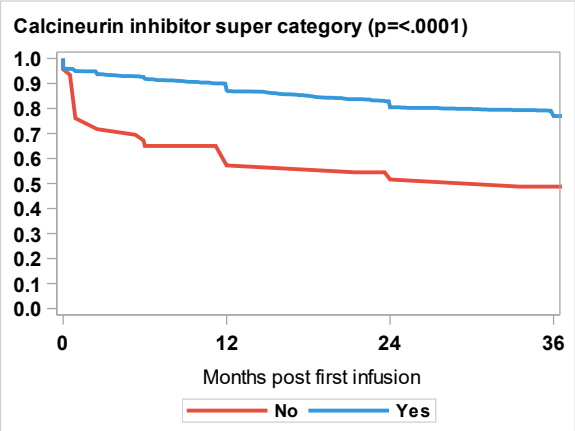


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients





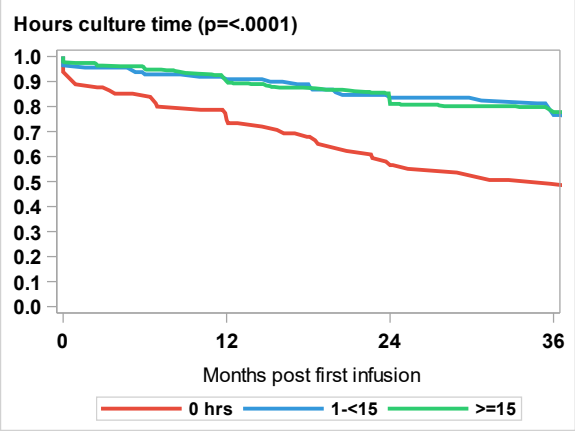


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

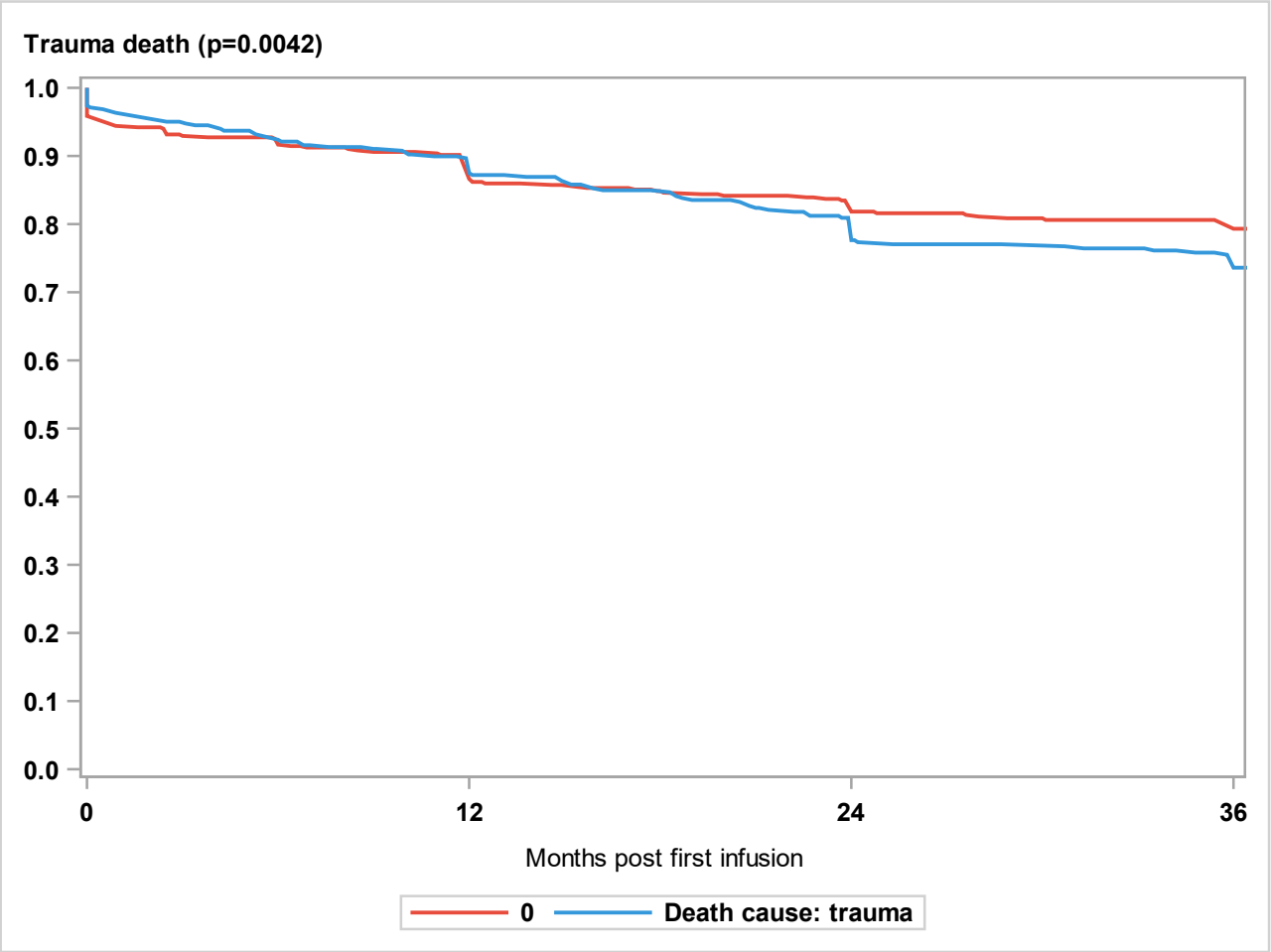


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

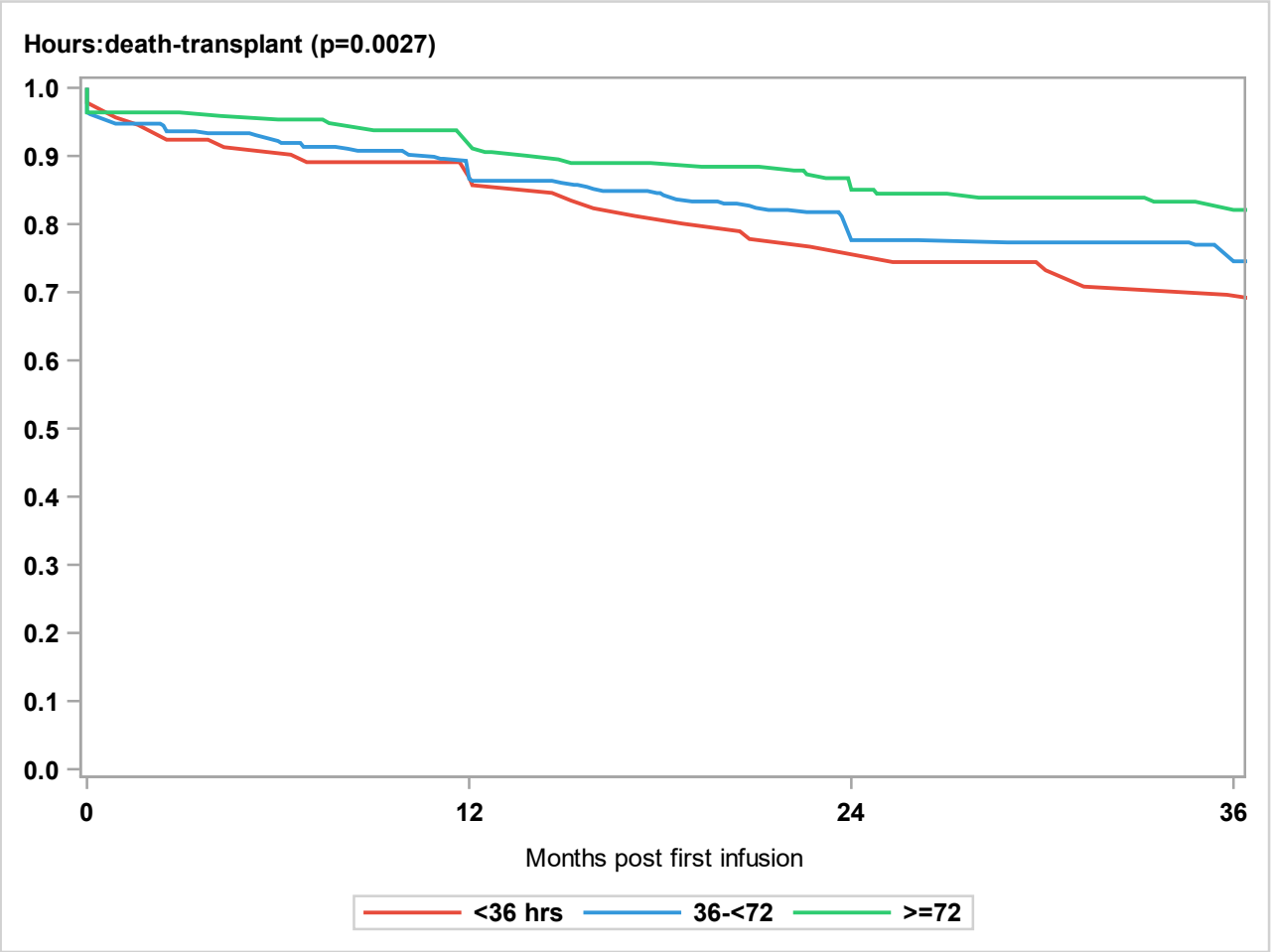
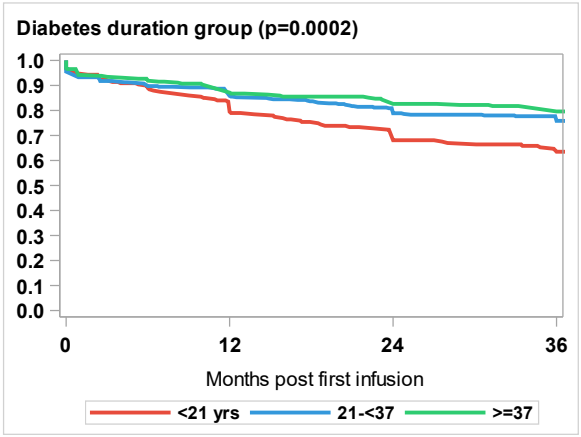
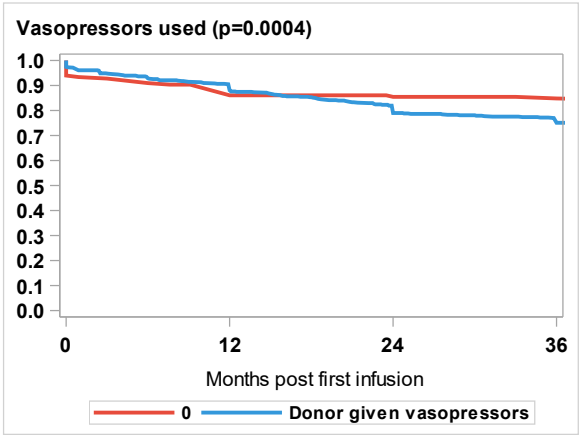


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients





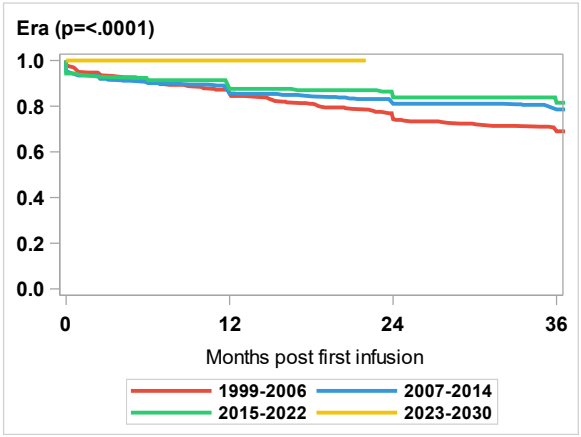


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

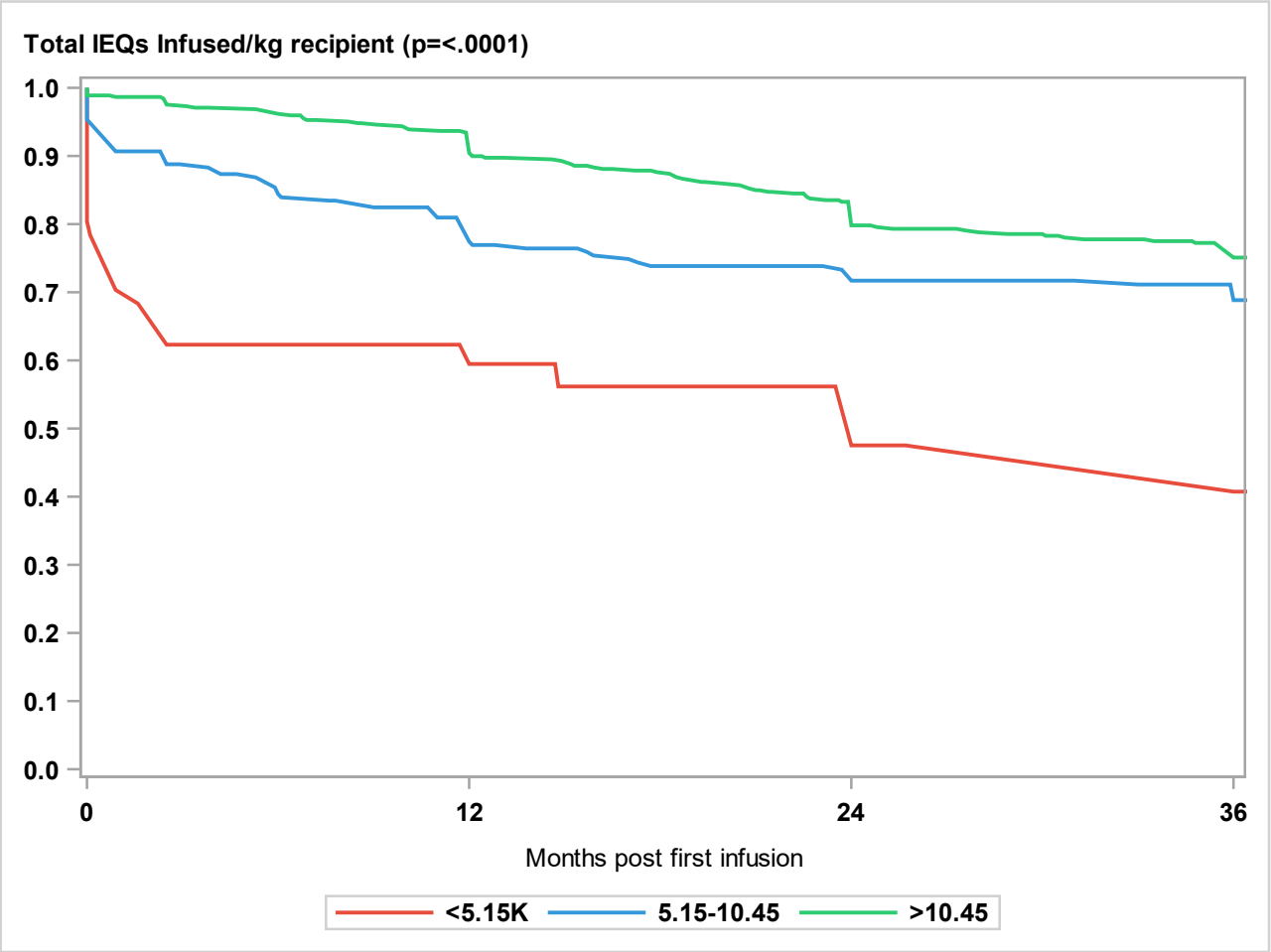


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

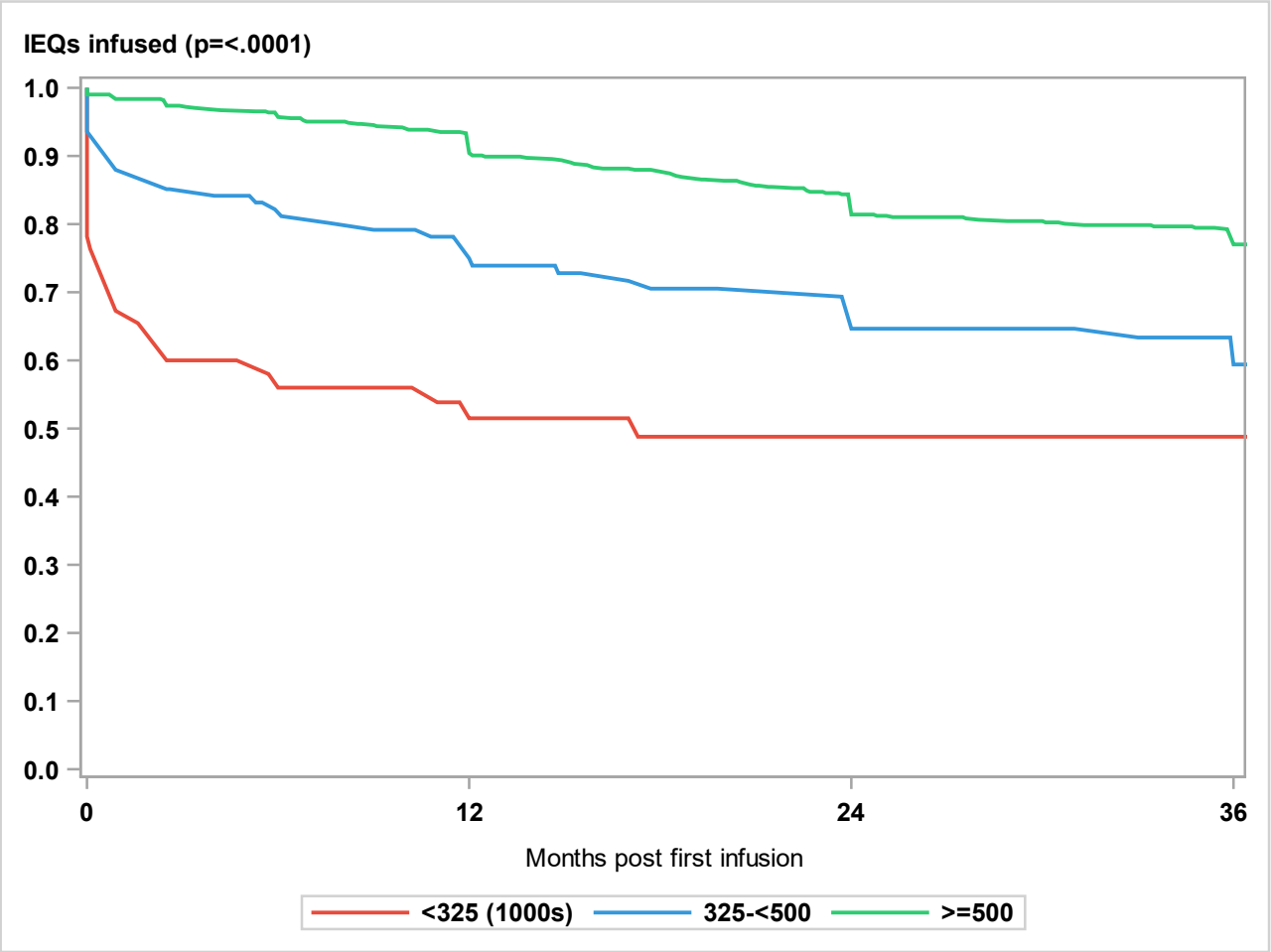
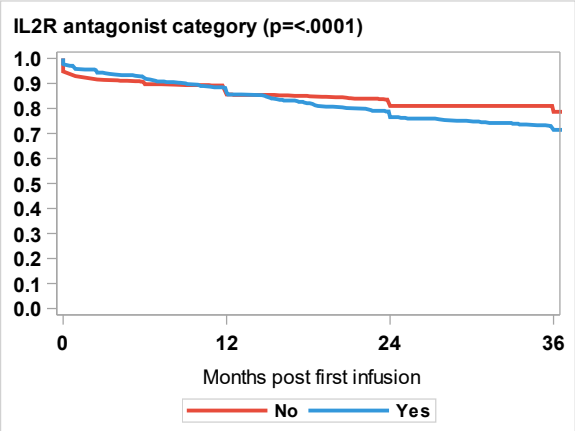
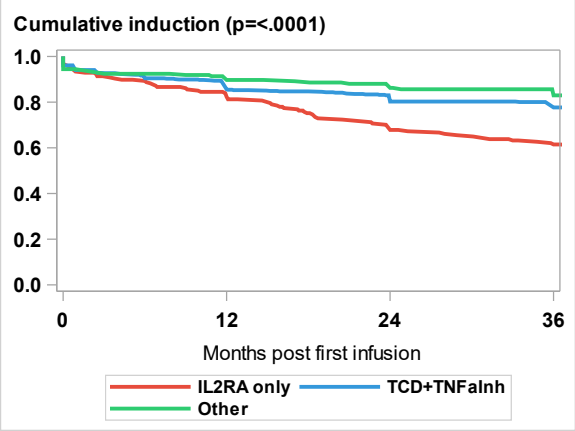


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients





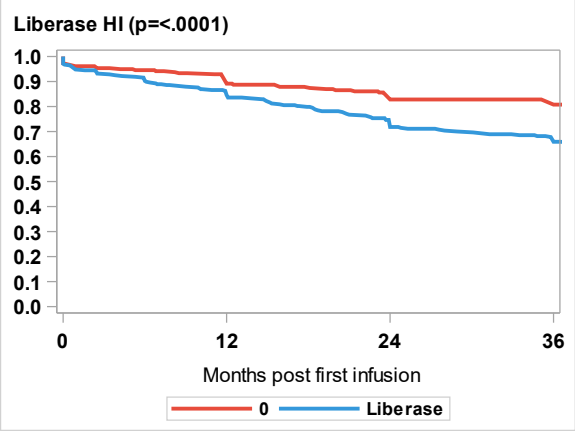


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

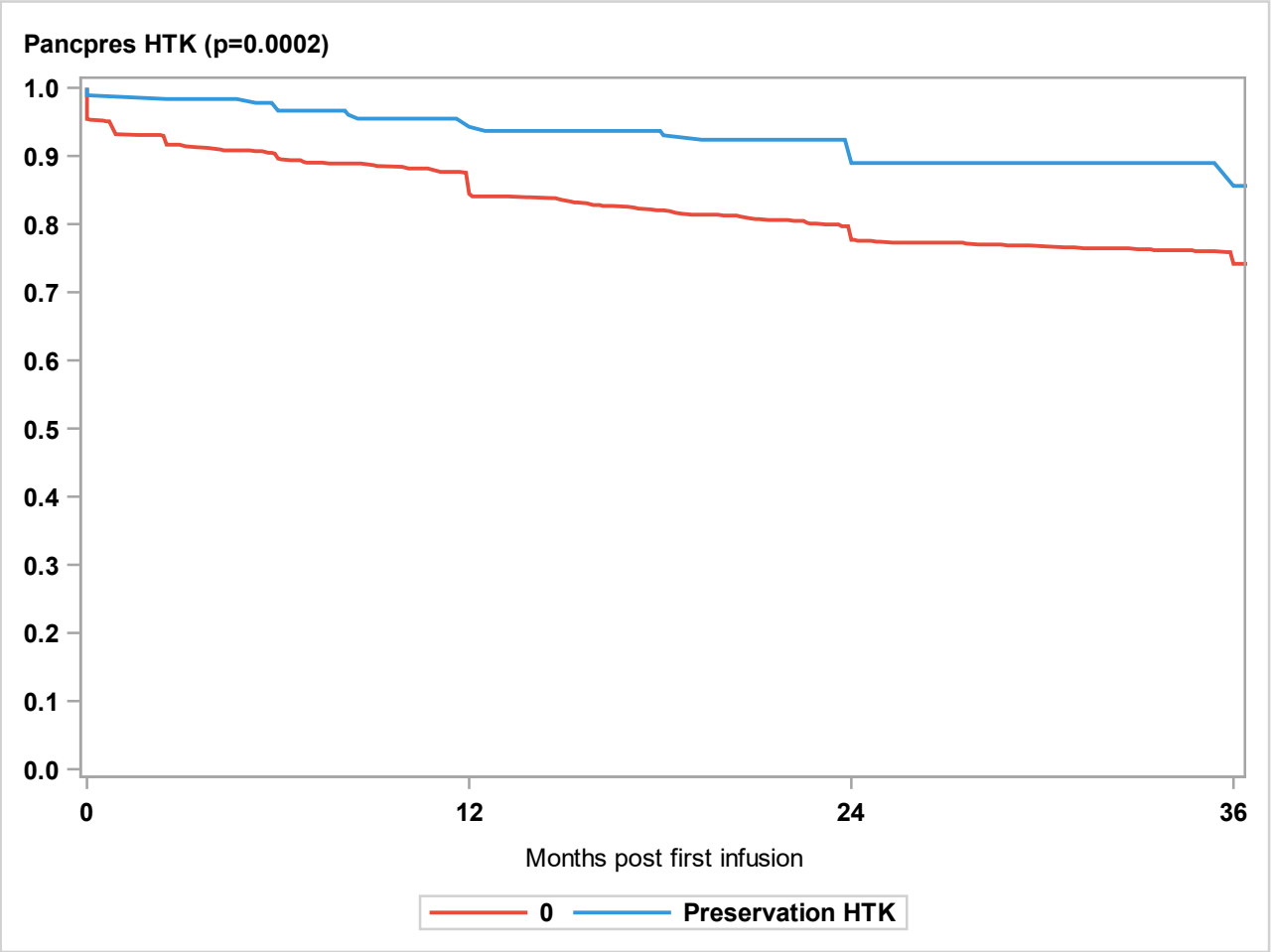


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

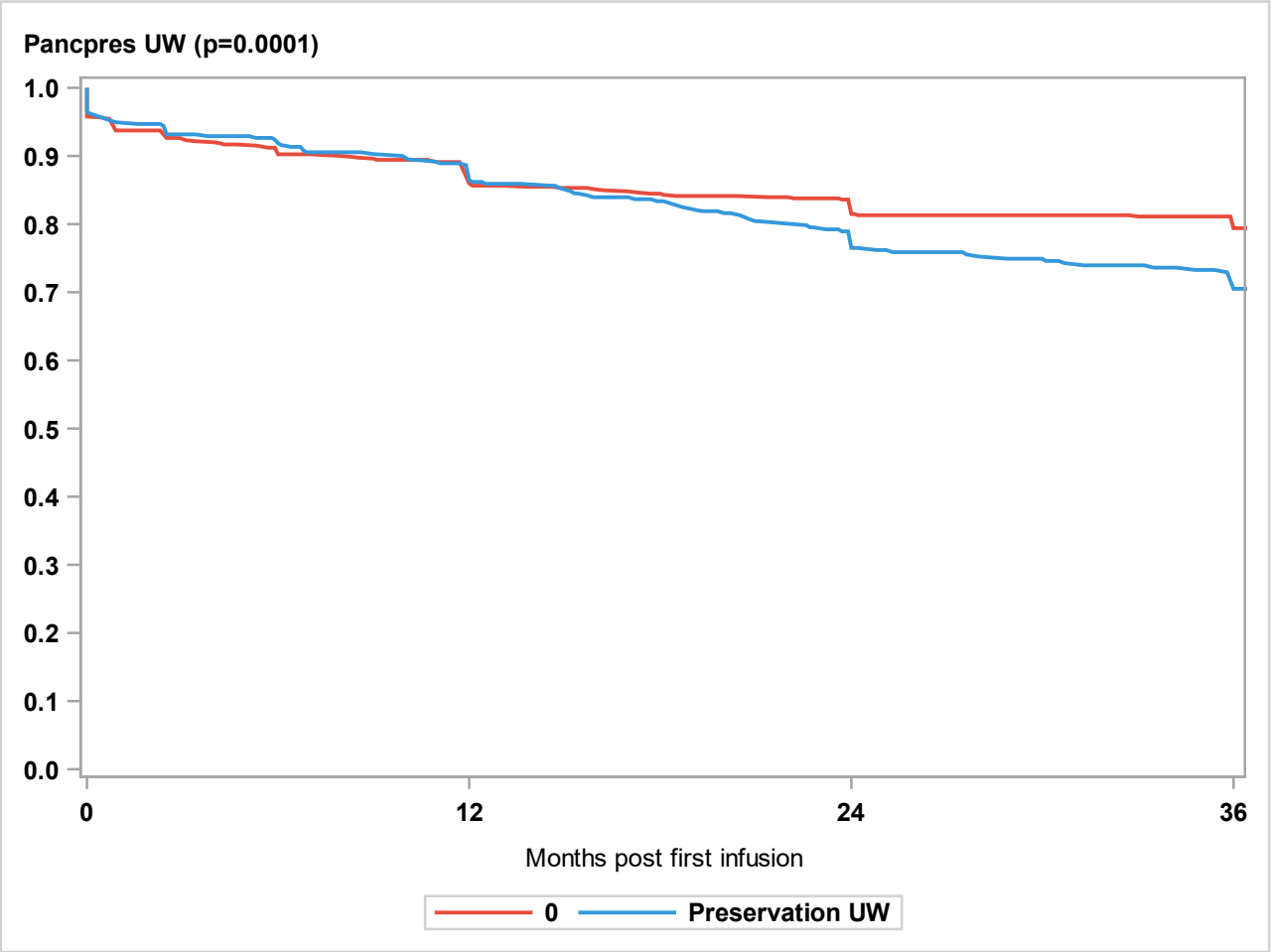
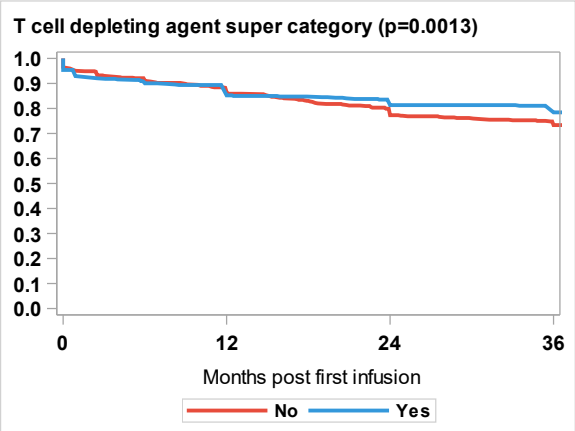
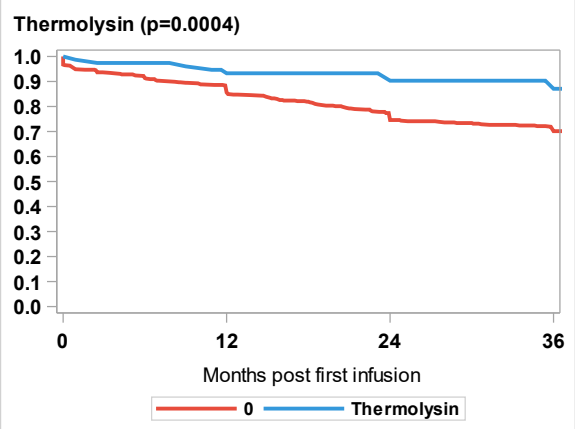


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients





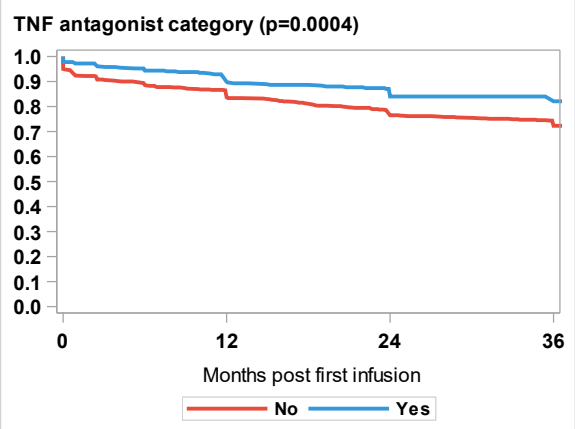


Exhibit 5-3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

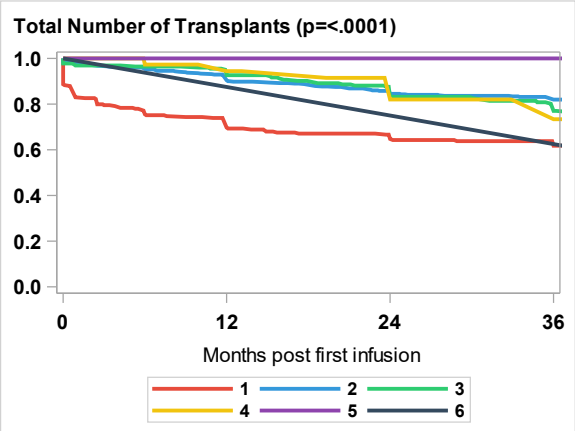
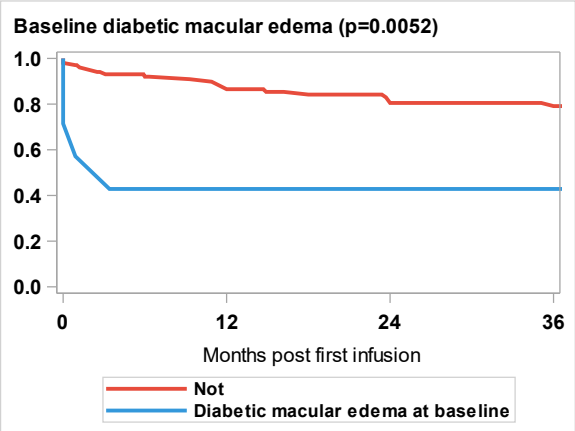
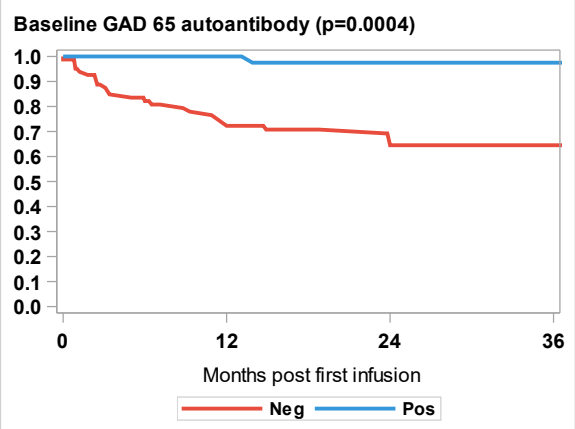


Exhibit 5-3B
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients





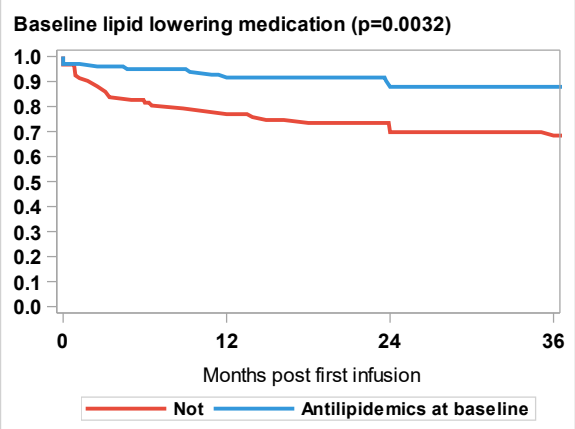


Exhibit 5-3B
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

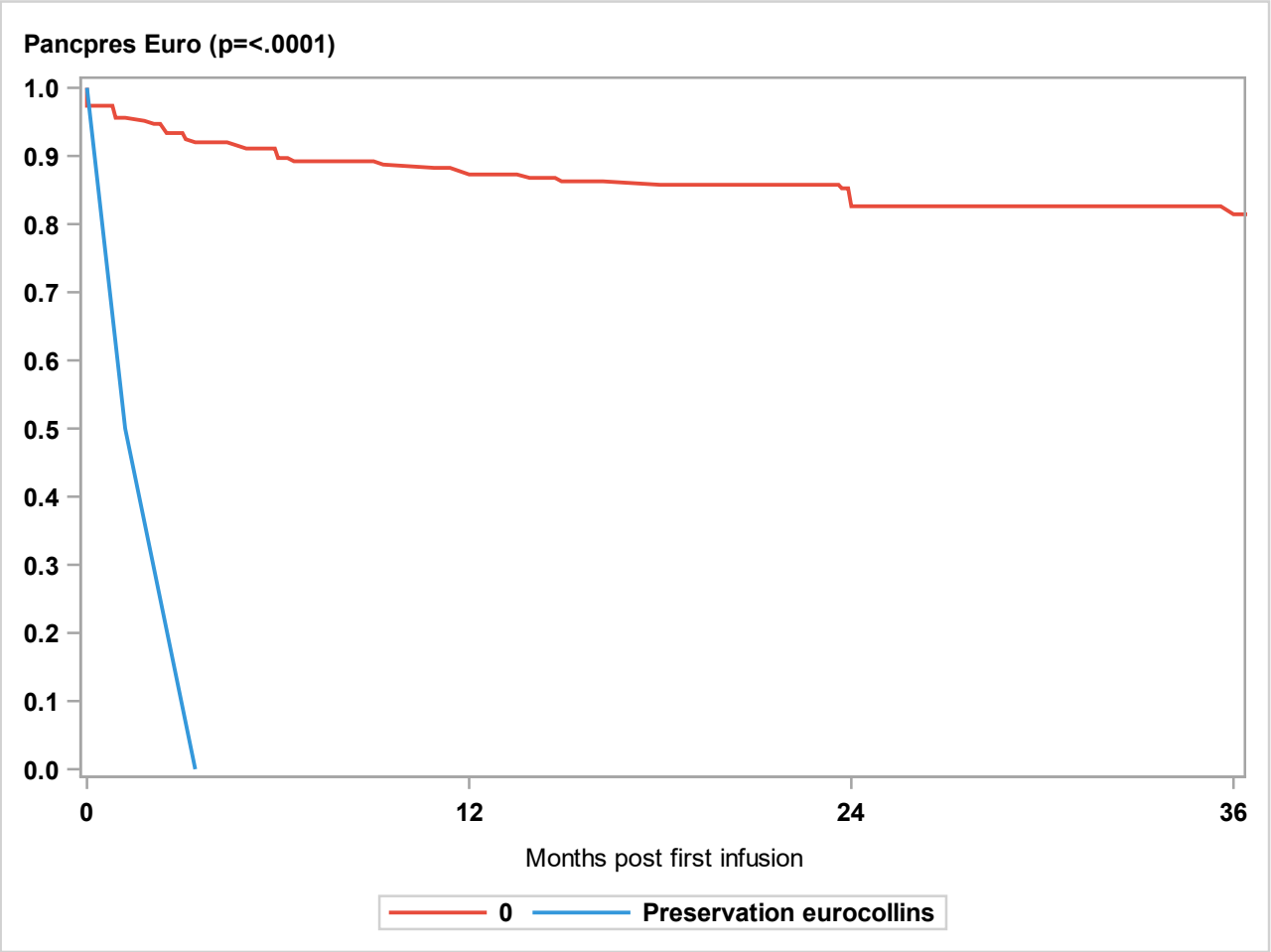


Exhibit 5-3B
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

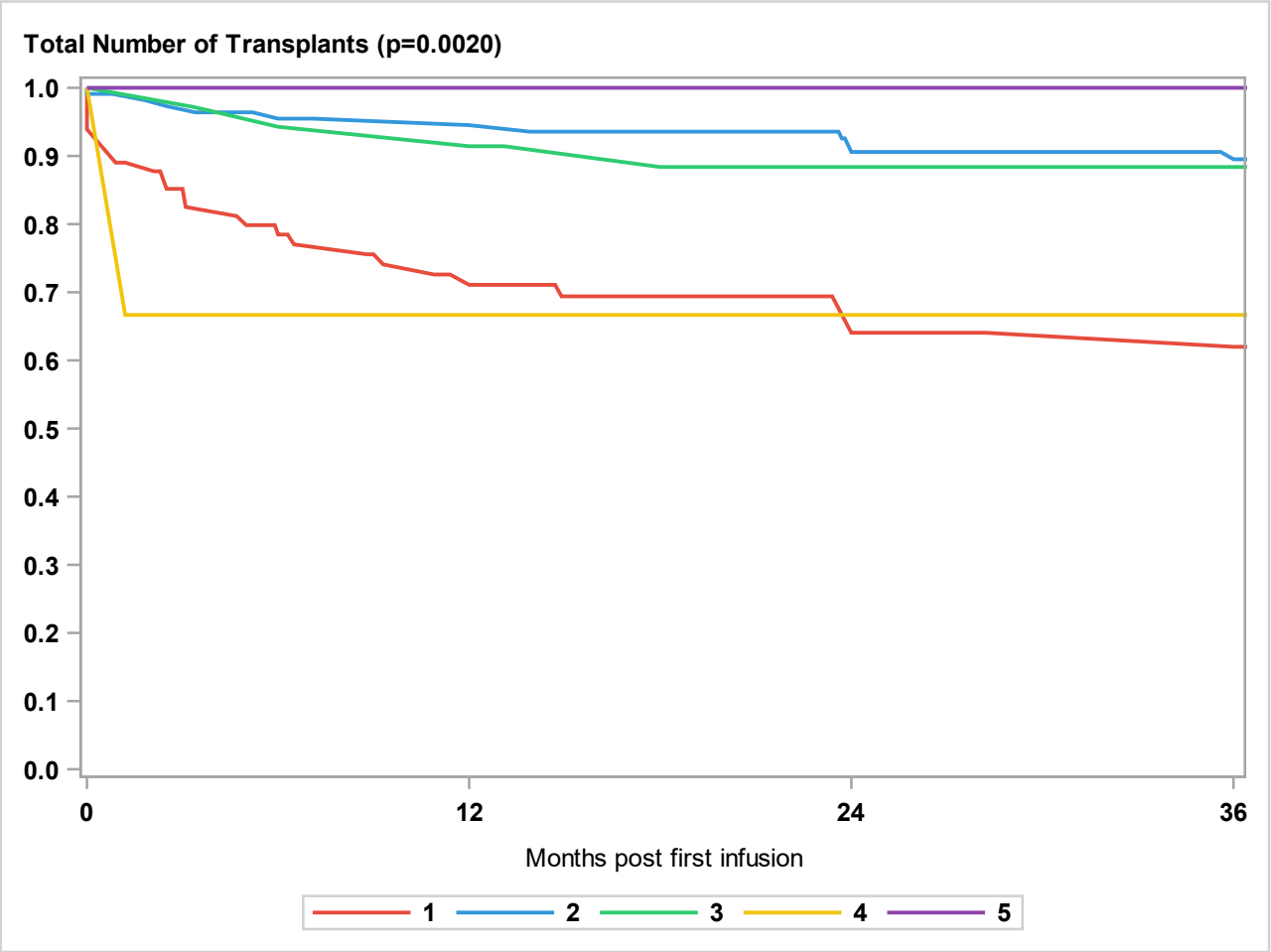
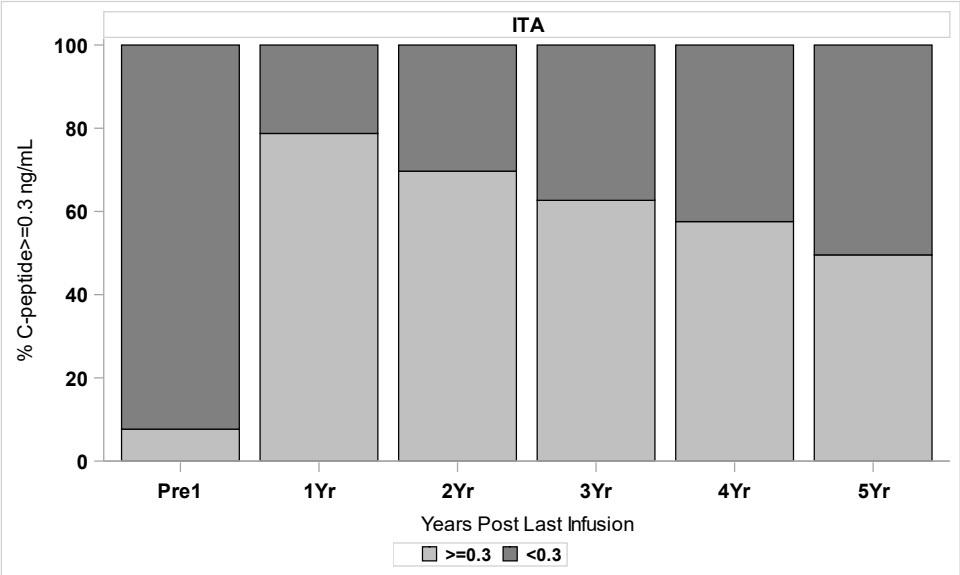


Exhibit 5-4A
Unadjusted Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion



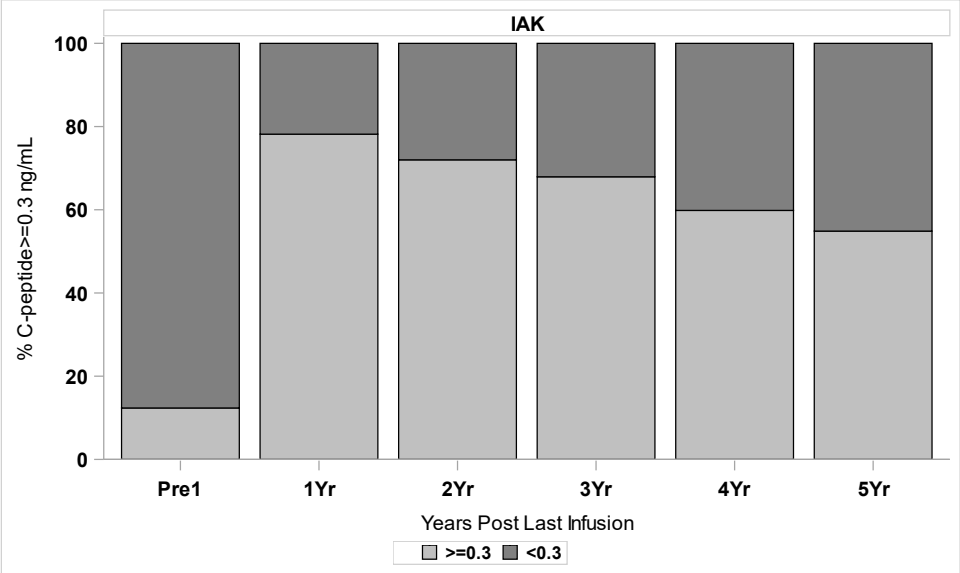
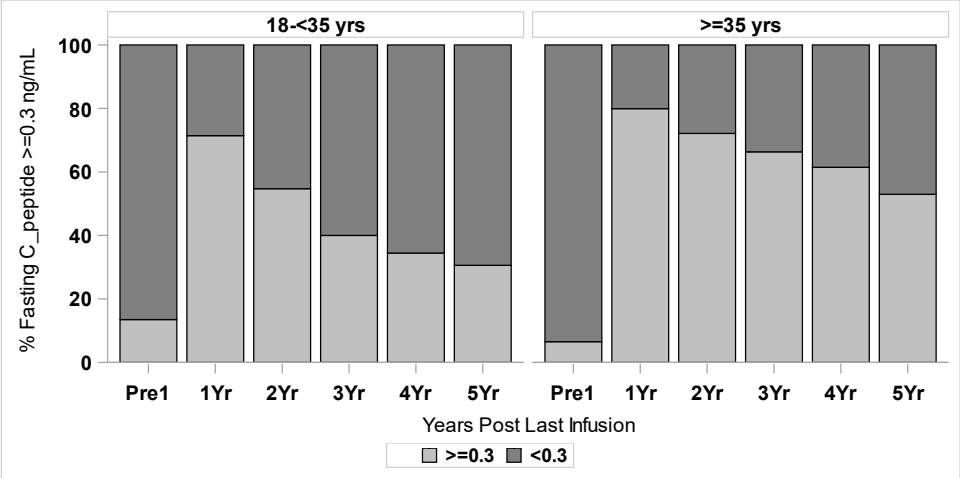
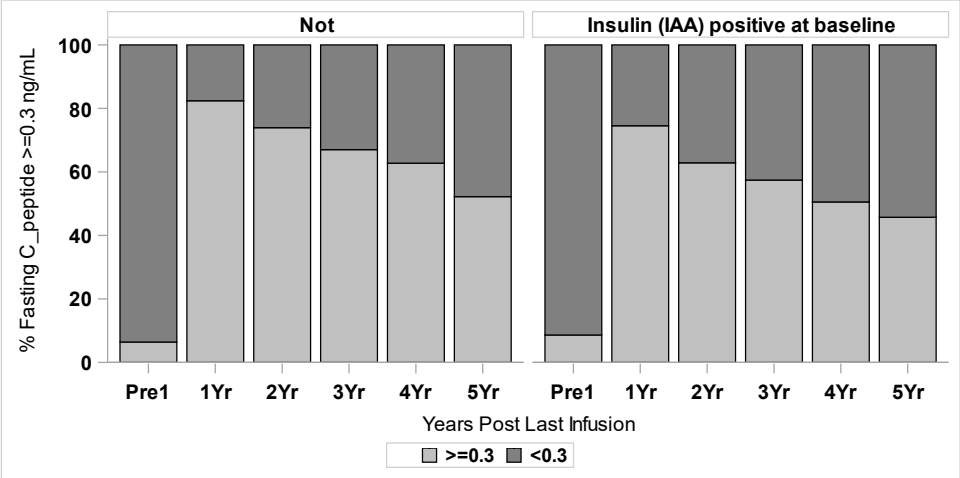


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Age (p=<.0001)



Baseline +insulin AAB (p=0.0095)



Baseline total bilirubin (p=0.0092)

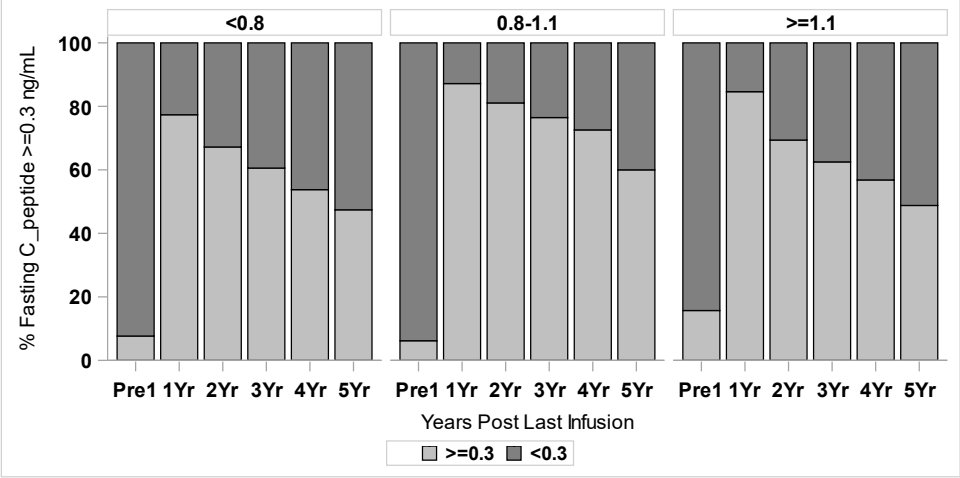
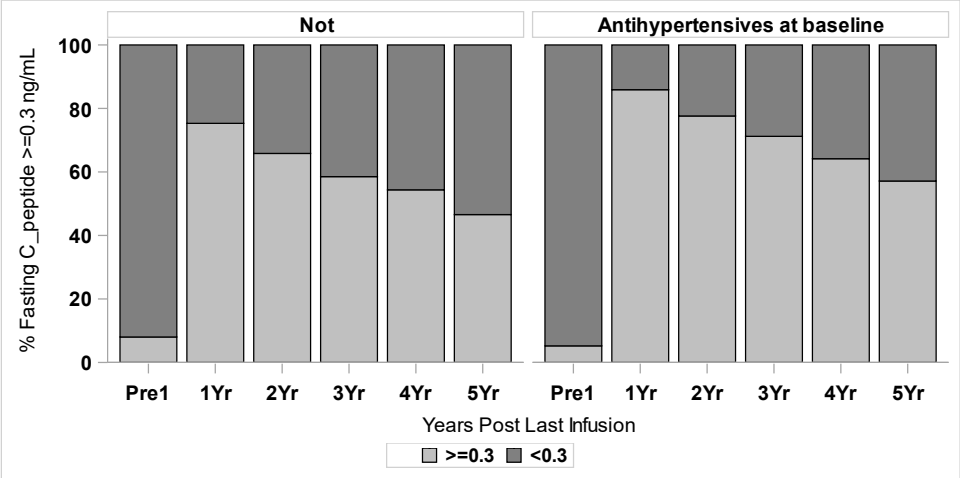
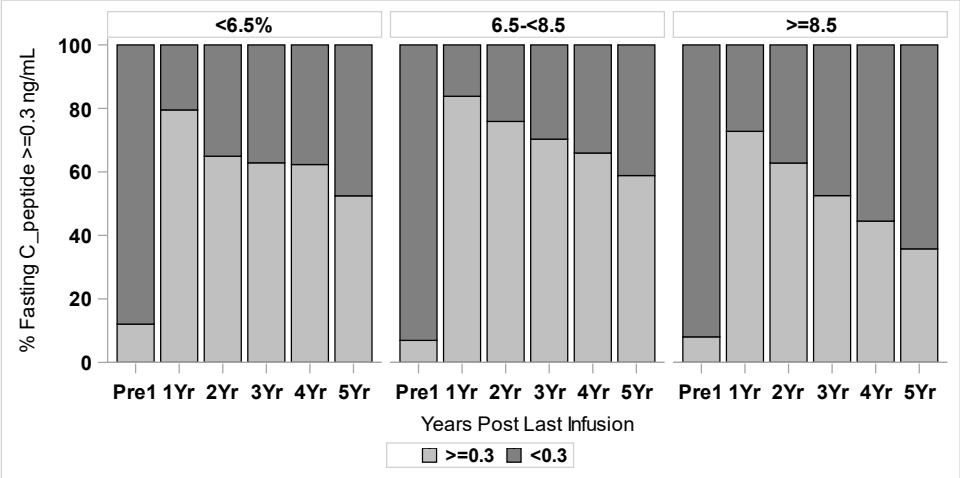


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Baseline BP meds (p=0.0010)



Baseline HbA1c (p=<.0001)



Baseline antilipidemics (p=0.0030)

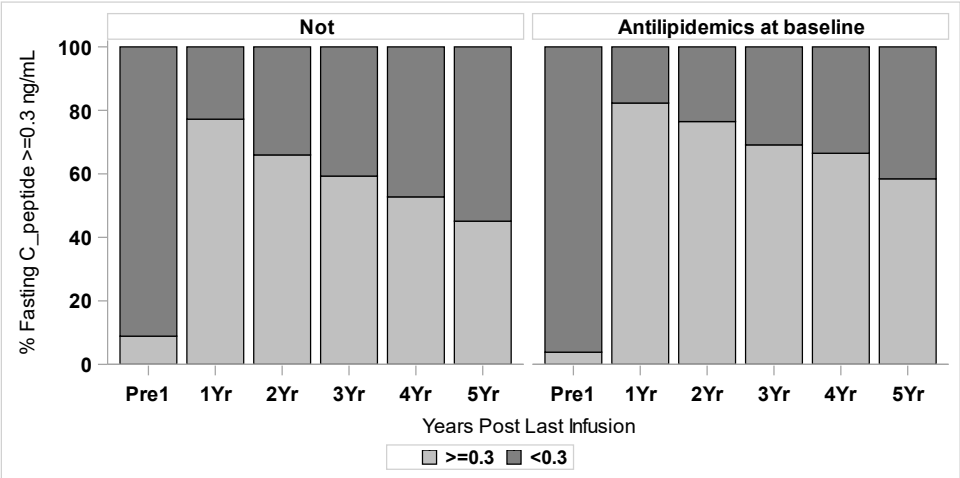
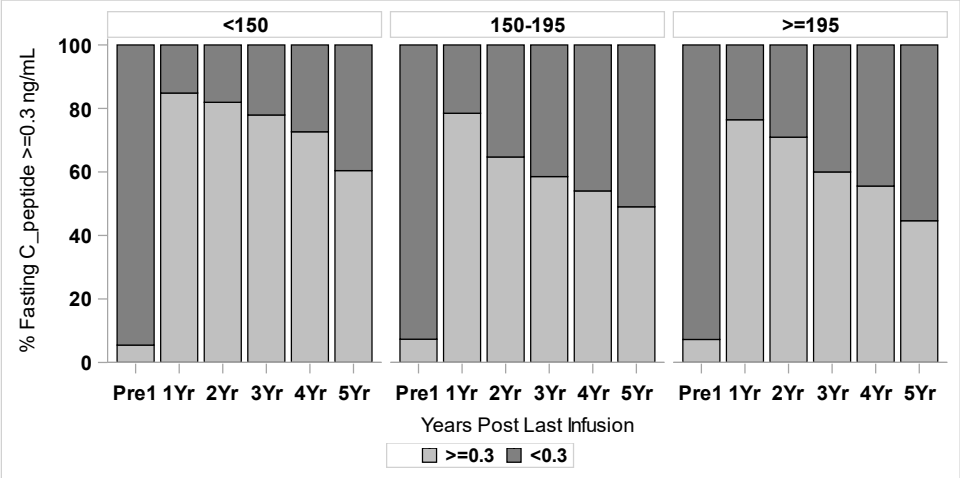
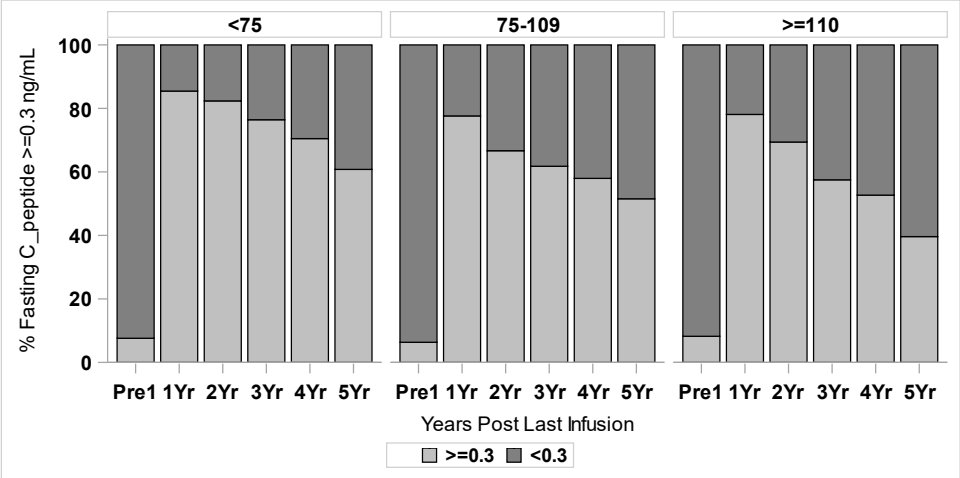


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Baseline total cholesterol (p=0.0003)



Baseline LDL (p=0.0013)



Calcineurin inhibitor (p=0.0005)

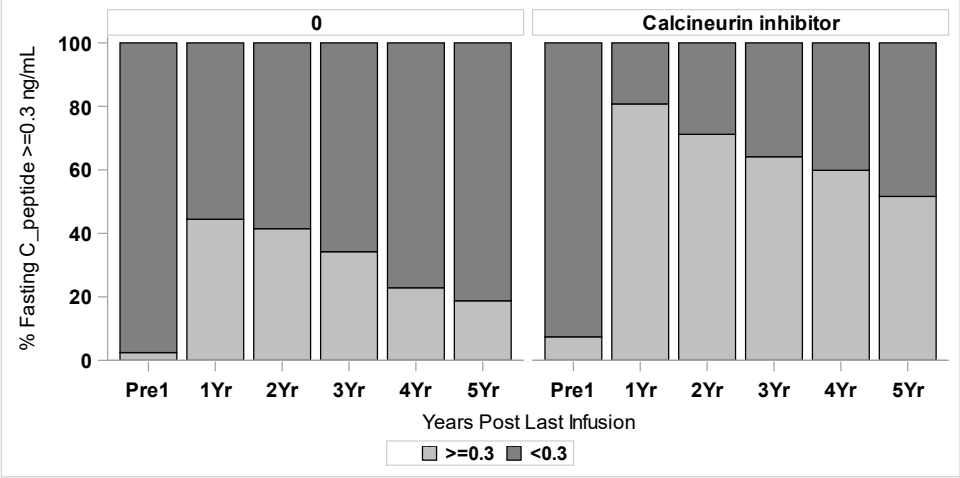
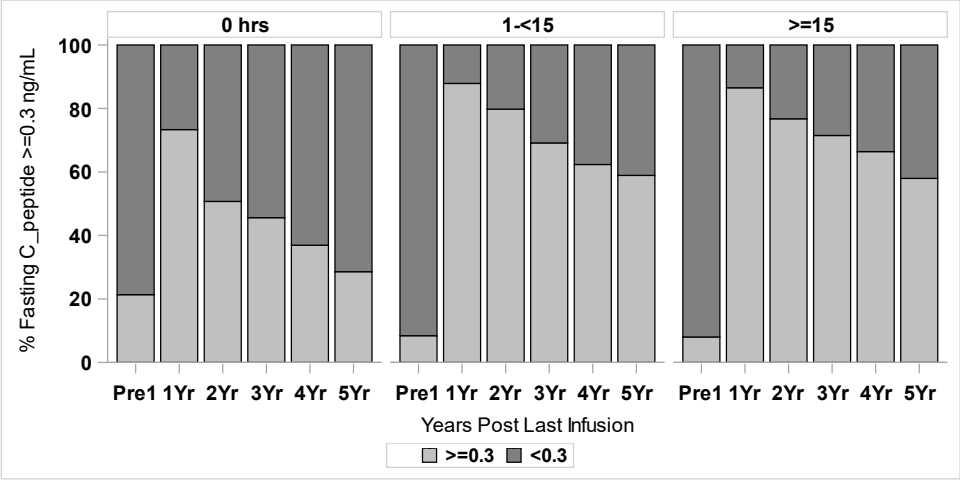
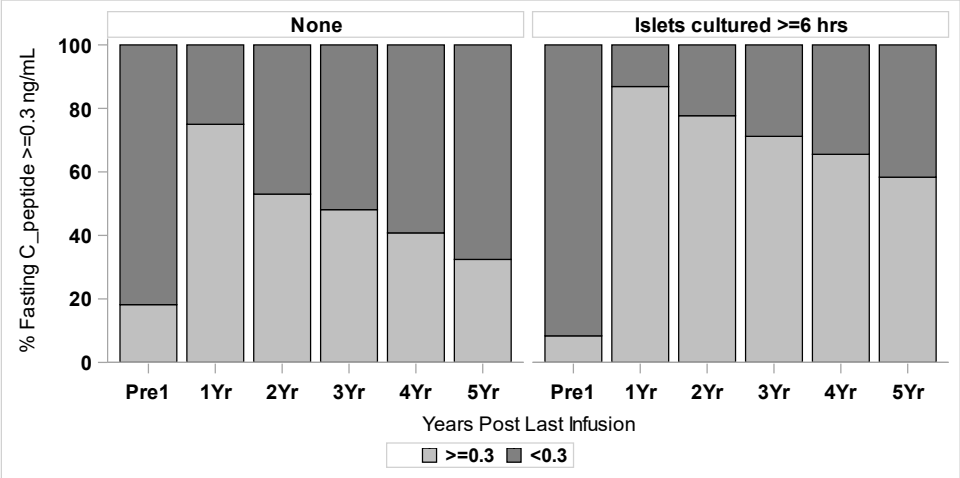


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Hours: cultured 0-6 included (p=0.0005)



Cultured >=6 hrs (p=0.0001)



Donor hx alcohol (p=0.0071)

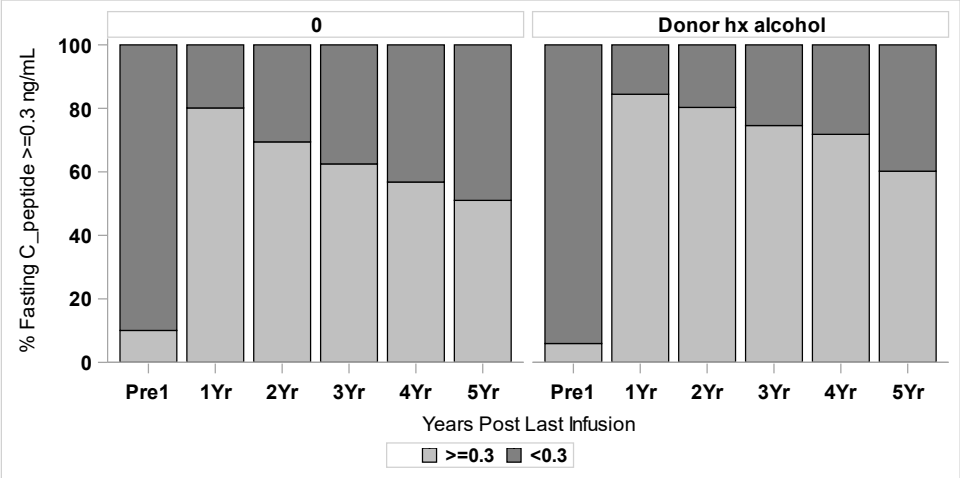
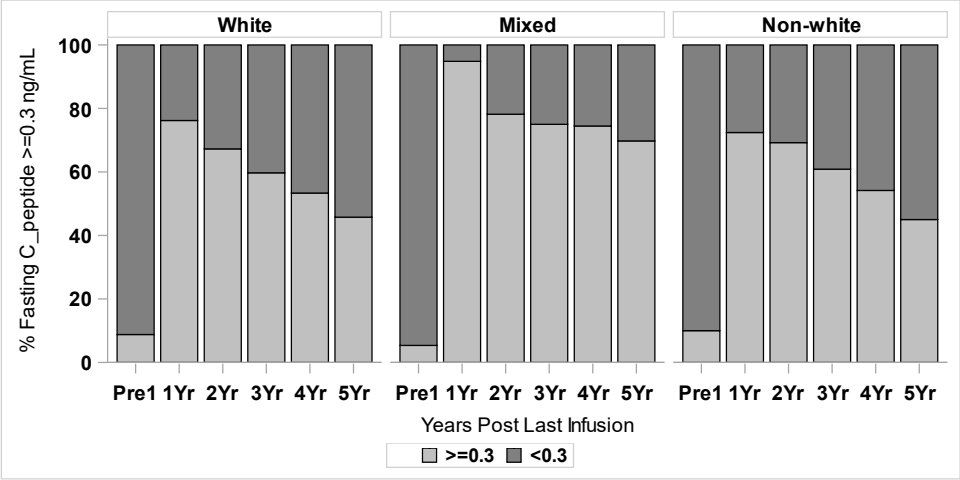
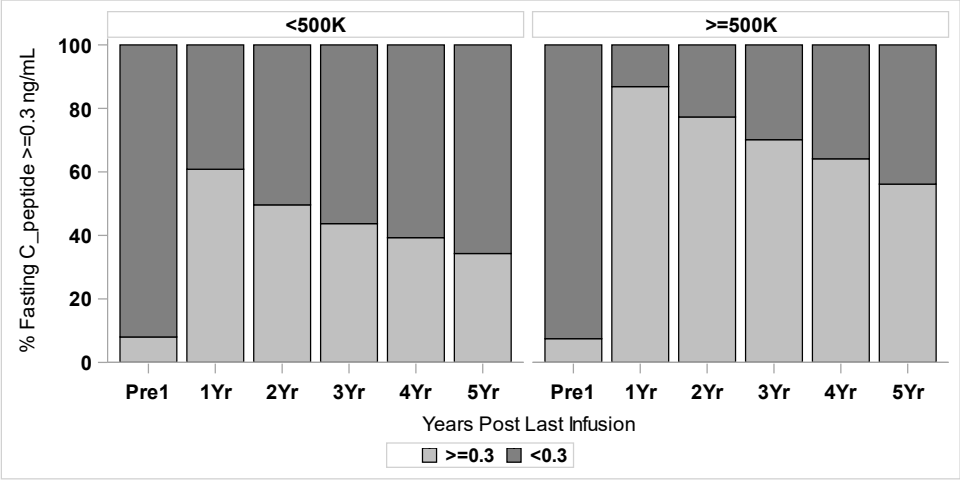


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Donor race (p=0.0012)



Islets IEQs all infusions (p=<.0001)



Islets IEQs/kg recipient (p=<.0001)

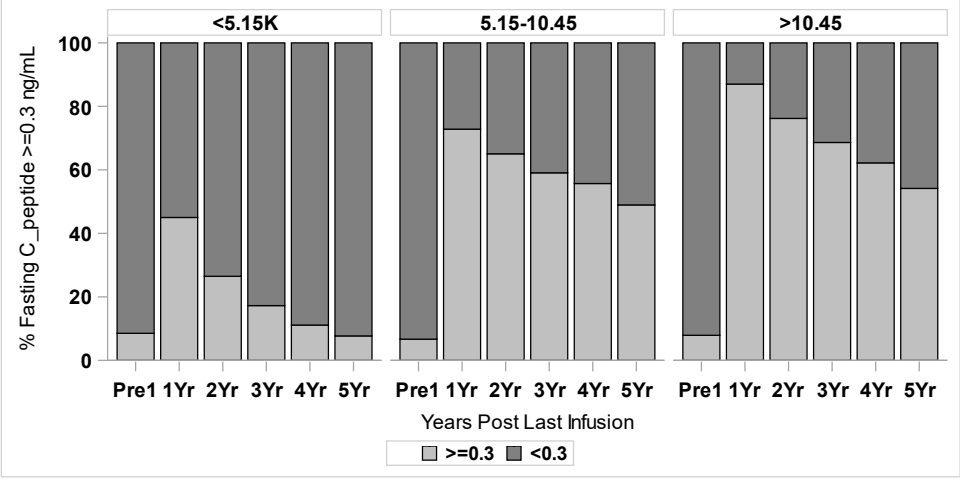
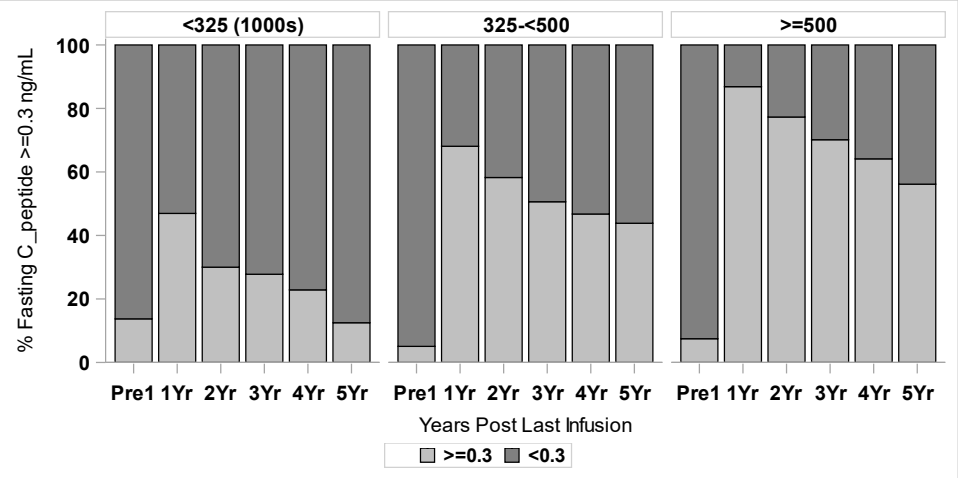
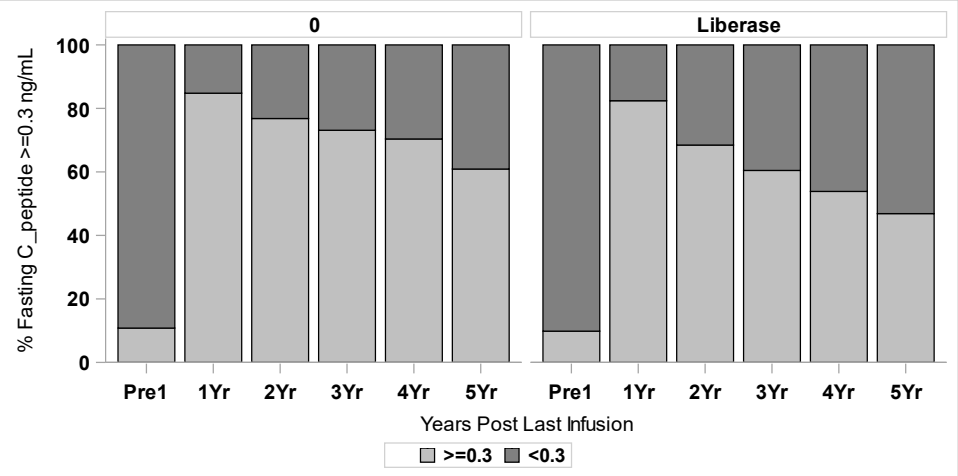


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Islets IEQs infused (p=<.0001)



Liberase (p=0.0053)



Maintenance combination (p=0.0005)

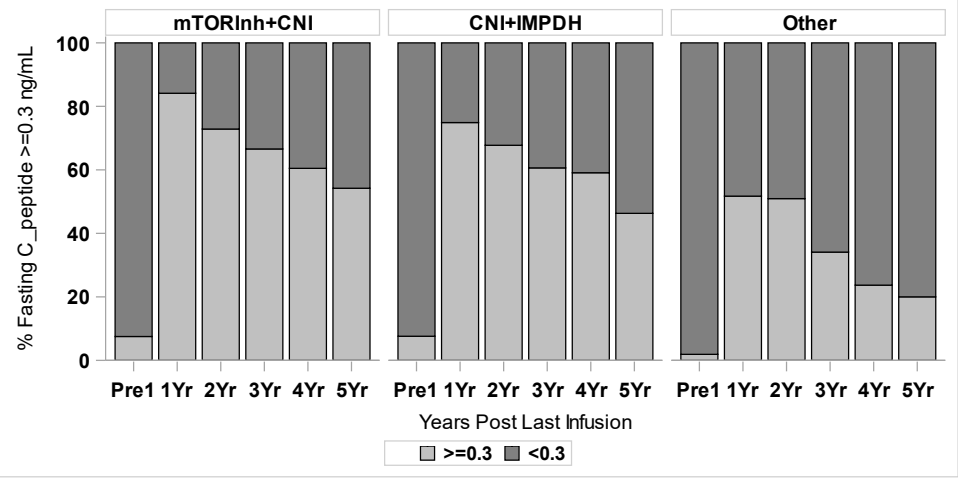
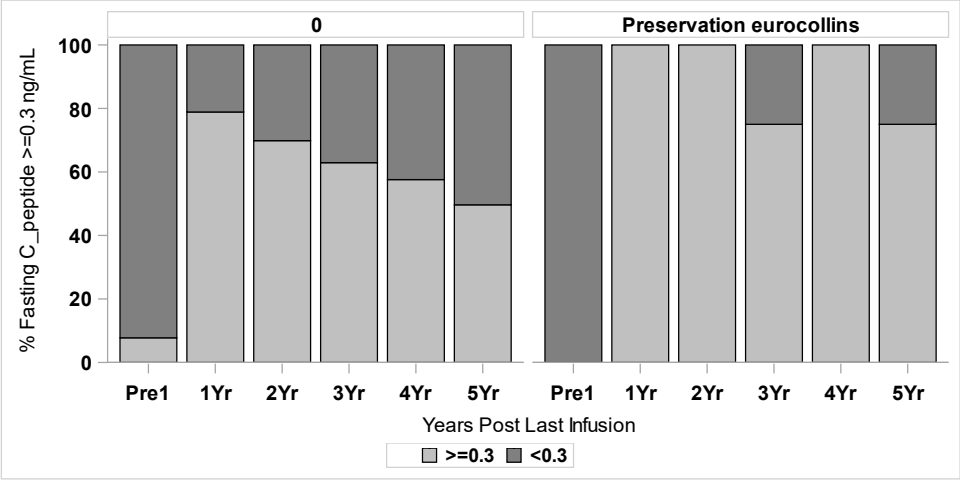
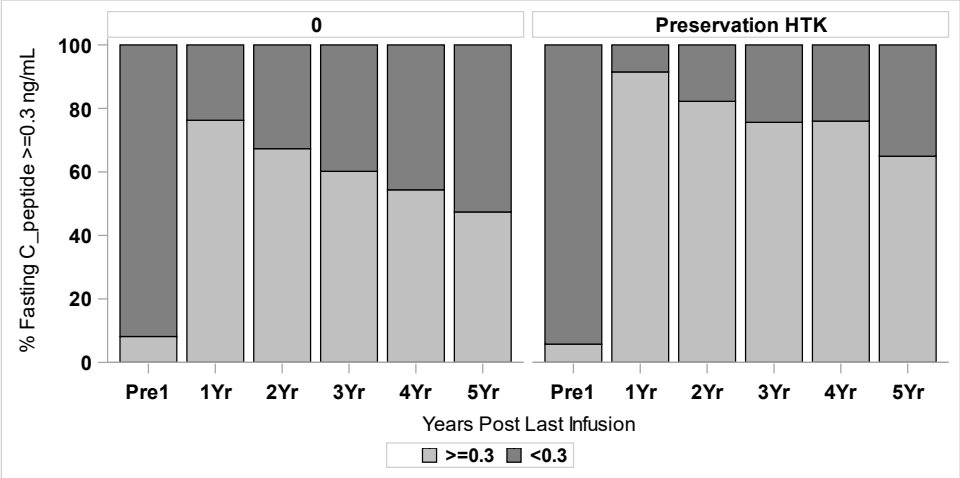


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

Eurocollins presrvation (p=<.0001)



HTK preservation (p=<.0001)



Thermolysin (p=<.0001)

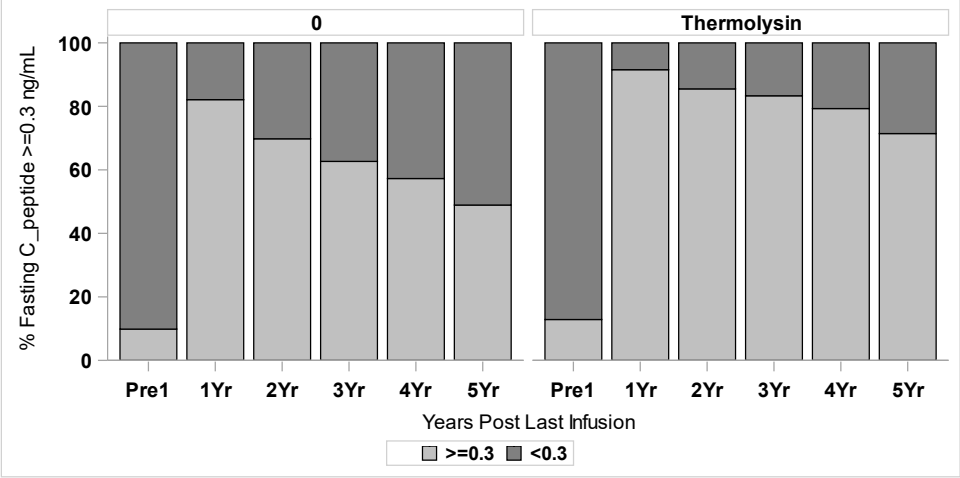
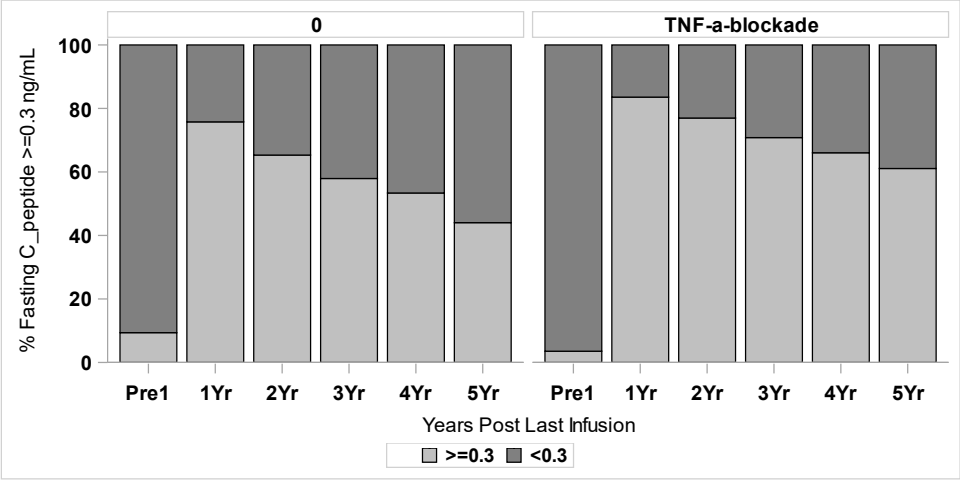
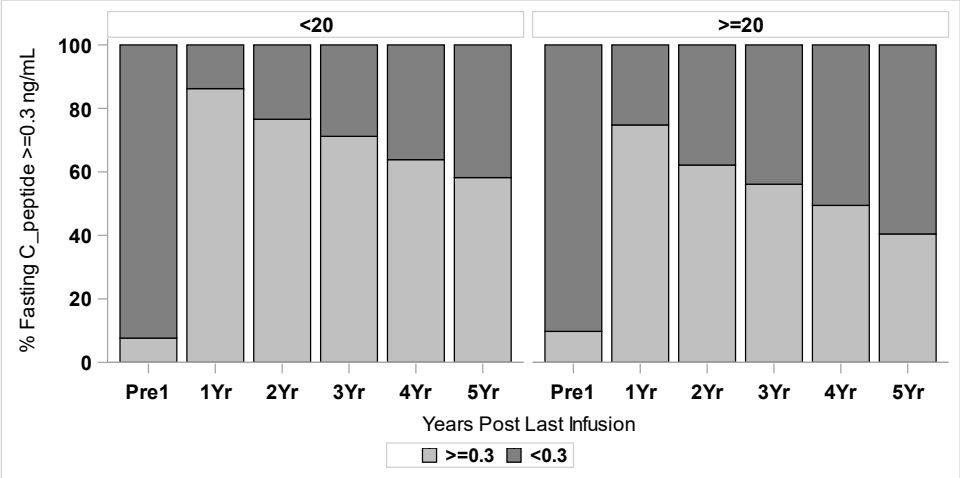


Exhibit 5-4B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among ITA Recipients

TNFa inhibitor (p=0.0001)



Islets total endotoxin (p=0.0033)



Total infusions (p=<.0001)

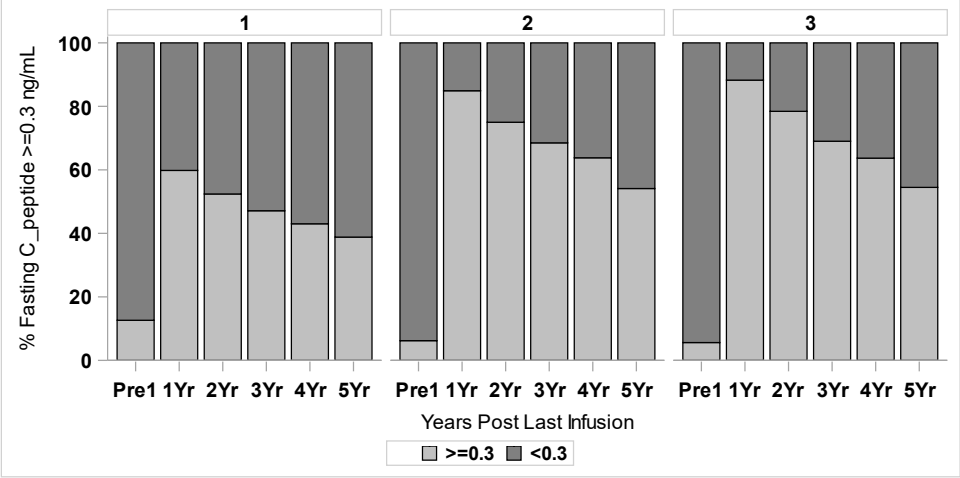
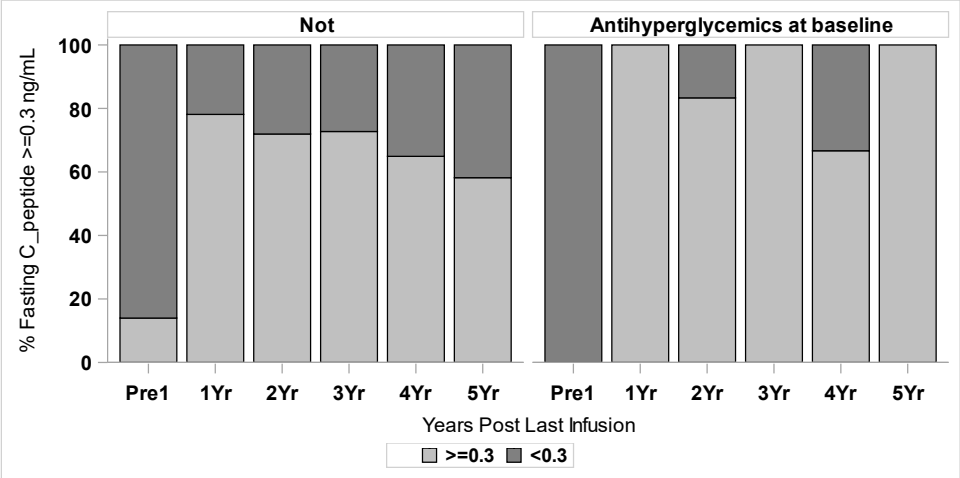
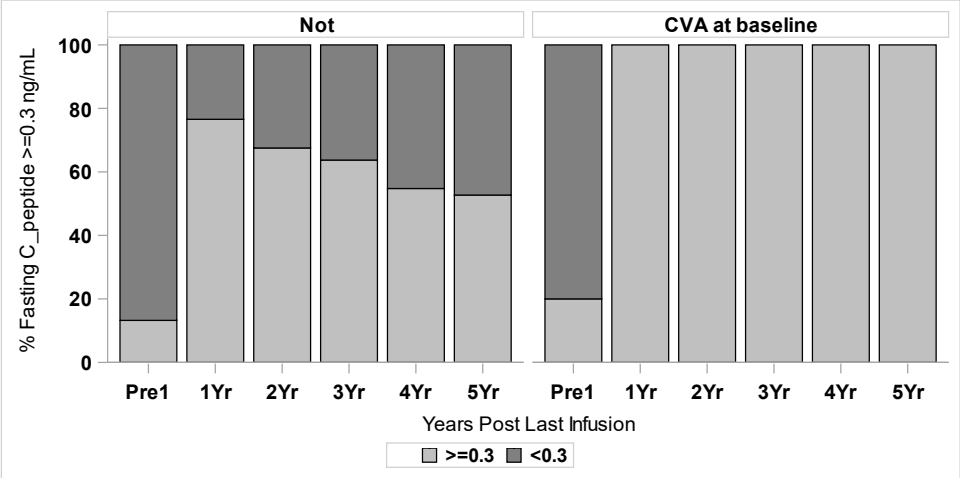


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

Baseline antihyperglycemics (p=0.0020)



Baseline CVA (p=<.0001)



Baseline +GAD (p=0.0001)

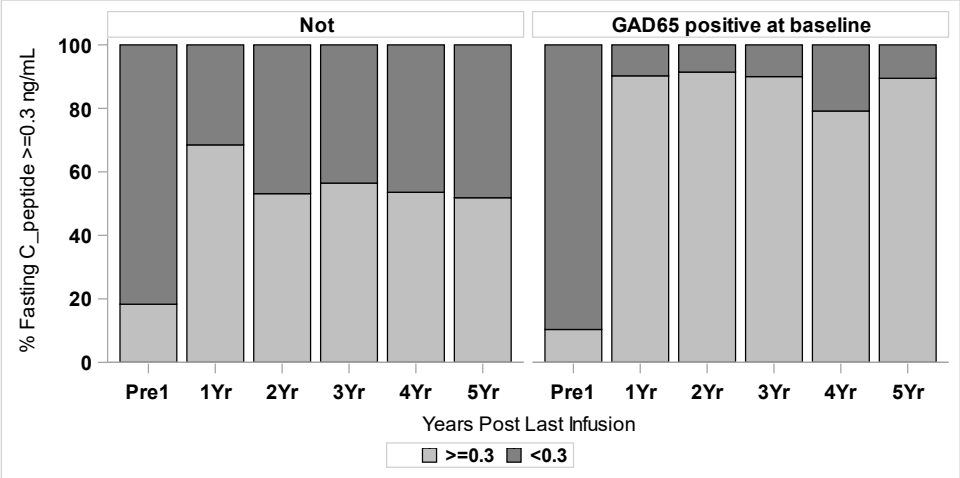
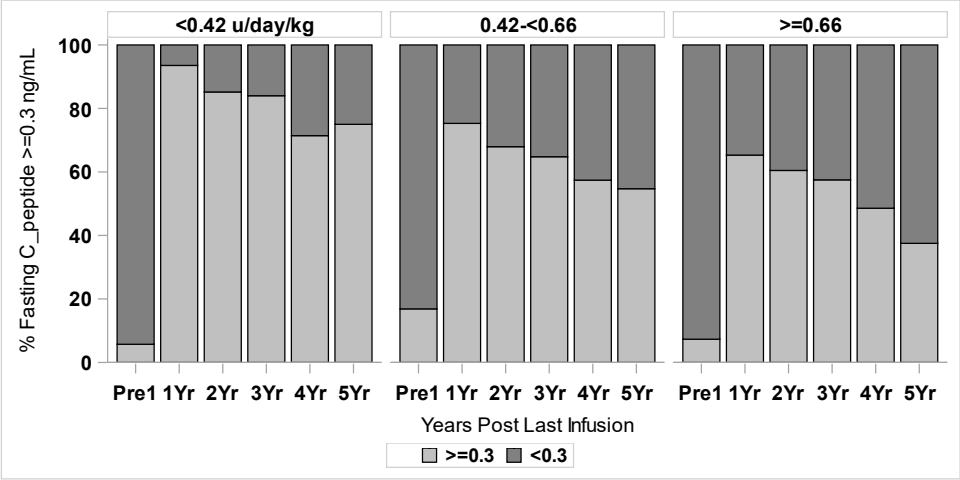
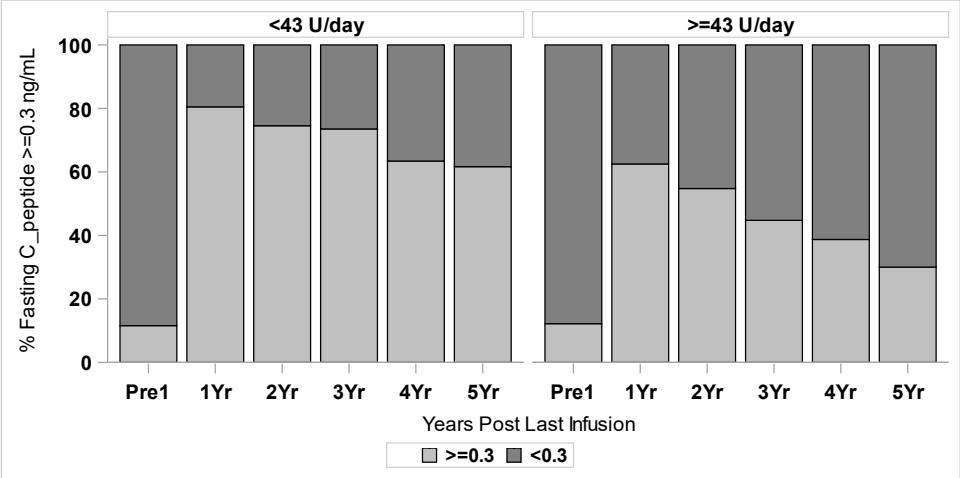


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

Baseline insulin (U/kg/day) (p=0.0073)



Baseline insulin (U/day) (p=0.0091)



Baseline antilipidemics (p=0.0047)

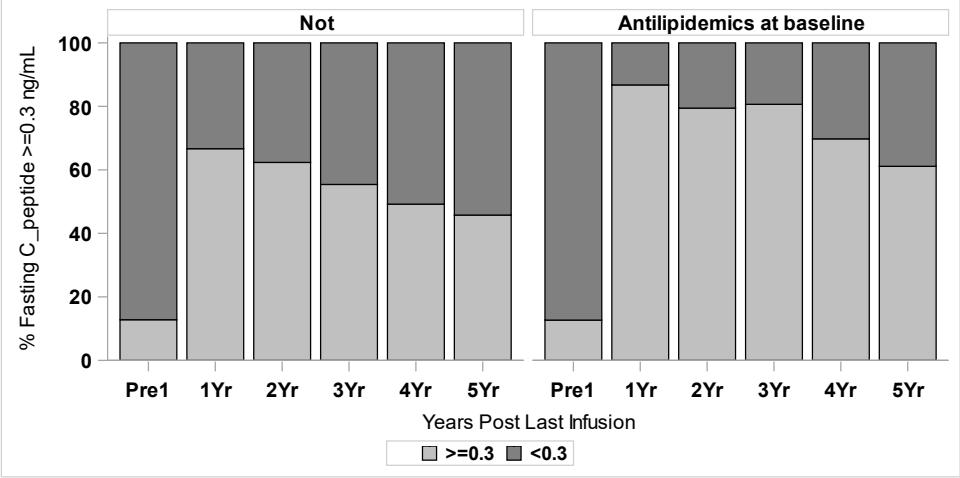
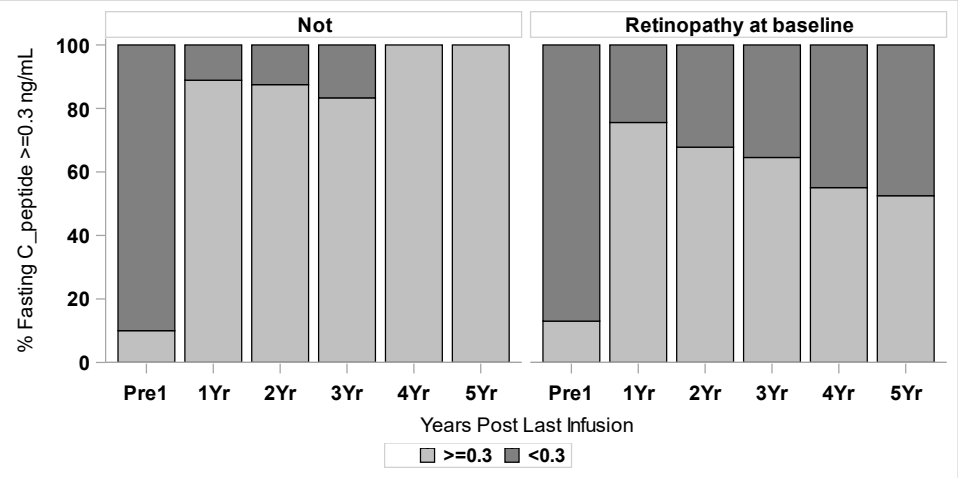
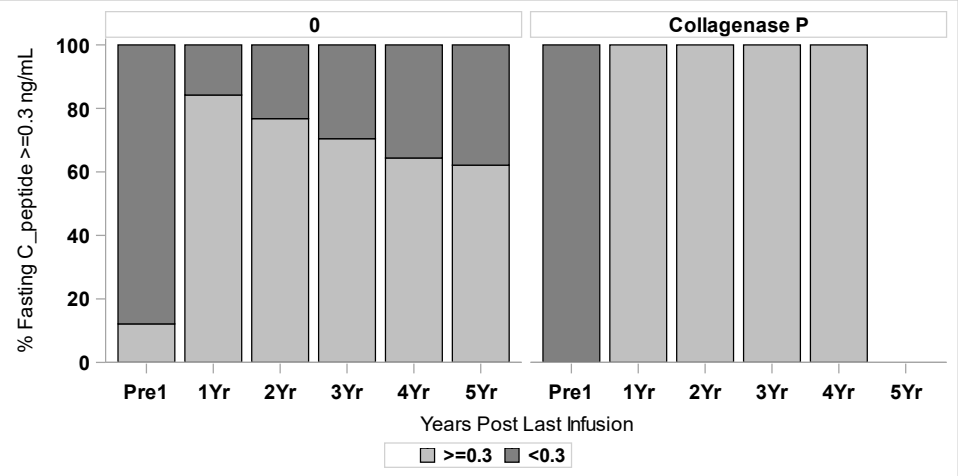


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

Baseline retinopathy (p=0.0032)



Collagenase P (p=<.0001)



Era (p=<.0001)

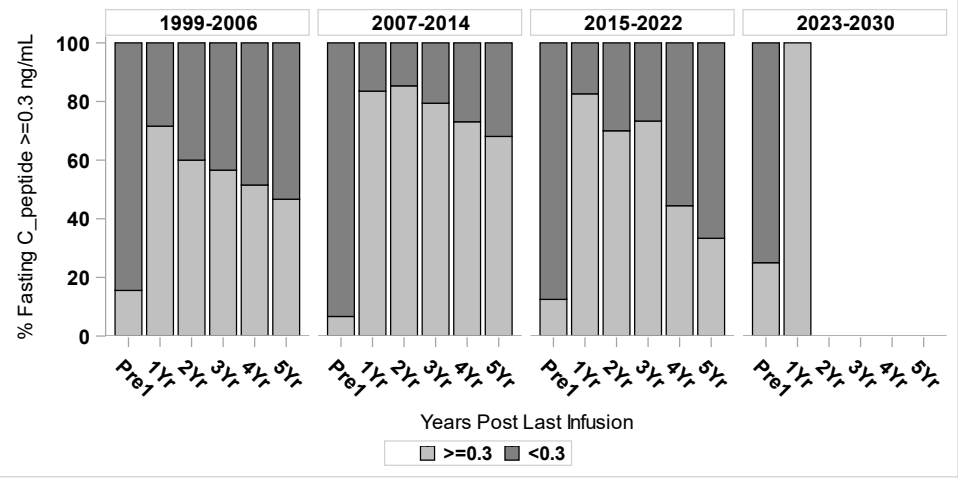
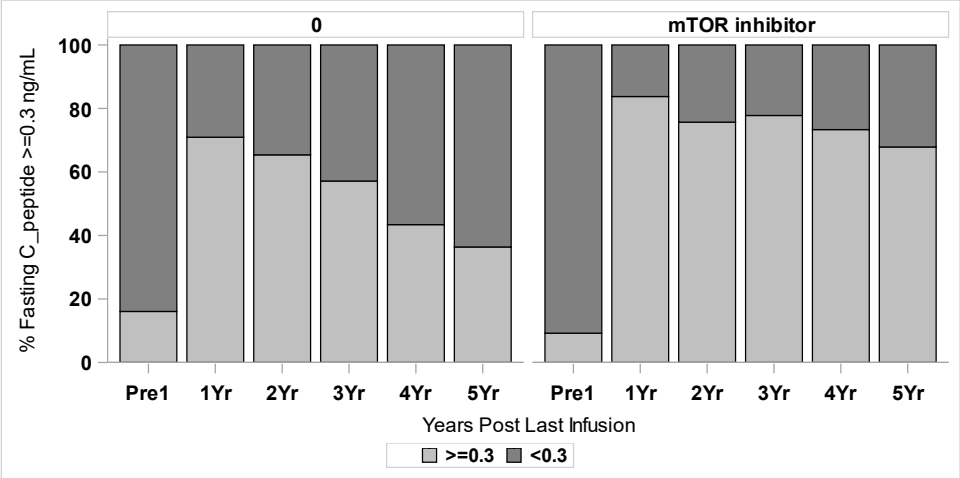
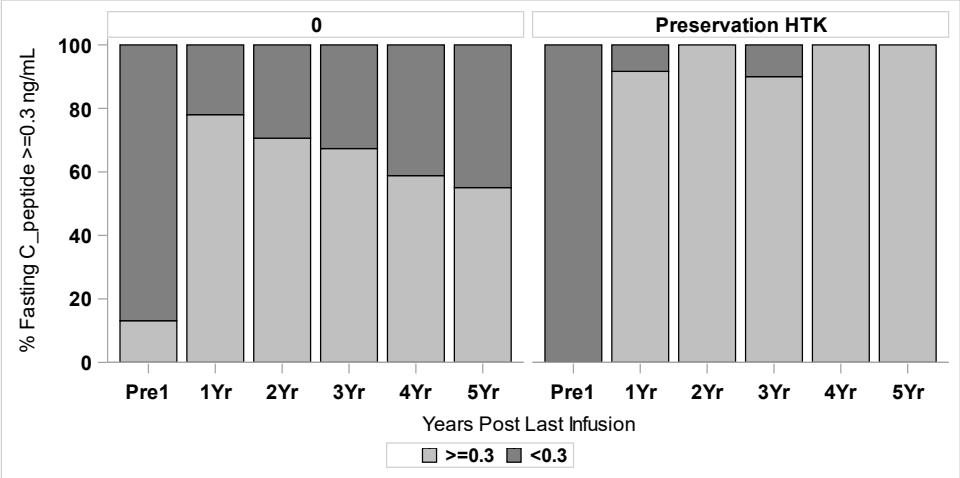


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

mTOR inhibitor (p=0.0077)



HTK preservation (p=<.0001)



Donor serum creatinine (p=0.0051)

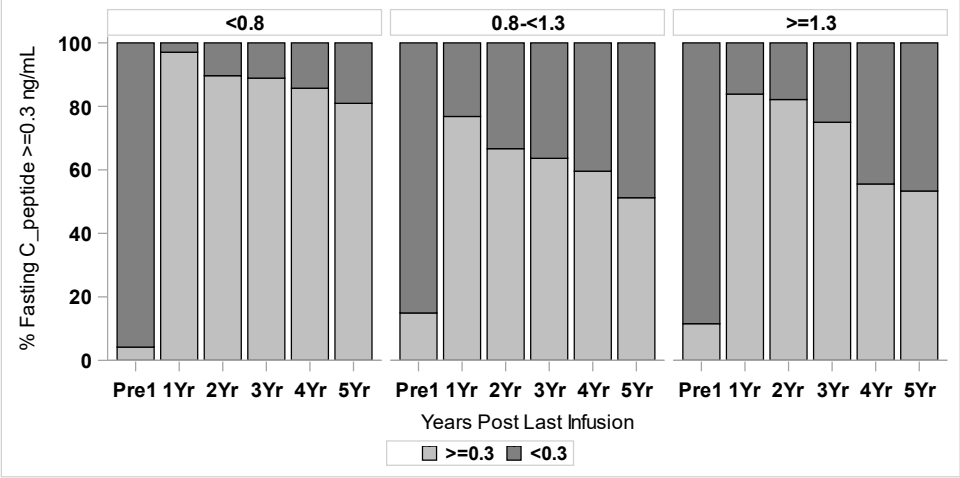


Exhibit 5-4C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting C-peptide>=0.3 ng/mL Post Last Infusion among IAK Recipients

Total infusions (p=<.0001)

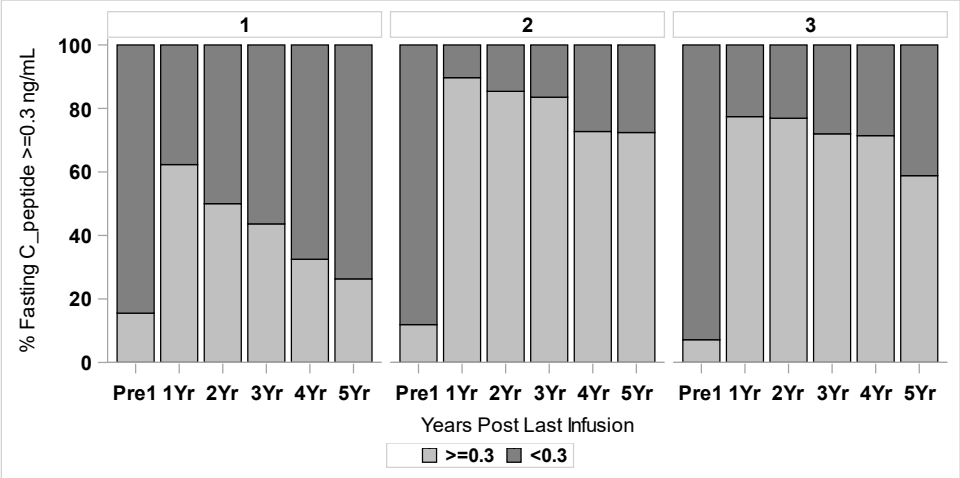
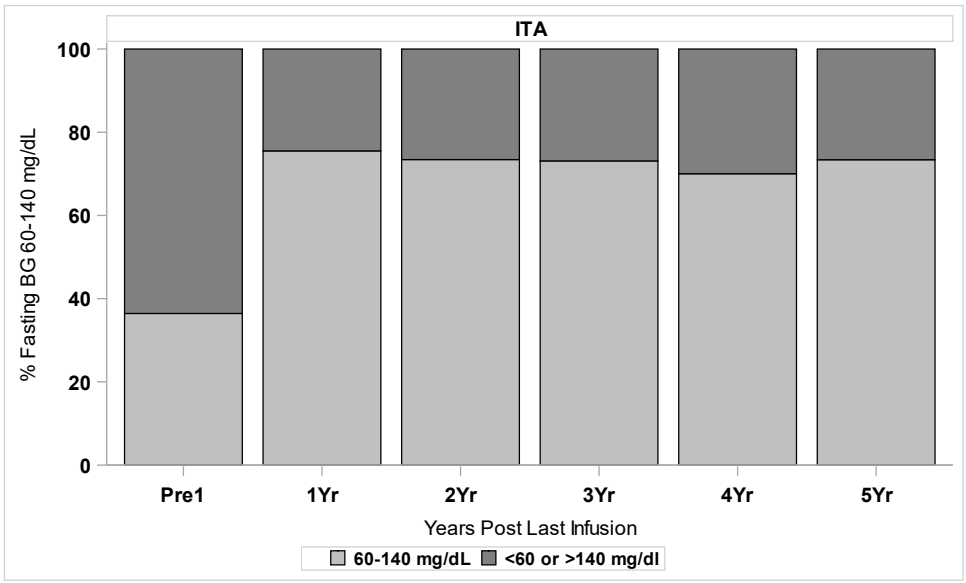


Exhibit 5-5A
Unadjusted Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion



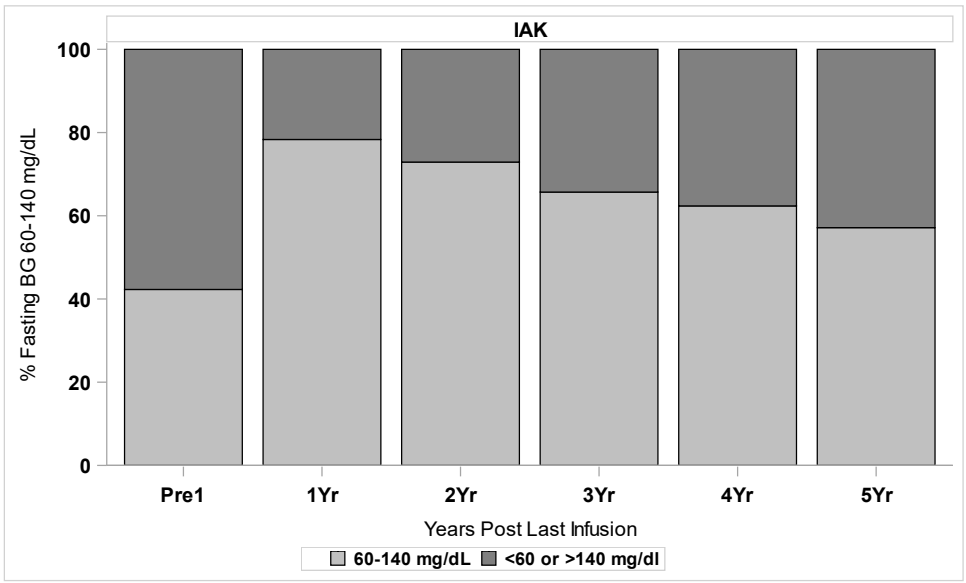
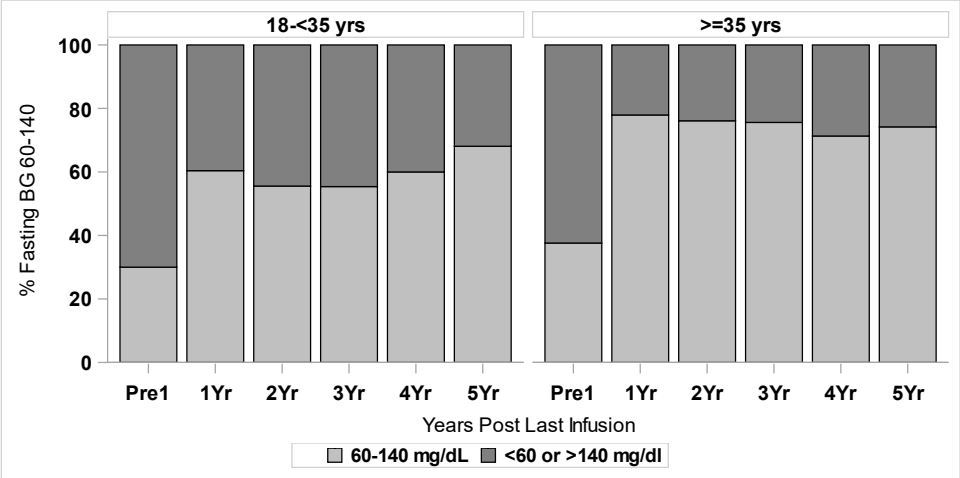
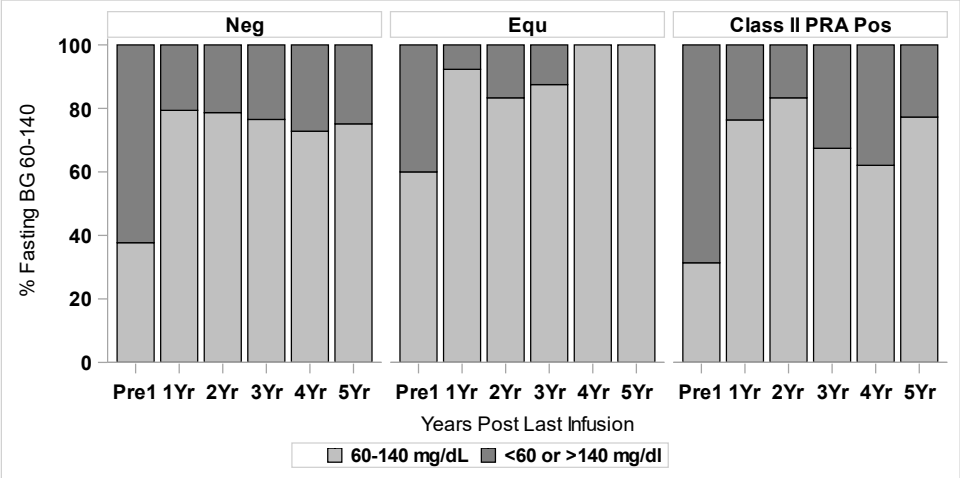


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

Age (p=0.0003)



Baseline Class II PRA (p=0.0025)



Baseline autonomic neuropathy (p=0.0024)

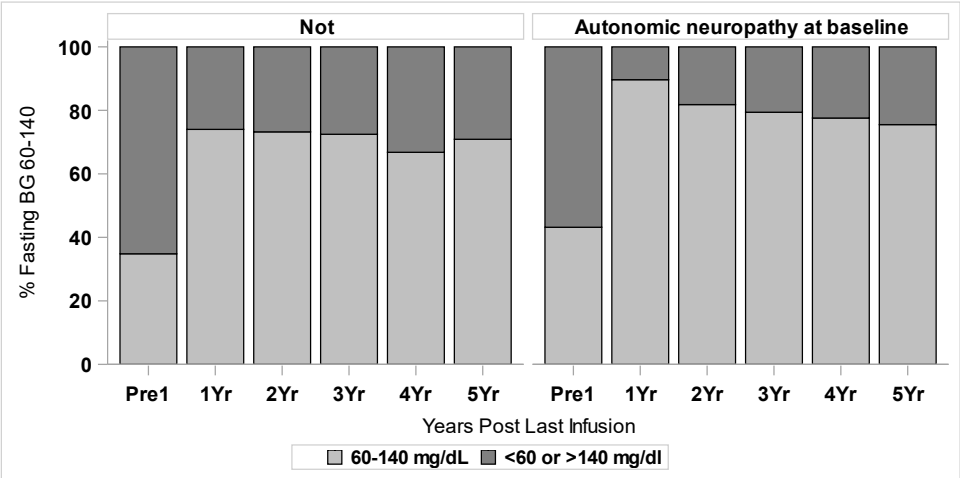
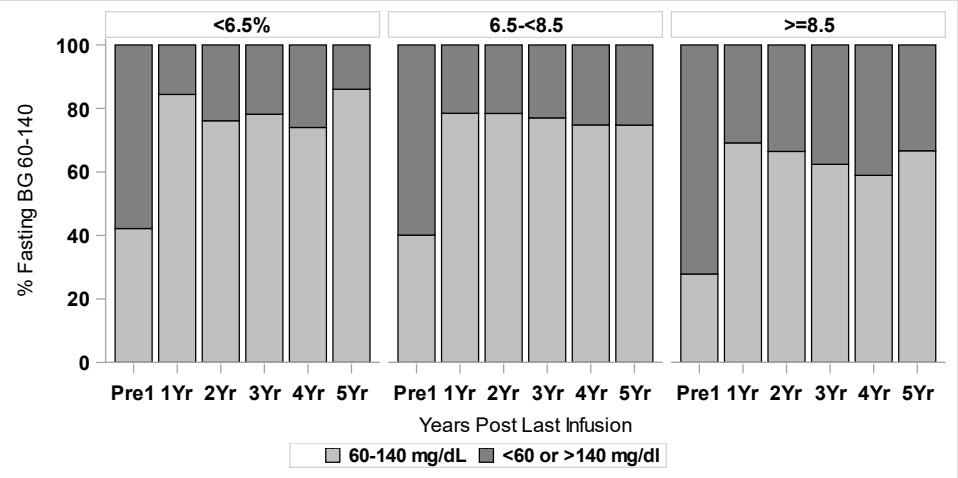
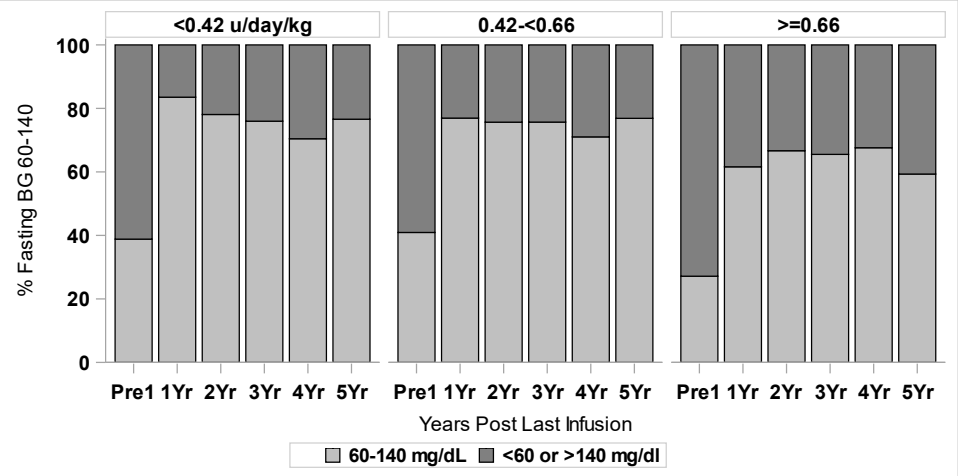


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

Baseline HbA1c (p=0.0002)



Baseline insulin (U/kg/day) (p=0.0052)



Baseline insulin (U/day) (p=0.0002)

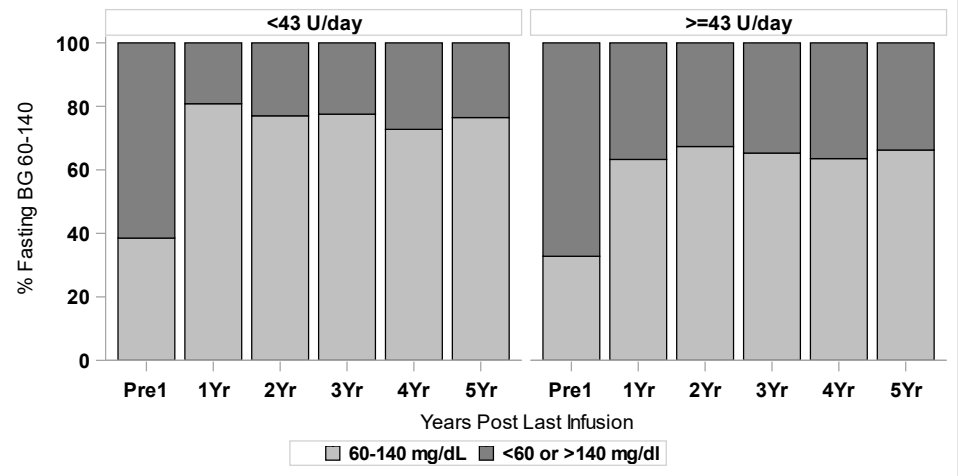
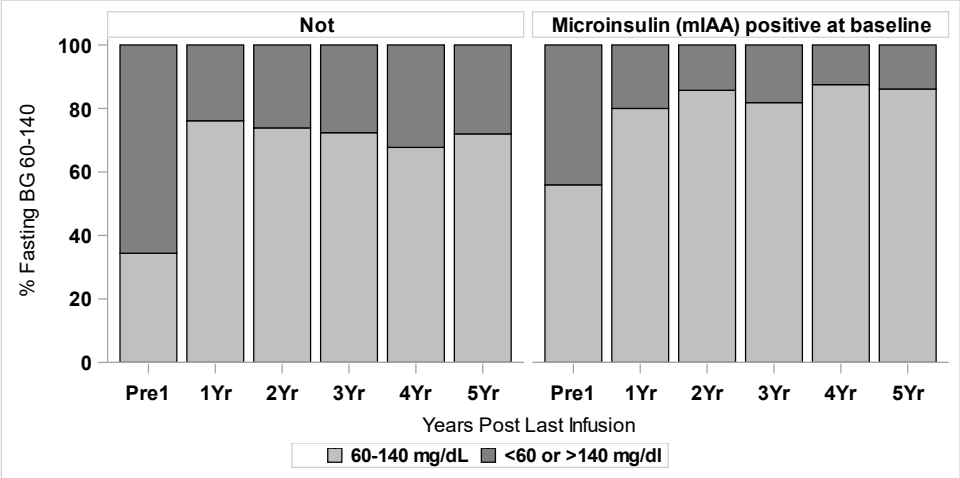
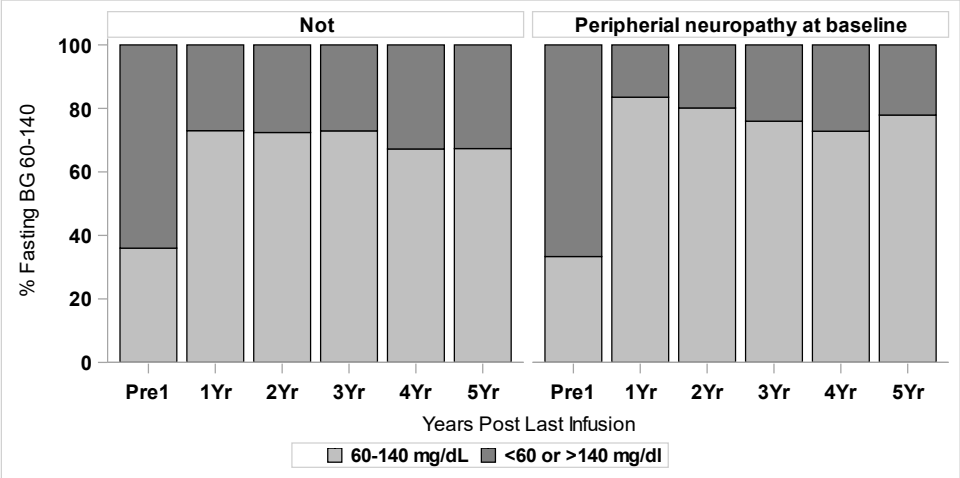


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

Baseline +microinsulin AAB (p=0.0017)



Baseline peripheral neuropathy (p=0.0073)



Baseline smoker (p=0.0056)

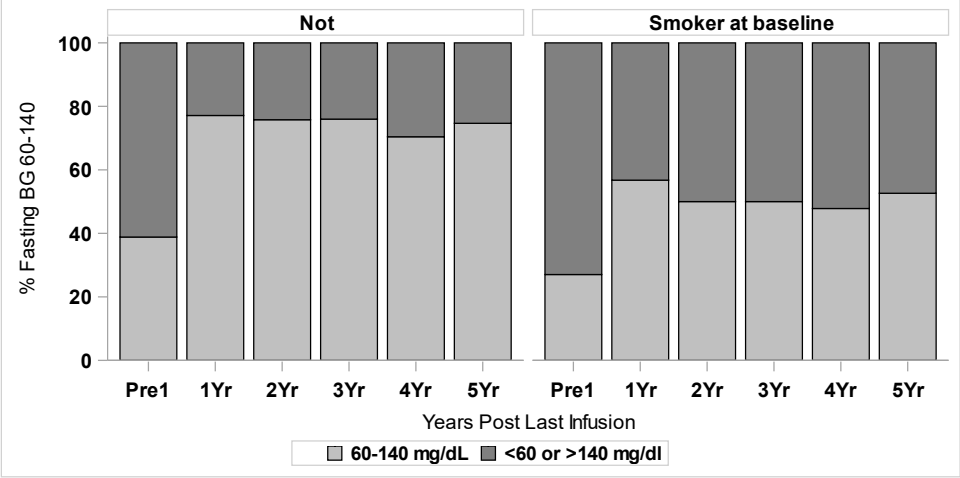
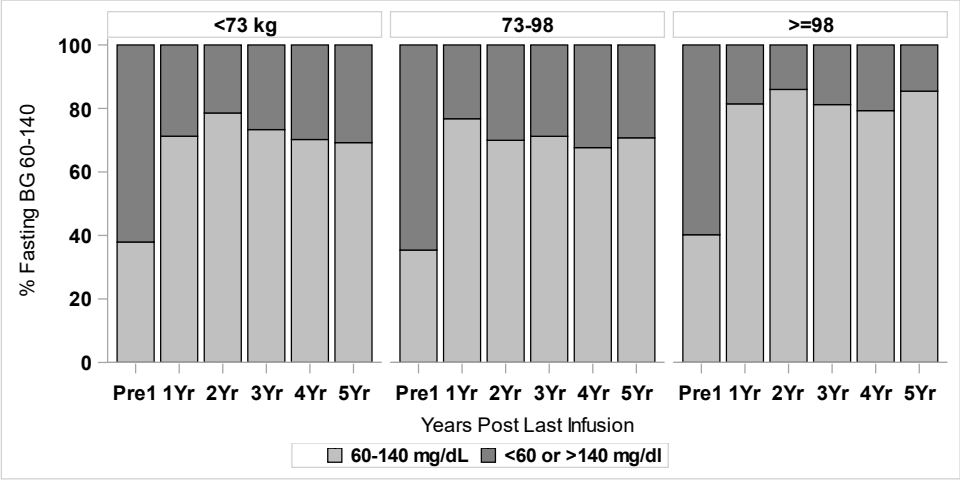
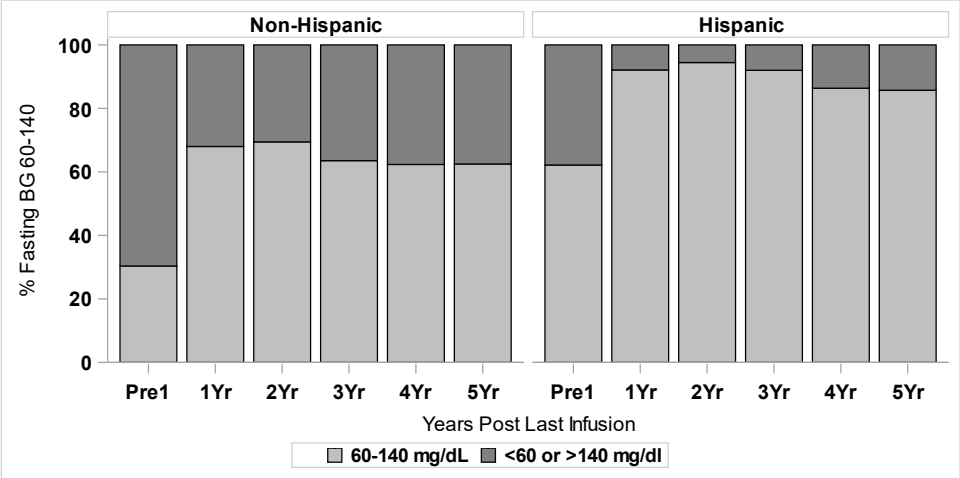


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

Donor weight (kg) (p=<.0001)



Donor Hispanic (p=<.0001)



Donor race (p=0.0059)

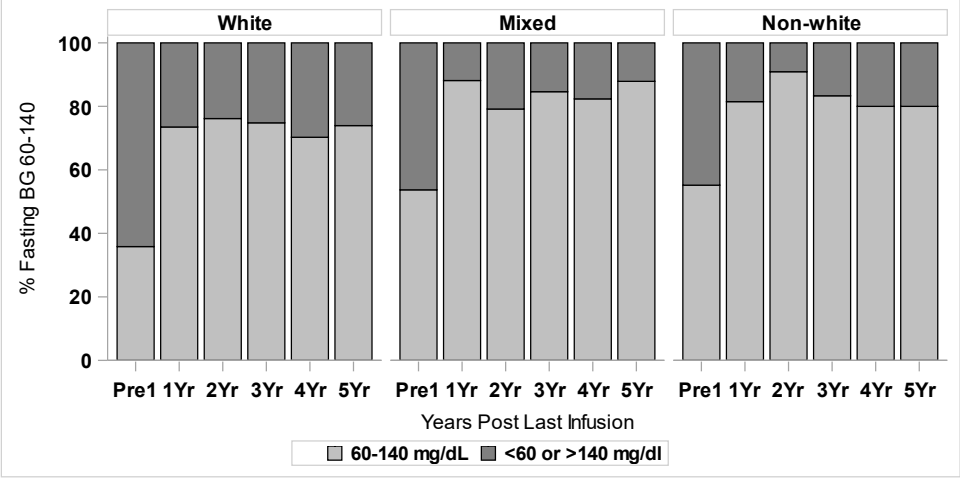
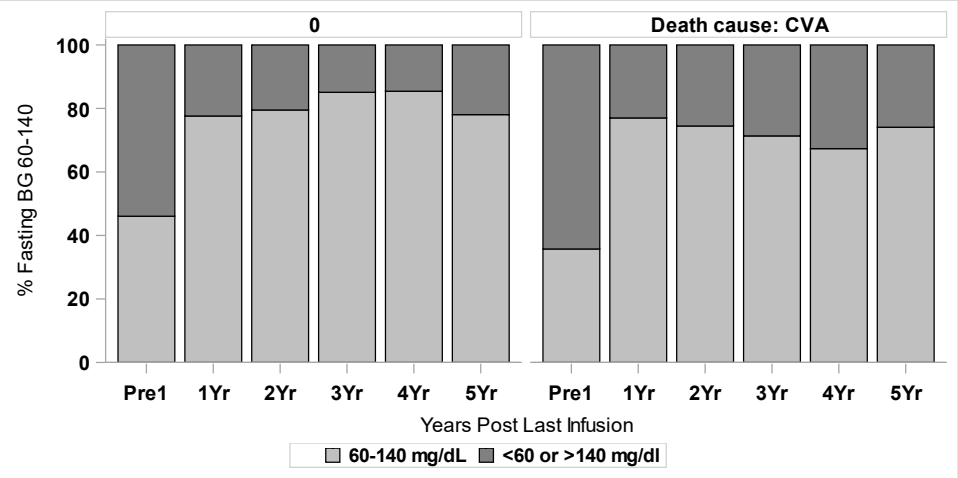
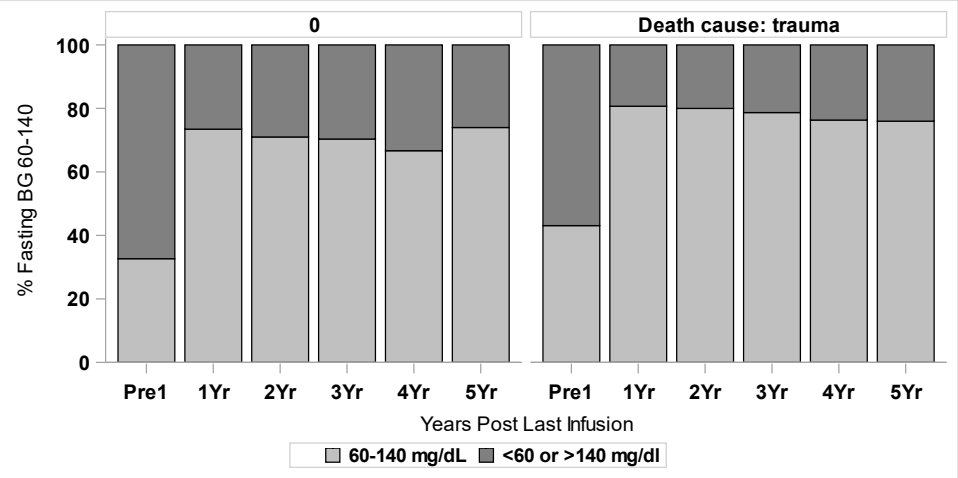


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

CVA death (p=0.0039)



Trauma death (p=0.0029)



Hours: Death to cross-clamp (p=0.0015)

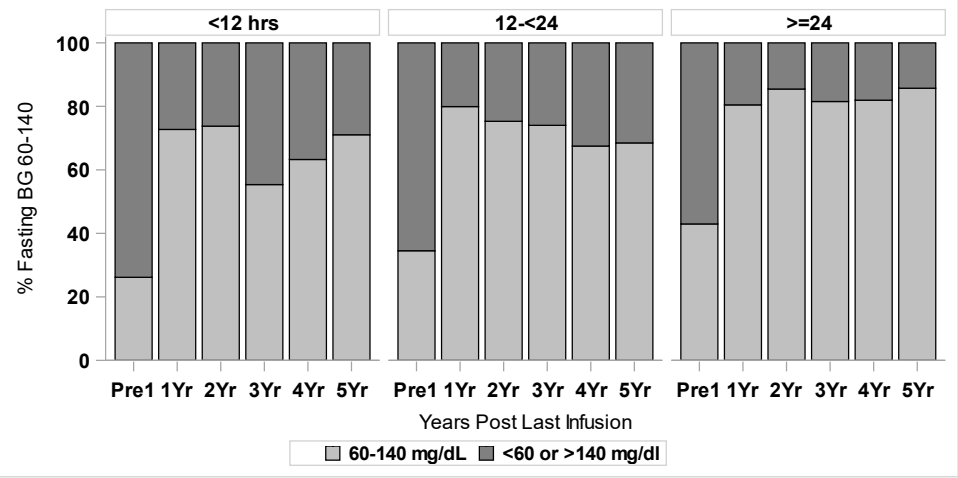
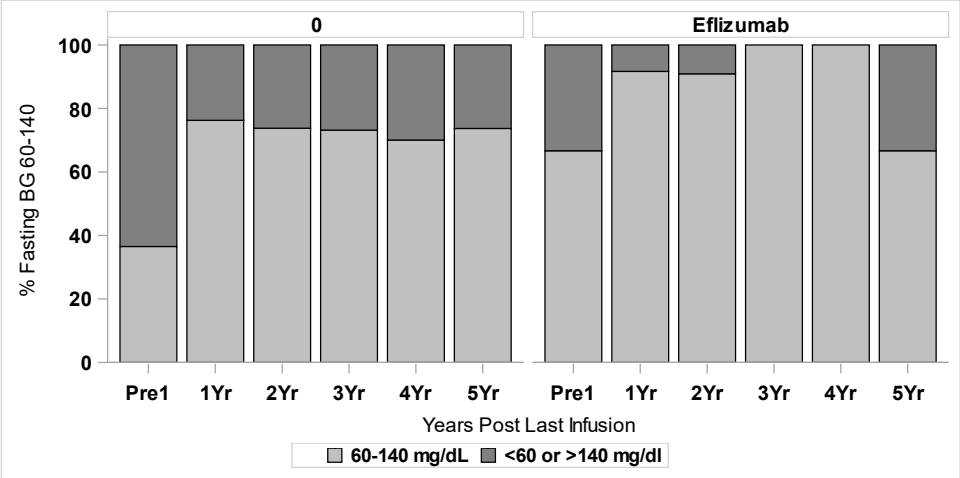
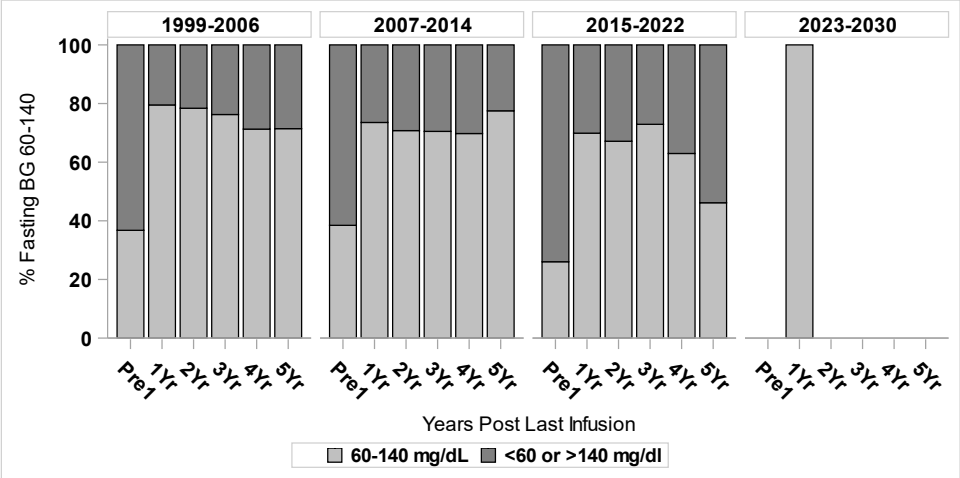


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

Eflizumab (p=<.0001)



Era (p=<.0001)



IL1-receptor antagonist (IL1R/DSG) (p=0.0005)

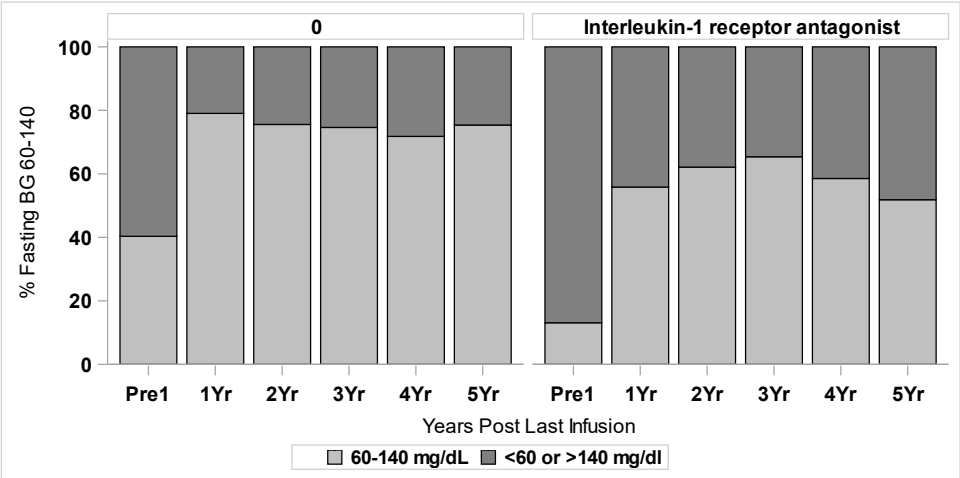
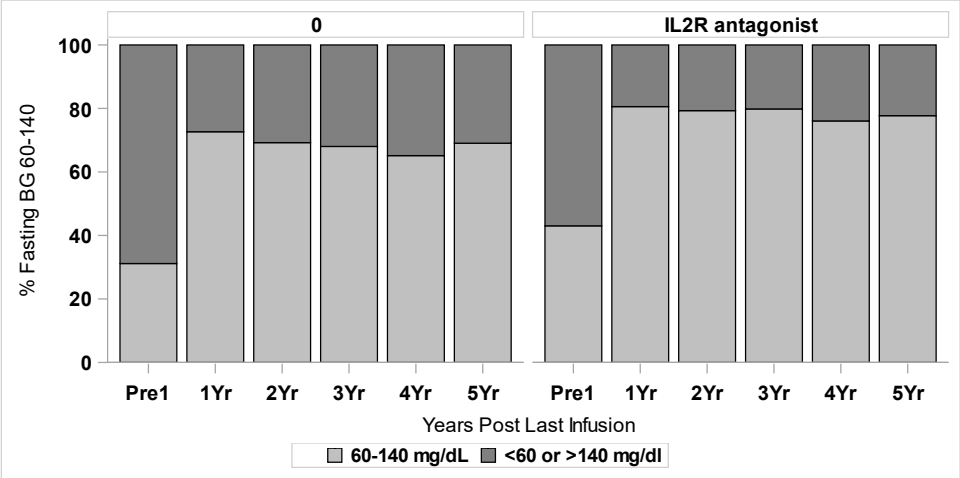
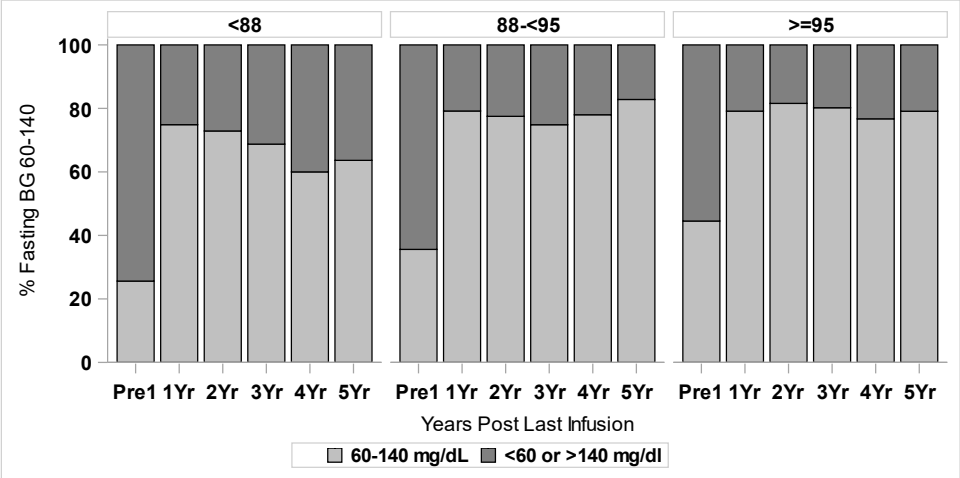


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

IL2RA inhibition (p=<.0001)



Islets viability (%) (p=0.0053)



Immunoglobulin (IVIG) (p=<.0001)

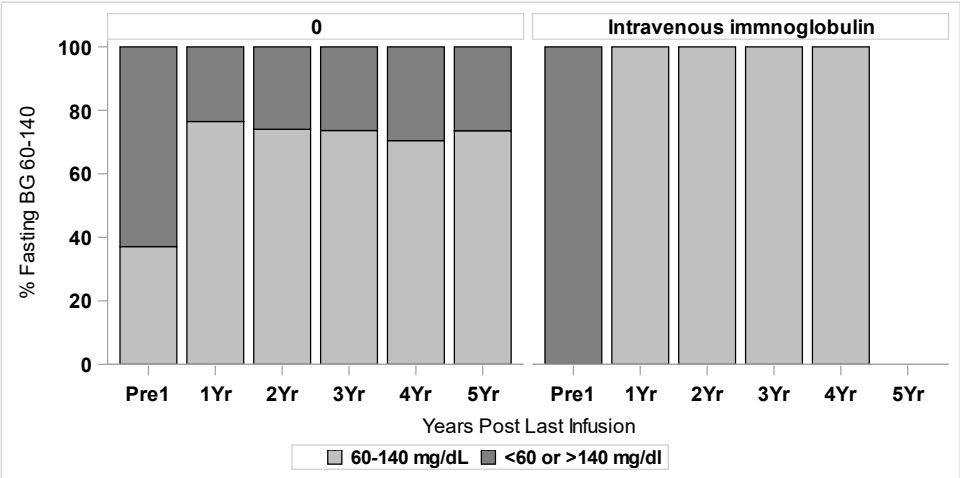
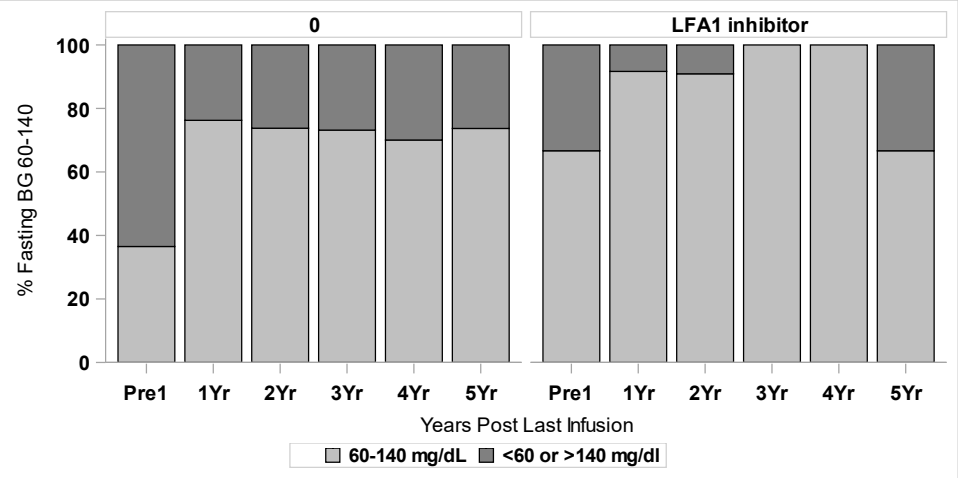
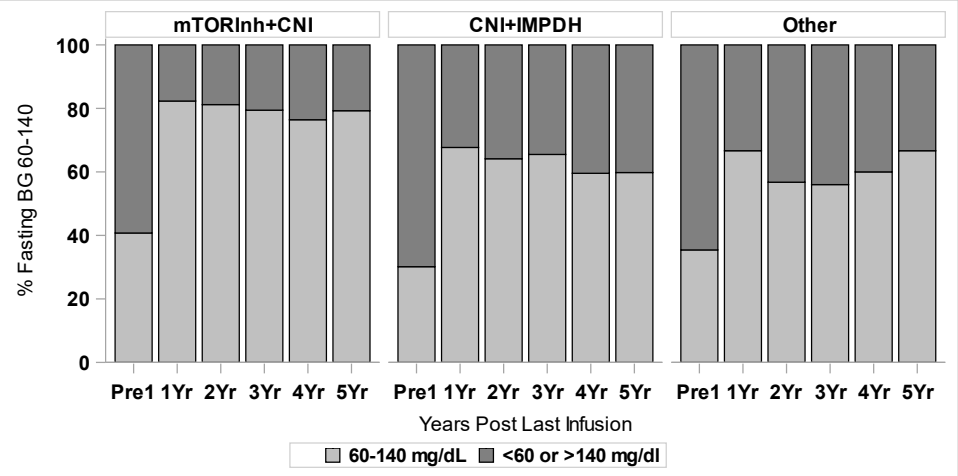


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

LFA-1 inhibitor (Efalizumab) (p=<.0001)



Maintenance combination (p=<.0001)



Donor max insulin blood glucose (p=0.0039)

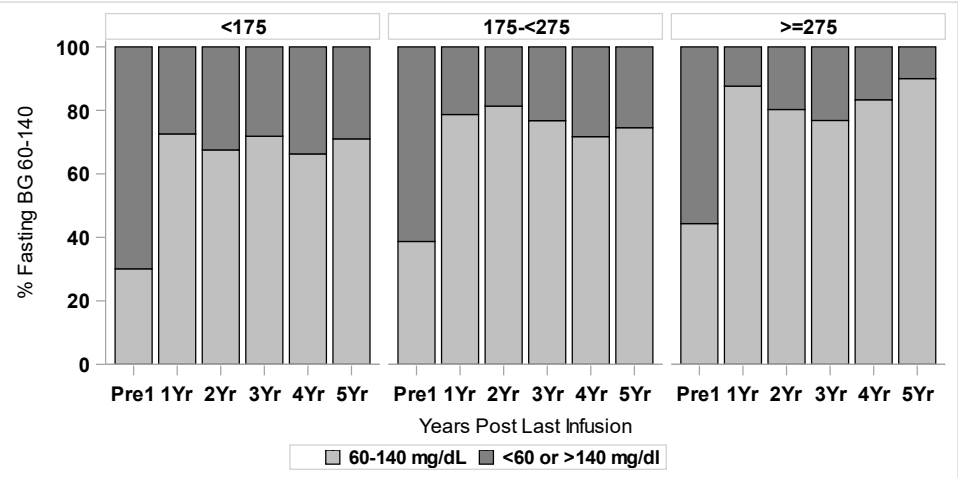
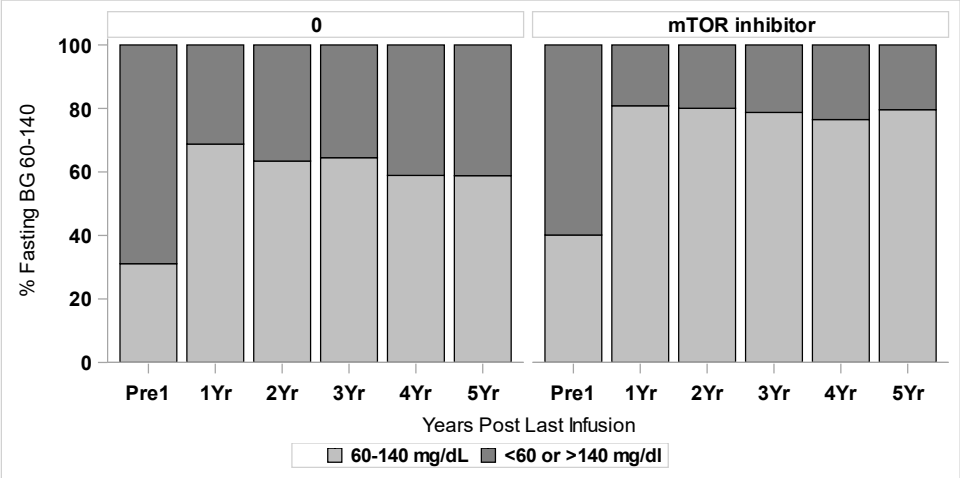
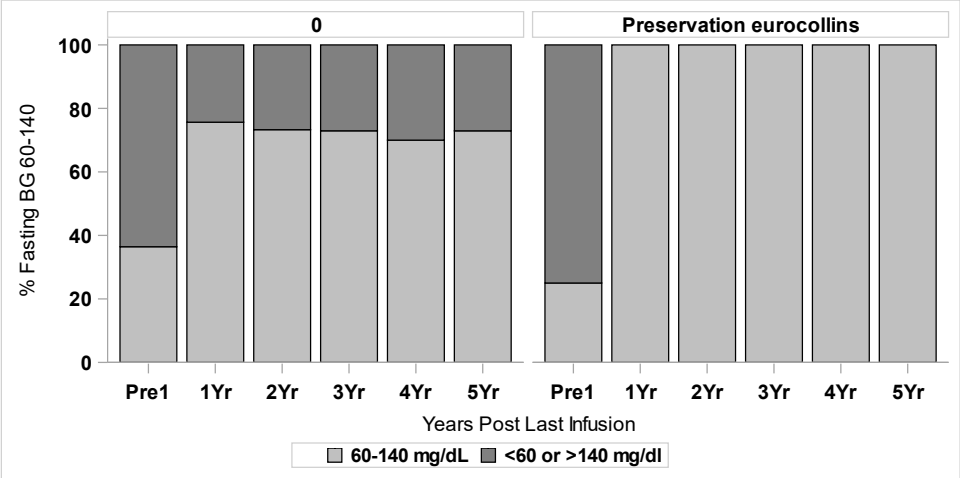


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

mTOR inhibitor (p=<.0001)



Eurocollins presrvation (p=<.0001)



Donor pre insulin blood glucose (p=0.0067)

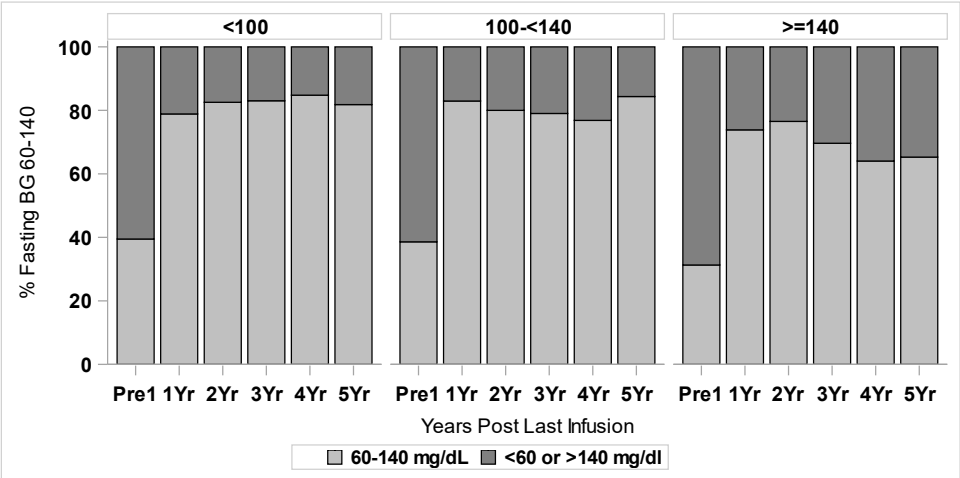
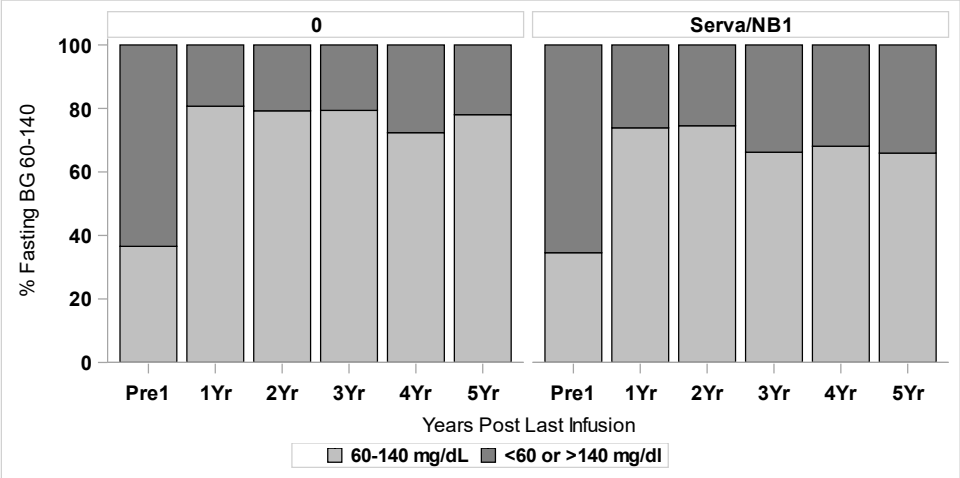


Exhibit 5-5B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among ITA Recipients

Serva/NB1 (p=0.0084)



TNFa inhibitor (p=0.0007)

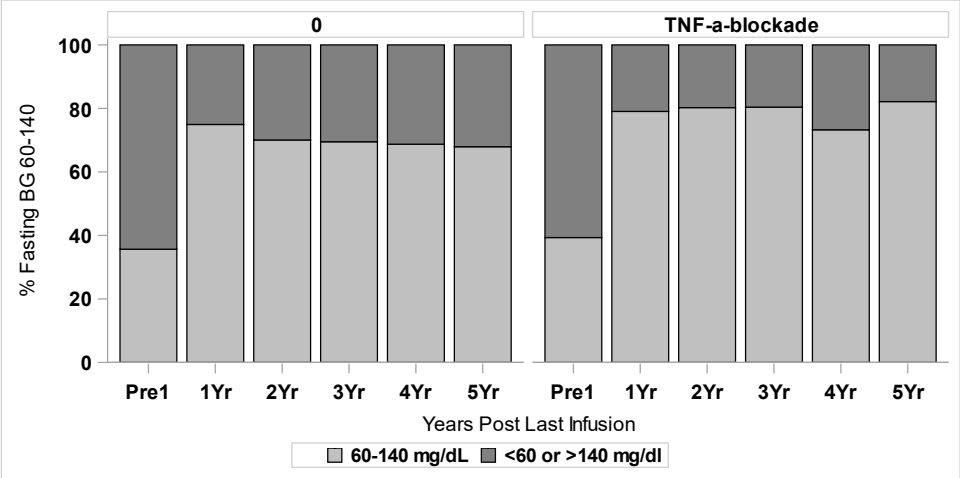
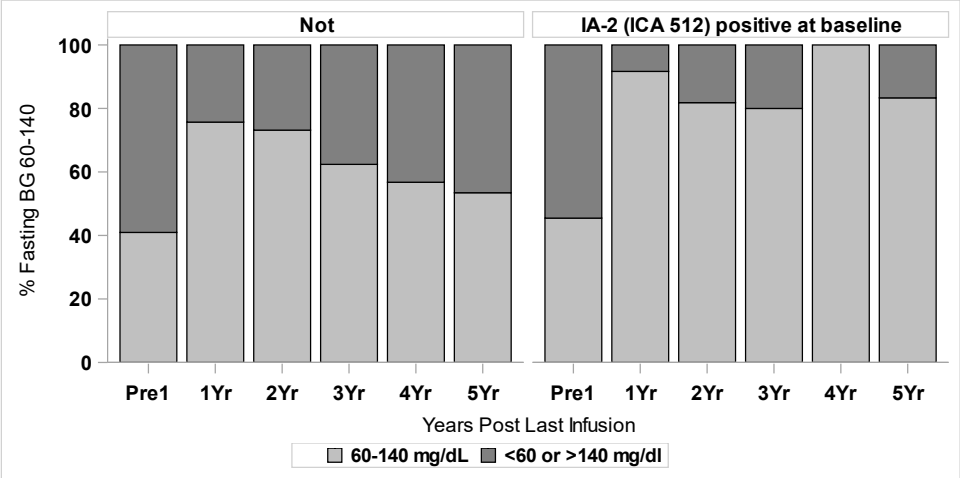
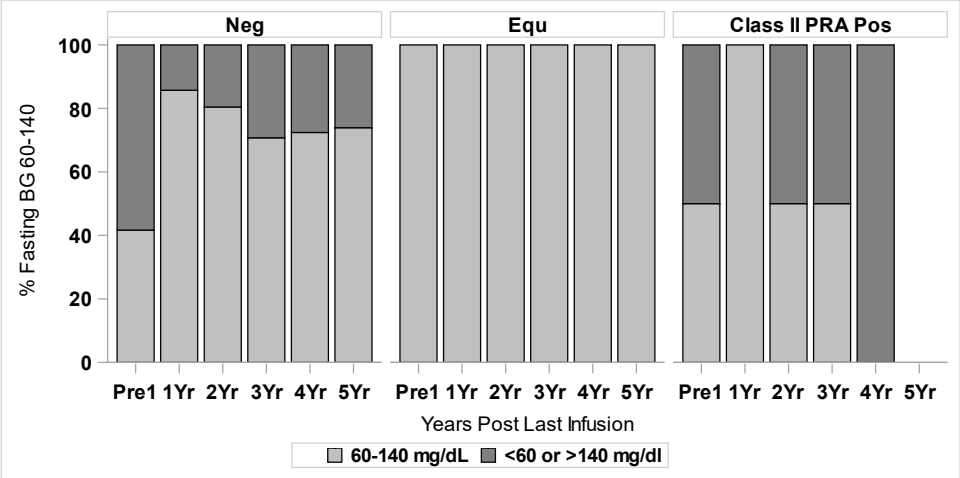


Exhibit 5-5C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among IAK Recipients

Baseline +IA2 (p=0.0028)



Baseline Class II PRA (p=<.0001)



Baseline +microinsulin AAB (p=<.0001)

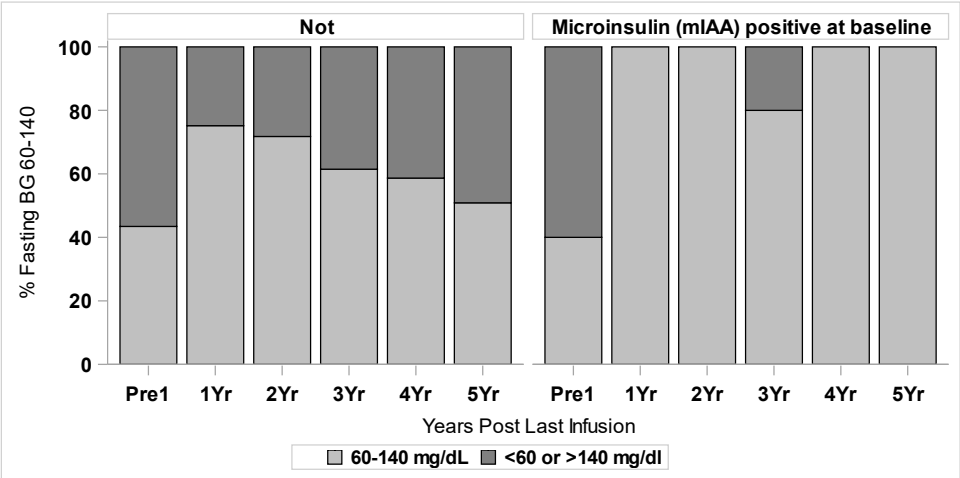
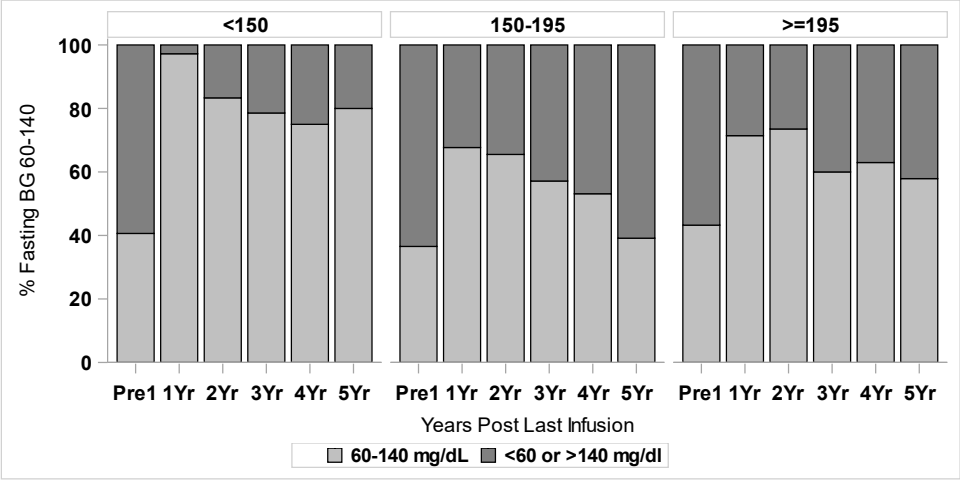
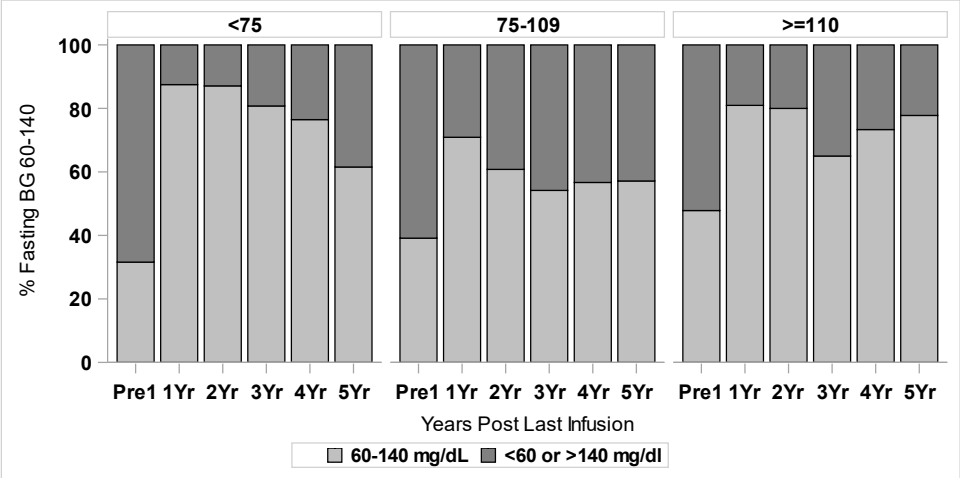


Exhibit 5-5C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among IAK Recipients

Baseline total cholesterol (p=<.0001)



Baseline LDL (p=0.0088)



Era (p=<.0001)

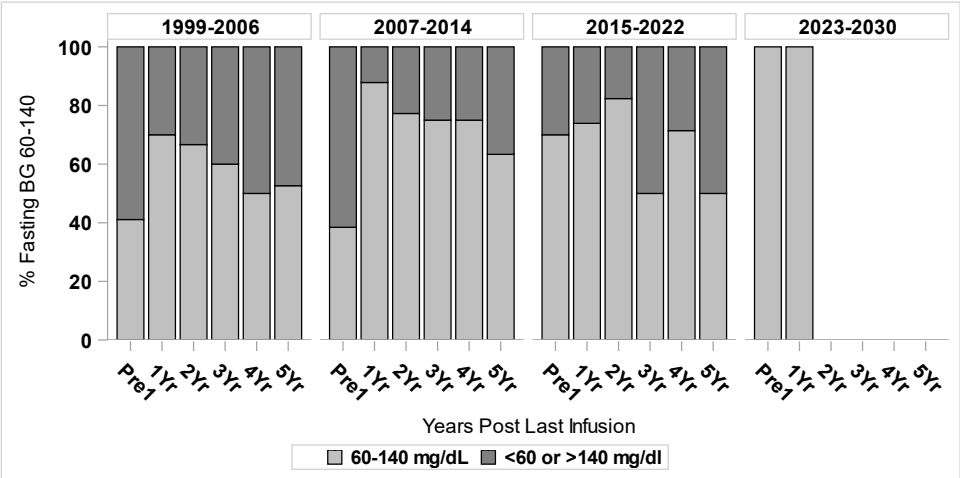
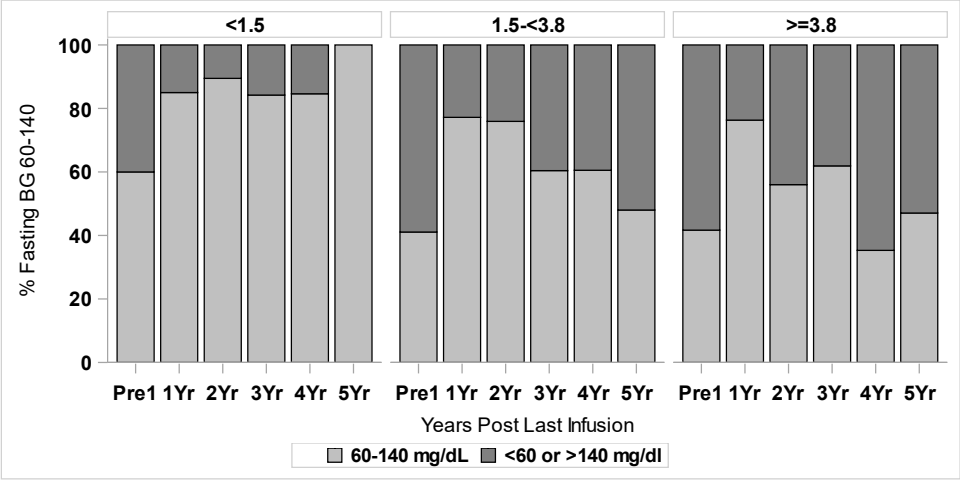
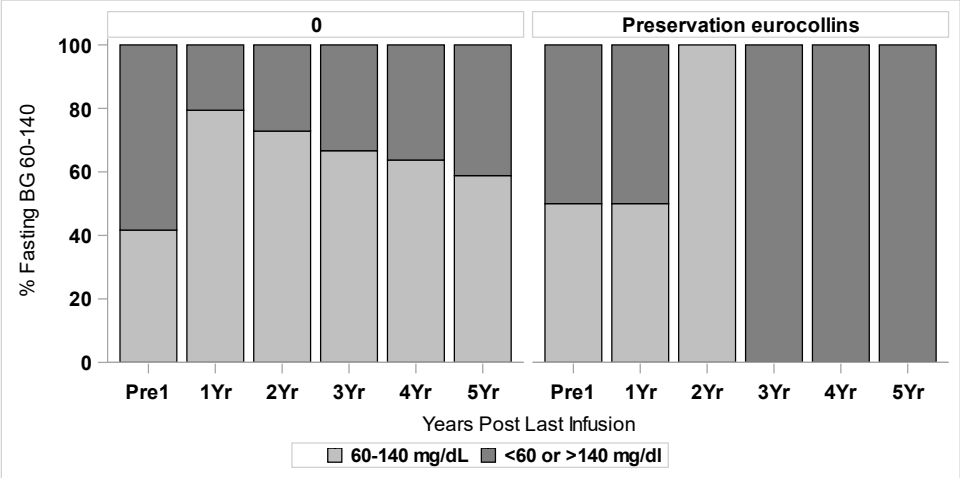


Exhibit 5-5C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among IAK Recipients

Islets stimulation index (p=0.0003)



Eurocollins presrvation (p=0.0007)



IMPDH inhibitor (MMF) (p=0.0008)

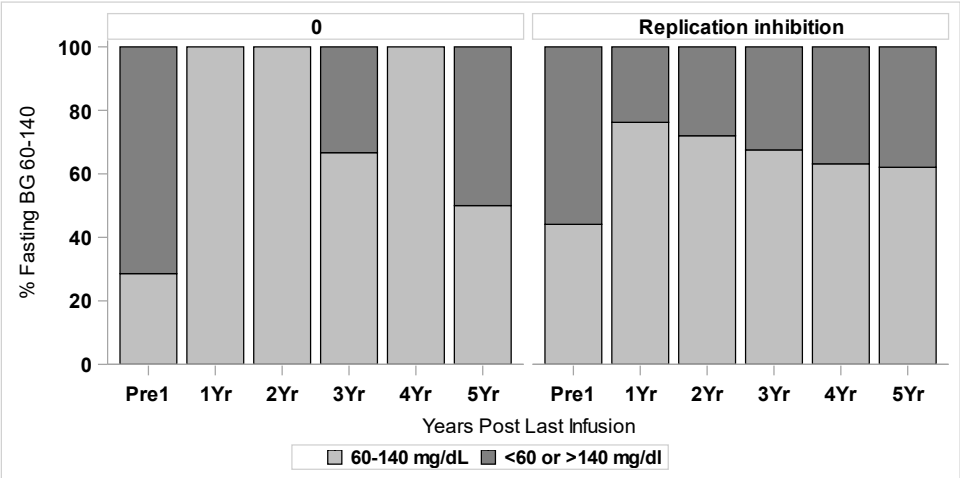
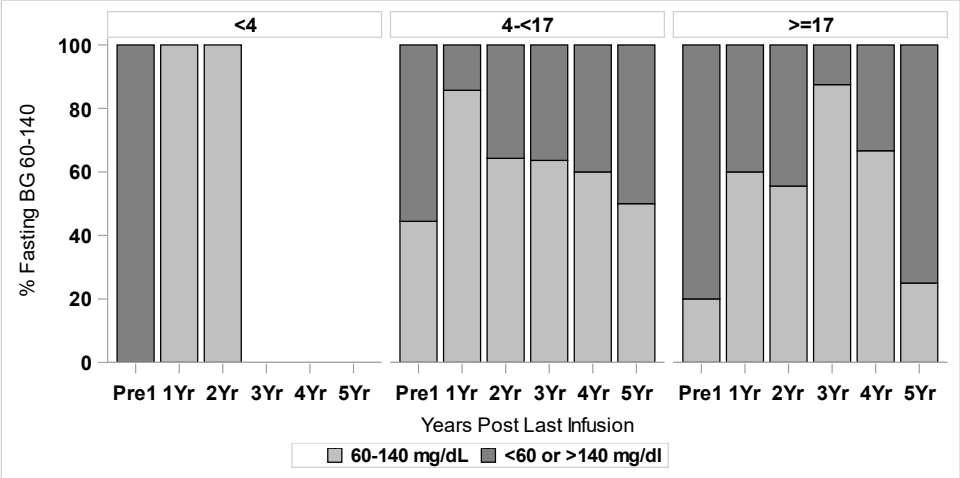


Exhibit 5-5C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/dL Post Last Infusion among IAK Recipients

Islets total DNA (p=0.0057)



Islets total insulin (p=0.0033)

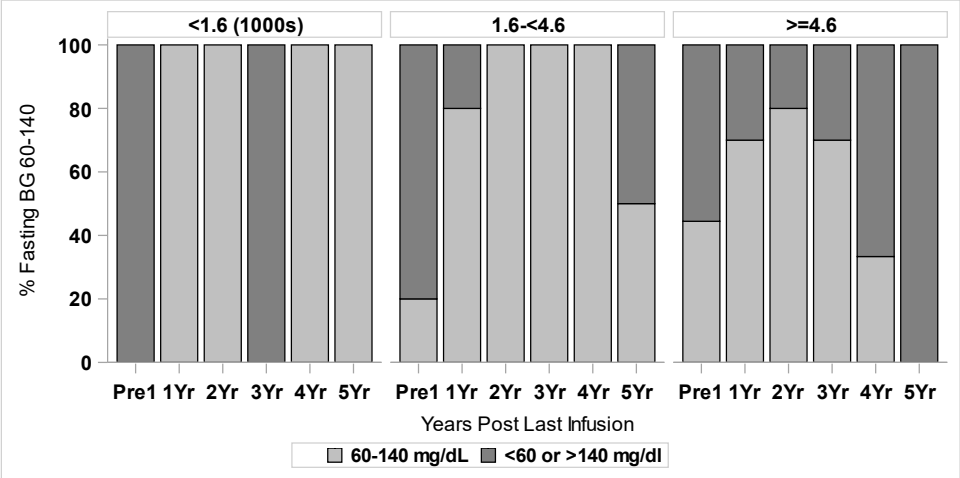
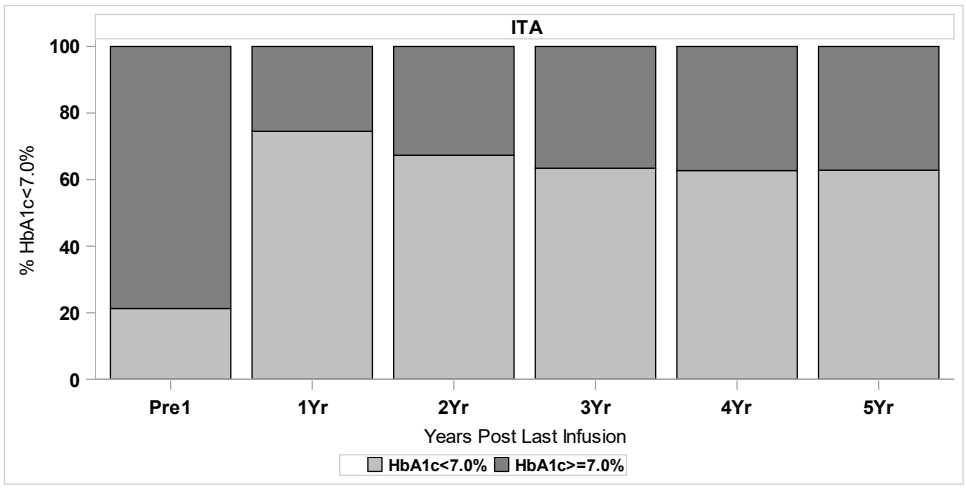


Exhibit 5-6A
Unadjusted Prevalence of HbA1c<7.0% Post Last Infusion



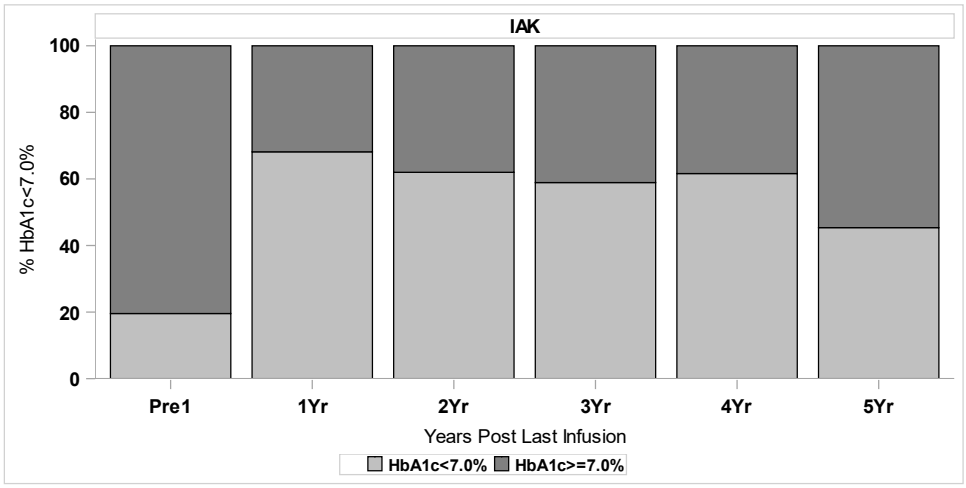
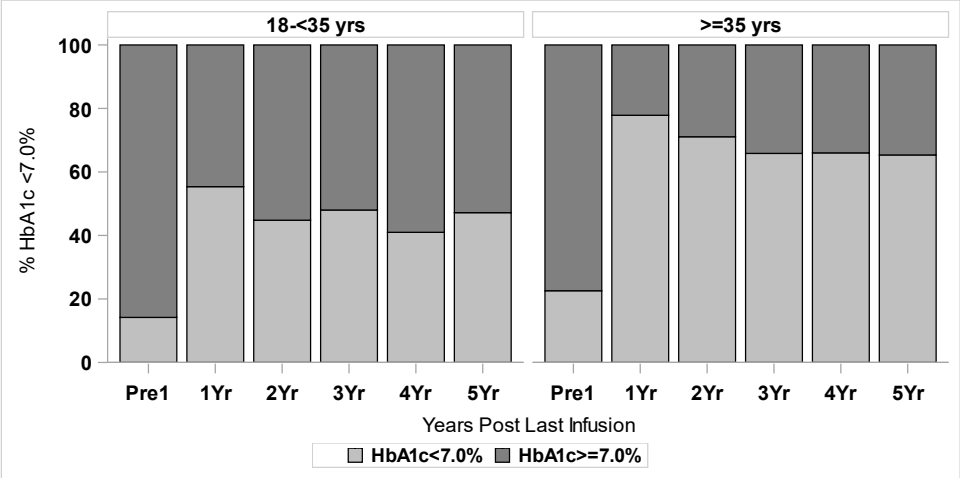
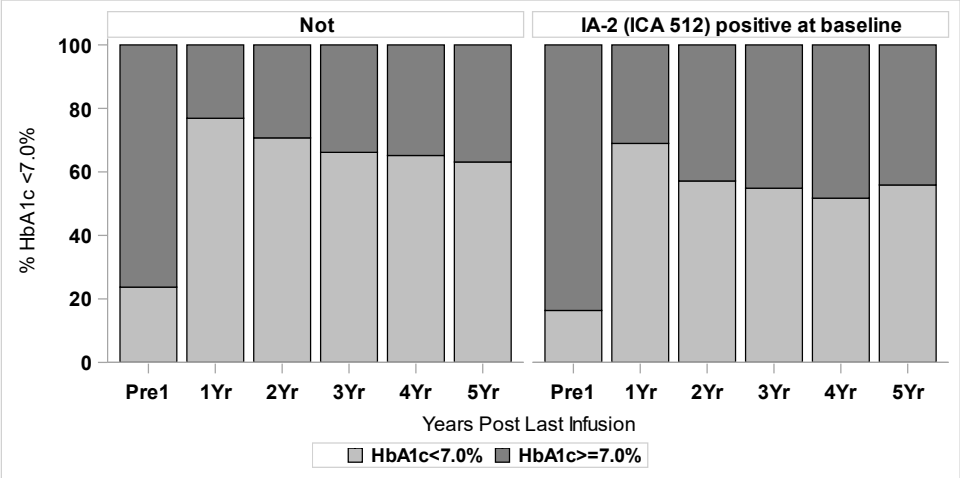


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Age (p=<.0001)



Baseline +IA2 (p=0.0090)



Baseline CVA (p=<.0001)

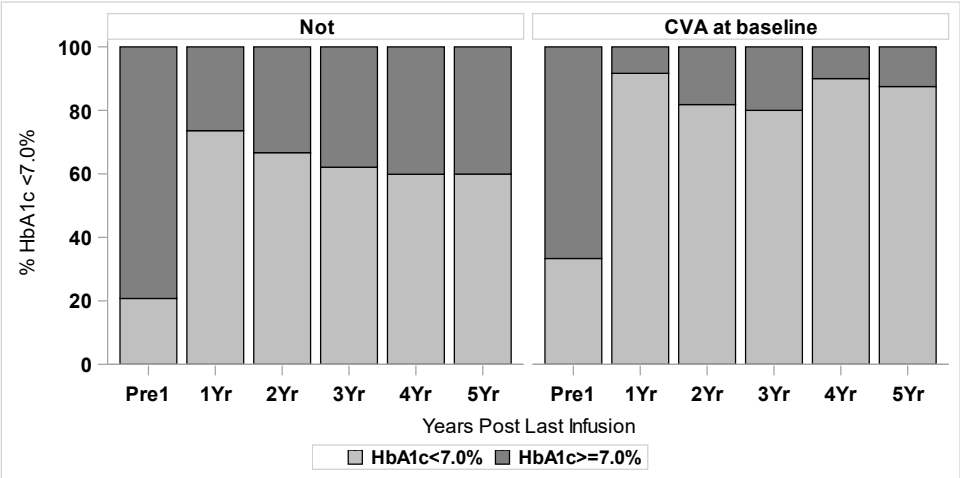
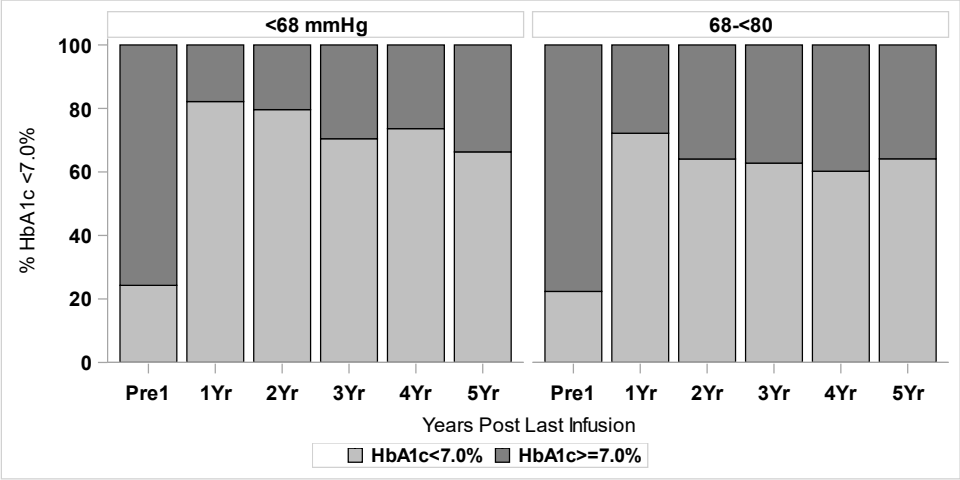
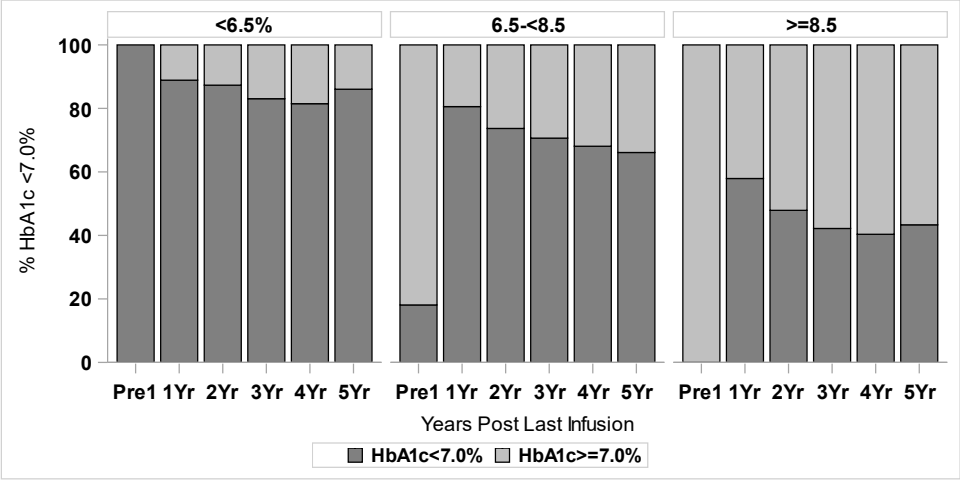


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Baseline DBP (p=0.0012)



Baseline HbA1c (p=<.0001)



Baseline insulin (U/kg/day) (p=0.0069)

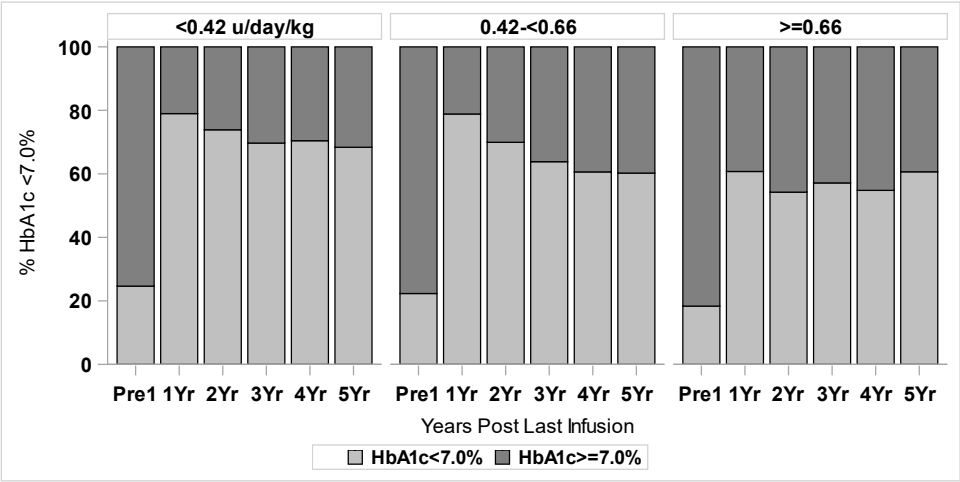
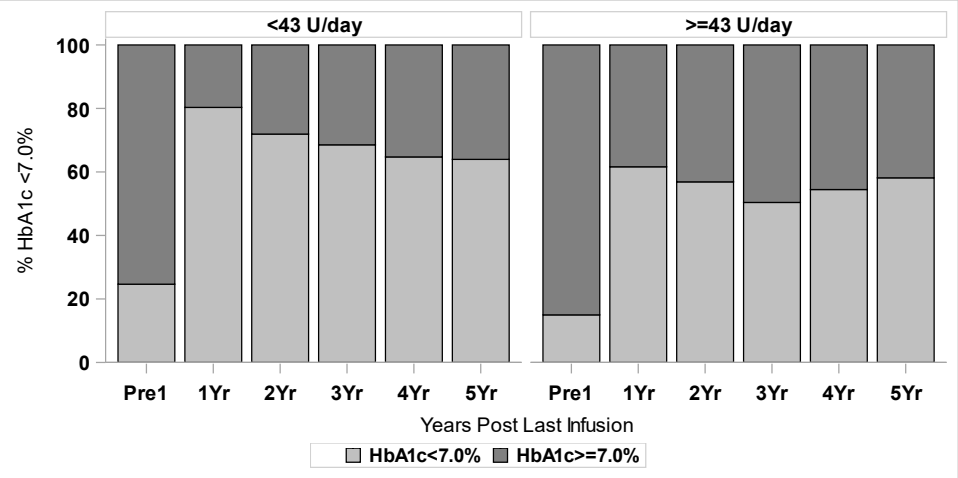
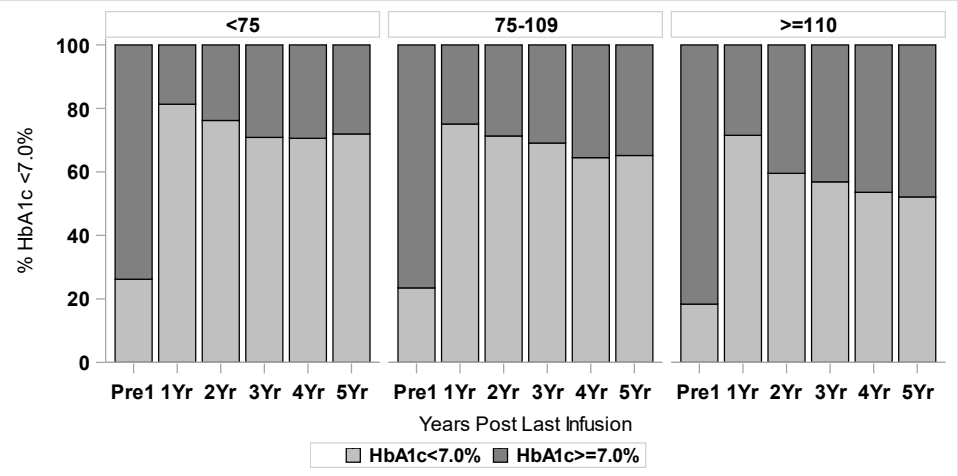


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Baseline insulin (U/day) (p=0.0003)



Baseline LDL (p=0.0064)



Donor weight (kg) (p=0.0005)

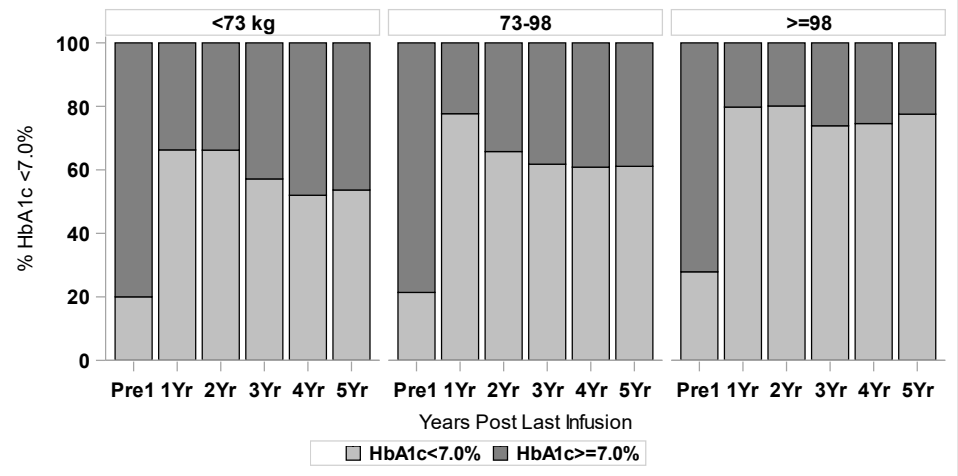
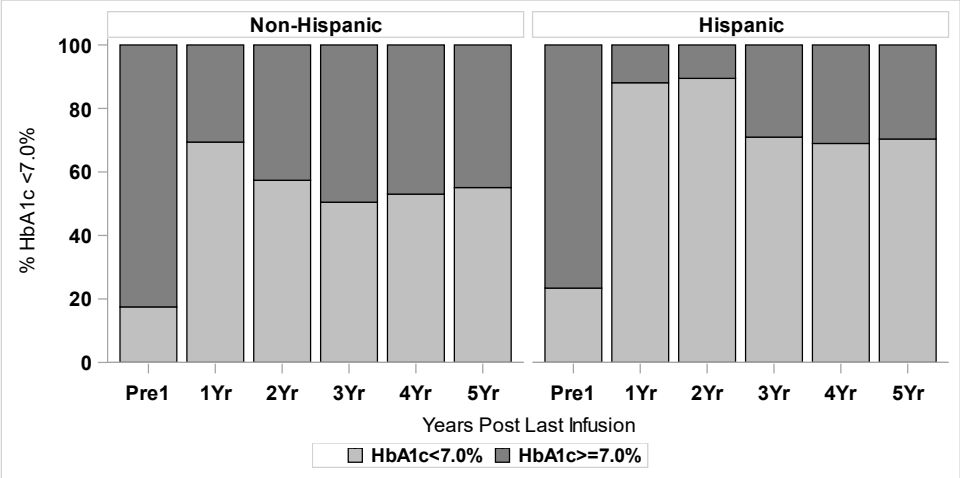
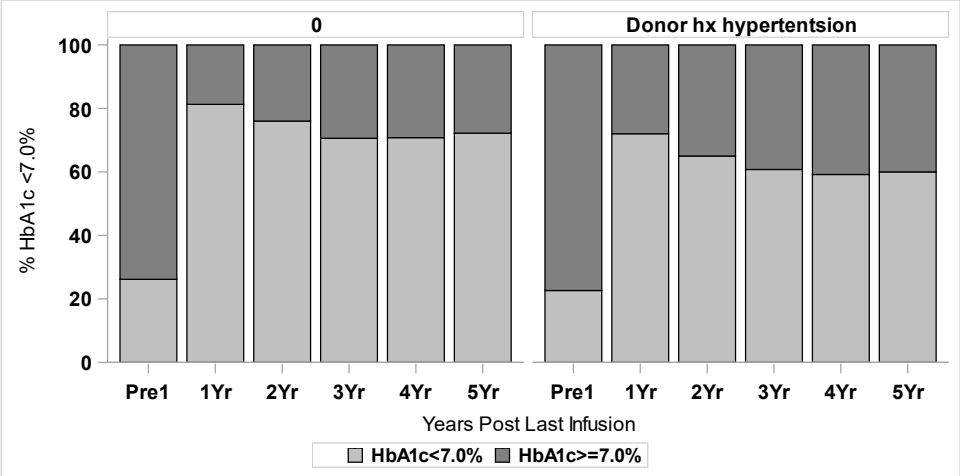


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Donor Hispanic (p=0.0005)



Donor hx hypertension (p=0.0009)



Donor age (p=0.0045)

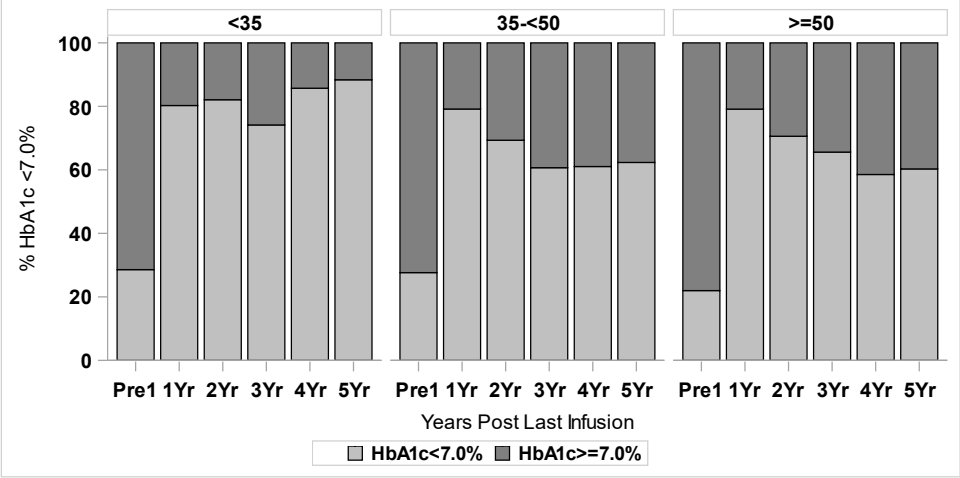
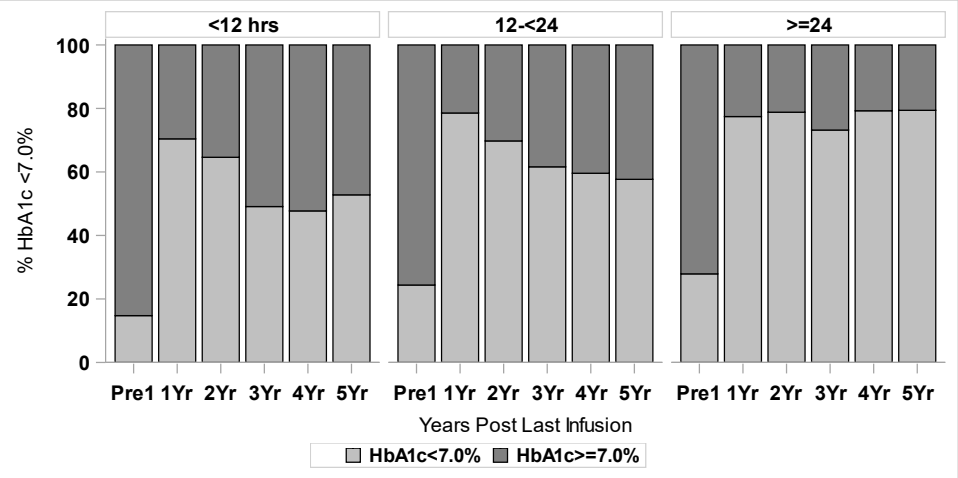
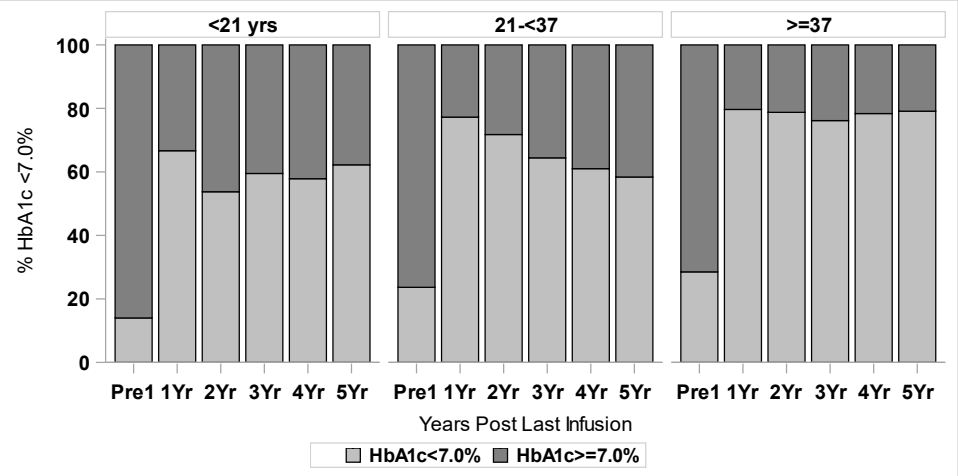


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Hours: Death to cross-clamp (p=0.0023)



Duration (p=<.0001)



Eflizumab (p=<.0001)

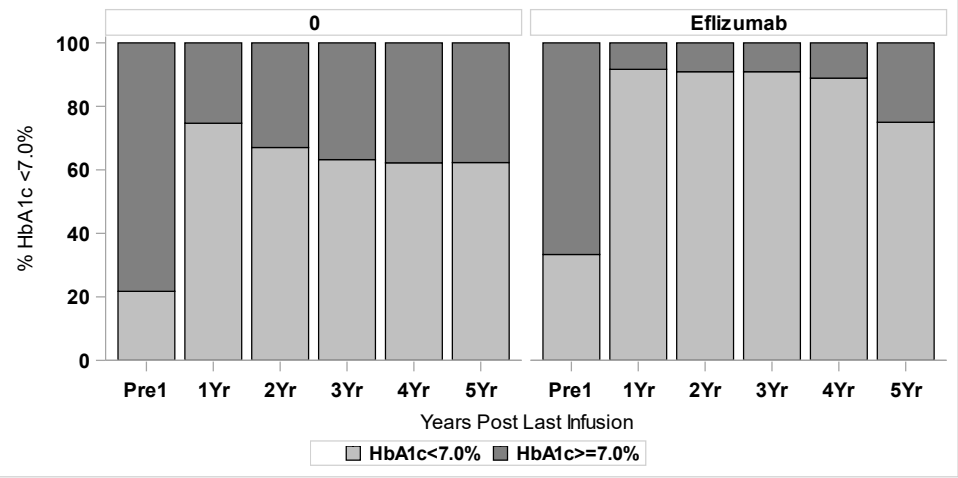
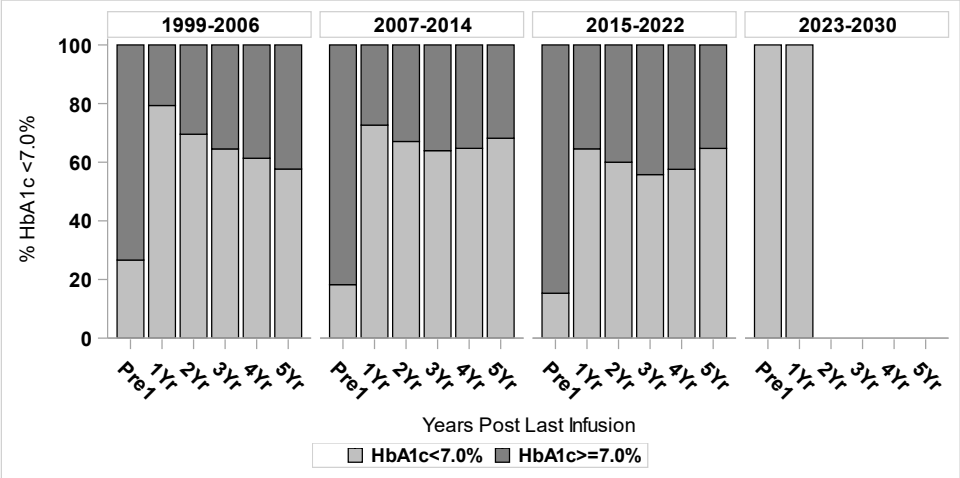
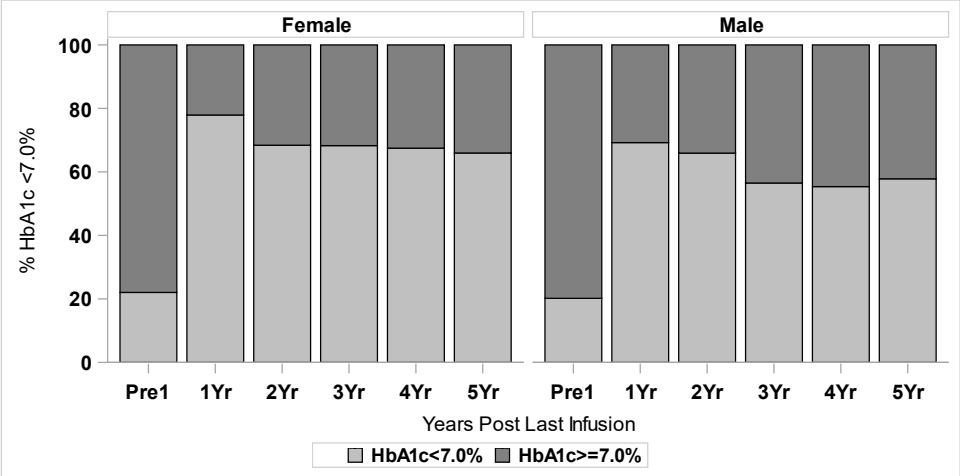


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Era (p=<.0001)



Gender (p=0.0074)



Islets viability (%) (p=0.0046)

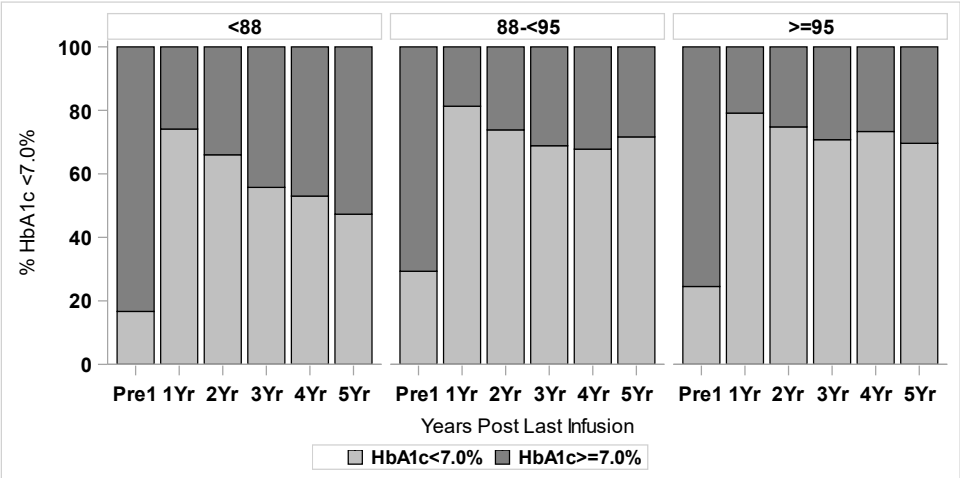
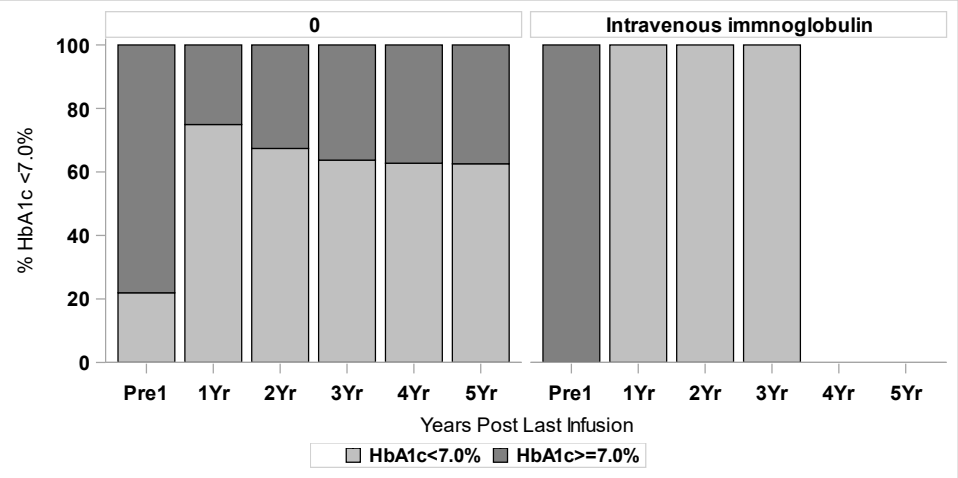
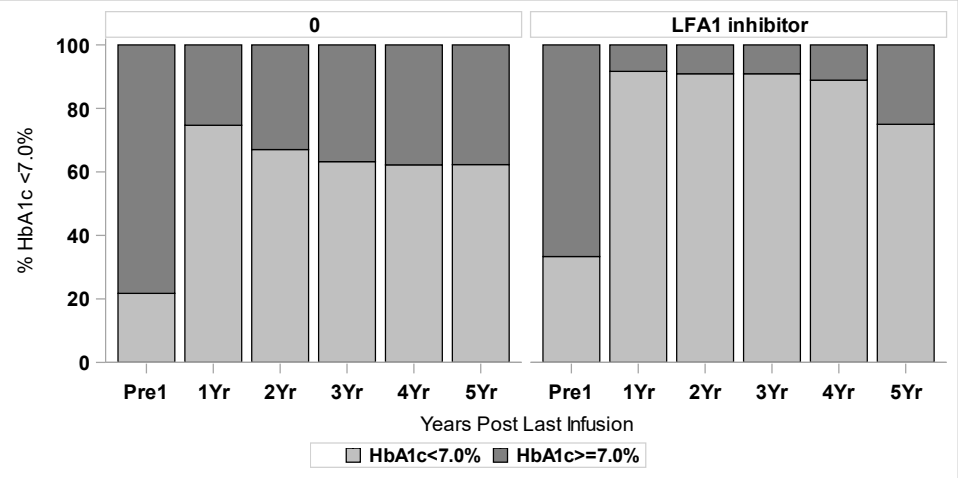


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Immunoglobulin (IVIG) (p=<.0001)



LFA-1 inhibitor (Efalizumab) (p=<.0001)



Maintenance combination (p=<.0001)

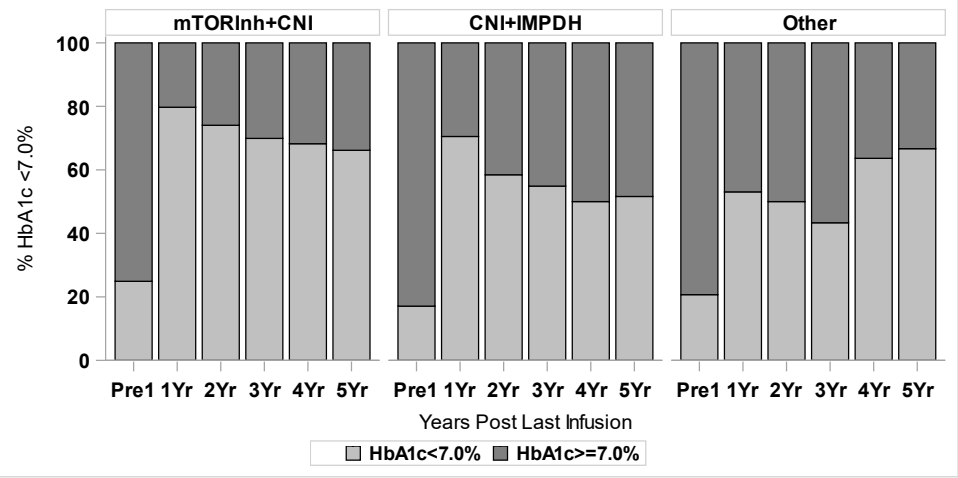
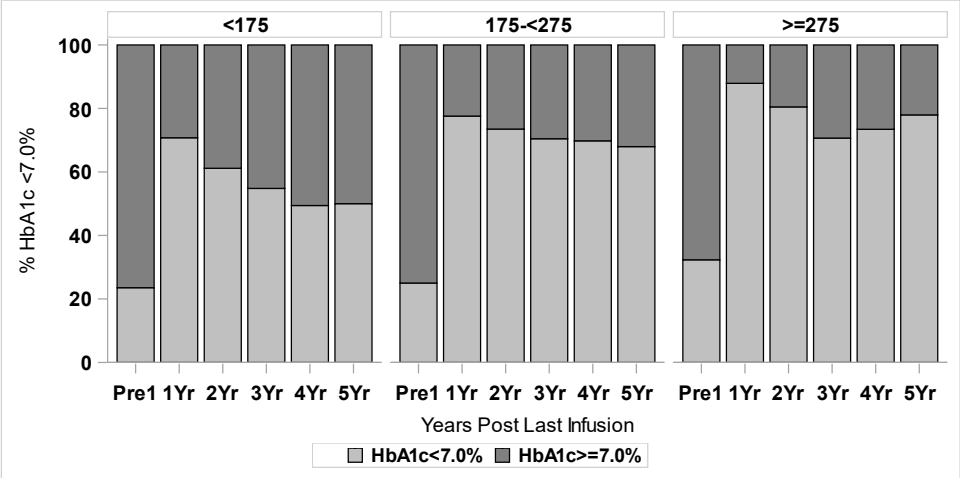
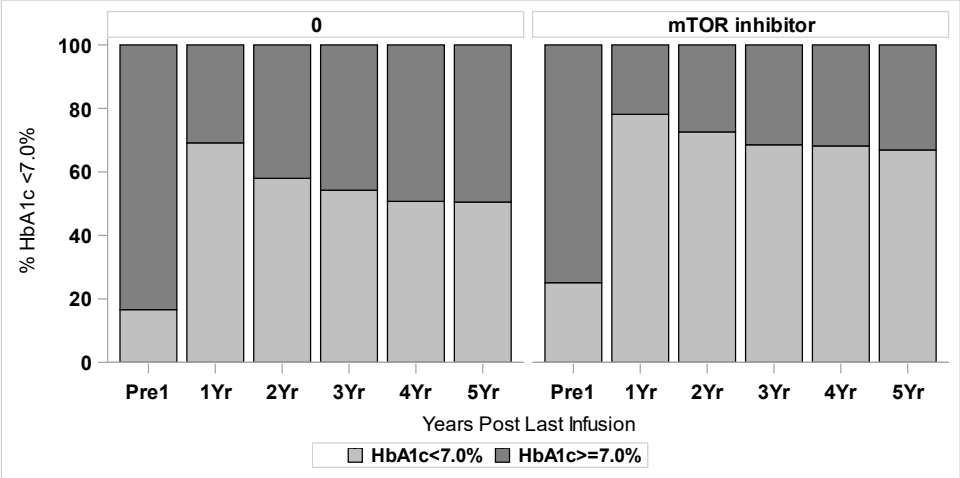


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Donor max insulin blood glucose (p=0.0006)



mTOR inhibitor (p=<.0001)



Eurocollins presrvation (p=<.0001)

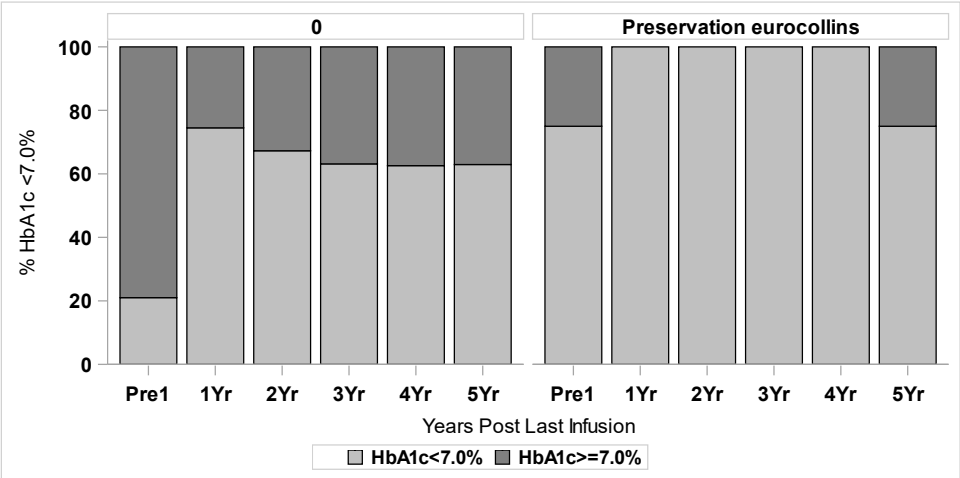
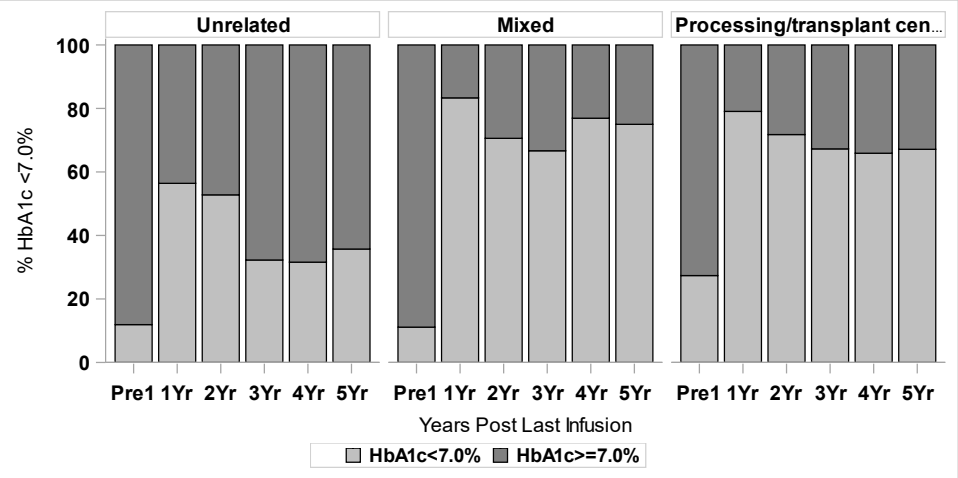
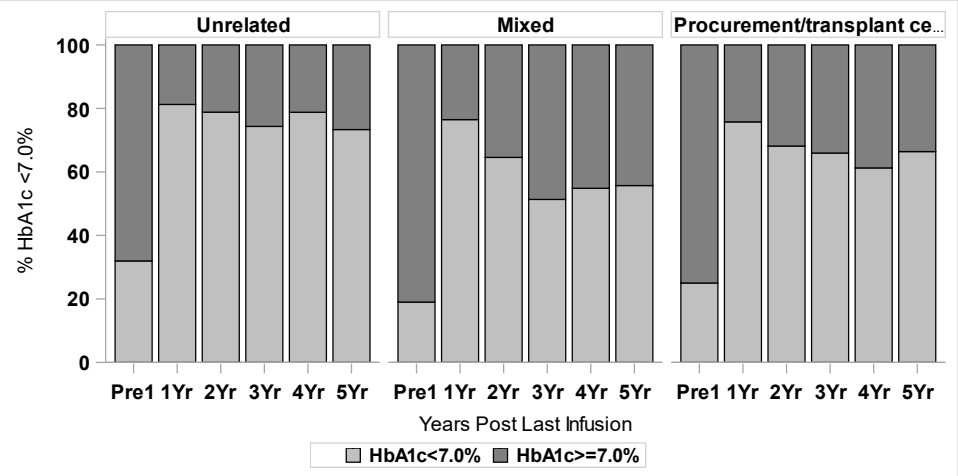


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Processing center (p=0.0067)



Procurement center (p=0.0035)



Islets purity (p=0.0054)

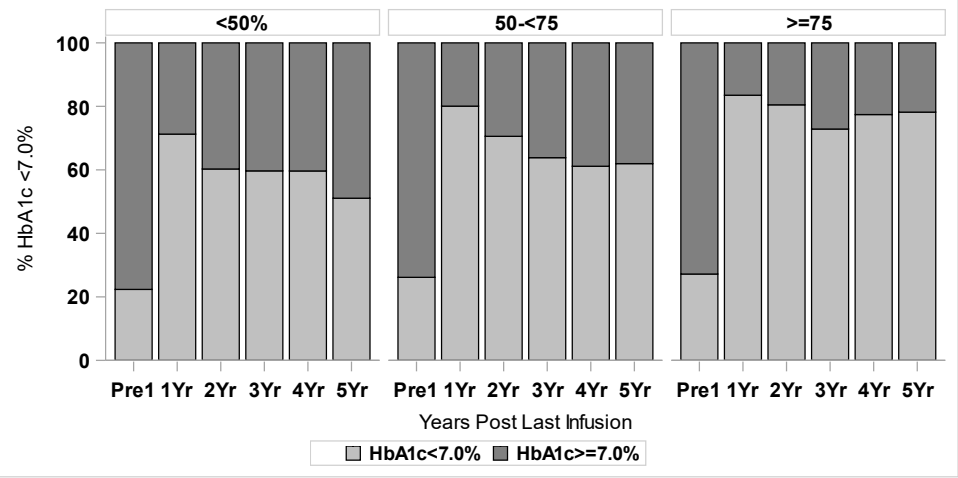
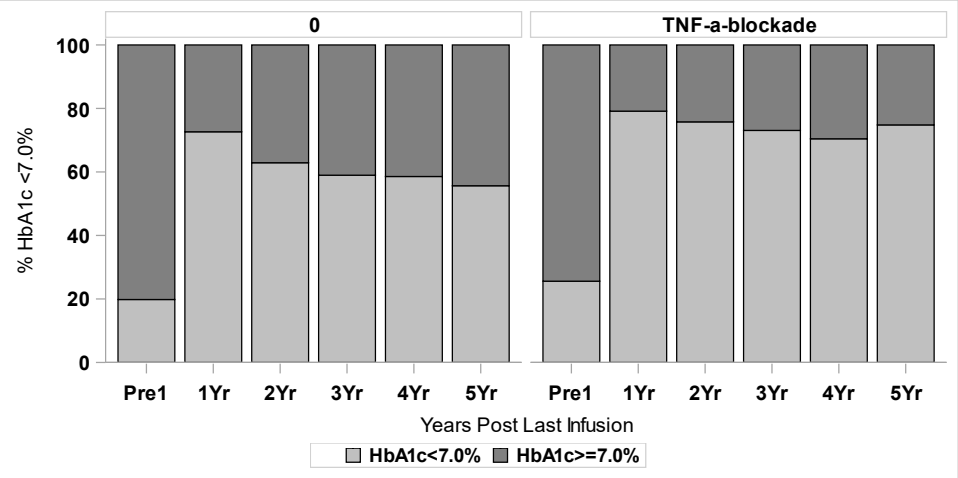
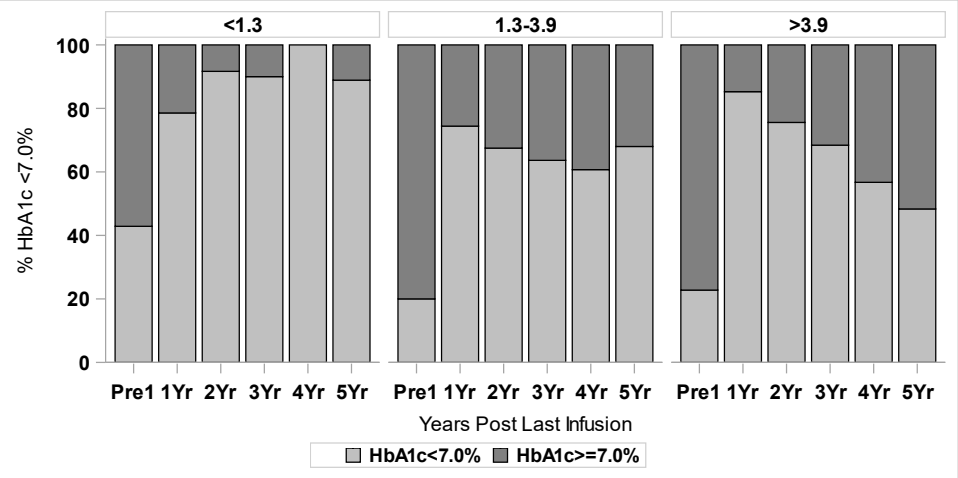


Exhibit 5-6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

TNFa inhibitor (p=<.0001)



Islets total beta cells/kg recipient (p=0.0034)



Islets total endotoxin/kg recipient (p=0.0091)

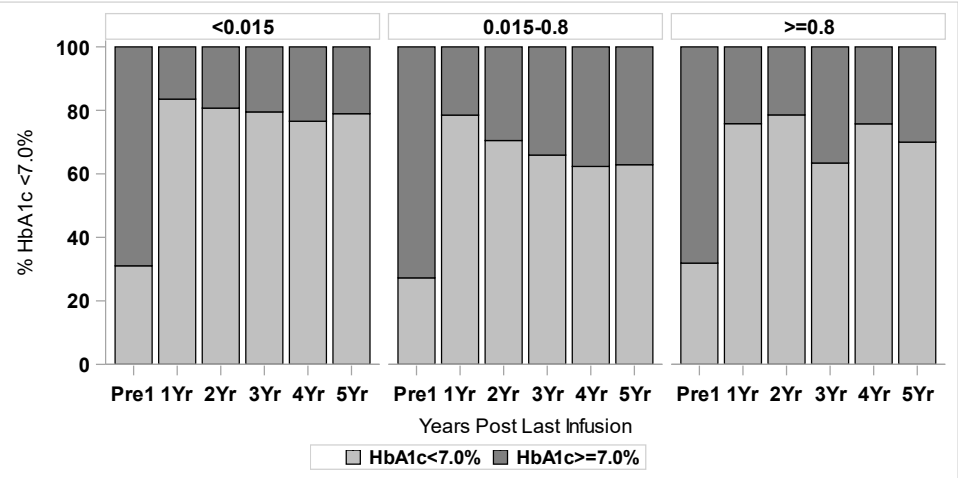
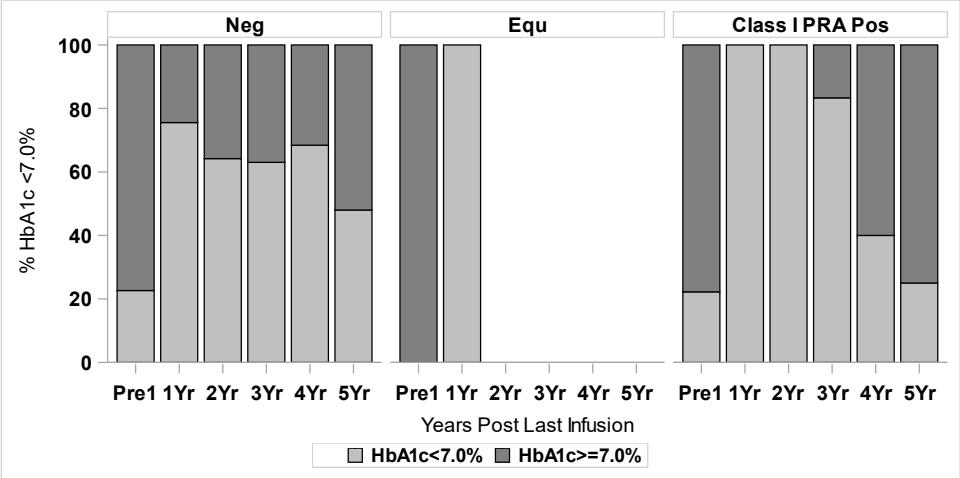
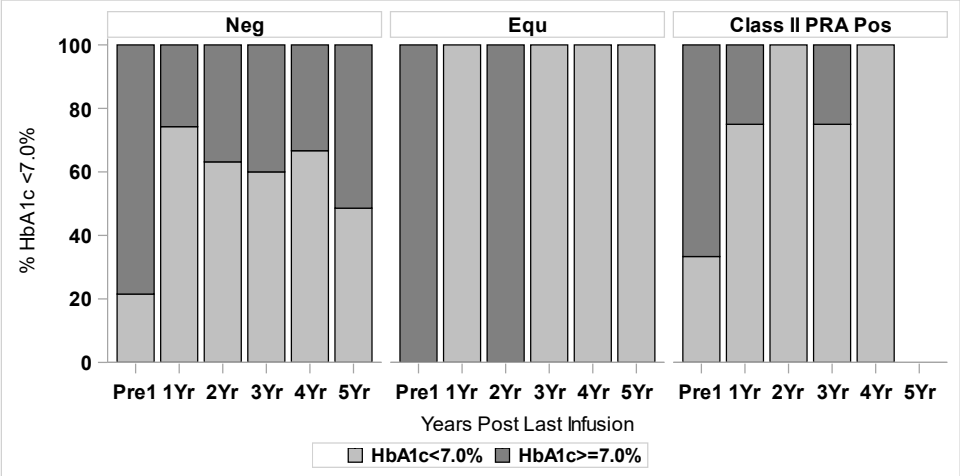


Exhibit 5-6C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

Baseline +Class I PRA (p=<.0001)



Baseline Class II PRA (p=0.0097)



Baseline HbA1c (p=<.0001)

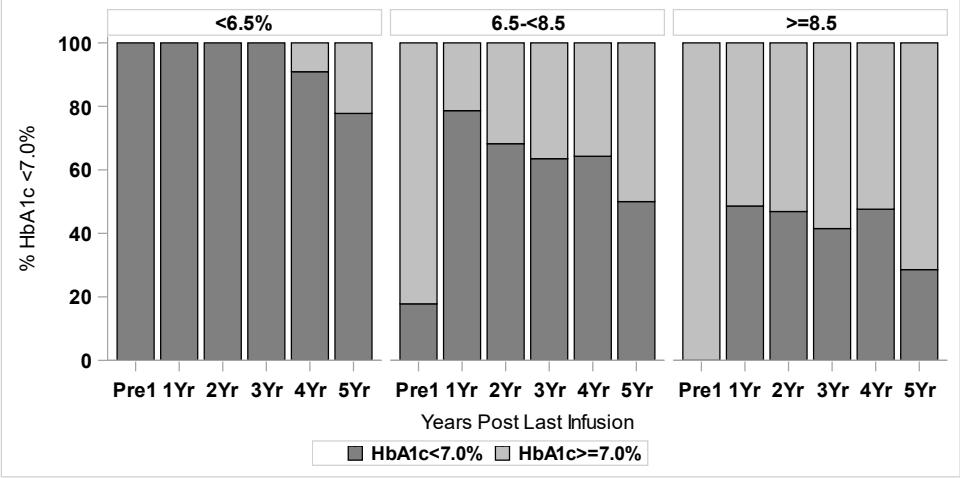
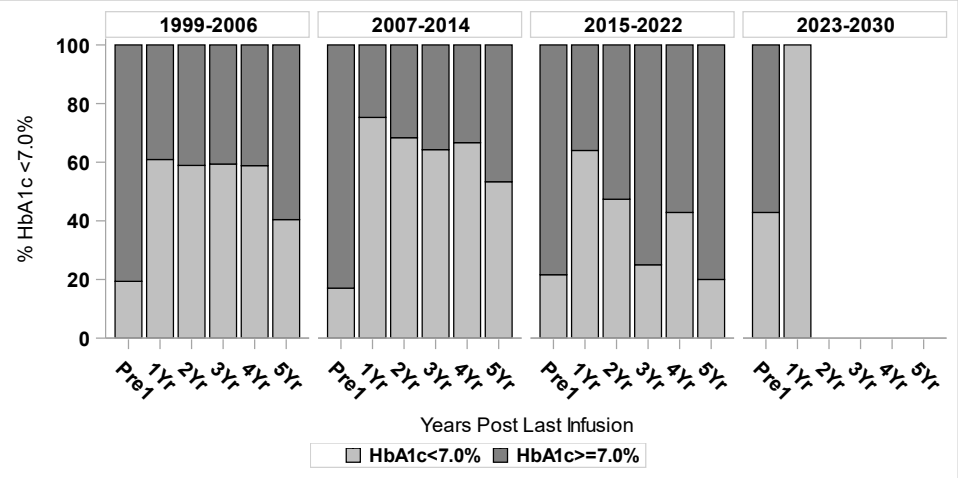


Exhibit 5-6C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

Era (p=<.0001)



Donor serum creatinine (p=0.0050)

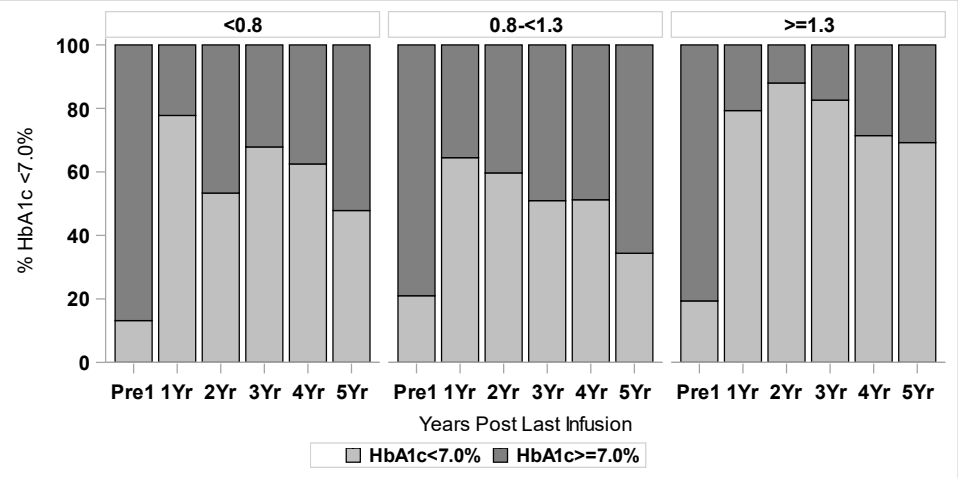
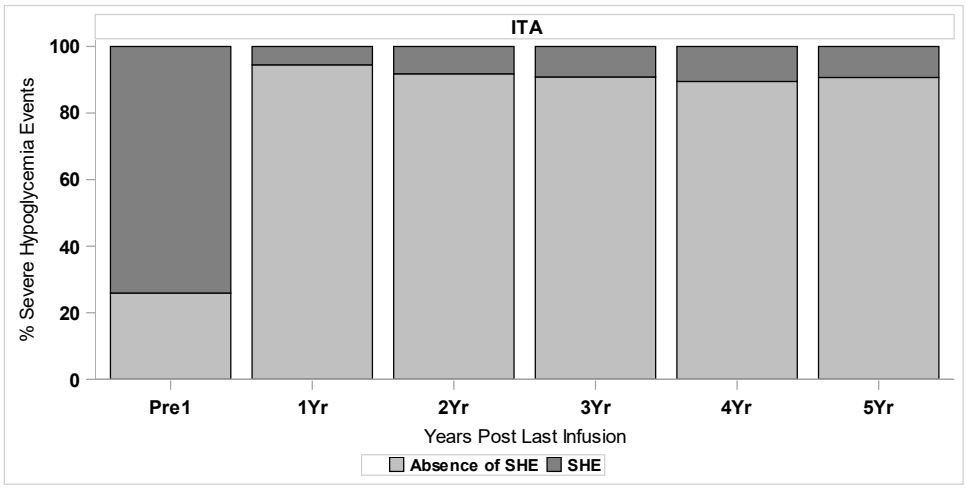


Exhibit 5-7A
Unadjusted Prevalence of Severe Hypoglycemia Events Post Last Infusion



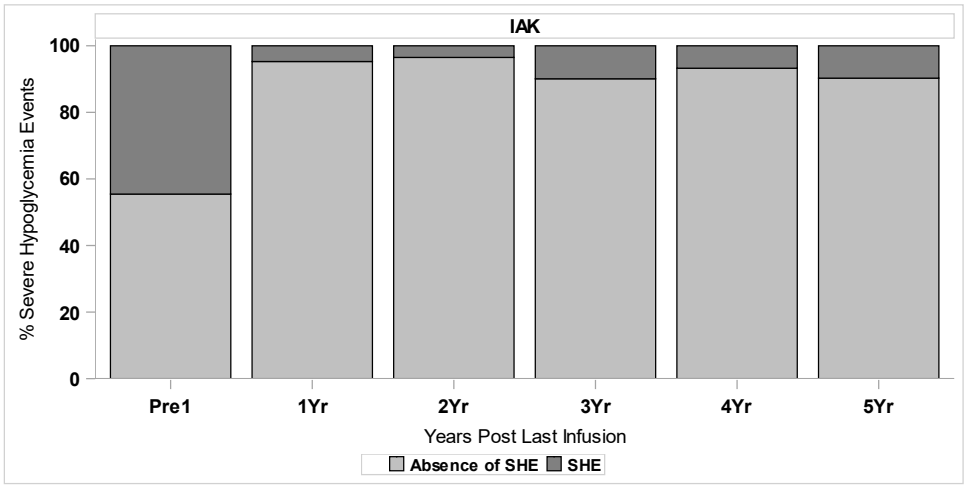
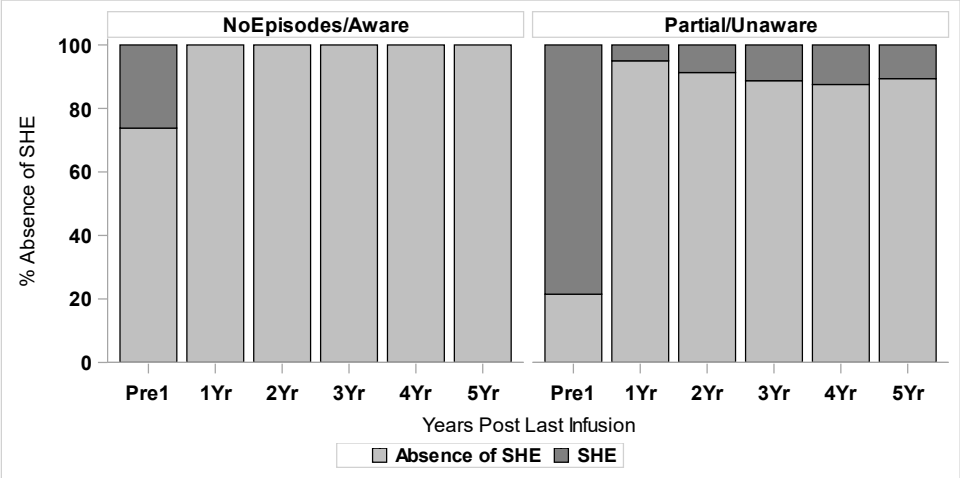
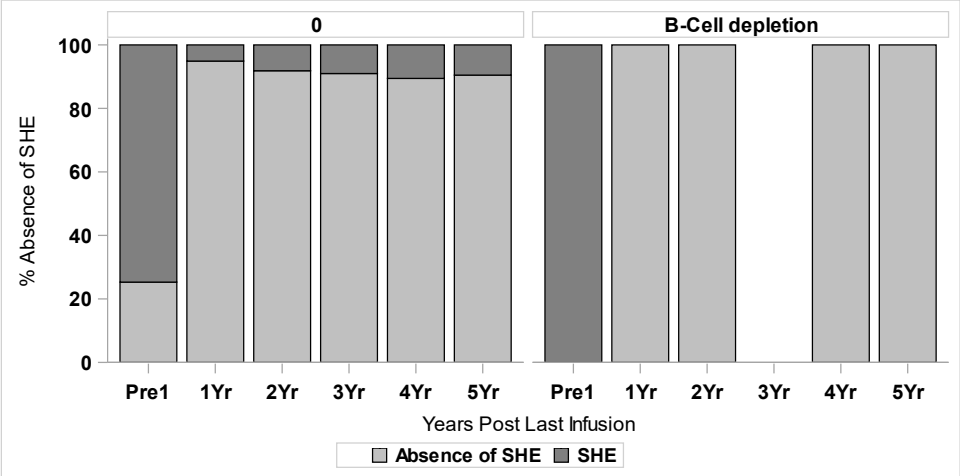


Exhibit 5-7B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among ITA Recipients

Baseline hypoglycemia (p=<.0001)



B-cell depletion (Rituximab) (p=<.0001)



Collagenase P (p=0.0002)

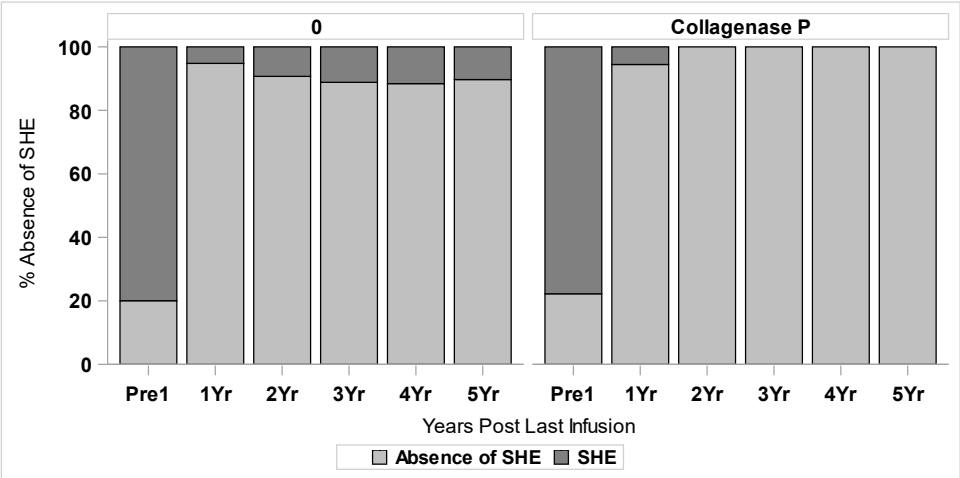
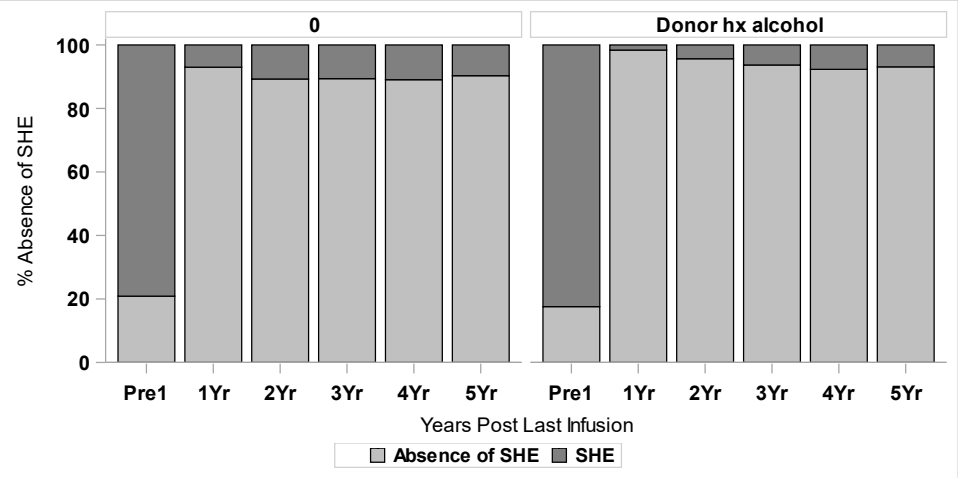
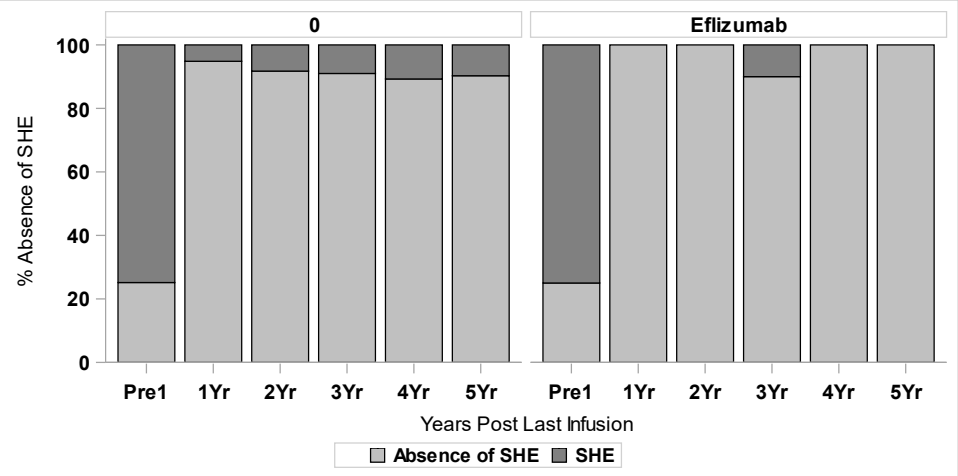


Exhibit 5-7B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among ITA Recipients

Donor hx alcohol (p=0.0091)



Eflizumab (p=0.0026)



Era (p=<.0001)

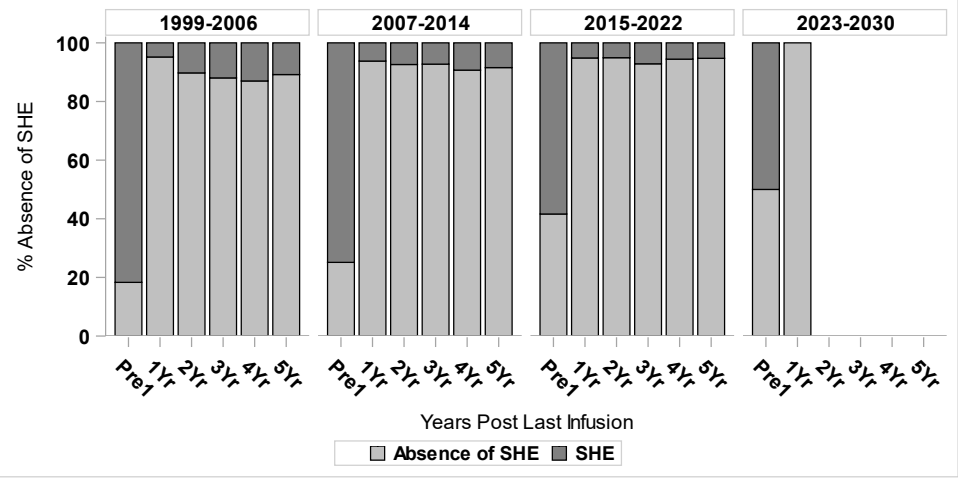
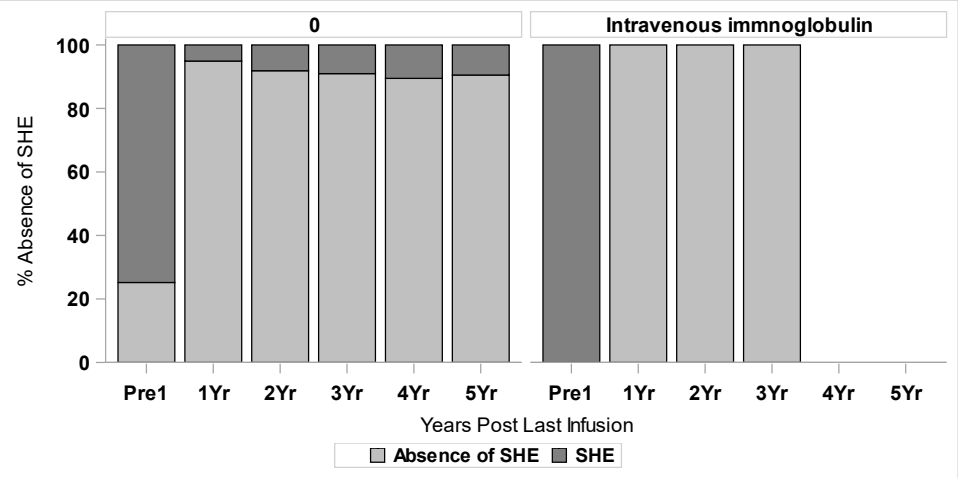
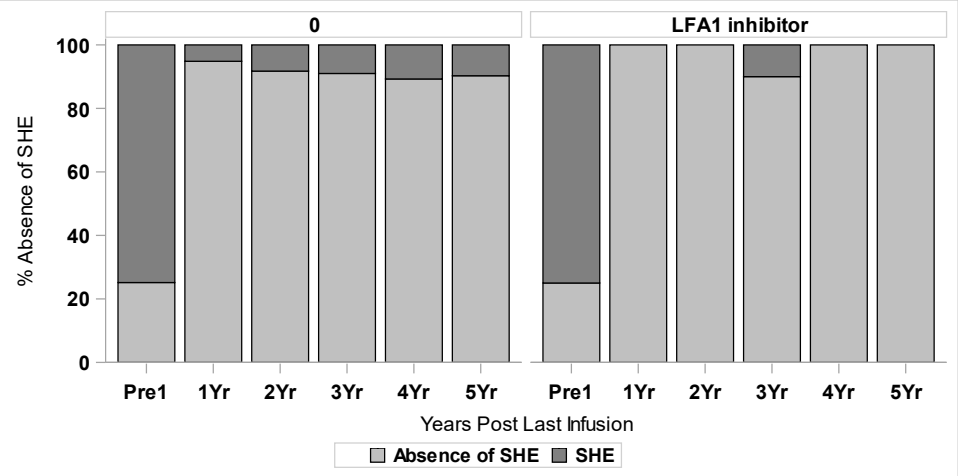


Exhibit 5-7B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among ITA Recipients

Immunoglobulin (IVIG) (p=<.0001)



LFA-1 inhibitor (Efalizumab) (p=0.0026)



Sigmablend (p=<.0001)

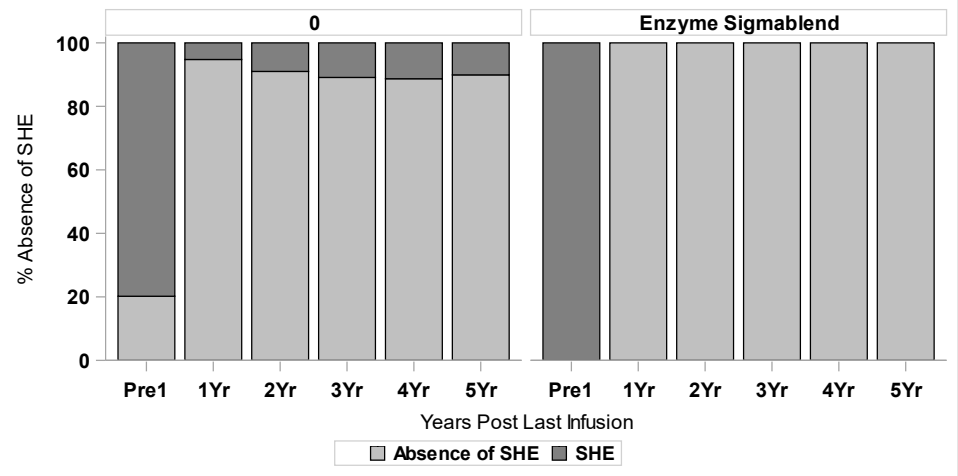
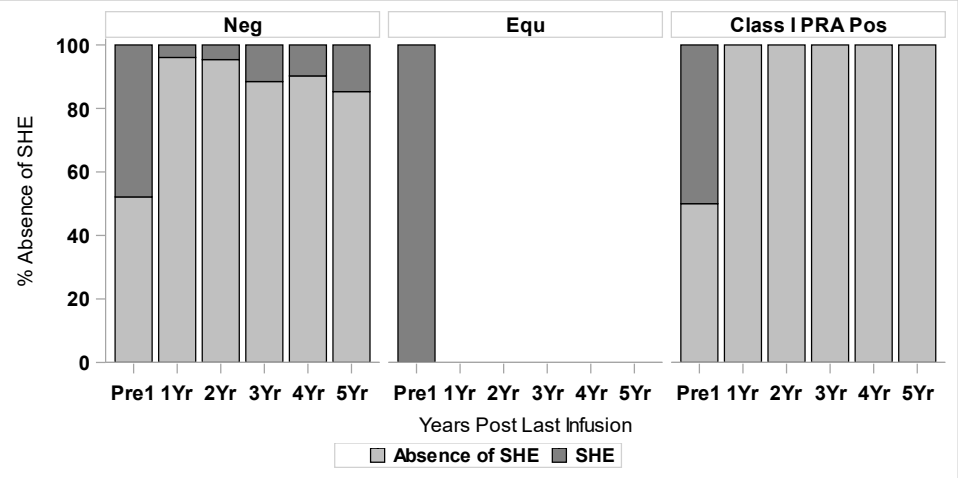
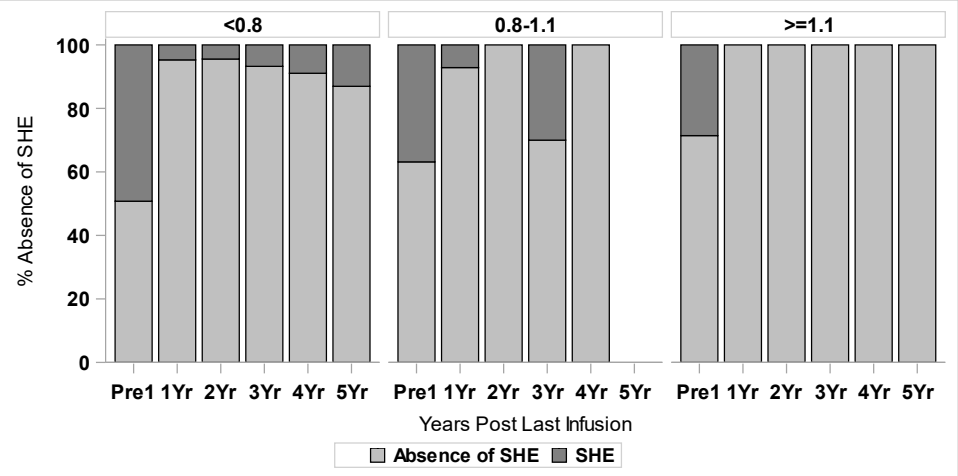


Exhibit 5-7C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among IAK Recipients

Baseline +Class I PRA (p=0.0021)



Baseline total bilirubin (p=0.0026)



Baseline CVA (p=<.0001)

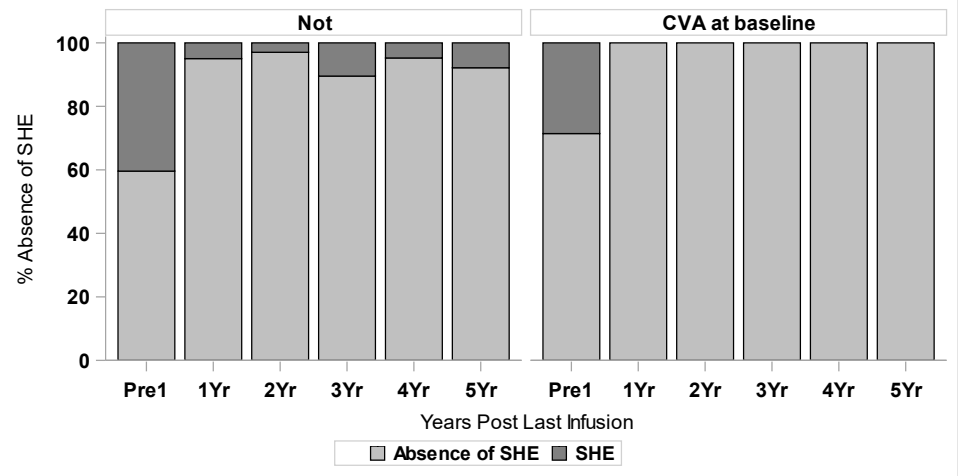
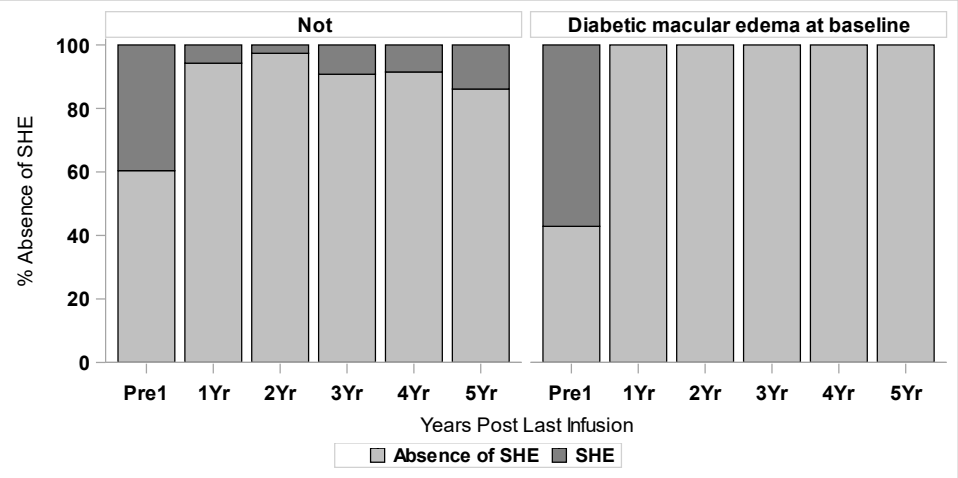
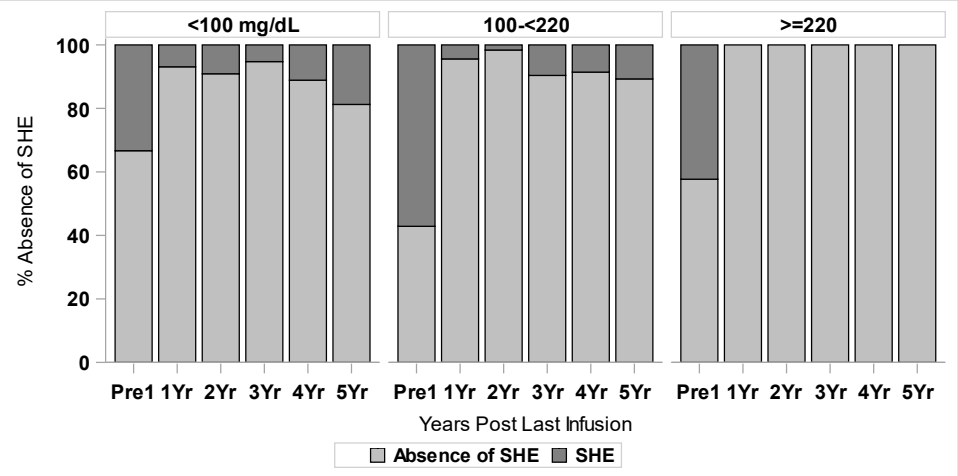


Exhibit 5-7C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among IAK Recipients

Baseline diabetic macular edema (p=0.0026)



Baseline fasting BG (p=0.0019)



Baseline +microinsulin AAB (p=<.0001)

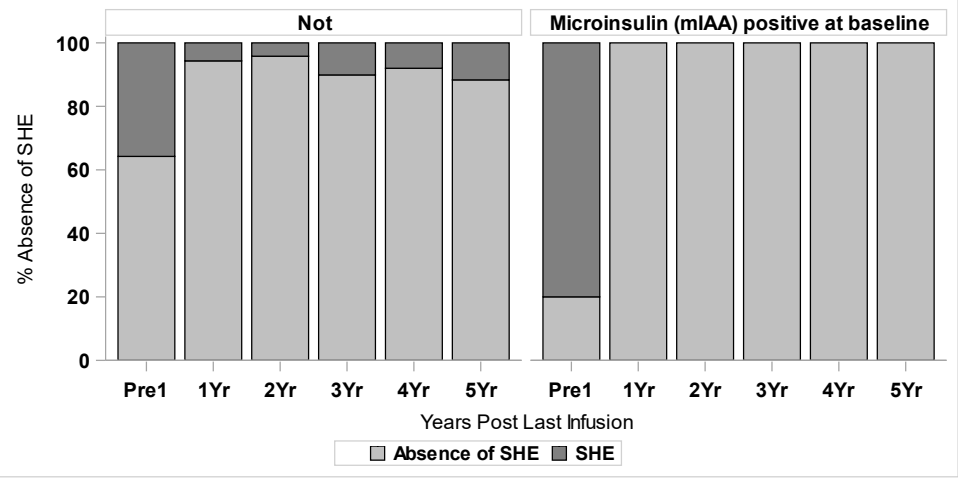
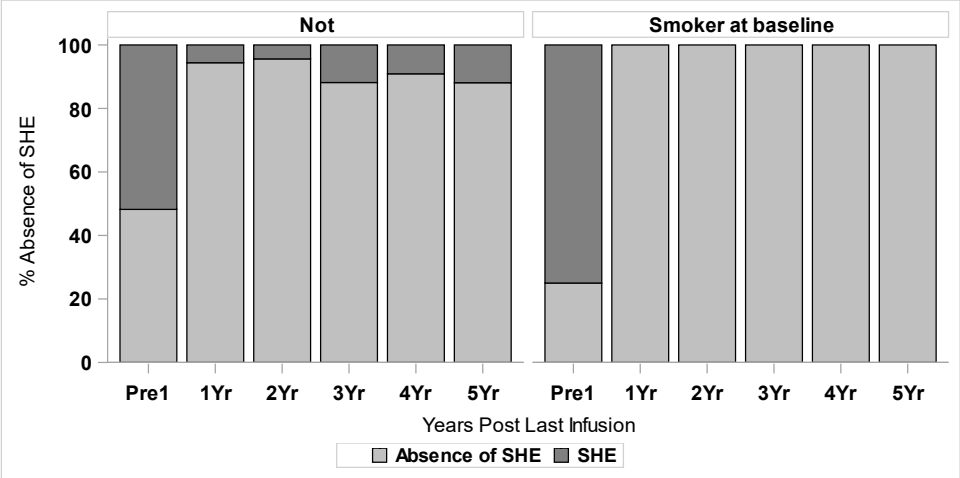
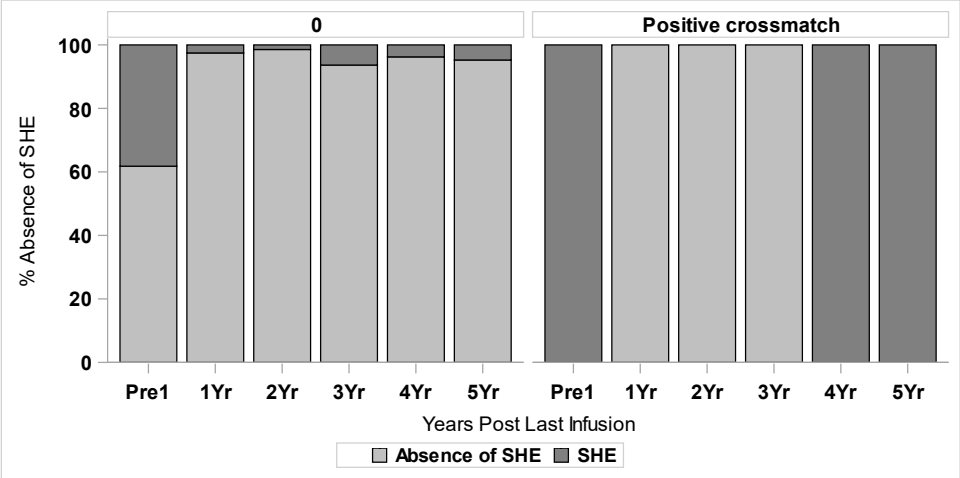


Exhibit 5-7C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among IAK Recipients

Baseline smoker (p=0.0008)



Positive crossmatch (p=0.0013)



IL1-receptor antagonist (IL1R/DSG) (p=<.0001)

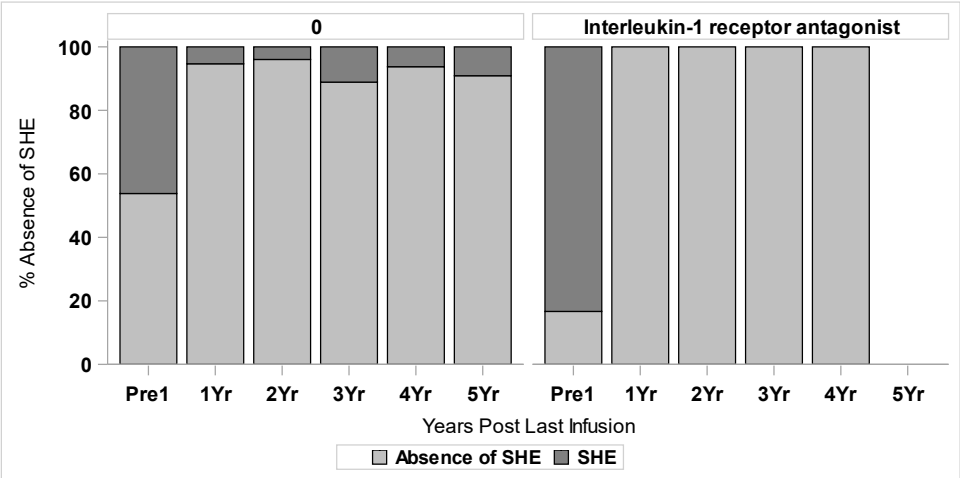
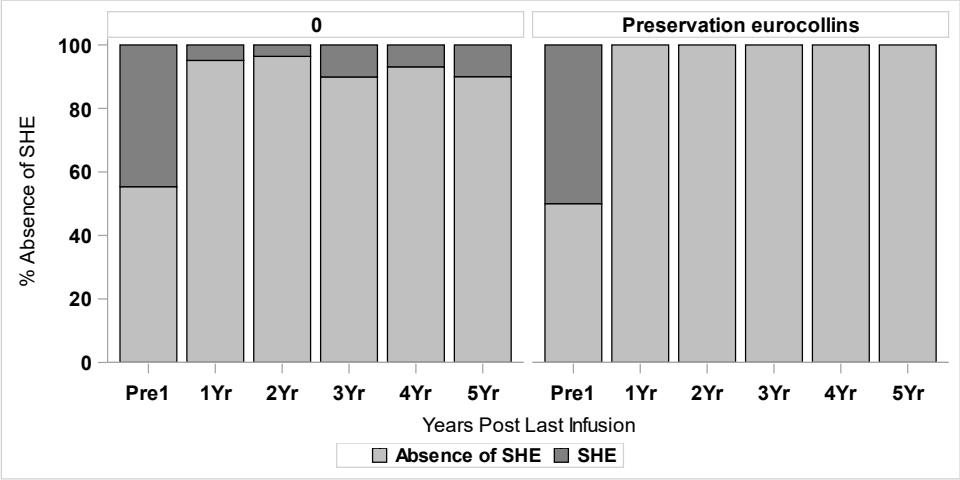
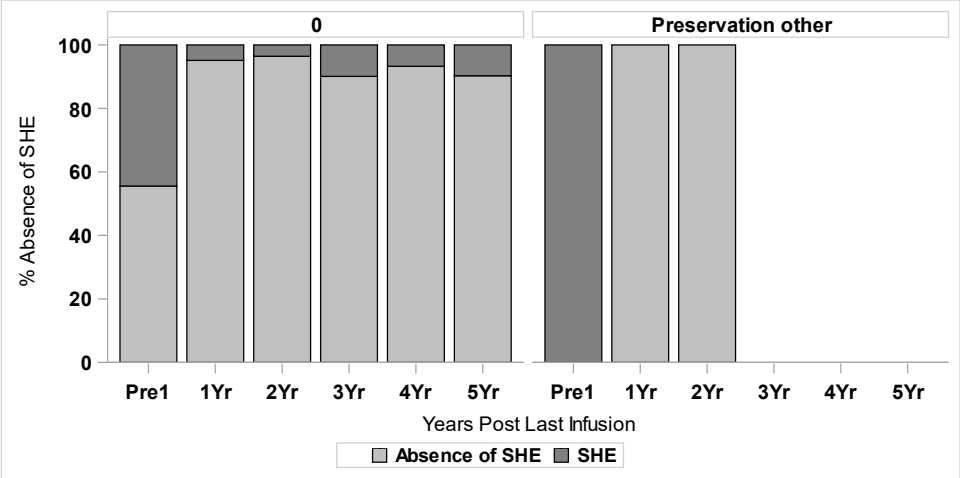


Exhibit 5-7C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among IAK Recipients

Eurocollins presrvation (p=<.0001)



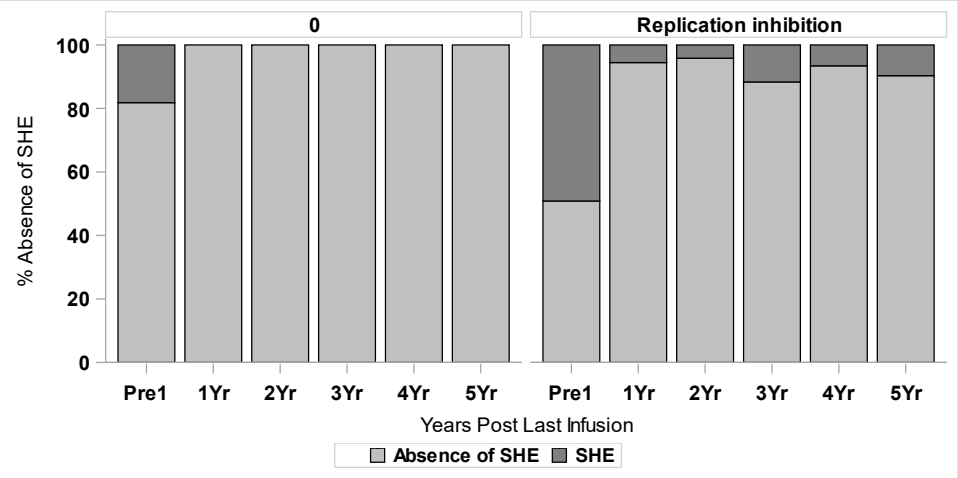
Other preservation (p=0.0010)



Processing center (p=0.0008)

Exhibit 5-7C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Severe Hypoglycemia Events Post Last Infusion among IAK Recipients

IMPDH inhibitor (MMF) (p=<.0001)



Total infusions (p=0.0001)

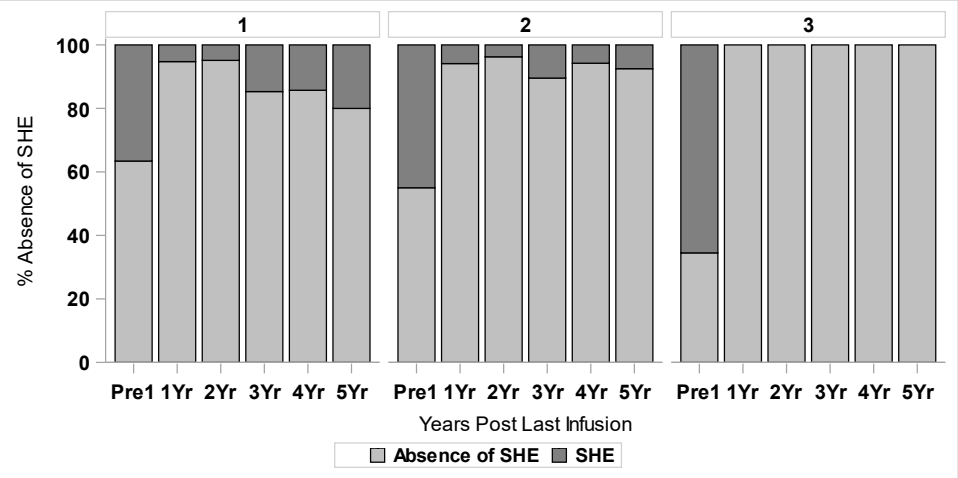
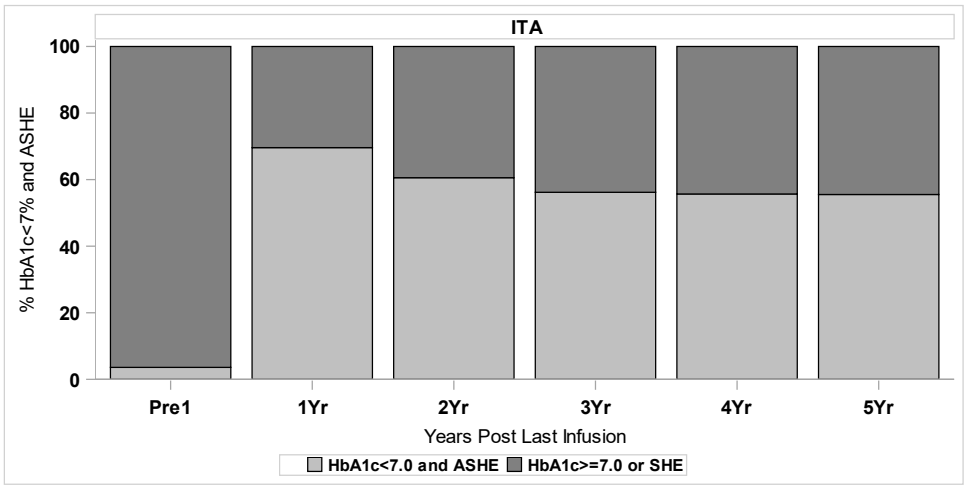


Exhibit 5-8A
Unadjusted Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion



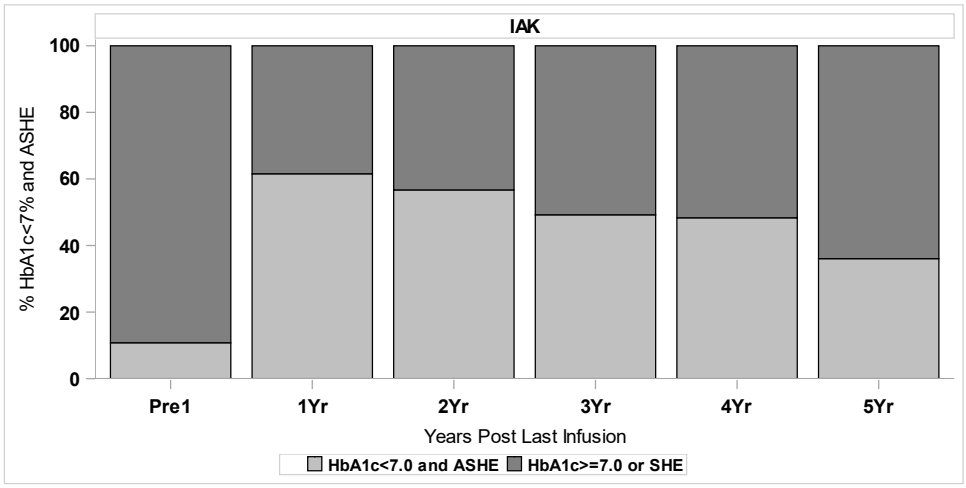
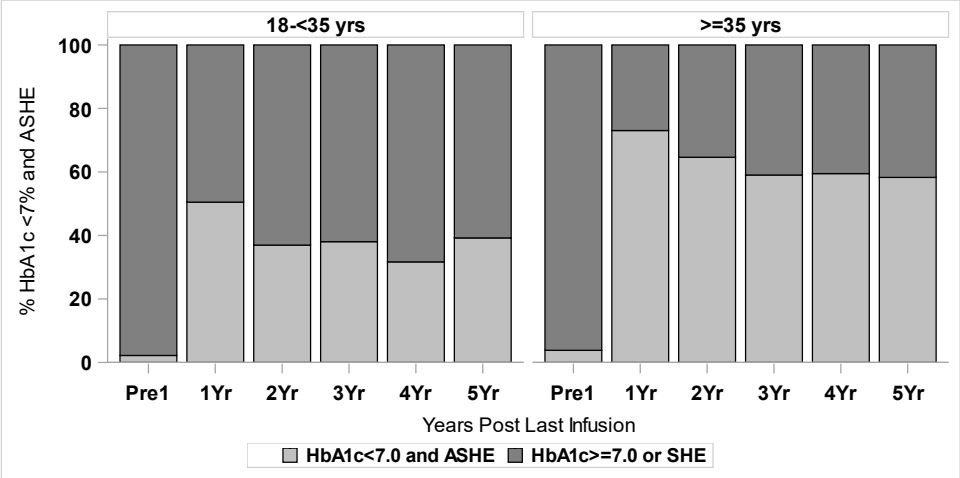
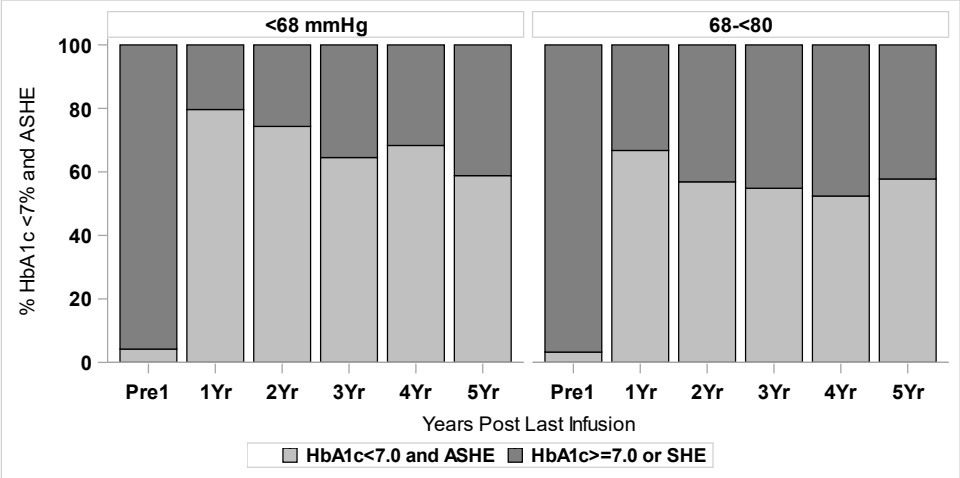


Exhibit 5-8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

Age (p=<.0001)



Baseline DBP (p=0.0005)



Baseline HbA1c (p=<.0001)

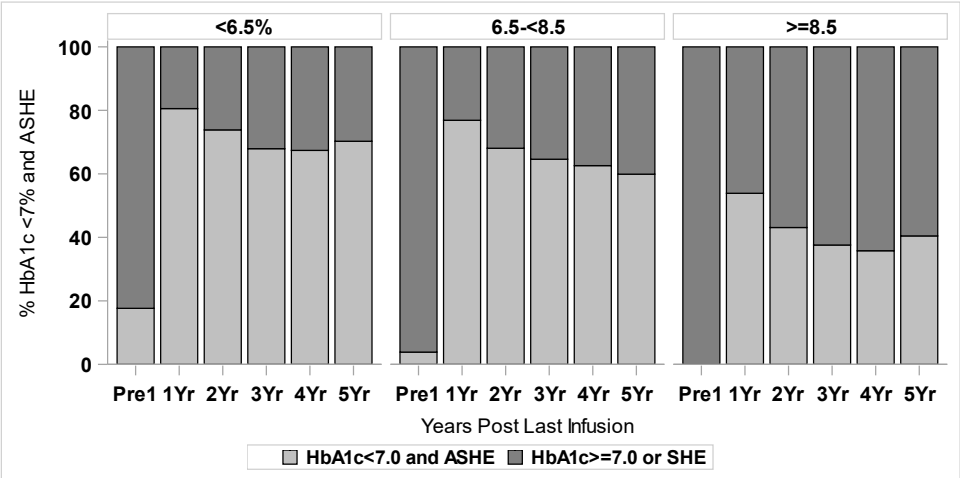
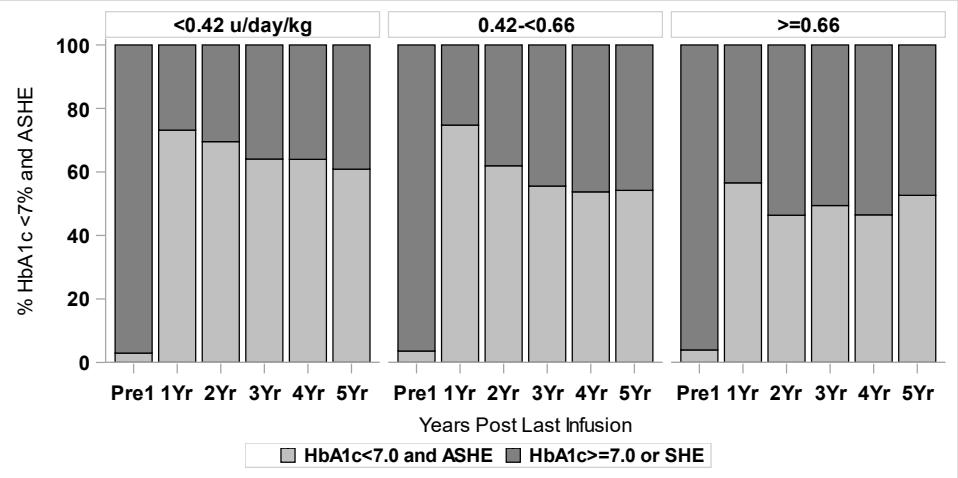
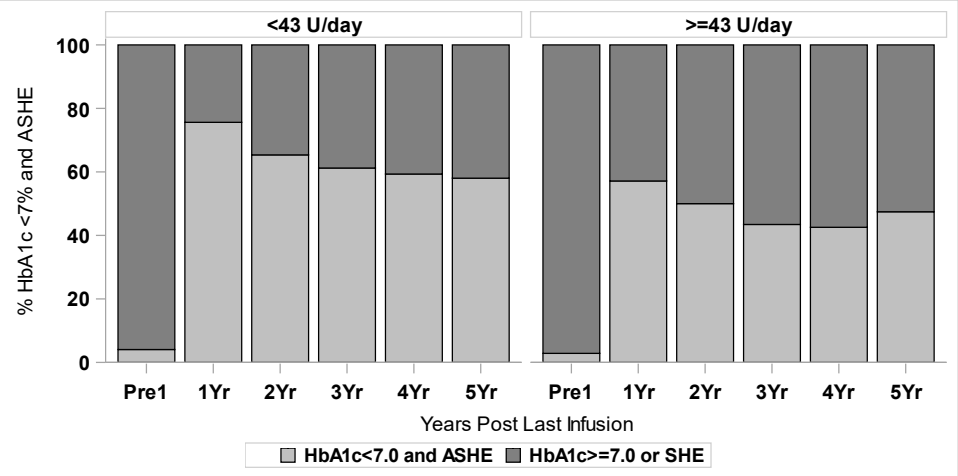


Exhibit 5-8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

Baseline insulin (U/kg/day) (p=0.0065)



Baseline insulin (U/day) (p=0.0001)



Baseline LDL (p=0.0023)

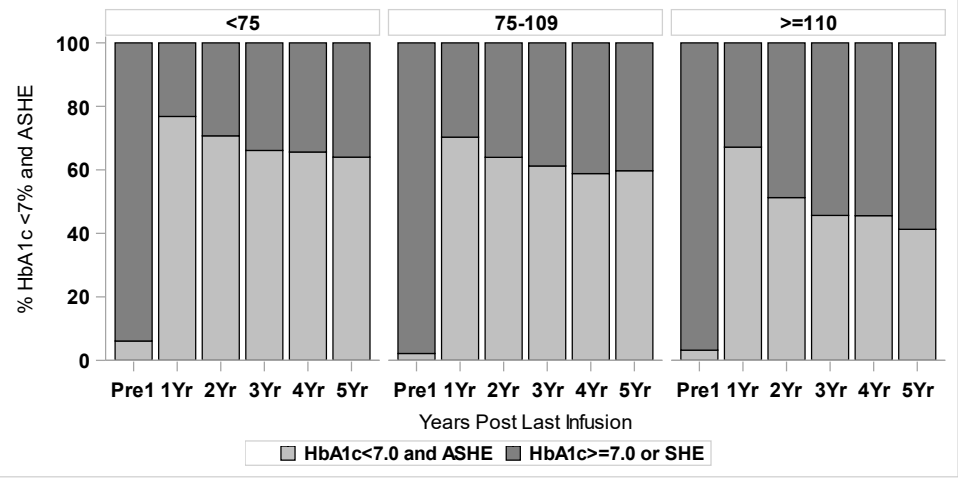
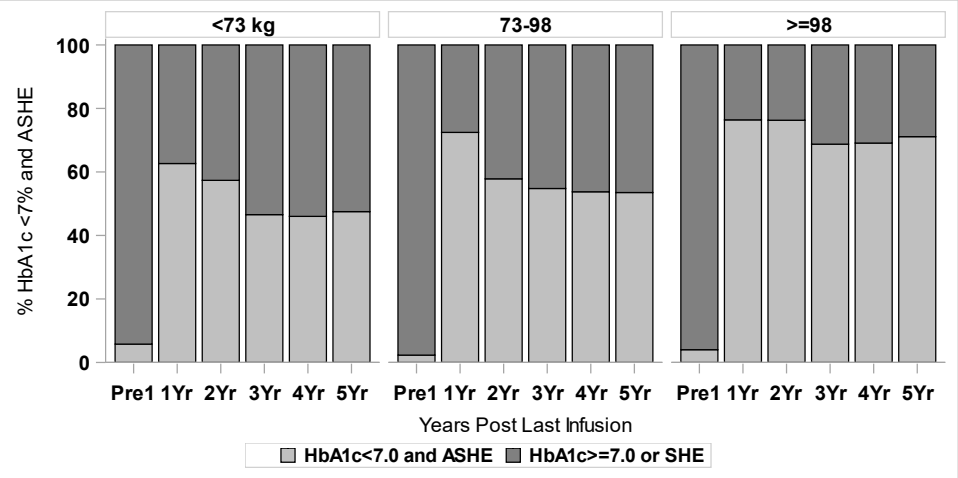
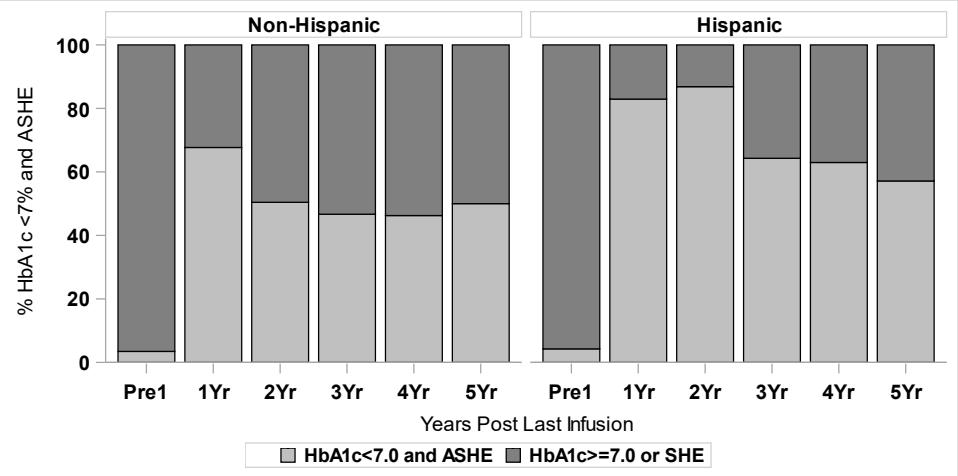


Exhibit 5-8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

Donor weight (kg) (p=0.0001)



Donor Hispanic (p=0.0018)



Donor age (p=0.0024)

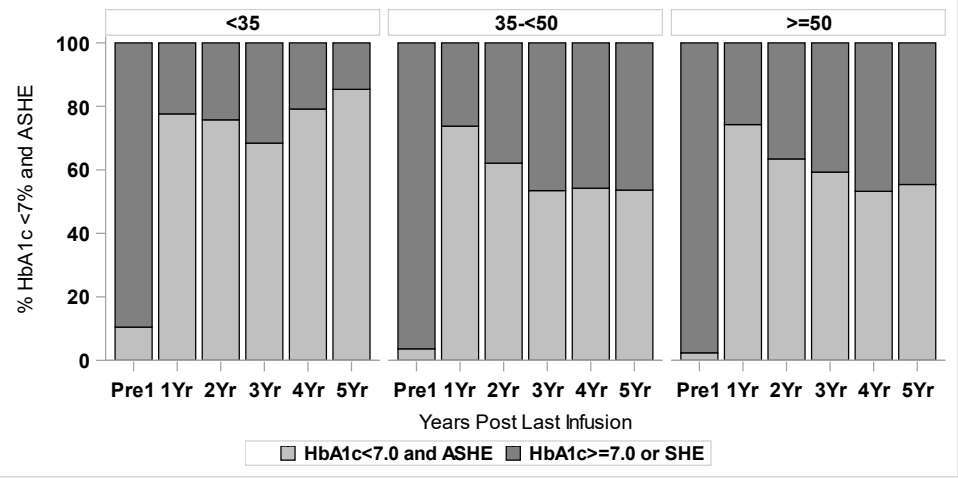
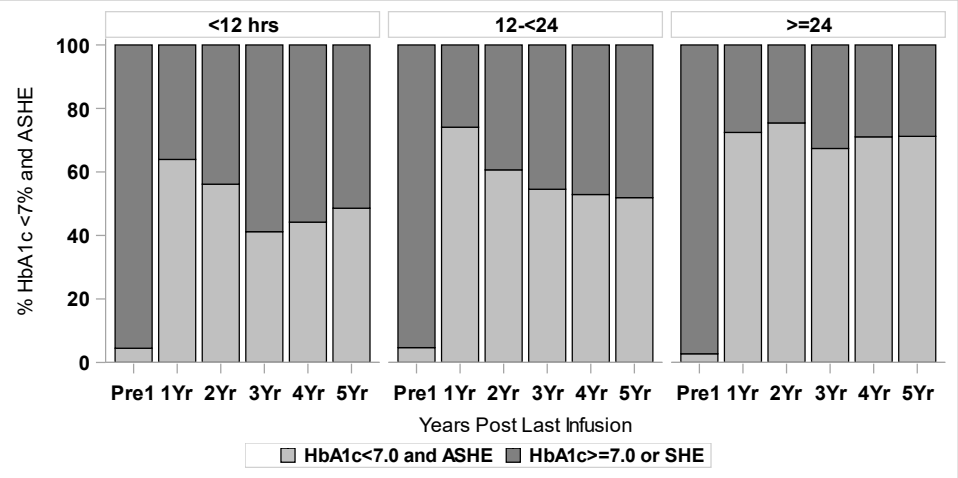
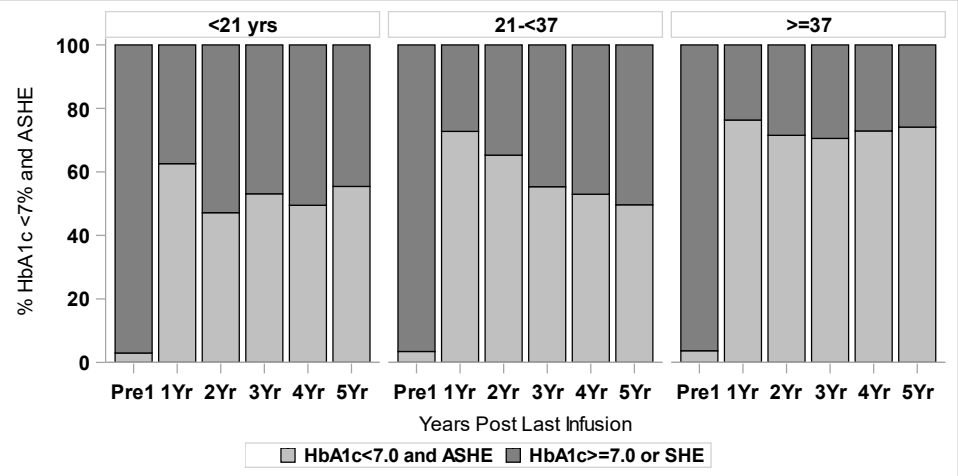


Exhibit 5-8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

Hours: Death to cross-clamp (p=0.0025)



Duration (p=<.0001)



Era (p=<.0001)

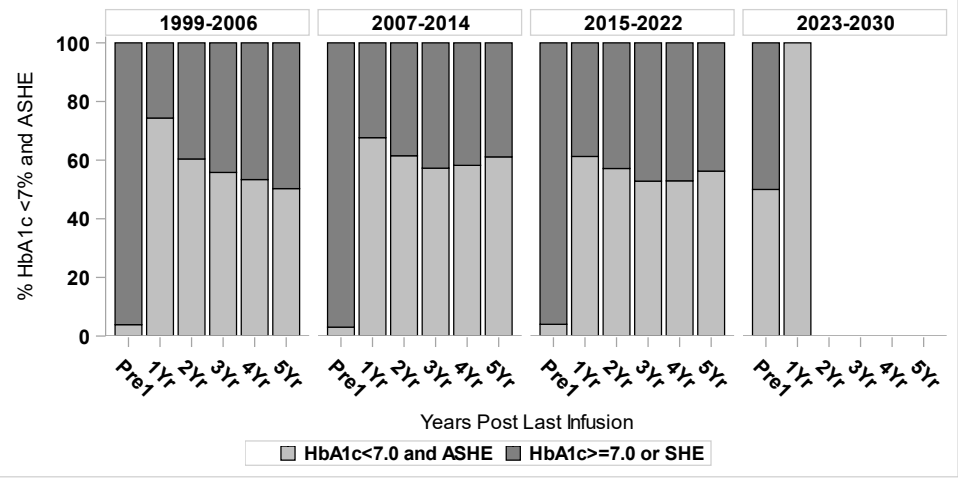
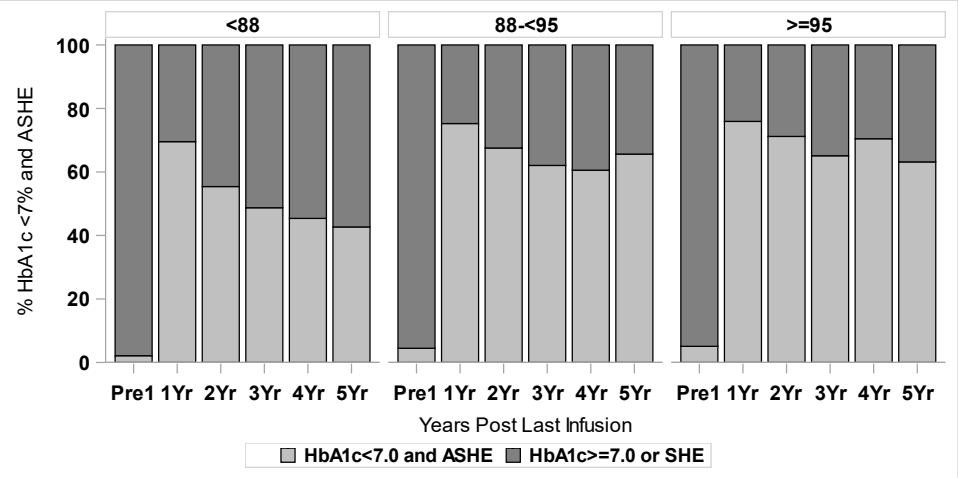
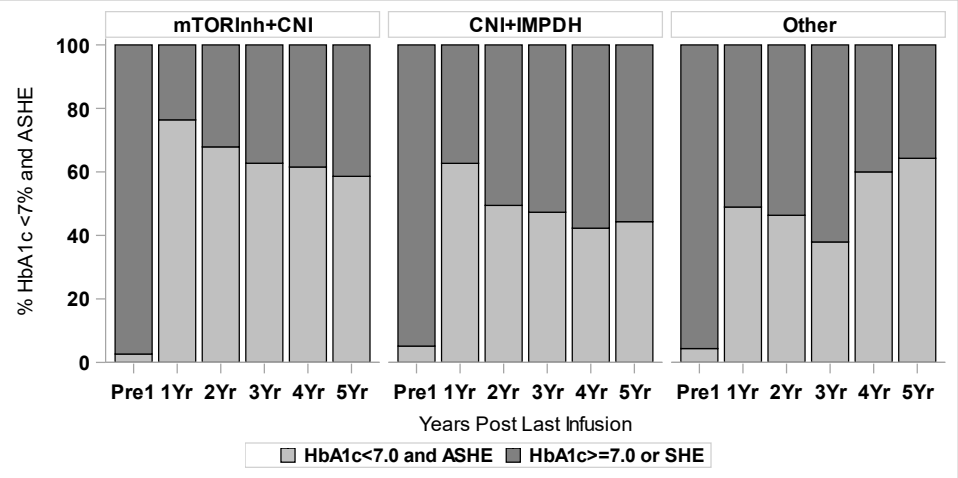


Exhibit 5-8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

Islets viability (%) (p=0.0016)



Maintenance combination (p=<.0001)



Donor max insulin blood glucose (p=0.0005)

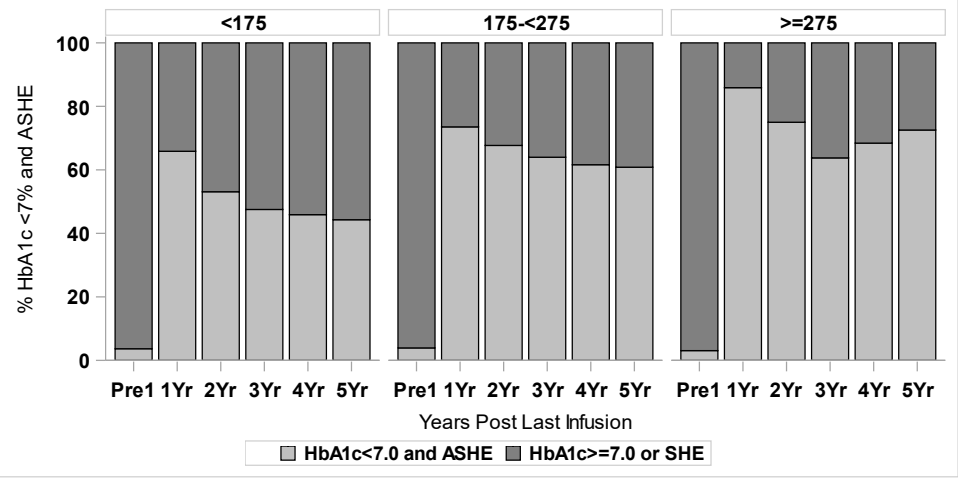
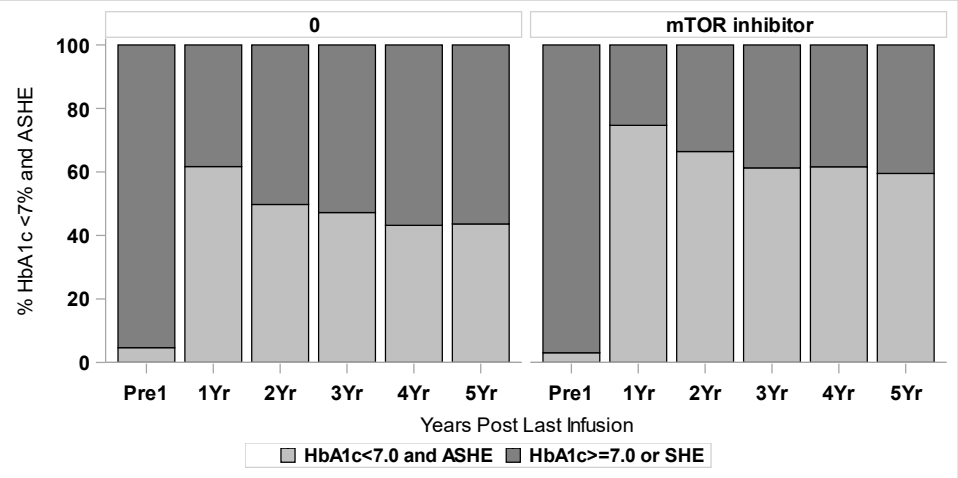
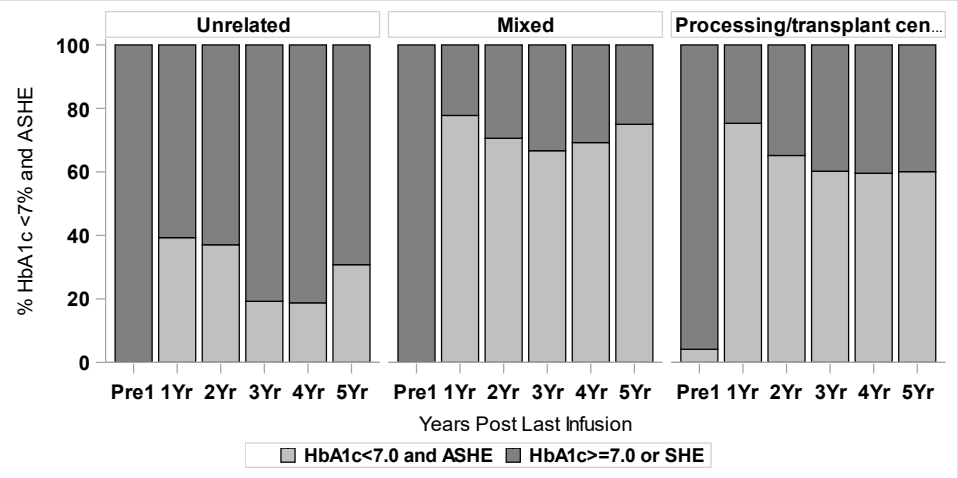


Exhibit 5-8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

mTOR inhibitor (p=<.0001)



Processing center (p=0.0039)



Procurement center (p=0.0015)

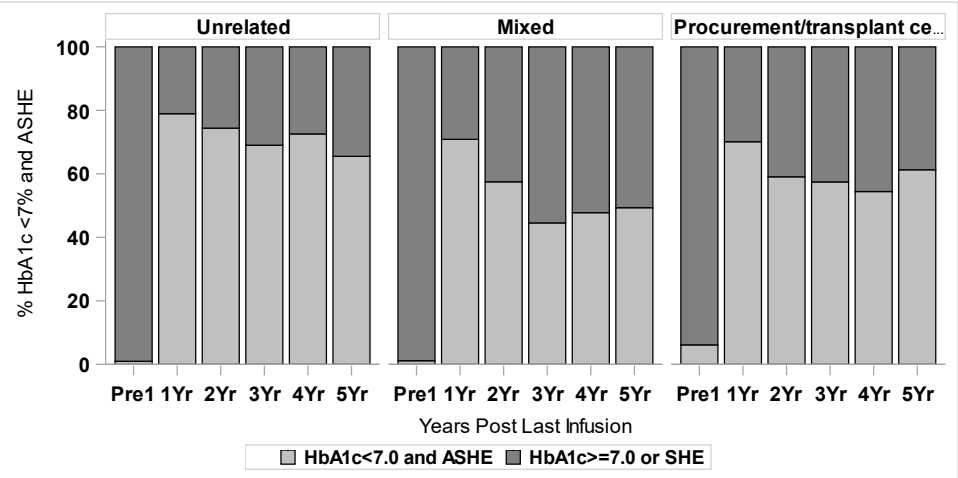
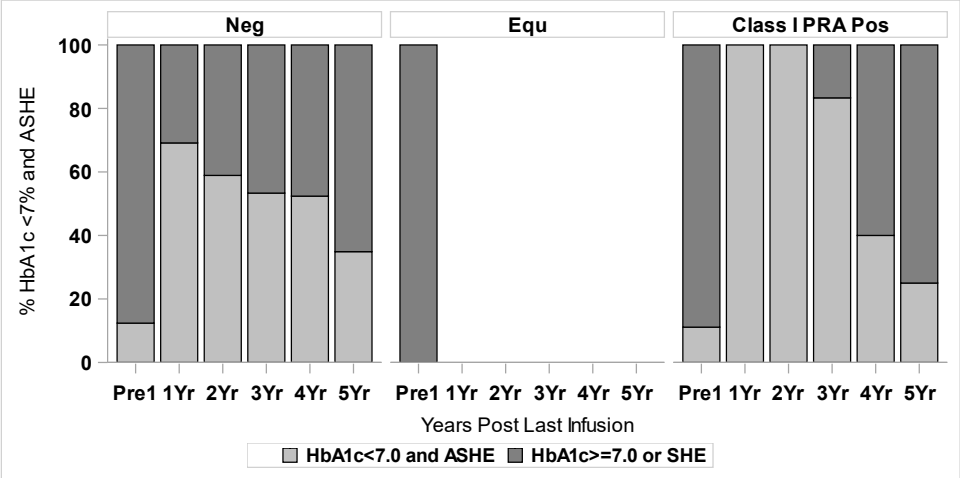
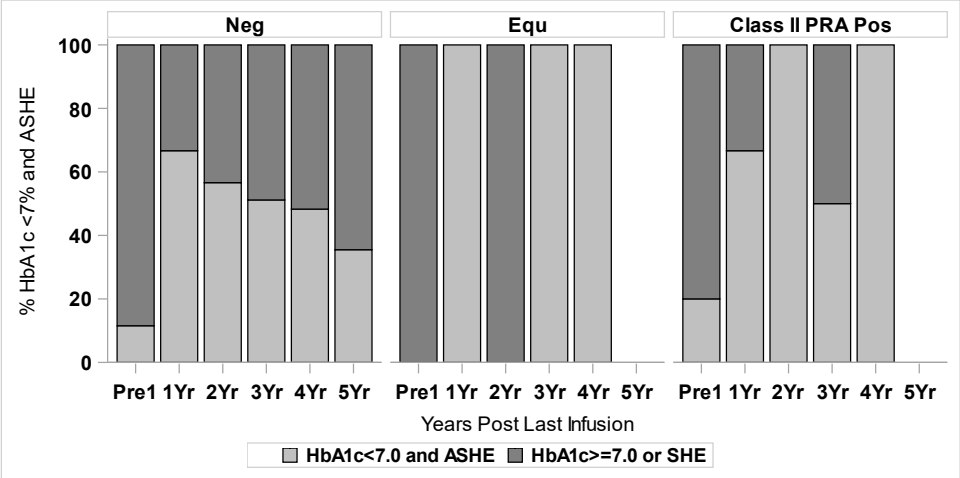


Exhibit 5-8C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

Baseline +Class I PRA (p=0.0051)



Baseline Class II PRA (p=0.0062)



Baseline HbA1c (p=0.0001)

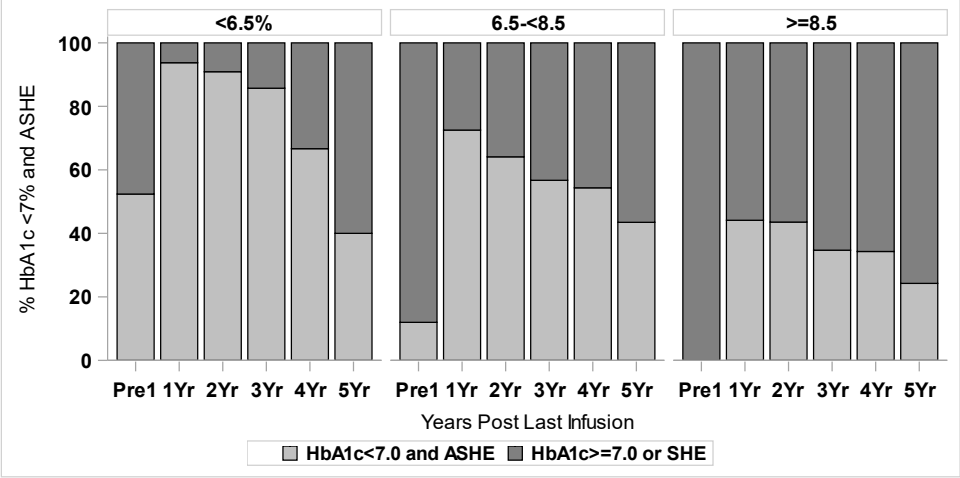
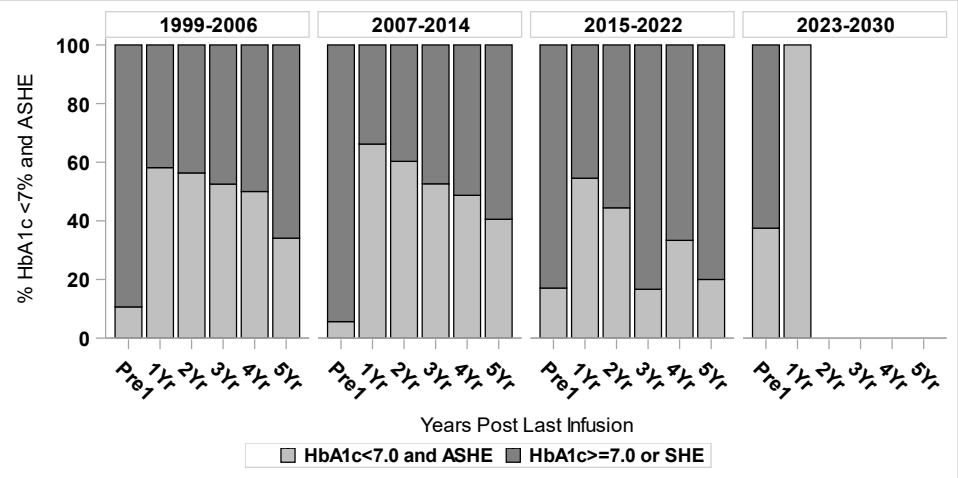
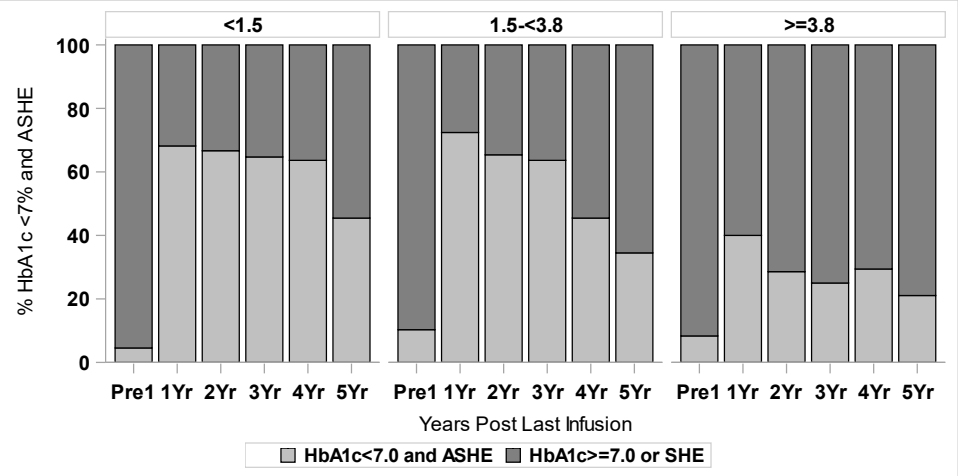


Exhibit 5-8C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

Era (p=<.0001)



Islets stimulation index (p=0.0084)



Donor pre insulin blood glucose (p=0.0065)

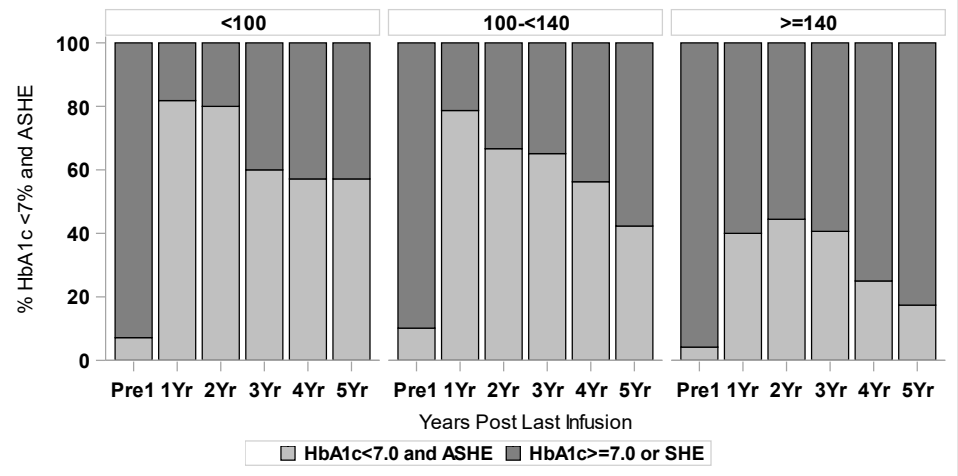
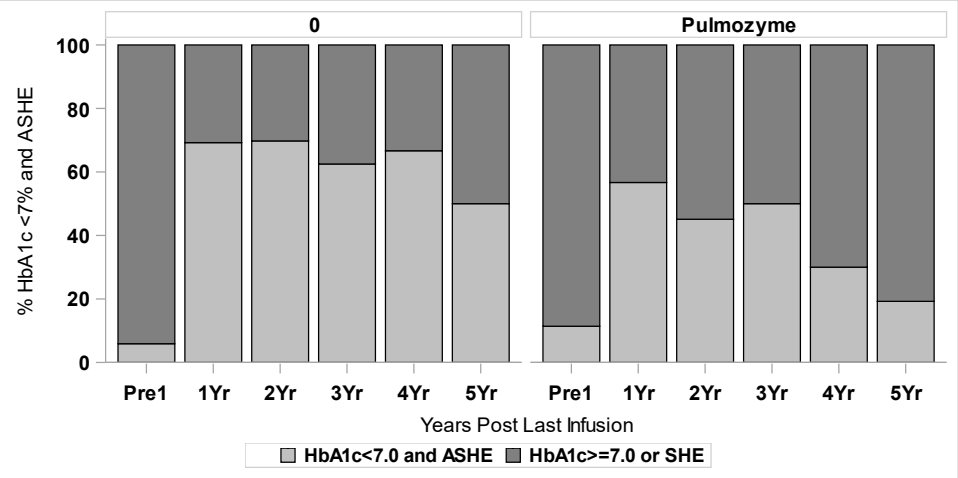
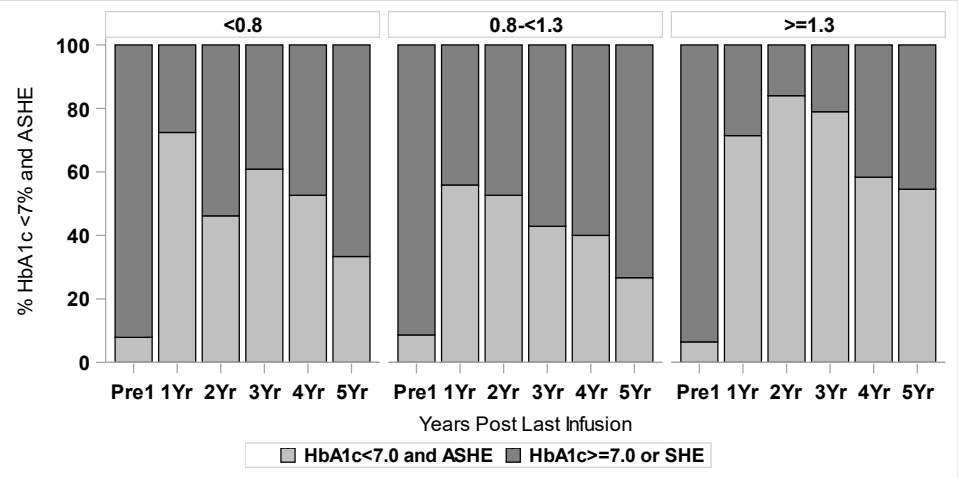


Exhibit 5-8C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

Pulmozyme (p=0.0063)



Donor serum creatinine (p=0.0091)



Thermolysin (p=0.0035)

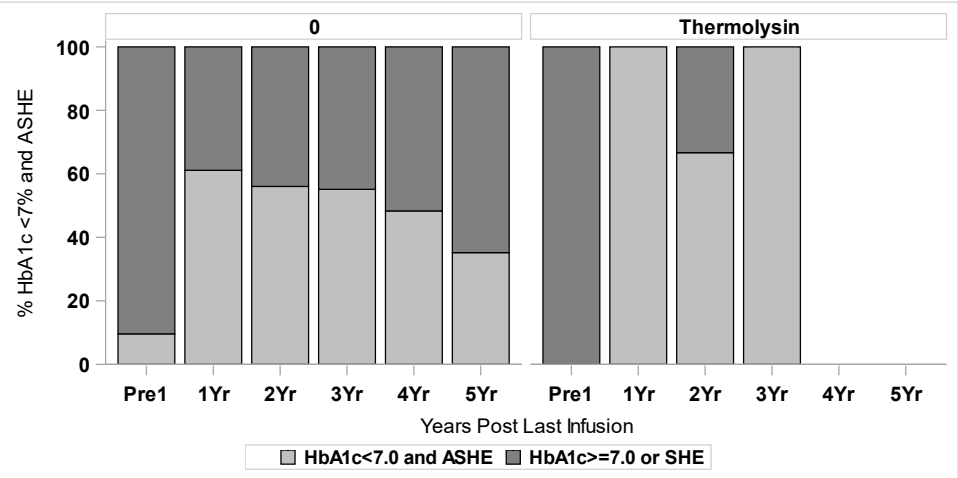


Exhibit 5-8C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

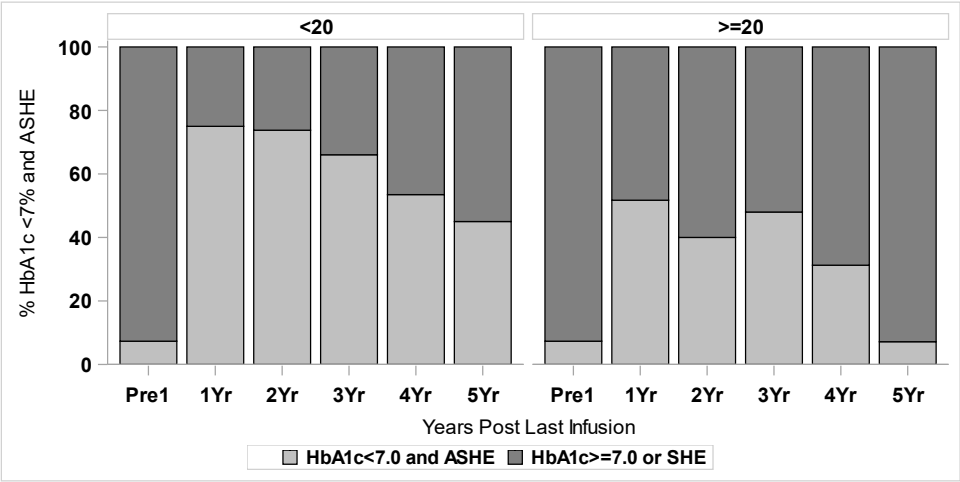


Exhibit 5-9
Insulin Dose (U/day) Post Last Infusion by Infusion Type

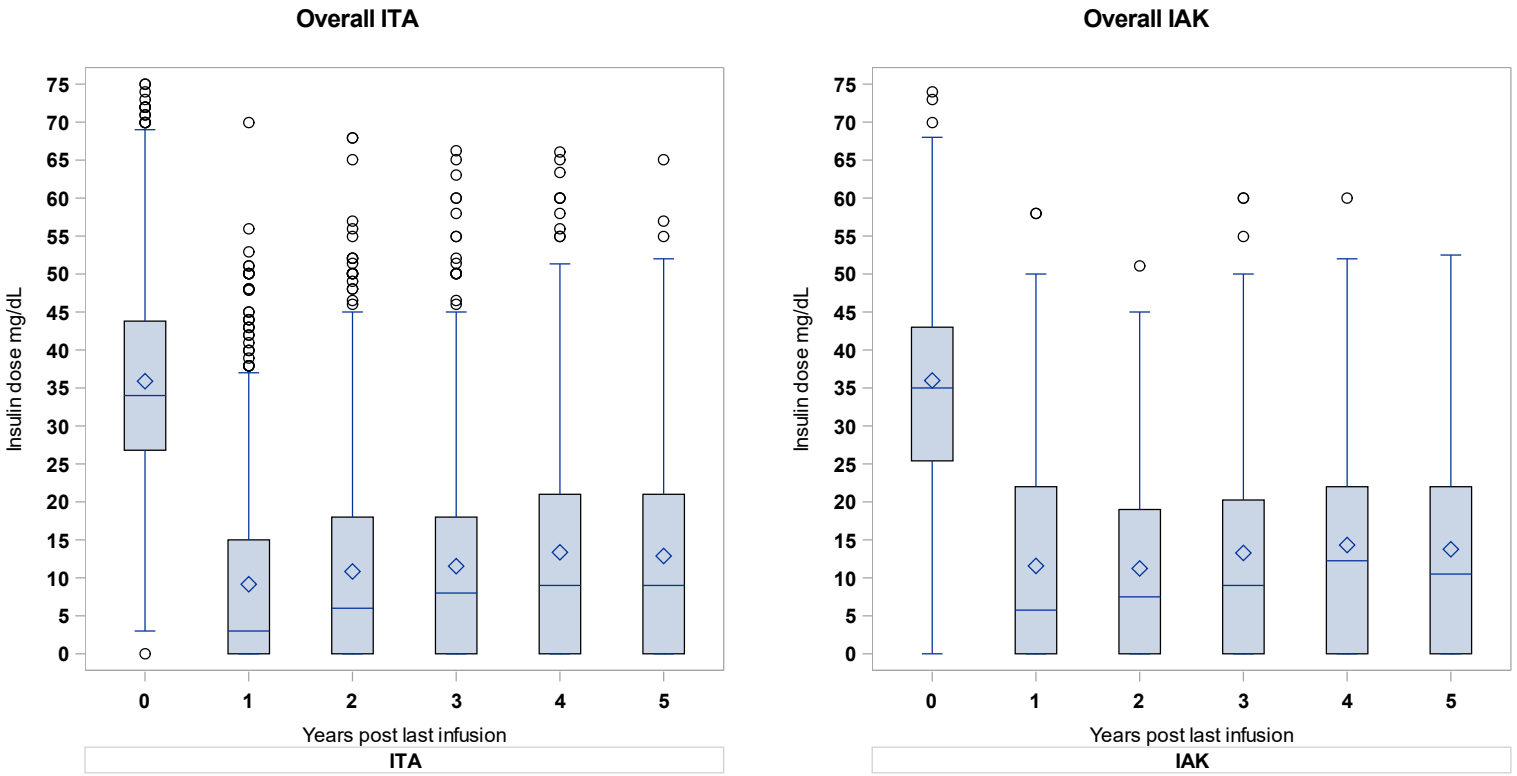


Exhibit 5-9
Insulin Dose (U/day) Post Last Infusion by Infusion Type

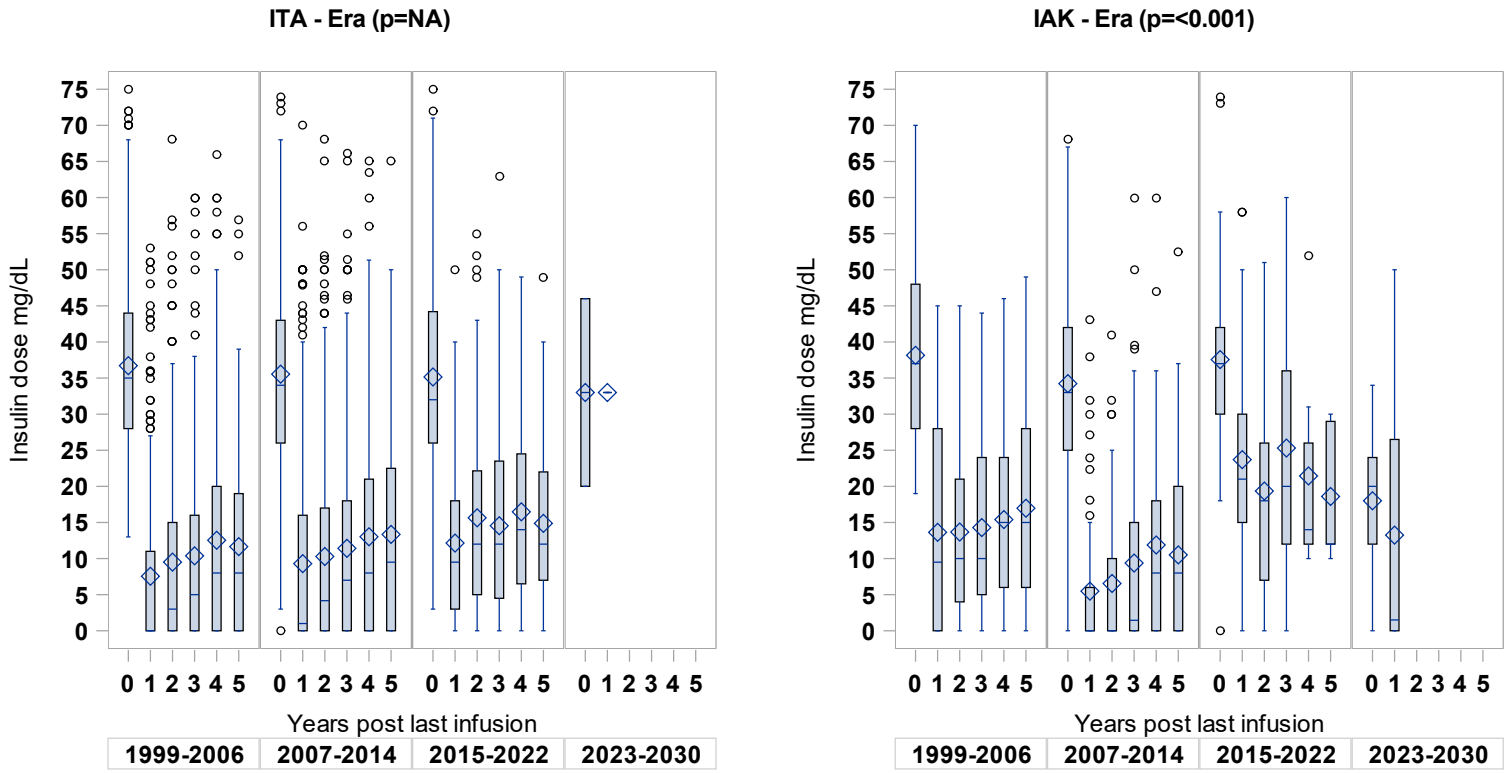


Exhibit 5-9
Insulin Dose (U/day) Post Last Infusion by Infusion Type

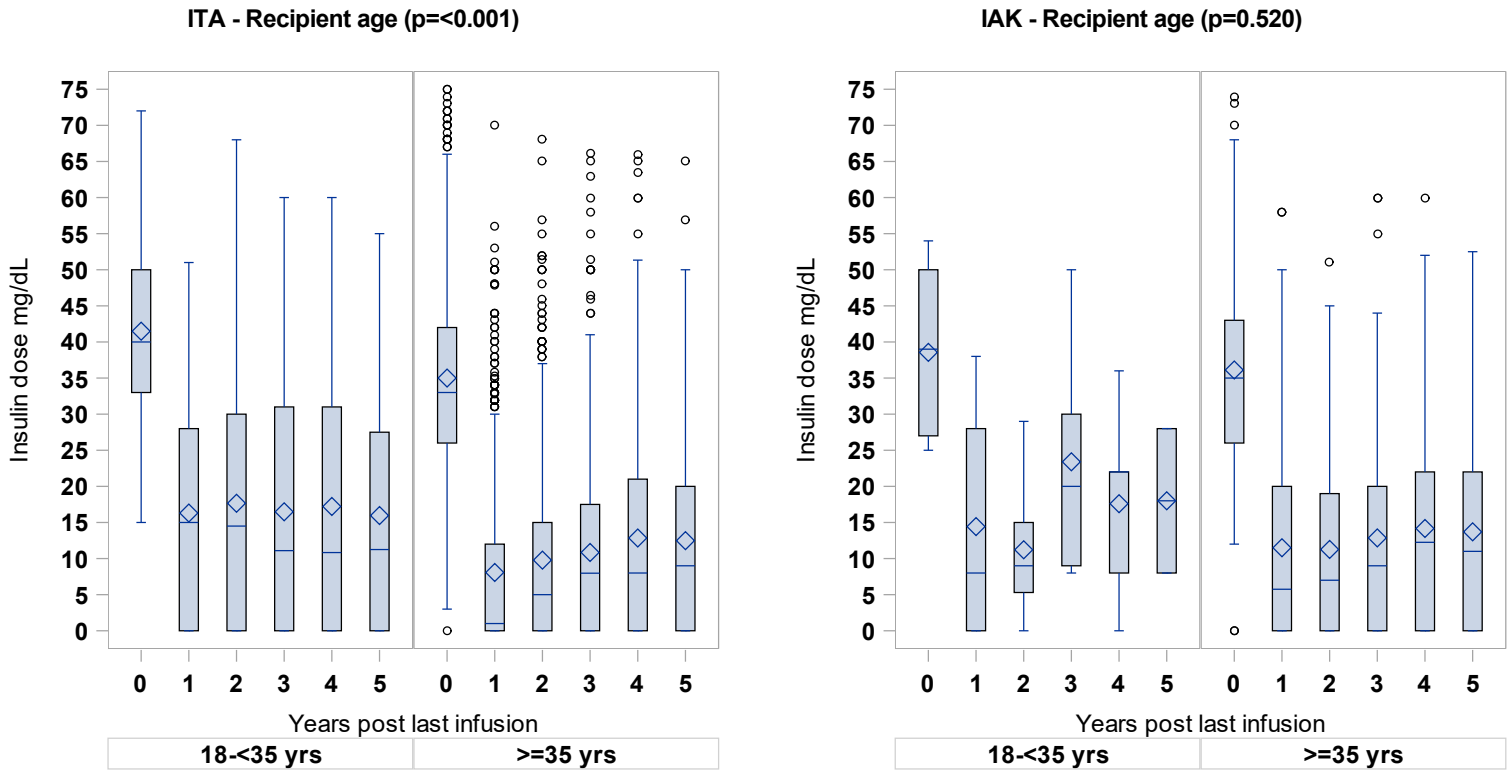


Exhibit 5-9
Insulin Dose (U/day) Post Last Infusion by Infusion Type

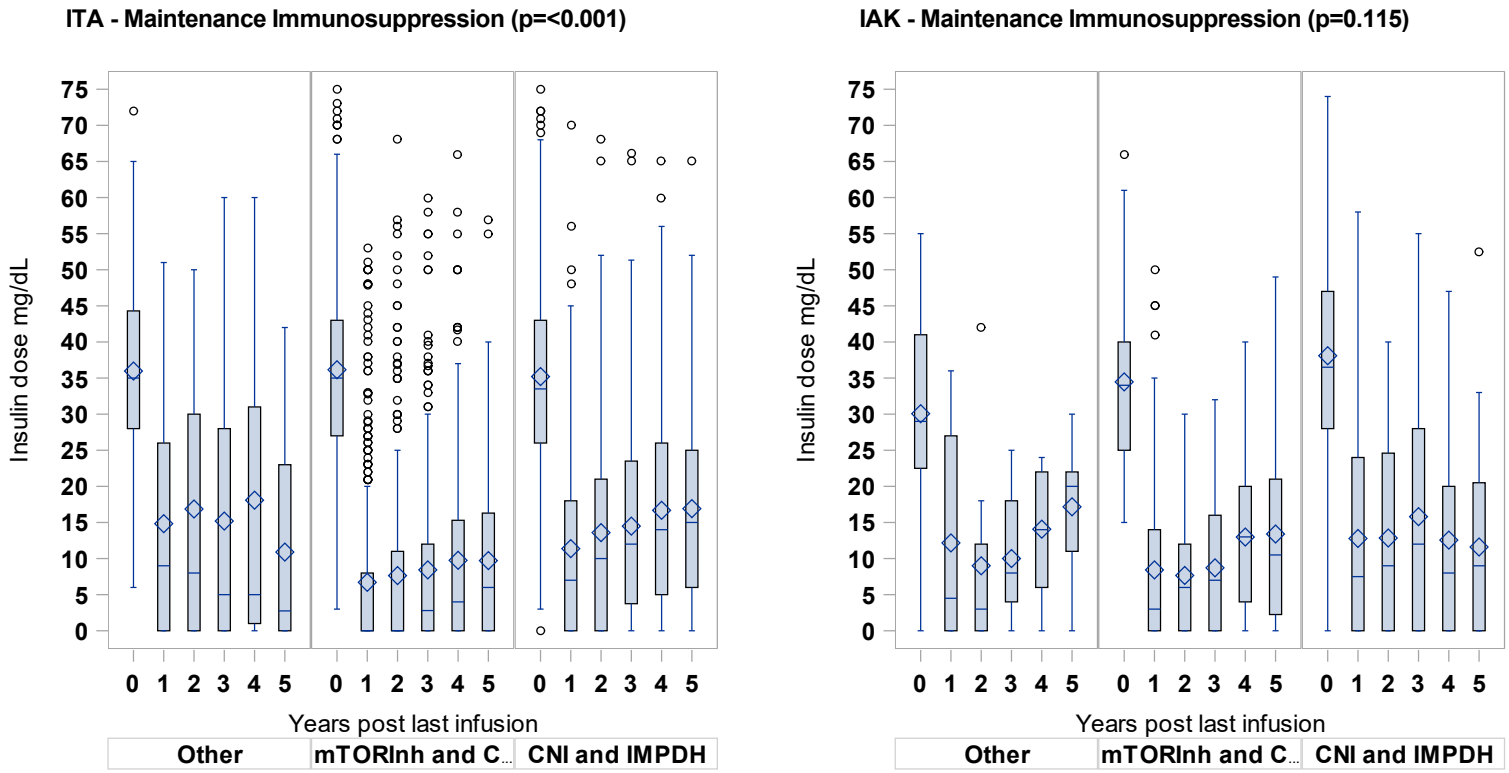


Exhibit 5-10
Fasting C-peptide (ng/mL) Post Last Infusion by Infusion Type

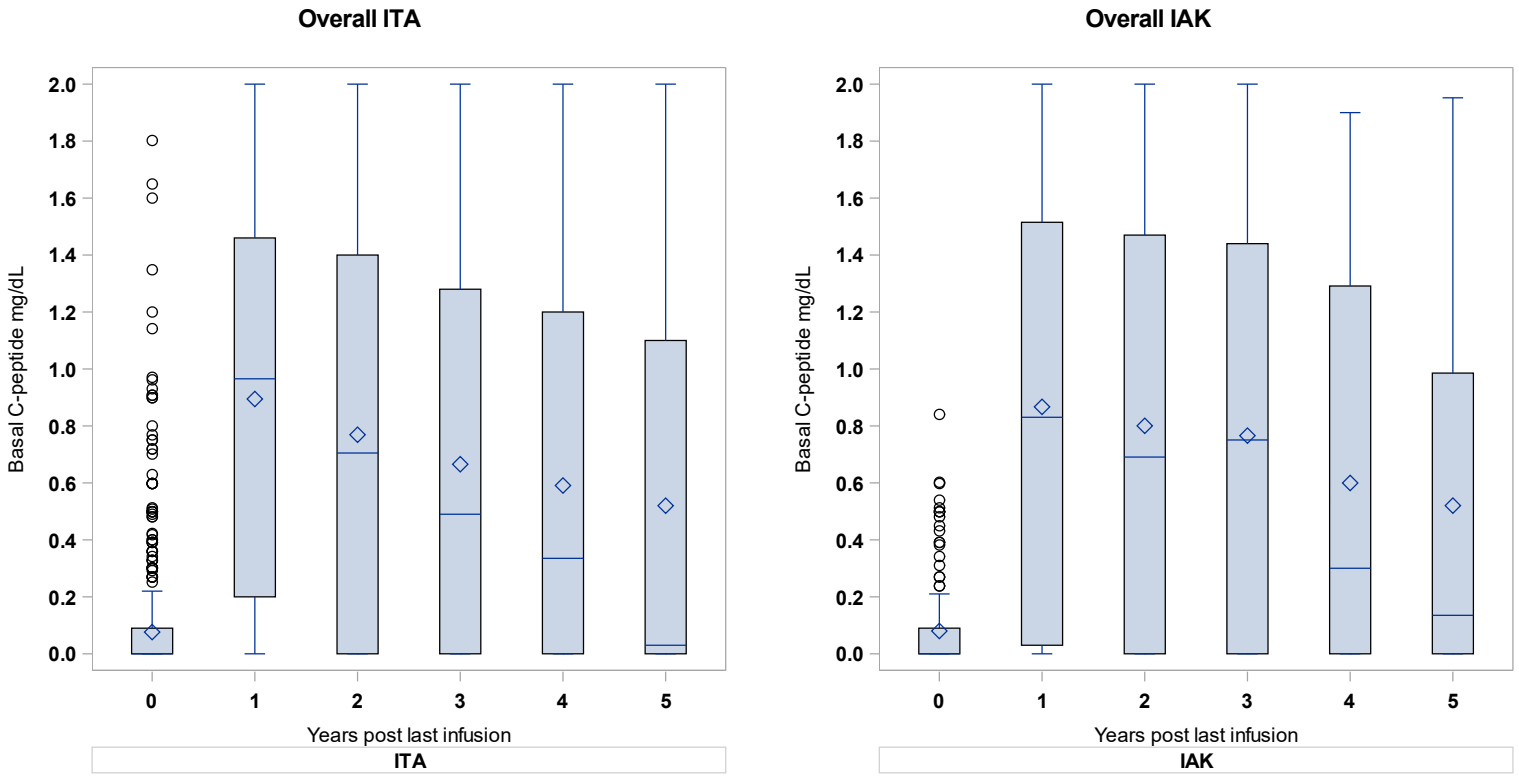


Exhibit 5-10
Fasting C-peptide (ng/mL) Post Last Infusion by Infusion Type

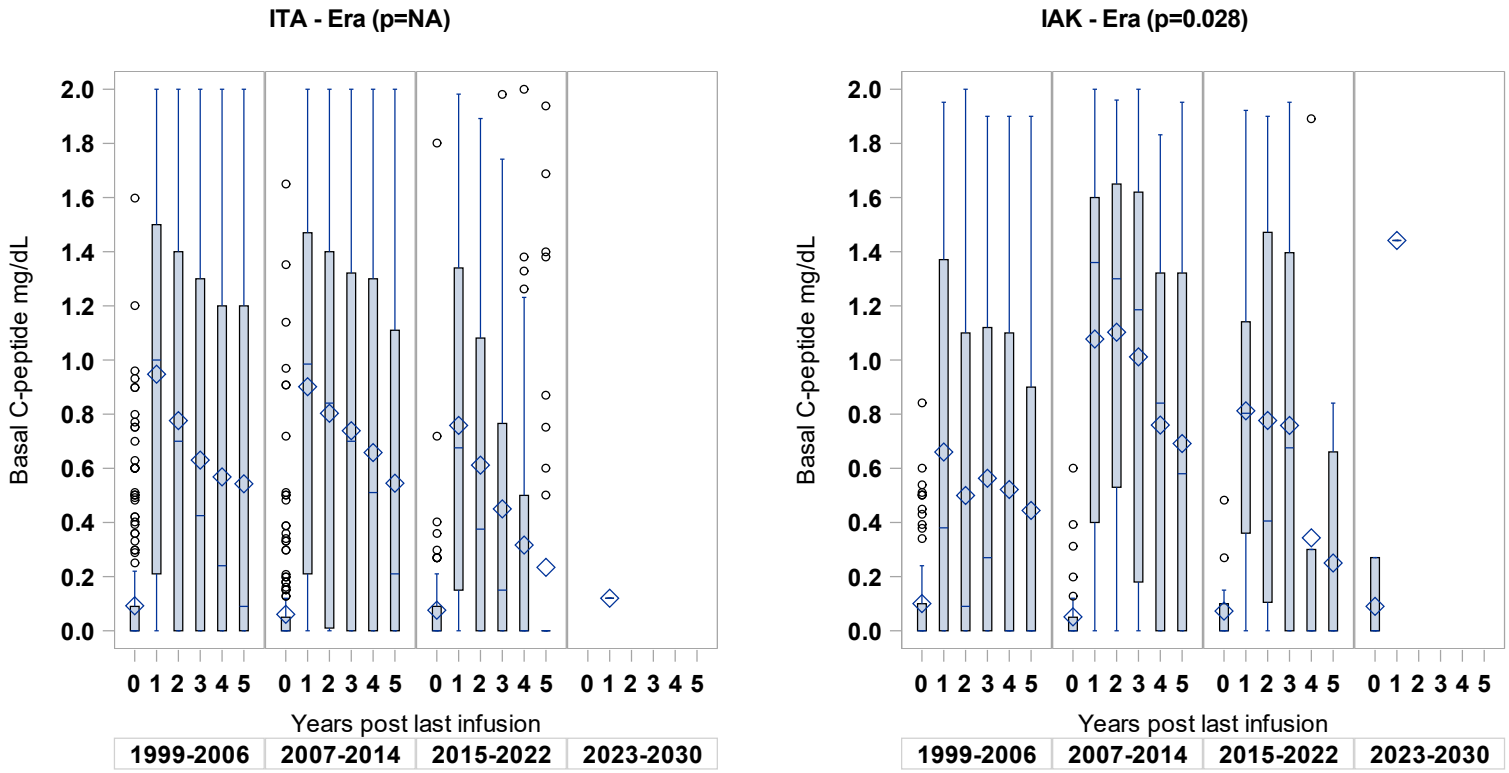


Exhibit 5-10
Fasting C-peptide (ng/mL) Post Last Infusion by Infusion Type

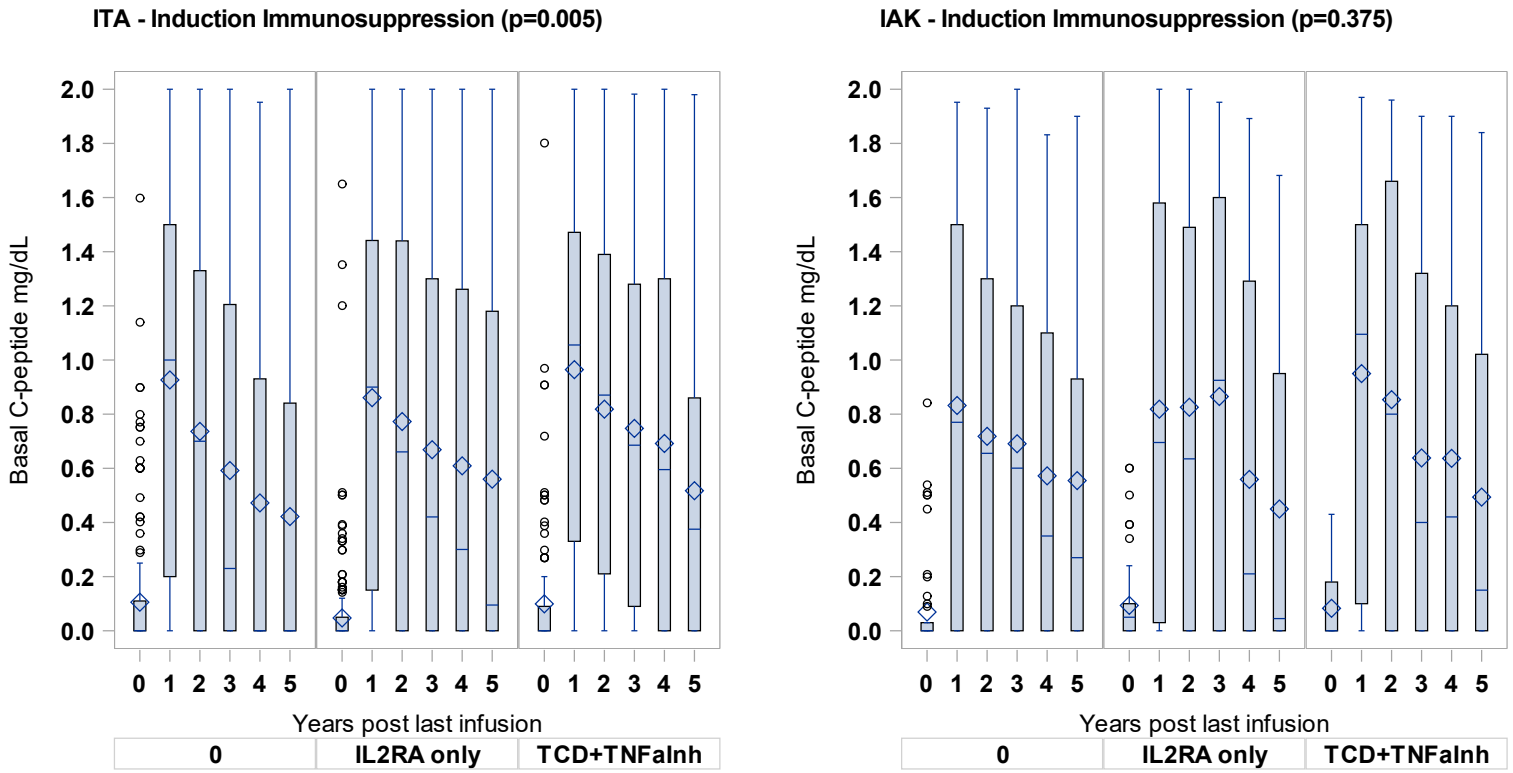


Exhibit 5-11
HbA1c (%) Post Last Infusion by Infusion Type

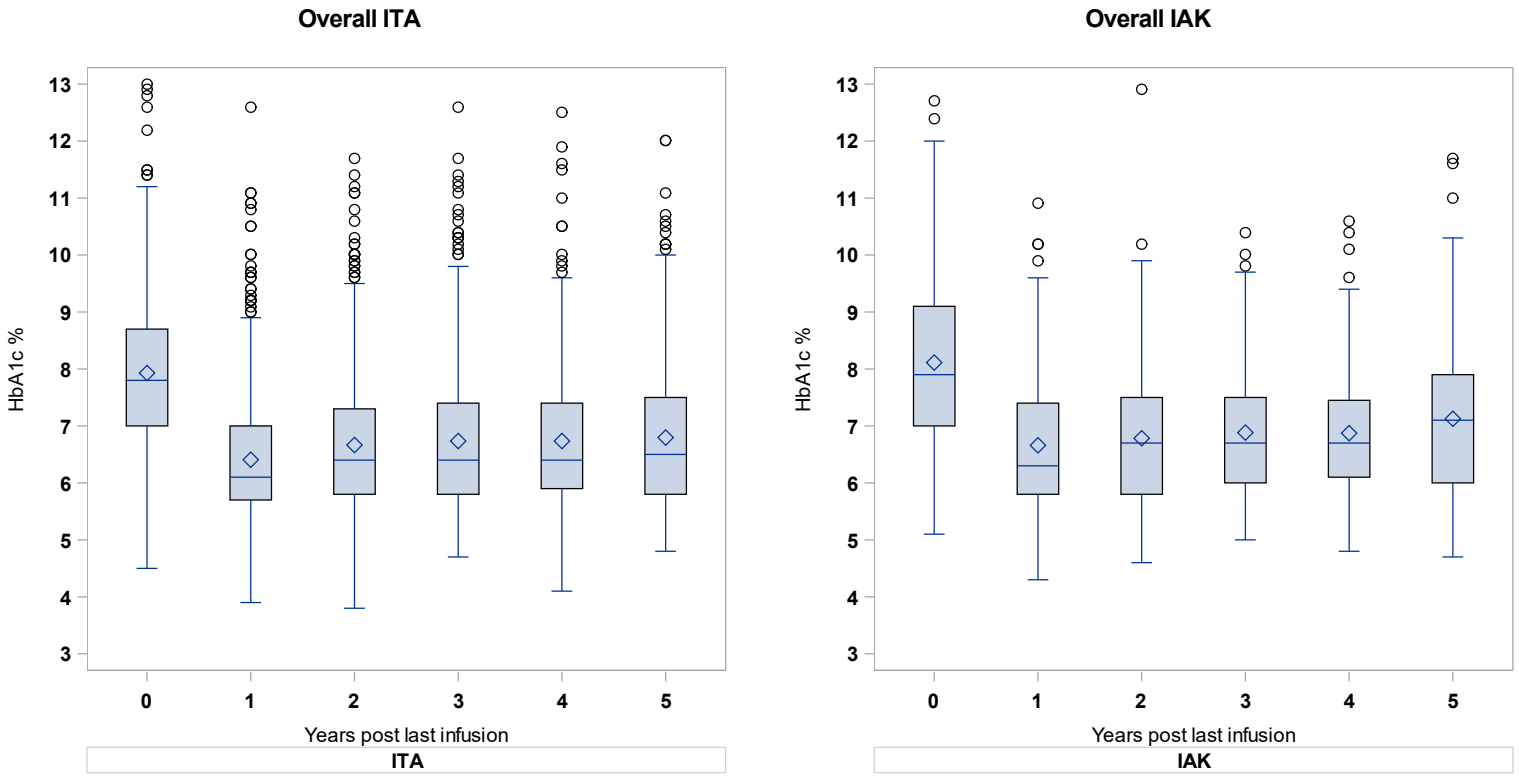


Exhibit 5-11
HbA1c (%) Post Last Infusion by Infusion Type

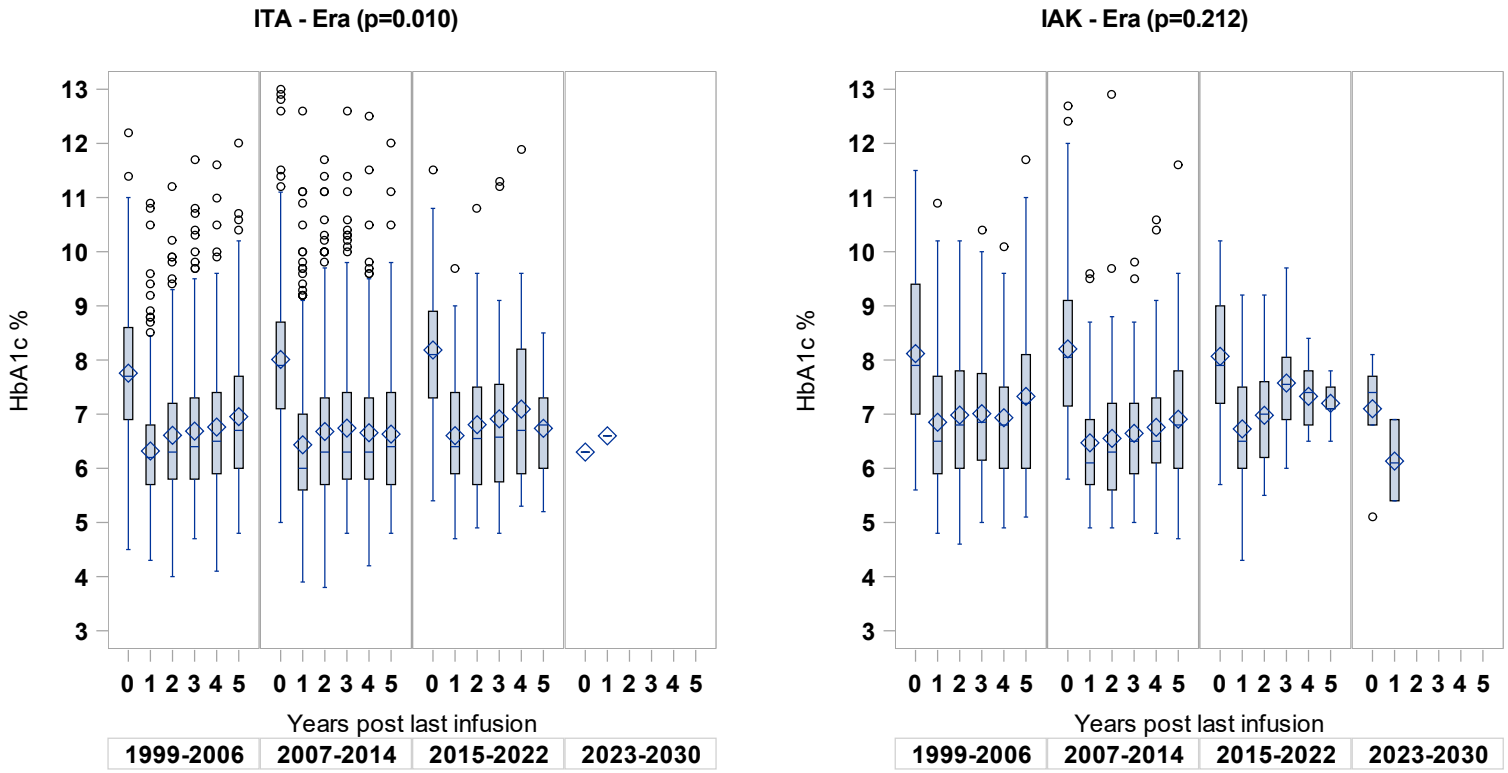


Exhibit 5-11
HbA1c (%) Post Last Infusion by Infusion Type

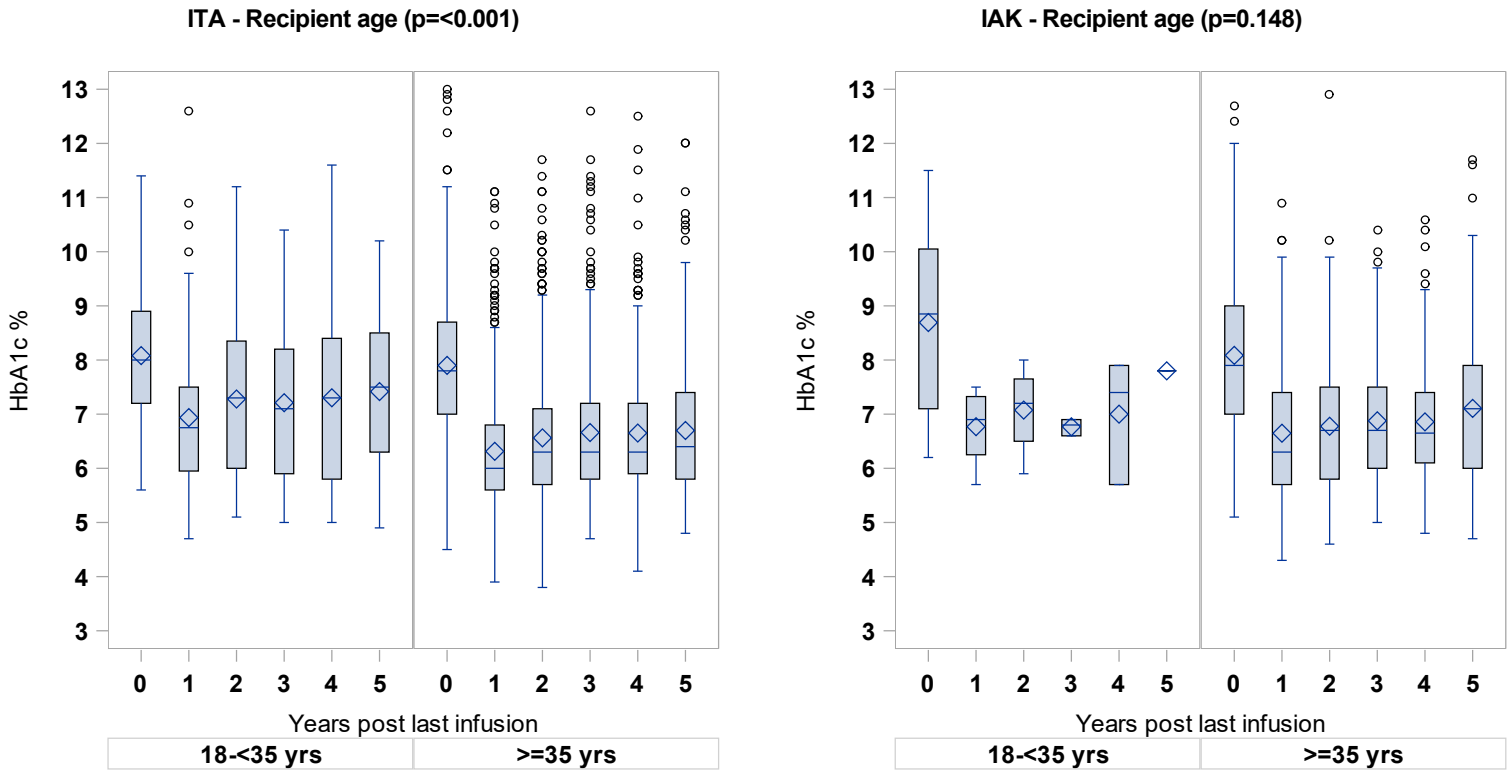


Exhibit 5-11
HbA1c (%) Post Last Infusion by Infusion Type

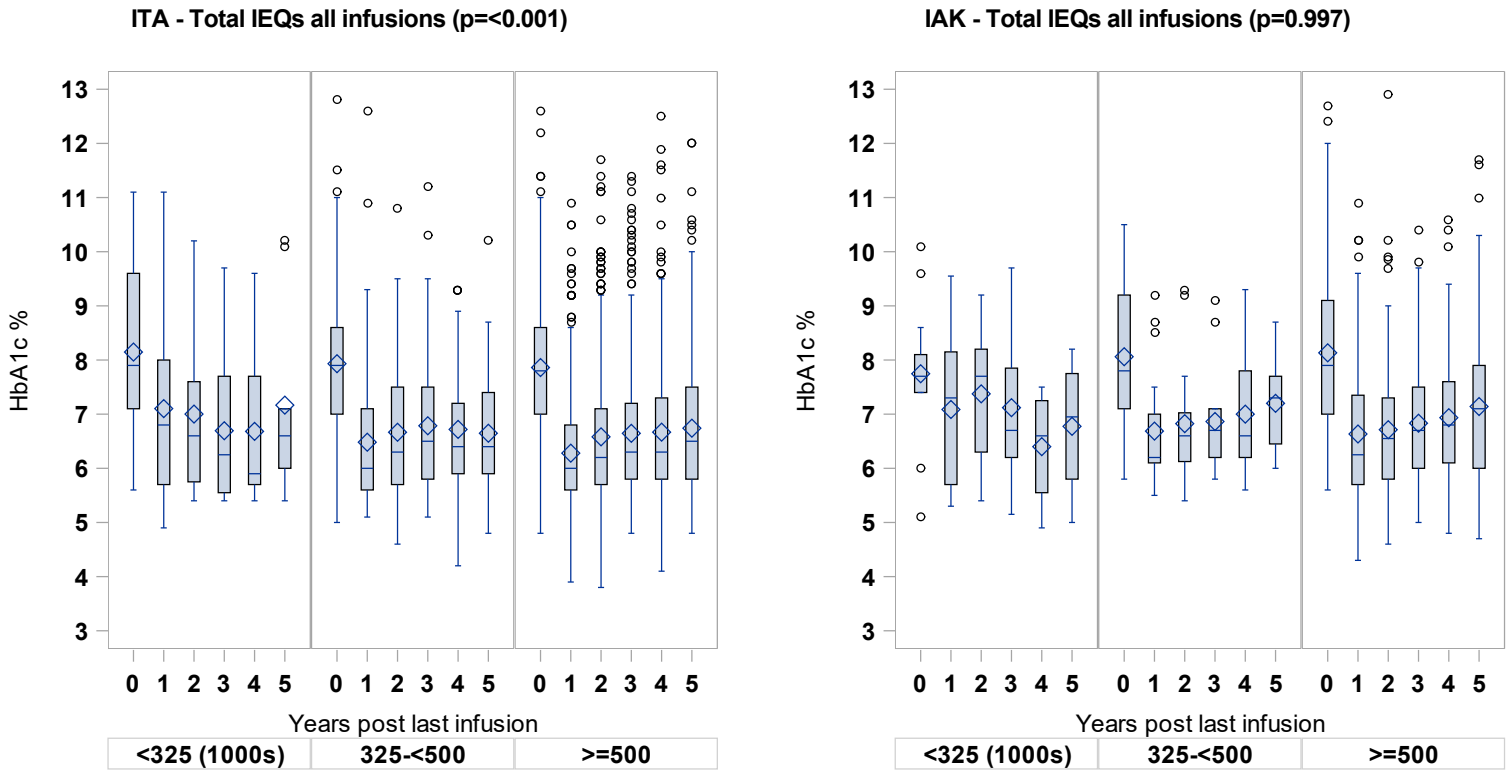


Exhibit 5-11
HbA1c (%) Post Last Infusion by Infusion Type

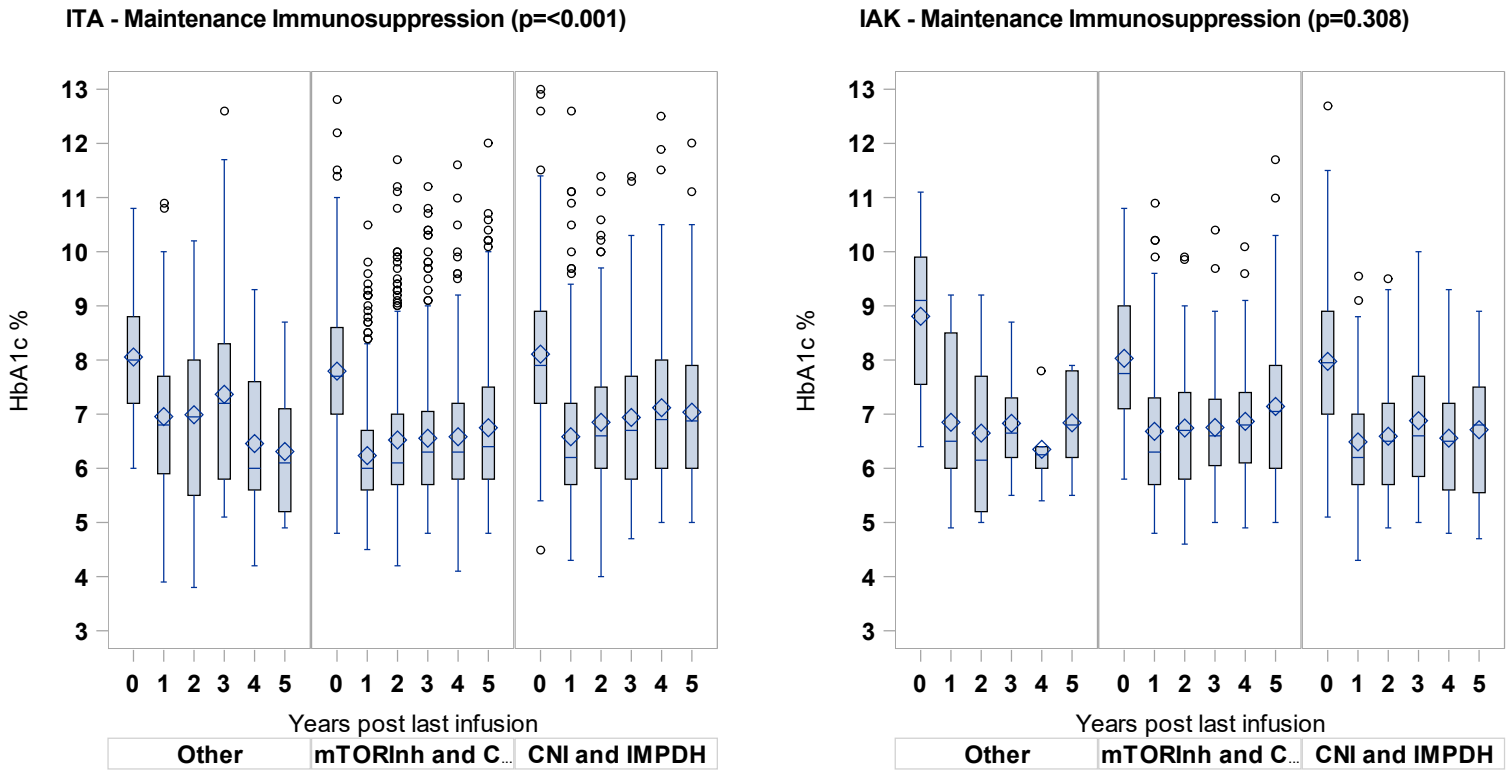


Exhibit 5-12
Fasting Blood Glucose (mg/dL) Post Last Infusion by Infusion Type

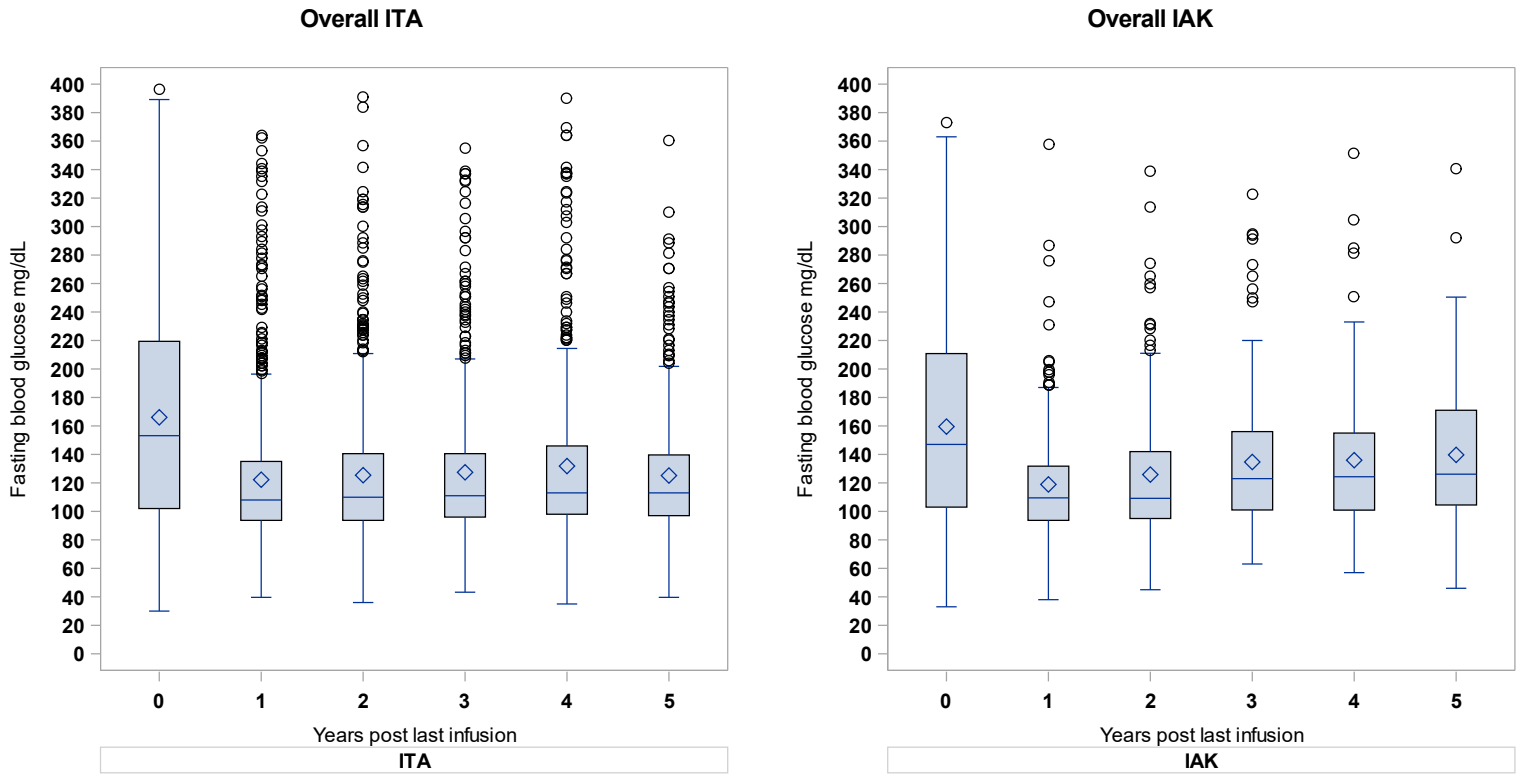


Exhibit 5-12
Fasting Blood Glucose (mg/dL) Post Last Infusion by Infusion Type

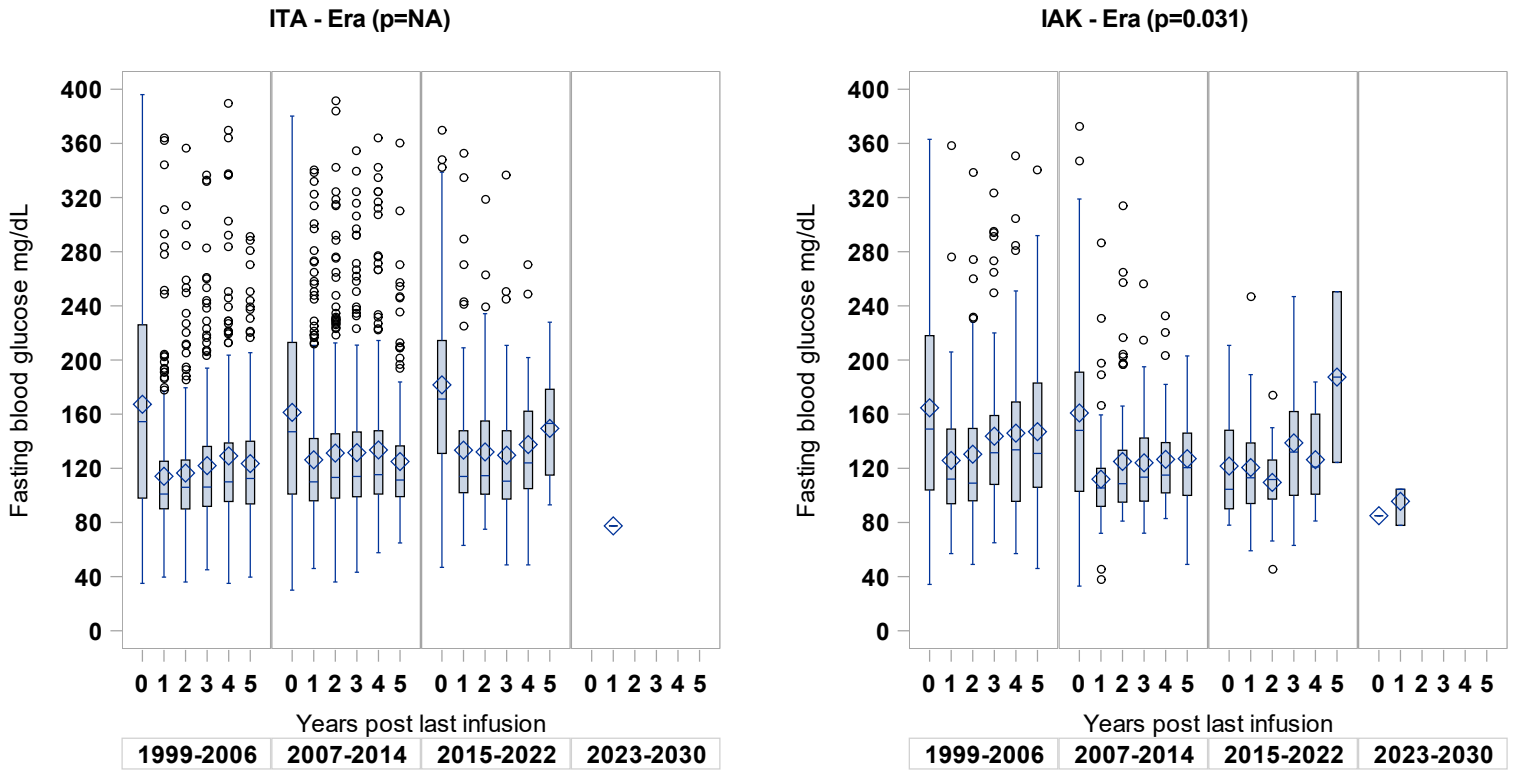


Exhibit 5-12
Fasting Blood Glucose (mg/dL) Post Last Infusion by Infusion Type

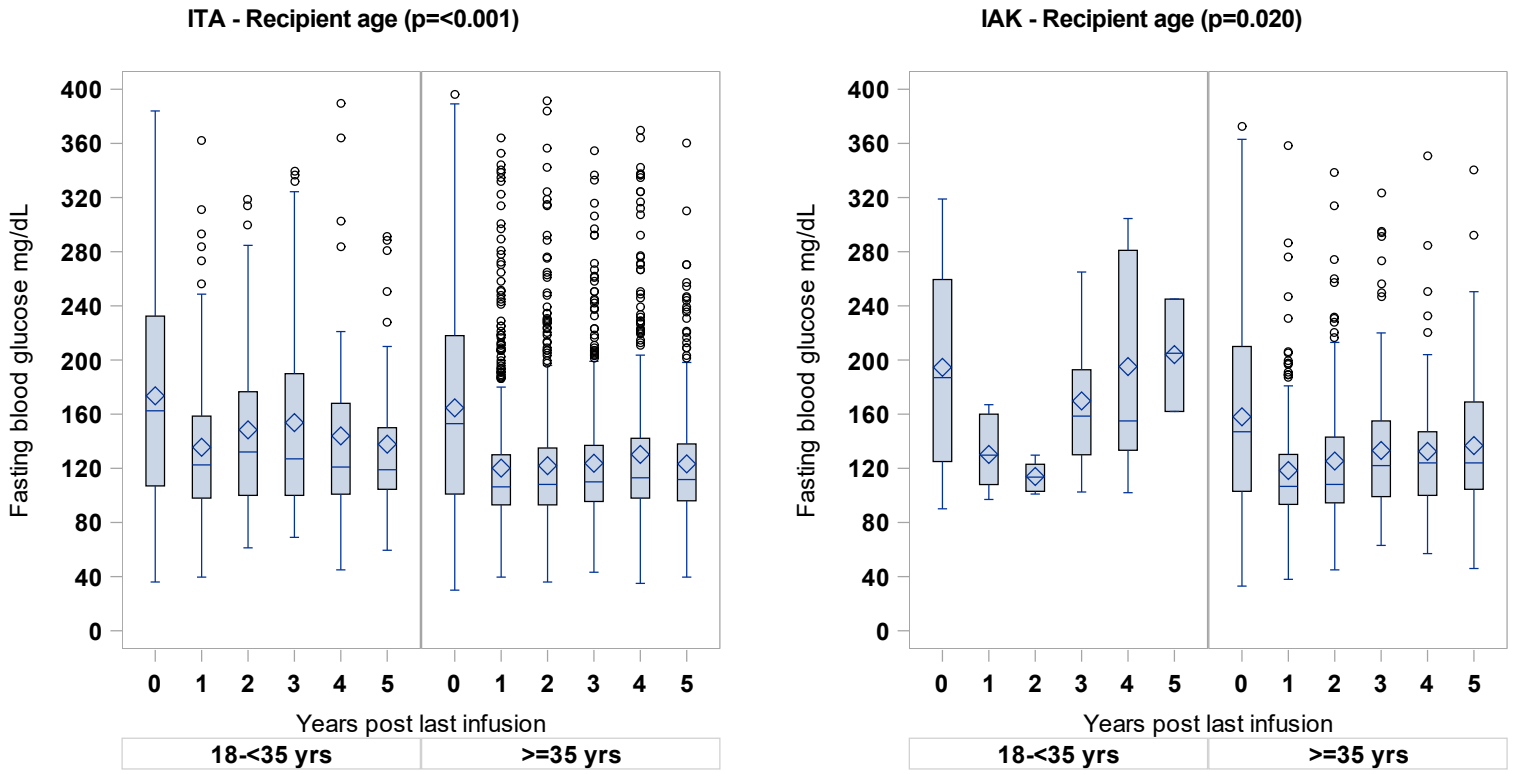


Exhibit 5-12
Fasting Blood Glucose (mg/dL) Post Last Infusion by Infusion Type

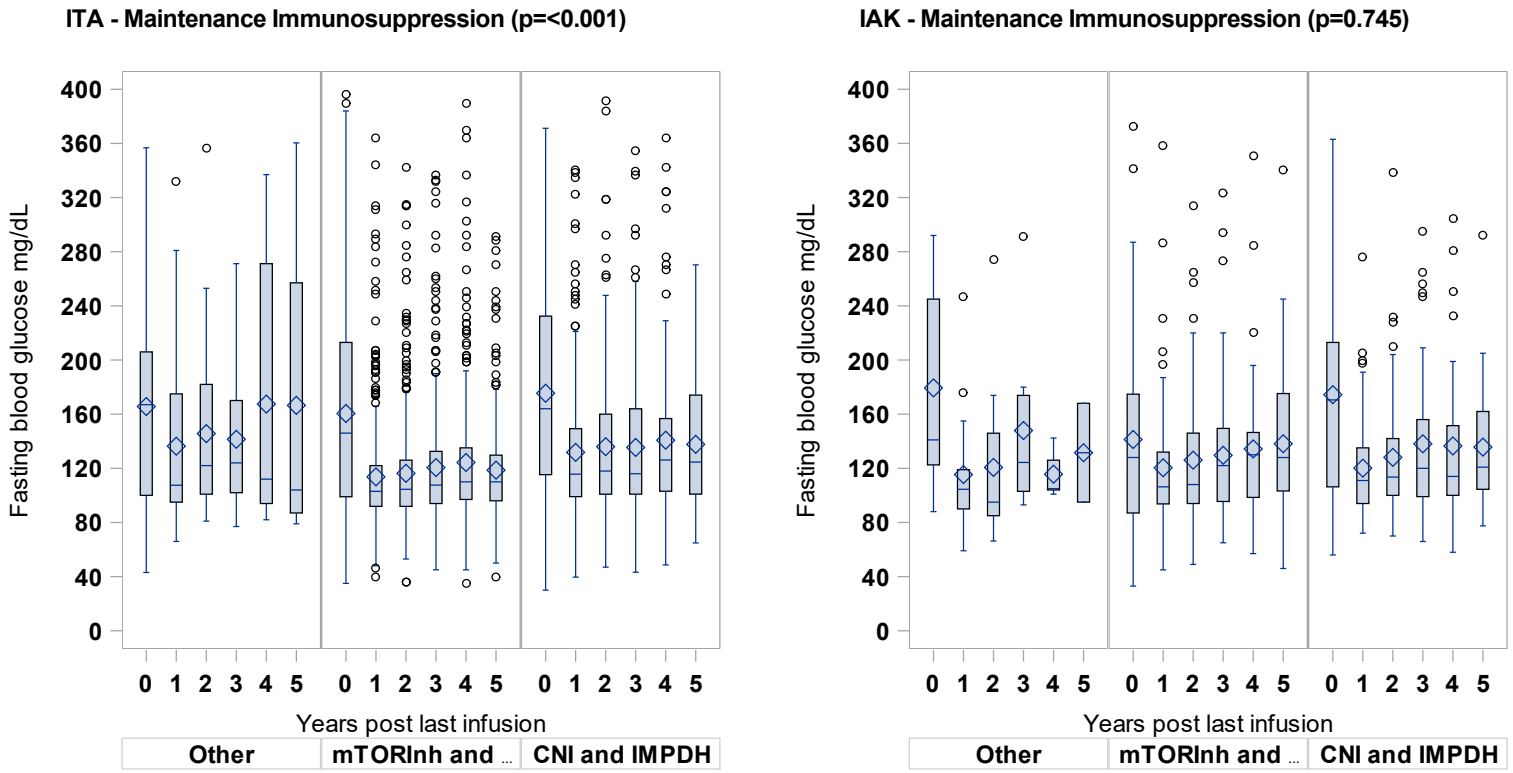
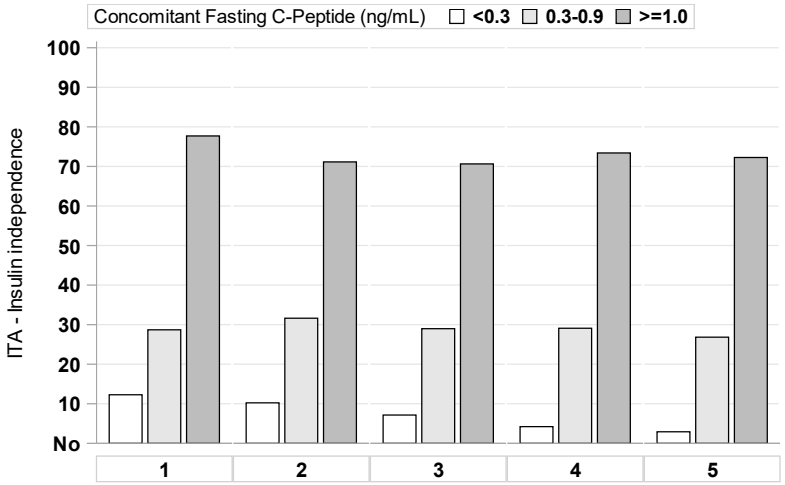
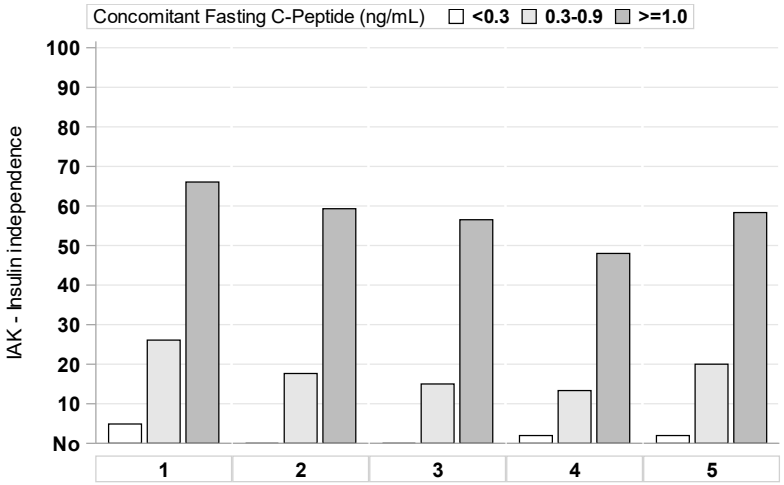


Exhibit 5-13
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion by Infusion Type

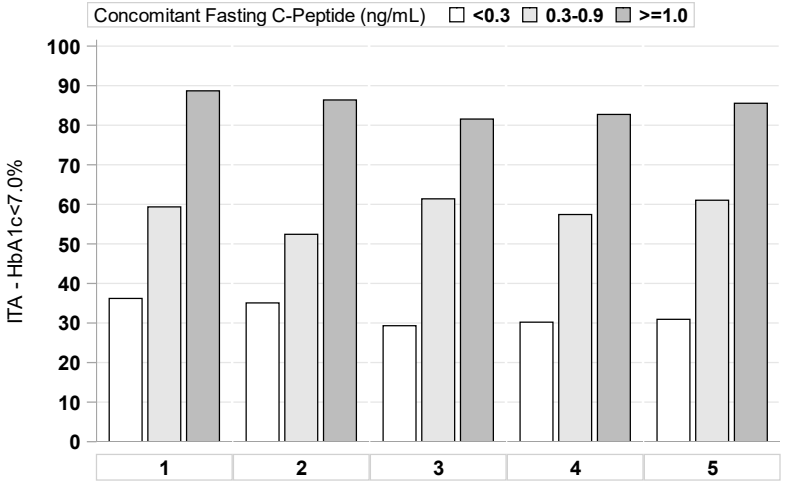
ITA - Insulin independence



IAK - Insulin independence



ITA - HbA1c<7.0%



IAK - HbA1c<7.0%

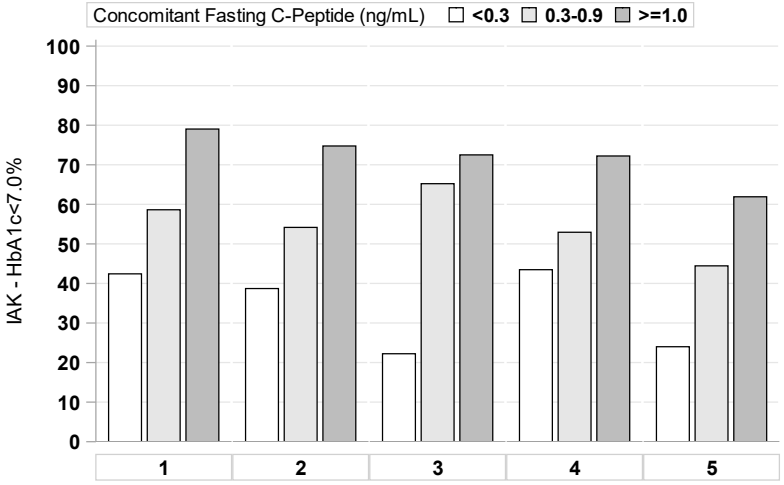
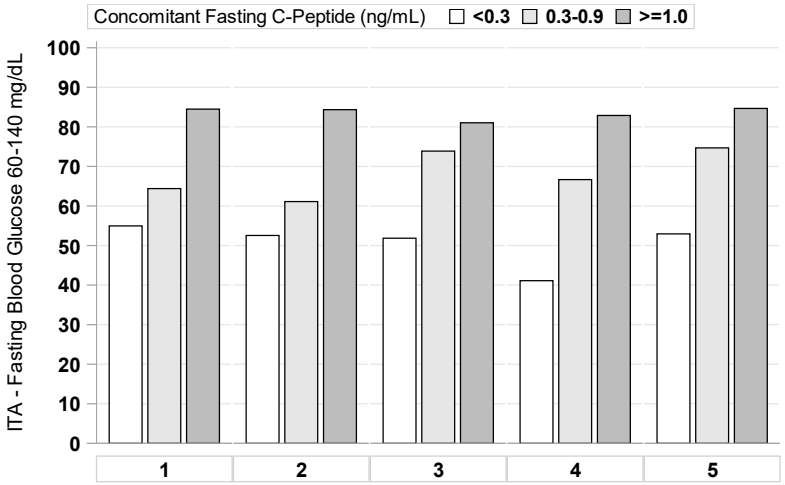
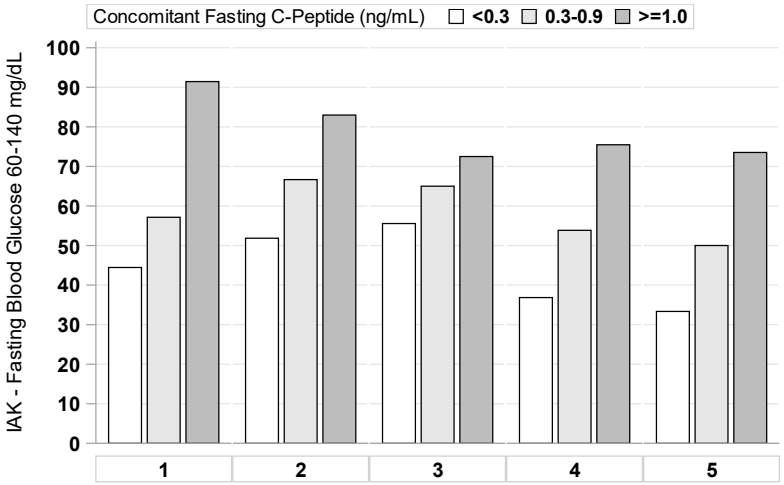


Exhibit 5-13
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion by Infusion Type

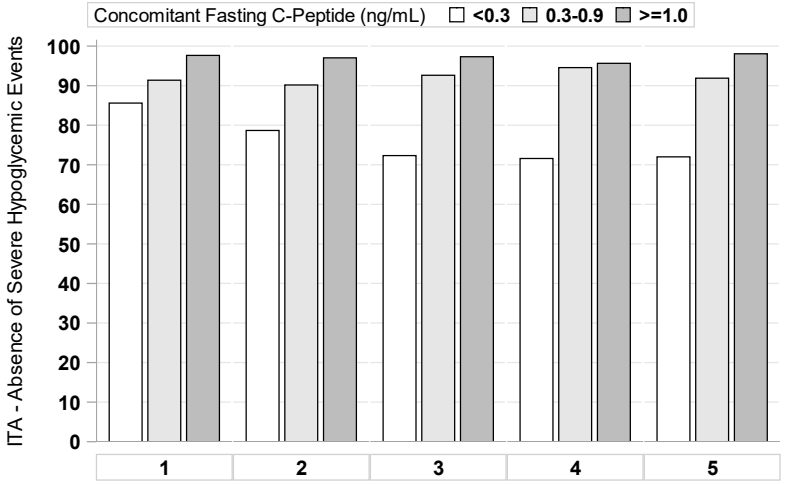
ITA - Fasting Blood Glucose 60-140 mg/dL



IAK - Fasting Blood Glucose 60-140 mg/dL



ITA - Absence of Severe Hypoglycemic Events



IAK - Absence of Severe Hypoglycemic Events

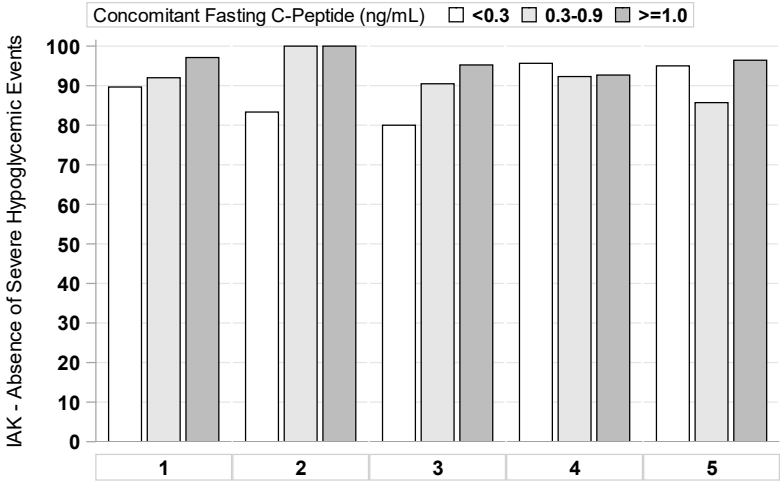
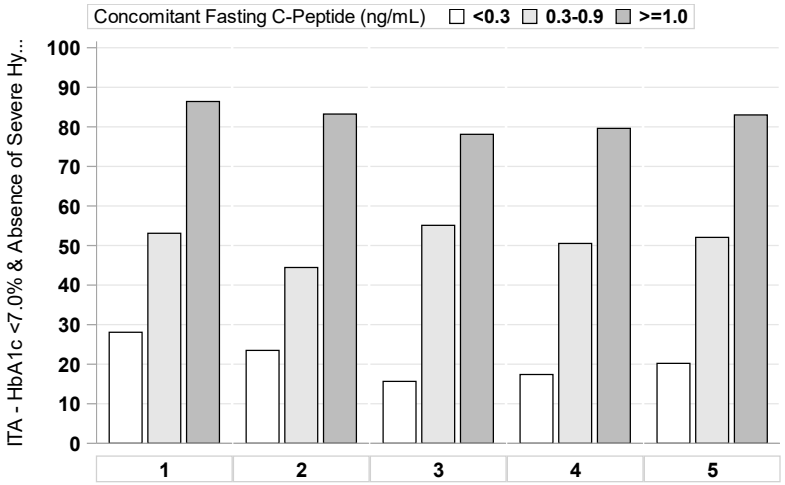


Exhibit 5-13
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion by Infusion Type

ITA - HbA1c <7.0% & Absence of Severe Hypoglycemic Events



IAK - HbA1c <7.0% & Absence of Severe Hypoglycemic Events

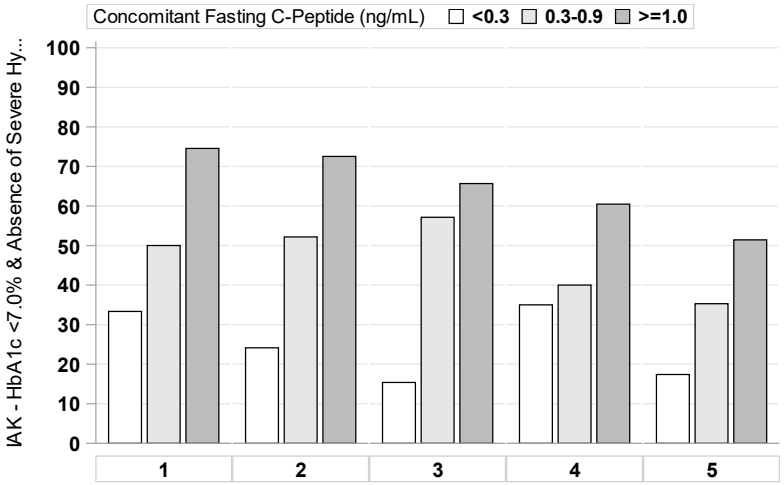
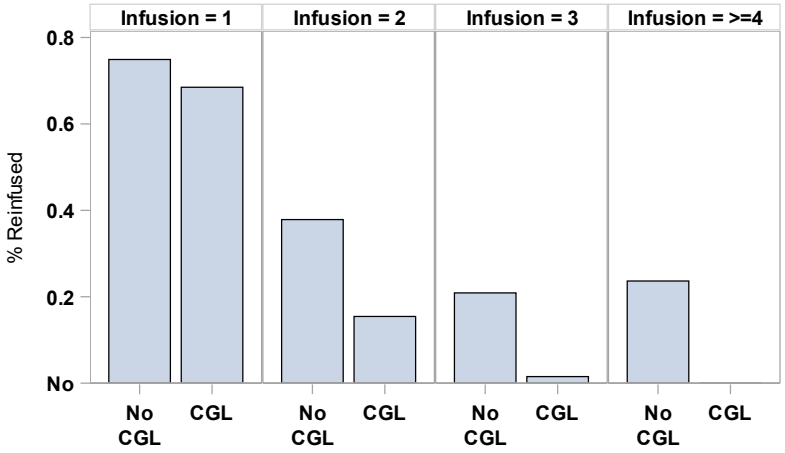
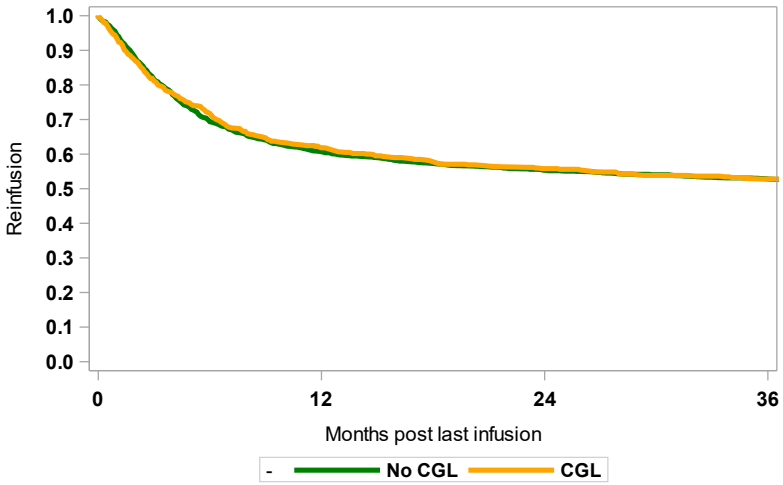


Exhibit 5-14
Re-Infusion (after each infusion sequence)

A. By previous complete graft loss (CGL) (p=0.606)

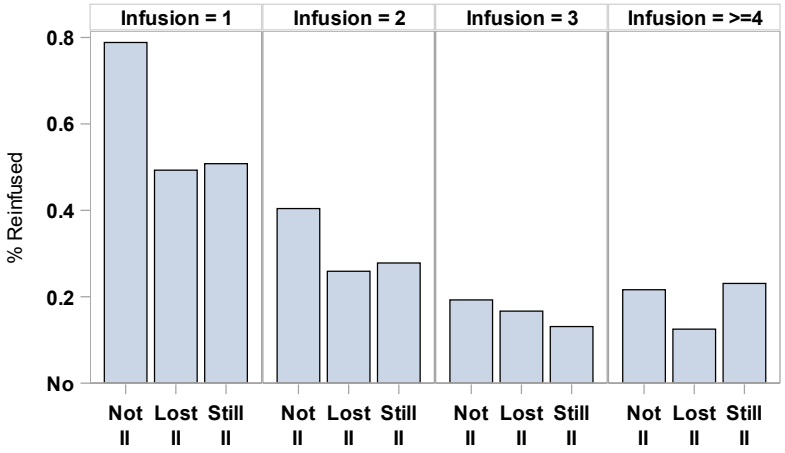


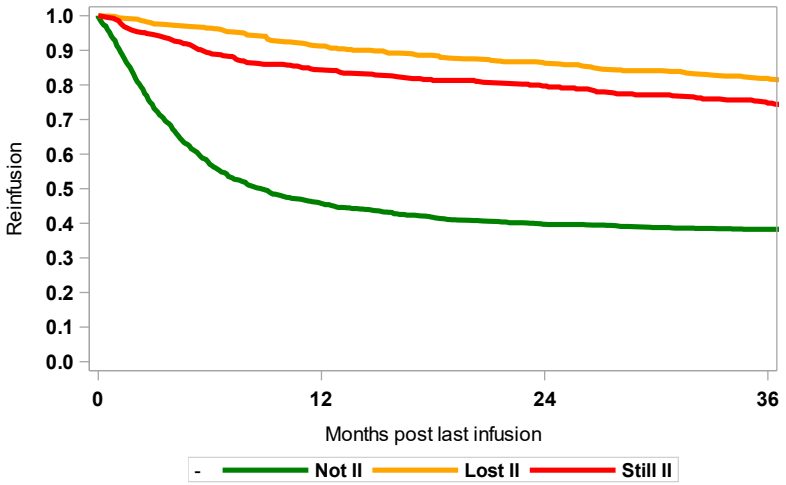


	Reinfusion		
	No	Yes	Total
	N	N	N
Infusion 1	347	928	1275
Infusion 2	613	315	928
Infusion 3	262	53	315
Infusion >=4	53	13	66
All	1275	1309	2584

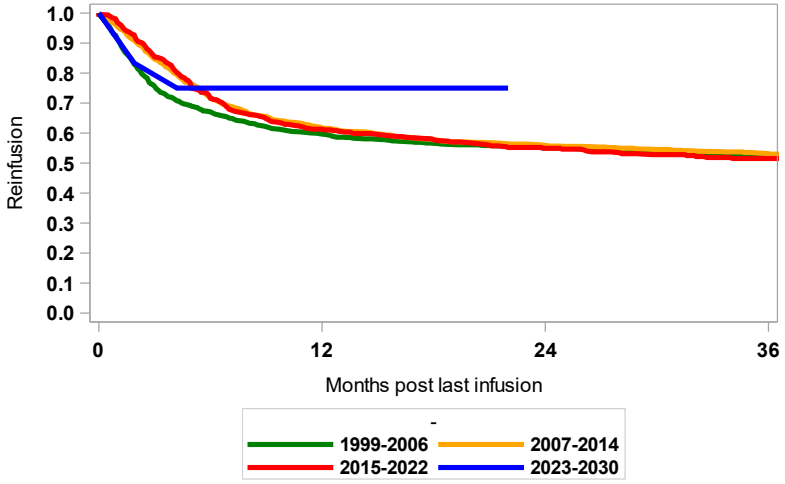
Exhibit 5-14
Re-Infusion (after each infusion sequence)

B. By concurrent insulin independence (II) (p=<0.001)

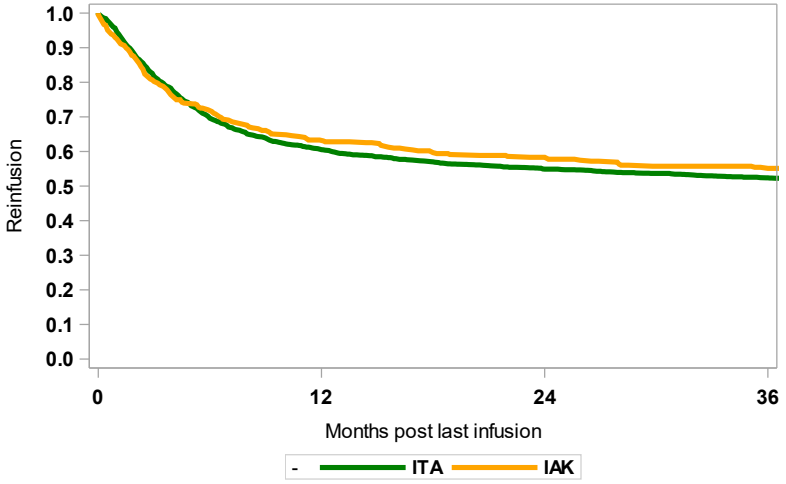




C. By Era (p=0.011)



D. By Transplant Type (p=0.193)



Chapter 6
Liver, Kidney, Lipid, and PRA Effects

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 ($p<0.01$).

ALT and AST levels typically rise after islet transplantation and then level off. ALT levels (Exhibit 6-1A) decreased after the first year post-last infusion among recipients who received maintenance immunosuppression with CNI+IMPDH, but ALT remained elevated among those who received other regimens ($p=0.0057$). A similar trend ($p=0.0013$) with respect to rise after islet transplantation and maintenance immunosuppression regimen is observed for AST (Exhibit 6-1B). AST levels over 5 years post-last infusion were highest in those who received IL2RA only for induction immunosupression ($p=0.0006$), while those receiving other regimens gradually returned to baseline levels after an increase in Year 1.

There is limited change in alkaline phosphatase in follow-up after islet transplantation (Exhibit 6-2); however, across eras there have been changes in initial – and hence follow-up – levels ($p <0.0001$). Initial levels are higher in IAK compared to ITA, and these levels persist over follow-up ($p<0.0001$). Recipients given induction with IL2RA-alone had higher initial levels which then persisted over long-term follow-up ($p<0.0001$), but effects of immunosuppression are likely confounded because different regimens were common in different eras.

Total bilirubin varied somewhat over years of follow-up after islet transplantation, but in no consistent upward or downward trend (Exhibit 6-3). Total bilirubin was significantly higher in ITA than IAK ($p=0.0016$).

There is a mild, not statistically significant, decline in HDL cholesterol over the years following islet transplantation in both ITA and IAK, which was generally consistent across the eras with an uptick in recent years (Exihibit 6-4). The decline over follow-up time was less pronounced in subjects who received induction immunosuppression with TCD+TNFaInh ($p=0.0009$).

In the earlier eras, a decline in LDL cholesterol in follow-up was noted, as well as an uptick in recent years (Exhibit 6-5). Among recipients under 35 LDL cholesterol rose peaking at year 2 post-last infusion and then gradually declined while in recipients 35 and over levels remained fairly stable with a slight decline at 5 years post-last infusion; initial LDL levels were higher in recipients aged<35 years, though the subsequent rate of decline was comparable ($p<0.0001$). Decline in LDL cholesterol was less pronounced in recipients who received induction immunosuppression with TCD+TNFaInh ($p<0.0001$). LDL cholesterol was initially higher in recipients who received maintenance immunosuppression with mTOR+CNI, but declined to a similar level as that observed among recipients who received CNI+IMPDH ($p=0.0014$).

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 or other regimens compared to CNI+IMPDH regimen (p=0.0003), and for induction with IL2RA alone or TCD+TNFa inhibition compared to other induction immunosuppression regimens (p=0.0009).

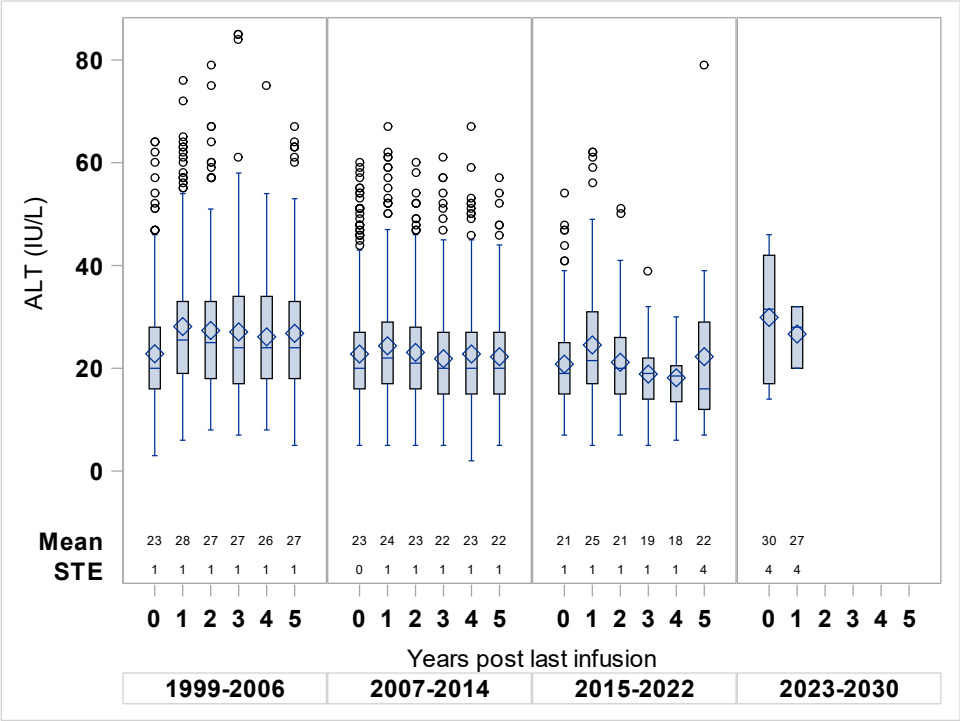
Total cholesterol was generally higher at baseline and declined in follow-up after islet transplantation in early eras, but in recent years has increased over follow-up (Exhibit 6-7). Induction with TCD+TNFa inhibition was associated with significantly less decline over follow-up time (p<0.0001).

Serum creatinine rose over years of follow-up after initial islet transplant. This trend was observed in both ITA and IAK, with the IAKs starting at higher levels (Exhibit 6-8). Those 35 and over also had higher initial levels (p=0.0002).

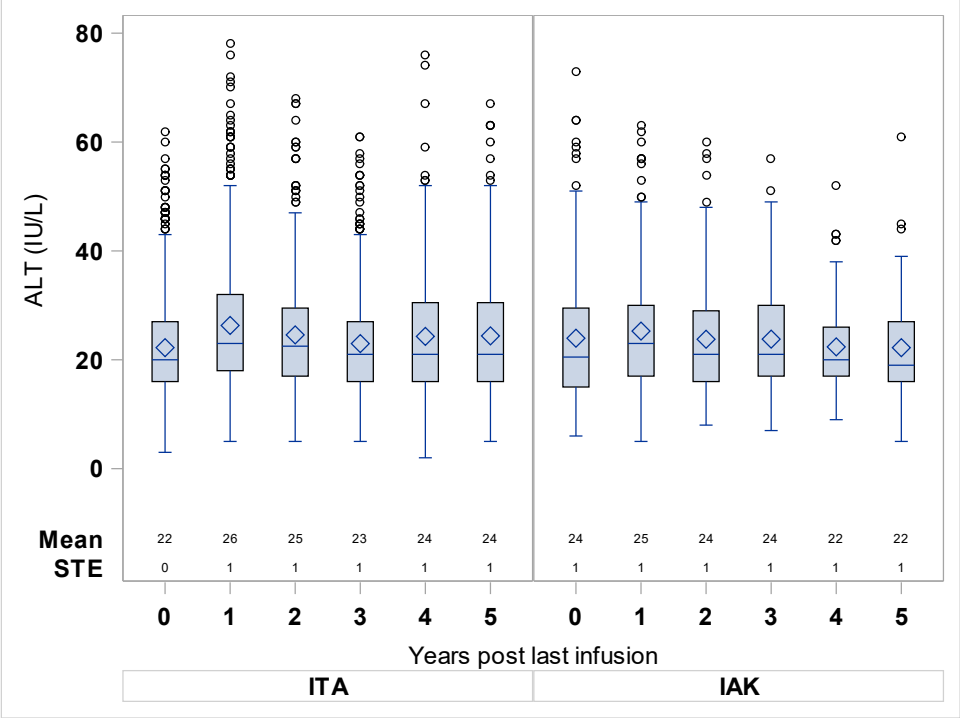
The decline in CKD-Epi eGFR after islet transplantation differing by transplant type is both statistically significant and clinically important (p<0.0001, Exhibit 6-9). IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate. Initial levels were also lower in recipients age ≥ 35 and declined at a slower rate compared to younger recipients (p<0.0001). Levels were generally lower among recipients managed with CNI+IMPDH compared to other maintenance immunosuppression regimens (p=0.0002).

Exhibit 6-1A
ALT (IU/mL)

A. Era (p=NS)



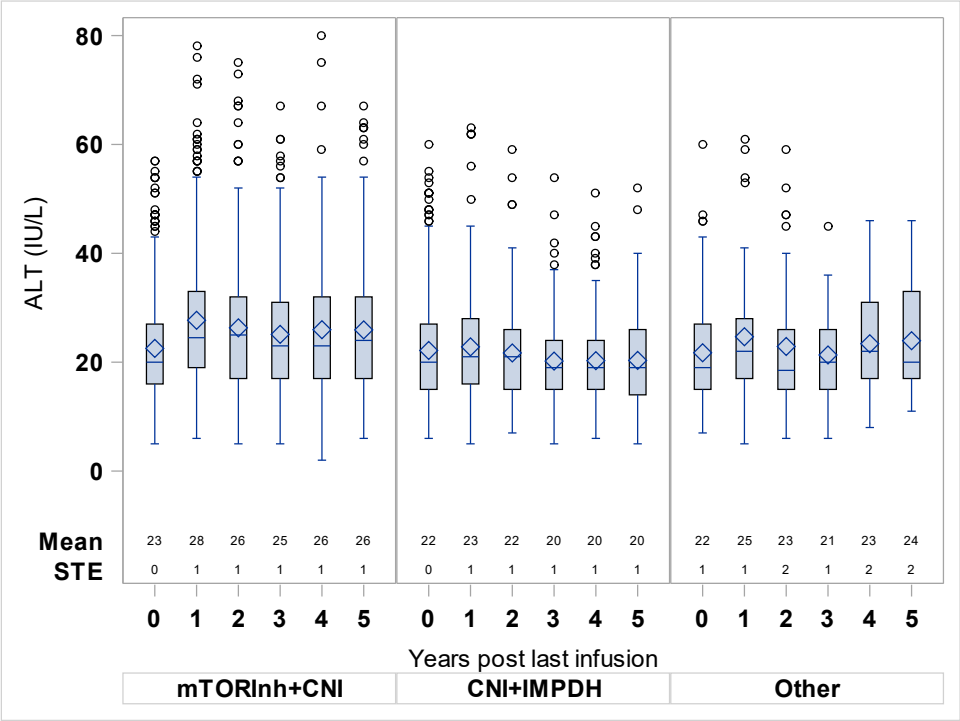
B. Type of Transplant (p=NS)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-1A
ALT (IU/mL)

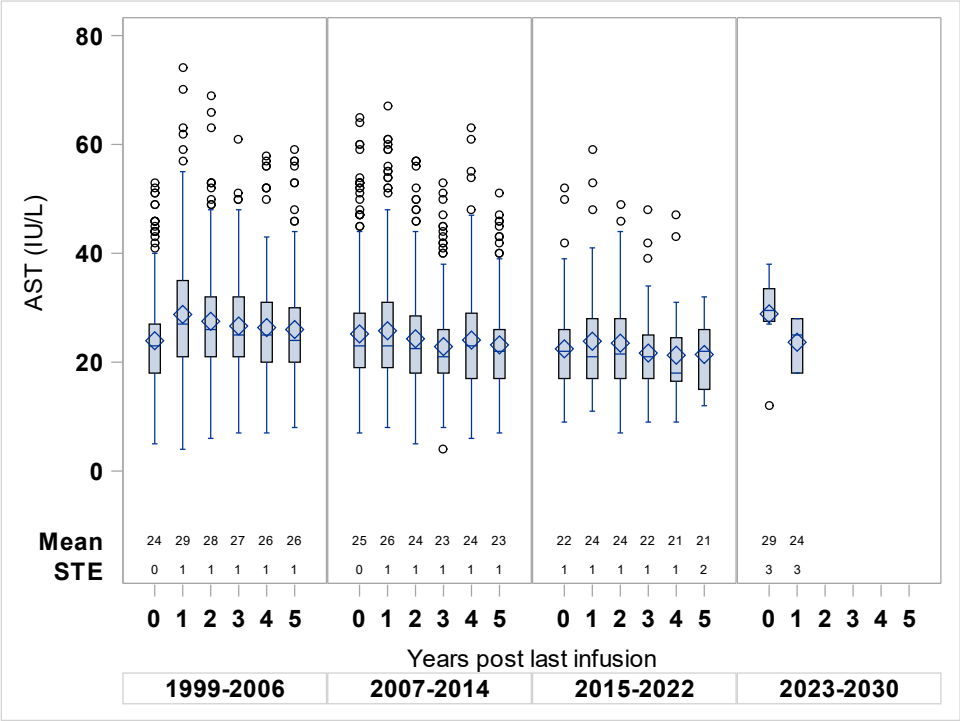
C. Maintenance Immunosuppression (p=0.0057)



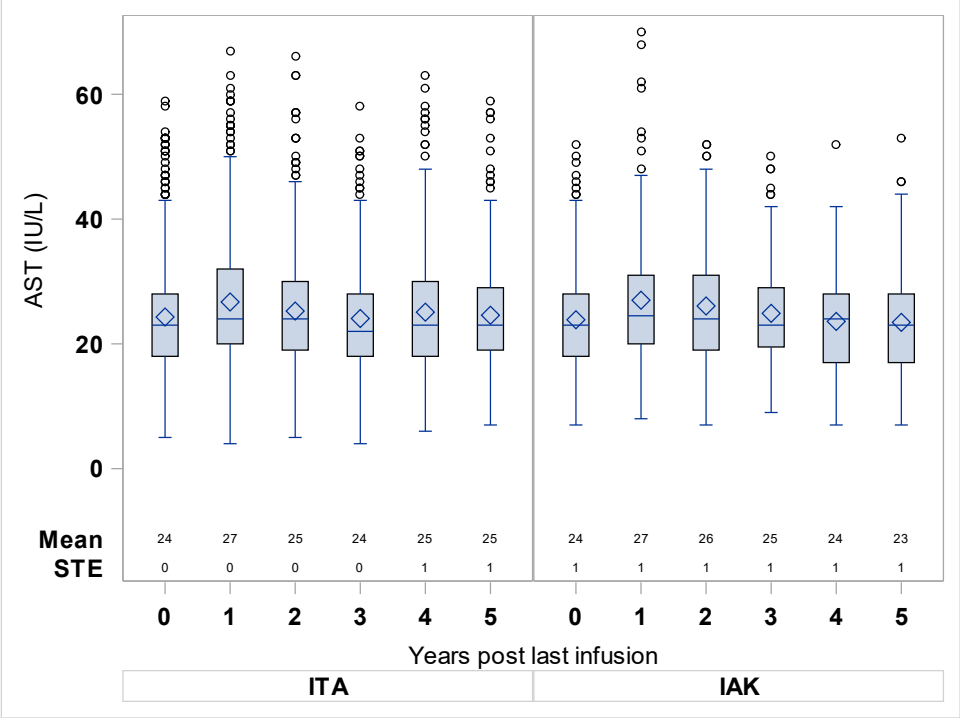
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-1B
AST (IU/mL)

A. Era (p=NS)



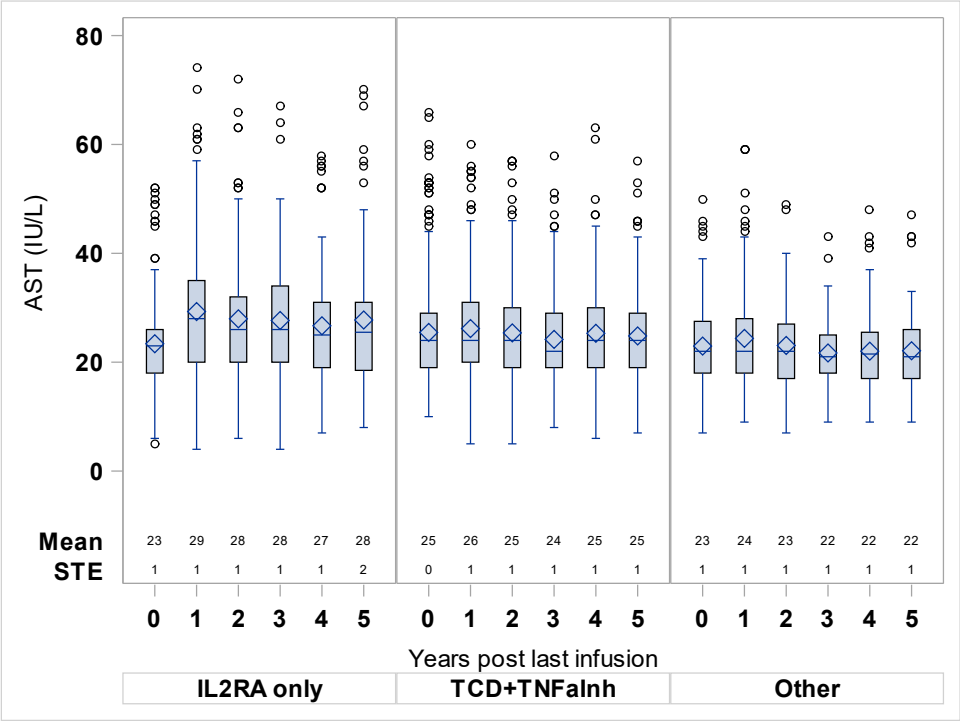
B. Type of Transplant (p=NS)



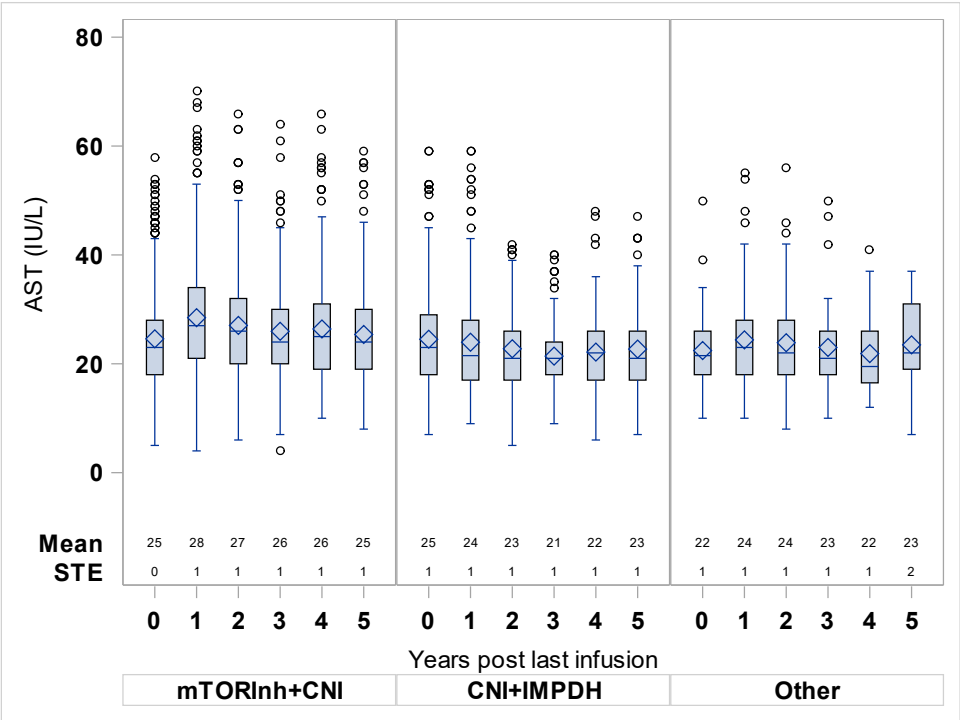
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-1B
AST (IU/mL)

C. Induction Immunosuppression (p=0.0006)



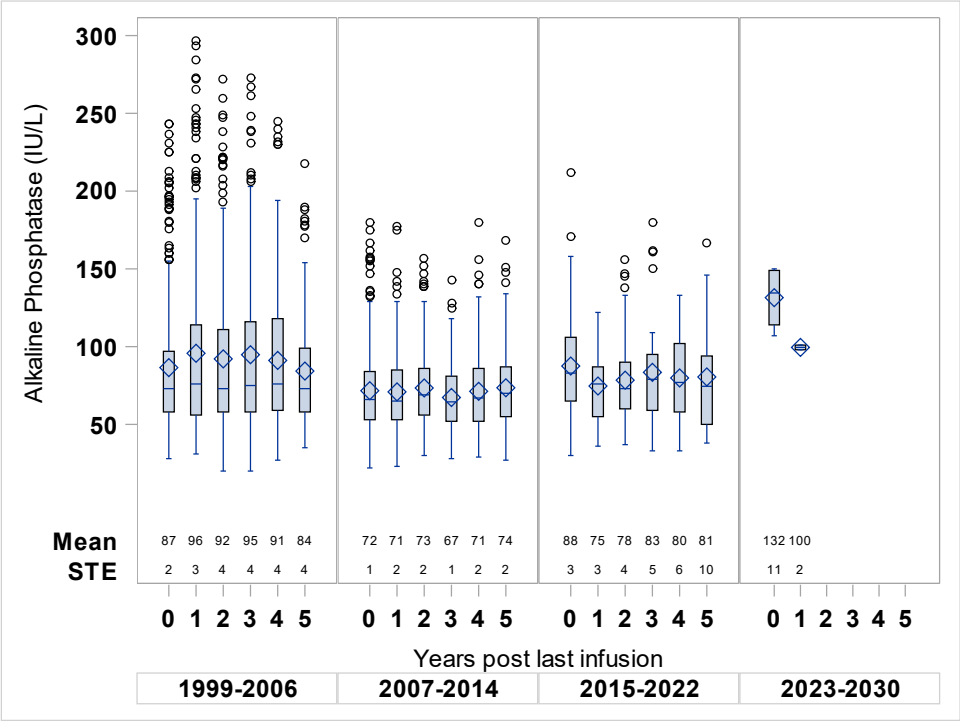
D. Maintenance Immunosuppression (p=0.0013)



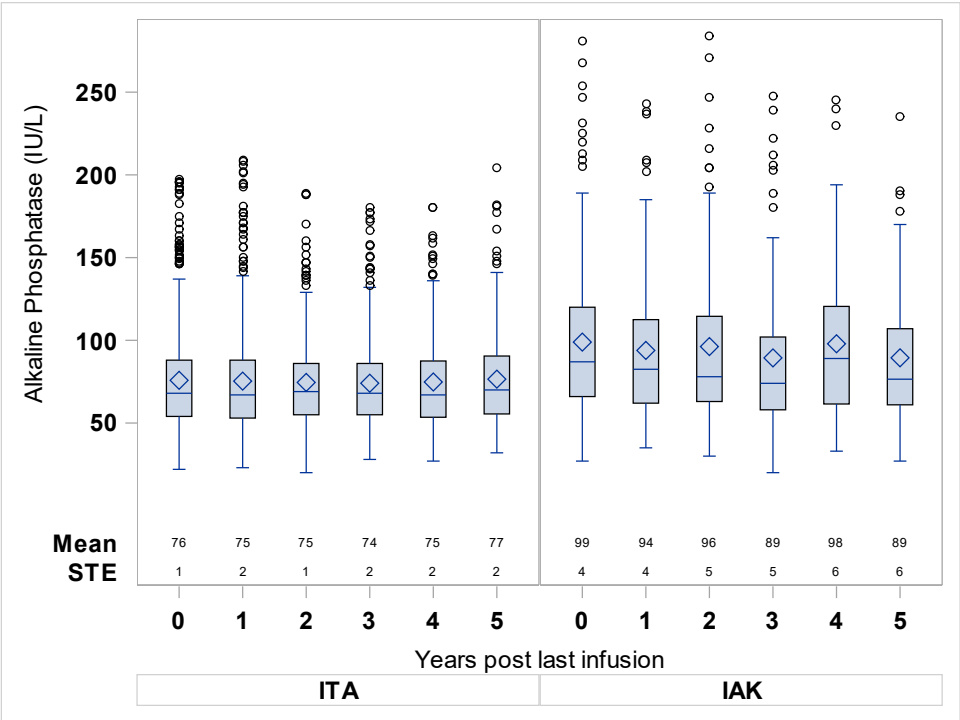
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-2
Alkaline Phosphatase (IU/L)

A. Era (p=<.0001)



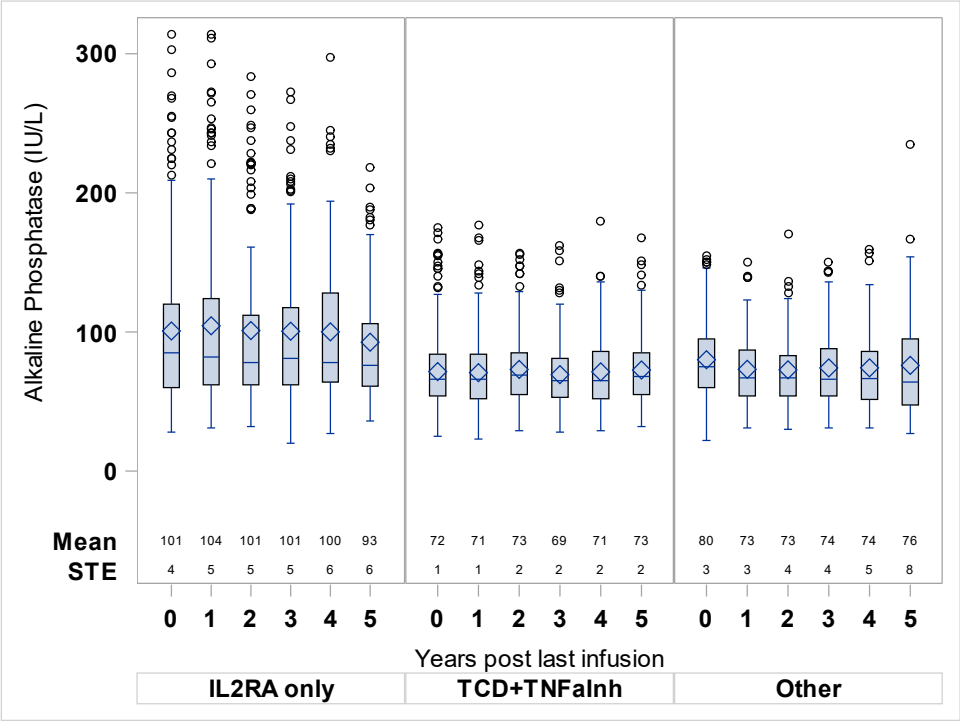
B. Type of Transplant (p=<.0001)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-2
Alkaline Phosphatase (IU/L)

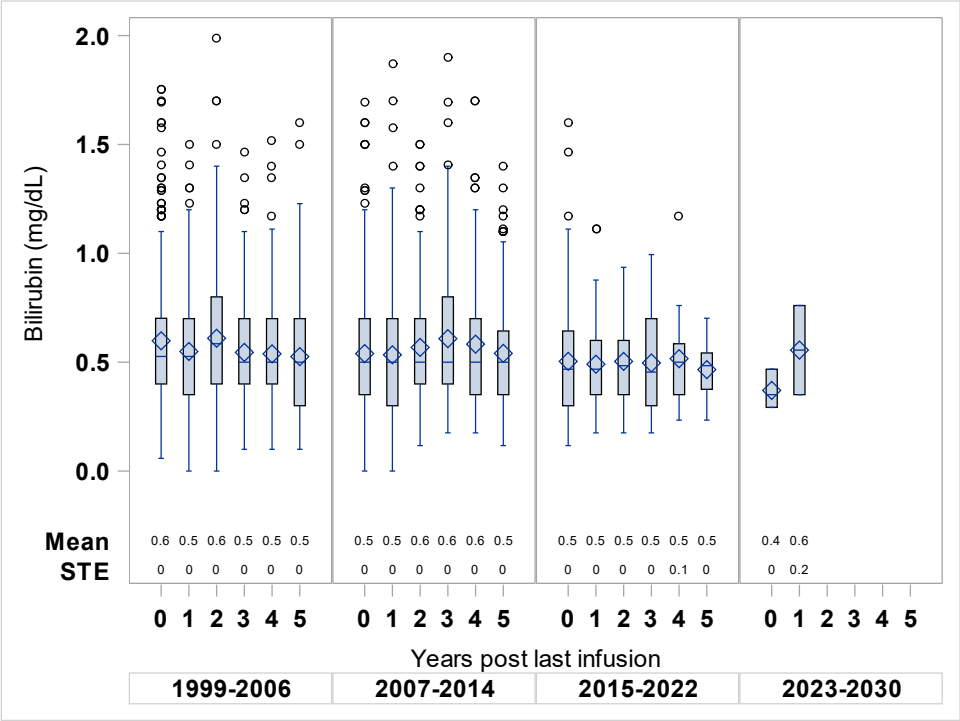
C. Induction Immunosuppression (p=<.0001)



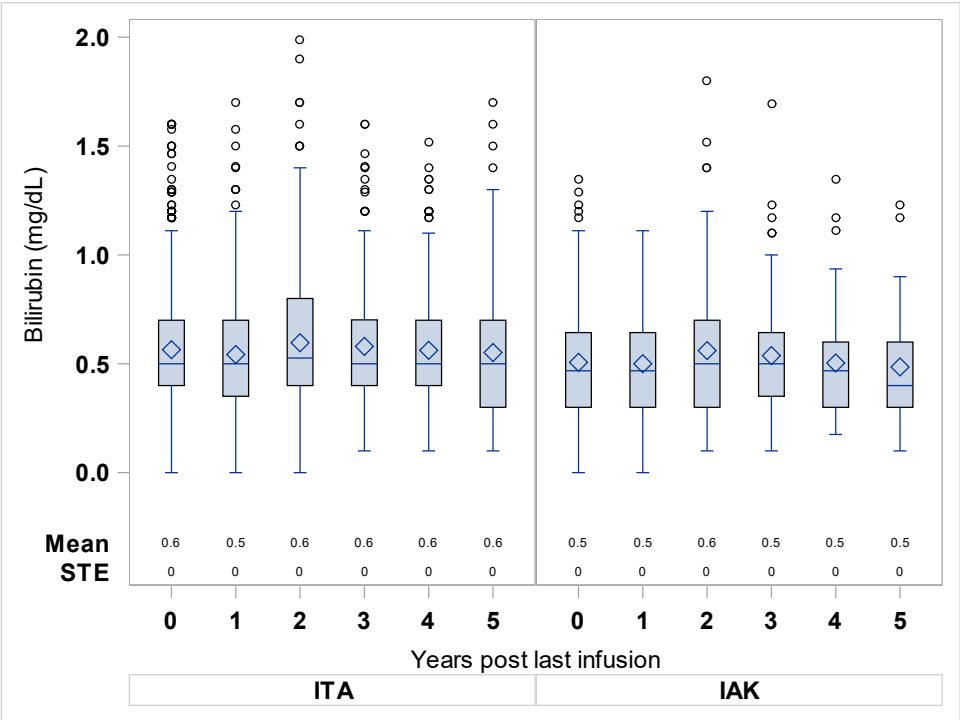
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-3
Total Bilirubin (mg/dL)

A. Era (p=NS)



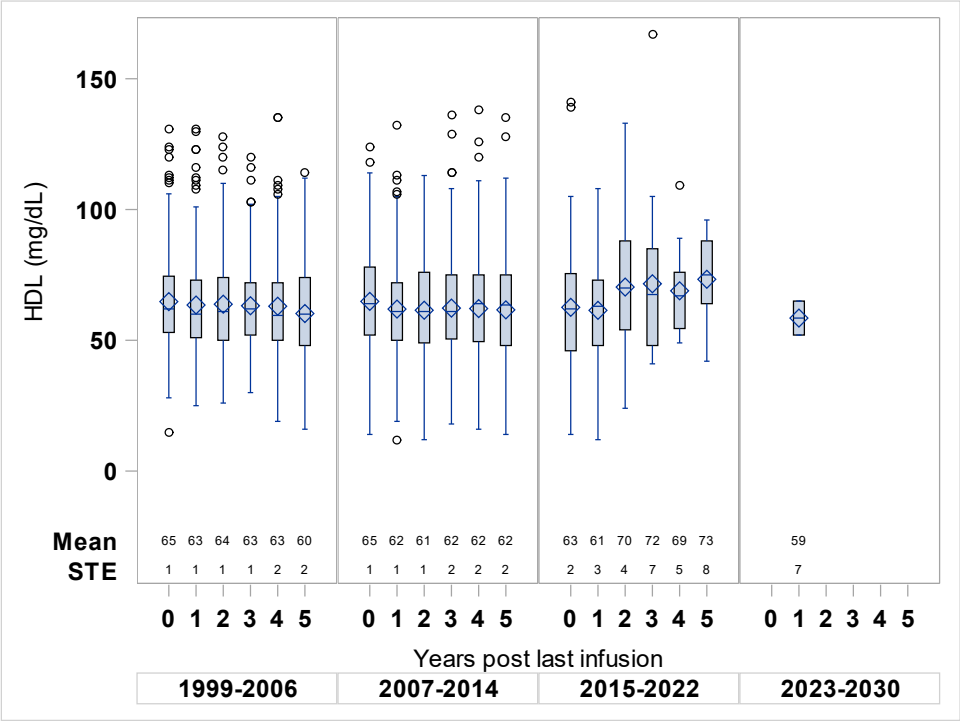
B. Type of Transplant (p=0.0016)



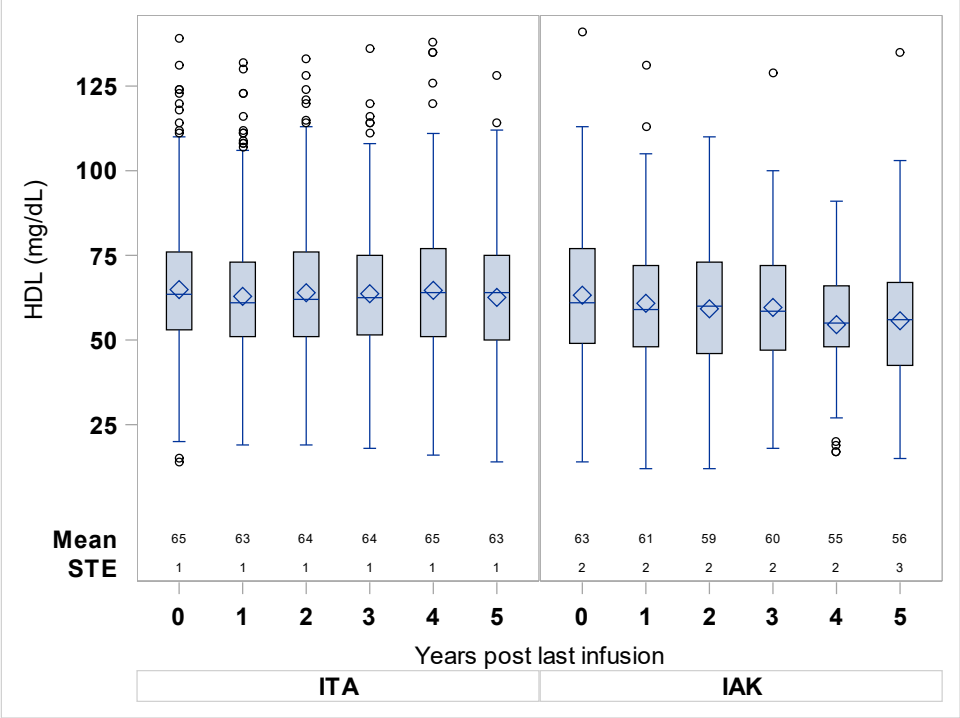
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-4
HDL Cholesterol (mg/dL)

A. Era (p=NS)



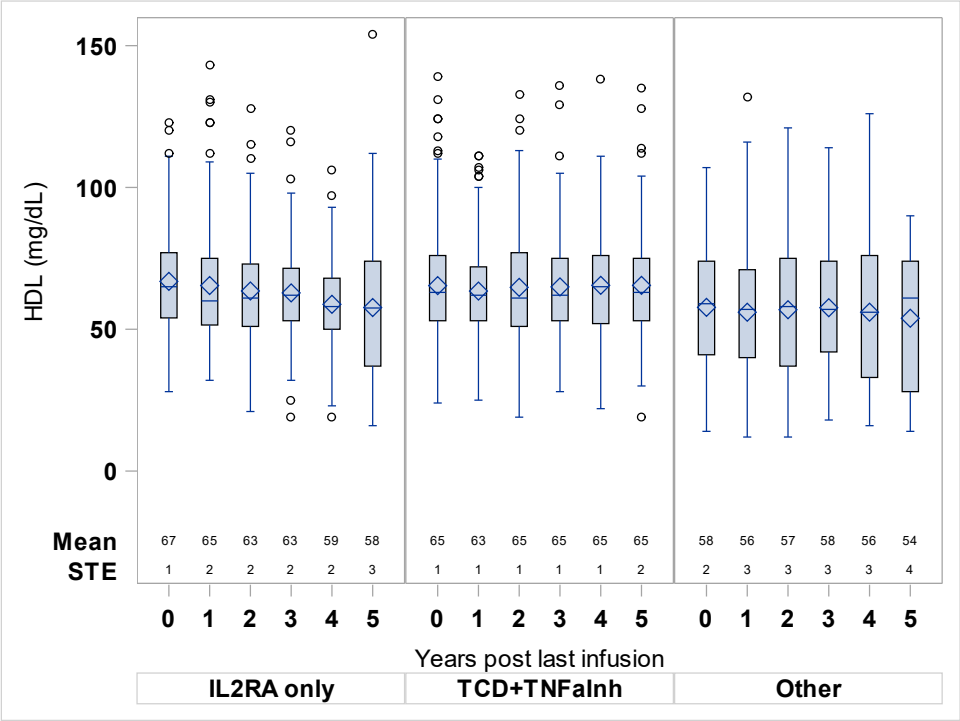
B. Type of Transplant (p=NS)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-4
HDL Cholesterol (mg/dL)

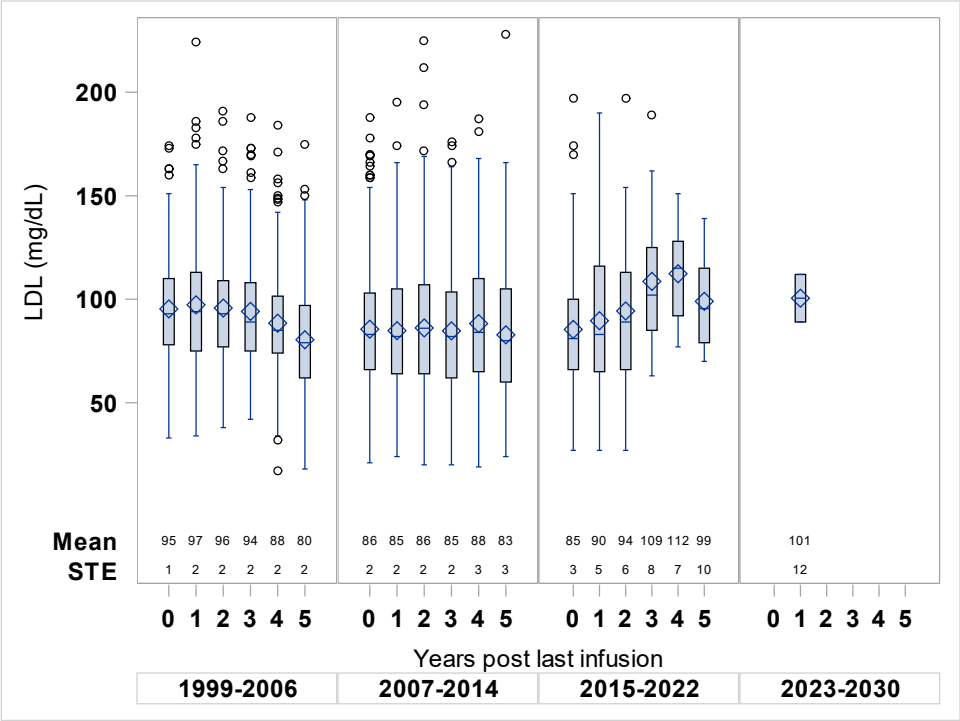
C. Induction Immunosuppression (p=0.0009)



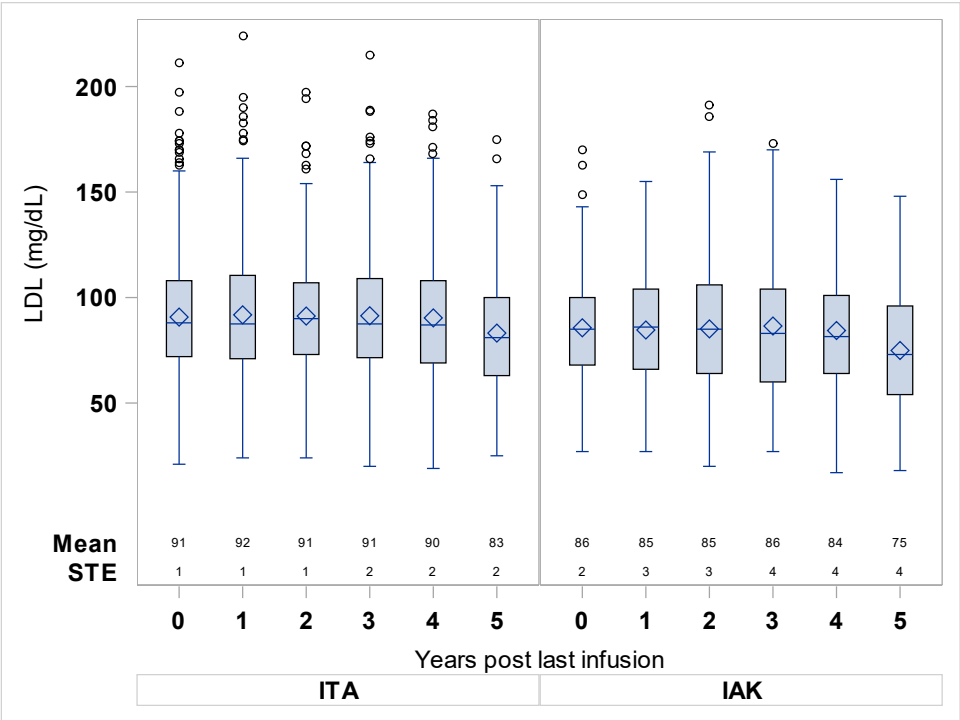
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-5
LDL Cholesterol (mg/dL)

A. Era (p=<.0001)



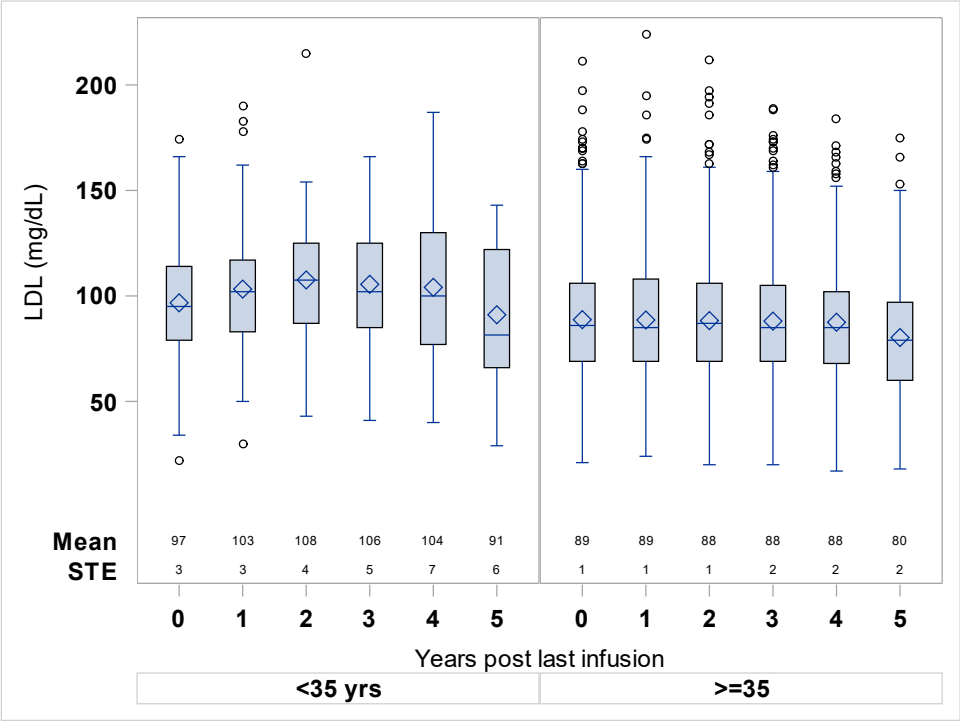
B. Type of Transplant (p=NS)



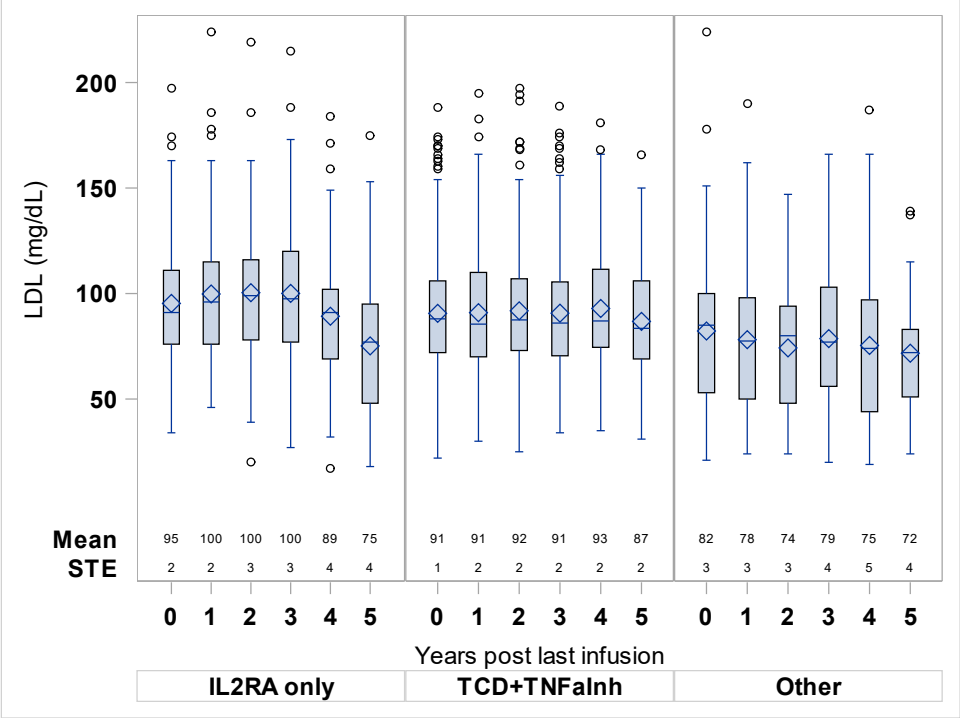
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-5
LDL Cholesterol (mg/dL)

C. Age (p=<.0001)



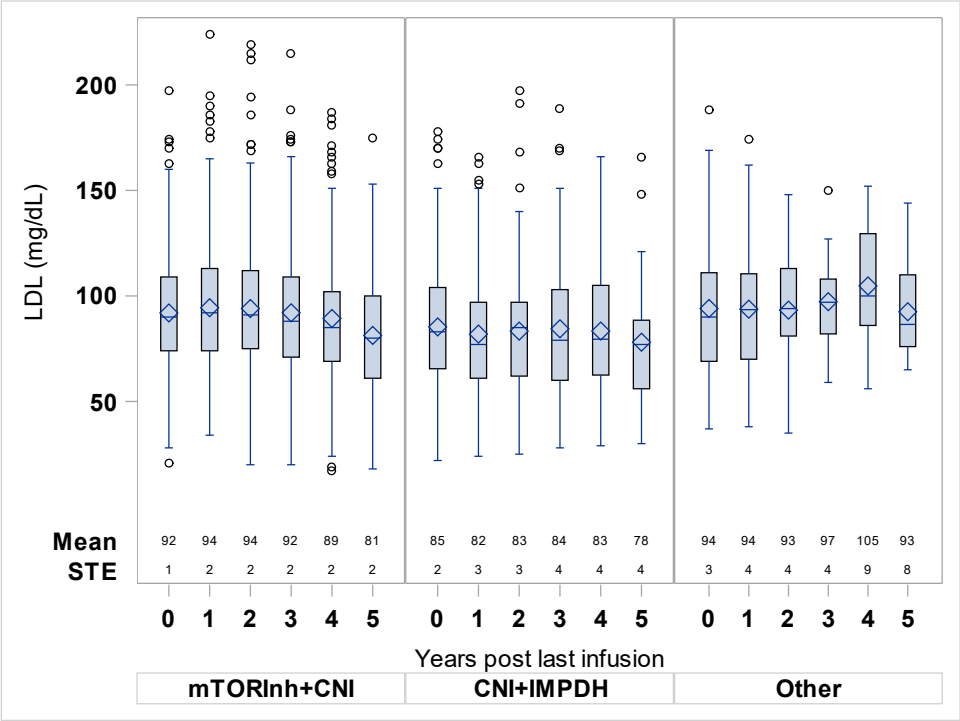
D. Induction Immunosuppression (p=<.0001)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-5
LDL Cholesterol (mg/dL)

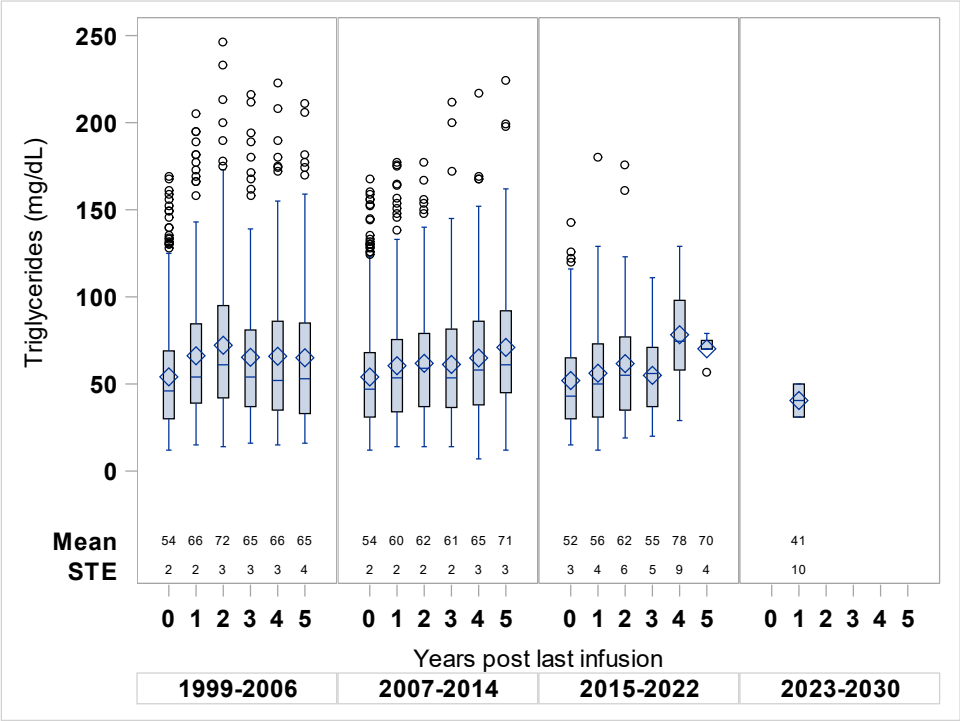
E. Maintenance Immunosuppression (p=0.0014)



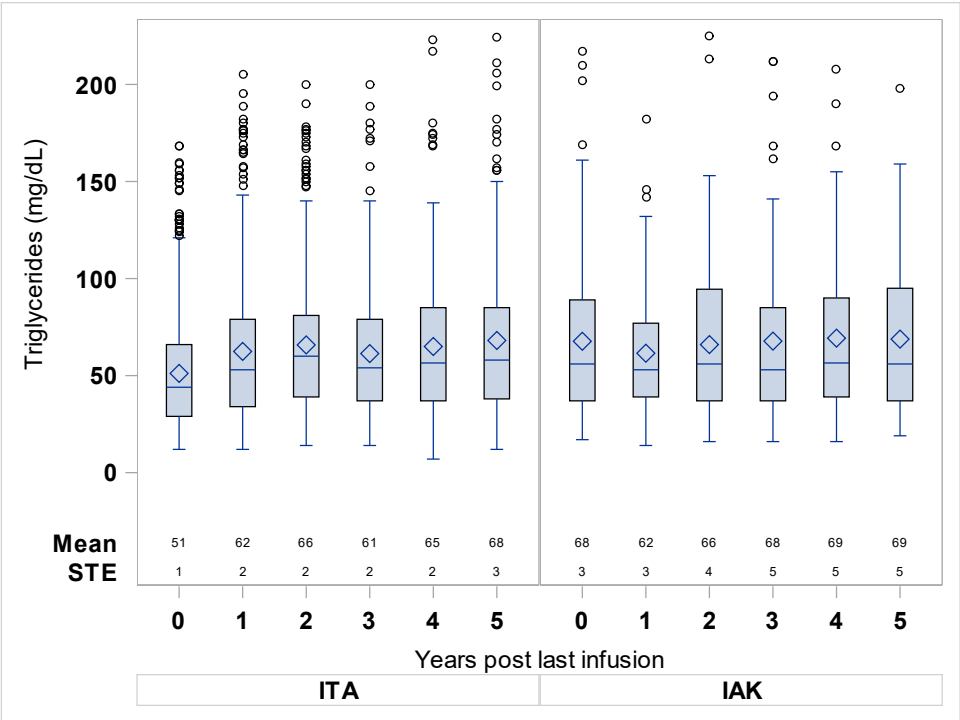
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-6
Triglycerides (mg/dL)

A. Era (p=NS)



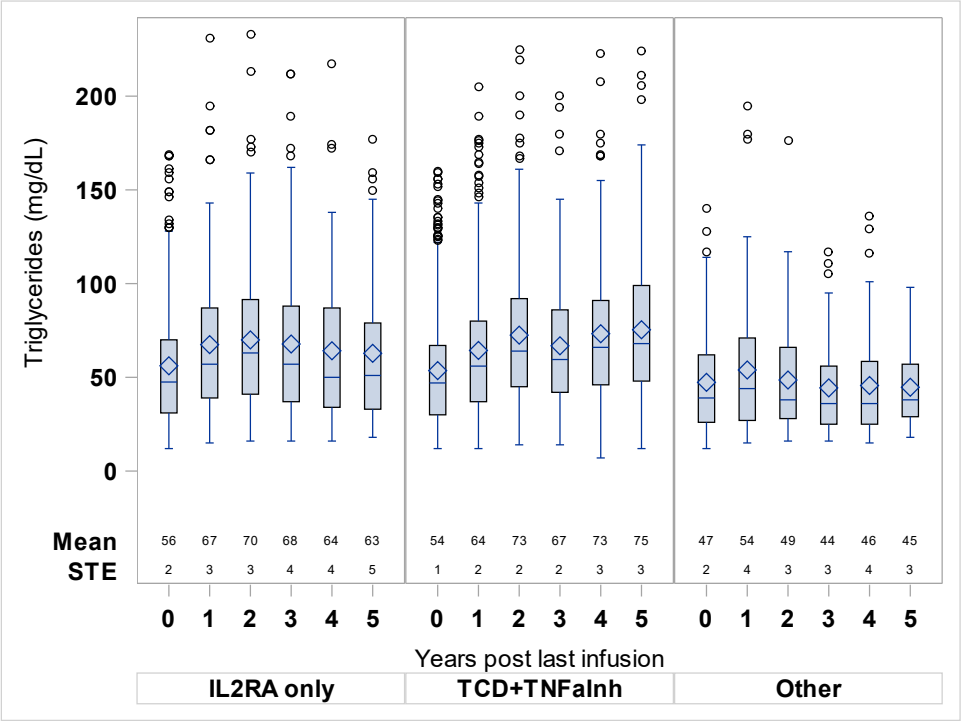
B. Type of Transplant (p=<.0001)



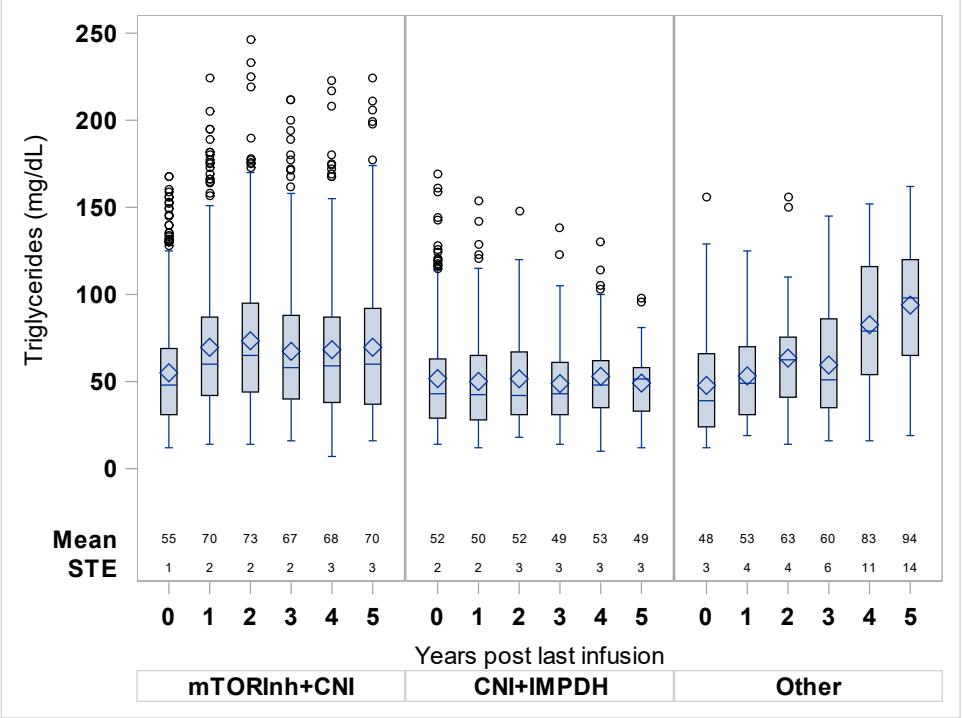
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-6
Triglycerides (mg/dL)

C. Induction Immunosuppression (p=0.0009)



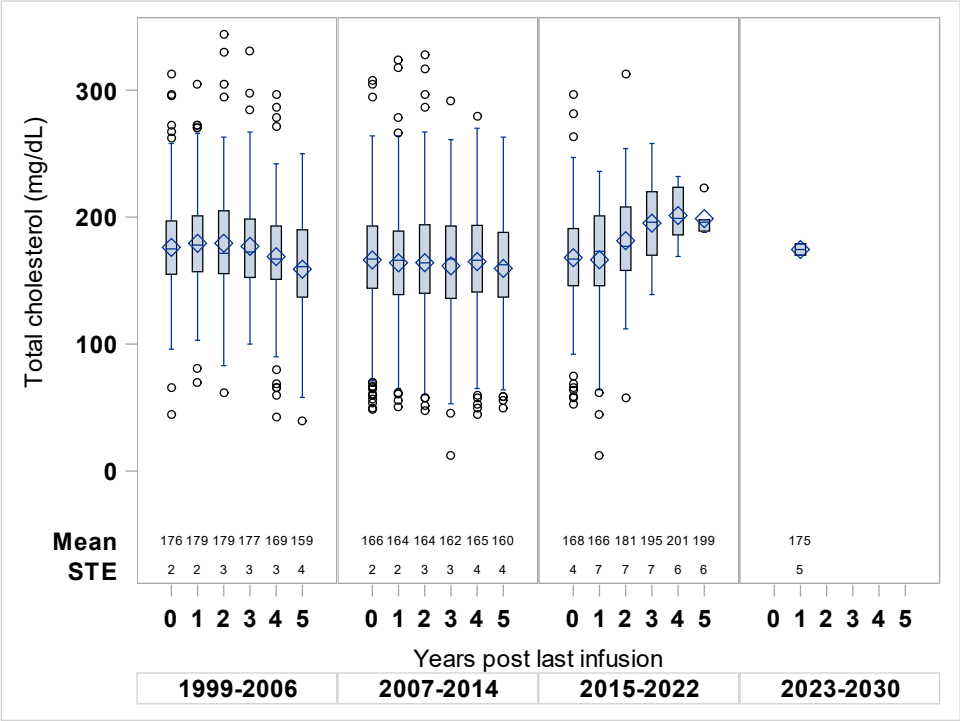
D. Maintenance Immunosuppression (p=0.0003)



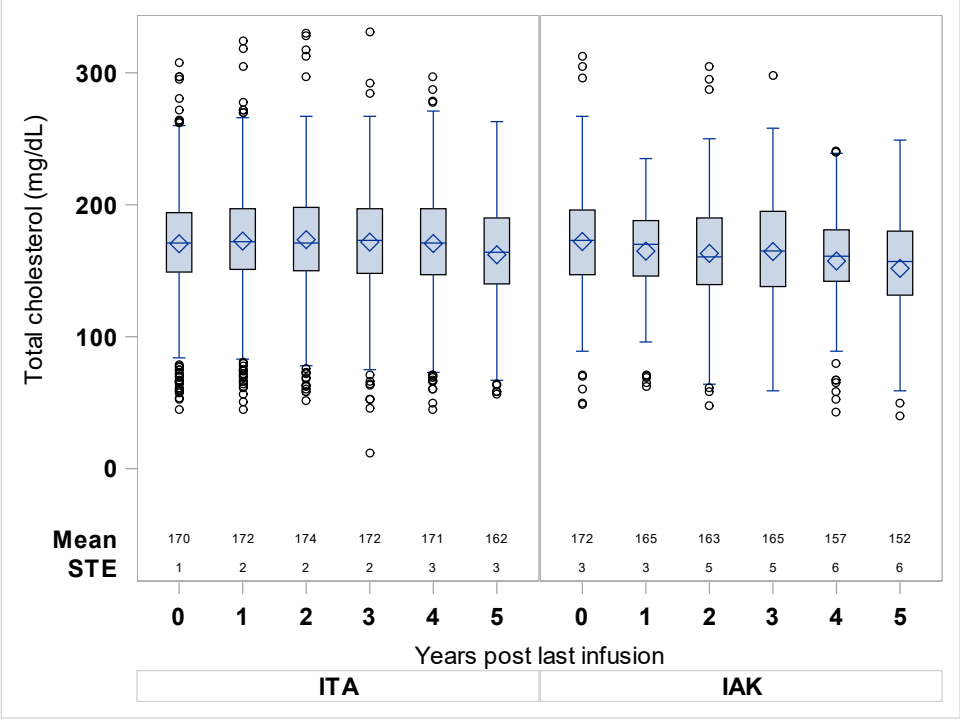
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-7
Total Cholesterol (mg/dL)

A. Era (p=0.0003)



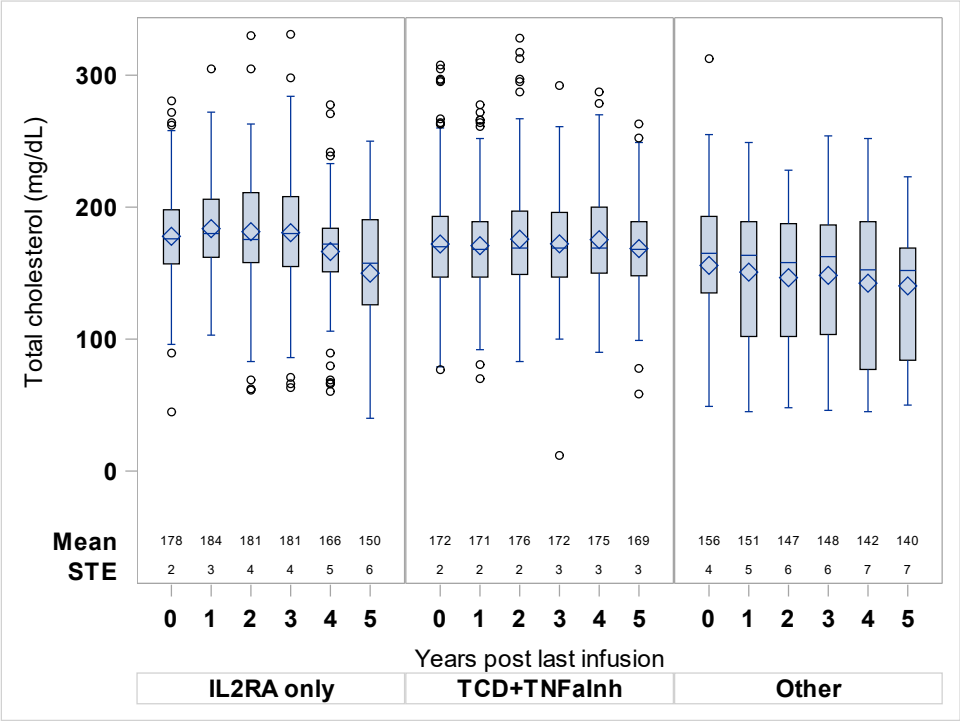
B. Type of Transplant (p=NS)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-7
Total Cholesterol (mg/dL)

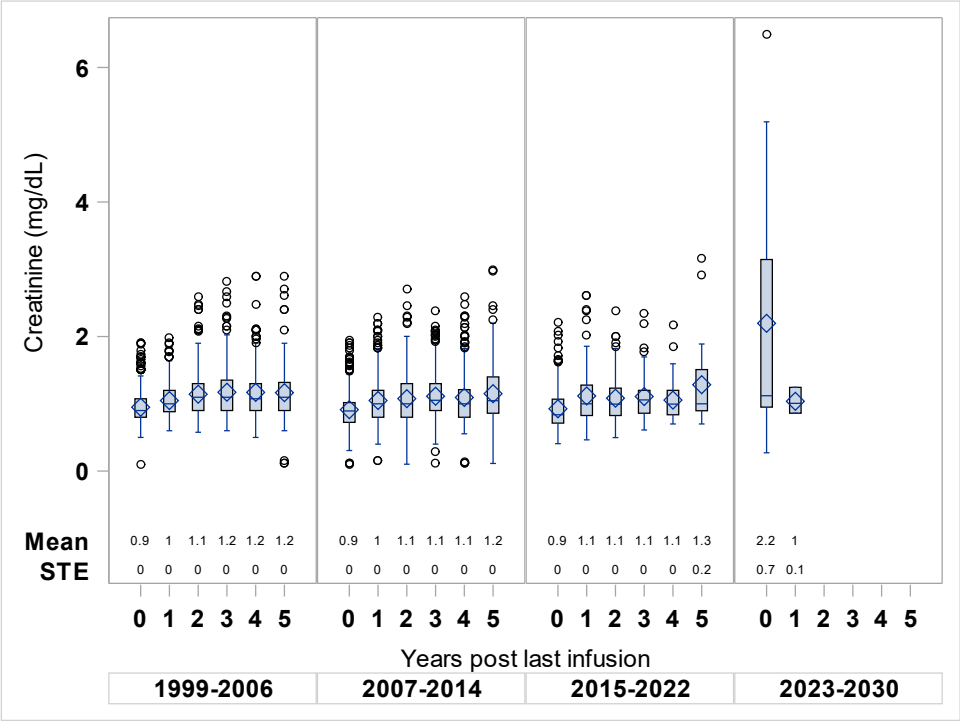
C. Induction Immunosuppression (p=<.0001)



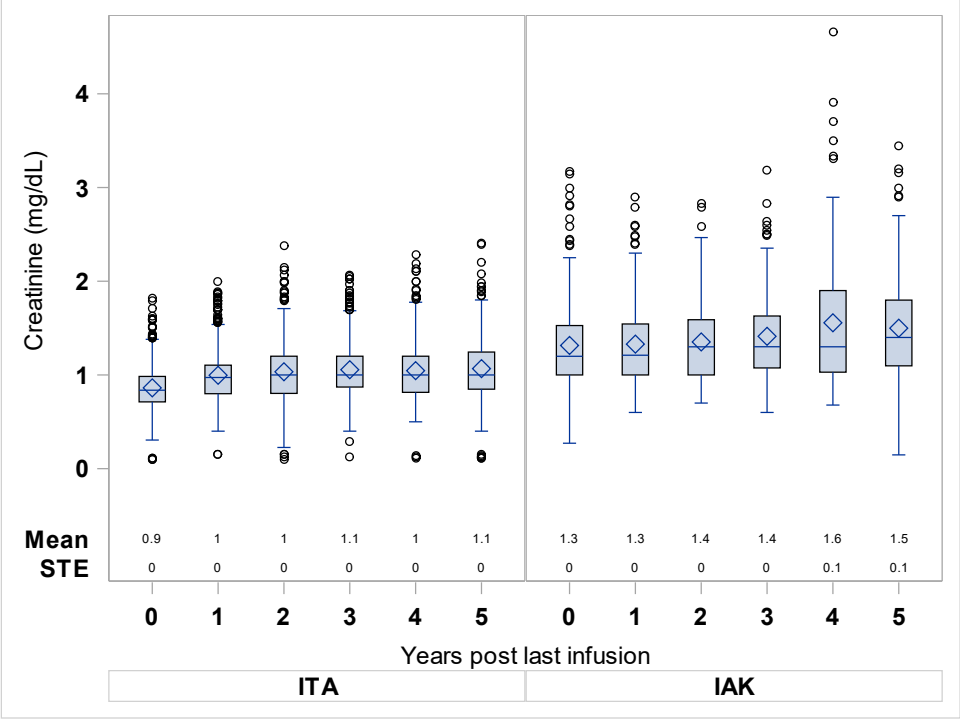
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-8
Serum Creatinine (mg/dL)

A. Era (p=<.0001)



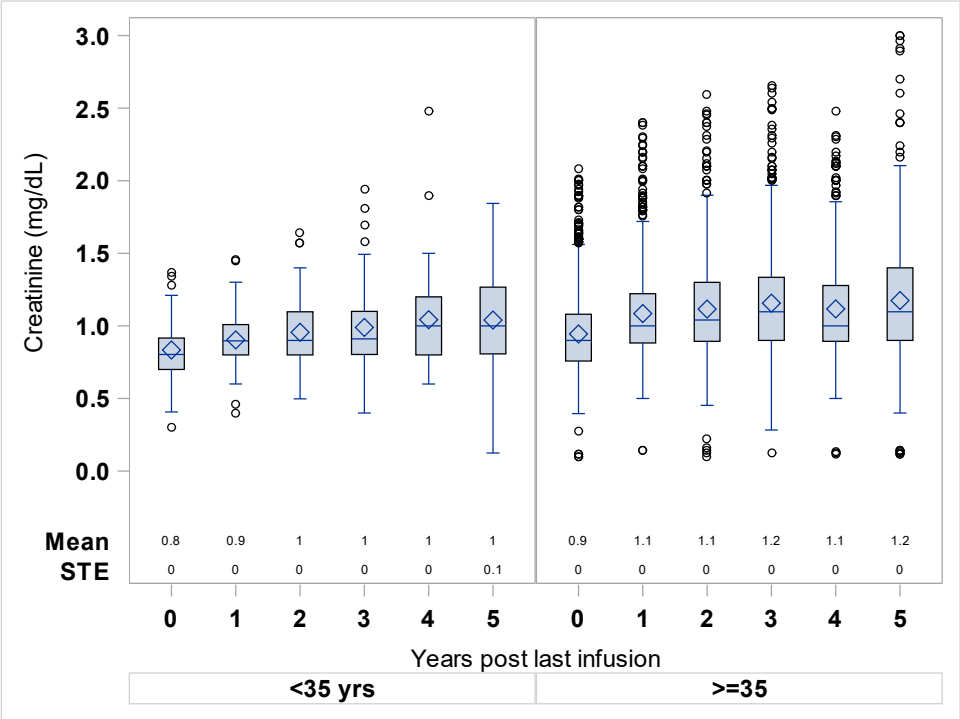
B. Type of Transplant (p=<.0001)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-8
Serum Creatinine (mg/dL)

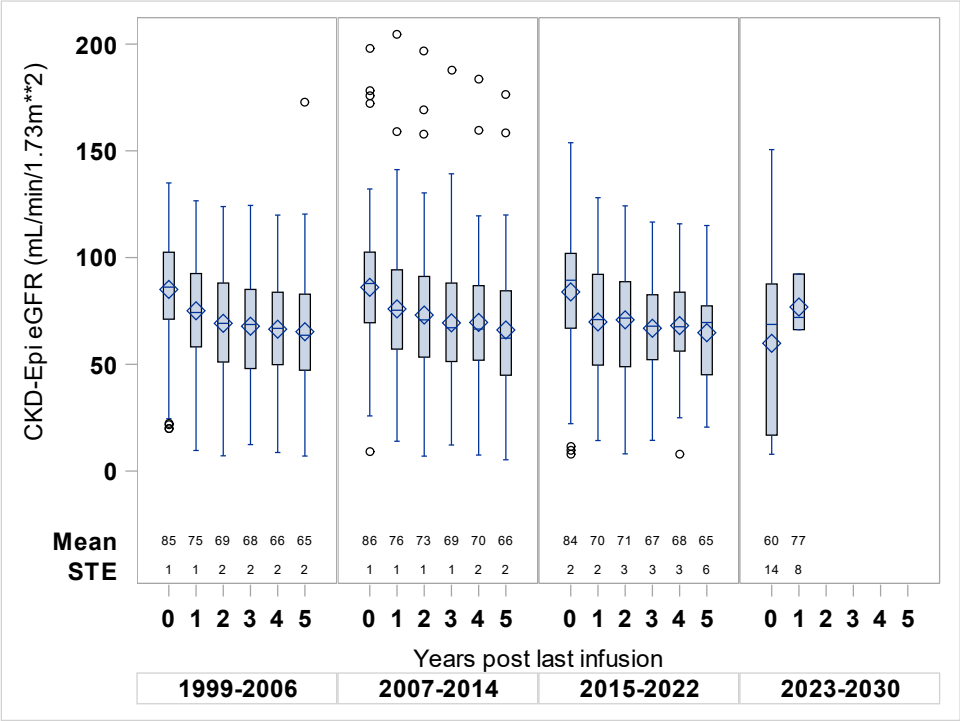
C. Age (p=0.0002)



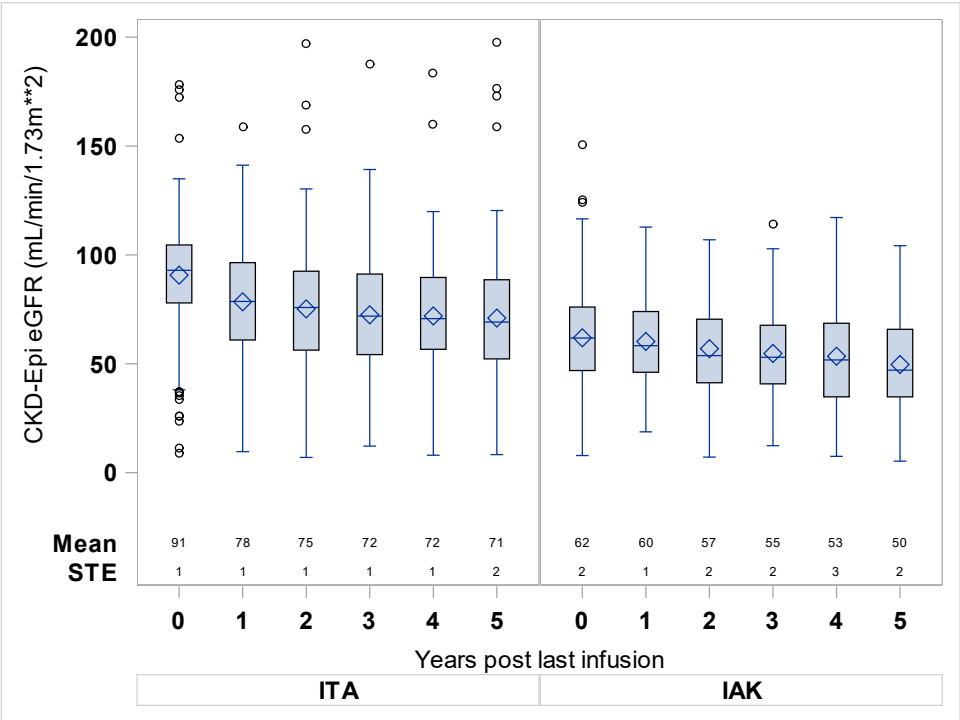
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-9
CKD-Epi eGFR (mL/min/1.73m ²)

A. Era (p=NS)



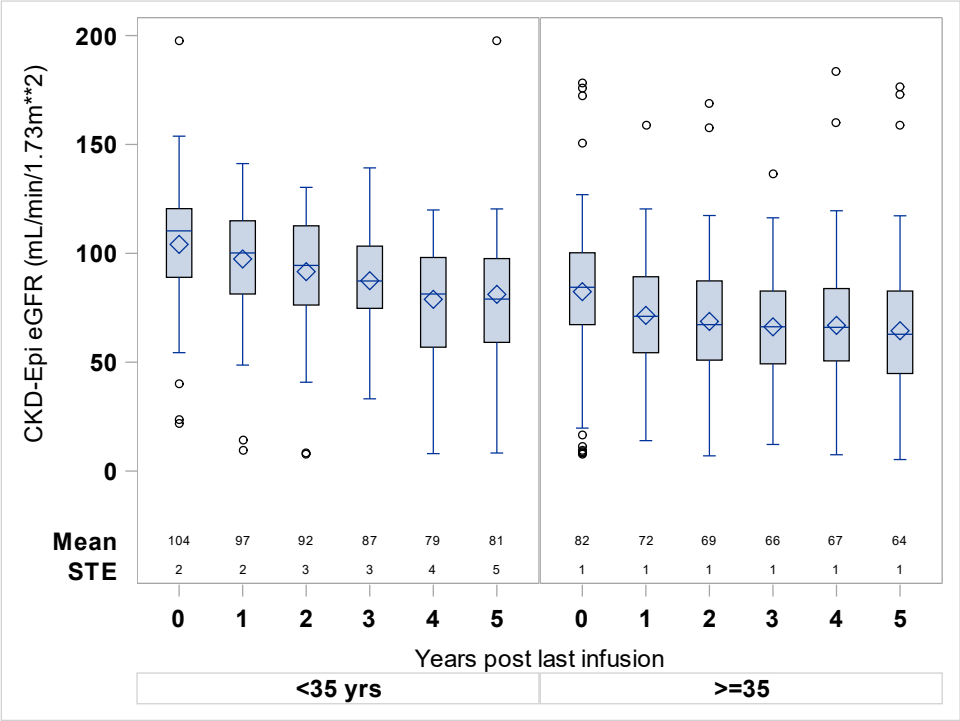
B. Type of Transplant (p=<.0001)



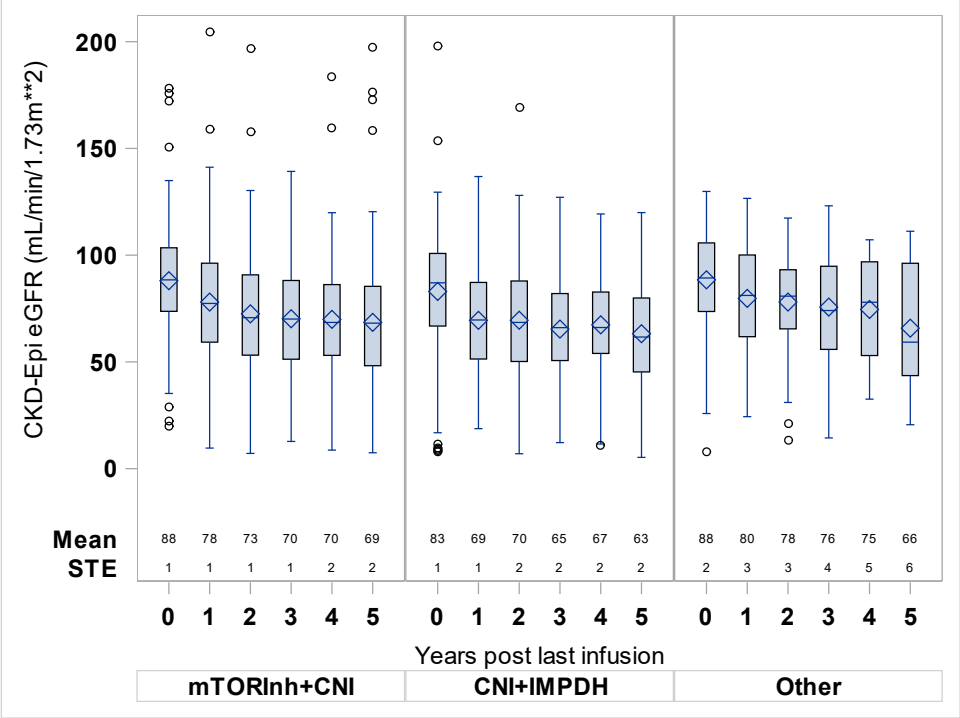
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Exhibit 6-9
CKD-Epi eGFR (mL/min/1.73m ²)

C. Age (p=<.0001)



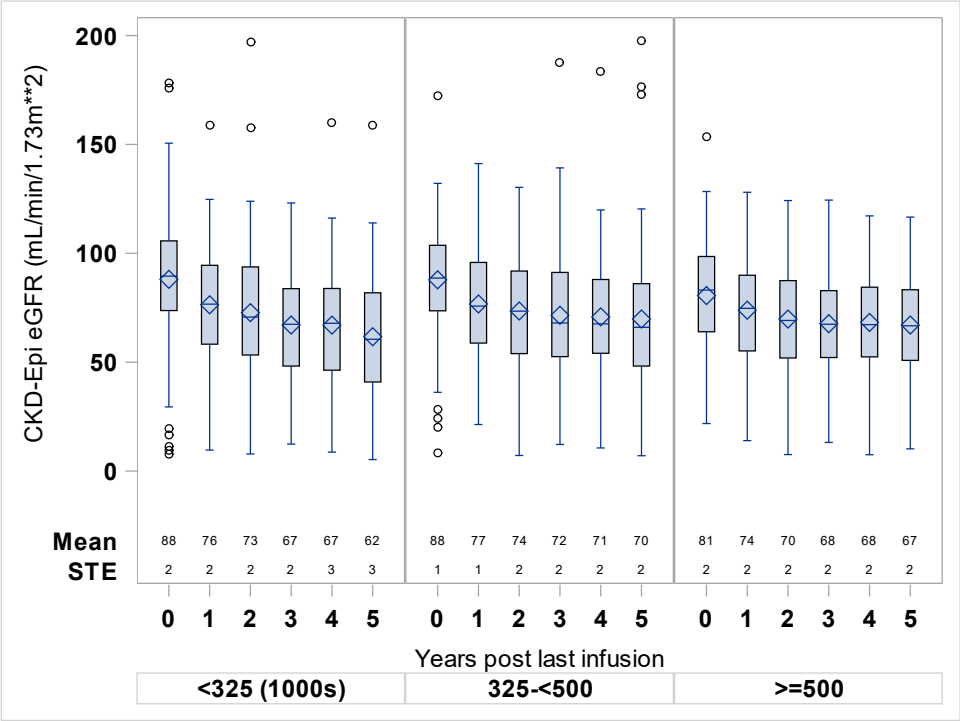
D. Maintenance Immunosuppression (p=0.0002)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

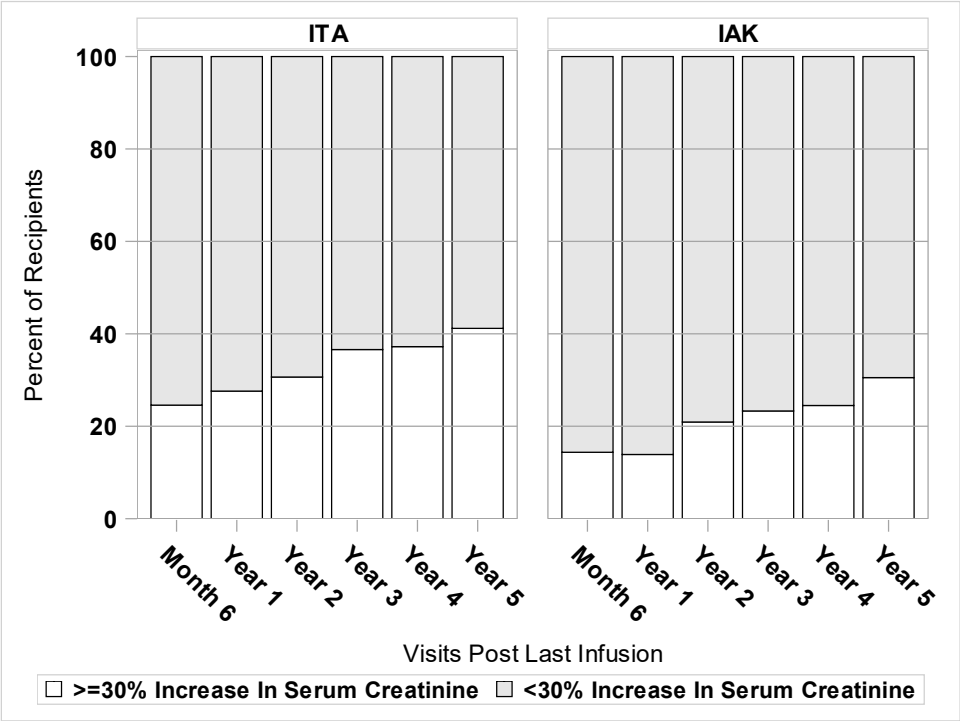
Exhibit 6-9
CKD-Epi eGFR (mL/min/1.73m ²)

E. IEQs Infused (p=0.0097)



Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

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



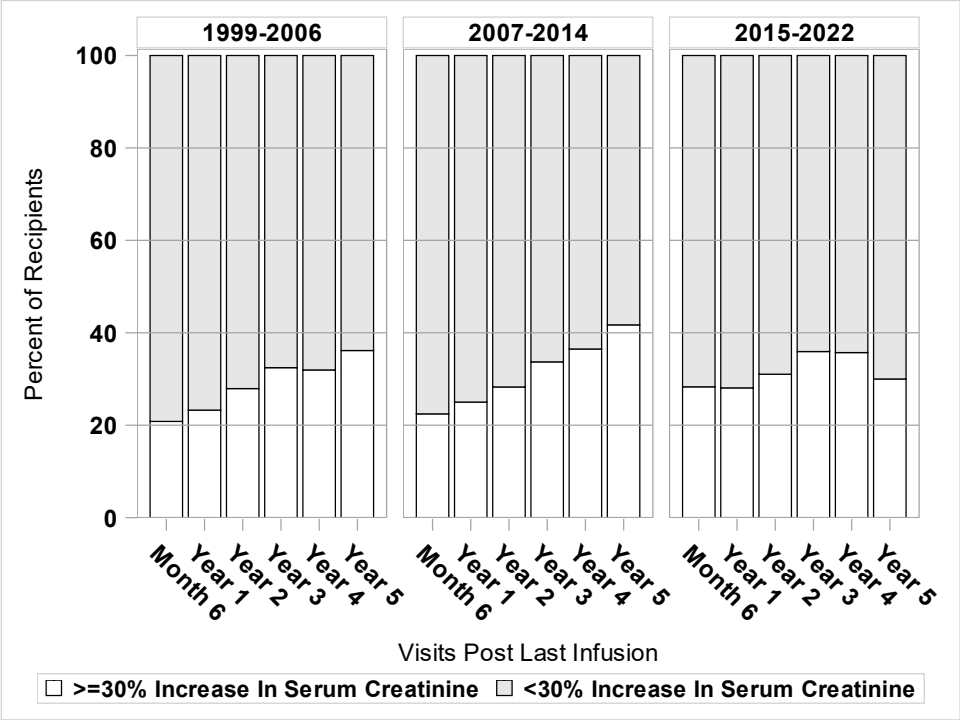
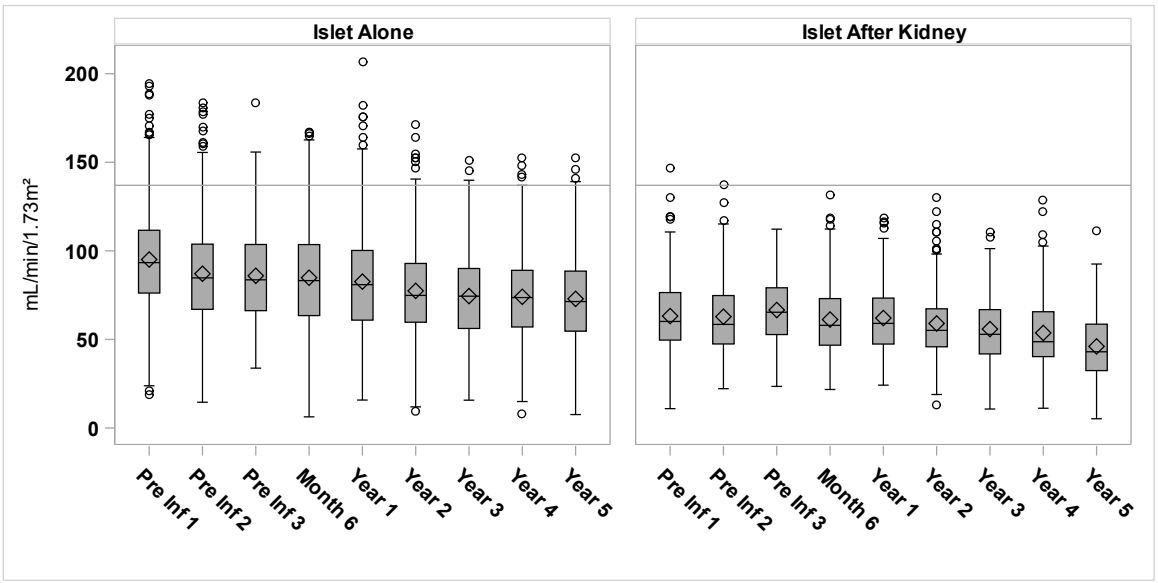
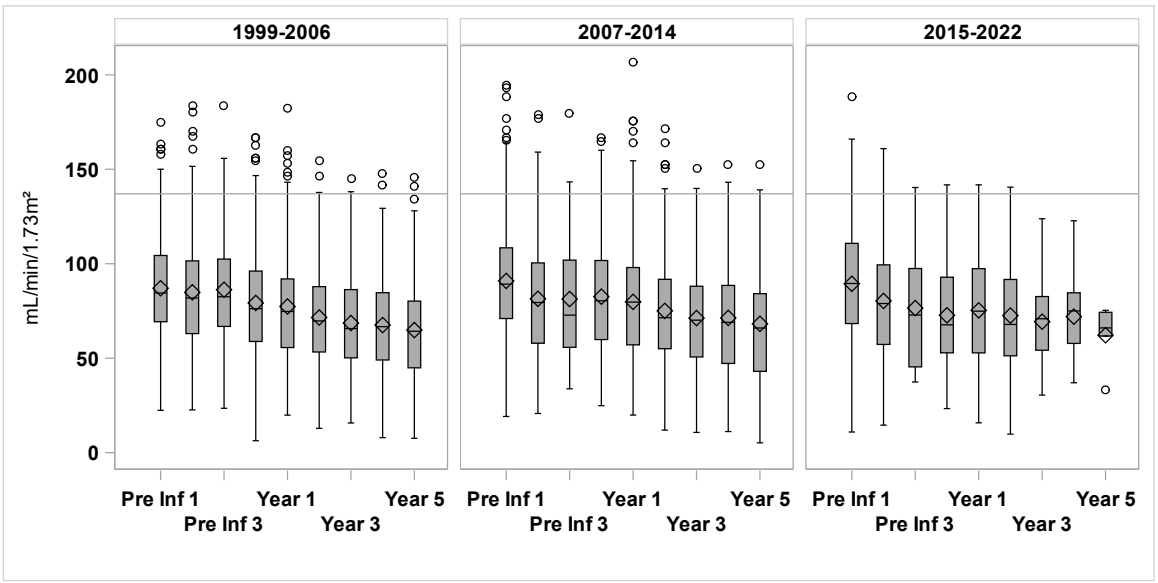


Exhibit 6-10
Percent of Recipients with a 30% increase in Serum Creatinine at each Follow-up Time Point by Infusion Type and Era

	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	639	652	535	429	360	289
Islet After Kidney	174	180	153	133	98	95
1999-2006	317	331	265	225	194	177
2007-2014	383	384	336	273	222	187
2015-2022	106	114	87	64	42	20
2023-2030	7	3	0	0	0	0

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





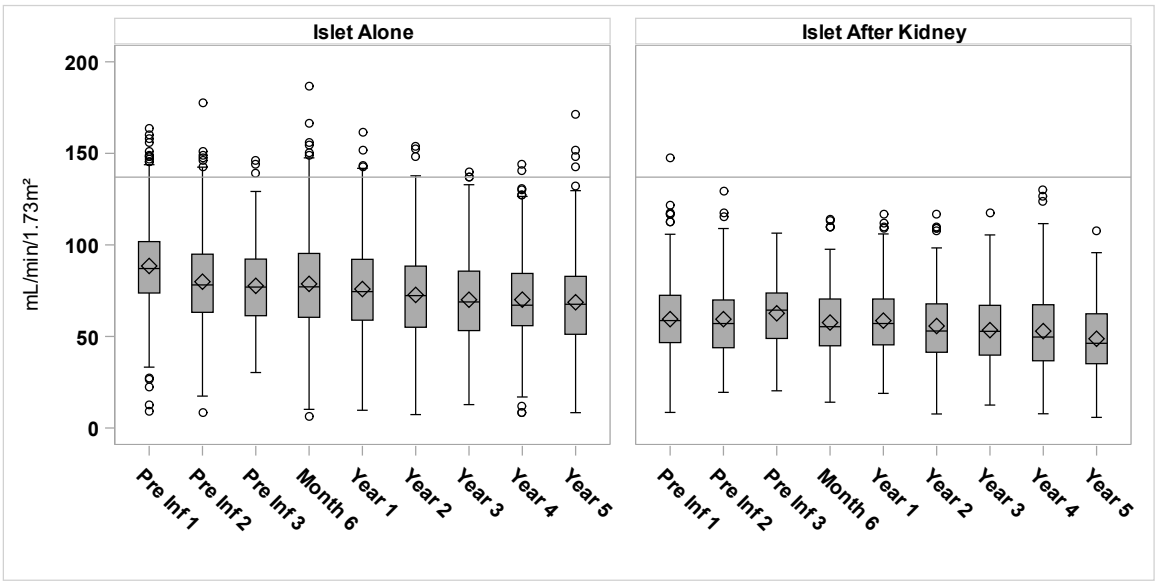
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

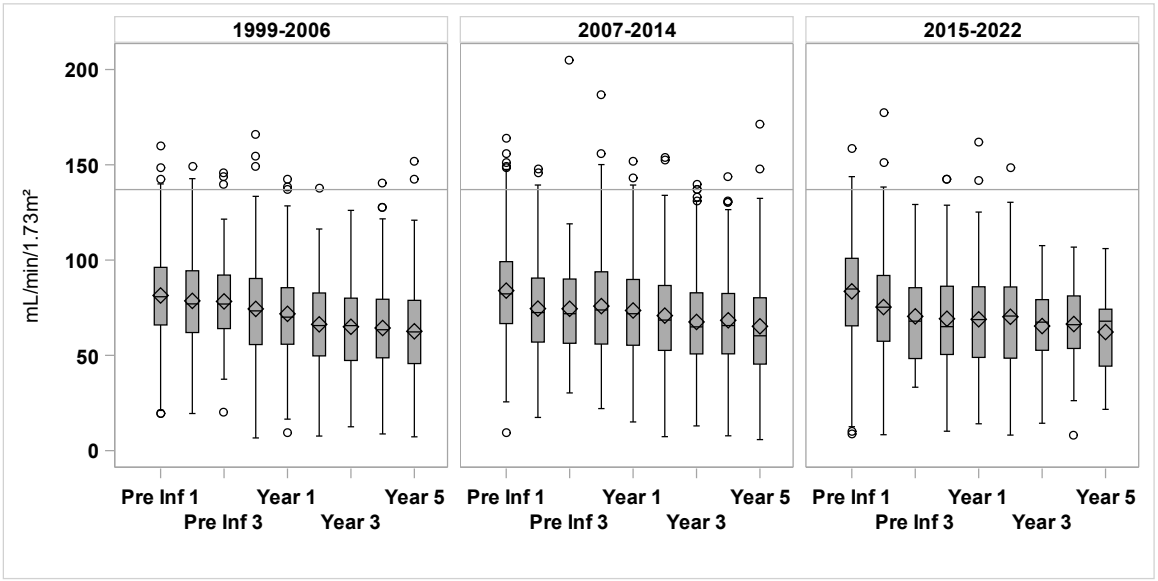
Exhibit 6-11
Cockgroft-Gault Calculated Clearance (mL/min/1.73m ^{2}) by Infusion Type and Era

	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	916	563	160	587	560	447	339	273	209
Islet After Kidney	220	125	25	145	149	126	108	76	62
1999-2006	411	298	109	300	300	239	199	160	126
2007-2014	514	273	60	353	332	281	220	174	139
2015-2022	201	114	16	79	77	53	28	15	6
2023-2030	10	3	0	0	0	0	0	0	0

Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

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





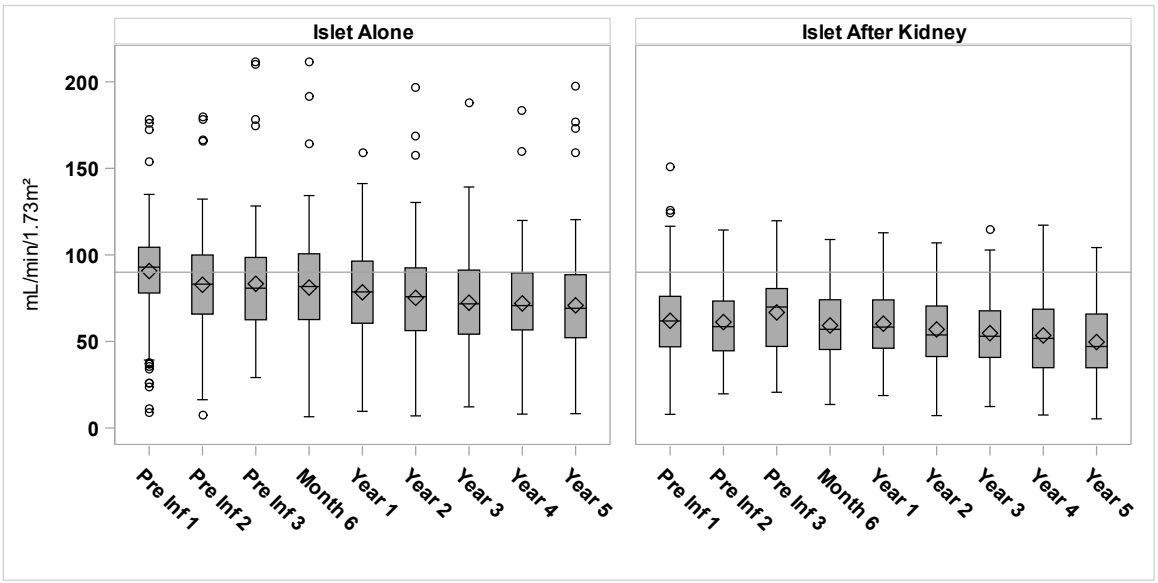
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

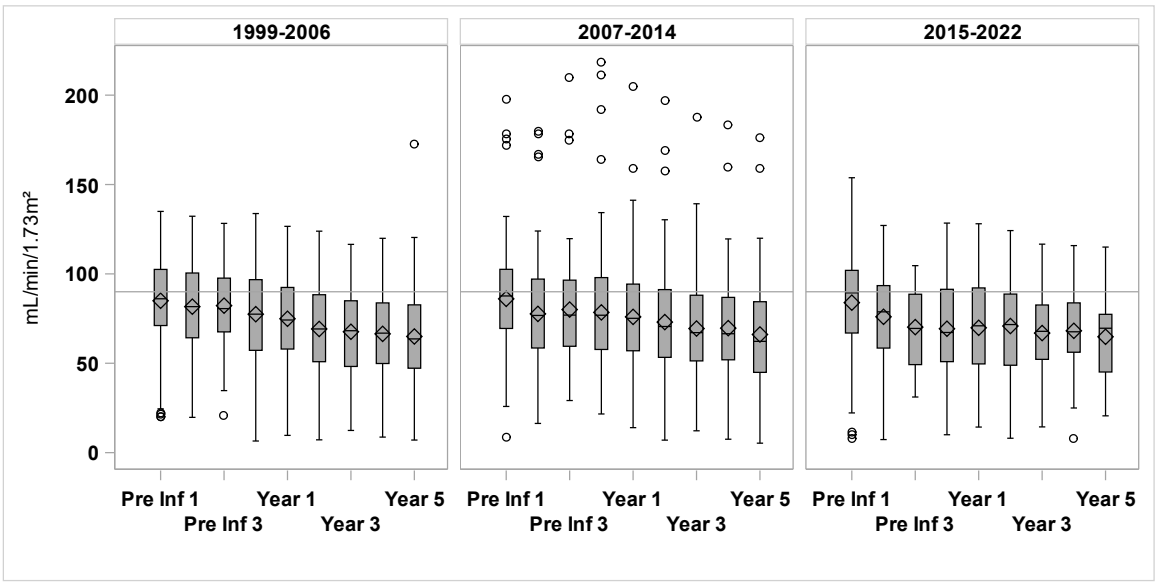
Exhibit 6-12
MDRD Estimated Cockgroft-Gault (mL/min/1.73m ^{2}) by Infusion Type and Era

	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	946	606	180	662	684	570	459	380	305
Islet After Kidney	235	130	27	176	182	152	132	97	94
1999-2006	420	308	116	319	331	264	225	193	176
2007-2014	541	307	75	402	415	365	301	241	203
2015-2022	210	118	16	110	117	93	65	43	20
2023-2030	10	3	0	7	3	0	0	0	0

Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

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





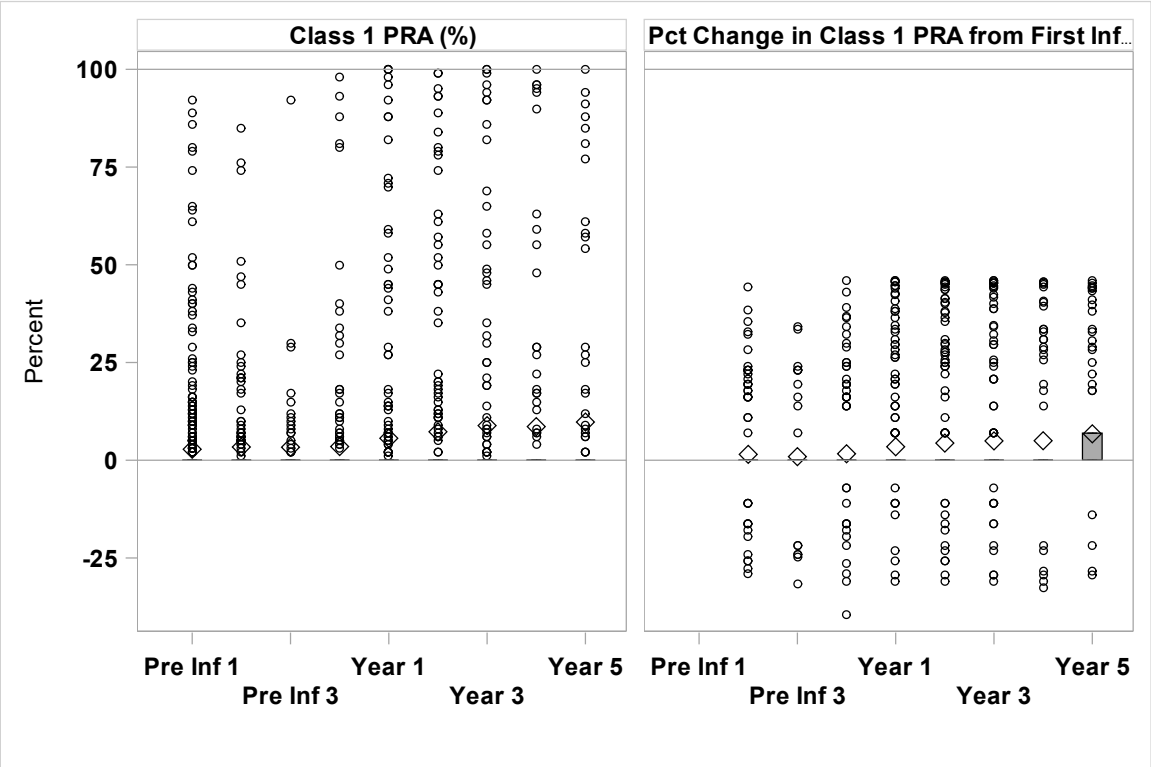
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

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	946	606	180	662	684	570	459	380	305
Islet After Kidney	235	130	27	176	182	152	132	97	94
1999-2006	420	308	116	319	331	264	225	193	176
2007-2014	541	307	75	402	415	365	301	241	203
2015-2022	210	118	16	110	117	93	65	43	20
2023-2030	10	3	0	7	3	0	0	0	0

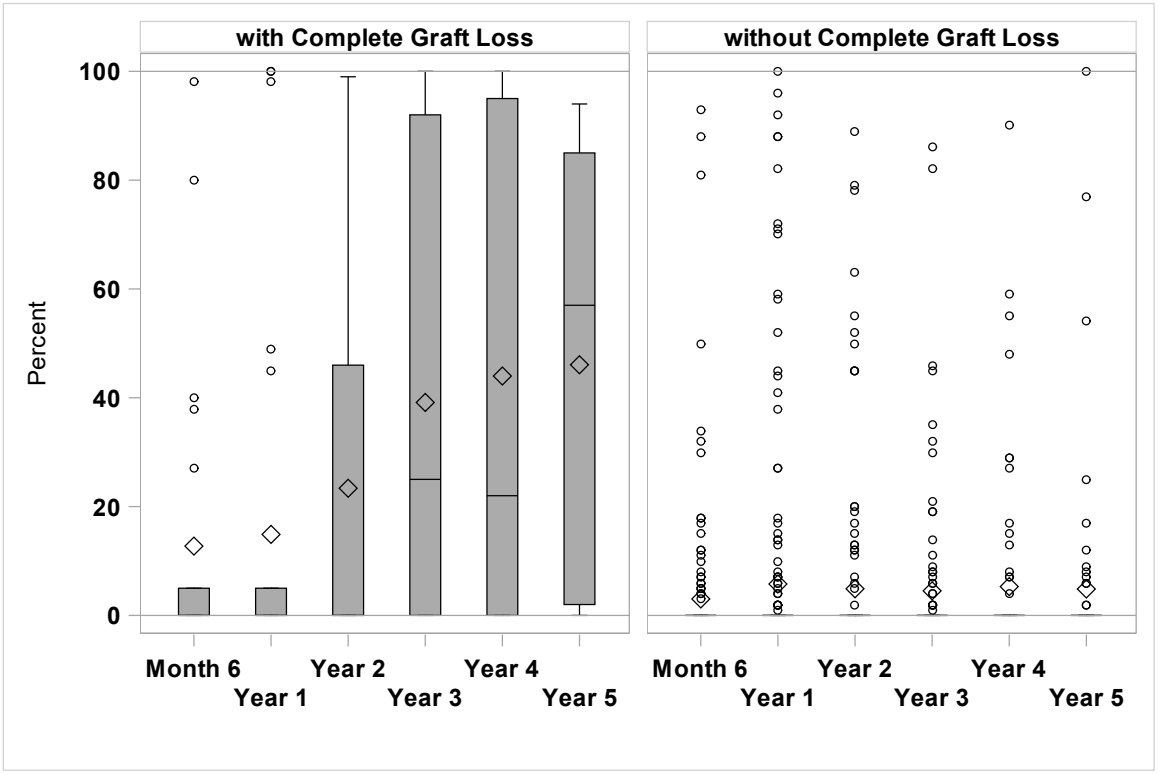
Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

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 (%)	678	227	79	253	315	251	177	118	104
Pct Change in Class 1 PRA from First Infusion	0	205	75	224	277	214	160	101	91

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	23	27	32	21	13	15
without Complete Graft Loss	192	228	158	111	77	67

Extreme outliers (outside of 3*IQR less than the lower quartile or 3*IQR more than the upper quartile) are excluded from box plots.

Chapter 7
Adverse Events

Introduction

As of 2021, by decision of the Executive Committee, only serious adverse events (SAEs) are reportable to CITR. All SAEs reported to CITR since inception were updated for MedDRA coding (version 19.0 or above) in the analysis file for this report. All SAEs reported from the MedDRA classifications were reviewed and either confirmed, revised or left unclassified. Consequently, some adverse events may have changed classification from previous Annual Reports. This chapter provides safety summaries for participants with ITA or IAK transplant types.

Tabulations of all SAEs by MedDRA System Organ Class (SOC) and Preferred Term (PT) transplant type are provided in Exhibit 7-9 (stratified by transplant type) and Exhibit 7-10 (stratified by era).

A total of 10.9% of ITA and 12.7% of IAK allo-islet recipients experienced a serious adverse event in the first 30 days following transplantation (Exhibit 7-1). There was a sharp decline in the number of patients who experienced SAEs post-2010, with 18.5% of patients experiencing such SAEs in 1999-2006 compared to 9.4% in 2007-2014 and 4.2% in 2015-2022. There is likely some lag in reporting for recent years.

In the first year after islet transplantation, which includes a majority of the re-infusions that were performed, about one-fourth of participants have experienced an SAE (Exhibit 7-2). SAE within 1-year was slightly more common in IAK (30.4%) than ITA (22.7%) and there was a significant decline post-2010. There is a similar pattern for SAEs in all follow-up after islet transplantation (Exhibit 7-3).

Exhibit 7-5 displays trends in SAE incidence according to type of transplant, era and relatedness to the infusion procedure and immunosuppression. While significant differences are noted by era (see above), there may be differences according to immunosuppression strategies and patient characteristics that deserve further investigation.

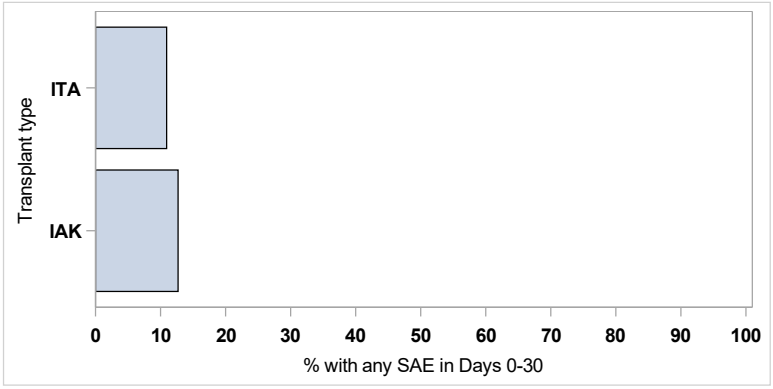
The total cohort of 1360 allo-islet recipients were followed for a mean of 7.7±4.4 SD years, comprising 10,472 person-years of follow-up from first infusion (Exhibit 7-6A). A total of 188 events in 100 recipients were classified malignancies. Of the total 188 events, 60.1% were deemed possibly related to immunosuppression, and 12.2% definitely related. Of the total events, 72.3% recovered, 8.5% did not recover, 4.8% recovered with sequelae, and 4.3% resulted in fatality. There were 41 instances in 28 patients of basal carcinoma of the skin and 84 instances in 43 patients of squamous carcinoma of the skin (Exhibit 7-6B).

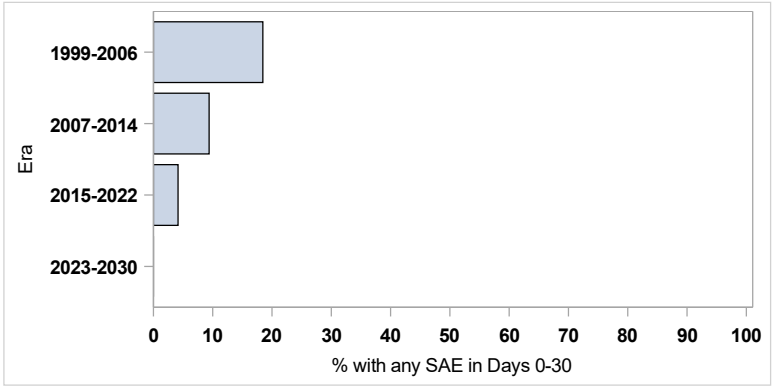
There have been 70 or 5.0% deaths in ITA/IAK participants; cumulative mortality rate was higher for IAK but appears consistent by era (Exhibit 7-7A). Ten deaths due to cancer occurred (see Exhibit 7-7B for details). Of the reported deaths, eleven were deemed possibly related or definitely related to islet transplantation or immunosuppression (Exhibit 7-7B).

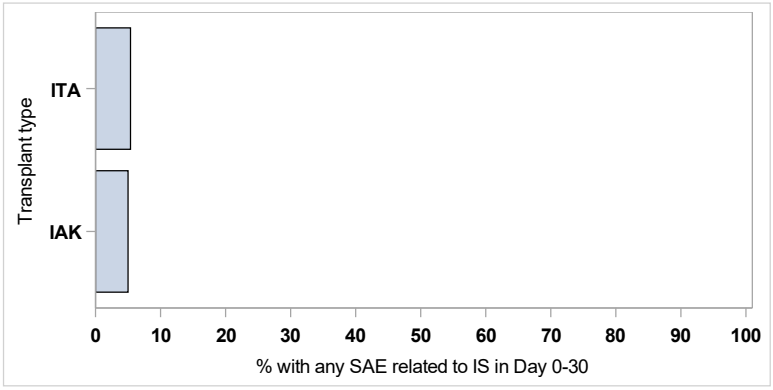
Life-threatening events have occurred in 13.4% of islet-alone and in 16.9% of IAK recipients (Exhibit 7-8A). Recent eras have seen a substantial decline in the incidence of life-threatening events. The most common life-threatening events reported were abnormal granulocytes (24 events) followed by abnormal liver function (23 events) and hypoglycaemia (14 events). A total of 80% of life-threatening events resolved with a full recovery, 8% recovered with sequelae, 3% did not recover, and 6% died as a result of the event.

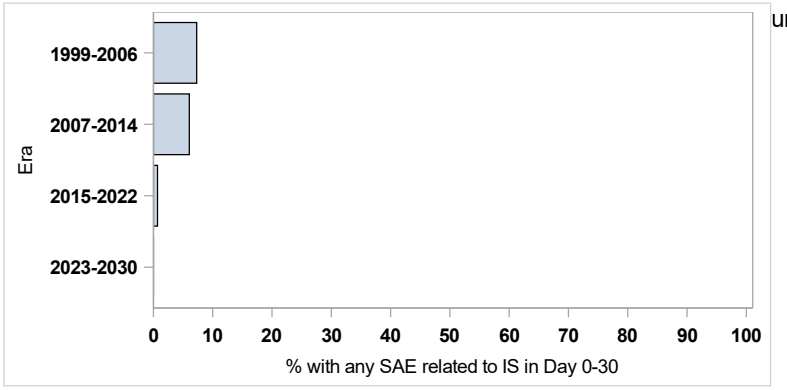
Exhibit 7-1
Serious Adverse Events (SAEs) in Days 0-30 Post 1st Infusion

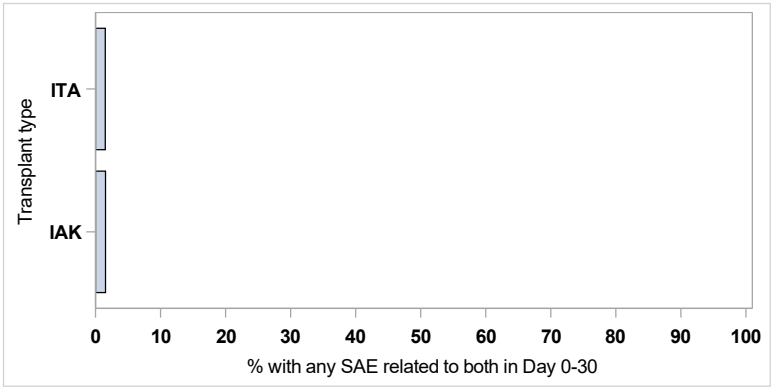
	Transplant Type				Era							
	ITA (N=1134)		IAK (N=260)		Era 1 1999-2006 (N=466)		Era 2 2007-2014 (N=628)		Era 3 2015-2022 (N=289)		Era 4 2023-2030 (N=11)	
Percent of Recipients with:	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N
Any SAE in Day 0-30	124	10.9	33	12.7	86	18.5	59	9.4	12	4.2	0	0.0
Any SAE related to IS in Day 0-30	61	5.4	13	5.0	34	7.3	38	6.1	2	0.7	0	0.0
Any SAE related to both in Day 0-30	17	1.5	4	1.5	7	1.5	14	2.2	0	0.0	0	0.0
Any SAE related to infusion in Day 0-30	72	6.3	22	8.5	57	12.2	31	4.9	6	2.1	0	0.0
Any SAE related to neither in Day 0-30	19	1.7	5	1.9	9	1.9	11	1.8	4	1.4	0	0.0






Transplant type
ITA
IAK
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to IS in Day 0-30


Era
1999-2006
2007-2014
2015-2022
2023-2030
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to IS in Day 0-30


Transplant type
ITA
IAK
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to both in Day 0-30

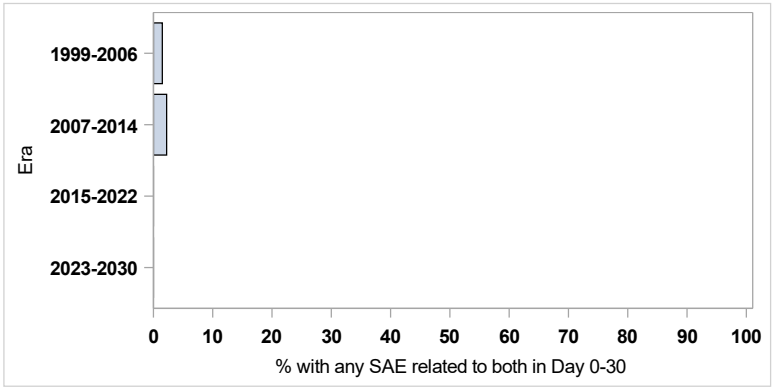
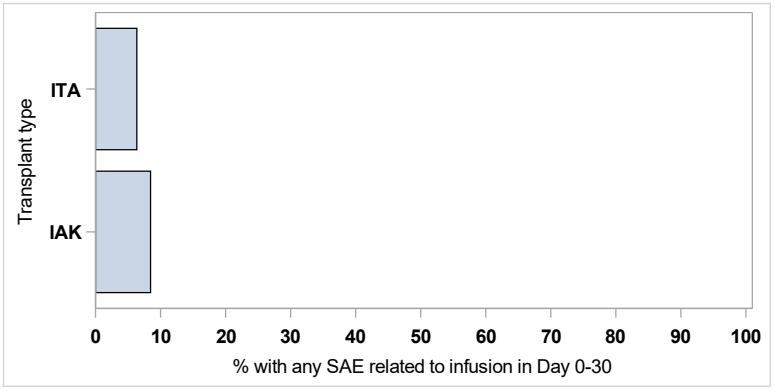
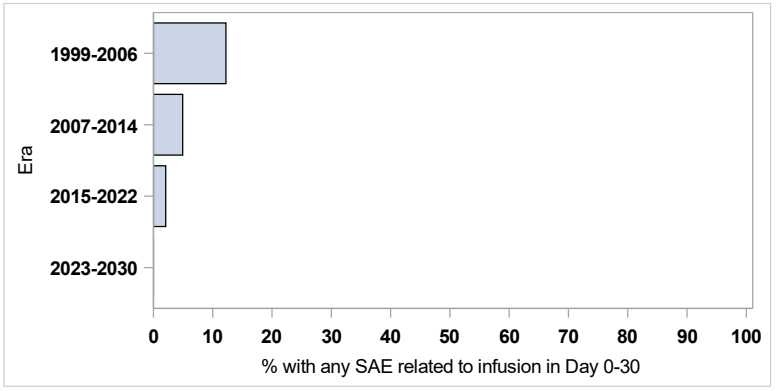
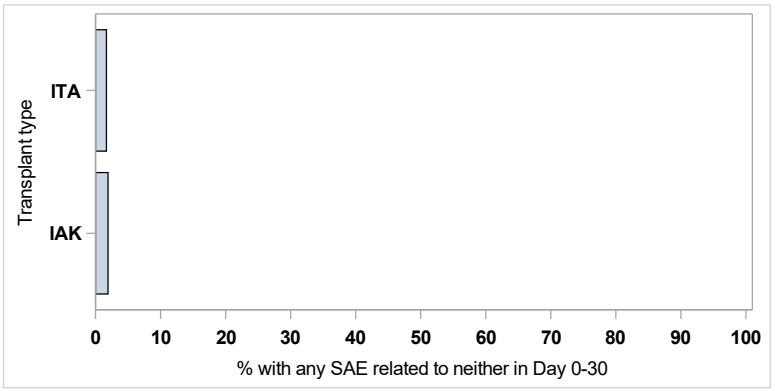

Era
1999-2006
2007-2014
2015-2022
2023-2030
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to both in Day 0-30

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







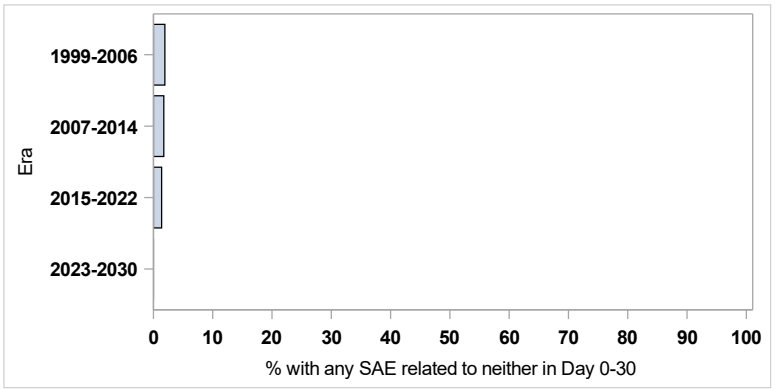
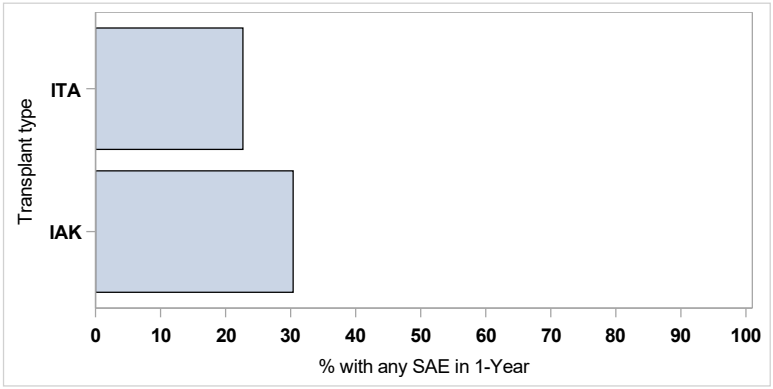
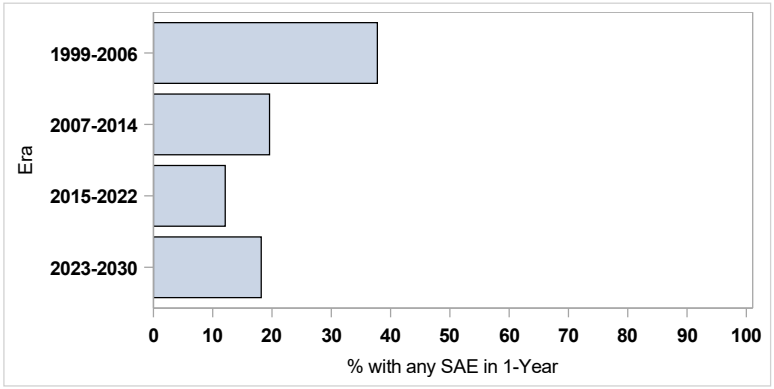
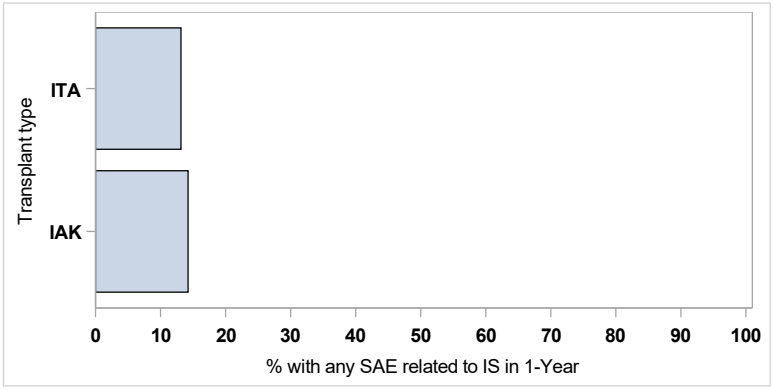


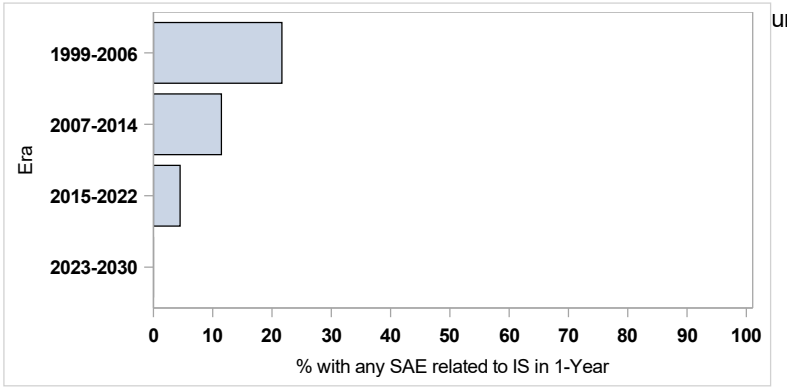
Exhibit 7-2
Serious Adverse Events (SAEs) in 1-Year Post 1st Infusion

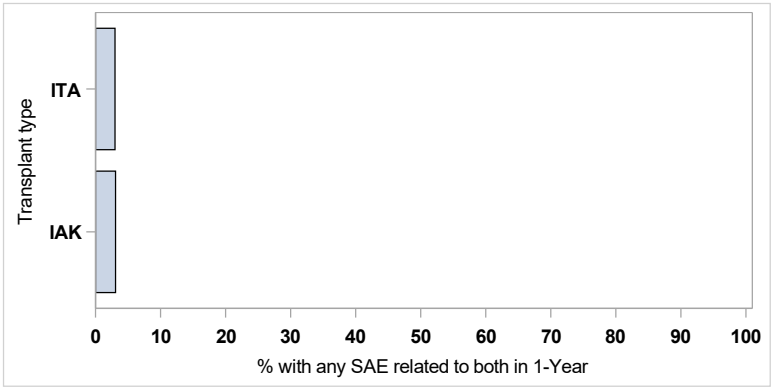
	Transplant Type				Era							
	ITA (N=1134)		IAK (N=260)		Era 1 1999-2006 (N=466)		Era 2 2007-2014 (N=628)		Era 3 2015-2022 (N=289)		Era 4 2023-2030 (N=11)	
Percent of Recipients with:	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N
Any SAE in 1-year	257	22.7	79	30.4	176	37.8	123	19.6	35	12.1	2	18.2
Any SAE related to IS in 1-year	149	13.1	37	14.2	101	21.7	72	11.5	13	4.5	0	0.0
Any SAE related to both in 1-year	34	3.0	8	3.1	16	3.4	23	3.7	3	1.0	0	0.0
Any SAE related to infusion in 1-year	121	10.7	39	15.0	90	19.3	57	9.1	12	4.2	1	9.1
Any SAE related to neither in 1-year	78	6.9	28	10.8	43	9.2	45	7.2	17	5.9	1	9.1






Transplant type
ITA
IAK
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to IS in 1-Year


Era
1999-2006
2007-2014
2015-2022
2023-2030
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to IS in 1-Year


Transplant type
ITA
IAK
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to both in 1-Year

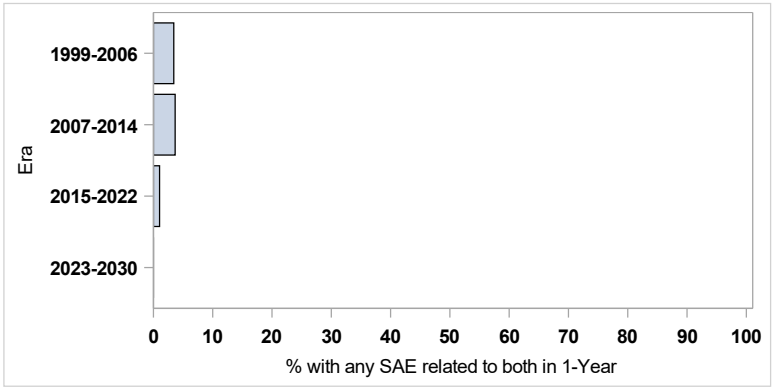
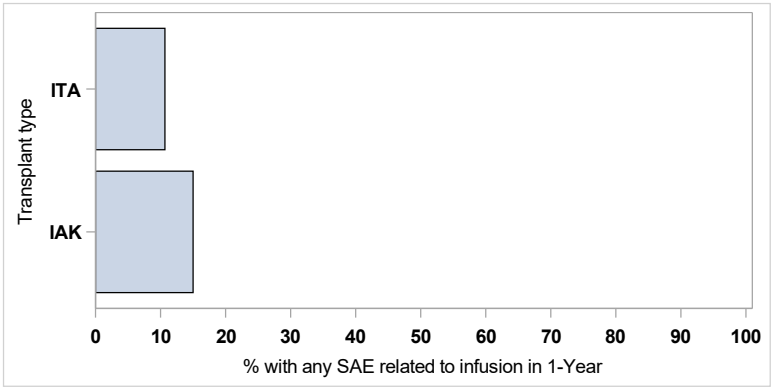
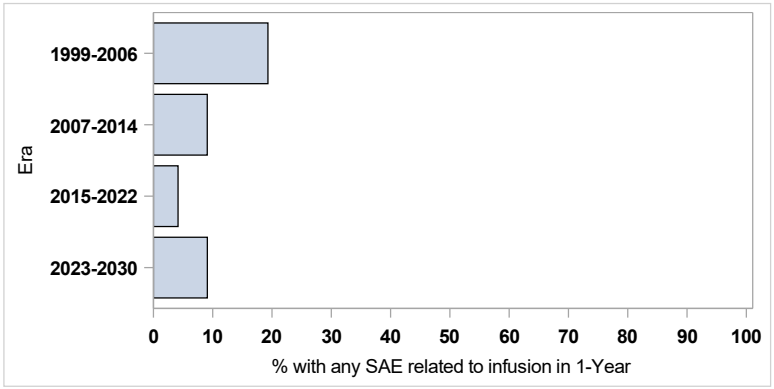
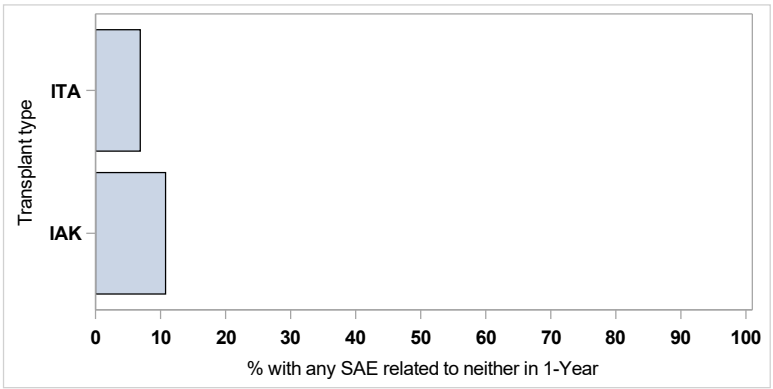

Era
1999-2006
2007-2014
2015-2022
2023-2030
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to both in 1-Year

Exhibit 7-2
Serious Adverse Events (SAEs) in 1-Year Post 1st Infusion







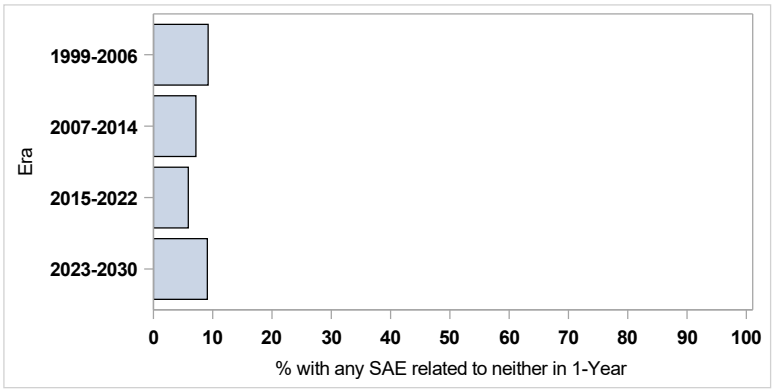
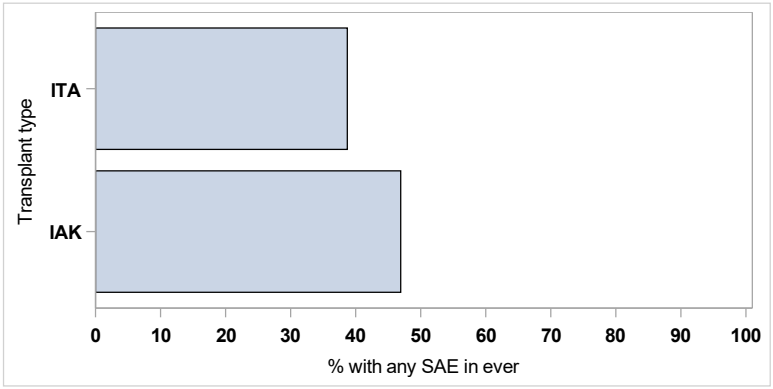
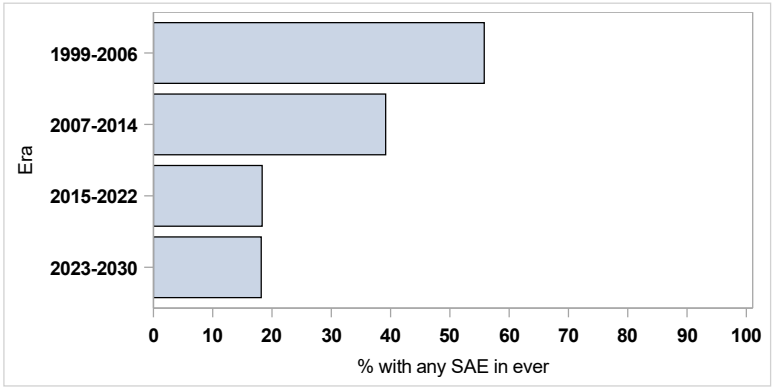
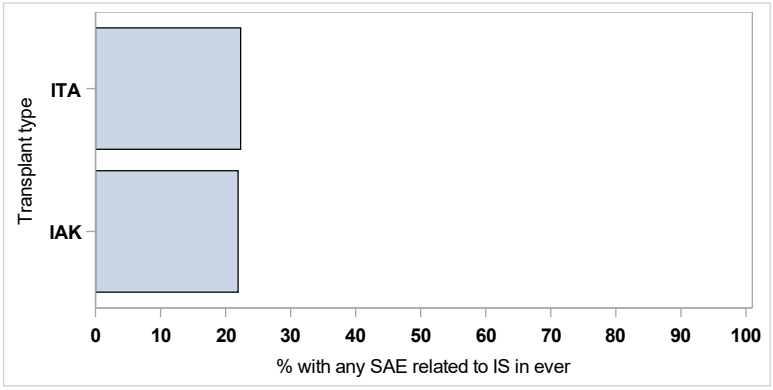


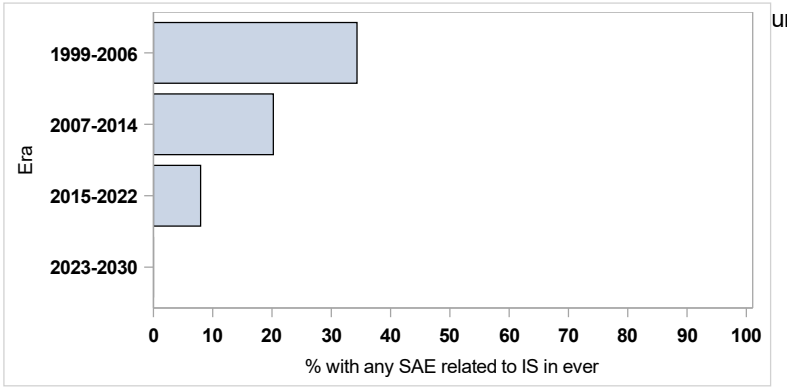
Exhibit 7-3
Recipients with a Serious Adverse Event (SAE) Any Time Post Islet Transplant

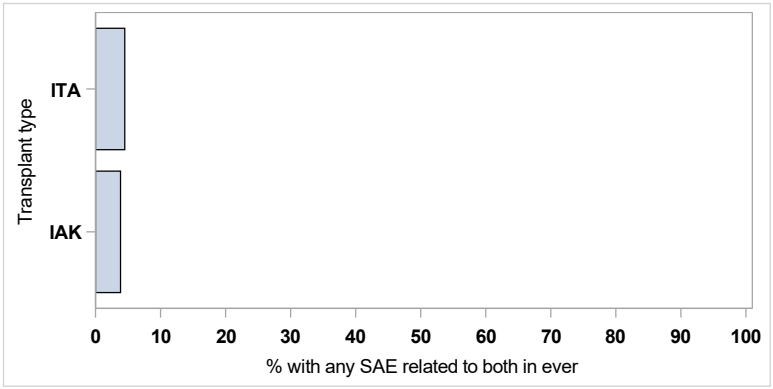
	Transplant Type				Era							
	ITA (N=1134)		IAK (N=260)		Era 1 1999-2006 (N=466)		Era 2 2007-2014 (N=628)		Era 3 2015-2022 (N=289)		Era 4 2023-2030 (N=11)	
Percent of Recipients with:	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N
Any SAE in ever	439	38.7	122	46.9	260	55.8	246	39.2	53	18.3	2	18.2
Any SAE related to IS in ever	253	22.3	57	21.9	160	34.3	127	20.2	23	8.0	0	0.0
Any SAE related to both in ever	51	4.5	10	3.8	24	5.2	32	5.1	5	1.7	0	0.0
Any SAE related to infusion in ever	157	13.8	43	16.5	107	23.0	76	12.1	16	5.5	1	9.1
Any SAE related to neither in ever	247	21.8	81	31.2	141	30.3	160	25.5	26	9.0	1	9.1






Transplant type
ITA
IAK
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to IS in ever


Era
1999-2006
2007-2014
2015-2022
2023-2030
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to IS in ever


Transplant type
ITA
IAK
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to both in ever

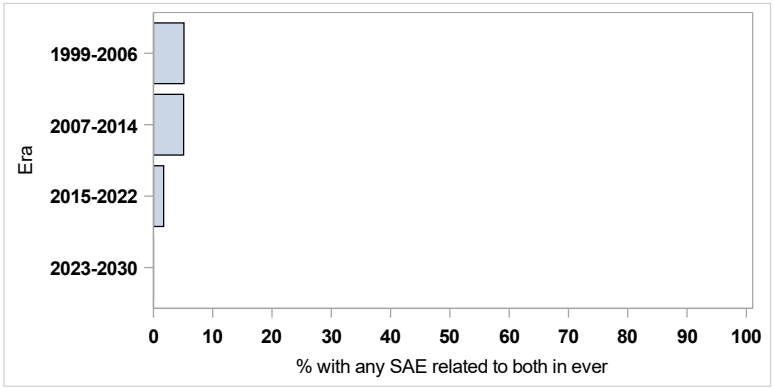
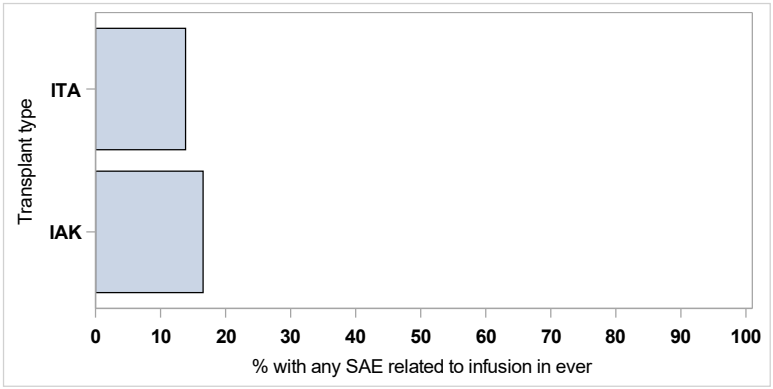
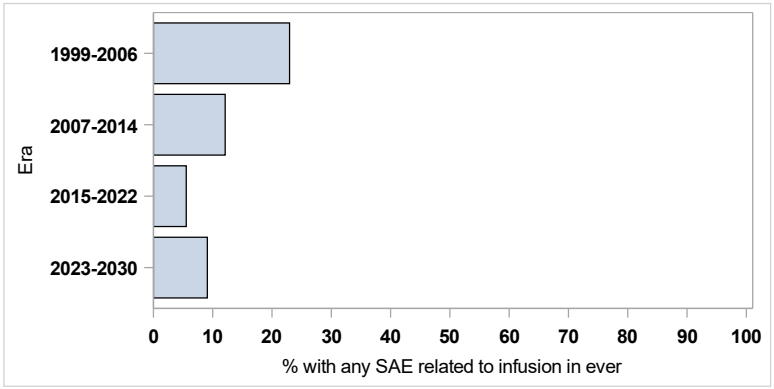
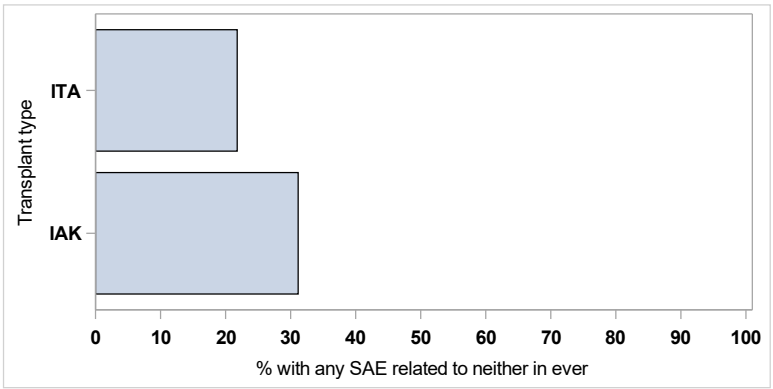

Era
1999-2006
2007-2014
2015-2022
2023-2030
0
10
20
30
40
50
60
70
80
90
100
% with any SAE related to both in ever

Exhibit 7-3
Recipients with a Serious Adverse Event (SAE) Any Time Post Islet Transplant







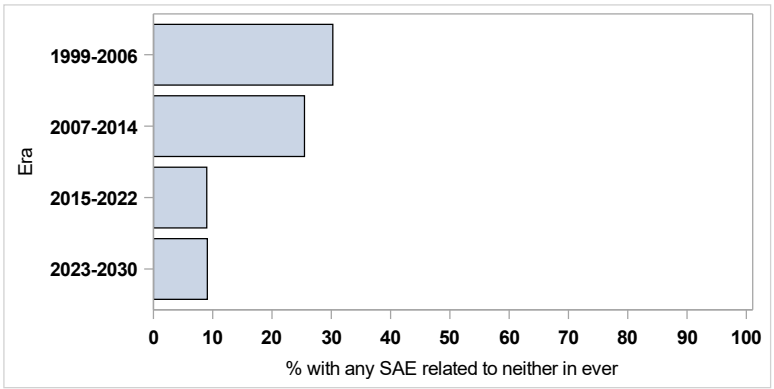


Exhibit 7-4
SAE Criteria

	Transplant Type				Era							
	ITA (N=1134)		IAK (N=260)		Era 1 1999-2006 (N=466)		Era 2 2007-2014 (N=628)		Era 3 2015-2022 (N=289)		Era 4 2023-2030 (N=11)	
Percent of Recipients with:	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N	n	% of N
Congenital abnormality	2	0.2	0	0.0	1	0.2	1	0.2	0	0.0	0	0.0
Death	39	3.4	34	13.1	33	7.1	32	5.1	7	2.4	1	9.1
Hospitilization	323	28.5	84	32.3	219	47.0	146	23.2	41	14.2	1	9.1
Life Threatening	150	13.2	42	16.2	126	27.0	48	7.6	18	6.2	0	0.0
Long term disability	35	3.1	17	6.5	22	4.7	26	4.1	4	1.4	0	0.0
PI Indicated Serious	80	7.1	22	8.5	53	11.4	40	6.4	9	3.1	0	0.0

Exhibit 7-5
Incidence of SAEs per Recipient by Type of Transplant and Era

Any SAE in First Year Post Transplant
Era: p=<0.001 Type: p=<0.05

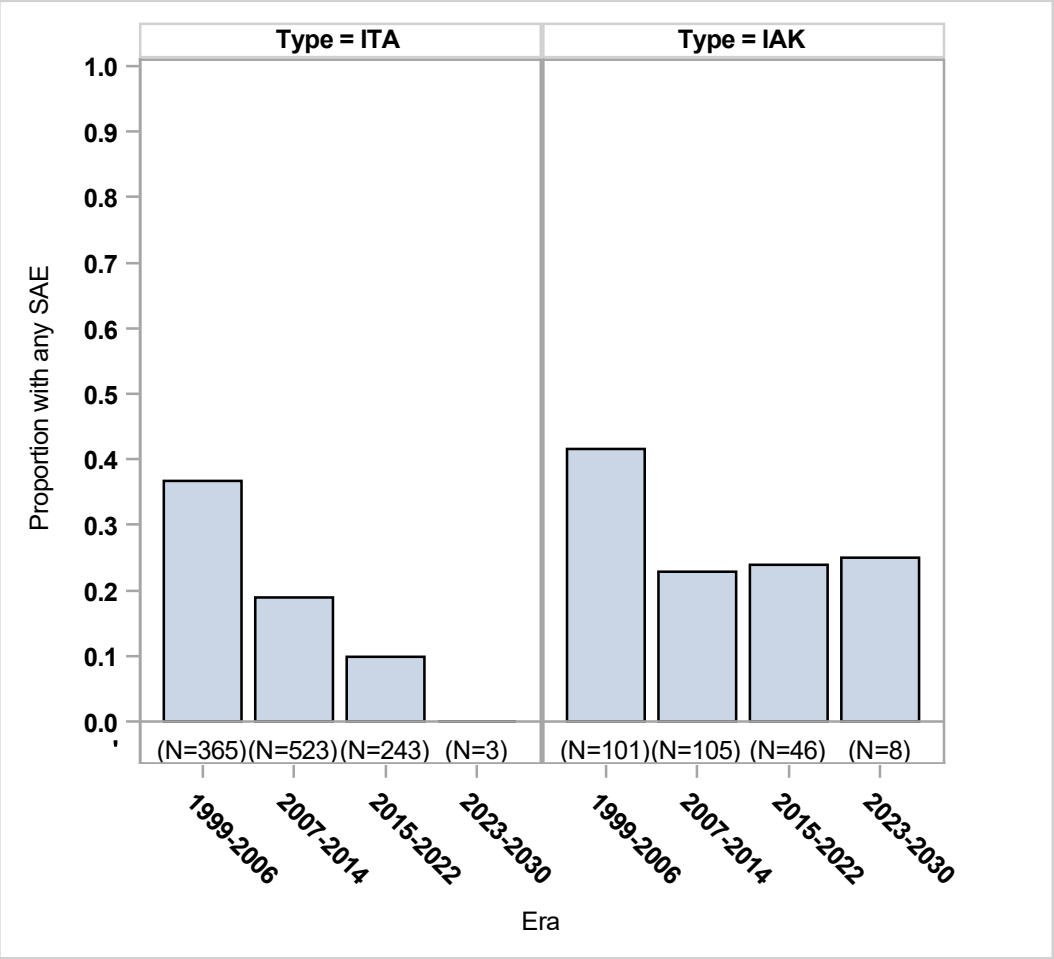


Exhibit 7-5
Incidence of SAEs per Recipient by Type of Transplant and Era

Any SAE in First Year Post Transplant Related to Infusion
Era: p=<0.001 Type: p=0.09

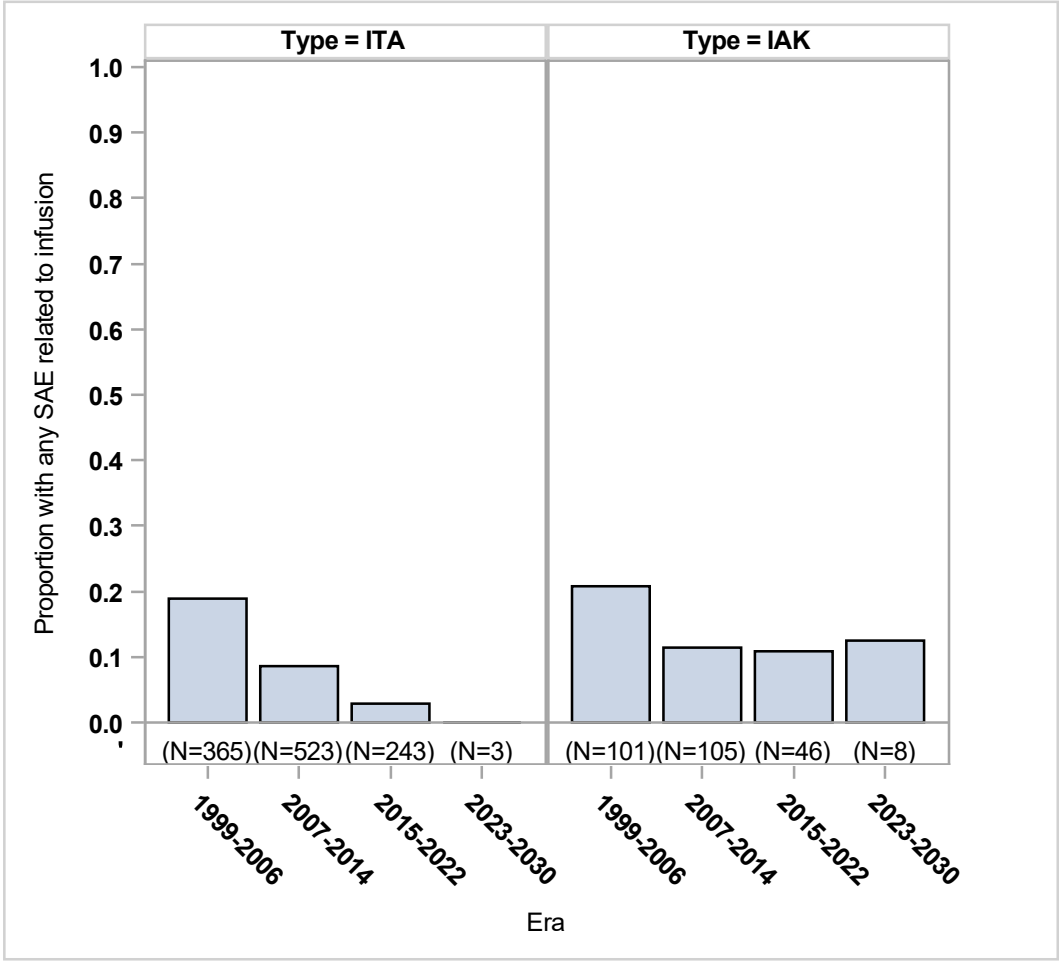


Exhibit 7-5
Incidence of SAEs per Recipient by Type of Transplant and Era

Any SAE in First Year Post Transplant Related to Immunosuppression
Era: p=<0.001 Type: p=0.87

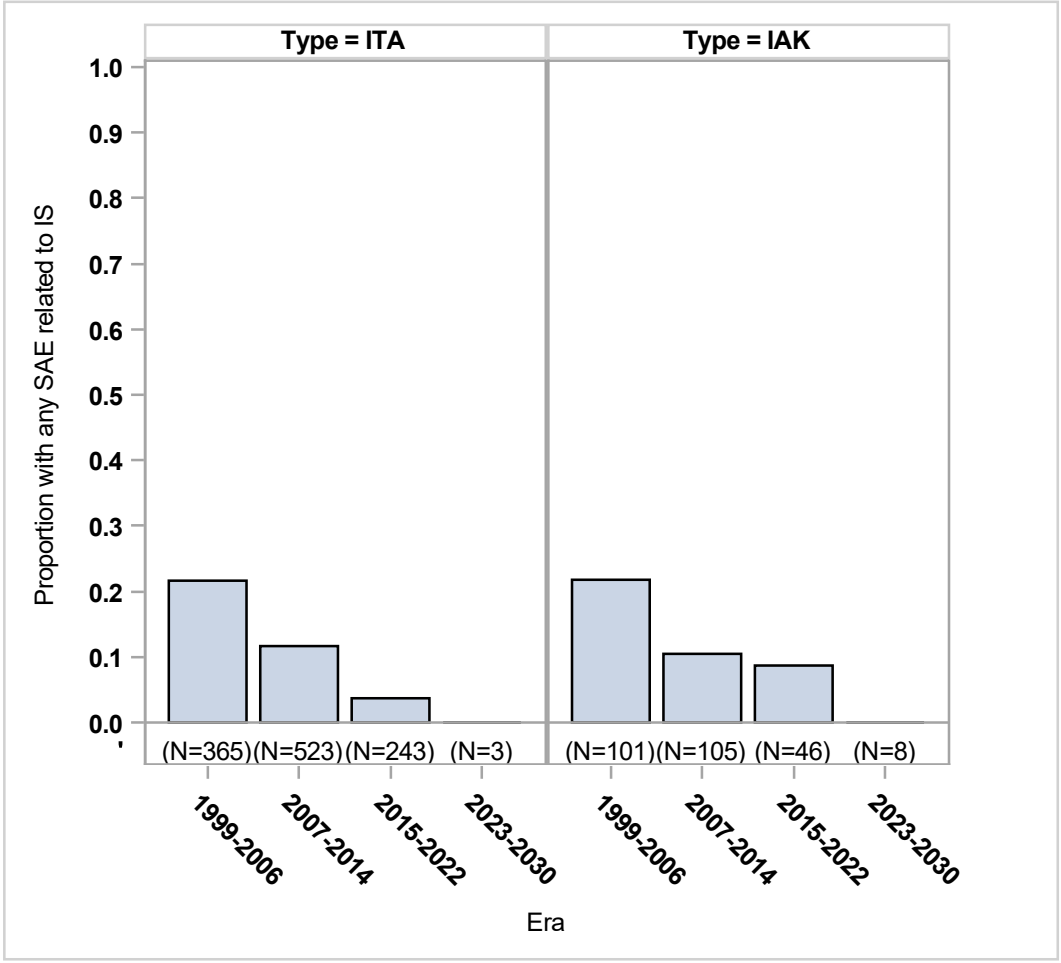


Exhibit 7-6A
Total years of follow-up

	N	Mean	Std
Total years of follow-up	1360	7.7	4.4

Exhibit 7-6B
All Malignancies

			Relatedness to Immunosuppression					Outcome					
Events	N of Pts	N of Events	Unk.	Possibly Related	Unlikely Related	Related	Not Related	Unk.	Recovering/ Resolving	Recovered/ Resolved	Not Recovered/Not Resolved	Recovered with sequelae	Fatal
TOTAL	100	188	18.6	60.1	3.2	12.2	5.9	6.4	3.7	72.3	8.5	4.8	4.3
ADENOCARCINOMA	1	2			100.0					50.0	50.0		
BASAL CELL CARCINOMA	28	41	12.2	68.3		19.5		7.3		82.9		9.8	
BREAST CANCER	4	6		50.0	16.7		33.3		50.0	16.7	16.7	16.7	
BREAST CANCER STAGE I	1	1					100.0				100.0		
CERVIX CARCINOMA	1	1		100.0							100.0		
COLON ADENOMA	1	1	100.0							100.0			
DUCTAL CARCINOMA	5	5		40.0	40.0		20.0			60.0	40.0		
GASTROINTESTINAL CARCINOMA	1	1		100.0									100.0
GERM CELL NEOPLASM	1	1	100.0							100.0			
LUNG CARCINOMA	2	2	50.0		50.0			50.0					50.0

			Relatedness to Immunosuppression					Outcome					
Events	N of Pts	N of Events	Unk.	Possibly Related	Unlikely Related	Related	Not Related	Unk.	Recovering/ Resolving	Recovered/ Resolved	Not Recovered/Not Resolved	Recovered with sequelae	Fatal
MALIGNANT MELANOMA	3	3	66.7	33.3				33.3		66.7			
MELANOCYTIC NAEVUS	1	1	100.0							100.0			
MELANOMA SHOULDER	1	1		100.0						100.0			
METASTASIS	3	3	33.3	66.7							33.3	33.3	33.3
NEOPLASM	2	2	50.0	50.0						50.0			50.0
NEOPLASM MALIGNANT	5	7		100.0					14.3	57.1	14.3	14.3	
OVARIAN ADENOMA	1	1					100.0			100.0			
PAPILLARY	4	4	25.0	50.0			25.0			100.0			
PLASMA CELL MYELOMA	1	1		100.0							100.0		
POLYCYTHAEMIA VERA	1	1	100.0						100.0				
POST TRANSPLANT LYMPHOPROLIFERATIVE	5	9	22.2	33.3			44.4		11.1	44.4	33.3		11.1
PROSTATE CANCER	1	4		100.0						75.0	25.0		
SINONASAL PAPILLOMA	1	1		100.0						100.0			
SKIN CANCER	1	1	100.0							100.0			
SMALL INTESTINE CARCINOMA	1	1		100.0						100.0			
SQUAMOUS CELL	43	84	17.9	63.1		17.9	1.2	8.3	1.2	81.0	3.6	2.4	3.6
TESTIS CANCER	1	1	100.0							100.0			

			Relatedness to Immunosuppression					Outcome					
Events	N of Pts	N of Events	Unk.	Possibly Related	Unlikely Related	Related	Not Related	Unk.	Recovering/ Resolving	Recovered/ Resolved	Not Recovered/Not Resolved	Recovered with sequelae	Fatal
TRANSITIONAL CELL CARCINOMA	1	1	100.0							100.0			
UTERINE LEIOMYOMA	1	1		100.0						100.0			

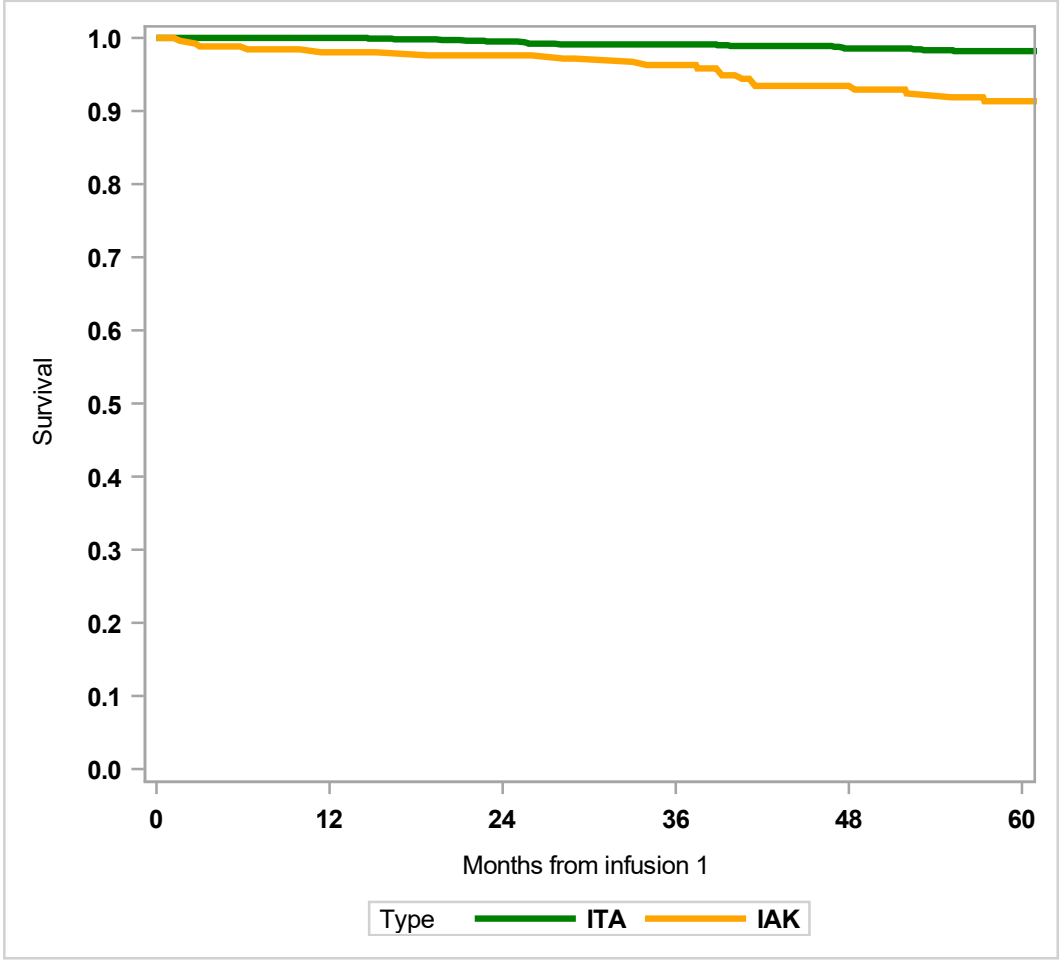
Exhibit 7-6C
First Malignancy in Patient

			Relatedness to Immunosuppression					Outcome					
Events	N of Pts	N of Events	Unk.	Possibly Related	Unlikely Related	Related	Not Related	Unk.	Recovering/ Resolving	Recovered/ Resolved	Not Recovered/Not Resolved	Recovered with sequelae	Fatal
TOTAL	100	100	20.0	65.0	4.0	4.0	7.0	6.0	4.0	68.0	9.0	7.0	6.0
BASAL CELL CARCINOMA	23	23	13.0	82.6		4.3		4.3		82.6		13.0	
BREAST CANCER	4	4		50.0	25.0		25.0		50.0		25.0	25.0	
BREAST CANCER STAGE I	1	1					100.0				100.0		
CERVIX CARCINOMA	1	1		100.0							100.0		
COLON ADENOMA	1	1	100.0							100.0			
DUCTAL CARCINOMA	4	4		25.0	50.0		25.0			50.0	50.0		
GASTROINTESTINAL CARCINOMA	1	1		100.0									100.0
LUNG CARCINOMA	2	2	50.0		50.0			50.0					50.0
MELANOMA SHOULDER	1	1		100.0						100.0			
METASTASIS	3	3	33.3	66.7							33.3	33.3	33.3
NEOPLASM	1	1		100.0						100.0			
NEOPLASM MALIGNANT	4	4		100.0						100.0			
OVARIAN ADENOMA	1	1					100.0			100.0			
PAPILLARY	4	4	25.0	50.0			25.0			100.0			
PLASMA CELL MYELOMA	1	1		100.0							100.0		

Exhibit 7-6C
First Malignancy in Patient

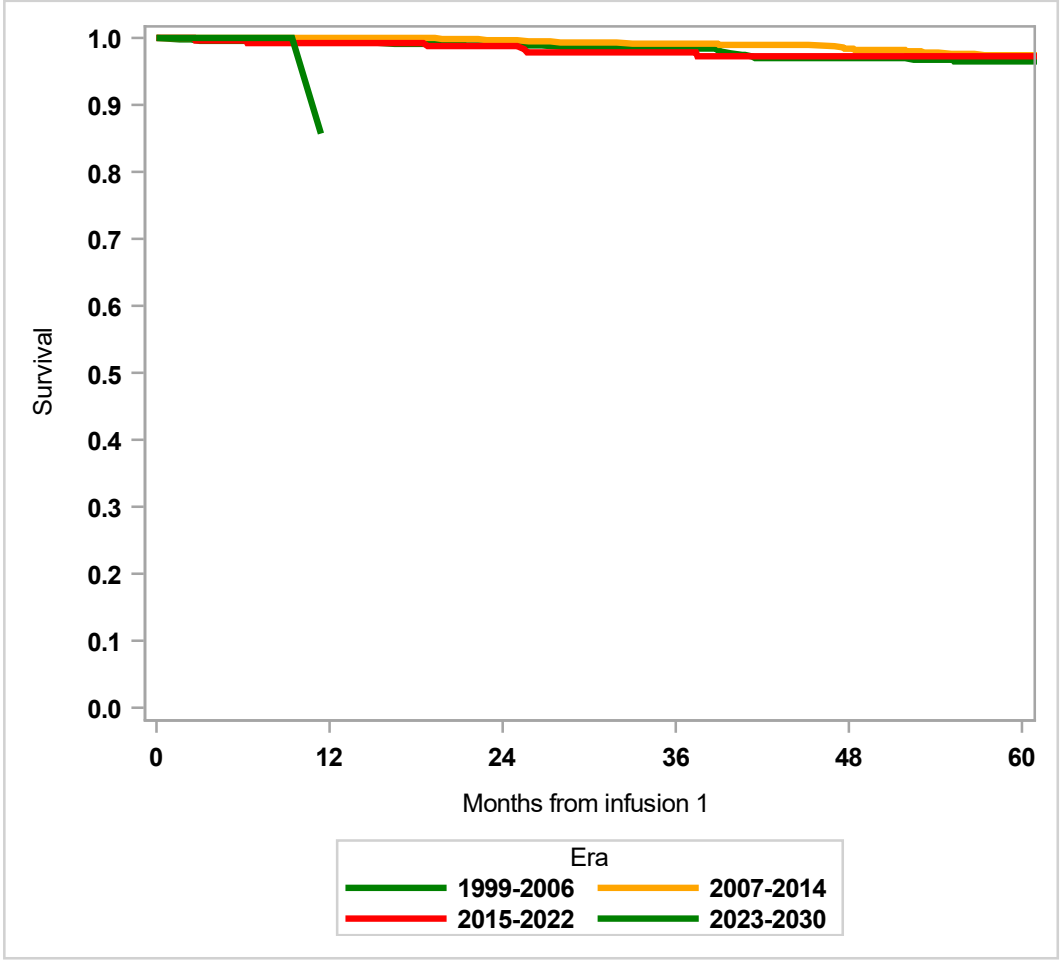
			Relatedness to Immunosuppression					Outcome					
Events	N of Pts	N of Events	Unk.	Possibly Related	Unlikely Related	Related	Not Related	Unk.	Recovering/ Resolving	Recovered/ Resolved	Not Recovered/Not Resolved	Recovered with sequelae	Fatal
POLYCYTHAEMIA VERA	1	1	100.0						100.0				
POST TRANSPLANT LYMPHOPROLIFERATIVE	5	5	20.0	60.0			20.0		20.0	40.0	20.0		20.0
PROSTATE CANCER	1	1		100.0							100.0		
SINONASAL PAPILLOMA	1	1		100.0						100.0			
SMALL INTESTINE CARCINOMA	1	1		100.0						100.0			
SQUAMOUS CELL	36	36	25.0	63.9		8.3	2.8	11.1		77.8		5.6	5.6
TESTIS CANCER	1	1	100.0							100.0			
TRANSITIONAL CELL CARCINOMA	1	1	100.0							100.0			
UTERINE LEIOMYOMA	1	1		100.0						100.0			

Exhibit 7-7A
Deaths by Type



	IAK	ITA
Deaths/N	34 /260	36 /1134

Exhibit 7-7A
Deaths by Era



	Era 1 1999-2006	Era 2 2007-2014	Era 3 2015-2022	Era 4 2023-2030
Deaths/N	32 /466	30 /628	7 /289	1 /11

Exhibit 7-7B
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	MedDRA Preferred Term	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immunosupression
ITA	.	2002	.		Neoplasm			.	Yes
ITA	.	2008	.		Lung neoplasm malignant	Not related	Unlikely related	.	Yes
ITA	.	2012	.		Renal failure	Not related	Unlikely related	.	Yes
ITA	.	2012	.		Cholangiocarcinoma	Not related	Possibly related	.	Yes
ITA	1.2	2002	44					.	Not Reported
ITA	1.4	2005	46	Atherosclerotic Coronary Artery Disease	Death	Not related	Not related	.	Yes
ITA	1.7	2008	63	Multiorgan failure infxn unk orig	Multiple organ dysfunction syndrome	Not related	Related	.	Yes
ITA	1.8	2003	43	Acute Methadone and Diphenhydramine Toxicity	Hypersensitivity	Not related	Not related	.	Yes
ITA	1.9	2012	59	myocardial infarction	Myocardial infarction	Not related	Not related	.	Yes
ITA	2.1	2009	45					.	Yes
ITA	2.1	2022	48	squamous cell carcinoma of tongue and metasthasis	Squamous cell carcinoma of the tongue	Unlikely related	Possibly related	.	Yes
ITA	2.1	2022	54	heart failure	heart failure			.	Yes
ITA	2.3	2014	67					.	Yes
ITA	3.2	2002	45	viral meningitis	Infection	Not related	Possibly related	.	Yes
ITA	3.3	2006	58		Death			.	Yes
ITA	3.9	2010	66					.	Not Reported
ITA	4	2010	50					.	Not Reported
ITA	4	2012	48	Nocturnal hypoglycemia	Nocturnal hypoglycemia			.	Not Reported
ITA	4.4	2001	40	Unknown	Death	Not related	Unlikely related	.	Yes
ITA	4.4	2007	62					.	Not Reported
ITA	4.6	2006	71	Cardiac failure	Death	Related	Not related	.	Yes
ITA	5.3	2003	30	infection	Acute respiratory distress syndrome	Not related	Unlikely related	.	Not Reported
ITA	5.9	2013	69					.	Yes
ITA	5.9	2014	63	Lung Cancer	Lung Cancer			.	Yes
ITA	6.5	2000	46	Diabetic Ketoacidosis due to Diabetes Mellitus	Death	Not related	Not related	.	Yes
ITA	7.7	2005	68					.	Yes
ITA	8.1	2016	74	Head Injury	Head injury	Not related	Not related	.	Not Reported
ITA	8.2	2000	40	Pneumonia	Death	Not related	Not related	.	Yes
ITA	8.8	2010	63					.	Yes
ITA	9.8	2009	70	advanced dementia	Amnesia	Not related	Possibly related	.	Yes
ITA	10	2006	77	Sepsis	Clostridium difficile colitis			.	Yes
ITA	10	2010	66	Respiratory failure related to Pneumocystis Pneumo	Diffuse large B-cell lymphoma	Not related	Possibly related	.	Yes

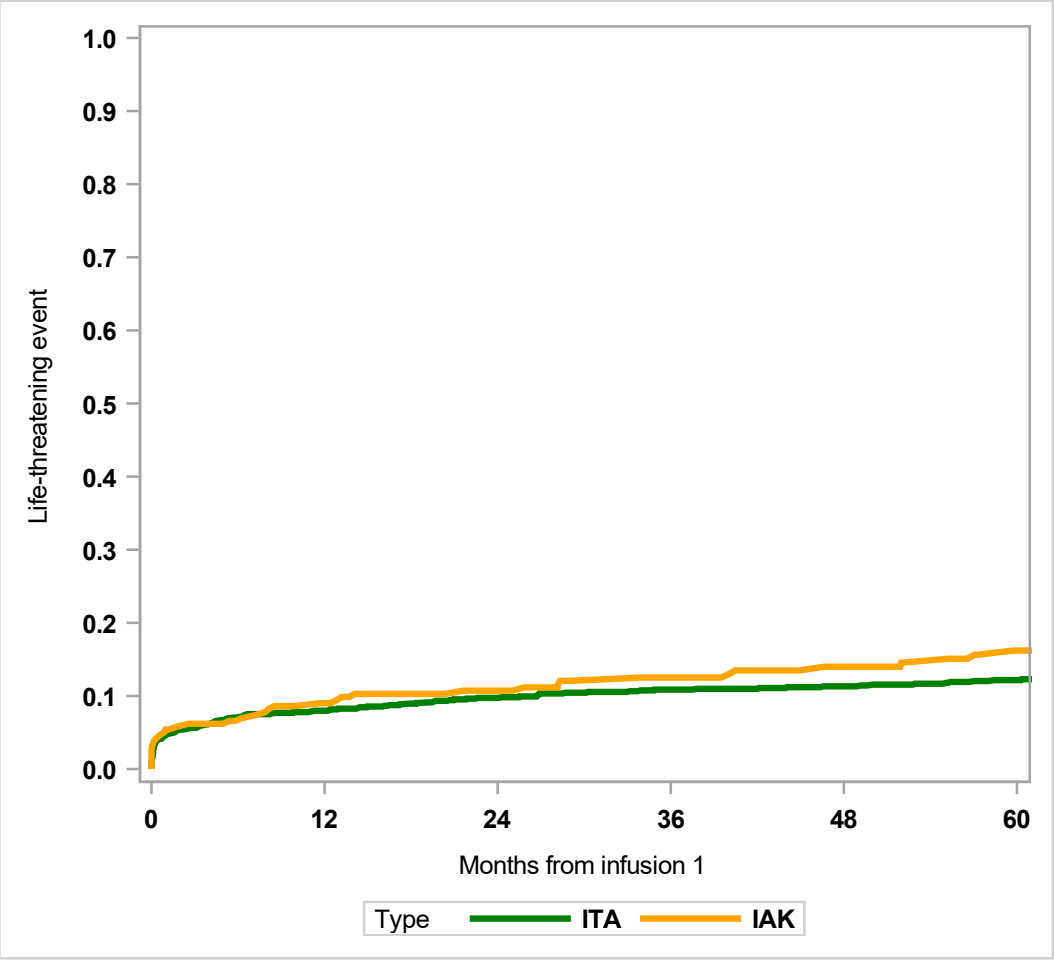
Exhibit 7-7B
Deaths by Cause and Relatedness to Procedure or Immunosuppression

Type of Transplant	Years post infusion 1	Year of Transplant	Age at Death	Primary Cause of Death	MedDRA Preferred Term	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immunosupression
ITA	10.7	2005	55	Diabetes complications	Diabetes complications			.	Yes
ITA	10.7	2007	69	CARDIAC CATH	Death	Not related	Not related	.	Yes
ITA	12.8	2002	57					.	Yes
ITA	13	2004	50					.	Yes
ITA	14.6	2009	58	Unknown	Unknown			.	Yes
ITA	14.7	2004	59	Tumor on head	Tumor on head			.	Yes
ITA	19.8	2000	51	subarachnoid hemorrhage	subarachnoid hemorrhage			.	Yes
ITA	20.8	2000	56	Cancer	Dyspnoea	Not related	Not related	.	Yes
IAK	0.1	2002	52	Infectious pneumopathy	Death		Related	.	Yes
IAK	0.2	2018	47	Ischemic coronary disease	Ischemic coronary disease			.	Not Reported
IAK	0.3	2001	35	CARDIO RESPIRATORY ARREST	Death	Unlikely related	Unlikely related	.	Yes
IAK	0.5	2022	58	Myocard infarct	Myocardial infarction	Unlikely related	Unlikely related	.	Yes
IAK	1	2023	70	sepsis	sepsis			.	Yes
IAK	1.6	2021	56	unknown	unknown			.	Yes
IAK	2.3	1999	53	Congestive heart failure	Cardio-respiratory arrest	Not related	Not related	.	Not Reported
IAK	2.7	2010	61	Cerebrovascular accident	Cerebrovascular accident			.	Not Reported
IAK	2.8	2000	36	Respiratory arrest	Respiratory arrest			.	Not Reported
IAK	3.1	2017	73					.	Not Reported
IAK	3.2	2008	55					.	Not Reported
IAK	3.3	2004	46	Brain hemorrhage	Haemorrhage	Not related	Not related	.	Yes
IAK	3.4	2004	54	Digestive cancer	Gastrointestinal carcinoma	Not related	Possibly related	.	Yes
IAK	3.4	2000	52		Death	Not related	Not related	.	Yes
IAK	3.5	2001	52	massive Hemorrhagic Infarct	Cerebral ischaemia	Not related	Not related	.	Yes
IAK	4	2012	40					.	Yes
IAK	4.3	2008	51	Squamous cell	Squamous cell carcinoma	Unlikely related	Possibly related	.	Yes
IAK	4.6	2007	56	severe chronic cardiovascular complications	Acute kidney injury	Not related	Not related	.	Yes
IAK	4.8	2010	63	pneumonia	pneumonia			.	Not Reported
IAK	5.5	2012	60	Cardiac arrest	Cardiac arrest	Not related	Not related	.	Yes
IAK	5.5	2010	65	ischemic cardiomyopathy	ischemic cardiomyopathy			.	Not Reported
IAK	5.7	2000	40	Acute myocardial infarction	Acute myocardial infarction	Not related	Not related	.	Not Reported
IAK	5.9	2011	60	cardiac arrest	cardiac arrest			.	Not Reported
IAK	6.3	2003	62	pneumonia	Infection	Not related	Not related	.	Yes
IAK	6.5	2011	48					.	Not Reported
IAK	8.9	2009	64					.	Yes

Exhibit 7-7B
Deaths by Cause and Relatedness to Procedure or Immunosuppression

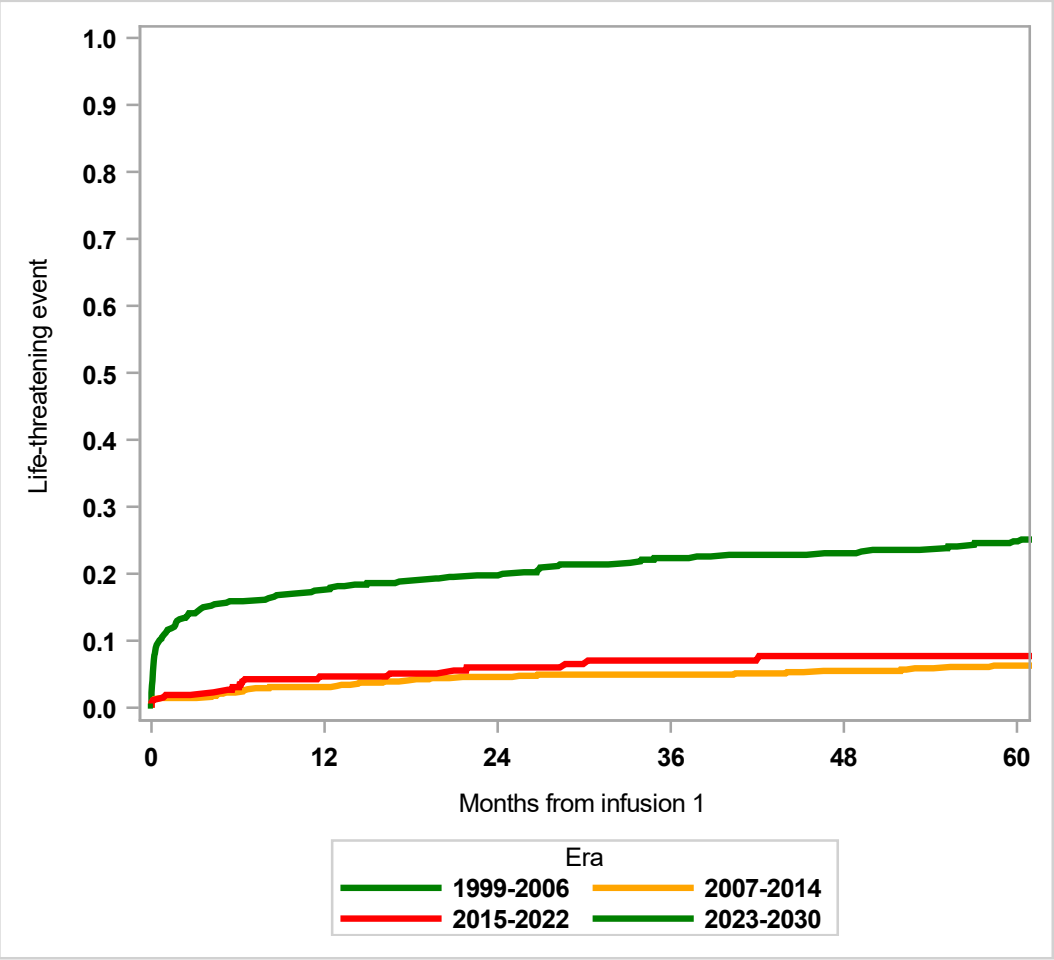
Type of Transplant	Years post infusion 1	Year of Transplant	Age at Death	Primary Cause of Death	MedDRA Preferred Term	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immunosupression
IAK	10.2	2003	55	Cardiac decomposition	Cardiac decomposition			.	Yes
IAK	10.7	2007	62	Unknown	Death			.	Yes
IAK	11	1999	60	Acute myocardial infarction	Acute myocardial infarction			.	Yes
IAK	11.3	2006	62	Unknown	Death	Unlikely related	Unlikely related	.	Yes
IAK	11.3	2010	63		Death			.	Yes
IAK	11.8	2006	56	Lung carcinoma	Squamous cell carcinoma of lung	Not related	Possibly related	.	Yes
IAK	12.2	2009	69	Heart attack	Myocardial infarction			.	Not Reported
IAK	14.7	2007	54	COVID-19	COVID-19	Not related		.	Not Reported

Exhibit 7-8A
Life-Threatening Events by Type



	IAK	ITA
Lifethreatening events/N	44 /260	152 /1134

Exhibit 7-8A
Life-Threatening Events by Era



	Era 1 1999-2006	Era 2 2007-2014	Era 3 2015-2022	Era 4 2023-2030
Lifethreatening events/N	128 /466	48 /628	20 /289	. /11

Exhibit 7-8B
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
IAK	Not related	Not related	Cardiac disorders	Cardio-respiratory arrest	1999-2006	28.2
			Cardiac disorders	Myocardial ischaemia	1999-2006	59.8
			Investigations	Troponin I	1999-2006	57.1
			Nervous system disorders	Cerebral ischaemia	2007-2014	13.2
			Vascular disorders	Haematoma	1999-2006	25.8
		Possibly related	Blood and lymphatic system disorders	Neutropenia	1999-2006	0.4
			Infections and infestations	Opportunistic infection	2007-2014	12.8
			Investigations	Granulocytes abnormal	1999-2006	2.5
			Investigations	Granulocytes abnormal	1999-2006	7.9
			Investigations	Haemoglobin	1999-2006	46.6
			Renal and urinary disorders	Proteinuria	1999-2006	28.3
		Related	Respiratory, thoracic and mediastinal disorders	Pneumonitis	1999-2006	0.6
		Unlikely related	Blood and lymphatic system disorders	Blood disorder	1999-2006	8.5
			General disorders and administration site conditions	Generalised oedema	2007-2014	40.5
			Infections and infestations	Gangrene	2007-2014	21.6
	Possibly related	Not related	Nervous system disorders	Cerebrovascular accident	2015-2022	11.7
		Possibly related	Blood and lymphatic system disorders	Neutropenia	1999-2006	0.2
		Unlikely related	Investigations	Haemoglobin	1999-2006	0.9
			Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	2015-2022	0.1
	Related	Not related	Gastrointestinal disorders	Pancreatic haemorrhage	1999-2006	0.0
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2006	0.0
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2006	1.8

Exhibit 7-8B
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
			Hepatobiliary disorders	Hepatic haematoma	2007-2014	0.0
			Vascular disorders	Haematoma	1999-2006	0.0
			Vascular disorders	Haemorrhage	2007-2014	0.0
			Vascular disorders	Shock haemorrhagic	2015-2022	0.0
		Unlikely related	Gastrointestinal disorders	Gastrointestinal haemorrhage	1999-2006	0.0
			Vascular disorders	Haemorrhage	1999-2006	5.4
			Vascular disorders	Haemorrhage	1999-2006	0.0
	Unlikely related	Not related	Nervous system disorders	Cerebral ischaemia	1999-2006	66.6
		Possibly related	Immune system disorders	Hypersensitivity	1999-2006	34.0
			Infections and infestations	Infection	1999-2006	14.1
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	2007-2014	52.0
			Renal and urinary disorders	Renal failure	1999-2006	8.1
		Unlikely related	Cardiac disorders	Cardio-respiratory arrest	1999-2006	55.2
			Cardiac disorders	Myocardial infarction	2015-2022	6.3
			Cardiac disorders	Myocardial ischaemia	1999-2006	40.0
ITA	Not related	Not related	Cardiac disorders	Coronary artery disease	1999-2006	131.0
			Cardiac disorders	Myocardial ischaemia	1999-2006	87.5
			Cardiac disorders	Myocardial ischaemia	2007-2014	0.7
			Infections and infestations	Infection	1999-2006	106.8
			Injury, poisoning and procedural complications	Head injury	2015-2022	97.0
			Injury, poisoning and procedural complications	Subdural haemorrhage	2007-2014	113.5
			Metabolism and nutrition disorders	Diabetic ketoacidosis	2007-2014	5.2

Exhibit 7-8B
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
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	26.9
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	8.7
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	14.9
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	11.1
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	34.9
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	12.4
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	-8.1
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	-9.8
			Metabolism and nutrition disorders	Hypoglycaemia	2007-2014	58.4
			Metabolism and nutrition disorders	Hypoglycaemia	2015-2022	28.7
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	1999-2006	105.9
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1999-2006	4.4
			Nervous system disorders	Cerebellar ischaemia	2007-2014	55.4
			Nervous system disorders	Hypoglycaemic coma	2007-2014	46.6
			Nervous system disorders	Hypoglycaemic coma	2007-2014	14.4
		Possibly related	Blood and lymphatic system disorders	Neutropenia	1999-2006	26.7
			Cardiac disorders	Pericardial effusion	1999-2006	96.6
			Infections and infestations	Infection	1999-2006	20.7
			Infections and infestations	Infection	1999-2006	33.9
			Infections and infestations	Pyelonephritis	2015-2022	6.1
			Investigations	Granulocytes abnormal	1999-2006	1.9

Exhibit 7-8B
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
			Investigations	Granulocytes abnormal	1999-2006	2.5
			Investigations	Granulocytes abnormal	1999-2006	1.4
			Investigations	Granulocytes abnormal	1999-2006	4.1
			Investigations	Granulocytes abnormal	1999-2006	1.7
			Investigations	Granulocytes abnormal	1999-2006	49.2
			Investigations	Granulocytes abnormal	1999-2006	0.5
			Investigations	Granulocytes abnormal	1999-2006	3.4
			Investigations	Haemoglobin decreased	1999-2006	1.7
			Investigations	Neutrophil count decreased	2007-2014	110.6
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	11.3
			Metabolism and nutrition disorders	Hypoglycaemia unawareness	2007-2014	125.2
			Metabolism and nutrition disorders	Hypophosphataemia	1999-2006	2.3
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	1999-2006	22.6
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant pleural effusion	1999-2006	228.3
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1999-2006	26.9
			Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	2015-2022	30.3
			Vascular disorders	Hypertension	1999-2006	50.0
		Related	Blood and lymphatic system disorders	Lymphopenia	1999-2006	0.0
			Blood and lymphatic system disorders	Lymphopenia	1999-2006	0.0
			Blood and lymphatic system disorders	Lymphopenia	1999-2006	-1.2

Exhibit 7-8B
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
			Blood and lymphatic system disorders	Lymphopenia	1999-2006	0.0
			Blood and lymphatic system disorders	Lymphopenia	2007-2014	18.4
			Blood and lymphatic system disorders	Pancytopenia	2007-2014	6.3
			General disorders and administration site conditions	Multiple organ dysfunction syndrome	2007-2014	19.4
			Infections and infestations	Cytomegalovirus viraemia	2015-2022	21.0
			Investigations	Granulocytes abnormal	1999-2006	37.8
			Investigations	Granulocytes abnormal	1999-2006	9.8
			Investigations	Granulocytes abnormal	1999-2006	0.2
			Investigations	Granulocytes abnormal	1999-2006	0.7
			Investigations	Granulocytes abnormal	1999-2006	5.2
			Investigations	Granulocytes abnormal	1999-2006	3.6
			Psychiatric disorders	Insomnia	1999-2006	19.7
			Renal and urinary disorders	Proteinuria	1999-2006	24.3
		Unlikely related	Cardiac disorders	Acute myocardial infarction	2007-2014	65.9
			Cardiac disorders	Myocardial ischaemia	2007-2014	4.1
			General disorders and administration site conditions	Pyrexia	2007-2014	25.5
	Possibly related	Not related	Gastrointestinal disorders	Gastrointestinal disorder	2015-2022	5.3
		Possibly related	Blood and lymphatic system disorders	Lymphadenopathy	2007-2014	114.6
			Cardiac disorders	Myocardial ischaemia	1999-2006	0.0
			Investigations	Liver function test abnormal	1999-2006	0.2
			Investigations	Liver function test abnormal	1999-2006	0.1
			Respiratory, thoracic and mediastinal disorders	Aspiration	2007-2014	0.1

Exhibit 7-8B
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
		Related	Blood and lymphatic system disorders	Lymphopenia	2007-2014	0.0
		Unlikely related	Hepatobiliary disorders	Cholecystitis	1999-2006	12.4
			Investigations	Blood alkaline phosphatase	1999-2006	0.2
			Investigations	Blood alkaline phosphatase	1999-2006	0.1
			Investigations	Blood alkaline phosphatase	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	0.3
			Investigations	Liver function test abnormal	1999-2006	0.2
			Investigations	Liver function test abnormal	1999-2006	0.2
			Investigations	Liver function test abnormal	1999-2006	0.0
			Investigations	Liver function test abnormal	1999-2006	0.3
			Investigations	Liver function test abnormal	1999-2006	0.2
			Investigations	Liver function test abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	0.0
			Investigations	Liver function test abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	12.9
			Investigations	Liver function test abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	0.3
			Investigations	Liver function test abnormal	1999-2006	0.3
			Investigations	Liver function test abnormal	1999-2006	0.2

Exhibit 7-8B
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
			Investigations	Liver function test abnormal	1999-2006	0.0
			Investigations	Liver function test abnormal	1999-2006	0.0
			Metabolism and nutrition disorders	Ketoacidosis	2007-2014	4.5
	Related	Not related	Cardiac disorders	Cardio-respiratory arrest	2007-2014	0.0
			Gastrointestinal disorders	Gastrointestinal obstruction	1999-2006	1.6
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2006	0.0
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2006	17.2
			Gastrointestinal disorders	Peritoneal haemorrhage	2007-2014	8.2
			Gastrointestinal disorders	Peritoneal haemorrhage	2007-2014	16.2
			General disorders and administration site conditions	Death	1999-2006	55.1
			Hepatobiliary disorders	Hepatic haematoma	1999-2006	0.0
			Hepatobiliary disorders	Portal vein thrombosis	1999-2006	3.3
			Hepatobiliary disorders	Subcapsular hepatic haematoma	2007-2014	0.1
			Hepatobiliary disorders	Subcapsular hepatic haematoma	2015-2022	42.1
			Immune system disorders	Anaphylactic shock	2015-2022	0.0
			Infections and infestations	Infection	1999-2006	1.6
			Investigations	Liver function test abnormal	1999-2006	0.1
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2006	2.6
		Possibly related	Gastrointestinal disorders	Peritoneal haemorrhage	1999-2006	1.1
		Related	Investigations	Granulocytes abnormal	1999-2006	0.1
			Investigations	Liver function test abnormal	1999-2006	1.1
			Nervous system disorders	Neuroleptic malignant syndrome	2007-2014	0.0

Exhibit 7-8B
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
		Unlikely related	Gastrointestinal disorders	Haemoperitoneum	2007-2014	6.4
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2006	1.0
			Gastrointestinal disorders	Peritoneal haemorrhage	2007-2014	6.7
			Hepatobiliary disorders	Portal vein thrombosis	2015-2022	21.8
	Unlikely related	Not related	Vascular disorders	Hypotension	2015-2022	6.5
		Possibly related	Gastrointestinal disorders	Abdominal pain	2007-2014	0.2
			Infections and infestations	Infection	1999-2006	33.2
			Investigations	Granulocytes abnormal	1999-2006	0.9
			Investigations	Granulocytes abnormal	1999-2006	19.7
			Investigations	Granulocytes abnormal	1999-2006	0.1
			Investigations	Granulocytes abnormal	1999-2006	0.7
			Investigations	Granulocytes abnormal	1999-2006	0.3
			Investigations	Haemoglobin	1999-2006	3.3
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma of the tongue	2015-2022	16.5
		Related	Infections and infestations	Pneumonia cytomegaloviral	1999-2006	60.3
			Investigations	Granulocytes abnormal	1999-2006	0.1
			Investigations	Granulocytes abnormal	2007-2014	4.8
		Unlikely related	Infections and infestations	Infection	2007-2014	14.3
			Injury, poisoning and procedural complications	Overdose	2007-2014	98.9
			Nervous system disorders	Serotonin syndrome	1999-2006	77.5

Exhibit 7-8C
Life-Threatening Events (Outcome by System/Organ Class)

		Total	Outcome of event				
			Not recovered	Recovering	Recovered	Sequelae	Fatal
		N	%	%	%	%	%
System/Organ Class	Preferred Term						
Blood and lymphatic system disorders	Blood disorder	1	.	.	100.0	.	.
	Lymphadenopathy	1	.	.	100.0	.	.
	Lymphopenia	6	.	.	100.0	.	.
	Neutropenia	3	.	.	100.0	.	.
	Pancytopenia	1	.	.	100.0	.	.
Cardiac disorders	Acute myocardial infarction	1	.	.	.	100.0	.
	Cardio-respiratory arrest	2	.	.	50.0	.	50.0
	Coronary artery disease	1	.	.	.	100.0	.
	Myocardial infarction	2	.	.	.	.	100.0
	Myocardial ischaemia	7	.	.	85.7	14.3	.
	Pericardial effusion	1	.	.	100.0	.	.
Gastrointestinal disorders	Abdominal pain	1	.	.	100.0	.	.
	Gastrointestinal disorder	1	.	.	100.0	.	.
	Gastrointestinal haemorrhage	1	.	.	100.0	.	.
	Gastrointestinal obstruction	1	.	.	100.0	.	.
	Haemoperitoneum	1	.	.	.	100.0	.
	Peritoneal haemorrhage	9	.	.	100.0	.	.
General disorders and administration site conditions	Death	2	.	.	.	.	100.0
	Generalised oedema	1	.	.	.	100.0	.
	Multiple organ dysfunction syndrome	1	.	.	.	.	100.0
	Pyrexia	1	.	.	100.0	.	.
	Unevaluable event	1	.	.	.	100.0	.
Hepatobiliary disorders	Cholecystitis	1	.	.	100.0	.	.
	Cholecystitis acute	1	.	.	100.0	.	.
	Hepatic haematoma	1	.	.	100.0	.	.
	Portal vein thrombosis	3	.	33.3	66.7	.	.
	Subcapsular hepatic haematoma	2	.	50.0	50.0	.	.
Immune system disorders	Anaphylactic shock	1	.	.	100.0	.	.
	Hypersensitivity	2	.	.	50.0	50.0	.

(Continued)

Exhibit 7-8C
Life-Threatening Events (Outcome by System/Organ Class)

		Total	Outcome of event				
			Not recovered	Recovering	Recovered	Sequelae	Fatal
		N	%	%	%	%	%
System/Organ Class	**Preferred Term**						
Infections and infestations	**BK virus infection**	1	.	.	100.0	.	.
	COVID-19	1	.	.	.	.	100.0
	Cytomegalovirus viraemia	1	.	.	100.0	.	.
	Gangrene	1	.	.	100.0	.	.
	Infection	7	.	.	57.1	42.9	.
	Opportunistic infection	1	.	.	100.0	.	.
	Pneumonia cytomegaloviral	1	.	.	100.0	.	.
Injury, poisoning and procedural complications	**Concussion**	1	.	.	100.0	.	.
	Head injury	1	.	.	.	.	100.0
	Overdose	2	.	.	100.0	.	.
	Subdural haemorrhage	1	.	.	100.0	.	.
Investigations	**BK polyomavirus test positive**	1	.	.	100.0	.	.
	Blood alkaline phosphatase	3	.	.	100.0	.	.
	Granulocytes abnormal	24	.	.	100.0	.	.
	Haemoglobin	3	.	.	100.0	.	.
	Haemoglobin decreased	1	.	.	100.0	.	.
	Liver function test abnormal	23	.	.	95.7	4.3	.
	Neutrophil count decreased	1	.	.	100.0	.	.
	Troponin I	1	.	.	100.0	.	.
Metabolism and nutrition disorders	**Diabetic ketoacidosis**	1	.	.	100.0	.	.
	Hypoglycaemia	14	.	.	100.0	.	.
	Hypoglycaemia unawareness	1	100.0	.	.	.	.
	Hypophosphataemia	1	.	.	100.0	.	.
	Ketoacidosis	1	.	.	100.0	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Basal cell carcinoma**	1	.	.	.	100.0	.
	Breast cancer	2	.	50.0	.	50.0	.
	Malignant melanoma	1	.	.	100.0	.	.
	Malignant pleural effusion	1	100.0	.	.	.	.
	Neoplasm malignant	2	50.0	.	50.0	.	.
	Polycythaemia vera	1	.	100.0	.	.	.

(Continued)

Exhibit 7-8C
Life-Threatening Events (Outcome by System/Organ Class)

		Total	Outcome of event				
			Not recovered	Recovering	Recovered	Sequelae	Fatal
		N	%	%	%	%	%
System/Organ Class	**Preferred Term**						
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Squamous cell carcinoma**	3	.	.	66.7	.	33.3
	Squamous cell carcinoma of the tongue	1	.	.	.	.	100.0
	Transitional cell carcinoma	1	.	.	100.0	.	.
Nervous system disorders	**Cerebellar ischaemia**	1	.	.	.	100.0	.
	Cerebral ischaemia	2	50.0	.	.	50.0	.
	Cerebrovascular accident	1	.	100.0	.	.	.
	Hypoglycaemic coma	2	.	.	100.0	.	.
	Neuroleptic malignant syndrome	1	.	.	100.0	.	.
	Serotonin 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	.
Respiratory, thoracic and mediastinal disorders	**Acute pulmonary oedema**	1	.	.	100.0	.	.
	Acute respiratory failure	1	.	.	100.0	.	.
	Aspiration	1	.	.	100.0	.	.
	Asthma	1	.	.	100.0	.	.
	Pneumonitis	1	.	.	.	.	100.0
Skin and subcutaneous tissue disorders	**Skin lesion**	1	.	.	100.0	.	.
Vascular disorders	**Haematoma**	2	.	.	100.0	.	.
	Haemorrhage	3	.	.	100.0	.	.
	Hypertension	1	.	.	100.0	.	.
	Hypotension	1	.	.	100.0	.	.
	Peripheral ischaemia	1	.	.	100.0	.	.
	Shock haemorrhagic	1	.	.	100.0	.	.
Total		191	2.6	3.1	80.1	8.4	5.8

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Blood and lymphatic system disorders	Anaemia	9	7	2
	Blood disorder	4	3	1
	Bone marrow disorder	2	2	.
	Febrile neutropenia	8	8	.
	Haemolysis	1	1	.
	Hypochromic anaemia	2	2	.
	Leukopenia	5	2	3
	Lymphadenopathy	2	2	.
	Lymphopenia	12	11	1
	Myelosuppression	2	2	.
	Neutropenia	34	28	6
	Pancytopenia	1	1	.
	Platelet disorder	1	1	.
	Thrombocytopenia	7	7	.
Cardiac disorders	Acute coronary syndrome	1	1	.
	Acute myocardial infarction	5	4	1
	Arrhythmia	1	.	1
	Atrial fibrillation	2	2	.
	Atrial flutter	1	1	.
	Atrioventricular block	1	1	.
	Bradycardia	1	1	.
	Brugada syndrome	1	.	1
	Cardiac arrest	1	.	1
	Cardiac disorder	2	2	.
	Cardiac failure congestive	2	.	2
	Cardio-respiratory arrest	3	1	2
	Coronary artery disease	4	2	2
	Left ventricular dysfunction	1	1	.
	Mitral valve incompetence	1	1	.
	Myocardial infarction	5	2	3
	Myocardial ischaemia	17	11	6

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Cardiac disorders	Myocarditis	2	2	.
	Pericardial effusion	2	.	2
	Pericarditis	1	1	.
Endocrine disorders	Endocrine disorder	4	2	2
	Hypoglycaemia	1	1	.
	Thyroiditis subacute	1	1	.
Eye disorders	Eye disorder	4	4	.
	Ocular surface disease	1	.	1
	Retinal detachment	5	4	1
	Retinal haemorrhage	1	1	.
	Vitreous haemorrhage	5	1	4
Gastrointestinal disorders	Abdominal pain	5	5	.
	Abdominal pain upper	1	1	.
	Appendix disorder	3	3	.
	Ascites	4	4	.
	Colitis	7	4	3
	Constipation	1	1	.
	Diarrhoea	49	45	4
	Food poisoning	1	1	.
	Gastritis	1	.	1
	Gastrointestinal disorder	20	14	6
	Gastrointestinal haemorrhage	5	2	3
	Gastrointestinal obstruction	8	4	4
	Gastrointestinal perforation	1	1	.
	Haemoperitoneum	7	7	.
	Haemorrhoids	1	1	.
	Ileus	1	1	.
	Intestinal obstruction	1	.	1
	Intra-abdominal haemorrhage	4	4	.
	Mouth ulceration	3	2	1
	Nausea	8	4	4

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Gastrointestinal disorders	Pancreatic haemorrhage	1	.	1
	Pancreatitis	1	1	.
	Peritoneal haemorrhage	42	32	10
	Small intestinal obstruction	9	9	.
	Umbilical hernia	1	1	.
	Vomiting	50	42	8
General disorders and administration site conditions	Adverse event	3	2	1
	Asthenia	1	1	.
	Chest pain	3	3	.
	Chills	1	1	.
	Death	13	7	6
	Fatigue	4	4	.
	Generalised oedema	1	.	1
	Impaired healing	1	.	1
	Influenza like illness	1	1	.
	Mucosal inflammation	7	6	1
	Multiple organ dysfunction syndrome	1	1	.
	Oedema peripheral	6	4	2
	Pain	28	25	3
	Pyrexia	9	9	.
	Systemic inflammatory response syndrome	4	1	3
	Ulcer	1	.	1
	Unevaluable event	4	4	.
Hepatobiliary disorders	Biliary tract disorder	1	1	.
	Cholecystitis	9	7	2
	Cholecystitis acute	1	1	.
	Hepatic haematoma	6	4	2
	Hepatic haemorrhage	4	4	.
	Hepatitis cholestatic	1	1	.
	Hepatobiliary disease	2	2	.
	Portal vein thrombosis	14	13	1

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Hepatobiliary disorders	Subcapsular hepatic haematoma	8	7	1
Immune system disorders	Anaphylactic shock	1	1	.
	Autoimmune disorder	1	1	.
	Cytokine release syndrome	1	1	.
	Graft versus host disease	2	2	.
	Hypersensitivity	19	17	2
	Pancreas transplant rejection	2	1	1
	Sensitisation	2	1	1
	Serum sickness	3	3	.
	Transplant rejection	4	3	1
Infections and infestations	Appendicitis	4	4	.
	Appendicitis perforated	2	2	.
	Arthritis bacterial	1	1	.
	BK virus infection	1	.	1
	Bacterial sepsis	1	.	1
	COVID-19	2	1	1
	COVID-19 pneumonia	2	1	1
	Clostridium difficile colitis	3	2	1
	Clostridium difficile infection	2	2	.
	Coccidioidomycosis	1	1	.
	Cytomegalovirus hepatitis	1	.	1
	Cytomegalovirus infection	1	1	.
	Cytomegalovirus viraemia	1	1	.
	Dermo-hypodermitis	1	1	.
	Encephalitis cytomegalovirus	1	1	.
	Epididymitis	2	2	.
	Erysipelas	1	1	.
	Escherichia pyelonephritis	1	.	1
	Escherichia sepsis	2	.	2
	Gangrene	1	.	1
	Gastroenteritis	1	.	1

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Infections and infestations	Herpes simplex	1	1	.
	Infection	86	59	27
	Influenza	1	.	1
	Joint abscess	1	1	.
	Kidney infection	2	2	.
	Klebsiella sepsis	1	1	.
	Large intestine infection	2	2	.
	Localised infection	1	1	.
	Metapneumovirus infection	2	2	.
	Norovirus infection	4	4	.
	Oesophageal candidiasis	1	1	.
	Opportunistic infection	2	1	1
	Oral herpes	1	1	.
	Osteomyelitis	1	1	.
	Parainfluenzae virus infection	1	.	1
	Pneumonia	23	15	8
	Pneumonia cytomegaloviral	1	1	.
	Pneumonia legionella	1	1	.
	Polyomavirus viraemia	1	.	1
	Pyelonephritis	7	7	.
	Renal graft infection	1	.	1
	Sepsis	2	2	.
	Skin infection	4	.	4
	Staphylococcal bacteraemia	1	1	.
	Staphylococcal infection	1	1	.
	Trench fever	1	1	.
	Urinary tract infection	20	6	14
	Urosepsis	1	1	.
	Vestibular neuronitis	1	1	.
	Viral infection	1	1	.

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	**Preferred term**			
Injury, poisoning and procedural complications	**Combined tibia-fibula fracture**	1	1	.
	Complications of transplanted kidney	1	1	.
	Foot fracture	1	1	.
	Fracture	9	8	1
	Head injury	1	1	.
	Hip fracture	10	10	.
	Incision site pain	1	1	.
	Injury	3	2	1
	Intentional overdose	1	1	.
	Limb injury	1	1	.
	Lower limb fracture	1	1	.
	Overdose	2	2	.
	Post procedural haemorrhage	1	1	.
	Procedural pain	2	2	.
	Subdural haemorrhage	1	1	.
	Toxicity to various agents	2	2	.
	Upper limb fracture	1	1	.
	Vascular injury	1	1	.
	Wound	1	1	.
	Wound complication	11	8	3
Investigations	**BK polyomavirus test positive**	1	.	1
	Blood alkaline phosphatase	14	14	.
	Blood creatine phosphokinase	1	1	.
	Blood creatinine	13	6	7
	Blood creatinine increased	7	5	2
	Blood glucose abnormal	1	1	.
	Blood glucose increased	1	1	.
	Blood potassium increased	2	2	.
	Clostridium test	1	1	.
	Coagulation factor	1	1	.
	Donor specific antibody present	3	3	.

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	**Preferred term**			
Investigations	**Glomerular filtration rate**	1	.	1
	Glomerular filtration rate decreased	1	.	1
	Granulocytes abnormal	56	50	6
	Haemoglobin	16	13	3
	Haemoglobin decreased	4	2	2
	Hepatic enzyme increased	1	1	.
	Laboratory test	1	1	.
	Liver function test abnormal	36	36	.
	Neutrophil count	3	3	.
	Neutrophil count decreased	4	4	.
	Renin increased	1	1	.
	Troponin I	1	.	1
	Troponin T	1	1	.
	Weight decreased	1	1	.
Metabolism and nutrition disorders	**Dehydration**	8	6	2
	Diabetes mellitus	1	1	.
	Diabetic ketoacidosis	8	6	2
	Hyperglycaemia	6	4	2
	Hyperkalaemia	4	1	3
	Hypoglycaemia	82	56	26
	Hypoglycaemia unawareness	1	1	.
	Hypokalaemia	1	1	.
	Hypomagnesaemia	1	1	.
	Hyponatraemia	8	7	1
	Hypophosphataemia	1	1	.
	Hypovolaemia	2	.	2
	Ketoacidosis	17	14	3
	Malnutrition	1	.	1
	Metabolic disorder	1	.	1

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	**Preferred term**			
Musculoskeletal and connective tissue disorders	**Arthralgia**	2	2	.
	Arthritis	2	2	.
	Arthritis reactive	1	1	.
	Arthropathy	1	1	.
	Intervertebral disc protrusion	1	1	.
	Muscle necrosis	1	1	.
	Musculoskeletal disorder	5	5	.
	Myalgia	1	1	.
	Neuropathic arthropathy	3	.	3
	Osteoarthritis	1	.	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Adenocarcinoma**	2	.	2
	Basal cell carcinoma	15	14	1
	Basosquamous carcinoma	2	1	1
	Breast cancer	5	5	.
	Breast cancer stage I	1	1	.
	Cervix carcinoma	1	1	.
	Cholangiocarcinoma	1	1	.
	Colorectal cancer stage IV	1	1	.
	Diffuse large B-cell lymphoma	1	1	.
	Gastrointestinal carcinoma	1	.	1
	Intraductal papillary-mucinous carcinoma of	1	1	.
	Intraductal proliferative breast lesion	1	1	.
	Invasive ductal breast carcinoma	1	1	.
	Lung carcinoma cell type unspecified stage I	1	1	.
	Lung neoplasm malignant	2	2	.
	Lymphoma	1	1	.
	Malignant melanoma	2	2	.
	Malignant pleural effusion	1	1	.
	Neoplasm	2	1	1
	Neoplasm malignant	16	12	4
	Ovarian adenoma	1	1	.

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	**Preferred term**			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Papillary thyroid cancer**	1	1	.
	Plasma cell myeloma	1	1	.
	Polycythaemia vera	1	1	.
	Post transplant lymphoproliferative disorder	7	3	4
	Prostate cancer	4	4	.
	Small intestine carcinoma	1	1	.
	Squamous cell carcinoma	28	24	4
	Squamous cell carcinoma of head and neck	1	1	.
	Squamous cell carcinoma of lung	1	.	1
	Squamous cell carcinoma of skin	6	6	.
	Squamous cell carcinoma of the tongue	1	1	.
	Transitional cell carcinoma	2	2	.
	Uterine leiomyoma	1	1	.
Nervous system disorders	**Amnesia**	1	1	.
	Cerebellar ischaemia	1	1	.
	Cerebellar stroke	3	3	.
	Cerebral ischaemia	9	.	9
	Cerebrovascular accident	1	.	1
	Cognitive disorder	1	1	.
	Dizziness	3	3	.
	Frontotemporal dementia	1	1	.
	Generalised tonic-clonic seizure	1	1	.
	Headache	4	4	.
	Hydrocephalus	6	6	.
	Hypoglycaemic coma	2	2	.
	Hypoglycaemic seizure	1	.	1
	Loss of consciousness	1	1	.
	Nervous system disorder	6	6	.
	Neuroleptic malignant syndrome	1	1	.
	Neurological symptom	1	1	.
	Neuropathy peripheral	1	1	.

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Nervous system disorders	Optic neuritis	1	1	.
	Psychogenic seizure	2	2	.
	Seizure	5	5	.
	Serotonin syndrome	1	1	.
	Spinal cord compression	2	2	.
	Subarachnoid haemorrhage	1	.	1
	Syncope	8	8	.
	Transient ischaemic attack	2	1	1
	Tremor	1	1	.
Psychiatric disorders	Acute psychosis	1	1	.
	Anxiety	2	.	2
	Confusional state	3	3	.
	Delusion	9	9	.
	Insomnia	1	1	.
	Mood altered	3	3	.
	Psychotic disorder	1	1	.
	Suicidal ideation	1	1	.
	Suicide attempt	3	3	.
Renal and urinary disorders	Acute kidney injury	8	5	3
	End stage renal disease	1	1	.
	Ketonuria	1	1	.
	Nephropathy	1	1	.
	Proteinuria	3	2	1
	Renal artery stenosis	1	1	.
	Renal disorder	8	4	4
	Renal failure	25	15	10
	Renal infarct	1	1	.
	Tubulointerstitial nephritis	1	1	.
	Urinary bladder haemorrhage	3	1	2
	Urinary retention	1	1	.

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
		Overall	ITA	IAK
		N	N	N
System/Organ Class	Preferred term			
Reproductive system and breast disorders	Cervical dysplasia	1	1	.
	Lactation disorder	1	1	.
	Rectocele	1	1	.
	Sexual dysfunction	7	6	1
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	1	.	1
	Acute respiratory distress syndrome	1	1	.
	Acute respiratory failure	1	1	.
	Aspiration	2	2	.
	Asthma	1	1	.
	Cough	2	.	2
	Dyspnoea	5	3	2
	Hypoxia	4	4	.
	Lung disorder	8	5	3
	Lung infiltration	4	4	.
	Pleural effusion	2	2	.
	Pneumonitis	5	1	4
	Pulmonary embolism	1	1	.
	Pulmonary hypertension	3	1	2
Skin and subcutaneous tissue disorders	Decubitus ulcer	2	.	2
	Exfoliative rash	1	1	.
	Rash	1	1	.
	Skin disorder	1	1	.
	Skin lesion	1	1	.
Surgical and medical procedures	Amputation	1	.	1
	Brain operation	1	1	.
	Breast reconstruction	1	1	.
	Cholecystectomy	2	2	.
	Coronary arterial stent insertion	1	1	.
	Coronary artery bypass	3	2	1
	Hernia repair	1	.	1
	Ileostomy	1	1	.

(Continued)

Exhibit 7-9
All SAEs Classified by Transplant Type

		Overall	Transplant Type	
			ITA	IAK
		N	N	N
System/Organ Class	**Preferred term**			
Surgical and medical procedures	**Retinal laser coagulation**	1	1	.
	Skin neoplasm excision	2	2	.
	Surgery	6	3	3
	Toe amputation	1	1	.
Vascular disorders	**Arterial stenosis**	1	1	.
	Arterial thrombosis	1	1	.
	Blood pressure inadequately controlled	1	1	.
	Haematoma	10	7	3
	Haemorrhage	13	5	8
	Hypertension	5	3	2
	Intermittent claudication	1	1	.
	Lymphoedema	1	1	.
	Orthostatic hypotension	1	1	.
	Peripheral arterial occlusive disease	1	1	.
	Peripheral ischaemia	2	1	1
	Shock haemorrhagic	1	.	1
	Thrombosis	1	.	1
	Vascular occlusion	1	1	.

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Blood and lymphatic system disorders	Anaemia	9	1	8	.	.
	Blood disorder	4	1	1	2	.
	Bone marrow disorder	2	.	2	.	.
	Febrile neutropenia	8	1	7	.	.
	Haemolysis	1	1	.	.	.
	Hypochromic anaemia	2	.	2	.	.
	Leukopenia	5	.	3	2	.
	Lymphadenopathy	2	.	2	.	.
	Lymphopenia	12	6	6	.	.
	Myelosuppression	2	.	2	.	.
	Neutropenia	34	3	29	2	.
	Pancytopenia	1	.	1	.	.
	Platelet disorder	1	1	.	.	.
	Thrombocytopenia	7	.	7	.	.
Cardiac disorders	Acute coronary syndrome	1	.	1	.	.
	Acute myocardial infarction	5	1	4	.	.
	Arrhythmia	1	1	.	.	.
	Atrial fibrillation	2	.	2	.	.
	Atrial flutter	1	.	1	.	.
	Atrioventricular block	1	1	.	.	.
	Bradycardia	1	.	1	.	.
	Brugada syndrome	1	1	.	.	.
	Cardiac arrest	1	.	1	.	.
	Cardiac disorder	2	1	1	.	.
	Cardiac failure congestive	2	.	2	.	.
	Cardio-respiratory arrest	3	2	1	.	.
	Coronary artery disease	4	2	2	.	.
	Left ventricular dysfunction	1	.	1	.	.
	Mitral valve incompetence	1	.	1	.	.
	Myocardial infarction	5	1	3	1	.
	Myocardial ischaemia	17	10	6	1	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Cardiac disorders	Myocarditis	2	2	.	.	.
	Pericardial effusion	2	2	.	.	.
	Pericarditis	1	1	.	.	.
Endocrine disorders	Endocrine disorder	4	2	2	.	.
	Hypoglycaemia	1	.	1	.	.
	Thyroiditis subacute	1	1	.	.	.
Eye disorders	Eye disorder	4	3	1	.	.
	Ocular surface disease	1	1	.	.	.
	Retinal detachment	5	2	3	.	.
	Retinal haemorrhage	1	.	1	.	.
	Vitreous haemorrhage	5	2	3	.	.
Gastrointestinal disorders	Abdominal pain	5	.	4	1	.
	Abdominal pain upper	1	1	.	.	.
	Appendix disorder	3	.	3	.	.
	Ascites	4	4	.	.	.
	Colitis	7	6	1	.	.
	Constipation	1	.	1	.	.
	Diarrhoea	49	25	21	3	.
	Food poisoning	1	.	1	.	.
	Gastritis	1	.	1	.	.
	Gastrointestinal disorder	20	17	1	2	.
	Gastrointestinal haemorrhage	5	5	.	.	.
	Gastrointestinal obstruction	8	7	1	.	.
	Gastrointestinal perforation	1	.	1	.	.
	Haemoperitoneum	7	.	6	1	.
	Haemorrhoids	1	1	.	.	.
	Ileus	1	1	.	.	.
	Intestinal obstruction	1	.	1	.	.
	Intra-abdominal haemorrhage	4	1	2	1	.
	Mouth ulceration	3	.	.	3	.
	Nausea	8	2	5	1	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Gastrointestinal disorders	Pancreatic haemorrhage	1	1	.	.	.
	Pancreatitis	1	1	.	.	.
	Peritoneal haemorrhage	42	27	14	1	.
	Small intestinal obstruction	9	.	9	.	.
	Umbilical hernia	1	.	1	.	.
	Vomiting	50	13	24	13	.
General disorders and administration site conditions	Adverse event	3	1	2	.	.
	Asthenia	1	.	1	.	.
	Chest pain	3	.	3	.	.
	Chills	1	1	.	.	.
	Death	13	10	3	.	.
	Fatigue	4	1	3	.	.
	Generalised oedema	1	.	1	.	.
	Impaired healing	1	.	1	.	.
	Influenza like illness	1	.	1	.	.
	Mucosal inflammation	7	6	1	.	.
	Multiple organ dysfunction syndrome	1	.	1	.	.
	Oedema peripheral	6	3	3	.	.
	Pain	28	24	4	.	.
	Pyrexia	9	3	5	1	.
	Systemic inflammatory response syndrome	4	1	3	.	.
	Ulcer	1	1	.	.	.
	Unevaluable event	4	2	1	1	.
Hepatobiliary disorders	Biliary tract disorder	1	1	.	.	.
	Cholecystitis	9	7	2	.	.
	Cholecystitis acute	1	.	1	.	.
	Hepatic haematoma	6	3	2	.	1
	Hepatic haemorrhage	4	1	3	.	.
	Hepatitis cholestatic	1	.	1	.	.
	Hepatobiliary disease	2	1	1	.	.
	Portal vein thrombosis	14	9	2	3	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Hepatobiliary disorders	Subcapsular hepatic haematoma	8	.	7	1	.
Immune system disorders	Anaphylactic shock	1	.	.	1	.
	Autoimmune disorder	1	.	1	.	.
	Cytokine release syndrome	1	.	1	.	.
	Graft versus host disease	2	.	2	.	.
	Hypersensitivity	19	11	8	.	.
	Pancreas transplant rejection	2	.	2	.	.
	Sensitisation	2	1	1	.	.
	Serum sickness	3	.	2	1	.
	Transplant rejection	4	.	2	2	.
Infections and infestations	Appendicitis	4	.	4	.	.
	Appendicitis perforated	2	.	2	.	.
	Arthritis bacterial	1	1	.	.	.
	BK virus infection	1	.	.	1	.
	Bacterial sepsis	1	1	.	.	.
	COVID-19	2	1	1	.	.
	COVID-19 pneumonia	2	1	1	.	.
	Clostridium difficile colitis	3	1	1	1	.
	Clostridium difficile infection	2	1	1	.	.
	Coccidioidomycosis	1	.	1	.	.
	Cytomegalovirus hepatitis	1	.	1	.	.
	Cytomegalovirus infection	1	.	1	.	.
	Cytomegalovirus viraemia	1	.	.	1	.
	Dermo-hypodermitis	1	.	.	1	.
	Encephalitis cytomegalovirus	1	.	1	.	.
	Epididymitis	2	2	.	.	.
	Erysipelas	1	.	1	.	.
	Escherichia pyelonephritis	1	.	.	1	.
	Escherichia sepsis	2	2	.	.	.
	Gangrene	1	.	1	.	.
	Gastroenteritis	1	.	1	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Infections and infestations	Herpes simplex	1	.	1	.	.
	Infection	86	68	17	1	.
	Influenza	1	.	1	.	.
	Joint abscess	1	1	.	.	.
	Kidney infection	2	.	2	.	.
	Klebsiella sepsis	1	.	1	.	.
	Large intestine infection	2	.	1	1	.
	Localised infection	1	1	.	.	.
	Metapneumovirus infection	2	.	1	1	.
	Norovirus infection	4	.	4	.	.
	Oesophageal candidiasis	1	.	1	.	.
	Opportunistic infection	2	.	2	.	.
	Oral herpes	1	1	.	.	.
	Osteomyelitis	1	1	.	.	.
	Parainfluenzae virus infection	1	1	.	.	.
	Pneumonia	23	2	20	1	.
	Pneumonia cytomegaloviral	1	1	.	.	.
	Pneumonia legionella	1	1	.	.	.
	Polyomavirus viraemia	1	.	.	1	.
	Pyelonephritis	7	1	5	1	.
	Renal graft infection	1	.	.	1	.
	Sepsis	2	1	1	.	.
	Skin infection	4	.	4	.	.
	Staphylococcal bacteraemia	1	.	.	1	.
	Staphylococcal infection	1	1	.	.	.
	Trench fever	1	1	.	.	.
	Urinary tract infection	20	.	19	1	.
	Urosepsis	1	1	.	.	.
	Vestibular neuronitis	1	.	1	.	.
	Viral infection	1	.	1	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Injury, poisoning and procedural complications	Combined tibia-fibula fracture	1	1	.	.	.
	Complications of transplanted kidney	1	.	.	1	.
	Foot fracture	1	1	.	.	.
	Fracture	9	5	4	.	.
	Head injury	1	.	.	1	.
	Hip fracture	10	1	9	.	.
	Incision site pain	1	.	1	.	.
	Injury	3	2	1	.	.
	Intentional overdose	1	.	1	.	.
	Limb injury	1	1	.	.	.
	Lower limb fracture	1	1	.	.	.
	Overdose	2	.	1	1	.
	Post procedural haemorrhage	1	.	1	.	.
	Procedural pain	2	.	2	.	.
	Subdural haemorrhage	1	.	1	.	.
	Toxicity to various agents	2	.	2	.	.
	Upper limb fracture	1	.	1	.	.
	Vascular injury	1	.	1	.	.
	Wound	1	.	1	.	.
	Wound complication	11	5	6	.	.
Investigations	BK polyomavirus test positive	1	.	1	.	.
	Blood alkaline phosphatase	14	14	.	.	.
	Blood creatine phosphokinase	1	1	.	.	.
	Blood creatinine	13	10	3	.	.
	Blood creatinine increased	7	1	6	.	.
	Blood glucose abnormal	1	.	1	.	.
	Blood glucose increased	1	.	.	1	.
	Blood potassium increased	2	.	1	1	.
	Clostridium test	1	.	.	1	.
	Coagulation factor	1	.	1	.	.
	Donor specific antibody present	3	.	3	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	**Preferred term**					
Investigations	**Glomerular filtration rate**	1	1	.	.	.
	Glomerular filtration rate decreased	1	.	1	.	.
	Granulocytes abnormal	56	46	10	.	.
	Haemoglobin	16	12	4	.	.
	Haemoglobin decreased	4	2	2	.	.
	Hepatic enzyme increased	1	.	1	.	.
	Laboratory test	1	1	.	.	.
	Liver function test abnormal	36	36	.	.	.
	Neutrophil count	3	.	3	.	.
	Neutrophil count decreased	4	1	3	.	.
	Renin increased	1	.	1	.	.
	Troponin I	1	1	.	.	.
	Troponin T	1	.	1	.	.
	Weight decreased	1	1	.	.	.
Metabolism and nutrition disorders	**Dehydration**	8	4	4	.	.
	Diabetes mellitus	1	.	1	.	.
	Diabetic ketoacidosis	8	1	7	.	.
	Hyperglycaemia	6	1	5	.	.
	Hyperkalaemia	4	.	4	.	.
	Hypoglycaemia	82	29	49	4	.
	Hypoglycaemia unawareness	1	.	1	.	.
	Hypokalaemia	1	1	.	.	.
	Hypomagnesaemia	1	1	.	.	.
	Hyponatraemia	8	7	1	.	.
	Hypophosphataemia	1	1	.	.	.
	Hypovolaemia	2	.	2	.	.
	Ketoacidosis	17	11	6	.	.
	Malnutrition	1	1	.	.	.
	Metabolic disorder	1	1	.	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	**Preferred term**					
Musculoskeletal and connective tissue disorders	**Arthralgia**	2	.	1	1	.
	Arthritis	2	1	1	.	.
	Arthritis reactive	1	.	.	1	.
	Arthropathy	1	.	1	.	.
	Intervertebral disc protrusion	1	.	1	.	.
	Muscle necrosis	1	1	.	.	.
	Musculoskeletal disorder	5	5	.	.	.
	Myalgia	1	.	1	.	.
	Neuropathic arthropathy	3	.	3	.	.
	Osteoarthritis	1	1	.	.	.
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**Adenocarcinoma**	2	.	2	.	.
	Basal cell carcinoma	15	3	12	.	.
	Basosquamous carcinoma	2	1	1	.	.
	Breast cancer	5	3	2	.	.
	Breast cancer stage I	1	.	1	.	.
	Cervix carcinoma	1	.	.	1	.
	Cholangiocarcinoma	1	.	1	.	.
	Colorectal cancer stage IV	1	.	1	.	.
	Diffuse large B-cell lymphoma	1	.	1	.	.
	Gastrointestinal carcinoma	1	1	.	.	.
	Intraductal papillary-mucinous carcinoma of	1	1	.	.	.
	Intraductal proliferative breast lesion	1	.	1	.	.
	Invasive ductal breast carcinoma	1	1	.	.	.
	Lung carcinoma cell type unspecified stage I	1	.	1	.	.
	Lung neoplasm malignant	2	.	2	.	.
	Lymphoma	1	1	.	.	.
	Malignant melanoma	2	1	1	.	.
	Malignant pleural effusion	1	1	.	.	.
	Neoplasm	2	1	1	.	.
	Neoplasm malignant	16	14	2	.	.
	Ovarian adenoma	1	1	.	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Papillary thyroid cancer	1	1	.	.	.
	Plasma cell myeloma	1	.	.	1	.
	Polycythaemia vera	1	.	1	.	.
	Post transplant lymphoproliferative disorder	7	1	6	.	.
	Prostate cancer	4	.	4	.	.
	Small intestine carcinoma	1	.	1	.	.
	Squamous cell carcinoma	28	19	9	.	.
	Squamous cell carcinoma of head and neck	1	.	1	.	.
	Squamous cell carcinoma of lung	1	1	.	.	.
	Squamous cell carcinoma of skin	6	.	6	.	.
	Squamous cell carcinoma of the tongue	1	.	.	1	.
	Transitional cell carcinoma	2	1	1	.	.
	Uterine leiomyoma	1	.	.	1	.
Nervous system disorders	Amnesia	1	.	1	.	.
	Cerebellar ischaemia	1	.	1	.	.
	Cerebellar stroke	3	.	3	.	.
	Cerebral ischaemia	9	3	6	.	.
	Cerebrovascular accident	1	.	.	1	.
	Cognitive disorder	1	.	1	.	.
	Dizziness	3	2	1	.	.
	Frontotemporal dementia	1	.	1	.	.
	Generalised tonic-clonic seizure	1	.	1	.	.
	Headache	4	.	4	.	.
	Hydrocephalus	6	.	6	.	.
	Hypoglycaemic coma	2	.	2	.	.
	Hypoglycaemic seizure	1	.	1	.	.
	Loss of consciousness	1	1	.	.	.
	Nervous system disorder	6	4	2	.	.
	Neuroleptic malignant syndrome	1	.	1	.	.
	Neurological symptom	1	.	1	.	.
	Neuropathy peripheral	1	.	1	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Nervous system disorders	Optic neuritis	1	1	.	.	.
	Psychogenic seizure	2	.	2	.	.
	Seizure	5	1	4	.	.
	Serotonin syndrome	1	1	.	.	.
	Spinal cord compression	2	.	2	.	.
	Subarachnoid haemorrhage	1	.	1	.	.
	Syncope	8	3	4	1	.
	Transient ischaemic attack	2	.	2	.	.
	Tremor	1	1	.	.	.
Psychiatric disorders	Acute psychosis	1	.	1	.	.
	Anxiety	2	.	2	.	.
	Confusional state	3	1	2	.	.
	Delusion	9	.	9	.	.
	Insomnia	1	1	.	.	.
	Mood altered	3	3	.	.	.
	Psychotic disorder	1	1	.	.	.
	Suicidal ideation	1	.	1	.	.
	Suicide attempt	3	.	3	.	.
Renal and urinary disorders	Acute kidney injury	8	3	5	.	.
	End stage renal disease	1	1	.	.	.
	Ketonuria	1	1	.	.	.
	Nephropathy	1	1	.	.	.
	Proteinuria	3	2	1	.	.
	Renal artery stenosis	1	.	1	.	.
	Renal disorder	8	6	2	.	.
	Renal failure	25	15	10	.	.
	Renal infarct	1	.	1	.	.
	Tubulointerstitial nephritis	1	.	1	.	.
	Urinary bladder haemorrhage	3	2	1	.	.
	Urinary retention	1	.	1	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	Preferred term					
Reproductive system and breast disorders	Cervical dysplasia	1	.	1	.	.
	Lactation disorder	1	1	.	.	.
	Rectocele	1	.	.	1	.
	Sexual dysfunction	7	6	1	.	.
Respiratory, thoracic and mediastinal disorders	Acute pulmonary oedema	1	.	.	1	.
	Acute respiratory distress syndrome	1	1	.	.	.
	Acute respiratory failure	1	.	.	1	.
	Aspiration	2	1	1	.	.
	Asthma	1	1	.	.	.
	Cough	2	2	.	.	.
	Dyspnoea	5	3	2	.	.
	Hypoxia	4	1	3	.	.
	Lung disorder	8	5	3	.	.
	Lung infiltration	4	.	4	.	.
	Pleural effusion	2	.	1	1	.
	Pneumonitis	5	4	1	.	.
	Pulmonary embolism	1	.	1	.	.
	Pulmonary hypertension	3	.	3	.	.
Skin and subcutaneous tissue disorders	Decubitus ulcer	2	2	.	.	.
	Exfoliative rash	1	.	1	.	.
	Rash	1	.	1	.	.
	Skin disorder	1	1	.	.	.
	Skin lesion	1	1	.	.	.
Surgical and medical procedures	Amputation	1	.	1	.	.
	Brain operation	1	.	1	.	.
	Breast reconstruction	1	.	1	.	.
	Cholecystectomy	2	.	2	.	.
	Coronary arterial stent insertion	1	1	.	.	.
	Coronary artery bypass	3	1	2	.	.
	Hernia repair	1	.	1	.	.
	Ileostomy	1	1	.	.	.

(Continued)

Exhibit 7-10
All SAEs Classified by Era

		Overall	Era			
			1999-2006	2007-2014	2015-2022	2023-2030
		N	N	N	N	N
System/Organ Class	**Preferred term**					
Surgical and medical procedures	**Retinal laser coagulation**	1	.	1	.	.
	Skin neoplasm excision	2	.	2	.	.
	Surgery	6	3	3	.	.
	Toe amputation	1	1	.	.	.
Vascular disorders	**Arterial stenosis**	1	.	1	.	.
	Arterial thrombosis	1	1	.	.	.
	Blood pressure inadequately controlled	1	.	1	.	.
	Haematoma	10	7	3	.	.
	Haemorrhage	13	8	4	1	.
	Hypertension	5	2	3	.	.
	Intermittent claudication	1	1	.	.	.
	Lymphoedema	1	1	.	.	.
	Orthostatic hypotension	1	.	1	.	.
	Peripheral arterial occlusive disease	1	1	.	.	.
	Peripheral ischaemia	2	2	.	.	.
	Shock haemorrhagic	1	.	.	1	.
	Thrombosis	1	1	.	.	.
	Vascular occlusion	1	.	1	.	.

Chapter 8
Registry Data Quality Review

Introduction

The total number of patients expected at each follow-up visit post last infusion is provided in Exhibit 8.

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 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.

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Exhibit 8
CITR Missing Data Report

Ns	Overall						Europe/Australia/Asia						North America					
	Post Last Infusion						Post Last Infusion						Post Last Infusion					
	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
1999-2006	487	480	478	474	469	466	191	185	184	181	179	178	296	295	294	293	290	288
2007-2014	648	645	640	638	630	622	312	309	307	307	302	301	336	336	333	331	328	321
2015-2022	349	345	341	320	281	259	213	211	210	196	174	160	136	134	131	124	107	99
2023-2030	20	19	2	.	.	.	12	12	2	.	.	.	8	7	.	.	.	.

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

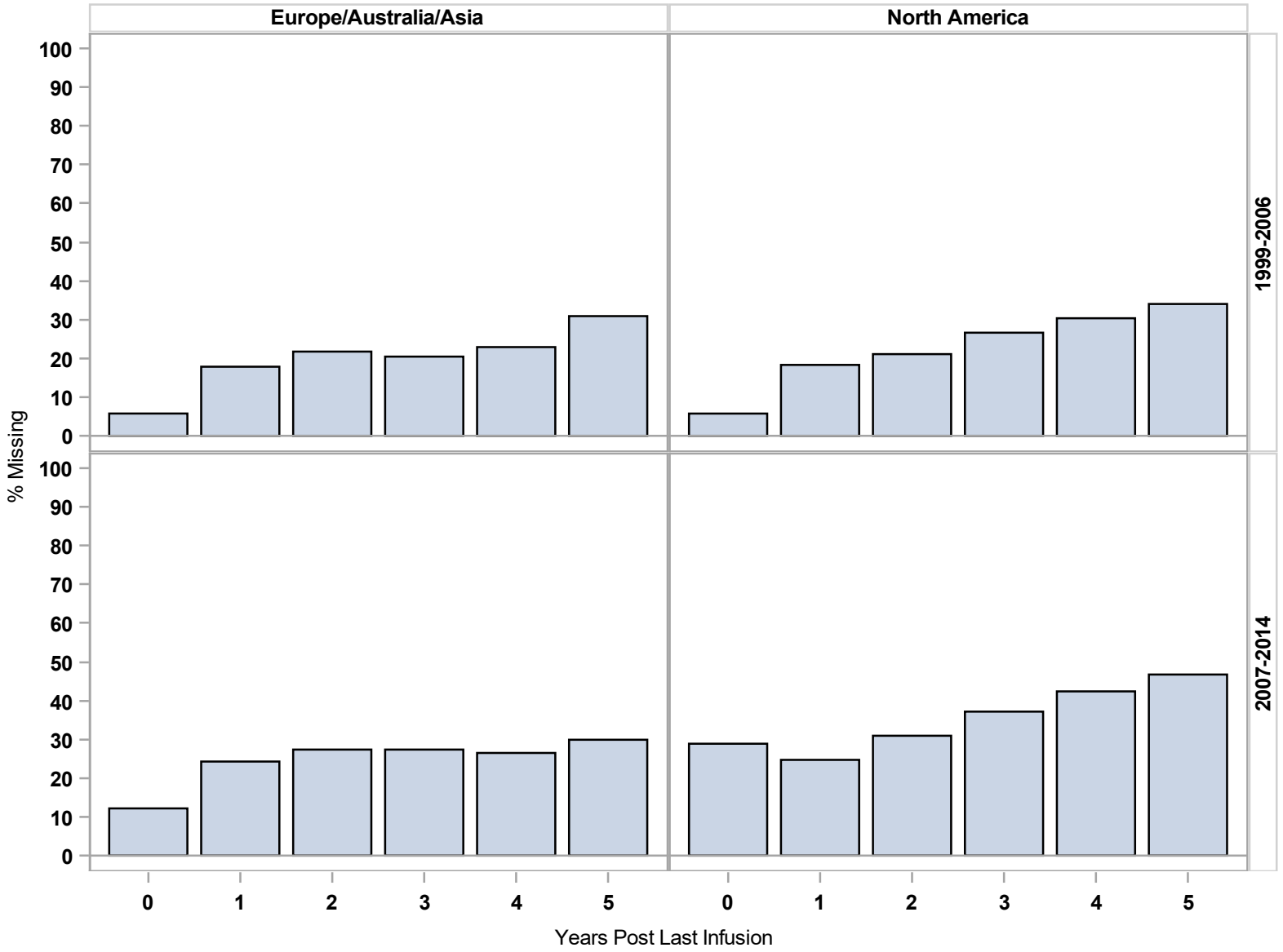

Exhibit 8 – 1
Missing Data for Insulin Independence by Era and Continent

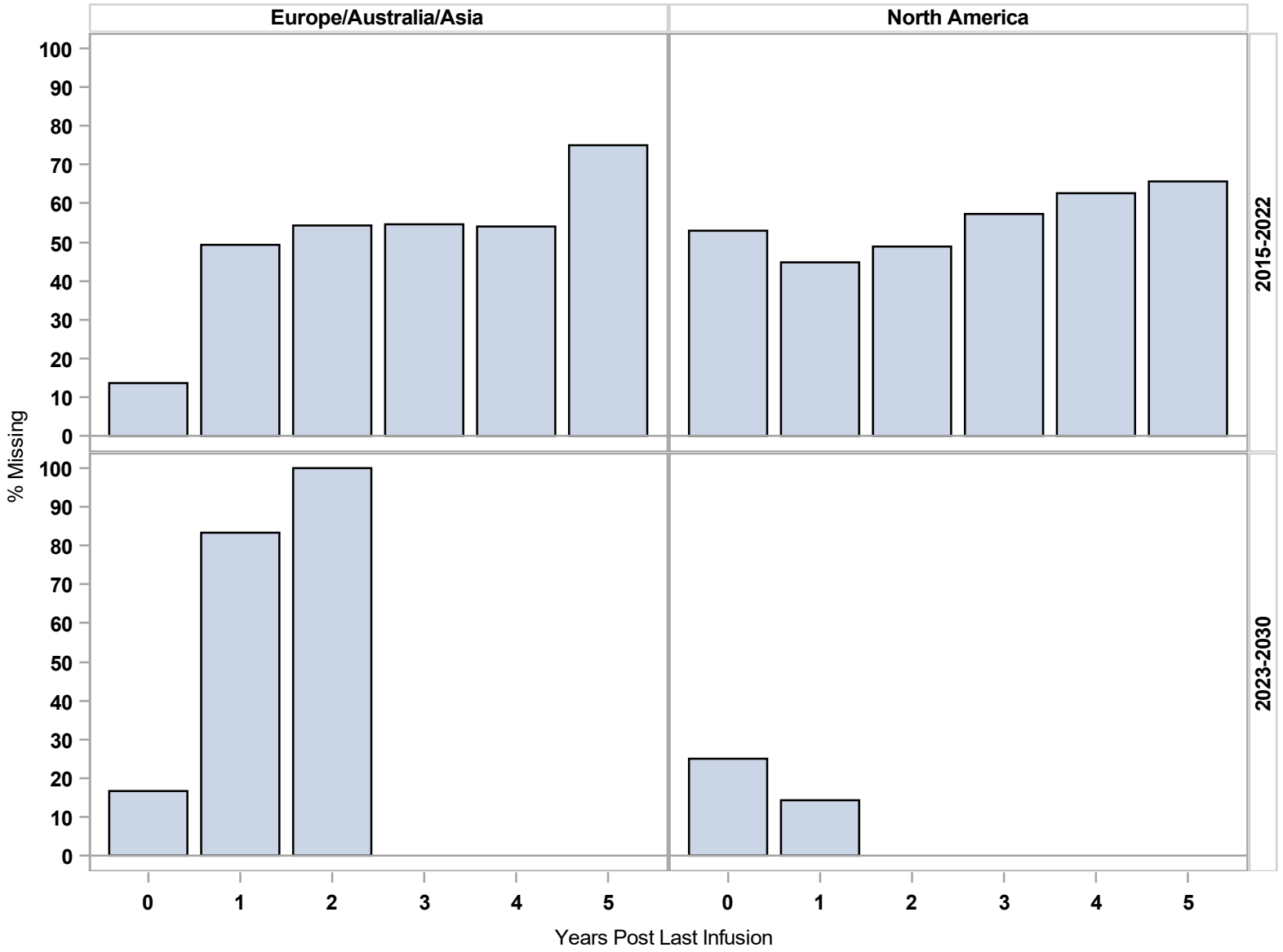

Exhibit 8 – 2
Missing Data for Fasting C-Peptide by Era and Continent

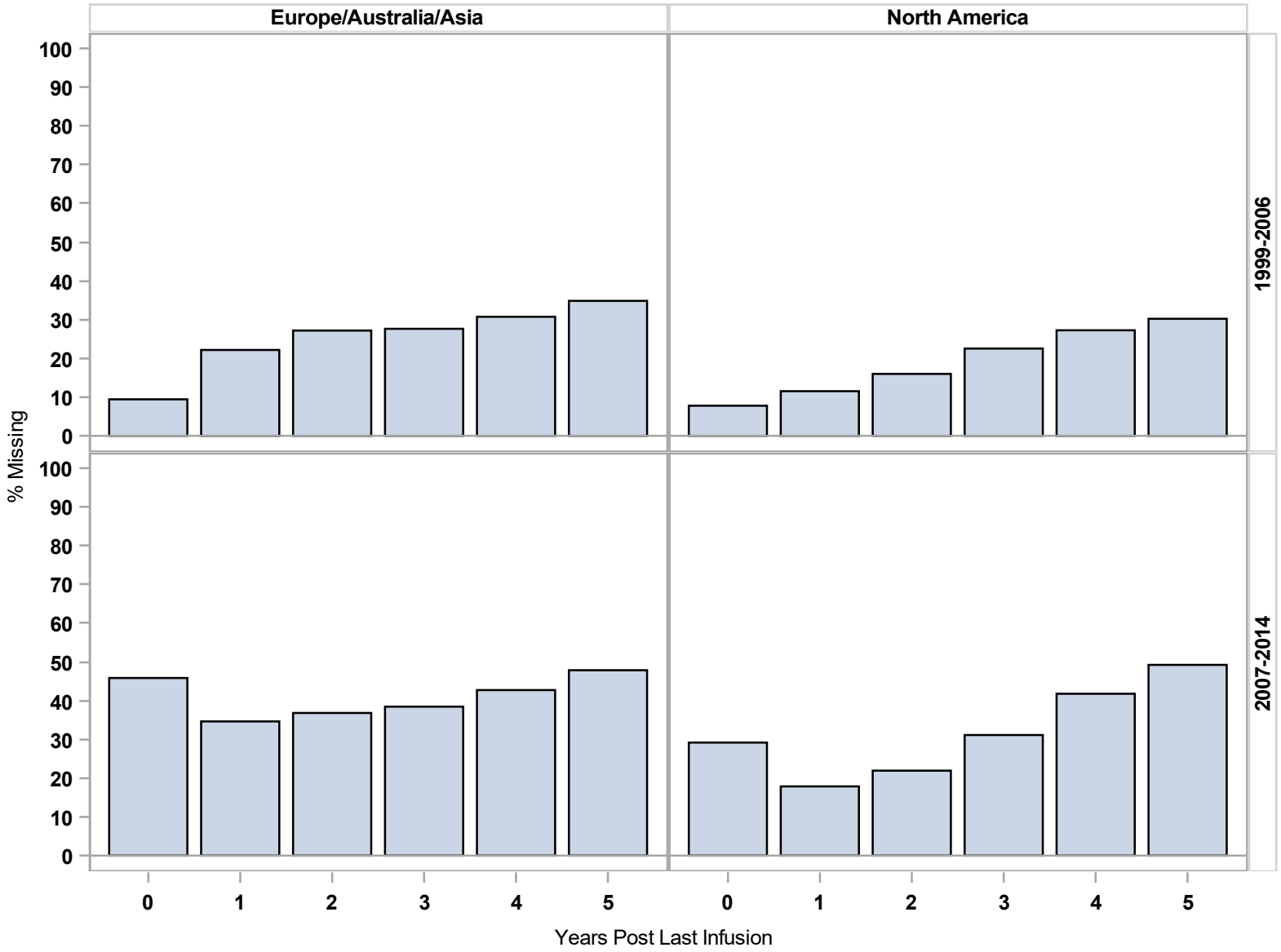

Exhibit 8 – 2
Missing Data for Fasting C-Peptide by Era and Continent

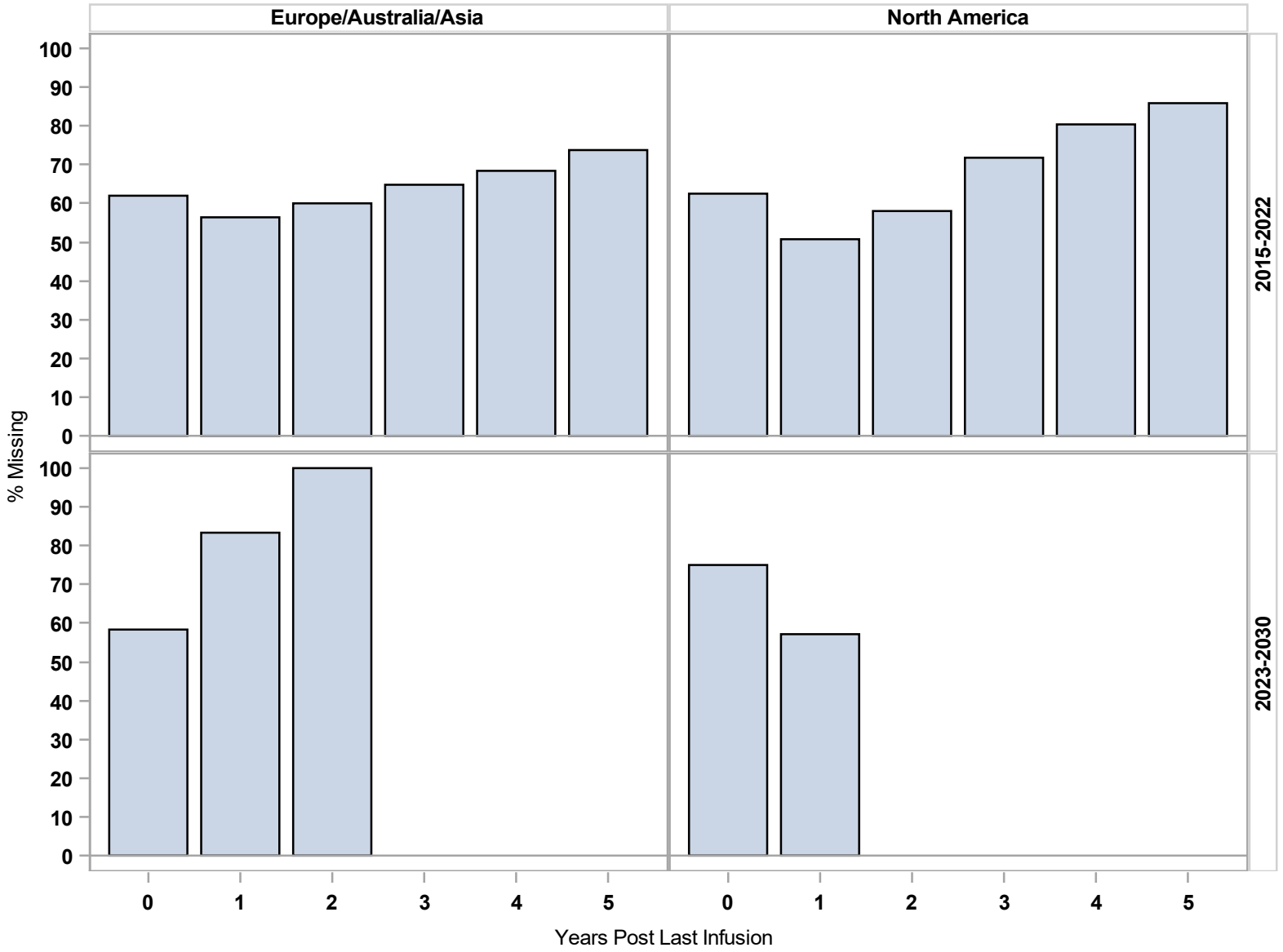

Exhibit 8 – 3
Missing Data for Hemoglobin A1c by Era and Continent

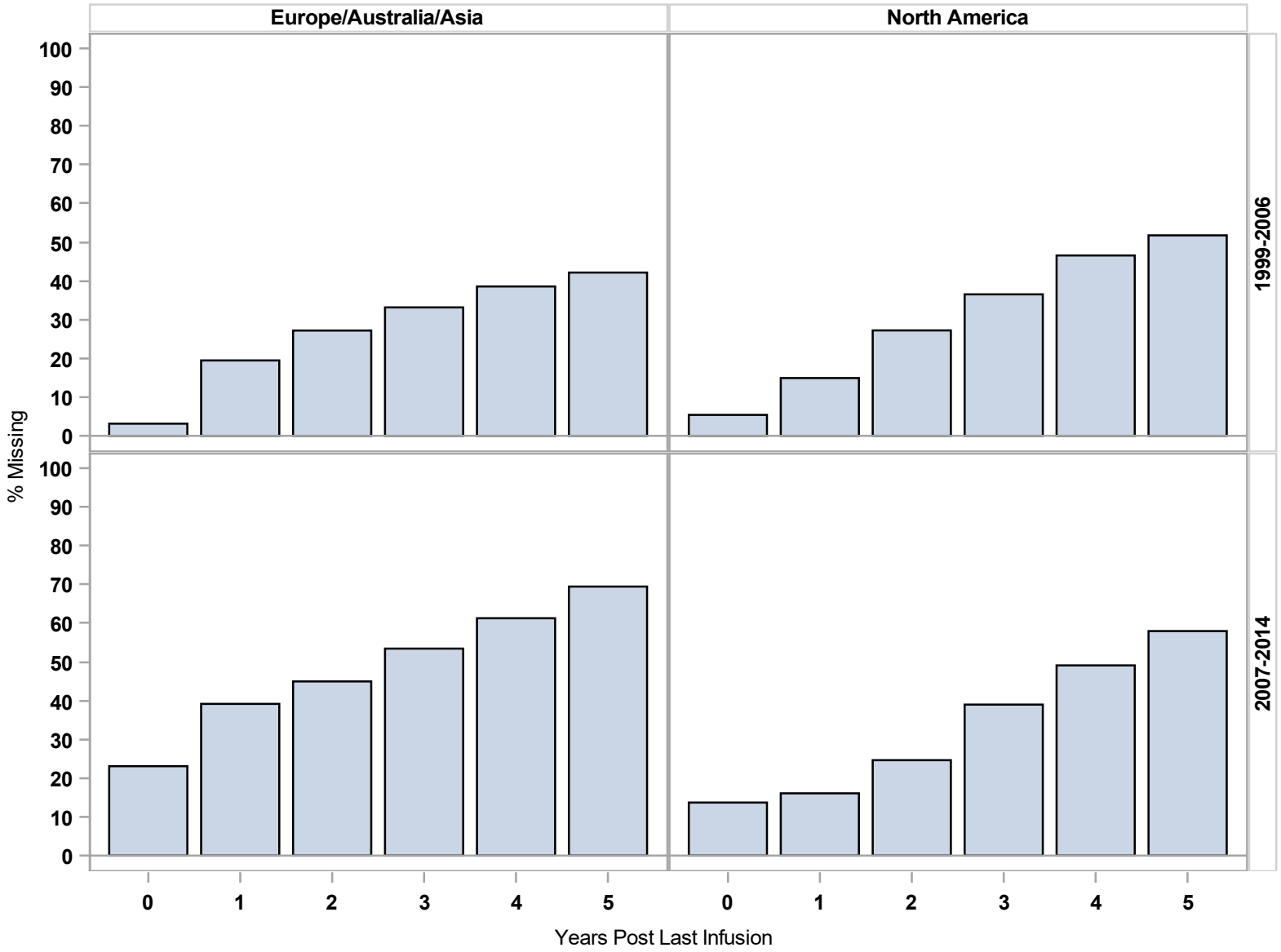

Exhibit 8 – 3
Missing Data for Hemoglobin A1c by Era and Continent

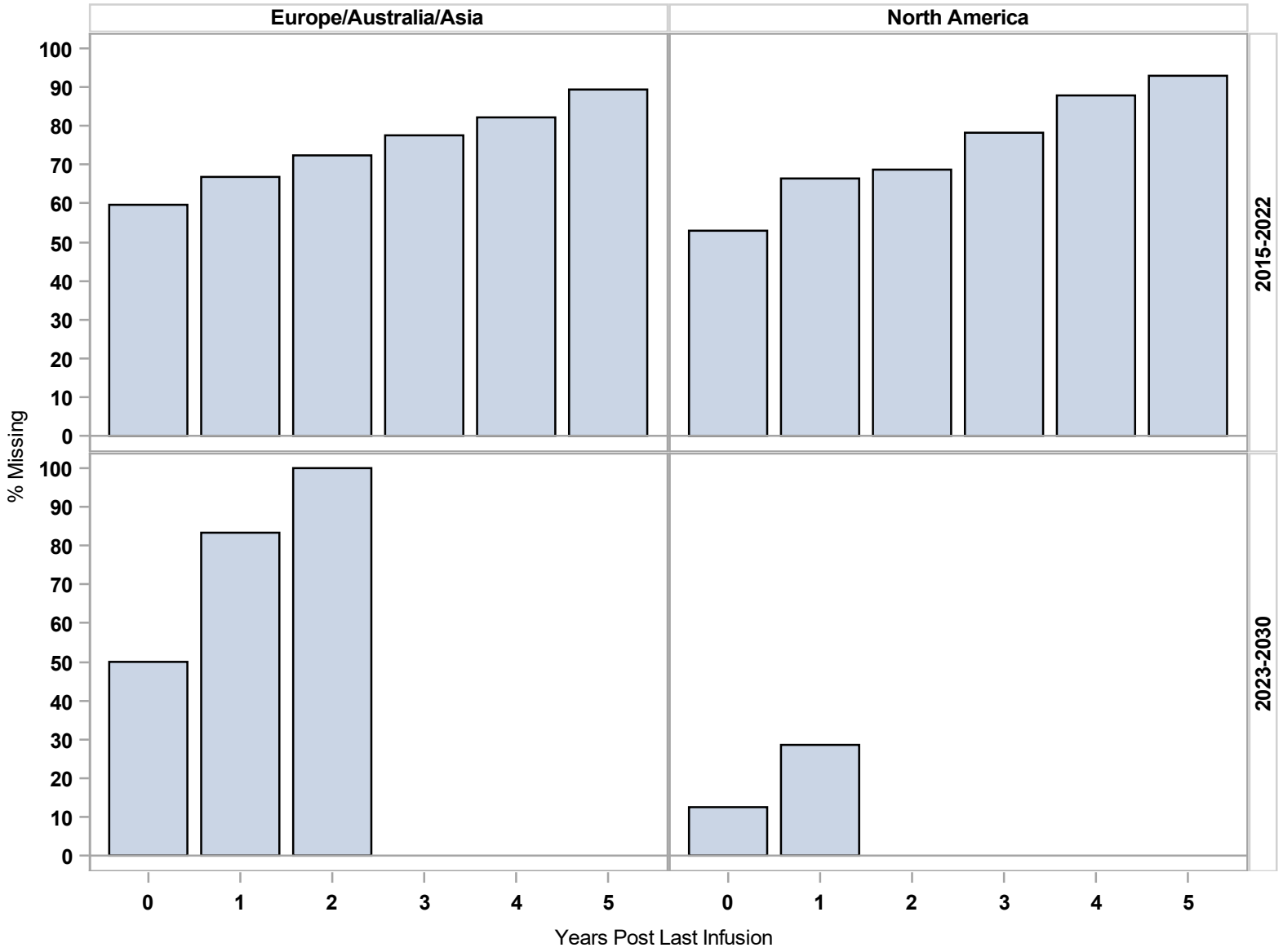

Exhibit 8 – 4
Missing Data for Fasting Blood Glucose by Era and Continent

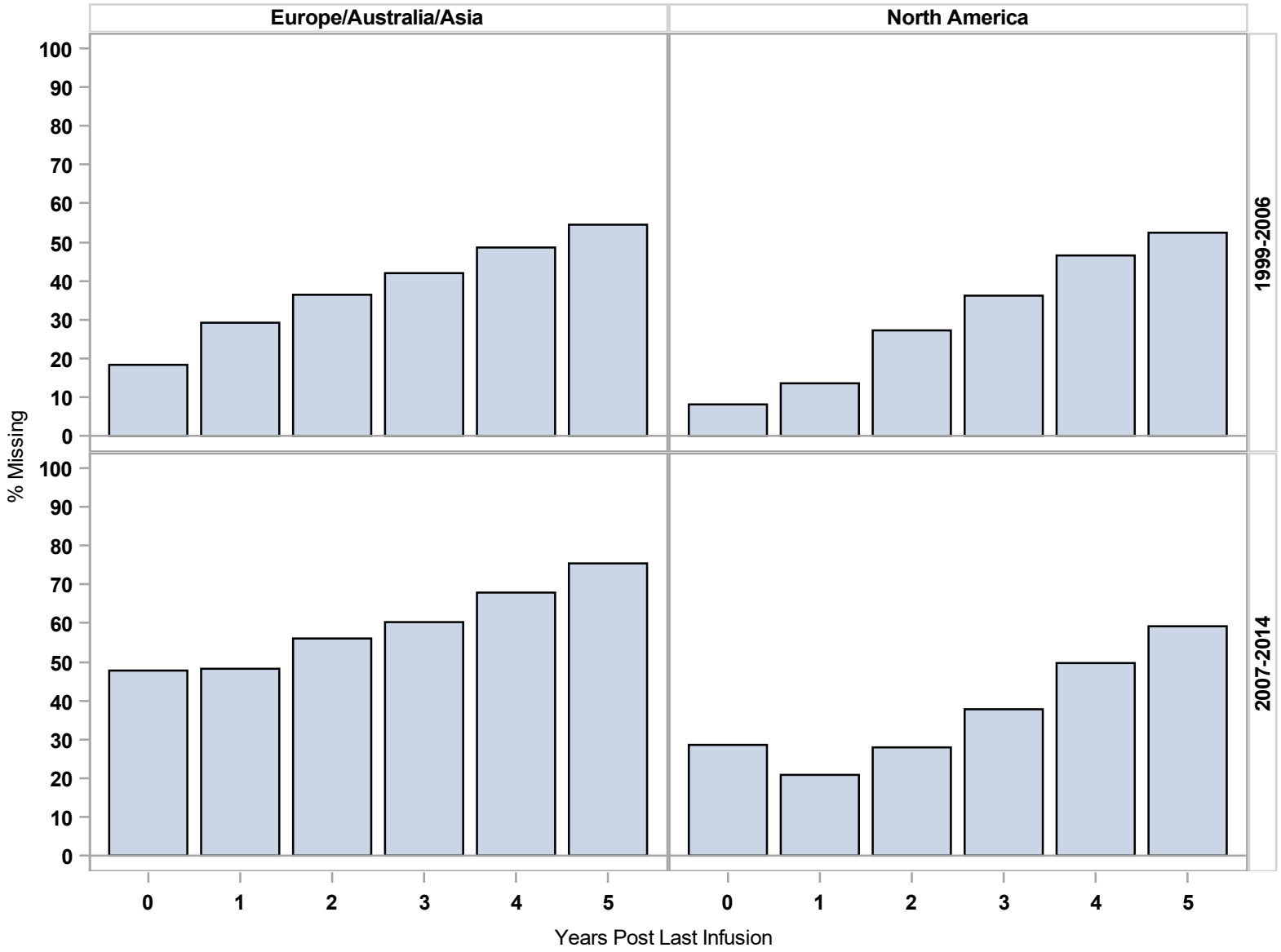

Exhibit 8 – 4
Missing Data for Fasting Blood Glucose by Era and Continent

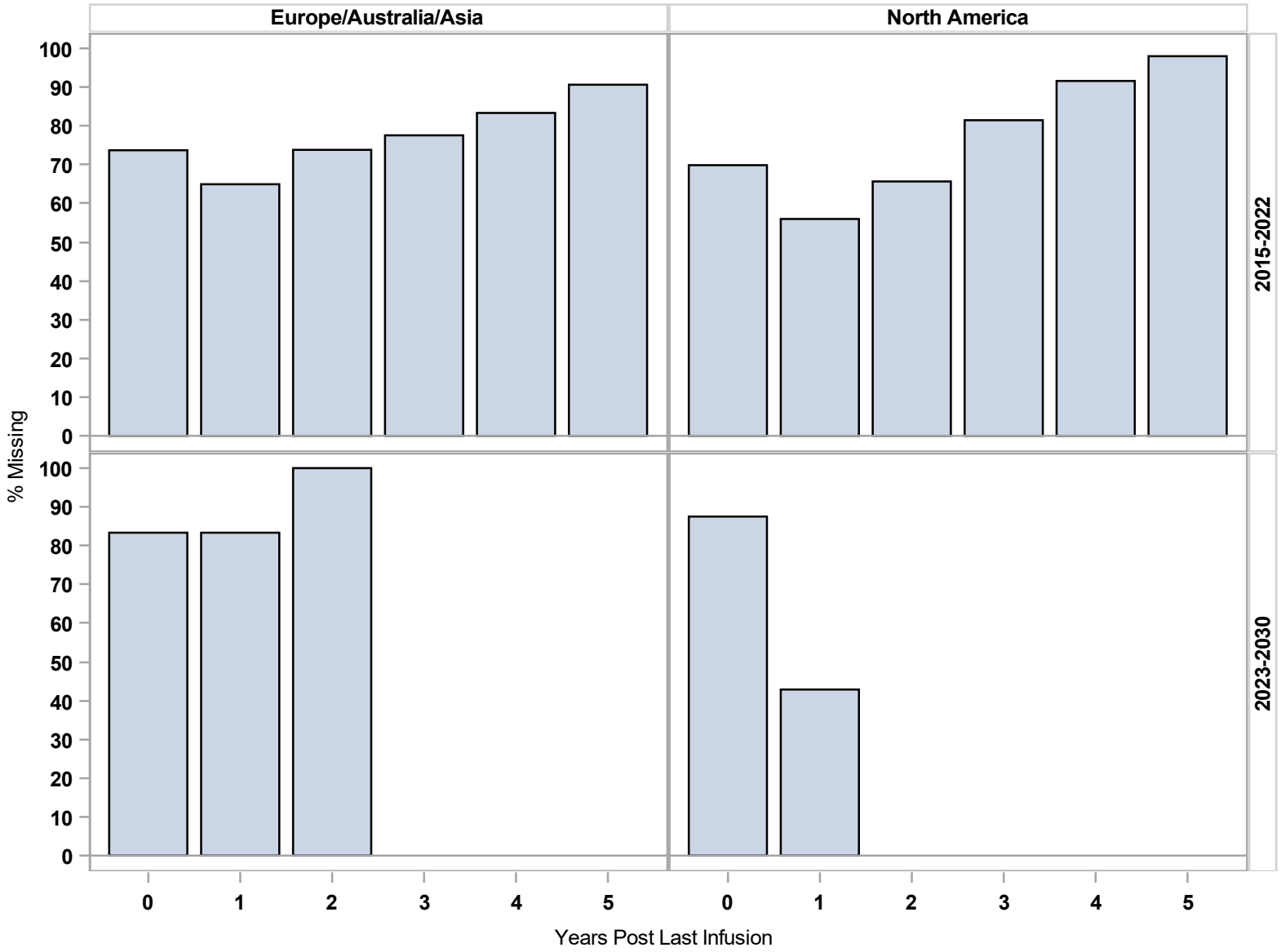

Exhibit 8 – 5
Missing Data for Severe HypoGlycemia by Era and Continent

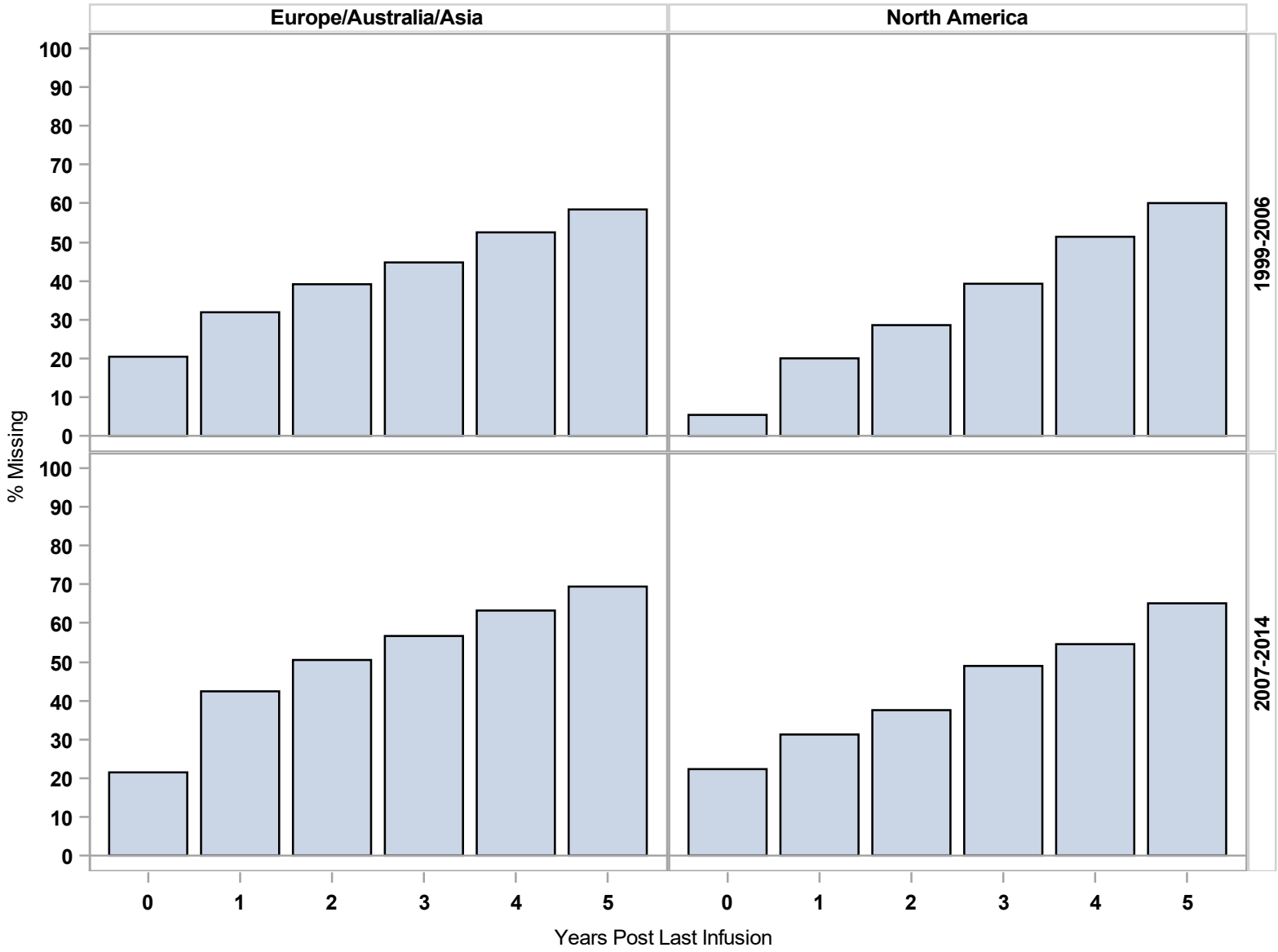

Exhibit 8 – 5
Missing Data for Severe HypoGlycemia by Era and Continent

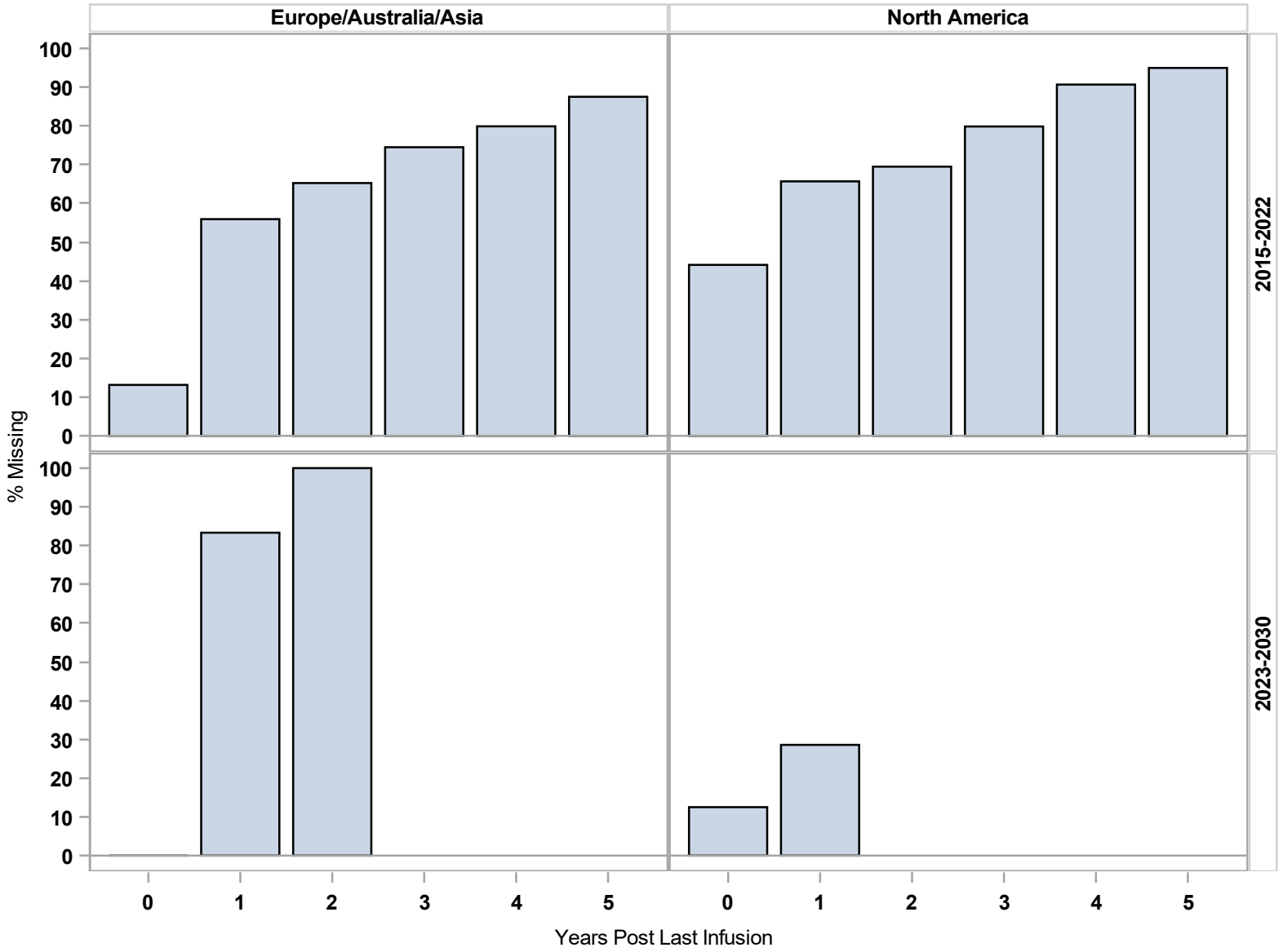

Exhibit 8 – 6
Missing Data for BMI by Era and Continent

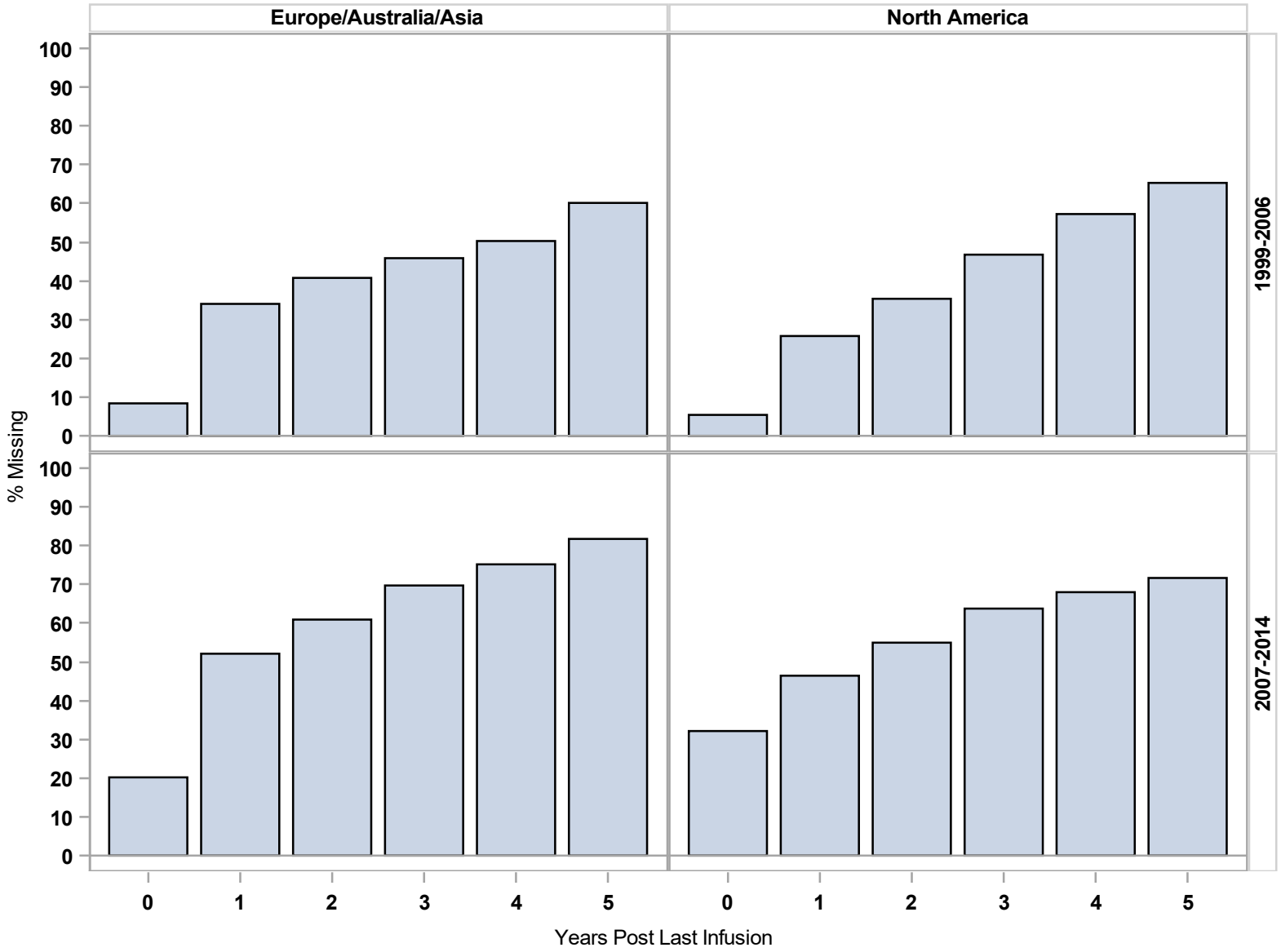

Exhibit 8 – 6
Missing Data for BMI by Era and Continent

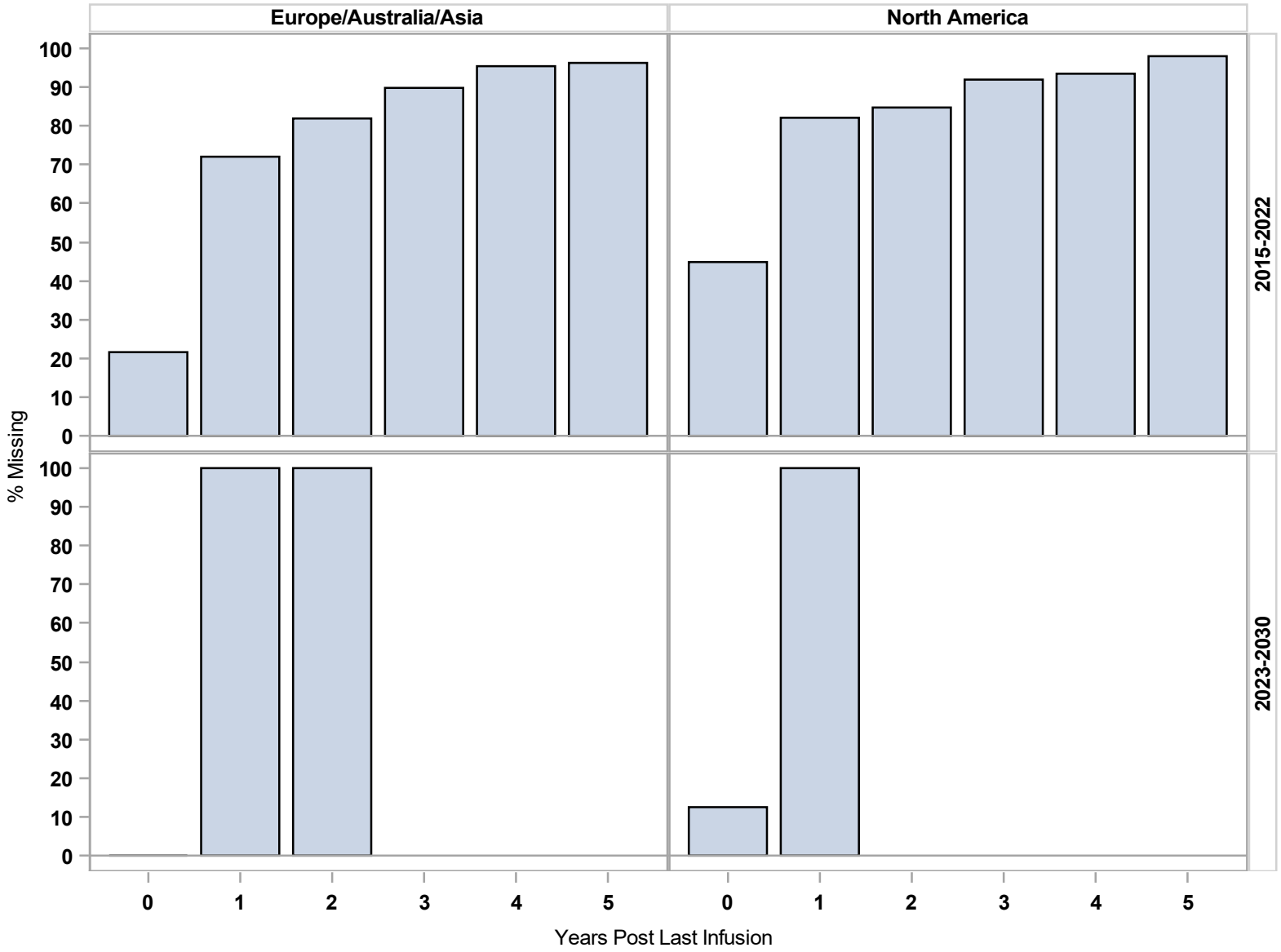

Exhibit 8 – 7
Missing Data for Clarke Score by Era and Continent

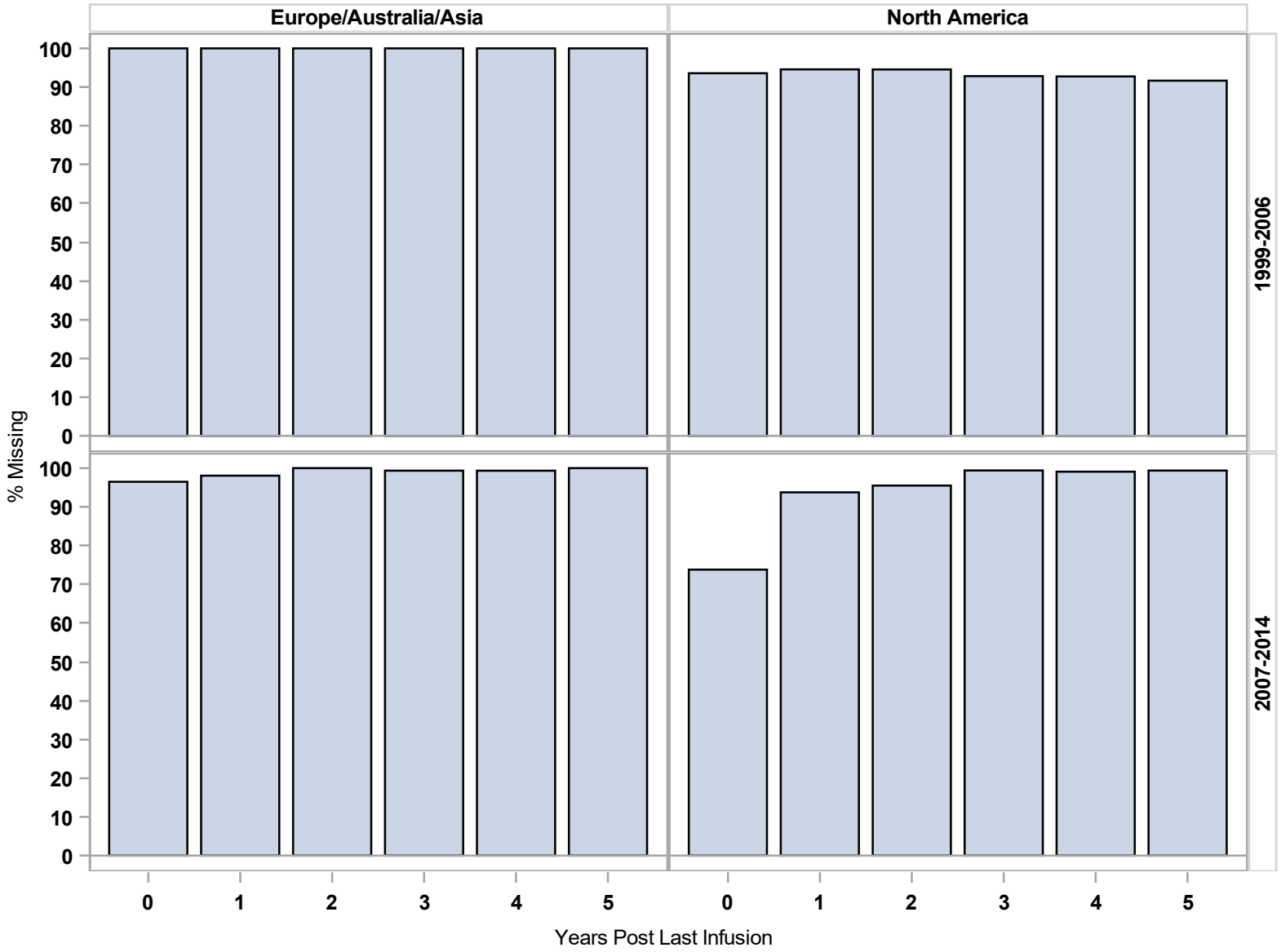

Exhibit 8 – 7
Missing Data for Clarke Score by Era and Continent

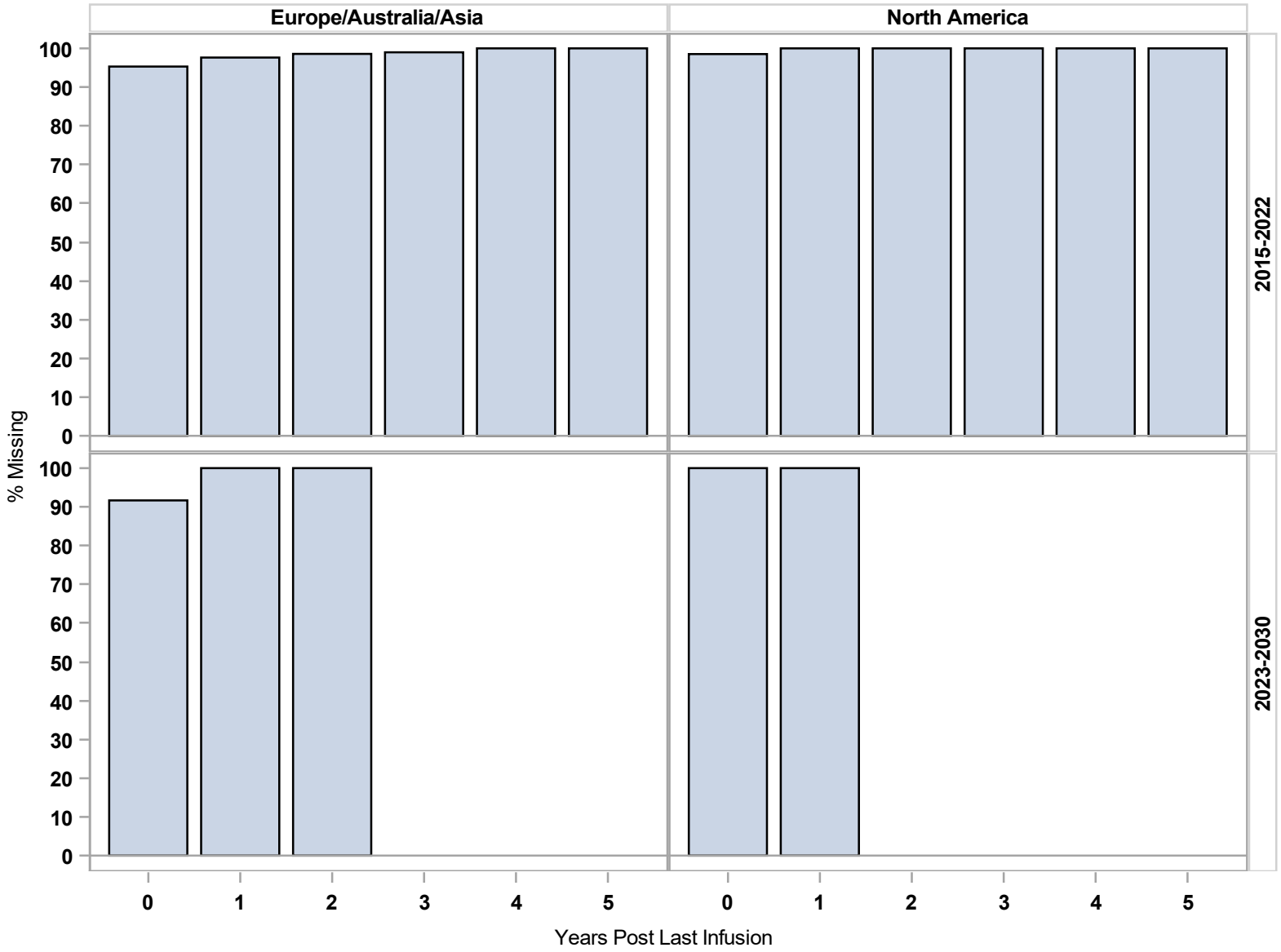

Exhibit 8 – 8
Missing Data for Ryan Hypo by Era and Continent

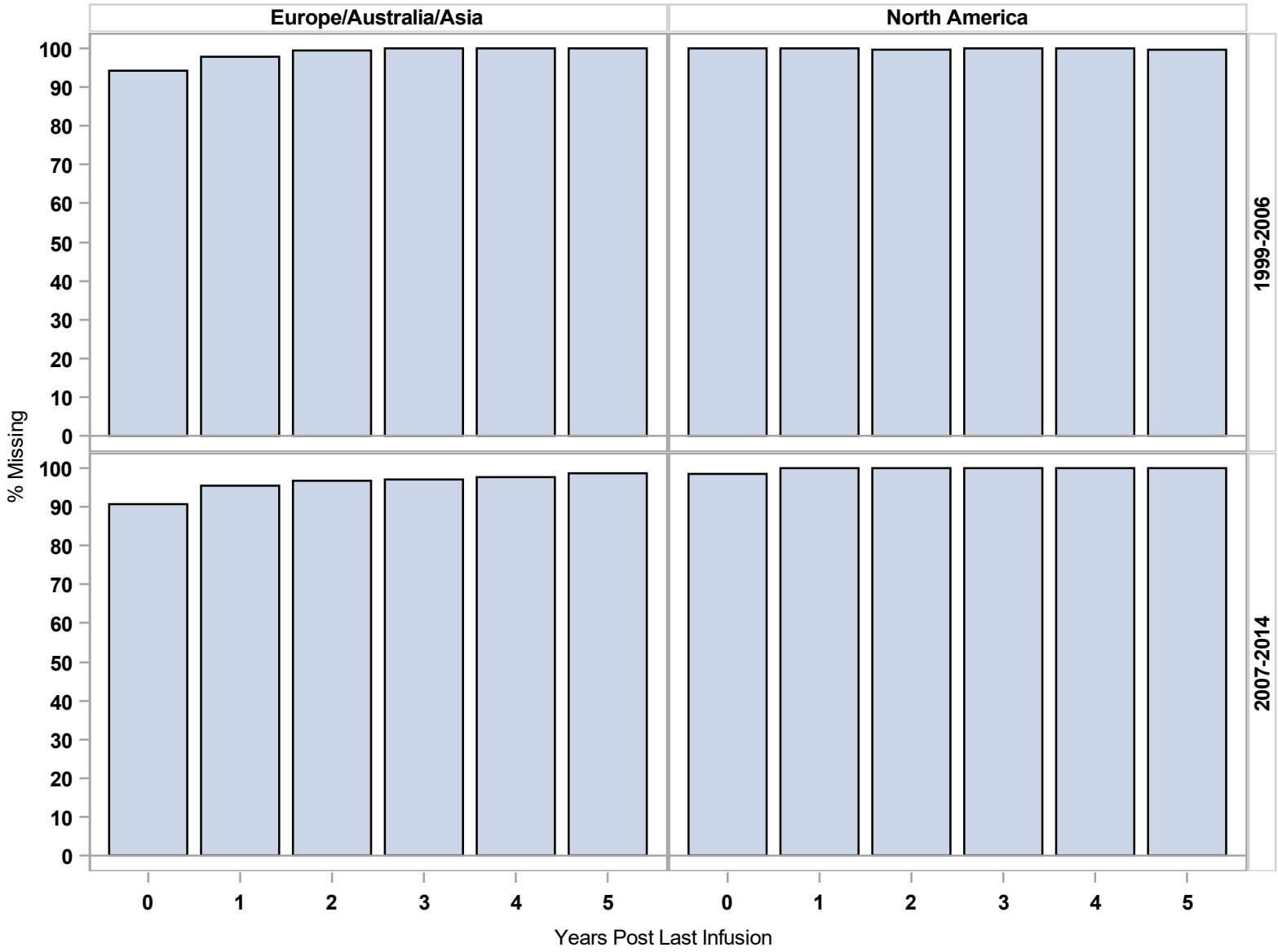

Exhibit 8 – 8
Missing Data for Ryan Hypo by Era and Continent

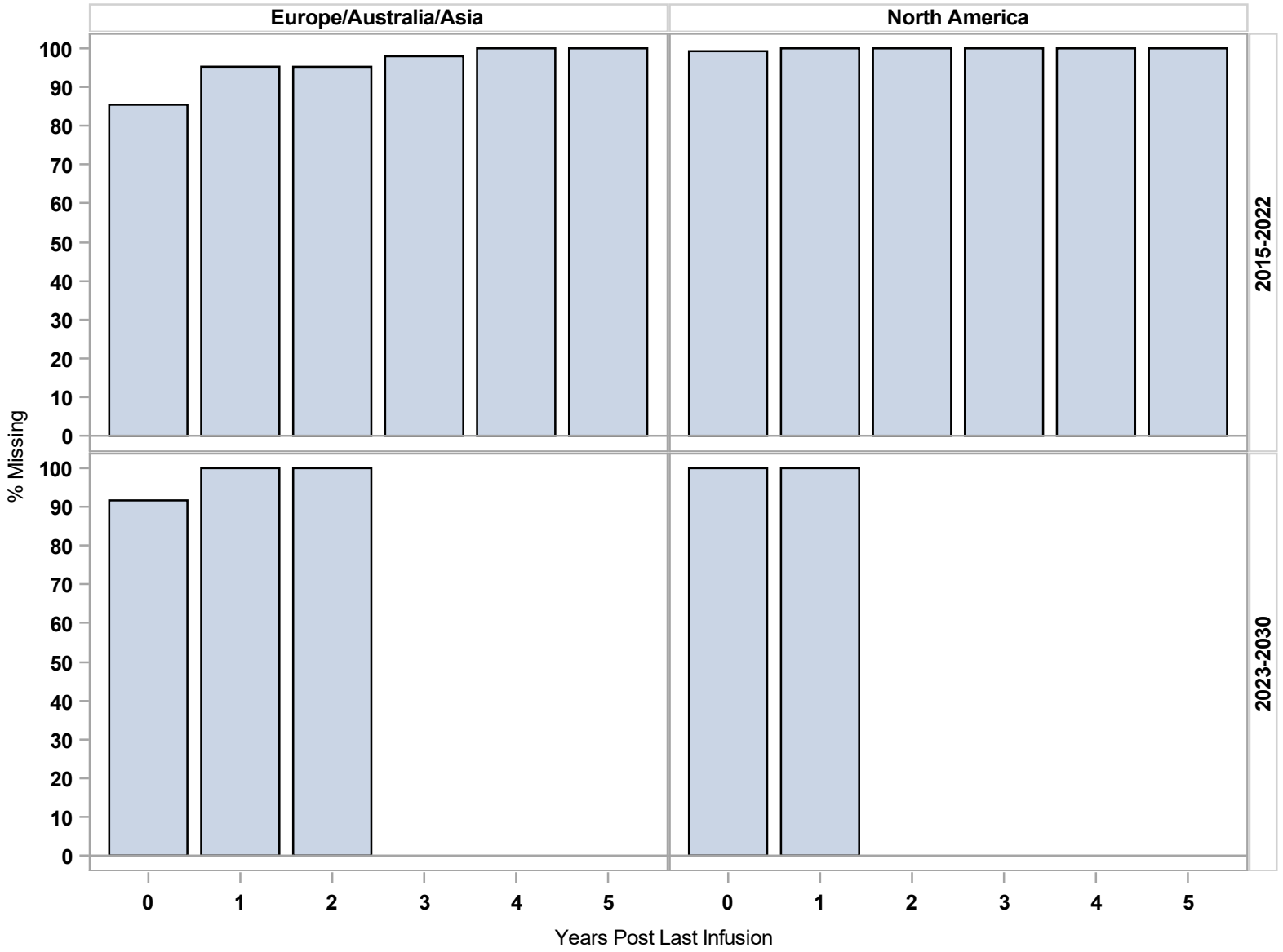

Exhibit 8 – 9
Missing Data for C-Peptide AUC by Era and Continent

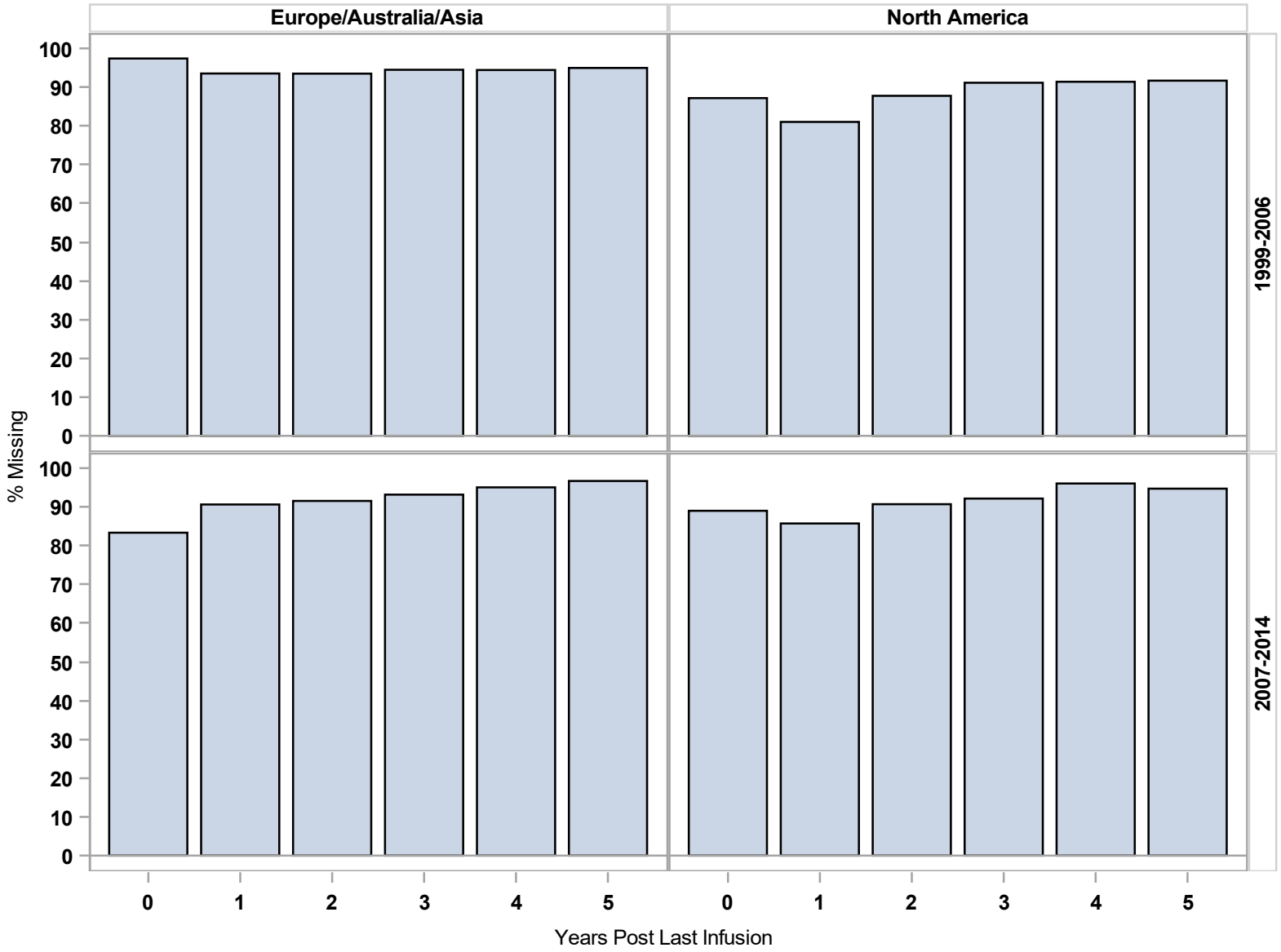

Exhibit 8 – 9
Missing Data for C-Peptide AUC by Era and Continent

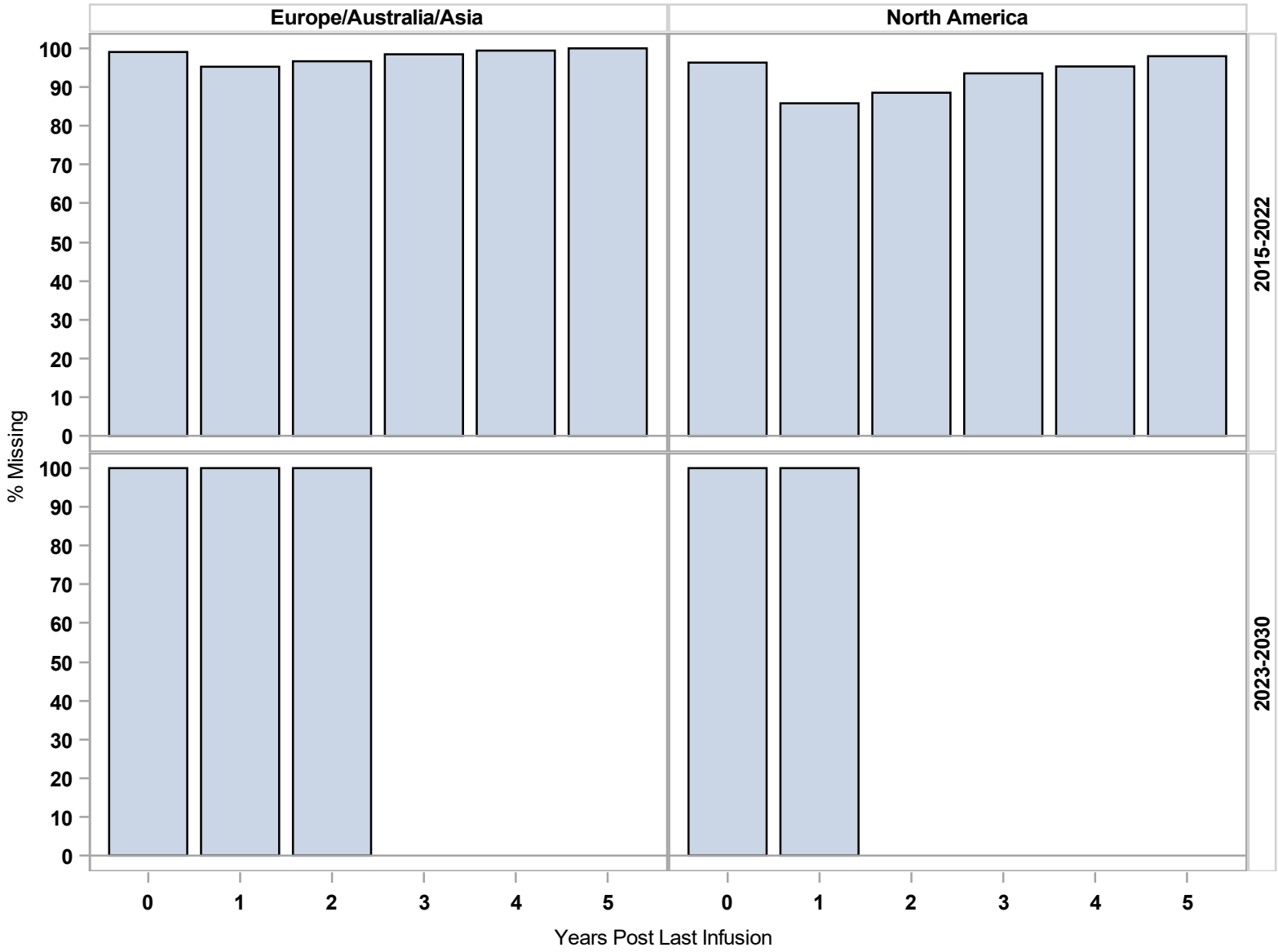

Exhibit 8 – 10
Missing Data for Cockcroft-Gaullt by Era and Continent

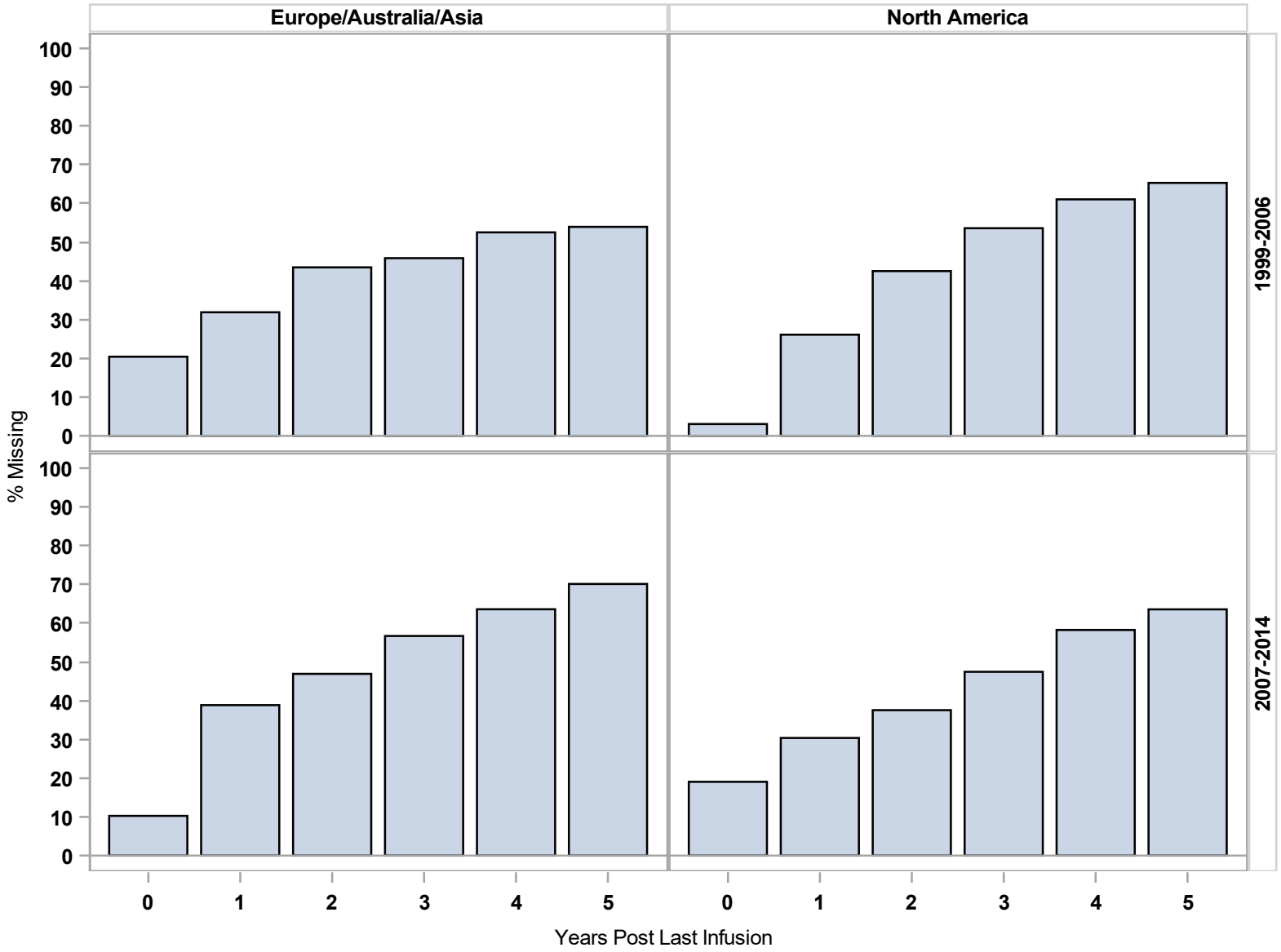

Exhibit 8 – 10
Missing Data for Cockcroft-Gaullt by Era and Continent

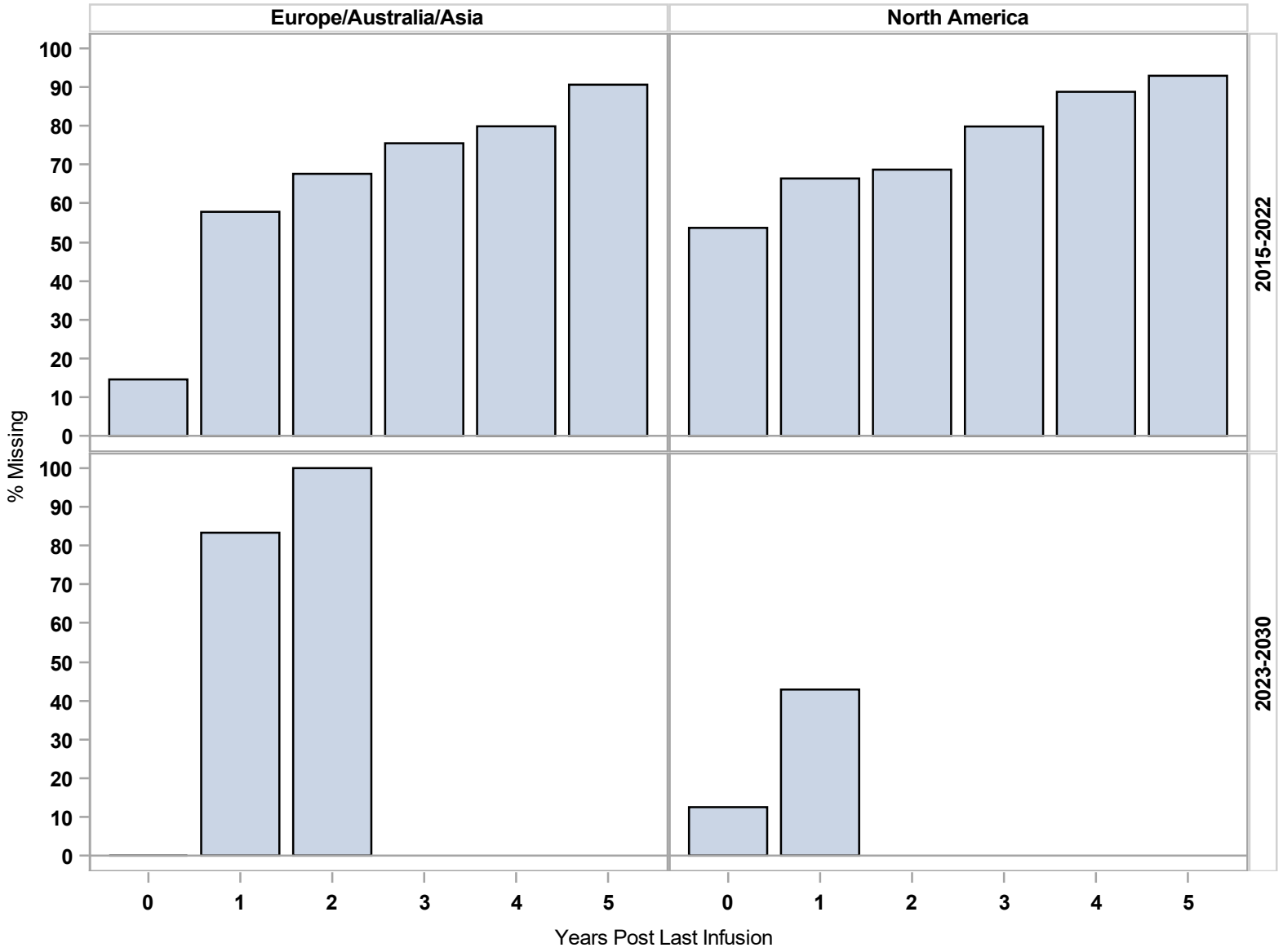

Exhibit 8 – 11
Missing Data for Creatinine by Era and Continent

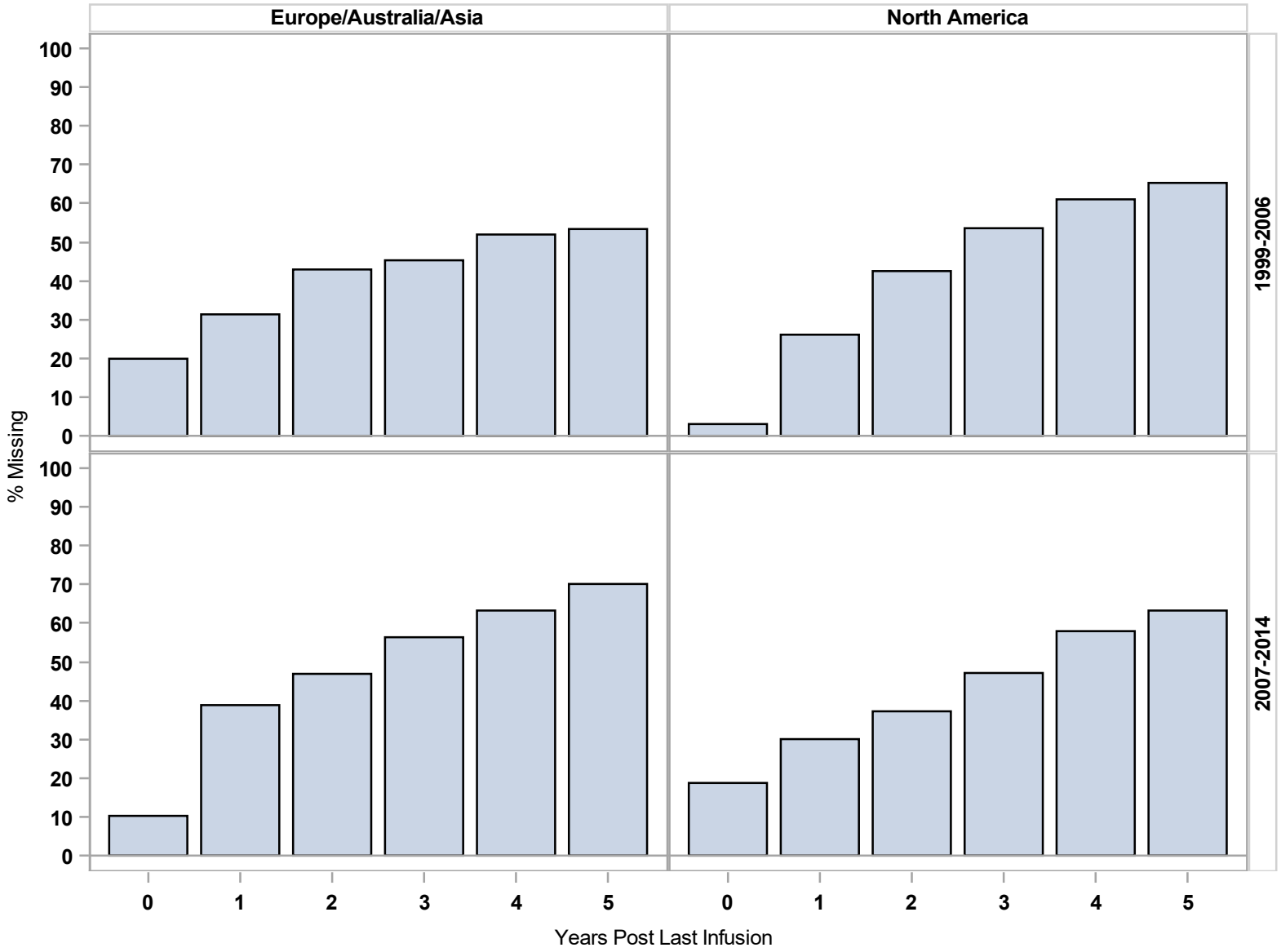

Exhibit 8 – 11
Missing Data for Creatinine by Era and Continent

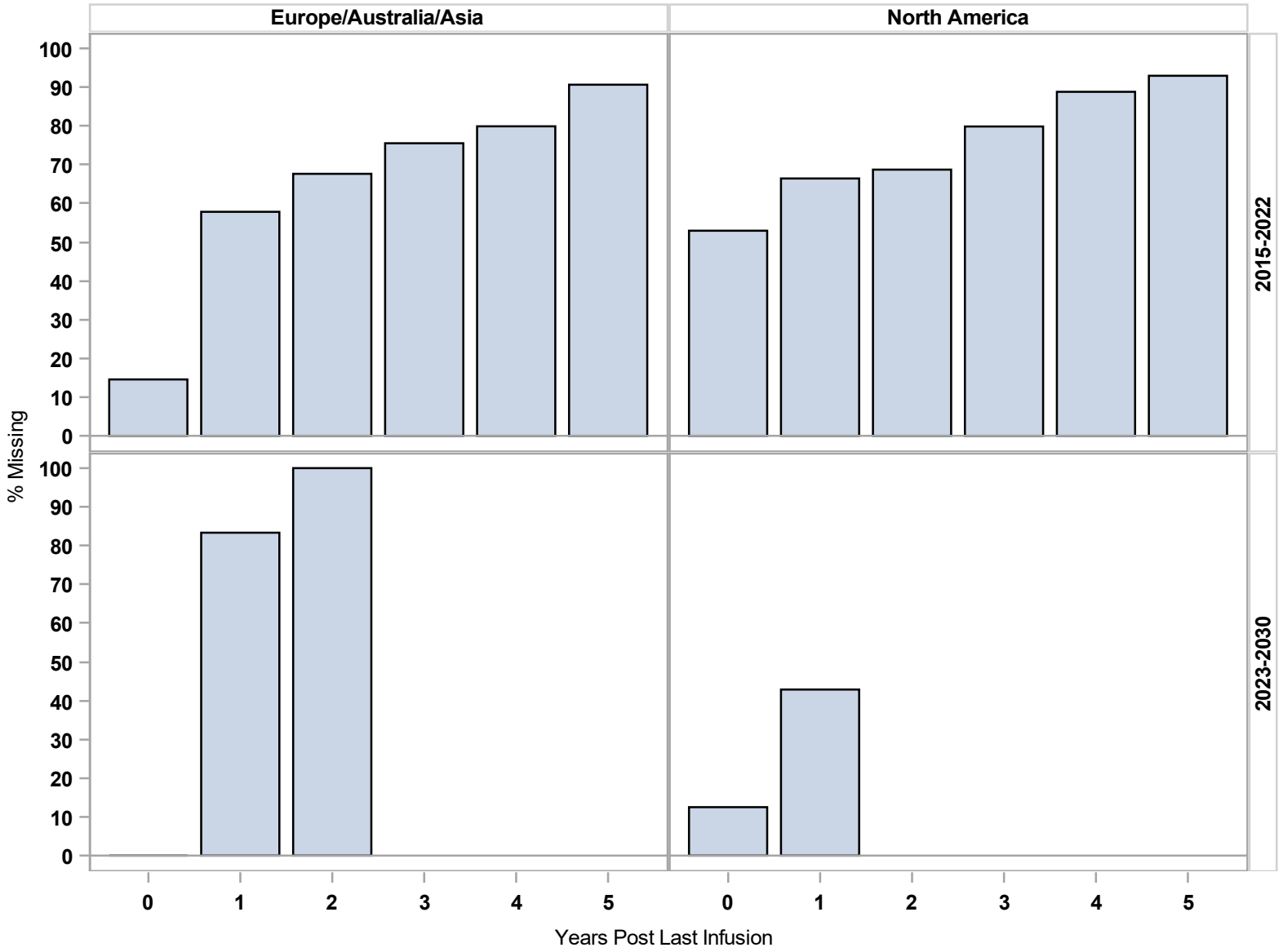

Exhibit 8 – 12
Missing Data for Cholesterol by Era and Continent

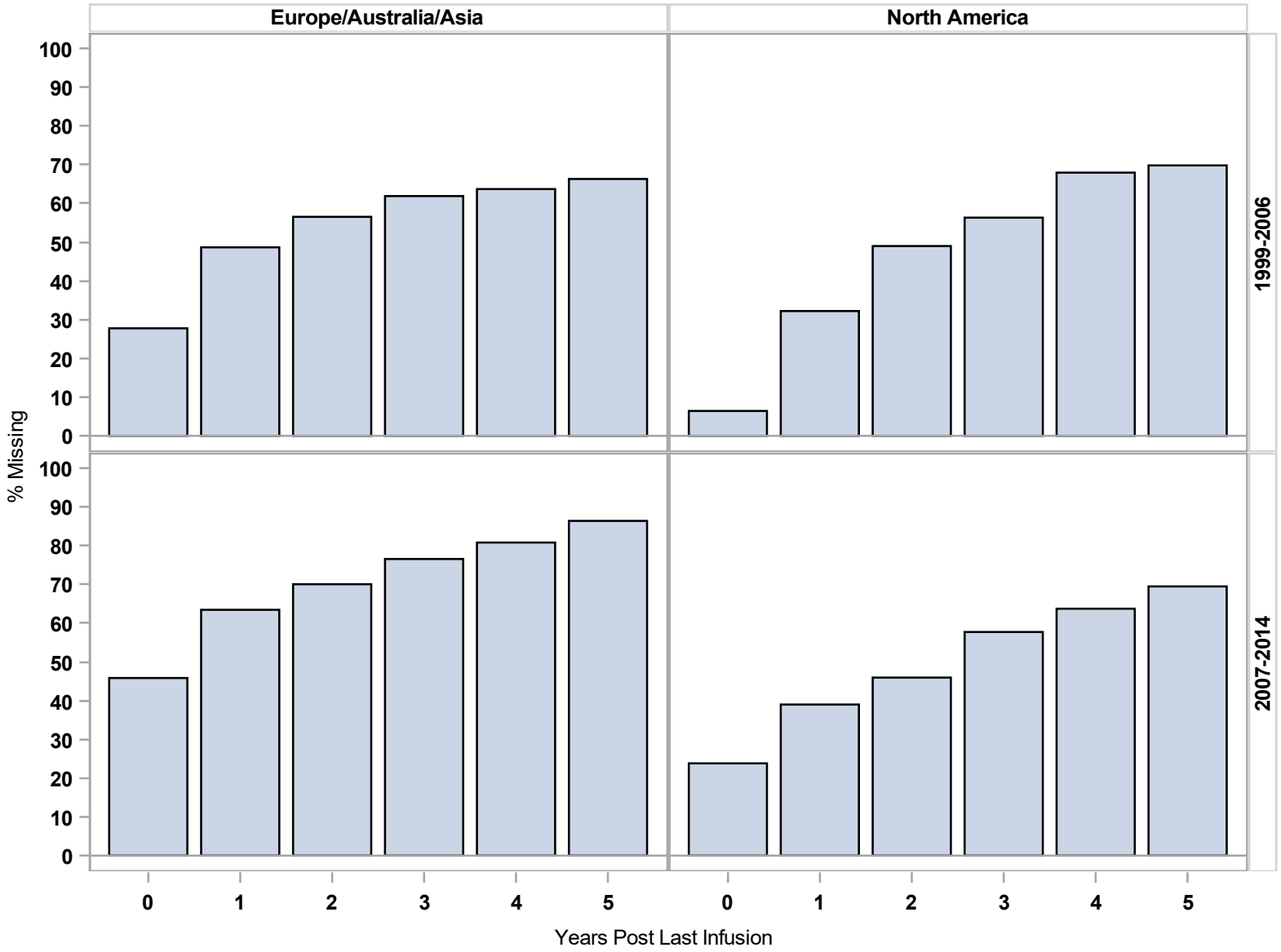

Exhibit 8 – 12
Missing Data for Cholesterol by Era and Continent

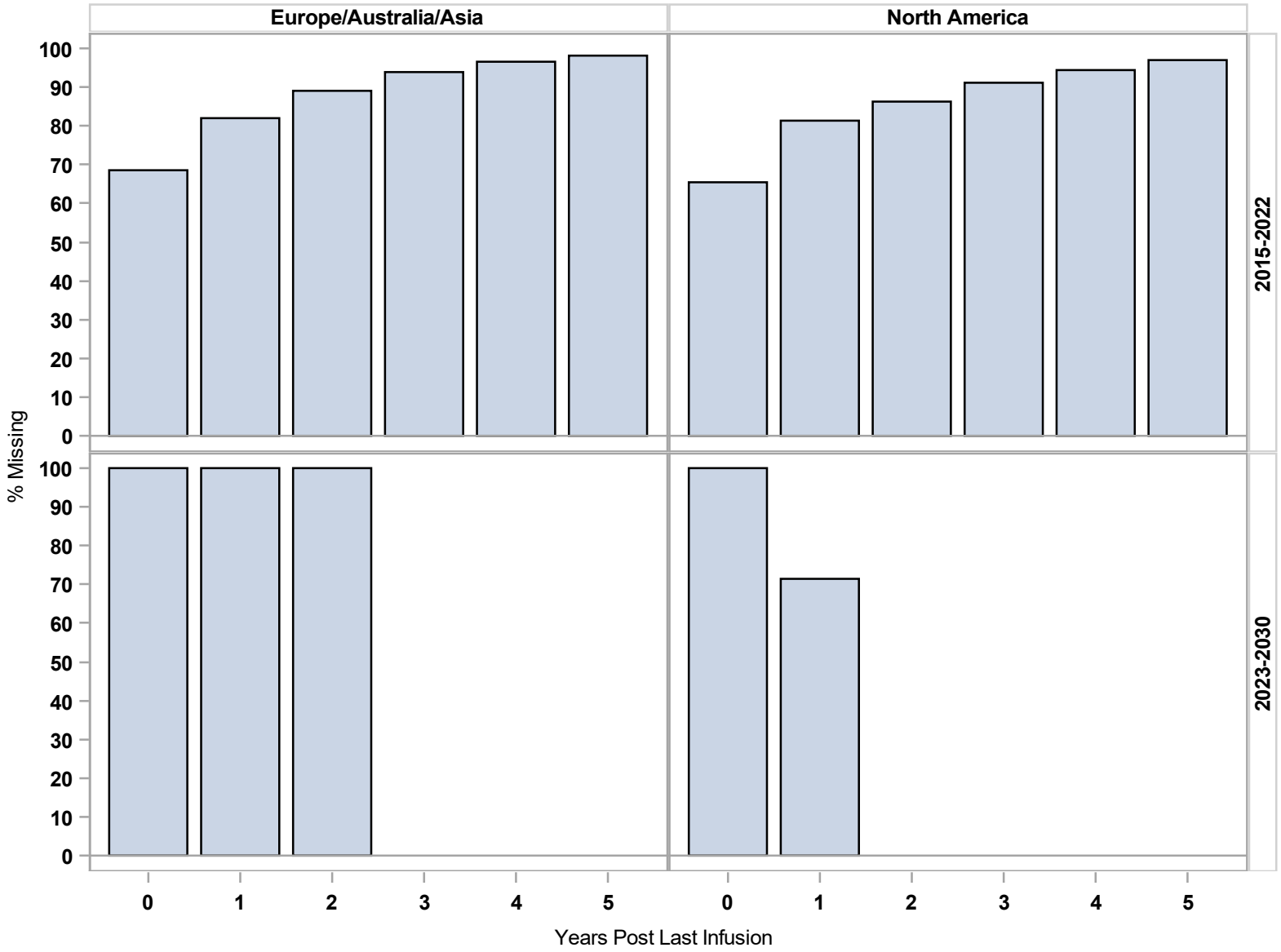

Exhibit 8 – 13
Missing Data for HDL by Era and Continent

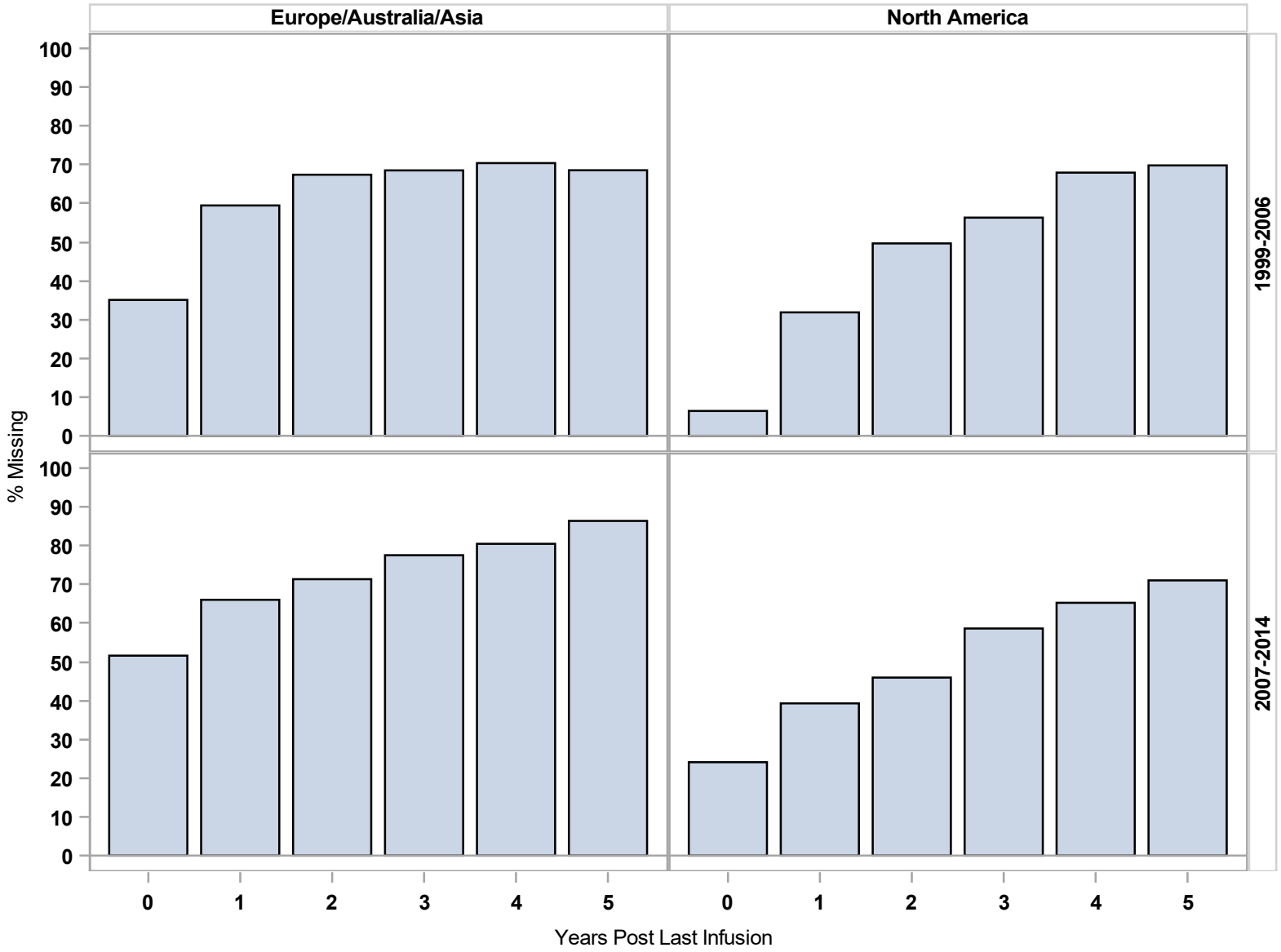

Exhibit 8 – 13
Missing Data for HDL by Era and Continent

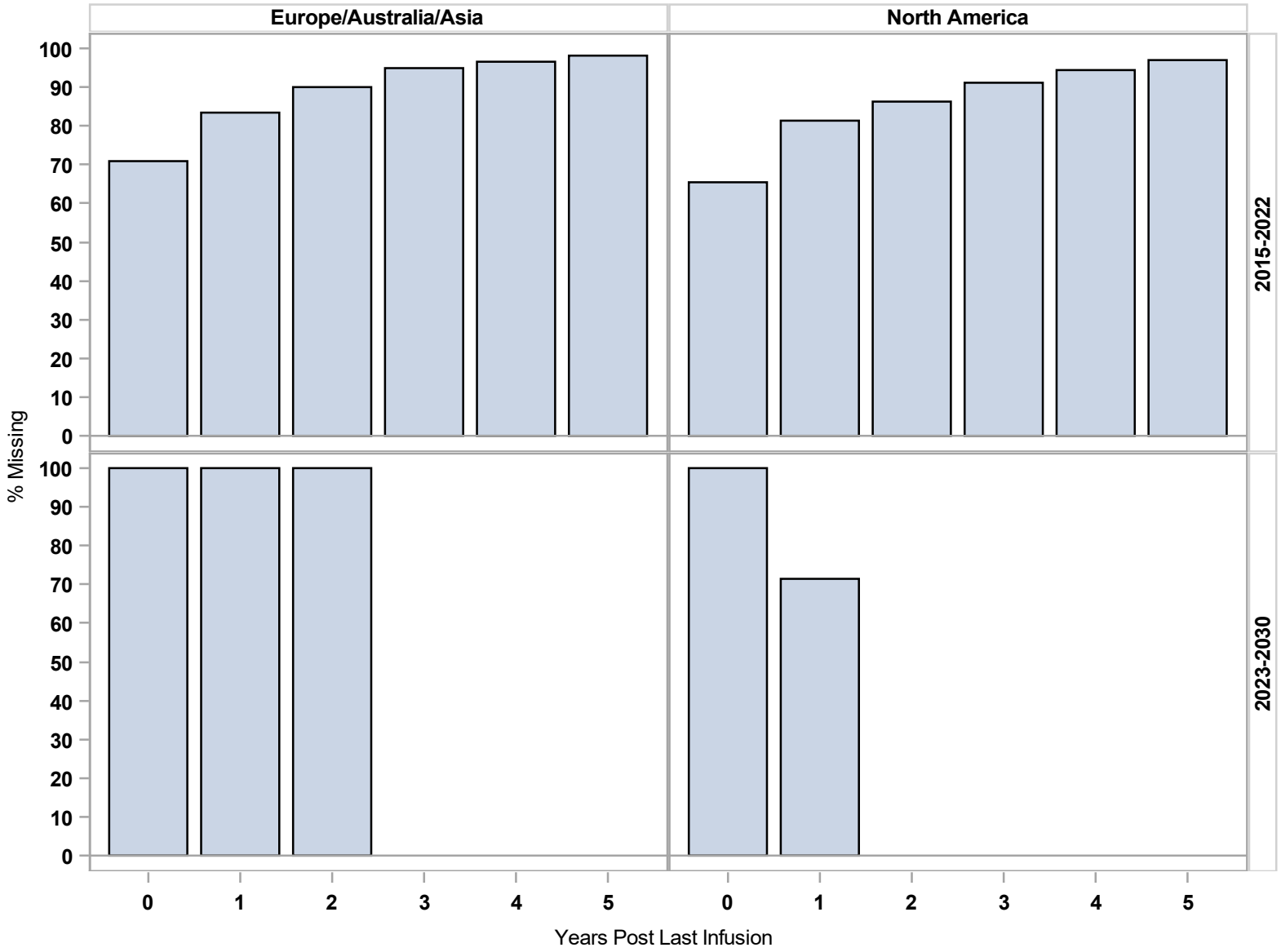

Exhibit 8 – 14
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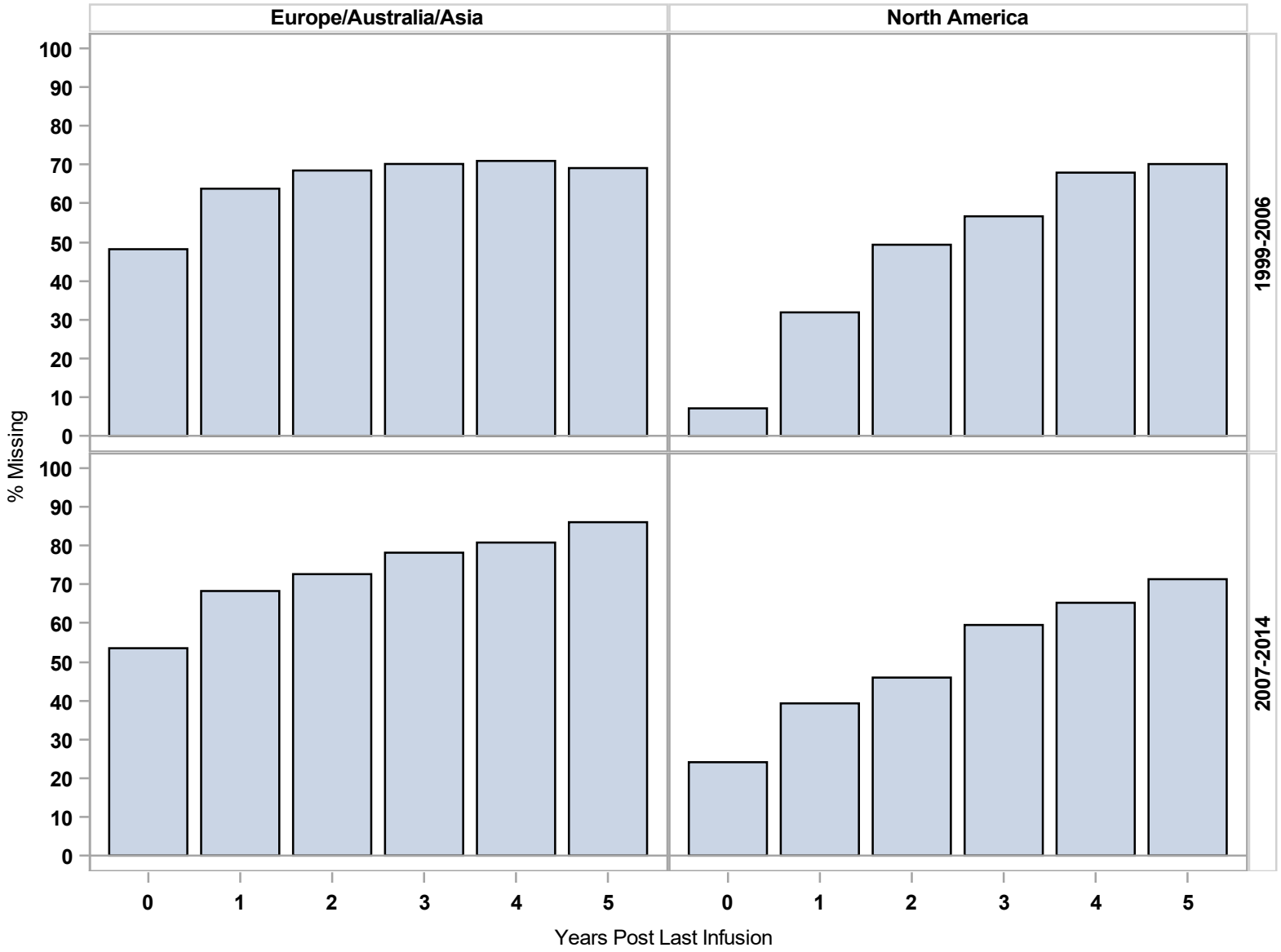

Exhibit 8 – 14
Missing Data for LDL by Era and Continent

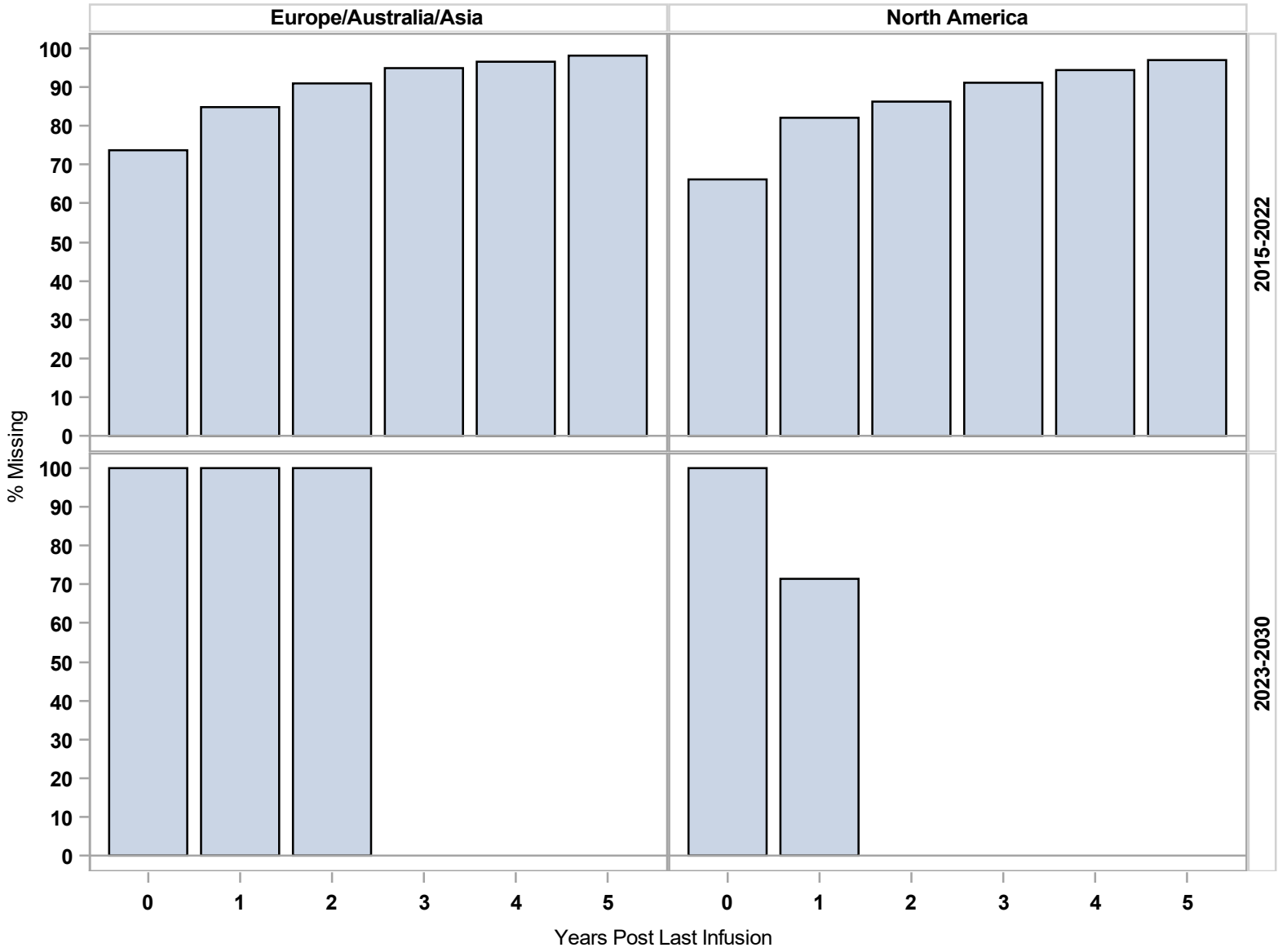

Exhibit 8 – 15
Missing Data for Triglycerides by Era and Continent

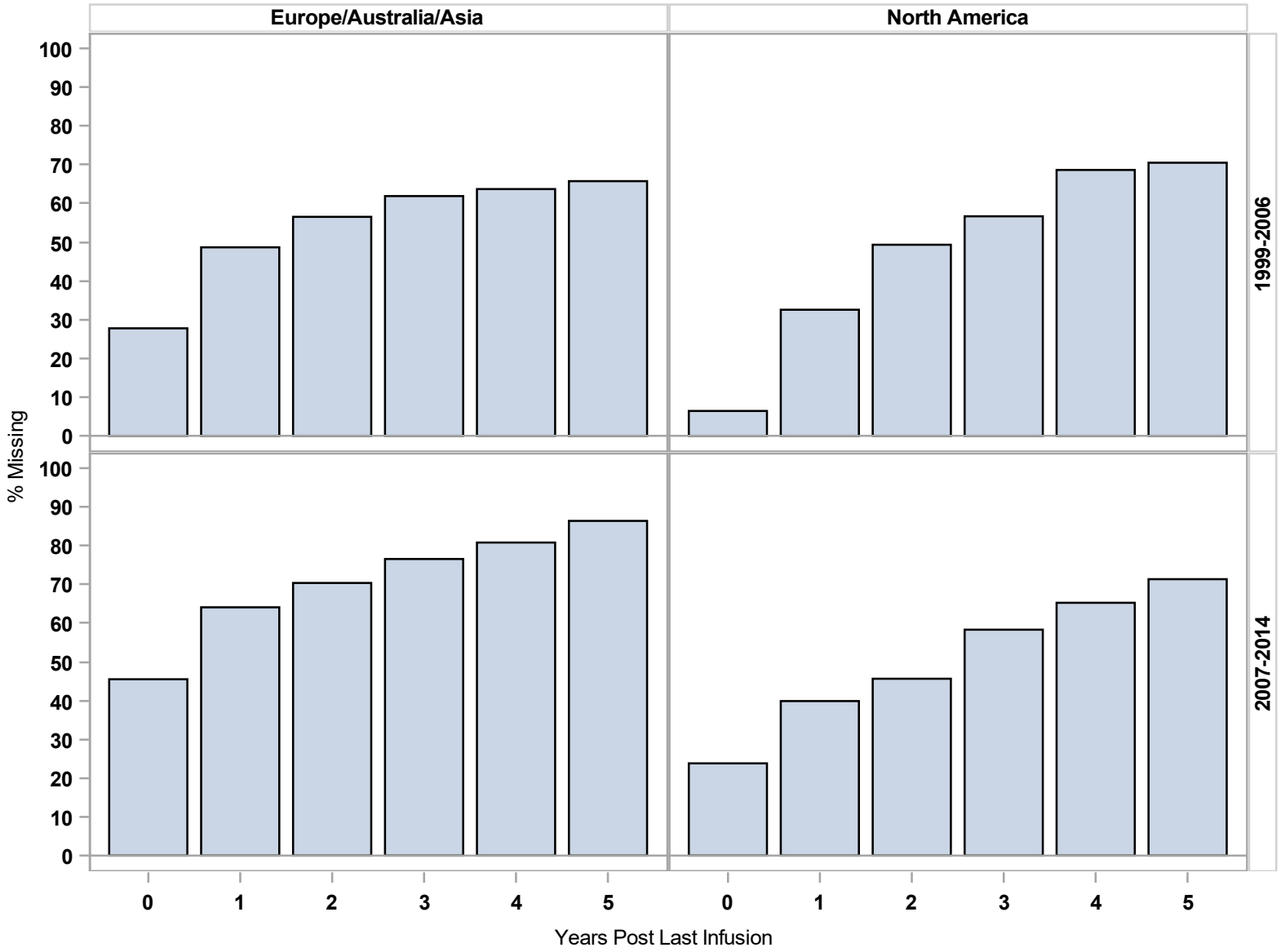

Exhibit 8 – 15
Missing Data for Triglycerides by Era and Continent

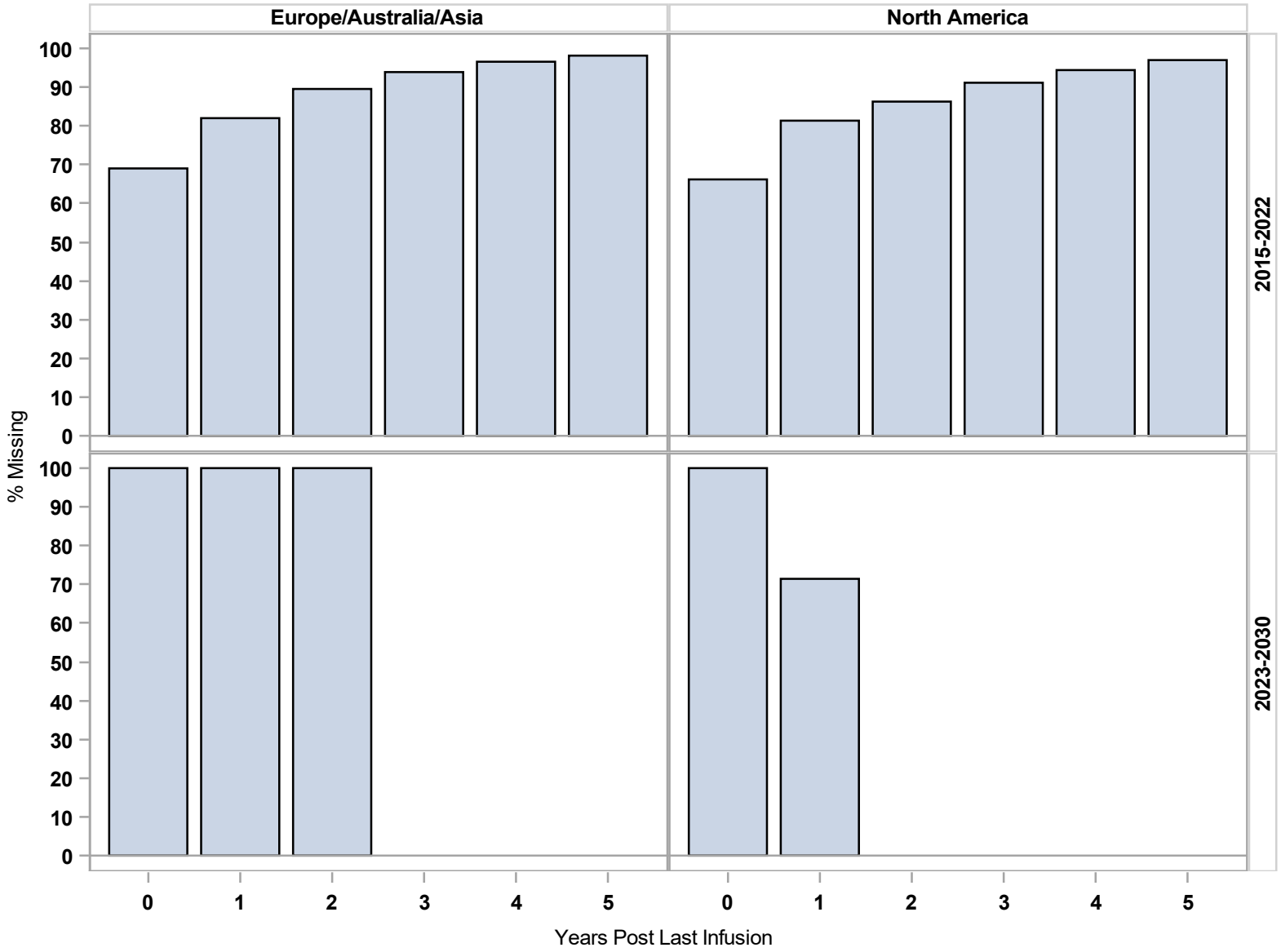

Exhibit 8 – 16
Missing Data for Bilirubin by Era and Continent

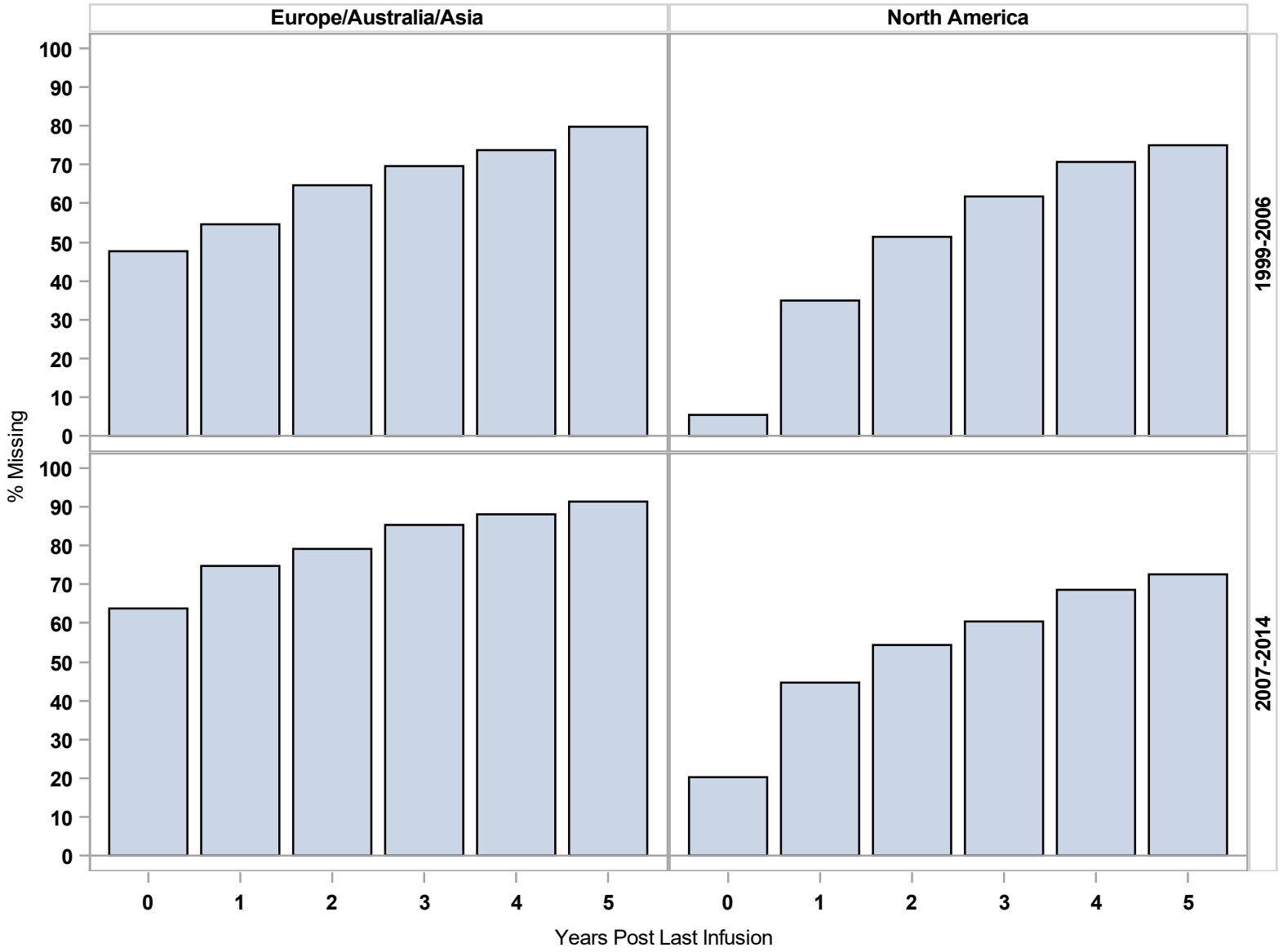

Exhibit 8 – 16
Missing Data for Bilirubin by Era and Continent

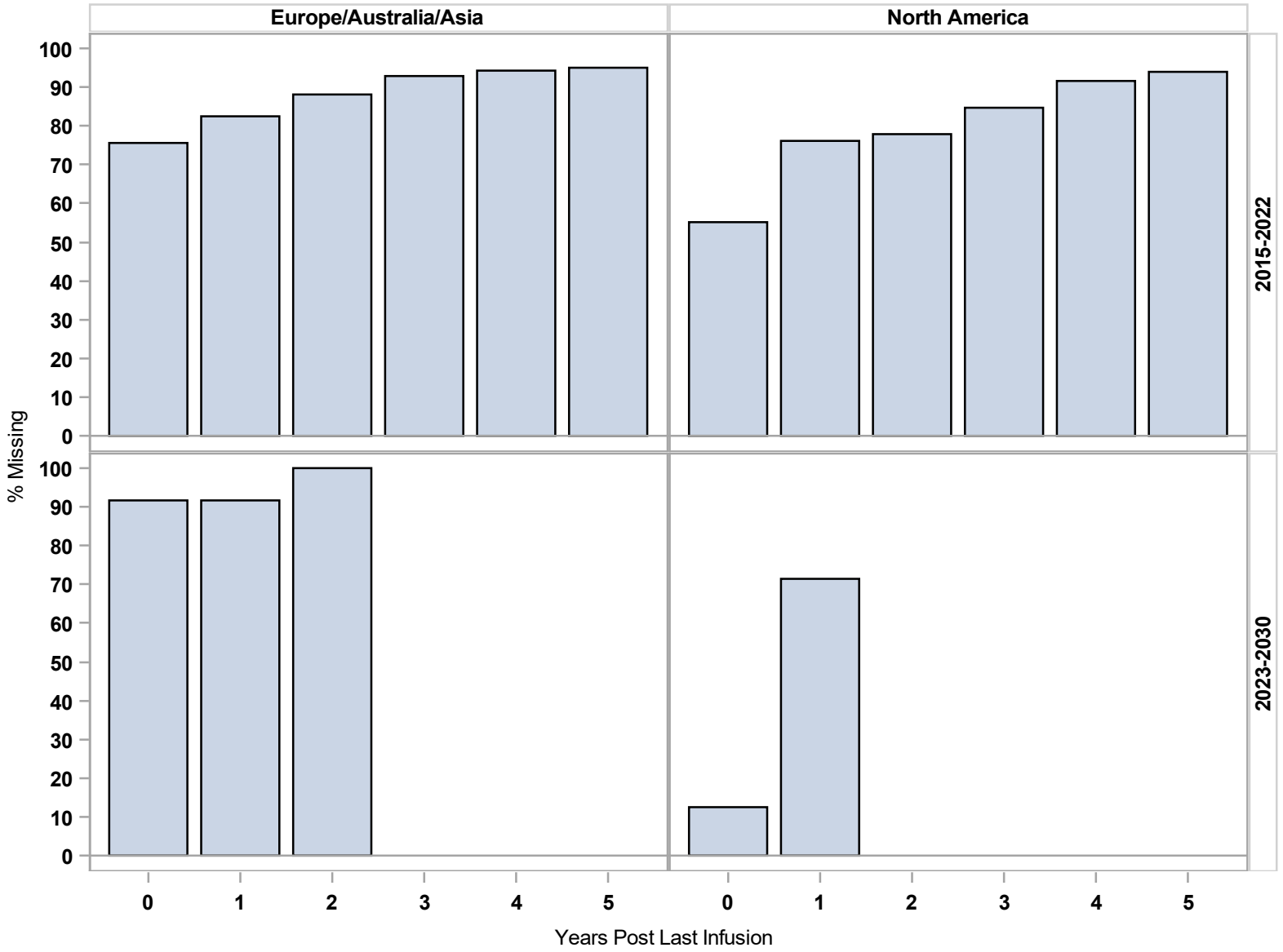

Exhibit 8 – 17
Missing Data for ALT by Era and Continent

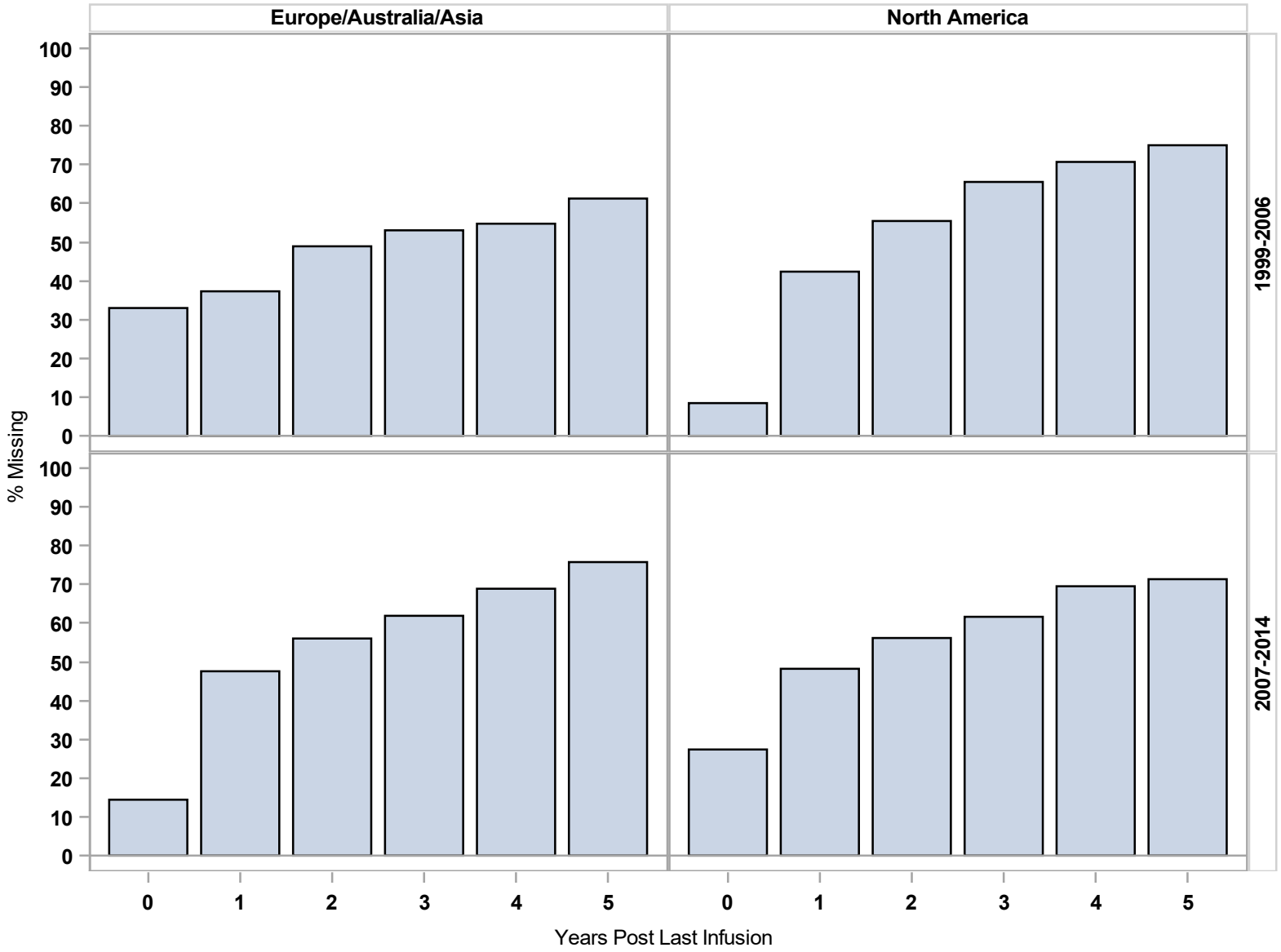

Exhibit 8 – 17
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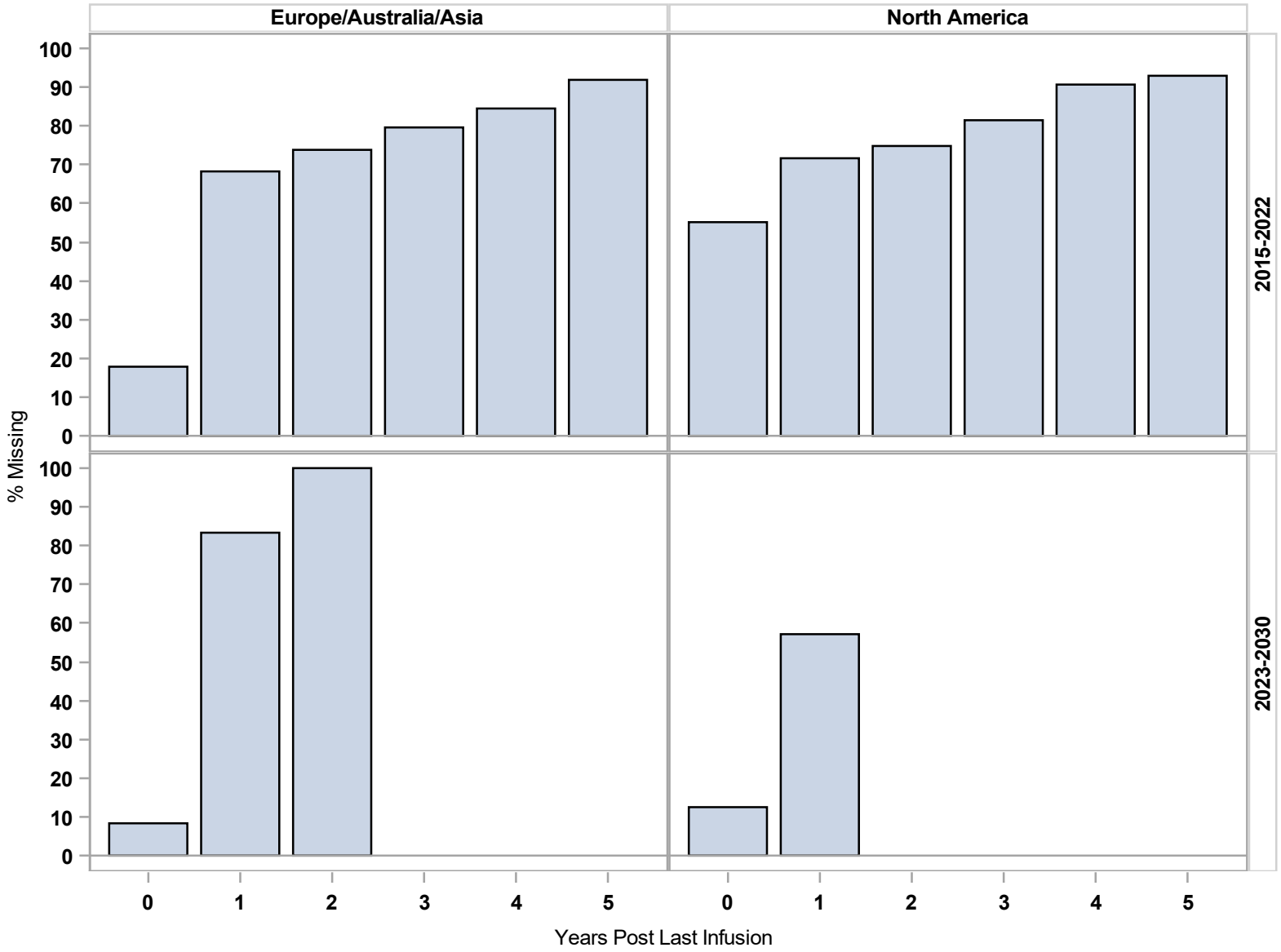


Exhibit 8 – 18
Missing Data for AST by Era and Continent

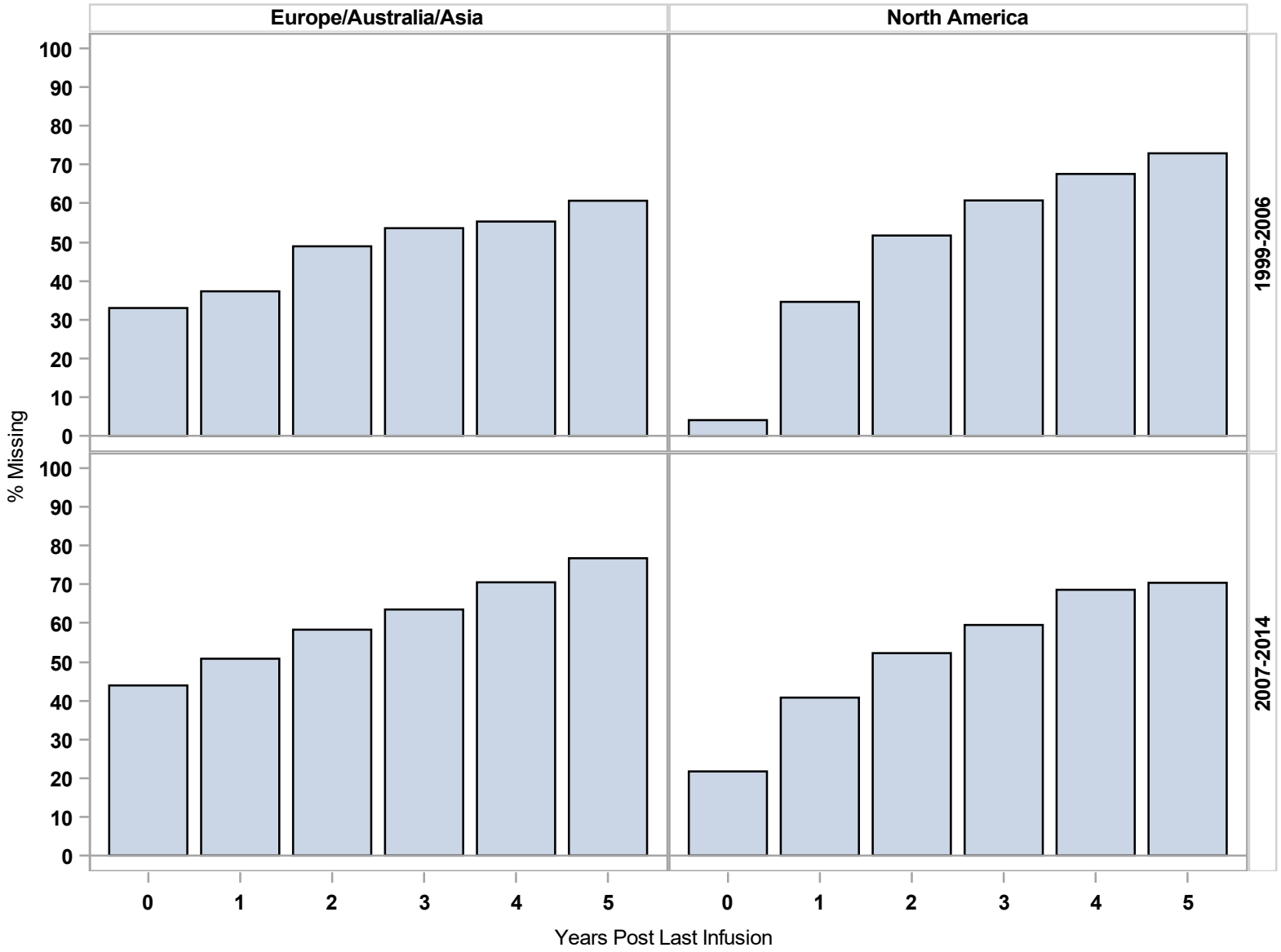


Exhibit 8 – 18
Missing Data for AST by Era and Continent

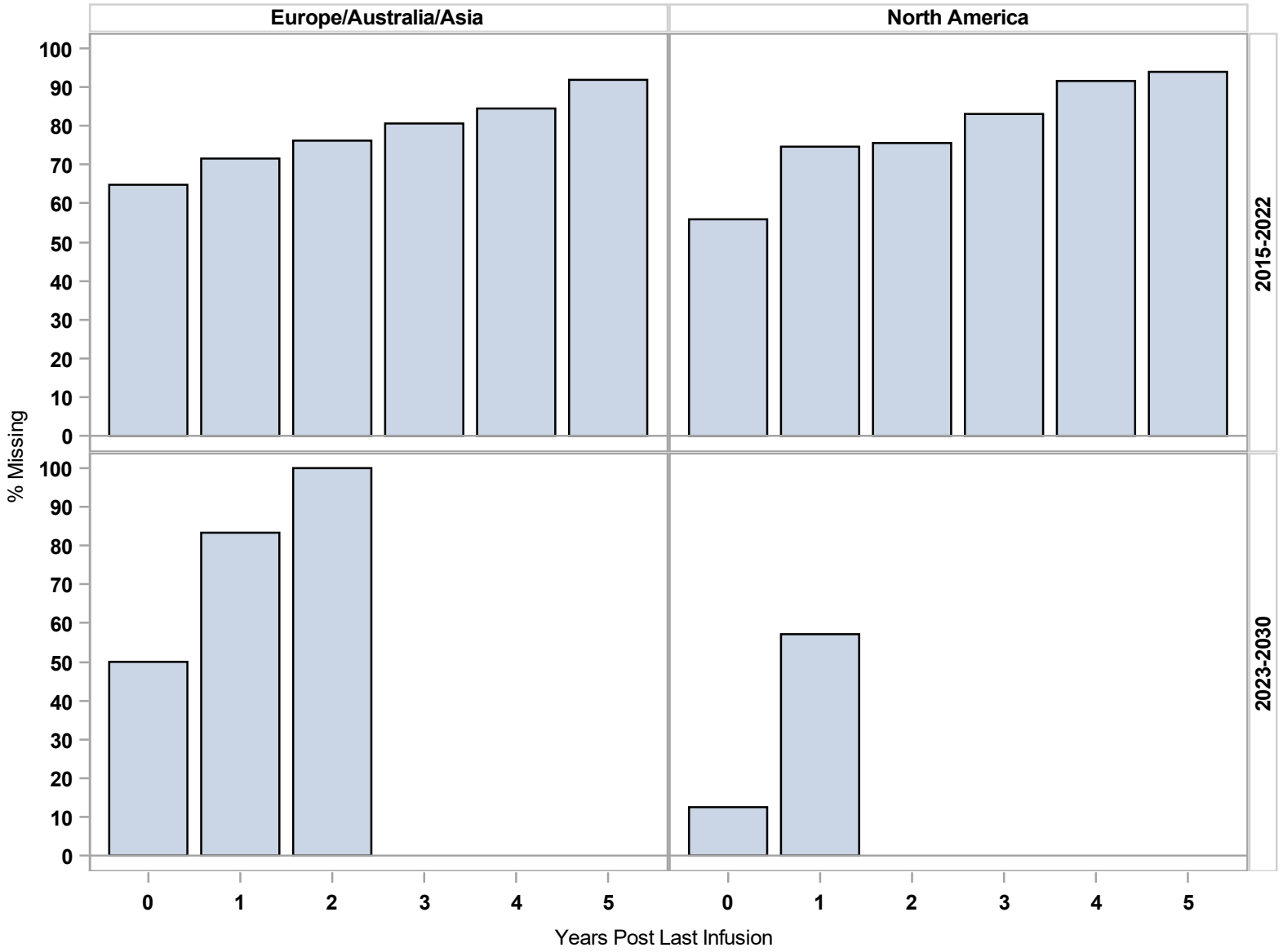


Exhibit 8 – 19
Missing Data for Alkaline Phosphate by Era and Continent

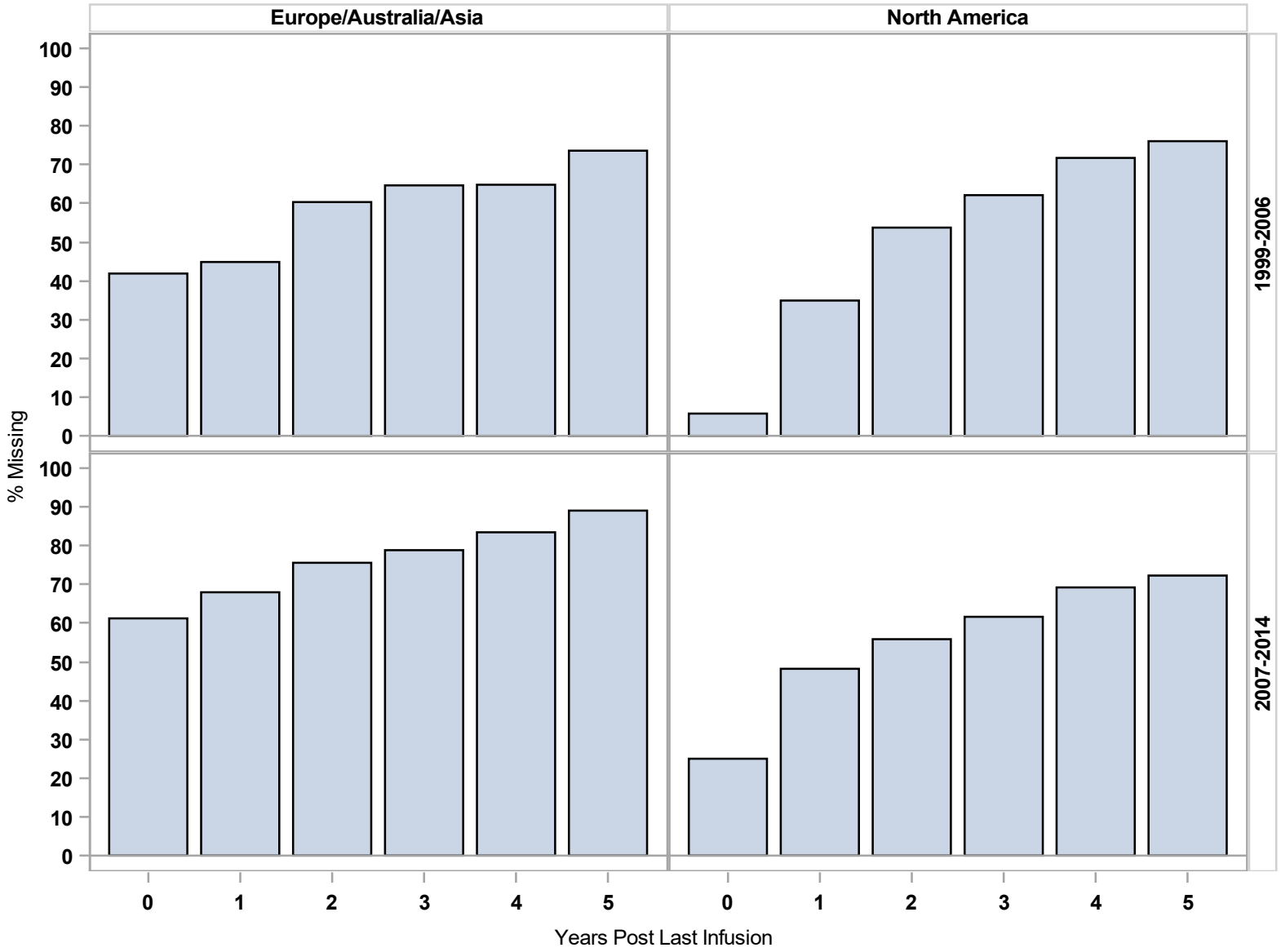
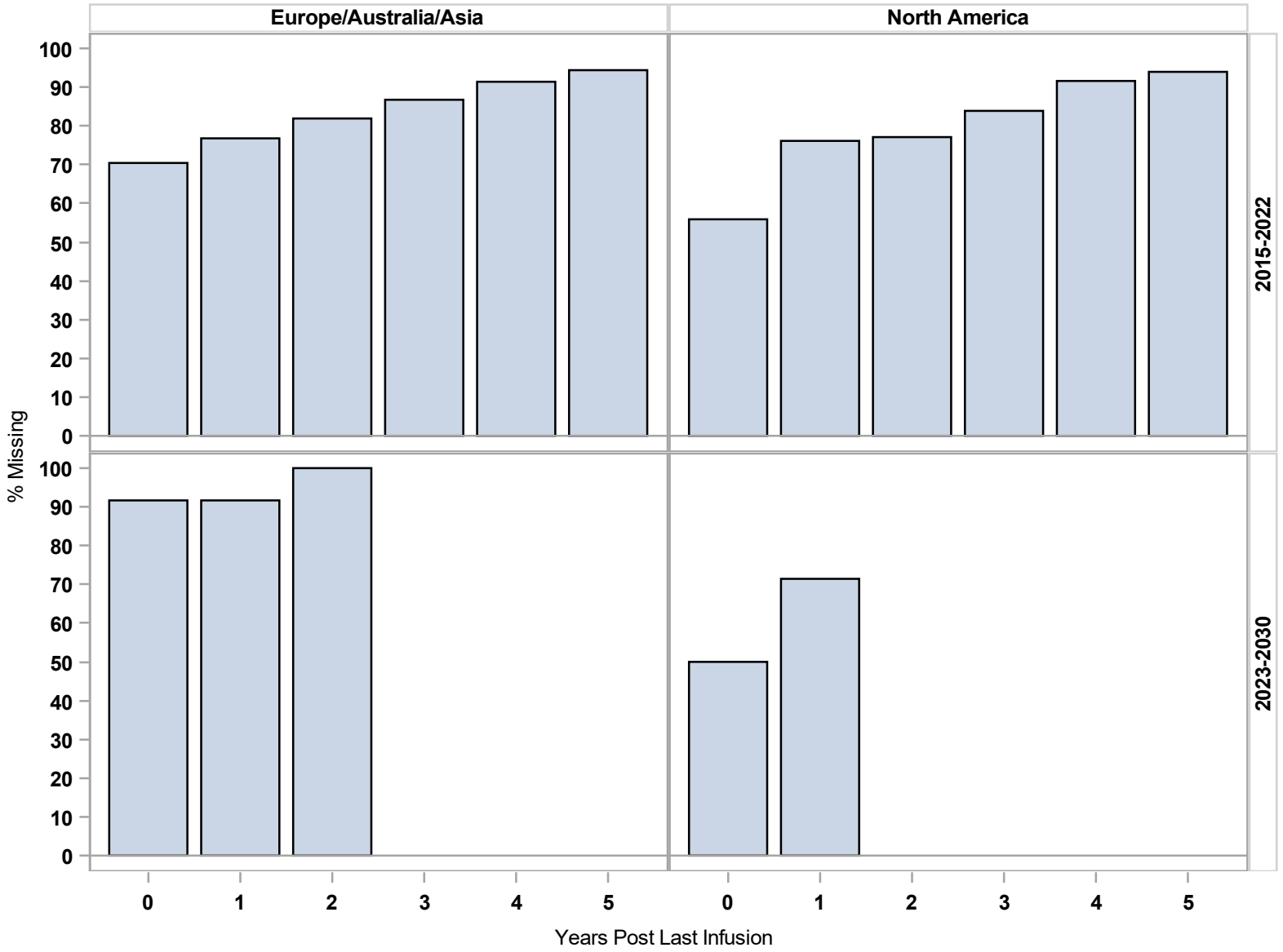


Exhibit 8 – 19
Missing Data for Alkaline Phosphate by Era and Continent



Appendix A: Islet Transplant Center Contributors

(Centers and Staff are listed in alphabetical order)
(=inactive sites; #=data not included in 12th Network Data Report)*

Baylor College of Medicine/
The Methodist Hospital*
Houston, Texas, USA
PI: John A. Goss
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Irene Harrison
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Paige Schock
Tiffany Zgabay

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Dallas, Texas, USA
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Michelle Acker
Jumana Ahmed
Jessica Clark
Lorie Estrada
Anne Farrow
Mariana Hurutado
Peter Kim
Taryn Kruse
Barbara Lilly
Bashoo Naziruddin
Sharon Primeaux
Ana Rahman
Mario Reyes
Madelyn Ricco
Rehma Shabbir
Ashanti Smith
Sammi Swaim
Morihito Takita
Edgar Vecino

Benaroya Research Institute*
Seattle, Washington, USA
PI: Carla Greenbaum
Marli McCulloch-Olson

Brussels Free University
Brussels, Belgium
PI: Robert Hilbrands
PI: Daniel Jacobs-Tulleneers-Thevissen
Pieter Gillard
Diedert De Paep
Veerle Kemels
Ursule Van de Velde

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PI: Paul Gores
Craig Halberstadt
Melissa McGraw
Grace Sauzier
Deana Williams

Columbia University
New York, New York, USA
PI: Beth Schrope
Jeanine Genkinger
Maya Ginsburg
Yi Lu
Vilma Rosario
Yvette Tanhehco
Kristin Shepperd

Emory Transplant Center
Atlanta, Georgia, USA
PI: Christian Larsen
Jose Cano
Sallie Carpentier
Erica Hudson
Lynn Layman
Nicole Turgeon

Geneva University Hospital/
GRAGIL Network
Geneva, Switzerland
Grenoble
PI: Pr Sandrine Lablanche
Data manager: Laure Nasse

Lyon
PI: Dr Fanny Buron
Data manager: Celine Dagot

Montpellier
PI: Dr Orianne Villard
Data manager: Mme Manal Al Masri

Geneva
PI: Thierry Bernet
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Institute for Clinical and Experimental
Medicine (IKEM)
Prague, Czechia
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