Eleventh Allograft Report

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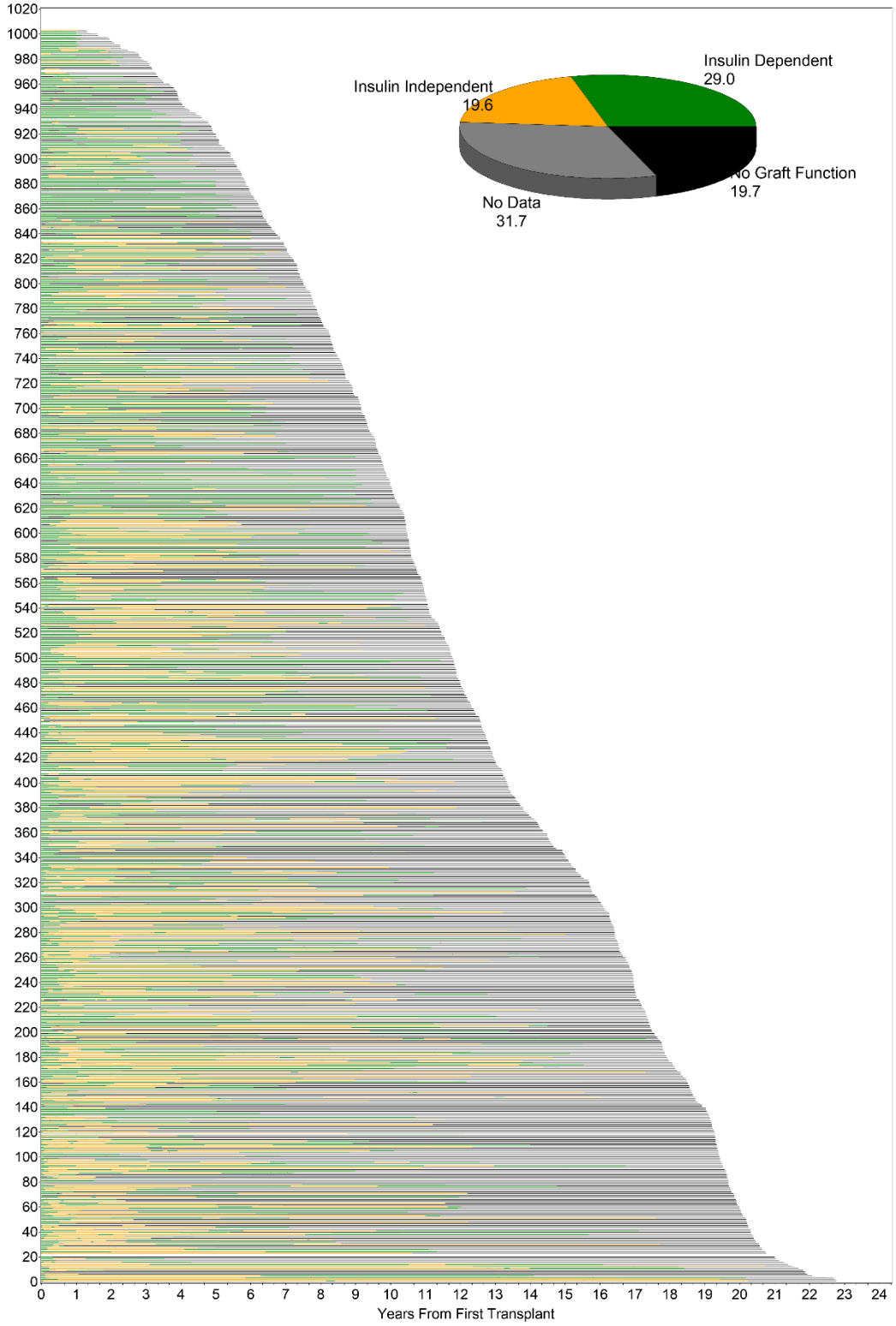


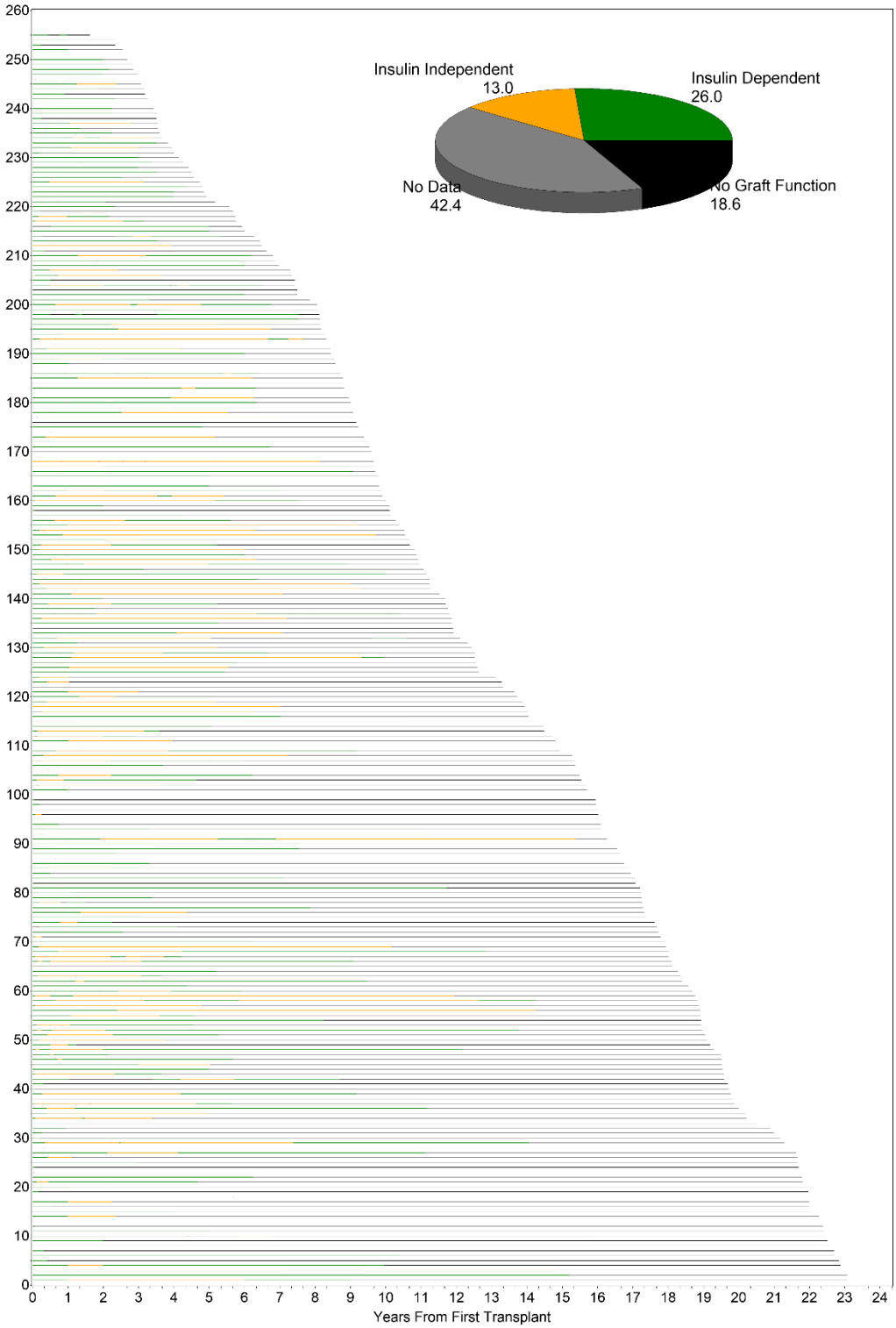
Collaborative Islet Transplant Registry 2022

Islet transplant alone (ITA, N=1,108)

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 2022

Islet after kidney, simultaneous islet-kidney, or kidney after islet (IAK/SIK/KAI, N=291)

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

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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 Annual Reports. This eleventh allograft report summarizing Registry progress summarizes information on patients who received one or more islet cell transplants between 1999 and 2020. All CITR Annual Reports are public and can be downloaded or requested in hard copy at www.citregistry.org.

Status and History

This report focuses on 1,399 islet allograft recipients (1,108 islet alone, 236 islet after kidney, 49 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 15, 2020, a total of 1,233 autologous islet transplant recipients were registered in CITR. Results on the autograft transplants are summarized in a separate report.

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

CITR 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

The current report represents a 29% increase in the number of recipients, a 32% increase in the number of infusion procedures, and 27% increase in donors, compared to the 10th Report.

Data Sources

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

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

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

Study Endpoints

The primary endpoints presented in this report are:

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

Secondary endpoints include:

- Average daily insulin and percent of baseline insulin
- Fasting plasma glucose
- Laboratory indicators of complications of diabetes and major organ function
- Metabolic testing
- 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 Kaplan-Meier time-to-event or Survival estimates and by Cox proportional hazards regression using relevant baseline factors as stratifying or adjusting covariates.

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

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

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

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

Statistical significance of univariate analyses not adjusted for repeated testing or other covariates, is shown for a number of the Exhibits. These are considered observed, nominal p-values outside of any pre-planned Type I error structure. In drawing any conclusions, readers should be mindful that the significance levels control for random variance, but not systematic biases in the data nor multiple testing. Nominal statistical significance of analyses presented in other CITR Annual 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 effects. The results of these models should be viewed as preliminary due to the relatively large number of factors, the effect of outliers and highly skewed distributions for many of the factors, and the associations among the factors.

The CITR data are analyzed to characterize the possible outcomes or states that an individual can experience following islet cell transplantation. Such analyses may help elucidate both biological factors affecting outcomes and clinically meaningful predictors of achievement and durability of success. Figure 1 presents one view of the possible states following the first of one to several infusions:

individuals can have immediate islet cell failure (primary non function), or they can enter either the insulin dependent or insulin independent states. An individual may change from one state to another before re-infusion: if insulin independence is achieved, it might be lost; other than primary non-function, islet failure can subsequently occur; finally, a subsequent infusion can be performed. Time-to-event models can be used to investigate the effect of pre-infusion patient, donor and islet characteristics on these outcomes after first infusion.

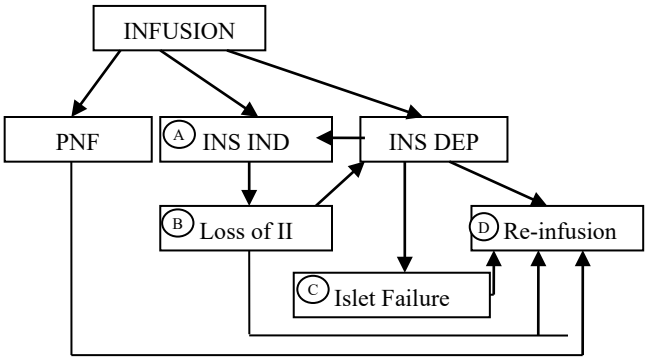


Figure 1. Possible states post first infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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

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

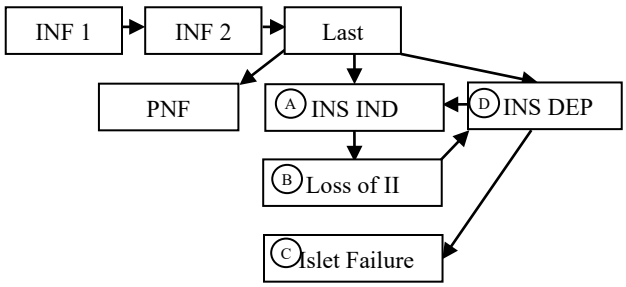


Figure 2. Possible states post last infusion (PNF=Primary non-function; INS IND, II=Insulin Independent; INS DEP=Insulin Dependent).

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

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 15, 2020**. 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 February 15, 2022 based on the recipients that had been registered for CITR at the December 15, 2020 participant registration closure date.**

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

Definitions

Several key terms used by CITR in the 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 2020, 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 1,108 islet transplant alone (ITA) and 285 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 1,399 allogeneic, human-to-human islet transplant recipients. In 2020, two North American sites reported performing allogeneic islet transplantation; both 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, 694 (91.4%) of 759 islet allograft recipients and 1,373 (88.9%) of all islet allograft infusion procedures performed in North America from 1999-2020 are included in this report.

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

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

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

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

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

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

Infusions

A summary of the total 2,832 North American and international islet allograft infusions by year of infusion is included in Exhibit 1-5. These infusions derived from 3,326 total donors: 2,540 (89.7%) were single donor preparations and 292 (10.3%) were multiple (2 or more) donor preparations.

Three hundred eighty-three (383) recipients (27.4%) have received a single islet infusion at the time of this report, 673 (48.1%) received a total of two infusions, 286 (20.4%) received three infusions, and 57 recipients (4.1%) received a total of four to six islet infusions (Exhibit 1-7).

Of the 1,399 islet allograft recipients presented in this report, 1,108 (79.2%) are islet alone recipients, 236 (16.9%) are islet after kidney recipients, 49 (3.5%) were islet simultaneous with kidney, and 6 (0.4%) were kidney after islet. Sixteen islet alone recipients and five islet after kidney recipients later received a pancreas transplant.

CITR Allografts Overall

There has been a 28.8% increase in the number of allograft recipients reported to the Registry since the last Annual Report, as well as a 31.7% increase in the total number of islet allograft infusion procedures reported.

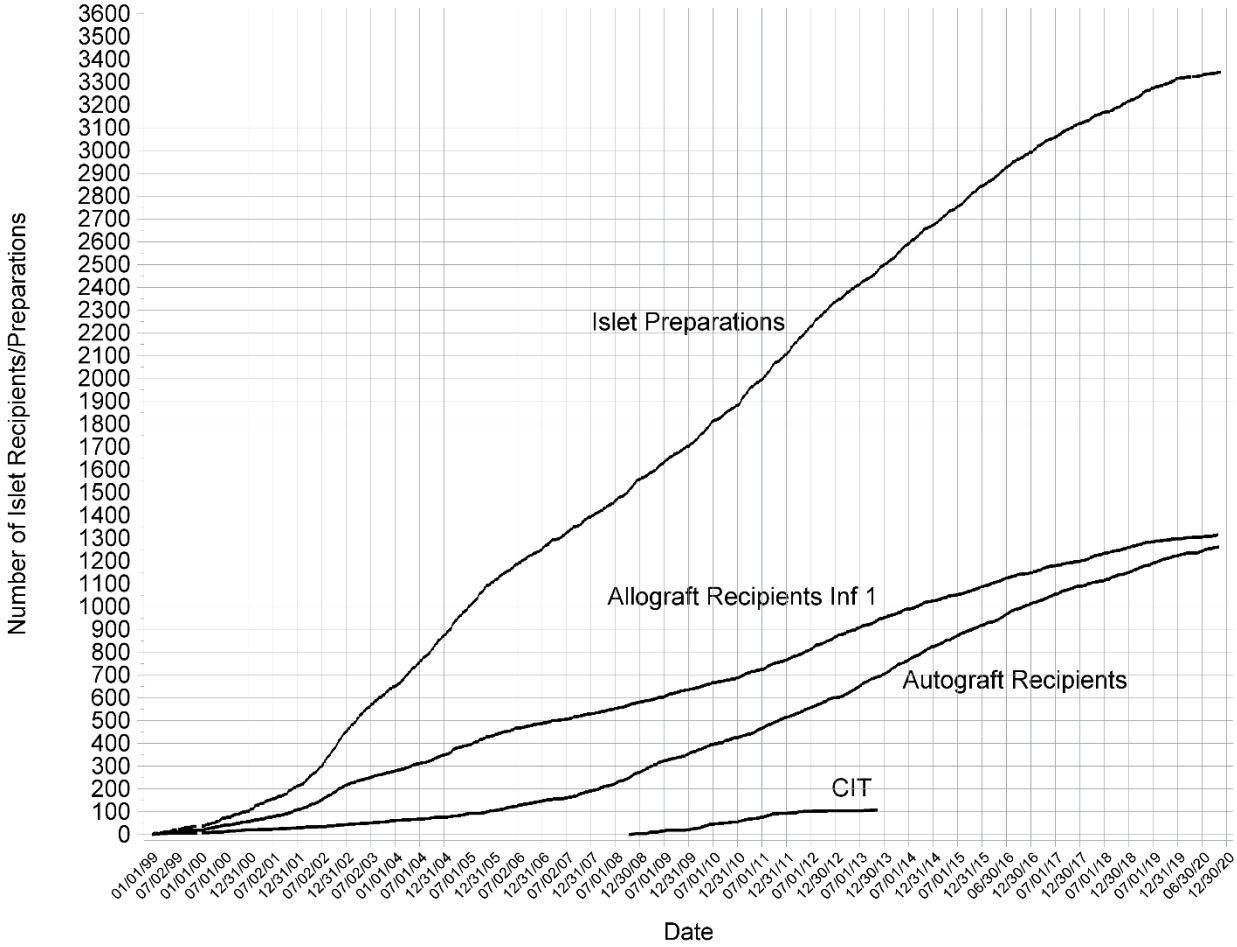
Autografts

There have been 1,123 North American and 110 international autograft consenting recipients registered in the Registry. A brief supplemental Report will present analyses for autologous islet transplants.

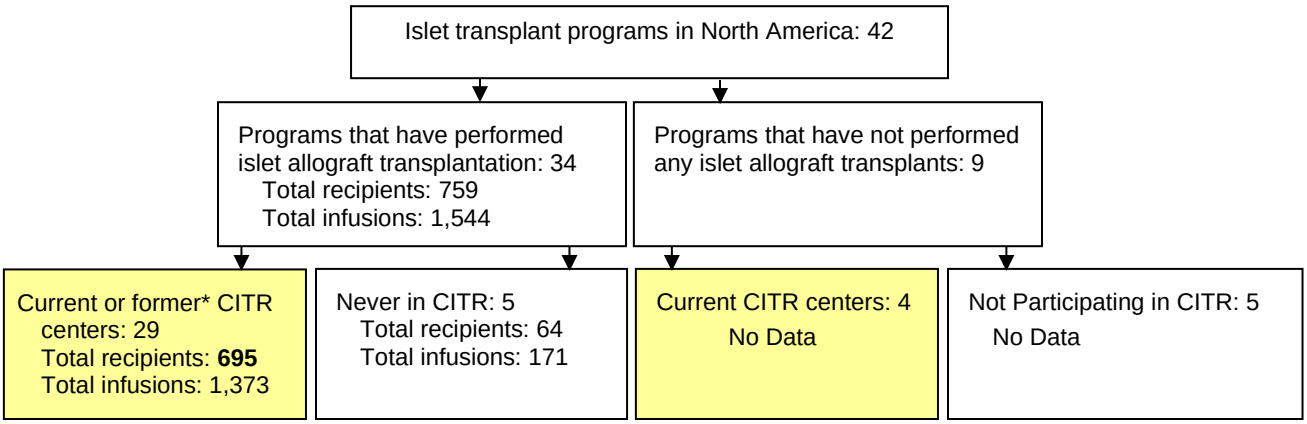
Exhibit 1 – 1A
CITR Allograft Recipients, Infusions and Donors by International Sites and by ITA/IAK/SIK/KAI
Consented, Registered and First Infused in 1999-2020

	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	**1108**	579	529	**236**	86	150	**49**	1	48	**6**	3	3	**1,399**
Infusions	**2,284**	1,208	1,076	**440**	157	283	**95**	1	94	**13**	7	6	**2,832**
Donors	**2,719**	1,271	1,448	**496**	167	329	**98**	1	97	**13**	7	6	**3,326**

Exhibit 1 – 1B
Cumulative Enrollment in CITR by Module



NORTH AMERICAN CENTERS
Total Performed and Total Reported to CITR 1999-2020



Three North American centers reported performing at least one islet allograft infusion procedure in 2020. All of these centers participated in and reported the information to CITR.

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

Exhibit 1 – 2A
Islet Transplant Centers Reporting Data to CITR
Participating North American Centers 1999-2020

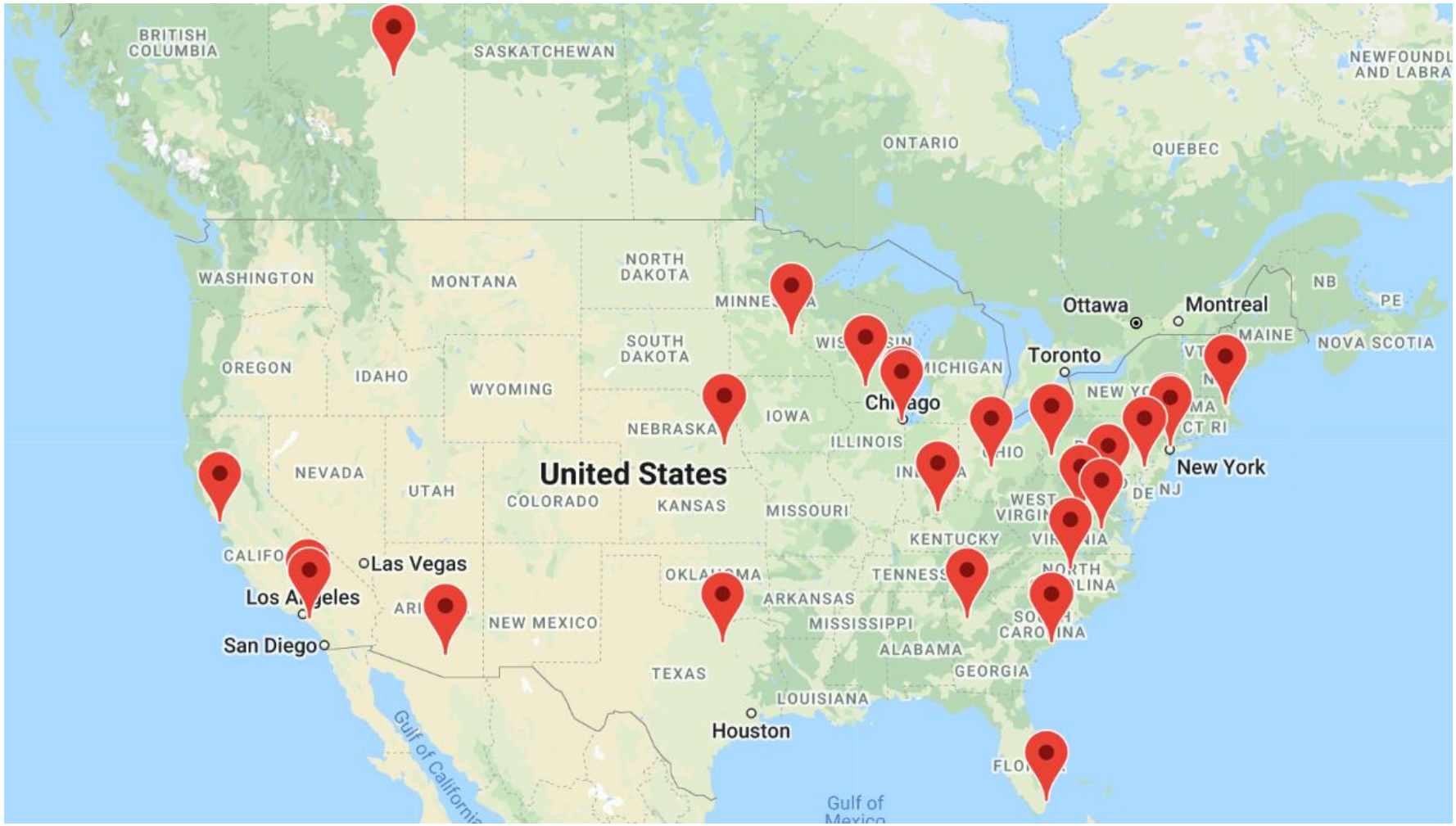


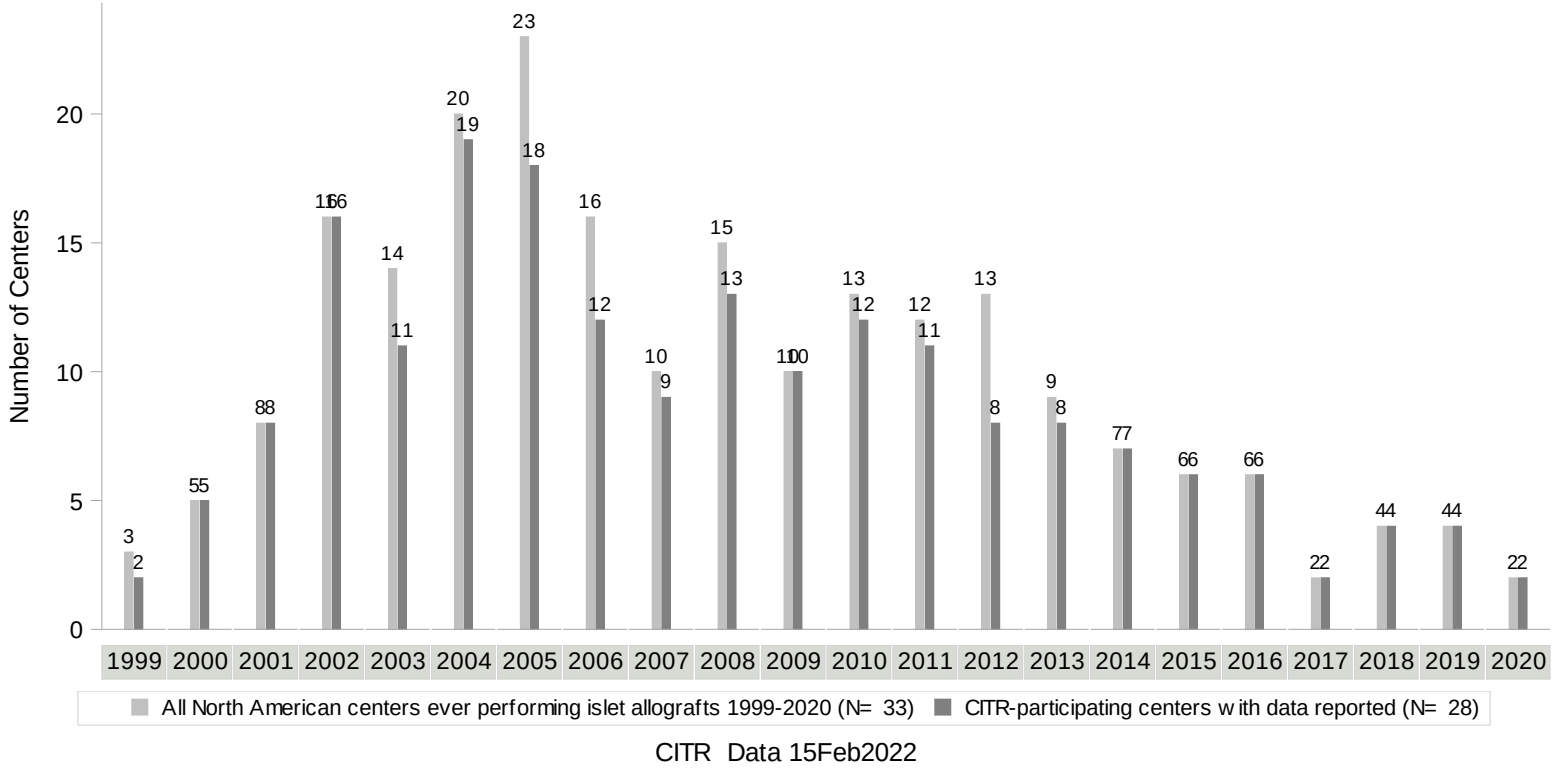
Exhibit 1 – 2B
Islet Transplant Centers Reporting Data to CITR
Participating European Centers 1999-2020

Exhibit 1 – 2C
Islet Transplant Centers Reporting Data to CITR
Participating Australian Centers 1999-2020

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 1999-2020



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

Exhibit 1 – 4A

Total Number of Islet Allograft Recipients Receiving Their First Islet Allograft Infusion and Number with Data Reported to CITR: Allograft recipients at CITR-Participating North American Islet Transplant Centers 1999-2020

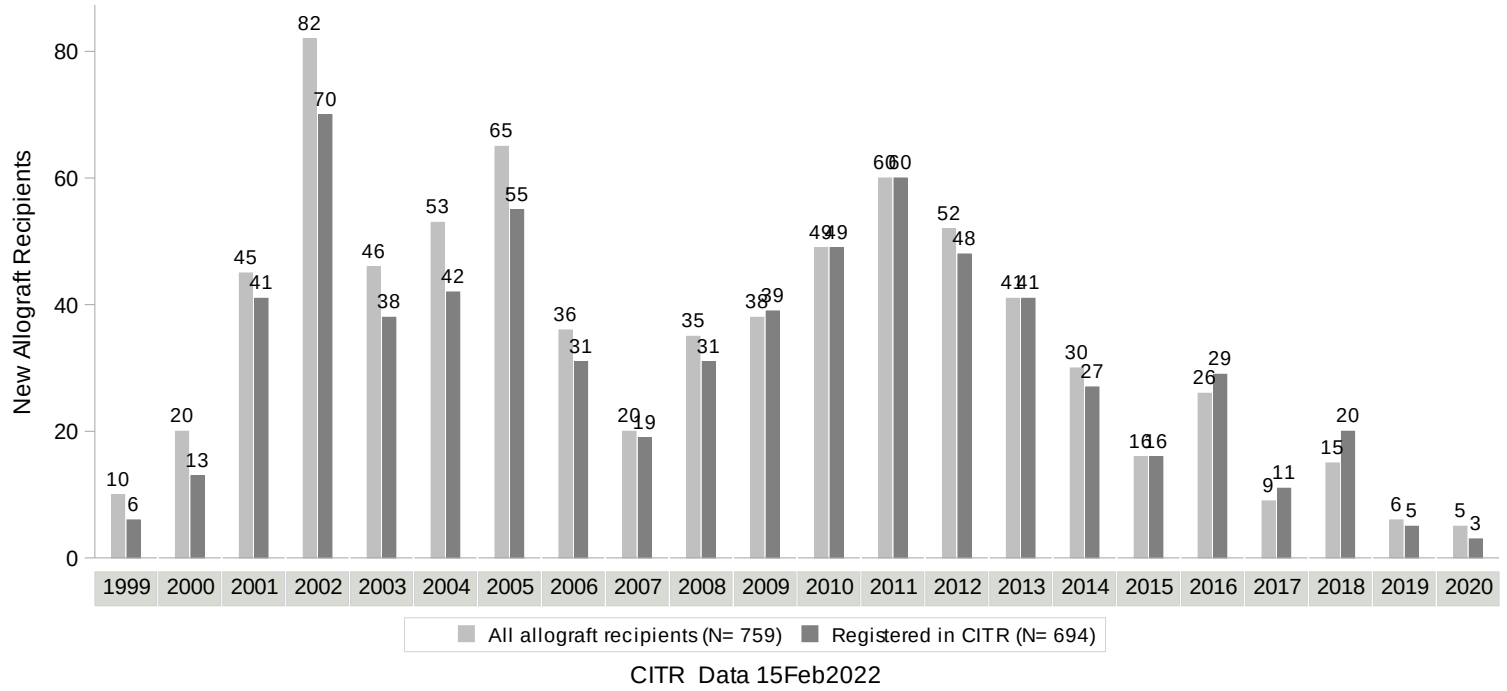
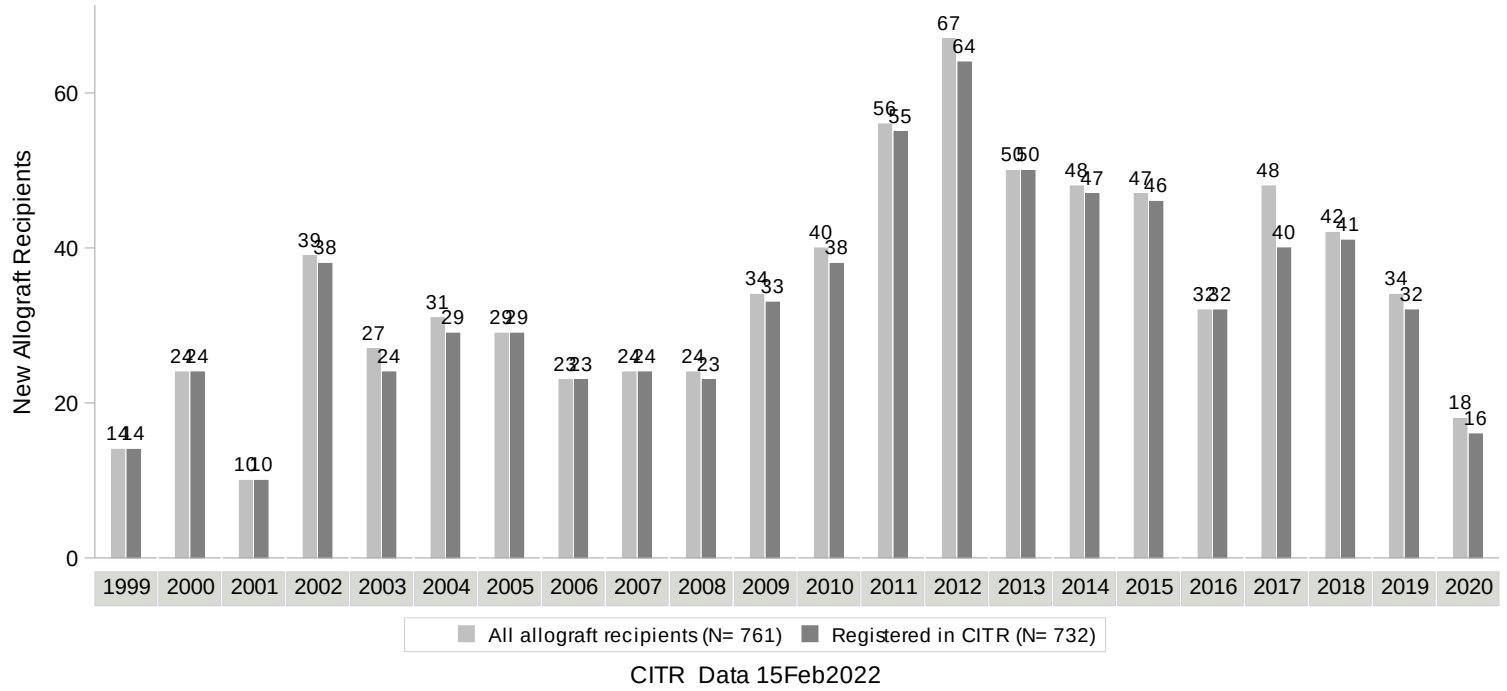


Exhibit 1 – 4B

Total Number of Islet Allograft Recipients Receiving Their First Islet Allograft Infusion and Number with Data Reported to CITR: Allograft recipients at CITR-Participating European and Australian Islet Transplant Centers 1999-2020



CITR Data 15Feb2022

Exhibit 1 – 5A

Total Number of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number: CITR-Participating North American Islet Transplant Centers, 1999-2021

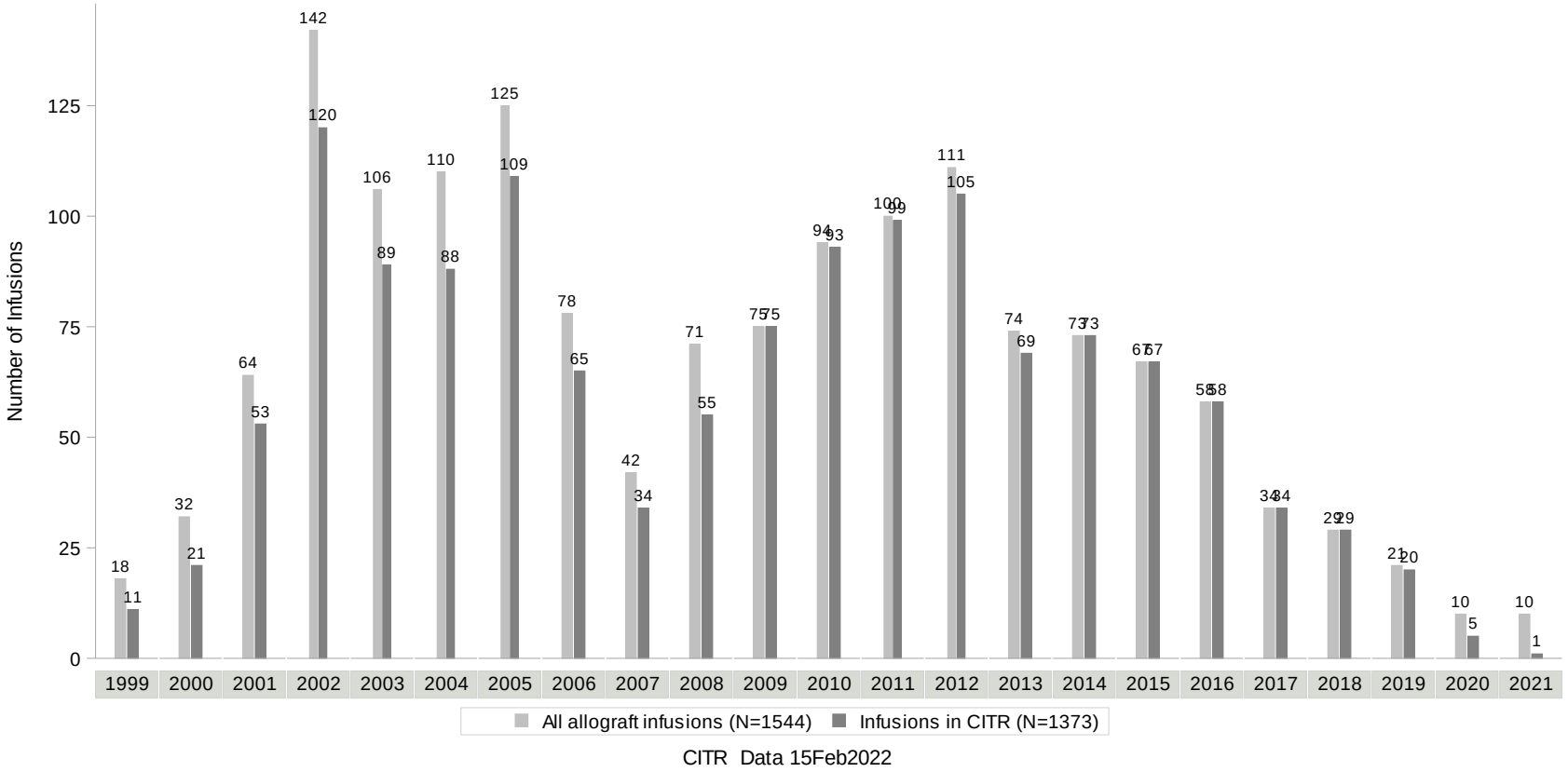


Exhibit 1 – 5B

Total Number of Islet Allograft Infusion Procedures Conducted and Entered in CITR Database, by Year and Infusion Procedure Number: CITR-Participating European and Australian Islet Transplant Centers, 1999-2021

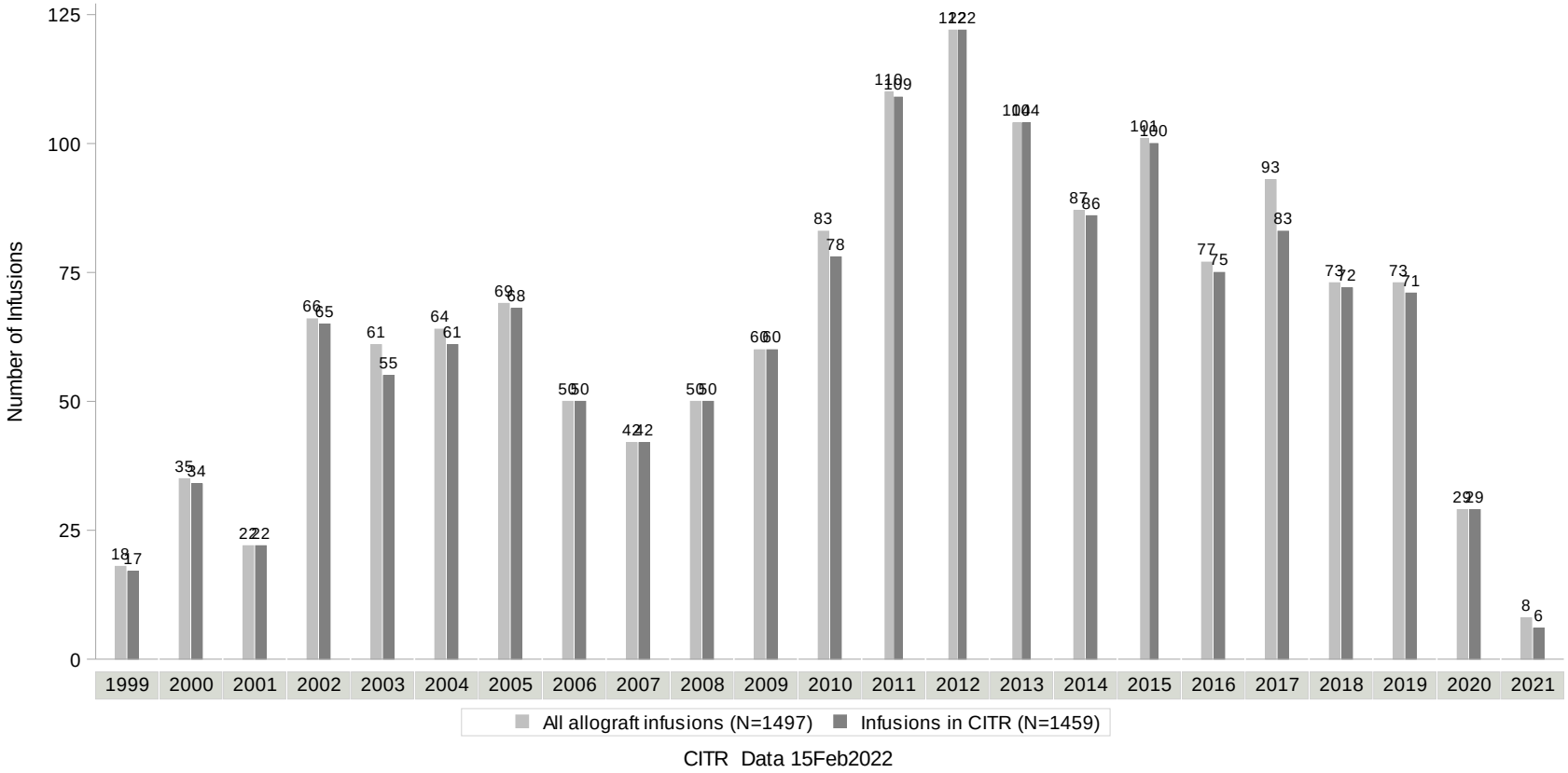


Exhibit 1 – 6A

<u>Islet Allograft Infusions</u> by Infusion Sequence Number and Year. CITR-Participating North American and International Centers, 1999-2021

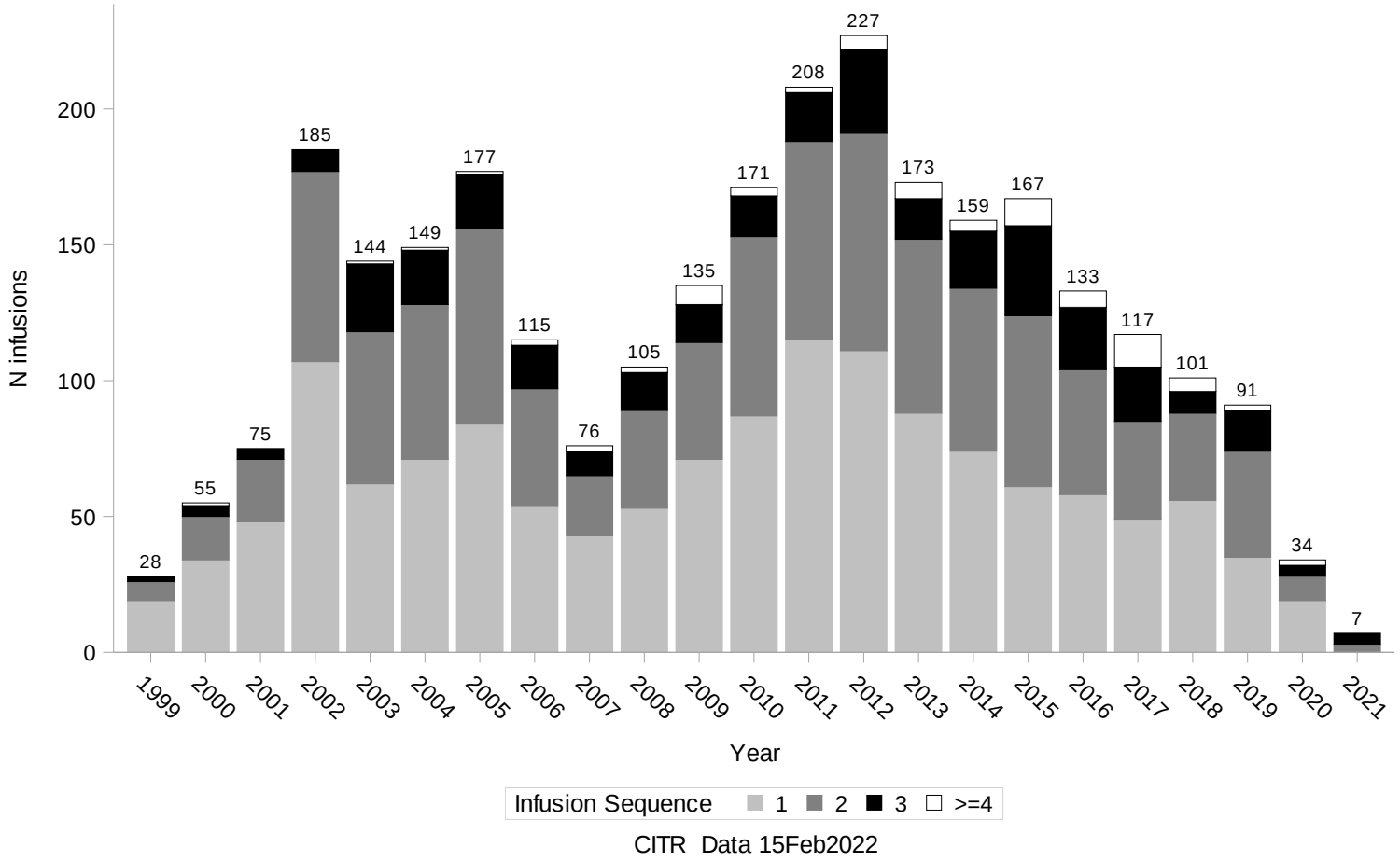


Exhibit 1 – 6B

Islet Allograft Recipients by Total Infusions to Date and Year. CITR-Participating North American and International Centers, 1999-2020

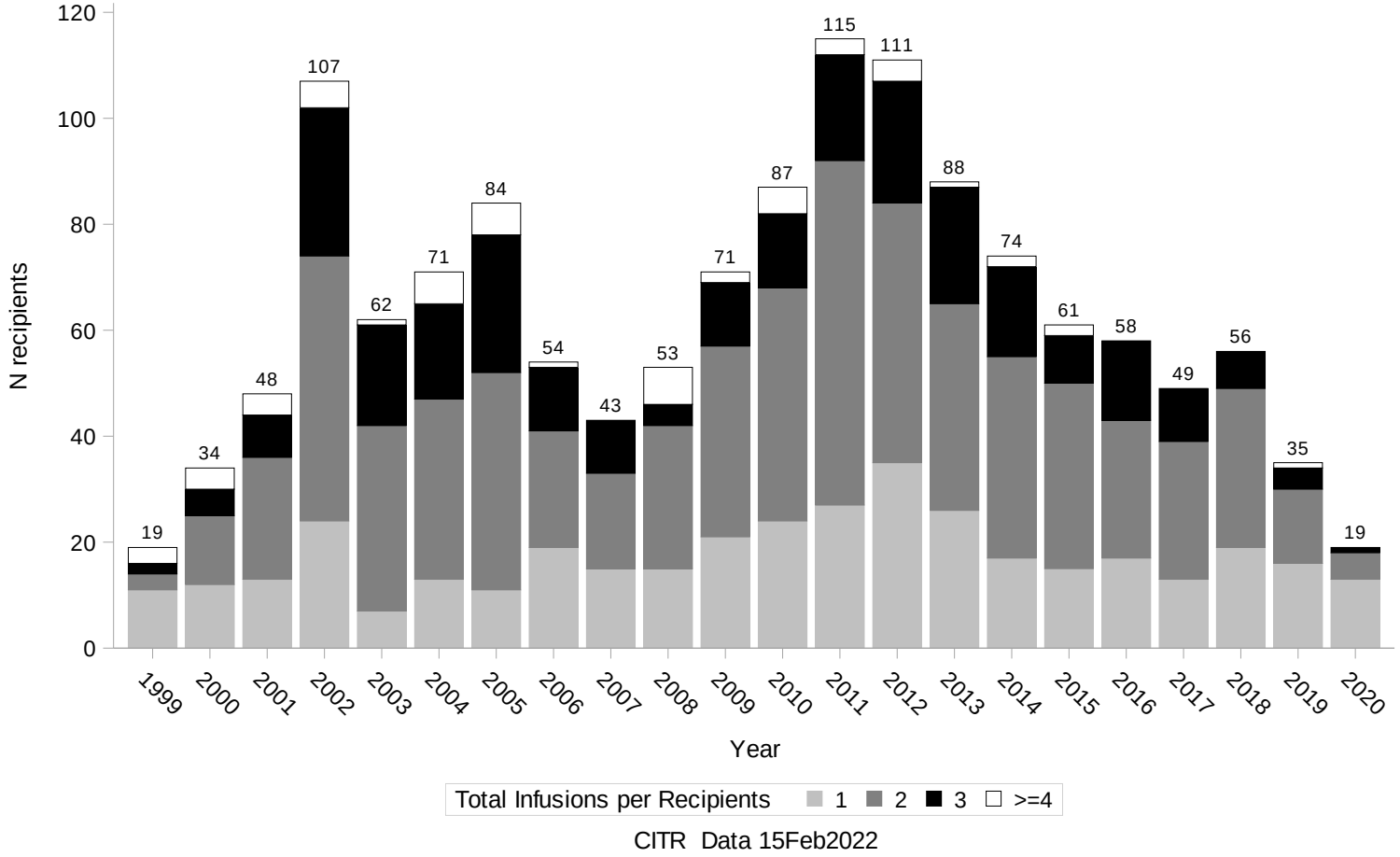


Exhibit 1 – 7
Total Number of Islet Allograft Infusion Procedures Per Recipient: CITR-Participating North American and International Centers, 1999-2021

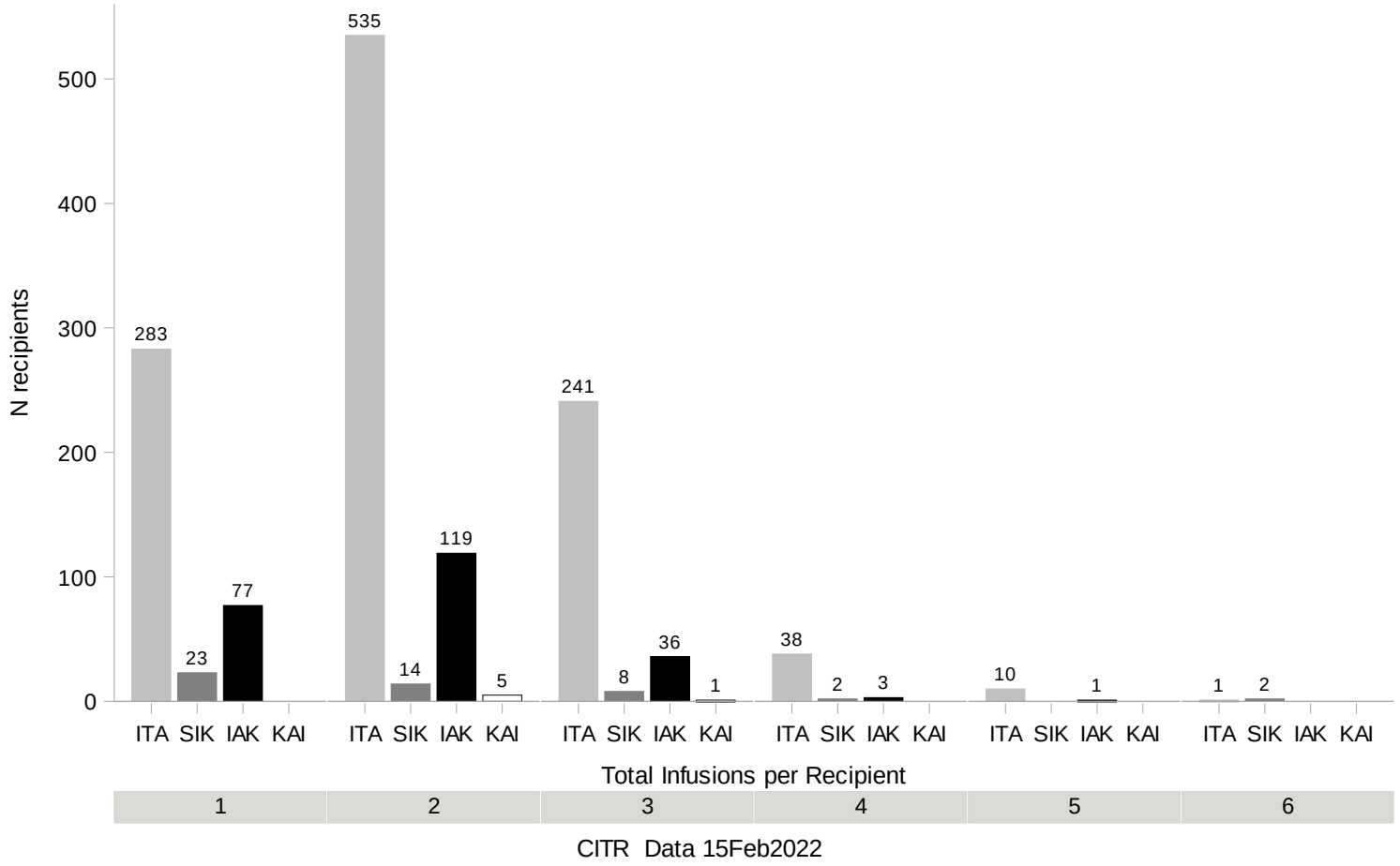
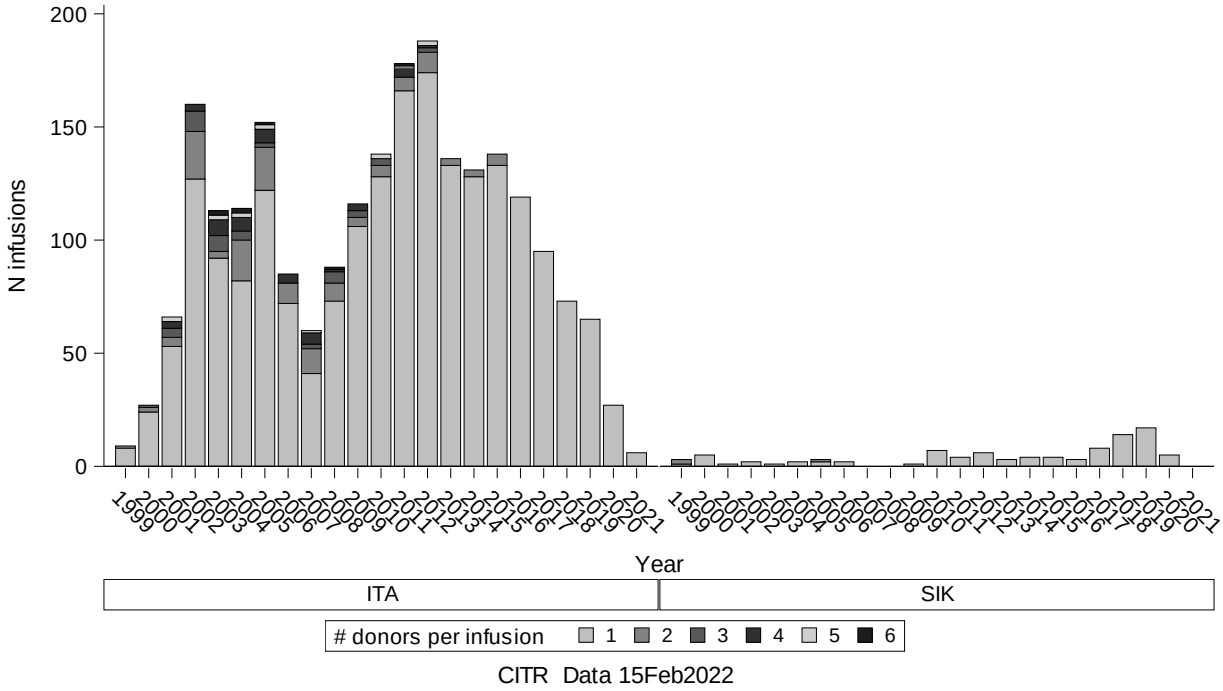
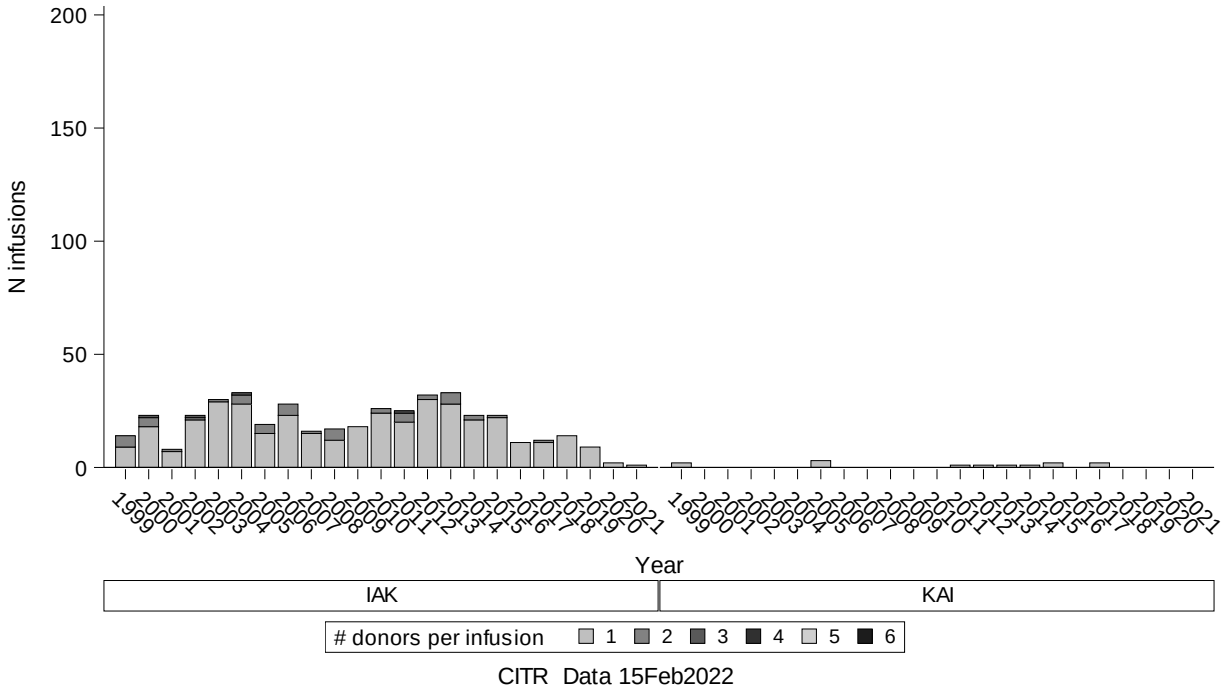


Exhibit 1 – 8

Total Number of Deceased Donors per Islet Allograft Infusion Procedure: CITR-Participating North American and International Centers, 1999-2021



CITR Data 15Feb2022



CITR Data 15Feb2022

Chapter 2
Recipient and Donor Characteristics

Introduction

All pre-infusion recipient characteristics are displayed in Exhibits 2-1 to 2-9. The distribution of each characteristic (variable) is shown according to transplant type (ITA or IAK) and era (1999-2002, 2003-2006, 2007-2010, 2011-2014, 2015-2018, and 2019-2022). In the first paired table per variable, the distribution of available data is shown and tested for differences by transplant type and era. Data availability is shown in the second, dimmed, paired table. Nominal p-values are calculated but are not based on experimental design.

In Exhibits 2-10 to 2-15, multiple donor information has been summarized over one to several donors/pancreata per islet infusion. There were 2,540 single-donor, 182 two-donor, 46 three-donor, 43 four-donor, 14 five-donor, and 7 six-donor, for a total of 3,326 donors and 2,832 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

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Gender	**Female**	684	60.3	120	51.3	*	119	57.5	158	59.4	152	60.8	220	57.6	130	59.6	25	55.6	
	Male	450	39.7	114	48.7		88	42.5	108	40.6	98	39.2	162	42.4	88	40.4	20	44.4	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Gender	Missing	1	0.1	2	0.8		0	0.0	1	0.4	1	0.4	1	0.3	0	0.0	0	0.0	
	Available	1134	99.9	234	99.2		207	100.0	266	99.6	250	99.6	382	99.7	218	100.0	45	100.0	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Race	**American Indian/Alaska Native**	2	0.3	0	0.0		0	0.0	1	0.5	1	0.5	0	0.0	0	0.0	0	0.0	
	Asian	3	0.4	0	0.0		0	0.0		0.0	0	0.0	2	0.8	1	0.7	0	0.0	
	Black or African American	7	0.9	2	1.1		0	0.0	1	0.5	5	2.6	3	1.2	0	0.0	0	0.0	
	Multiple	3	0.4	0	0.0		1	0.7	0	0.0	0	0.0	0	0.0	2	1.5	0	0.0	
	Other	1	0.1	1	0.6		0	0.0	0	0.0	0	0.0	1	0.4	0	0.0	1	2.4	
	White	775	98.0	172	98.3		142	99.3	195	99.0	189	96.9	247	97.6	134	97.8	40	97.6	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Race	Missing	344	30.3	61	25.8		64	30.9	70	26.2	56	22.3	130	33.9	81	37.2	4	8.9	
	Available	791	69.7	175	74.2		143	69.1	197	73.8	195	77.7	253	66.1	137	62.8	41	91.1	

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

Exhibit 2 – 1 (continued)
Recipient Demographics

		ITA		IAK		p	1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		p
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Ethnicity	**Hispanic or Latino**	7	1.1	5	3.0		1	0.7	7	3.6	2	1.1	2	1.1	0	0.0	0	0.0	
	Not Hispanic or Latino	621	98.9	163	97.0		141	99.3	190	96.4	175	98.9	180	98.9	72	100.0	26	100.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Ethnicity	**Missing**	507	44.7	68	28.8		65	31.4	70	26.2	74	29.5	201	52.5	146	67.0	19	42.2	
	Available	628	55.3	168	71.2		142	68.6	197	73.8	177	70.5	182	47.5	72	33.0	26	57.8	

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

Exhibit 2 – 1 (continued)
Recipient Demographics

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Employment	Unknown	205	22.9	71	38.2		44	24.6	30	12.7	77	37.6	93	32.0	26	19.5	6	16.7	
	N/A, less than 5 years old	0	0.0	1	0.5		1	0.6	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0	
	Not working by choice	37	4.1	4	2.2		5	2.8	13	5.5	10	4.9	11	3.8	2	1.5	0	0.0	
	Not working due to disease	138	15.4	41	22.0		19	10.6	41	17.3	20	9.8	52	17.9	32	24.1	15	41.7	
	Not working, reason unknown	7	0.8	8	4.3		1	0.6	4	1.7	4	2.0	5	1.7	1	0.8	0	0.0	
	Not working, unable to find employment	5	0.6	0	0.0	***	0	0.0	1	0.4	2	1.0	2	0.7	0	0.0	0	0.0	***
	Retired	46	5.1	7	3.8		3	1.7	13	5.5	12	5.9	16	5.5	6	4.5	3	8.3	
	Student	11	1.2	2	1.1		1	0.6	3	1.3	4	2.0	4	1.4	1	0.8		0.0	
	Working full time	362	40.4	38	20.4		85	47.5	111	46.8	59	28.8	88	30.2	49	36.8	8	22.2	
	Working part time by choice	41	4.6	9	4.8		7	3.9	11	4.6	13	6.3	10	3.4	7	5.3	2	5.6	
	Working part time due to disease	36	4.0	5	2.7		12	6.7	9	3.8	4	2.0	5	1.7	9	6.8	2	5.6	
	Working part time, reason unknown	7	0.8	0	0.0		1	0.6	1	0.4	0	0.0	5	1.7	0	0.0	0	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Employment	Missing	240	21.1	50	21.2		28	13.5	30	11.2	46	18.3	92	24.0	85	39.0	9	20.0	
	Available	895	78.9	186	78.8		179	86.5	237	88.8	205	81.7	291	76.0	133	61.0	36	80.0	

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

Exhibit 2 – 2

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

				ITA													
						Era											
				Total		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
				N	%	N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx				602	100.0	133	100.0	168	100.0	118	100.0	118	100.0	50	100.0	15	100.0
DiabHx	**SHE**	**C-peptide**	**Insulin**														
Cystic fibrosis related	**ASHE**	**<0.3**	**On Insulin**	1	0.2	-	-	-	-	-	-	1	0.8	-	-	-	-
		>=0.5	**On Insulin**	5	0.8	-	-	1	0.6	1	0.8	2	1.7	1	2.0	-	-
Pancreatectomy induced	**SHE**	**<0.3**	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		0.3-0.4	**On Insulin**	1	0.2	-	-	-	-	1	0.8	-	-	-	-	-	-
Type 1	**ASHE**	**<0.3**	**On Insulin**	136	22.6	26	19.5	25	14.9	15	12.7	39	33.1	25	50.0	6	40.0
		0.3-0.4	**On Insulin**	2	0.3	-	-	1	0.6	-	-	1	0.8	-	-	-	-
		>=0.5	**On Insulin**	4	0.7	2	1.5	-	-	2	1.7	-	-	-	-	-	-
	SHE	**<0.3**	**On Insulin**	415	68.9	88	66.2	129	76.8	93	78.8	74	62.7	23	46.0	8	53.3
		0.3-0.4	**On Insulin**	17	2.8	2	1.5	8	4.8	4	3.4	1	0.8	1	2.0	1	6.7
		>=0.5	**On Insulin**	21	3.5	15	11.3	4	2.4	2	1.7	-	-	-	-	-	-
Type 2	**ASHE**	**<0.3**	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-	-	-

Exhibit 2 – 2 (continued)

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

				IAK													
						Era											
				Total		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
				N	%	N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx				131	100.0	35	100.0	52	100.0	20	100.0	20	100.0	3	100.0	1	100.0
DiabHx	**SHE**	**C-peptide**	**Insulin**														
Cystic fibrosis related	**ASHE**	**<0.3**	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		>=0.5	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Pancreatectomy induced	**SHE**	**<0.3**	**On Insulin**	1	0.8	-	-	-	-	-	-	-	-	1	33.3	-	-
		0.3-0.4	**On Insulin**	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Type 1	**ASHE**	**<0.3**	**On Insulin**	52	39.7	17	48.6	21	40.4	10	50.0	4	20.0	-	-	-	-
		0.3-0.4	**On Insulin**	6	4.6	4	11.4	-	-	2	10.0	-	-	-	-	-	-
		>=0.5	**On Insulin**	8	6.1	3	8.6	4	7.7	-	-	1	5.0	-	-	-	-
	SHE	**<0.3**	**On Insulin**	59	45.0	11	31.4	24	46.2	8	40.0	13	65.0	2	66.7	1	100.0
		0.3-0.4	**On Insulin**	1	0.8	-	-	1	1.9	-	-	-	-	-	-	-	-
		>=0.5	**On Insulin**	3	2.3	-	-	2	3.8	-	-	1	5.0	-	-	-	-
Type 2	**ASHE**	**<0.3**	**On Insulin**	1	0.8	-	-	-	-	-	-	1	5.0	-	-	-	-

Exhibit 2 – 2 (continued)

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

				ITA													
						Era											
				TOTAL		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
				N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL				533	100.0	28	100.0	44	100.0	91	100.0	202	100.0	144	100.0	24	100.0
DiabHx	SHE	C-peptide	Insulin														
Missing	Missing	Missing	Missing	57	10.7	2	7.1	-	-	1	1.1	19	9.4	29	20.1	6	25.0
			Available	14	2.6	-	-	-	-	12	13.2	1	0.5	1	0.7	-	-
		Available	Missing	3	0.6	-	-	-	-	-	-	-	-	3	2.1	-	-
			Available	25	4.7	-	-	14	31.8	4	4.4	6	3.0	1	0.7	-	-
	Available	Missing	Missing	6	1.1	-	-	-	-	3	3.3	3	1.5	-	-	-	-
			Available	7	1.3	-	-	-	-	2	2.2	2	1.0	3	2.1	-	-
		Available	Missing	3	0.6	-	-	-	-	-	-	3	1.5	-	-	-	-
			Available	25	4.7	-	-	-	-	-	-	16	7.9	9	6.3	-	-
Available	Missing	Missing	Missing	26	4.9	3	10.7	1	2.3	5	5.5	9	4.5	6	4.2	2	8.3
			Available	24	4.5	7	25.0	2	4.5	1	1.1	9	4.5	4	2.8	1	4.2
		Available	Missing	31	5.8	3	10.7	1	2.3	5	5.5	5	2.5	16	11.1	1	4.2
			Available	39	7.3	4	14.3	11	25.0	6	6.6	17	8.4	1	0.7	-	-
	Available	Missing	Missing	16	3.0	-	-	-	-	1	1.1	8	4.0	6	4.2	1	4.2
			Available	206	38.6	7	25.0	8	18.2	23	25.3	92	45.5	63	43.8	13	54.2
		Available	Missing	51	9.6	2	7.1	7	15.9	28	30.8	12	5.9	2	1.4	-	-

Exhibit 2 – 2 (continued)

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

				IAK													
						Era											
				TOTAL		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
				N	%	N	%	N	%	N	%	N	%	N	%	N	%
TOTAL				105	100.0	11	100.0	3	100.0	22	100.0	43	100.0	21	100.0	5	100.0
DiabHx	SHE	C-peptide	Insulin														
Missing	Missing	Missing	Missing	12	11.4	3	27.3	-	-	3	13.6	6	14.0	-	-	-	-
			Available	-	-	-	-	-	-	-	-	-	-	-	-	-	-
		Available	Missing	1	1.0	1	9.1	-	-	-	-	-	-	-	-	-	-
			Available	1	1.0	-	-	-	-	-	-	1	2.3	-	-	-	-
	Available	Missing	Missing	1	1.0	-	-	-	-	-	-	1	2.3	-	-	-	-
			Available	3	2.9	-	-	-	-	-	-	2	4.7	1	4.8	-	-
		Available	Missing	-	-	-	-	-	-	-	-	-	-	-	-	-	-
			Available	14	13.3	-	-	-	-	3	13.6	10	23.3	1	4.8	-	-
Available	Missing	Missing	Missing	24	22.9	-	-	1	33.3	9	40.9	11	25.6	3	14.3	-	-
			Available	3	2.9	-	-	1	33.3	-	-	2	4.7	-	-	-	-
		Available	Missing	1	1.0	-	-	-	-	-	-	-	-	1	4.8	-	-
			Available	7	6.7	1	9.1	-	-	3	13.6	3	7.0	-	-	-	-
	Available	Missing	Missing	6	5.7	1	9.1	-	-	1	4.5	-	-	3	14.3	1	20.0
			Available	28	26.7	4	36.4	1	33.3	3	13.6	7	16.3	9	42.9	4	80.0
		Available	Missing	4	3.8	1	9.1	-	-	-	-	-	-	3	14.3	-	-

Exhibit 2 – 2 (continued)

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

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx	Cystic fibrosis related	10	1.0	-	-	-	-	1	0.4	2	0.9	6	1.9	1	0.6	-	-
	Other	1	0.1	-	-	-	-	-	-	-	-	-	-	1	0.6	-	-
	Pancreatectomy induced	1	0.1	1	0.5	-	-	-	-	1	0.4	-	-	1	0.6	-	-
	Type 1	982	98.7	202	99.0	201	100.0	252	99.6	220	98.7	305	97.4	167	98.2	39	100.0
	Type 2	1	0.1	1	0.5	-	-	-	-	-	-	2	0.6	-	-	-	-

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Indication for ITx	Missing	140	12.3	32	13.6	6	2.9	14	5.2	28	11.2	70	18.3	48	22.0	6	13.3
	Available	995	87.7	204	86.4	201	97.1	253	94.8	223	88.8	313	81.7	170	78.0	39	86.7

Exhibit 2 – 3

Recipient Characteristics at First Infusion

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Age at transplant	1135	47.0	0.3	235	48.2	0.6	
Days listed	721	341.3	13.8	164	416.4	39.0	*
Duration of Diabetes (yrs)	875	29.5	0.4	188	34.6	0.7	***
Weight (kg)	978	68.0	0.4	204	65.4	0.8	**
Body mass index (kg/m2)	694	23.8	0.1	169	23.1	0.2	*
Daily insulin requirement prior to infusion (units)	942	37.3	0.5	187	37.0	1.0	
Duration of intensive therapy (yrs)	425	20.5	0.7	33	26.9	2.3	**
Avg daily insulin / kg recipient body weight	900	0.5	0.0	179	0.6	0.0	*
Fasting plasma glucose (mg/dL)	745	170.5	3.2	143	166.4	7.1	
Basal C-Peptide (ng/mL)	779	0.1	0.0	159	0.2	0.1	**
HbA1C (%)	883	7.9	0.0	204	8.2	0.1	*
Class I PRA (%)	561	3.1	0.5	108	0.6	0.4	*
Class II PRA (%)	444	2.3	0.5	77	0.8	0.8	

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Age at transplant	207	41.5	0.6	267	44.6	0.6	251	48.5	0.6	382	49.1	0.6	218	50.3	0.8	45	52.1	1.6	***
Days listed	166	237.5	21.6	226	319.2	22.8	134	491.3	48.6	204	336.7	24.8	119	435.6	38.1	36	455.8	70.5	***
Duration of Diabetes (yrs)	193	27.2	0.7	250	29.6	0.6	208	31.4	0.8	257	30.6	0.7	119	34.2	1.1	36	33.9	1.9	***
Weight (kg)	193	65.8	0.8	258	65.3	0.6	223	67.4	0.8	322	69.1	0.7	152	69.8	1.0	34	70.9	2.5	***
Body mass index (kg/m2)	186	23.4	0.2	257	23.3	0.2	157	23.6	0.2	154	23.8	0.3	87	24.4	0.4	22	25.0	0.7	***
Daily insulin requirement prior to infusion (units)	191	39.1	1.1	257	37.6	0.9	195	35.6	1.0	306	37.0	0.9	146	37.1	1.4	34	37.2	2.7	
Duration of intensive therapy (yrs)	111	18.3	1.1	144	23.6	1.2	76	21.8	1.9	73	20.9	1.5	37	18.1	2.0	17	17.6	2.5	
Avg daily insulin / kg recipient body weight	189	0.6	0.0	251	0.6	0.0	189	0.5	0.0	282	0.5	0.0	135	0.5	0.0	33	0.5	0.0	**
Fasting plasma glucose (mg/dL)	168	181.1	7.2	248	169.4	5.8	196	156.0	5.8	197	171.8	6.0	68	180.1	9.0	11	154.5	23.5	
Basal C-Peptide (ng/mL)	180	0.2	0.0	253	0.1	0.0	187	0.1	0.0	211	0.1	0.0	90	0.2	0.1	17	0.1	0.0	
HbA1C (%)	192	7.9	0.1	261	7.8	0.1	227	7.9	0.1	292	8.2	0.1	95	8.2	0.1	20	7.9	0.3	**
Class I PRA (%)	134	1.2	0.4	192	4.2	1.0	130	1.7	0.6	151	3.7	1.0	44	0.6	0.4	18	2.2	2.2	
Class II PRA (%)	85	1.4	1.1	115	2.5	1.0	110	2.6	1.0	147	2.3	0.9	46	0.6	0.4	18	0.7	0.5	

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

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

Exhibit 2 – 3 (continued)

Recipient Characteristics at First Infusion

Significant trends in patient characteristics from table above

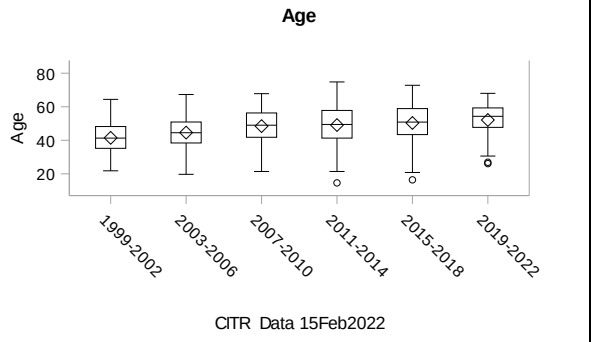
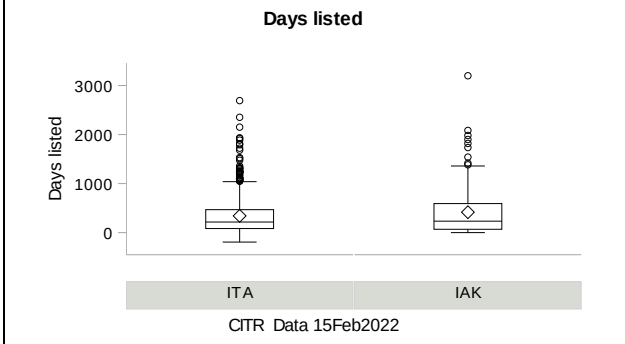
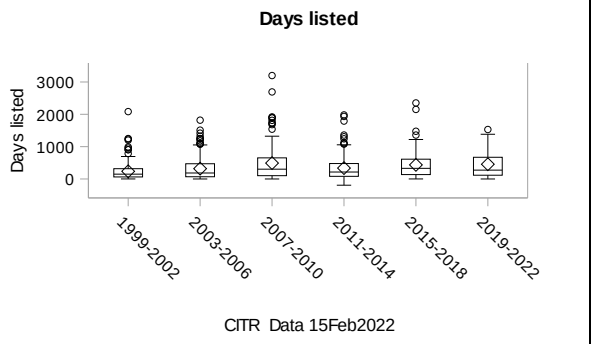
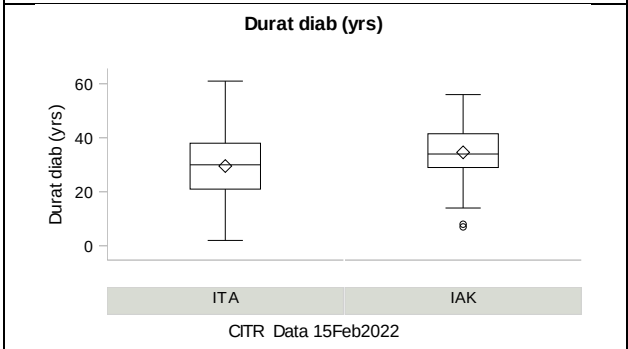
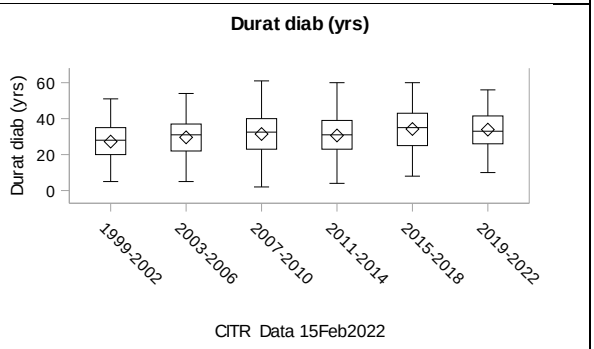
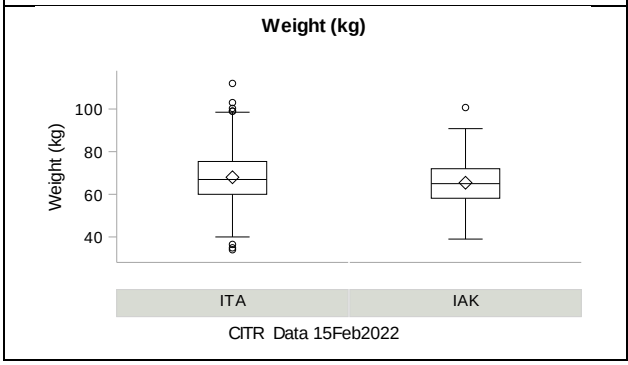
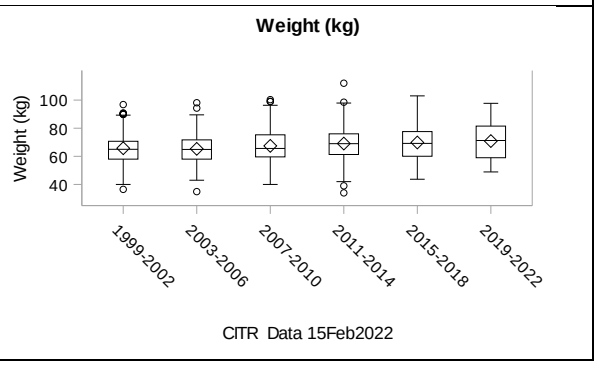
By ITA or IAK	By Era
	
	
	
	

Exhibit 2 – 3 (continued)

Recipient Characteristics at First Infusion

Significant trends in patient characteristics from table above

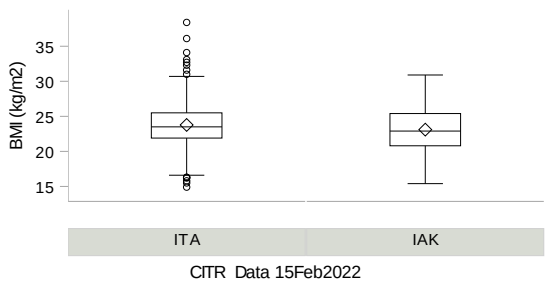
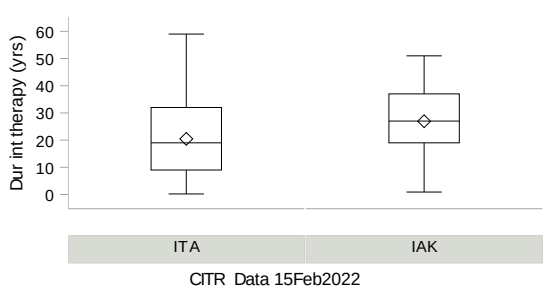
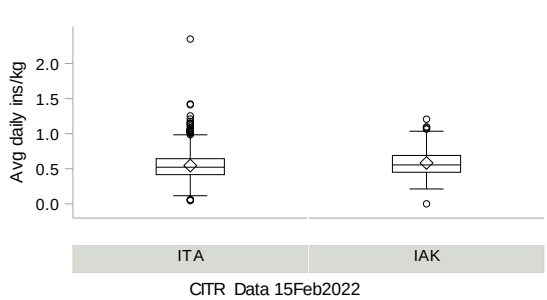
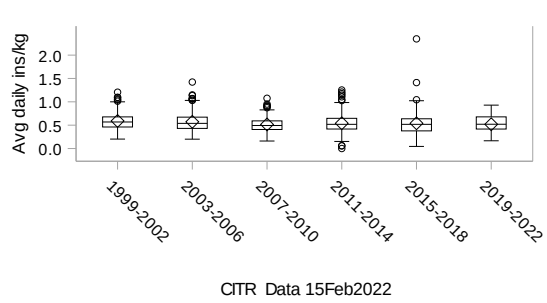
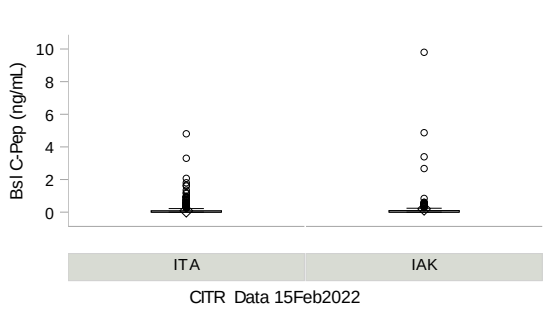
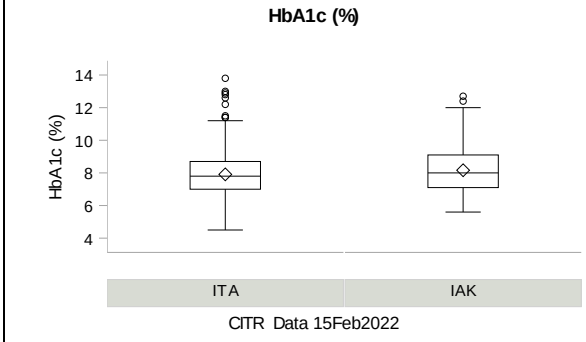
By ITA or IAK	By Era
	
	
	
	

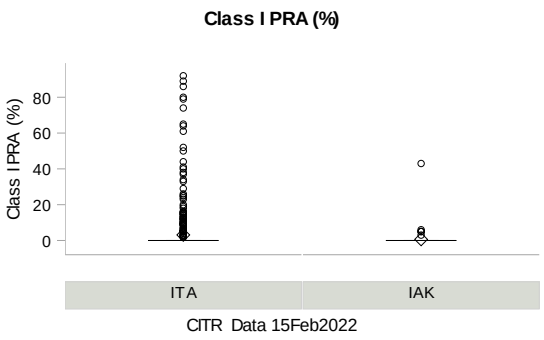
Exhibit 2 – 3 (continued)

Recipient Characteristics at First Infusion

Significant trends in patient characteristics from table above

By ITA or IAK





By Era

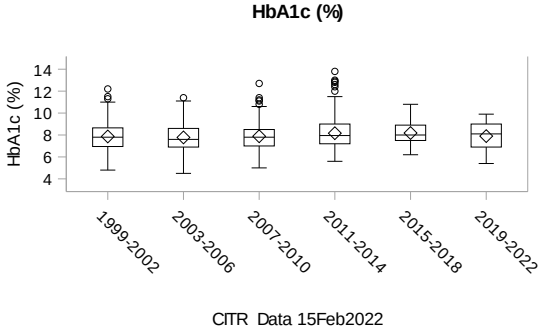


Exhibit 2 – 4

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Number of injections per day	**1-2**	10	3.1	6	6.5		7	6.1	3	2.0	2	3.4	3	5.7	0	0.0	1	10.0	
	3-5	300	94.0	83	90.2		107	93.0	143	96.0	50	86.2	49	92.5	25	96.2	9	90.0	*
	6 or more	9	2.8	3	3.3		1	0.9	3	2.0	6	10.3	1	1.9	1	3.8	0	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Number of injections per day	Missing	816	71.9	144	61.0		92	44.4	118	44.2	193	76.9	330	86.2	192	88.1	35	77.8	
	Available	319	28.1	92	39.0		115	55.6	149	55.8	58	23.1	53	13.8	26	11.9	10	22.2	

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

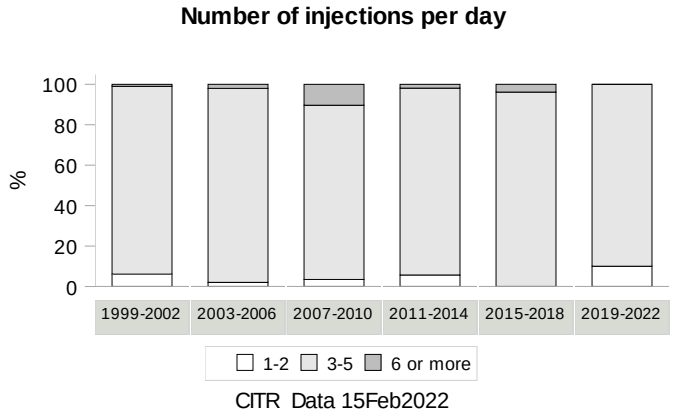


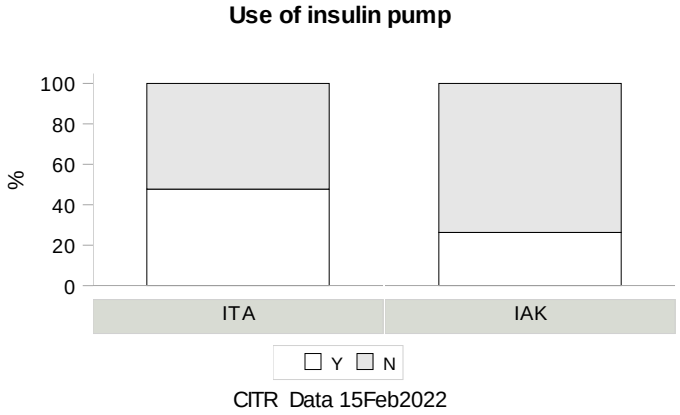
Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Use of insulin pump	**No**	378	52.3	115	73.7	***	129	69.4	164	62.4	71	46.7	75	44.6	44	50.6	10	43.5	***
	Yes	345	47.7	41	26.3		57	30.6	99	37.6	81	53.3	93	55.4	43	49.4	13	56.5	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Use of insulin pump	**Missing**	412	36.3	80	33.9		21	10.1	4	1.5	99	39.4	215	56.1	131	60.1	22	48.9	
	Available	723	63.7	156	66.1		186	89.9	263	98.5	152	60.6	168	43.9	87	39.9	23	51.1	

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



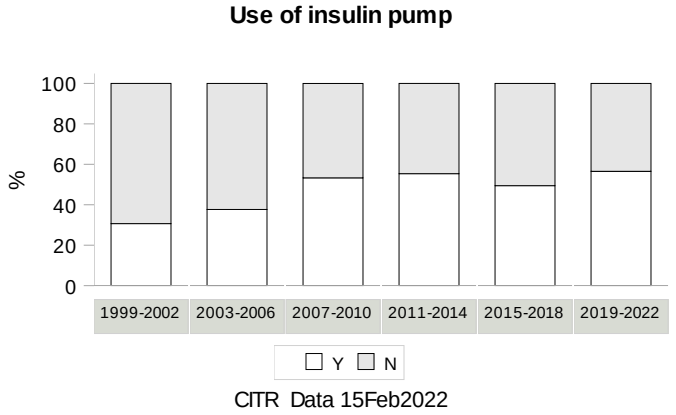


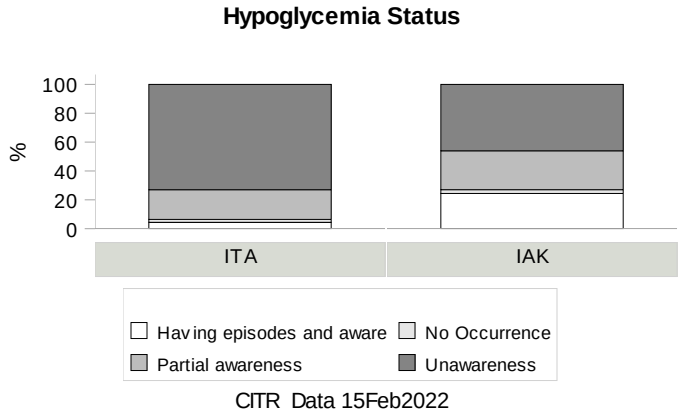
Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Hypoglycemia status	**Having episodes and aware**	30	4.3	37	24.3		14	8.3	10	3.9	12	8.6	18	10.7	10	11.0	3	13.6	
	No Occurrence	14	2.0	4	2.6	***	4	2.4	4	1.6	1	0.7	6	3.6	3	3.3	0	0.0	***
	Partial awareness	143	20.6	41	27.0		50	29.8	59	22.9	24	17.3	27	16.1	18	19.8	6	27.3	
	Unawareness	507	73.1	70	46.1		100	59.5	185	71.7	102	73.4	117	69.6	60	65.9	13	59.1	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Hypoglycemia status	**Available**	694	61.1	152	64.4		168	81.2	258	96.6	139	55.4	168	43.9	91	41.7	22	48.9	
	Missing	441	38.9	84	35.6		39	18.8	9	3.4	112	44.6	215	56.1	127	58.3	23	51.1	

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



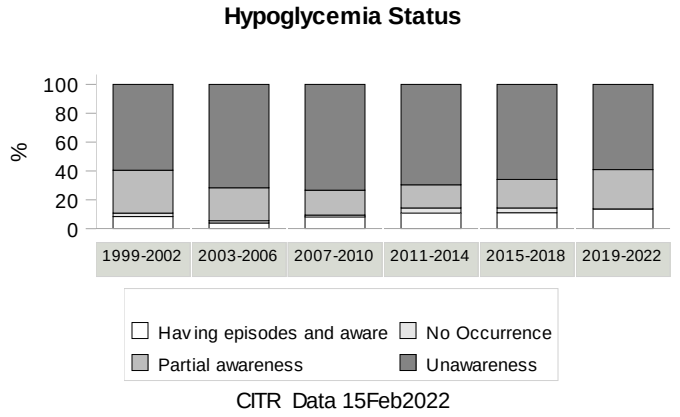


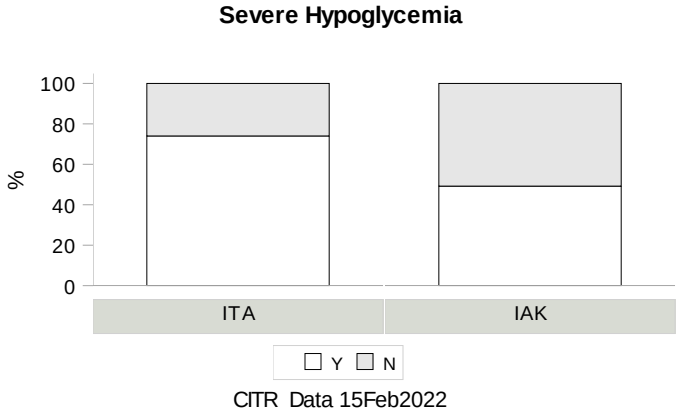
Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Severe hypoglycemia	**No**	238	26.0	95	50.8	***	60	32.8	56	23.7	41	20.3	92	31.3	70	45.8	14	40.0	***
	Yes	678	74.0	92	49.2		123	67.2	180	76.3	161	79.7	202	68.7	83	54.2	21	60.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Severe hypoglycemia	**Missing**	219	19.3	49	20.8		24	11.6	31	11.6	49	19.5	89	23.2	65	29.8	10	22.2	
	Available	916	80.7	187	79.2		183	88.4	236	88.4	202	80.5	294	76.8	153	70.2	35	77.8	

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



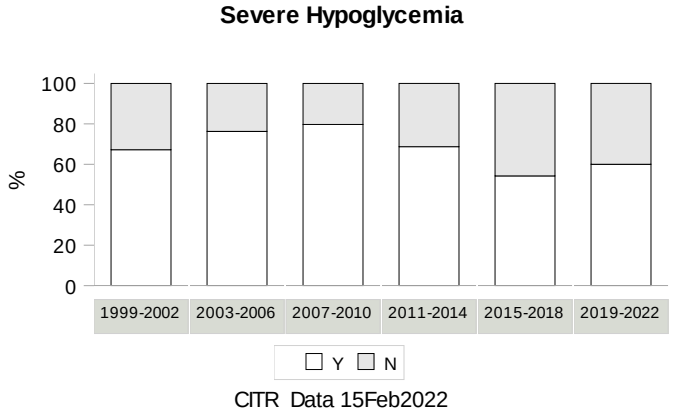


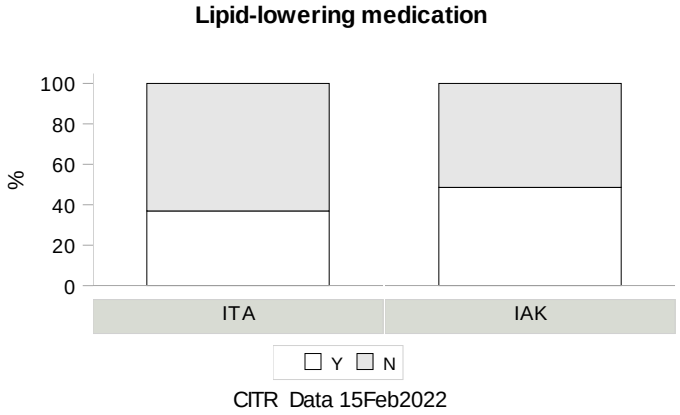
Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Lipid lowering medication	**No**	482	63.1	90	51.4	**	149	83.2	158	61.0	106	54.9	102	51.5	48	55.2	9	39.1	***
	Yes	282	36.9	85	48.6		30	16.8	101	39.0	87	45.1	96	48.5	39	44.8	14	60.9	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Lipid lowering medication	**Missing**	371	32.7	61	25.8		28	13.5	8	3.0	58	23.1	185	48.3	131	60.1	22	48.9	
	Available	764	67.3	175	74.2		179	86.5	259	97.0	193	76.9	198	51.7	87	39.9	23	51.1	

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



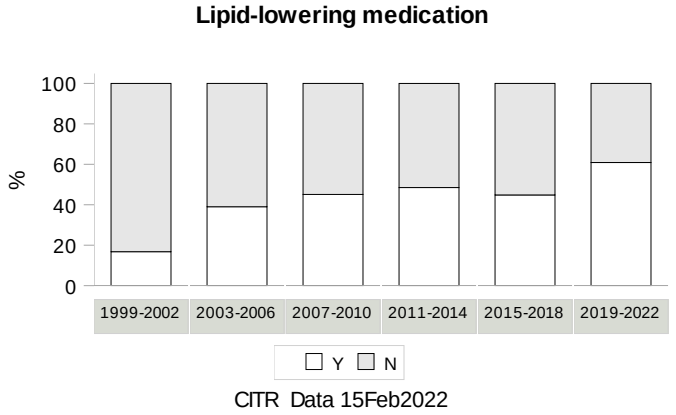


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Anti hypertension medication	**No**	495	64.5	55	31.6	***	114	62.3	155	59.8	103	52.6	114	58.5	52	60.5	12	52.2	
	Yes	273	35.5	119	68.4		69	37.7	104	40.2	93	47.4	81	41.5	34	39.5	11	47.8	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Anti hypertension medication	**Missing**	367	32.3	62	26.3		24	11.6	8	3.0	55	21.9	188	49.1	132	60.6	22	48.9	
	Available	768	67.7	174	73.7		183	88.4	259	97.0	196	78.1	195	50.9	86	39.4	23	51.1	

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

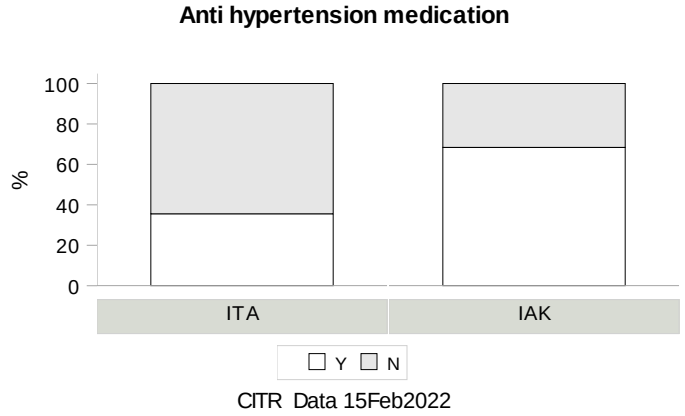


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Anti-hyperglycemia medication	**No**	459	92.2	103	94.5		63	95.5	100	95.2	149	95.5	162	93.1	67	80.7	21	91.3	***
	Yes	39	7.8	6	5.5		3	4.5	5	4.8	7	4.5	12	6.9	16	19.3	2	8.7	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Anti-hyperglycemia medication	**Missing**	637	56.1	127	53.8		141	68.1	162	60.7	95	37.8	209	54.6	135	61.9	22	48.9	
	Available	498	43.9	109	46.2		66	31.9	105	39.3	156	62.2	174	45.4	83	38.1	23	51.1	

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

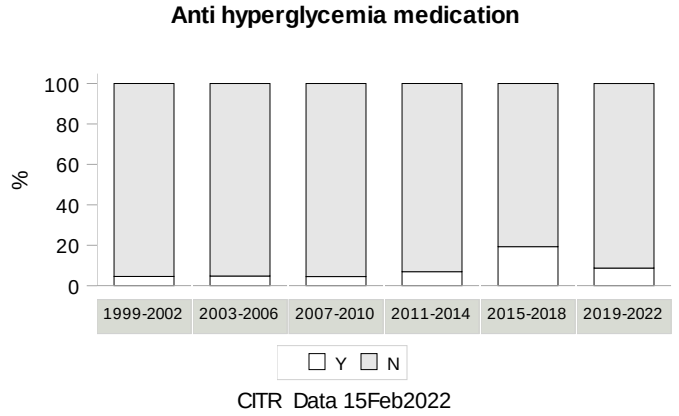


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

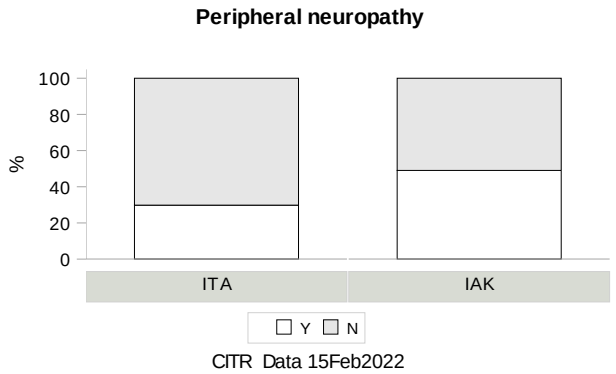
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Smoker	**No**	826	92.7	127	93.4		141	95.3	221	95.7	189	93.1	253	89.7	120	92.3	29	87.9	
	Yes	65	7.3	9	6.6		7	4.7	10	4.3	14	6.9	29	10.3	10	7.7	4	12.1	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Smoker	Missing	244	21.5	100	42.4		59	28.5	36	13.5	48	19.1	101	26.4	88	40.4	12	26.7	
	Available	891	78.5	136	57.6		148	71.5	231	86.5	203	80.9	282	73.6	130	59.6	33	73.3	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Peripheral neuropathy	**No**	570	70.2	77	51.0	***	110	60.1	165	65.5	105	67.3	166	74.8	75	65.2	26	74.3	*
	Yes	242	29.8	74	49.0		73	39.9	87	34.5	51	32.7	56	25.2	40	34.8	9	25.7	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Peripheral neuropathy	Missing	323	28.5	85	36.0		24	11.6	15	5.6	95	37.8	161	42.0	103	47.2	10	22.2	
	Available	812	71.5	151	64.0		183	88.4	252	94.4	156	62.2	222	58.0	115	52.8	35	77.8	

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



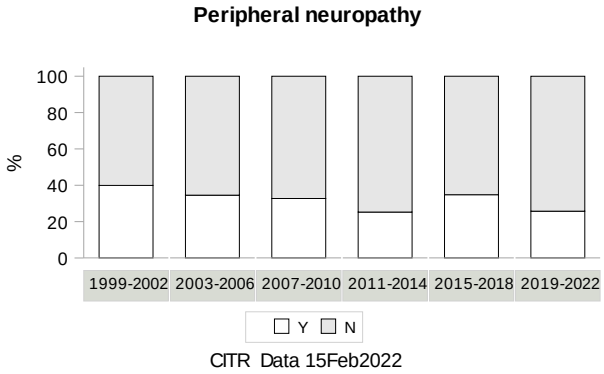


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Autonomic neuropathy	**No**	544	82.9	88	66.2	***	131	75.3	192	80.7	106	80.3	136	86.1	51	77.3	16	76.2	
	Yes	112	17.1	45	33.8		43	24.7	46	19.3	26	19.7	22	13.9	15	22.7	5	23.8	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Autonomic neuropathy	**Missing**	479	42.2	103	43.6		33	15.9	29	10.9	119	47.4	225	58.7	152	69.7	24	53.3	
	Available	656	57.8	133	56.4		174	84.1	238	89.1	132	52.6	158	41.3	66	30.3	21	46.7	

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

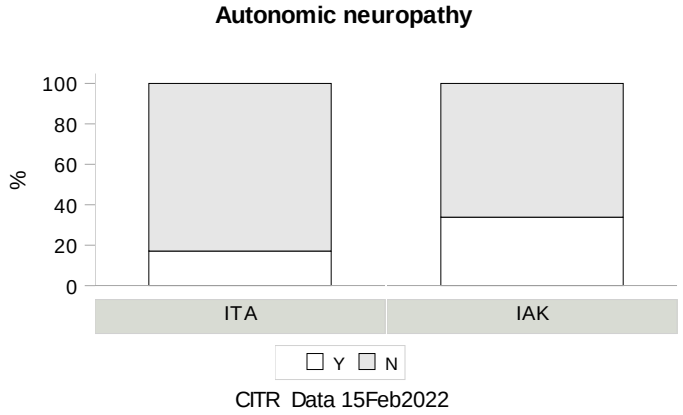


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
CAD history	**No**	744	92.4	121	78.6	***	173	94.0	229	89.1	133	86.9	201	91.0	98	90.7	31	86.1	
	Yes	61	7.6	33	21.4		11	6.0	28	10.9	20	13.1	20	9.0	10	9.3	5	13.9	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
CAD history	**Missing**	330	29.1	82	34.7		23	11.1	10	3.7	98	39.0	162	42.3	110	50.5	9	20.0	
	Available	805	70.9	154	65.3		184	88.9	257	96.3	153	61.0	221	57.7	108	49.5	36	80.0	

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

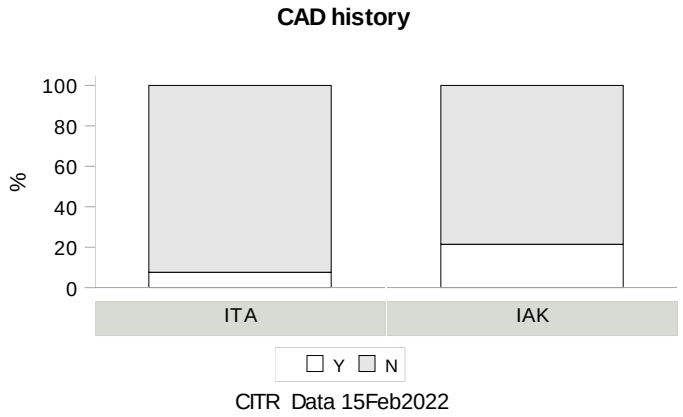


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
CVA history	**No**	773	97.6	138	94.5		180	100.0	248	99.2	142	94.0	207	96.3	102	96.2	32	88.9	***
	Yes	19	2.4	8	5.5		0	0.0	2	0.8	9	6.0	8	3.7	4	3.8	4	11.1	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
CVA history	Missing	343	30.2	90	38.1		27	13.0	17	6.4	100	39.8	168	43.9	112	51.4	9	20.0	
	Available	792	69.8	146	61.9		180	87.0	250	93.6	151	60.2	215	56.1	106	48.6	36	80.0	

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

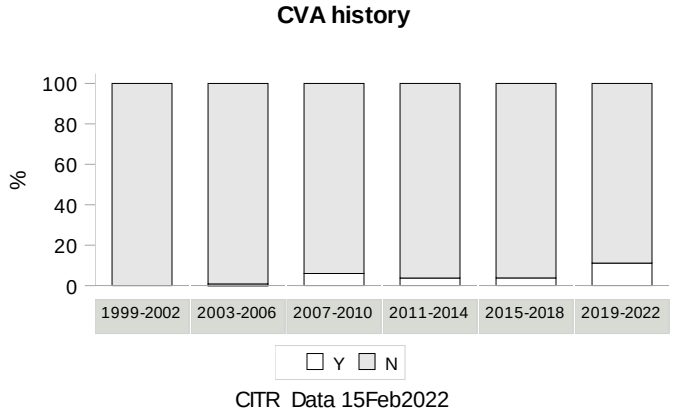


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
PVD history	**No**	617	96.1	98	83.8	***	160	95.8	231	94.7	116	92.1	129	92.1	57	96.6	22	95.7	
	Yes	25	3.9	19	16.2		7	4.2	13	5.3	10	7.9	11	7.9	2	3.4	1	4.3	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
PVD history	**Missing**	493	43.4	119	50.4		40	19.3	23	8.6	125	49.8	243	63.4	159	72.9	22	48.9	
	Available	642	56.6	117	49.6		167	80.7	244	91.4	126	50.2	140	36.6	59	27.1	23	51.1	

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

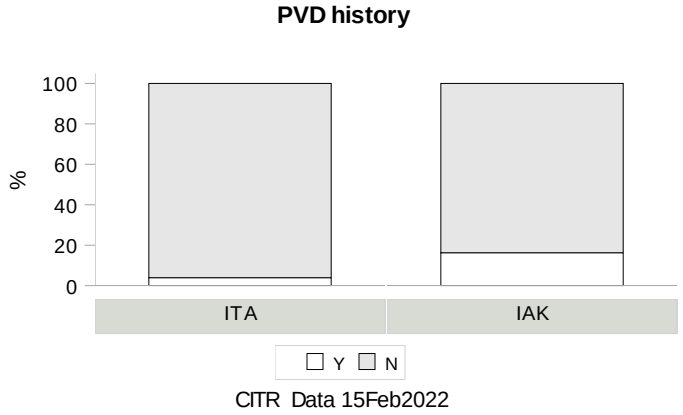


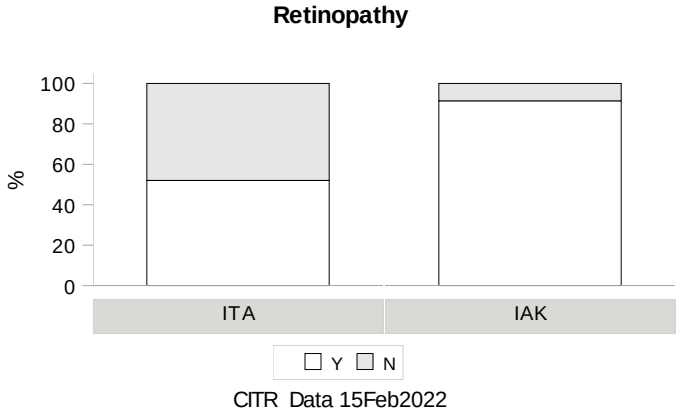
Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Retinopathy	**No**	322	48.0	13	8.6	***	58	31.2	96	38.7	53	38.7	78	50.3	37	50.0	13	59.1	**
	Yes	349	52.0	138	91.4		128	68.8	152	61.3	84	61.3	77	49.7	37	50.0	9	40.9	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Retinopathy	**Missing**	464	40.9	85	36.0		21	10.1	19	7.1	114	45.4	228	59.5	144	66.1	23	51.1	
	Available	671	59.1	151	64.0		186	89.9	248	92.9	137	54.6	155	40.5	74	33.9	22	48.9	

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



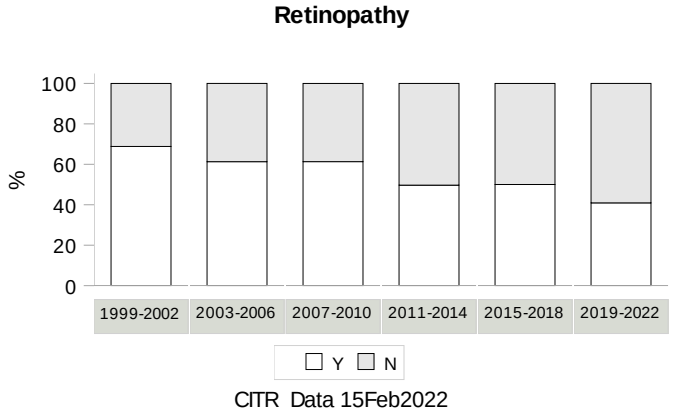


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Macular edema	**No**	563	97.9	92	92.9	*	140	97.2	201	96.6	102	95.3	134	98.5	56	98.2	22	100.0	
	Yes	12	2.1	7	7.1		4	2.8	7	3.4	5	4.7	2	1.5	1	1.8		0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Macular edema	**Missing**	560	49.3	137	58.1		63	30.4	59	22.1	144	57.4	247	64.5	161	73.9	23	51.1	
	Available	575	50.7	99	41.9		144	69.6	208	77.9	107	42.6	136	35.5	57	26.1	22	48.9	

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

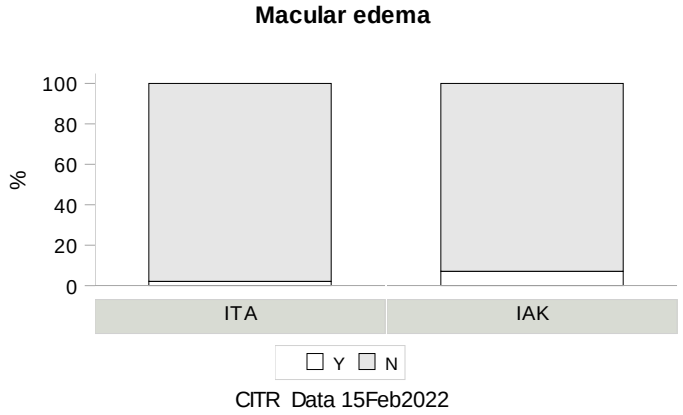


Exhibit 2 – 4 (continued)

Recipient Diabetes Characteristics and Medical History

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Blood group	**A**	430	37.9	103	43.6		102	49.3	130	48.7	105	41.8	127	33.2	57	26.1	12	26.7	
	A1	2	0.2	1	0.4		1	0.5	0	0.0	0	0.0	1	0.3	1	0.5	0	0.0	
	A2	1	0.1	0	0.0		0	0.0	0	0.0	1	0.4	0	0.0	0	0.0	0	0.0	
	AB	32	2.8	7	3.0		1	0.5	0	0.0	5	2.0	19	5.0	10	4.6	4	8.9	***
	B	116	10.2	23	9.7		23	11.1	26	9.7	24	9.6	48	12.5	14	6.4	4	8.9	
	O	405	35.7	78	33.1		68	32.9	96	36.0	91	36.3	124	32.4	85	39.0	19	42.2	
	Unknown	149	13.1	24	10.2		12	5.8	15	5.6	25	10.0	64	16.7	51	23.4	6	13.3	

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

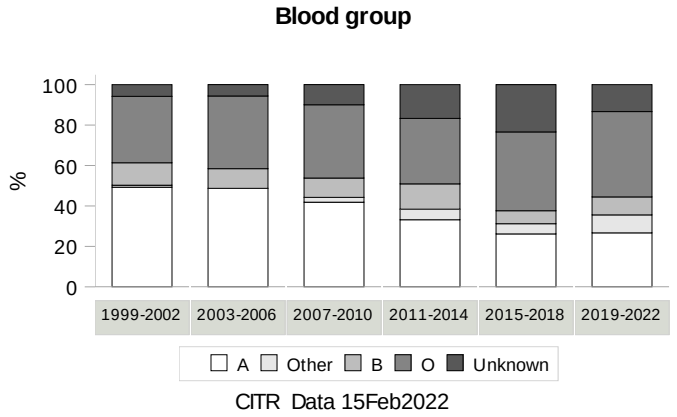


Exhibit 2 – 5

Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody GAD 65	**Negative**	279	54.6	76	60.3		101	66.4	115	62.8	62	53.0	47	42.3	22	40.7	8	40.0	***
	Positive	232	45.4	50	39.7		51	33.6	68	37.2	55	47.0	64	57.7	32	59.3	12	60.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Pre transplant autoantibody GAD 65	**Missing**	624	55.0	110	46.6		55	26.6	84	31.5	134	53.4	272	71.0	164	75.2	25	55.6	
	Available	511	45.0	126	53.4		152	73.4	183	68.5	117	46.6	111	29.0	54	24.8	20	44.4	

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

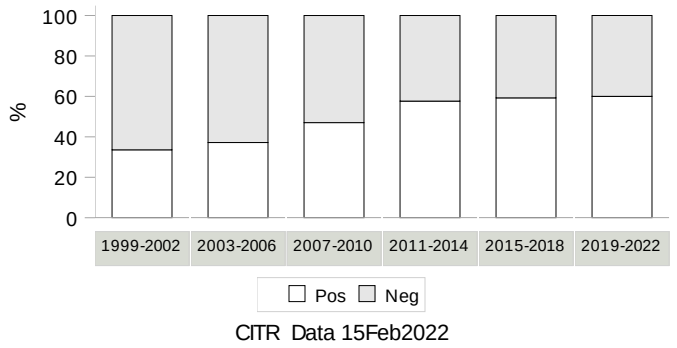


Exhibit 2 – 5 (continued)

Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody IA-2	**Negative**	639	79.5	171	90.5	***	163	82.7	217	81.9	170	81.3	189	81.1	53	79.1	18	81.8	
	Positive	165	20.5	18	9.5		34	17.3	48	18.1	39	18.7	44	18.9	14	20.9	4	18.2	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Pre transplant autoantibody IA-2	**Missing**	331	29.2	47	19.9		10	4.8	2	0.7	42	16.7	150	39.2	151	69.3	23	51.1	
	Available	804	70.8	189	80.1		197	95.2	265	99.3	209	83.3	233	60.8	67	30.7	22	48.9	

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

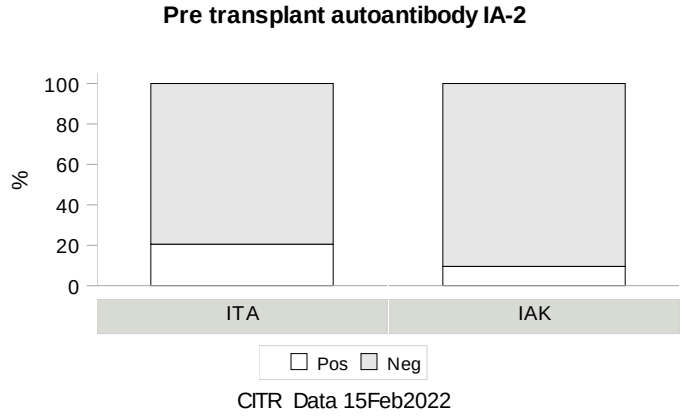


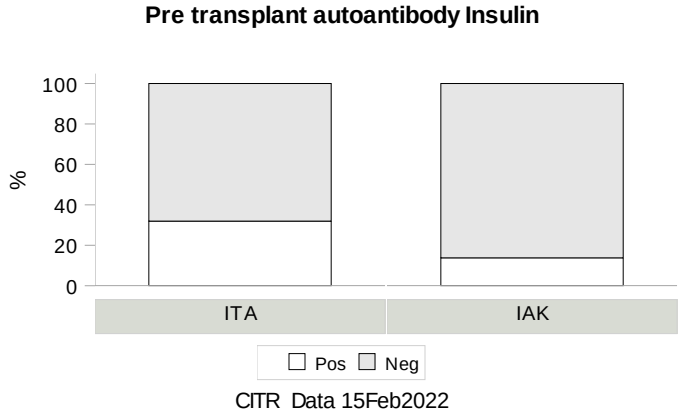
Exhibit 2 – 5 (continued)

Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Pre transplant autoantibody Insulin	**Negative**	548	68.1	163	86.2	***	136	69.0	154	58.1	171	81.4	191	82.0	42	62.7	17	77.3	***
	Positive	257	31.9	26	13.8		61	31.0	111	41.9	39	18.6	42	18.0	25	37.3	5	22.7	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Pre transplant autoantibody Insulin	**Missing**	330	29.1	47	19.9		10	4.8	2	0.7	41	16.3	150	39.2	151	69.3	23	51.1	
	Available	805	70.9	189	80.1		197	95.2	265	99.3	210	83.7	233	60.8	67	30.7	22	48.9	

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



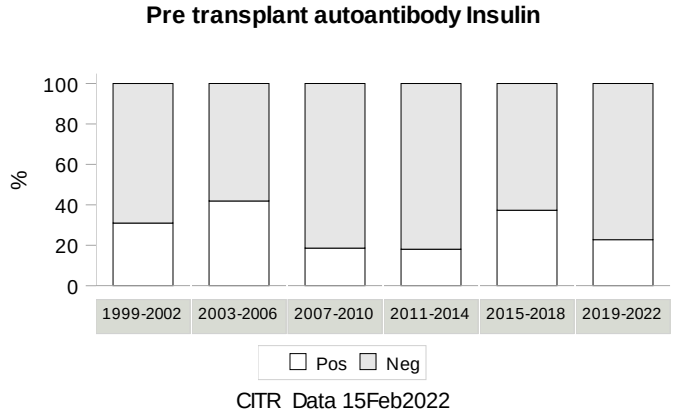


Exhibit 2 – 5 (continued)

Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Total Number of Positive Autoantibodies	**0**	330	41.0	108	57.1		84	42.6	119	44.9	94	44.8	114	48.9	20	29.9	7	31.8	
	1/4	269	33.4	60	31.7		72	36.5	73	27.5	74	35.2	73	31.3	27	40.3	10	45.5	
	1/2	156	19.4	15	7.9	***	36	18.3	57	21.5	27	12.9	31	13.3	16	23.9	4	18.2	
	2/3	2	0.2	2	1.1		0	0.0	1	0.4	2	1.0	1	0.4	0	0.0	0	0.0	
	3/4	48	6.0	4	2.1		5	2.5	15	5.7	13	6.2	14	6.0	4	6.0	1	4.5	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Total Number of Positive Autoantibodies	**Missing**	330	29.1	47	19.9		10	4.8	2	0.7	41	16.3	150	39.2	151	69.3	23	51.1	
	Available	805	70.9	189	80.1		197	95.2	265	99.3	210	83.7	233	60.8	67	30.7	22	48.9	

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

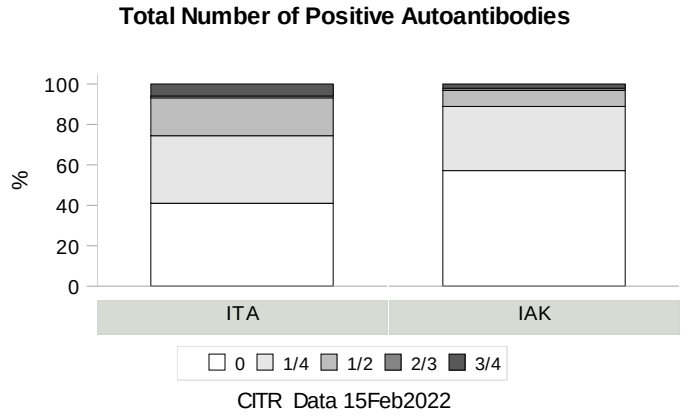


Exhibit 2 – 5 (continued)

Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
PRA-Class I	**Neg**	465	80.0	101	92.7		119	88.8	161	83.4	110	79.1	123	79.4	38	79.2	15	71.4	
	Pos	111	19.1	7	6.4	**	15	11.2	32	16.6	25	18.0	31	20.0	9	18.8	6	28.6	
	Equ	5	0.9	1	0.9		0	0.0	0	0.0	4	2.9	1	0.6	1	2.1	0	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
PRA-Class I	Missing	554	48.8	127	53.8		73	35.3	74	27.7	112	44.6	228	59.5	170	78.0	24	53.3	
	Available	581	51.2	109	46.2		134	64.7	193	72.3	139	55.4	155	40.5	48	22.0	21	46.7	

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

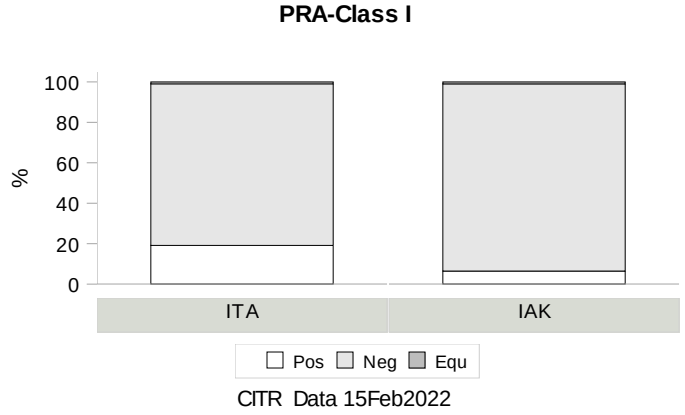


Exhibit 2 – 5 (continued)

Recipient Autoantibody and Sensitization at First Infusion

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
PRA-Class II	**Neg**	394	84.0	72	92.3		82	96.5	104	90.4	100	82.0	124	80.0	41	83.7	15	71.4	
	Pos	62	13.2	5	6.4		3	3.5	11	9.6	15	12.3	27	17.4	7	14.3	4	19.0	**
	Equ	13	2.8	1	1.3		0	0.0	0	0.0	7	5.7	4	2.6	1	2.0	2	9.5	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
PRA-Class II	**Missing**	666	58.7	158	66.9		122	58.9	152	56.9	129	51.4	228	59.5	169	77.5	24	53.3	
	Available	469	41.3	78	33.1		85	41.1	115	43.1	122	48.6	155	40.5	49	22.5	21	46.7	

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

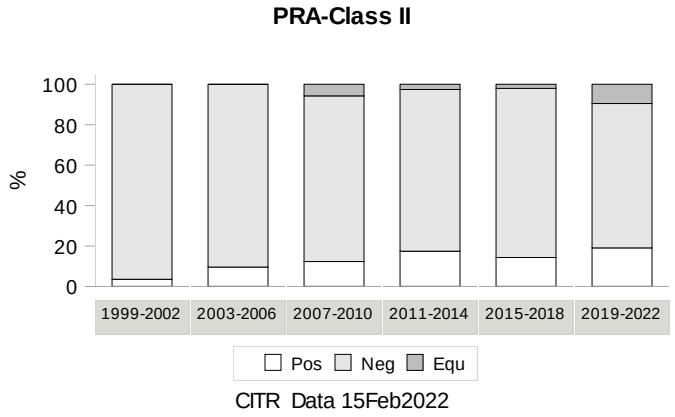


Exhibit 2 – 6

Recipient Infectious Disease Testing at First Infusion

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HIV	**Neg**	879	77.4	158	66.9	176	85.0	243	91.0	187	74.5	273	71.3	132	60.6	26	57.8
	Pos	-	0.0	1	0.4	-	0.0	-	0.0	1	0.4	-	0.0	-	0.0	-	0.0
	Unk	256	22.6	77	32.6	31	15.0	24	9.0	63	25.1	110	28.7	86	39.4	19	42.2

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HIV	Available	879	77.4	159	67.4	176	85.0	243	91.0	188	74.9	273	71.3	132	60.6	26	57.8
	Missing	256	22.6	77	32.6	31	15.0	24	9.0	63	25.1	110	28.7	86	39.4	19	42.2

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgG	**Neg**	502	44.2	68	28.8	91	44.0	134	50.2	107	42.6	151	39.4	73	33.5	14	31.1
	Pos	416	36.7	96	40.7	87	42.0	111	41.6	101	40.2	127	33.2	67	30.7	19	42.2
	Unk	217	19.1	72	30.5	29	14.0	22	8.2	43	17.1	105	27.4	78	35.8	12	26.7

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgG	Available	918	80.9	164	69.5	178	86.0	245	91.8	208	82.9	278	72.6	140	64.2	33	73.3
	Missing	217	19.1	72	30.5	29	14.0	22	8.2	43	17.1	105	27.4	78	35.8	12	26.7

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgM	**Neg**	629	55.4	81	34.3	104	50.2	160	59.9	138	55.0	218	56.9	76	34.9	14	31.1
	Pos	73	6.4	13	5.5	4	1.9	5	1.9	9	3.6	35	9.1	25	11.5	8	17.8
	Unk	433	38.1	142	60.2	99	47.8	102	38.2	104	41.4	130	33.9	117	53.7	23	51.1

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV-IgM	Available	702	61.9	94	39.8	108	52.2	165	61.8	147	58.6	253	66.1	101	46.3	22	48.9
	Missing	433	38.1	142	60.2	99	47.8	102	38.2	104	41.4	130	33.9	117	53.7	23	51.1

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Core	**Neg**	649	57.2	125	53.0	128	61.8	198	74.2	154	61.4	198	51.7	76	34.9	20	44.4
	Pos	20	1.8	5	2.1	2	1.0	4	1.5	6	2.4	9	2.3	4	1.8	-	0.0
	Unk	466	41.1	106	44.9	77	37.2	65	24.3	91	36.3	176	46.0	138	63.3	25	55.6

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Core	Available	669	58.9	130	55.1	130	62.8	202	75.7	160	63.7	207	54.0	80	36.7	20	44.4
	Missing	466	41.1	106	44.9	77	37.2	65	24.3	91	36.3	176	46.0	138	63.3	25	55.6

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

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Surface	**Neg**	298	26.3	43	18.2	39	18.8	49	18.4	64	25.5	127	33.2	51	23.4	11	24.4
	Pos	84	7.4	16	6.8	11	5.3	10	3.7	28	11.2	35	9.1	15	6.9	1	2.2
	Unk	753	66.3	177	75.0	157	75.8	208	77.9	159	63.3	221	57.7	152	69.7	33	73.3

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Hepatitis B Surface	**Available**	382	33.7	59	25.0	50	24.2	59	22.1	92	36.7	162	42.3	66	30.3	12	26.7
	Missing	753	66.3	177	75.0	157	75.8	208	77.9	159	63.3	221	57.7	152	69.7	33	73.3

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HCV	**Neg**	867	76.4	162	68.6	165	79.7	243	91.0	186	74.1	266	69.5	136	62.4	33	73.3
	Pos	9	0.8	6	2.5	4	1.9	1	0.4	1	0.4	6	1.6	2	0.9	1	2.2
	Unk	259	22.8	68	28.8	38	18.4	23	8.6	64	25.5	111	29.0	80	36.7	11	24.4

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HCV	**Available**	876	77.2	168	71.2	169	81.6	244	91.4	187	74.5	272	71.0	138	63.3	34	75.6
	Missing	259	22.8	68	28.8	38	18.4	23	8.6	64	25.5	111	29.0	80	36.7	11	24.4

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgG	**Neg**	87	7.7	8	3.4	10	4.8	17	6.4	19	7.6	32	8.4	14	6.4	3	6.7
	Pos	745	65.6	151	64.0	158	76.3	207	77.5	151	60.2	228	59.5	122	56.0	30	66.7
	Unk	303	26.7	77	32.6	39	18.8	43	16.1	81	32.3	123	32.1	82	37.6	12	26.7

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgG	**Available**	832	73.3	159	67.4	168	81.2	224	83.9	170	67.7	260	67.9	136	62.4	33	73.3
	Missing	303	26.7	77	32.6	39	18.8	43	16.1	81	32.3	123	32.1	82	37.6	12	26.7

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgM	**Neg**	467	41.1	83	35.2	94	45.4	135	50.6	95	37.8	159	41.5	59	27.1	8	17.8
	Pos	144	12.7	9	3.8	8	3.9	9	3.4	14	5.6	65	17.0	45	20.6	12	26.7
	Unk	524	46.2	144	61.0	105	50.7	123	46.1	142	56.6	159	41.5	114	52.3	25	55.6

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
EBV-IgM	**Available**	611	53.8	92	39.0	102	49.3	144	53.9	109	43.4	224	58.5	104	47.7	20	44.4
	Missing	524	46.2	144	61.0	105	50.7	123	46.1	142	56.6	159	41.5	114	52.3	25	55.6

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

	ITA									IAK								
	Total Number of Infusions Received									Total Number of Infusions Received								
	One Infusion			Two Infusions			>= Three Infusions			One Infusion			Two Infusions			>= Three Infusions		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Age (yrs)	298	46.9	0.7	545	47.5	0.5	292	46.2	0.6	77	48.3	1.1	118	48.5	0.8	40	47.4	1.5
Duration of Diabetes (yrs)	230	29.7	0.8	435	30.2	0.6	210	27.9	0.7	64	35.6	1.3	99	34.1	0.8	25	34.1	1.5
Weight (kg)	243	66.2	0.8	478	67.6	0.5	257	70.4	0.7	65	65.1	1.6	105	65.0	1.0	34	67.5	1.8
Body Mass Index (kg/m2)	166	23.2	0.2	308	23.7	0.2	220	24.3	0.2	54	23.2	0.4	86	22.9	0.3	29	23.7	0.5
Daily insulin requirement (units)	234	34.4	1.1	452	36.7	0.7	256	41.0	1.0	60	38.0	1.7	95	36.8	1.4	32	36.1	2.6
Average daily insulin / kg recipient body weight	221	0.5	0.0	436	0.5	0.0	243	0.6	0.0	57	0.6	0.0	91	0.6	0.0	31	0.5	0.0
Duration of intensive insulin therapy (yrs)	100	18.9	1.4	202	21.8	1.0	123	19.6	1.1	16	30.4	3.3	16	25.1	2.8	1	0.9	-
Fasting plasma glucose (mg/dL)	193	162.0	6.3	330	168.3	4.7	222	181.0	5.9	38	171.2	14.3	76	164.9	8.6	29	164.0	20.2
Basal C-Peptide (ng/mL)	202	0.1	0.0	343	0.1	0.0	234	0.1	0.0	50	0.2	0.1	81	0.3	0.1	28	0.1	0.0
HbA1C (%)	222	7.8	0.1	411	8.0	0.1	250	7.9	0.1	63	8.1	0.2	107	8.3	0.1	34	7.8	0.2

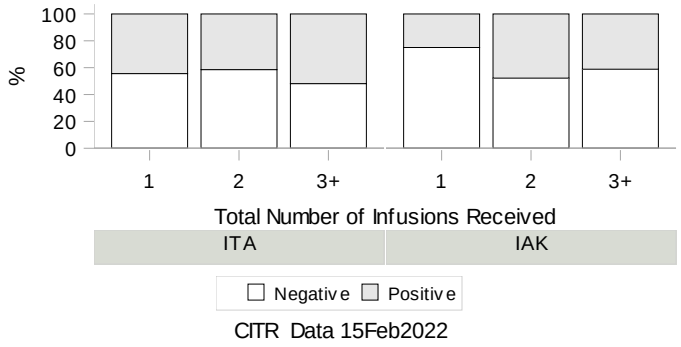
Exhibit 2 – 8

Recipient Baseline Autoantibodies by Total Infusions Received

		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - GAD 65	**Negative**	70	55.6	134	58.5	75	48.1	30	75.0	36	52.2	10	58.8
	Positive	56	44.4	95	41.5	81	51.9	10	25.0	33	47.8	7	41.2

Data completeness		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - GAD 65	Missing	172	57.7	316	58.0	136	46.6	37	48.1	50	42.0	23	57.5
	Available	126	42.3	229	42.0	156	53.4	40	51.9	69	58.0	17	42.5

Pre transplant autoantibody - GAD 65

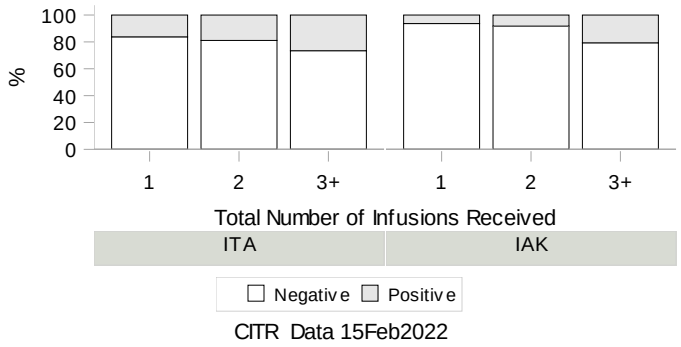


		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - IA-2	**Negative**	165	83.8	300	81.1	174	73.4	59	93.7	89	91.8	23	79.3
	Positive	32	16.2	70	18.9	63	26.6	4	6.3	8	8.2	6	20.7

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

Data completeness		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - IA-2	Missing	101	33.9	175	32.1	55	18.8	14	18.2	22	18.5	11	27.5
	Available	197	66.1	370	67.9	237	81.2	63	81.8	97	81.5	29	72.5

Pre transplant autoantibody - IA-2



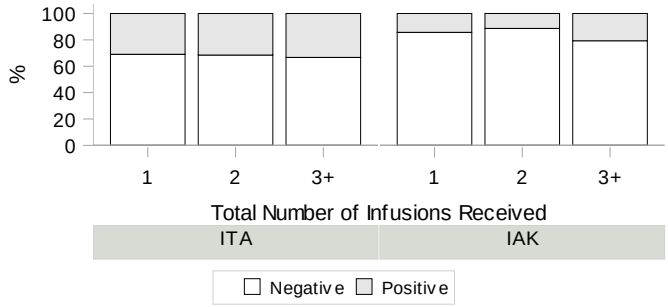
		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - Insulin	**Negative**	136	69.0	254	68.5	158	66.7	54	85.7	86	88.7	23	79.3
	Positive	61	31.0	117	31.5	79	33.3	9	14.3	11	11.3	6	20.7

Data completeness		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Pre transplant autoantibody - Insulin	Missing	101	33.9	174	31.9	55	18.8	14	18.2	22	18.5	11	27.5
	Available	197	66.1	371	68.1	237	81.2	63	81.8	97	81.5	29	72.5

Exhibit 2 – 8 (continued)

Recipient Baseline Autoantibodies by Total Infusions Received

Pre transplant autoantibody - Insulin

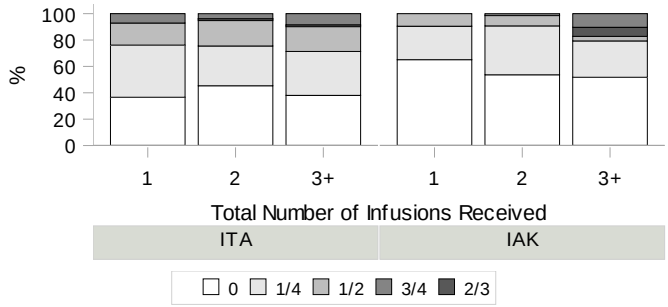


CITR Data 15Feb2022

		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Total Number of Positive Autoantibodies	**0**	72	36.5	168	45.3	90	38.0	41	65.1	52	53.6	15	51.7
	1/4	78	39.6	112	30.2	79	33.3	16	25.4	36	37.1	8	27.6
	1/2	33	16.8	76	20.5	47	19.8	6	9.5	8	8.2	1	3.4
	2/3	-	-	1	0.3	1	0.4	-	-	-	-	2	6.9
	3/4	14	7.1	14	3.8	20	8.4	-	-	1	1.0	3	10.3

Data completeness		ITA						IAK					
		Total Number of Infusions Received						Total Number of Infusions Received					
		One Infusion		Two Infusions		>= Three Infusions		One Infusion		Two Infusions		>= Three Infusions	
		N	%	N	%	N	%	N	%	N	%	N	%
Total Number of Positive Autoantibodies	**Missing**	101	33.9	174	31.9	55	18.8	14	18.2	22	18.5	11	27.5
	Available	197	66.1	371	68.1	237	81.2	63	81.8	97	81.5	29	72.5

Total Number of Positive Autoantibodies



CITR Data 15Feb2022

Exhibit 2 – 9

Recipient Laboratory Values at First Infusion

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
HbA1C (%)	883	7.9	0.0	204	8.2	0.1	*
Basal C-Peptide (ng/mL)	779	0.1	0.0	159	0.2	0.1	**
Fasting blood glucose (mg/dL)	745	170.5	3.2	143	166.4	7.1	
ALT (U/L)	880	24.1	0.7	174	23.8	1.0	
AST (U/L)	757	26.9	0.8	170	25.7	1.0	
Alkaline phosphatase (U/L)	678	80.0	1.6	158	108.8	5.8	***
Total bilirubin (mg/dL)	662	0.6	0.0	160	0.5	0.0	**
Total cholesterol (mg/dL)	748	170.4	1.4	172	171.9	3.2	
HDL (mg/dL)	723	65.1	0.7	161	63.3	1.7	
LDL (mg/dL)	705	90.7	1.1	146	86.7	2.5	
Triglycerides (mg/dL)	748	52.0	1.2	172	66.8	3.1	***
eGFR-CKD (mL/min/1.73m2)	936	91.3	0.7	211	62.2	1.5	***

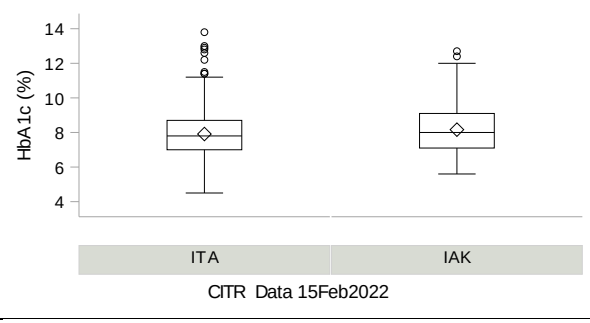
	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
HbA1C (%)	192	7.9	0.1	261	7.8	0.1	227	7.9	0.1	292	8.2	0.1	95	8.2	0.1	20	7.9	0.3	**
Basal C-Peptide (ng/mL)	180	0.2	0.0	253	0.1	0.0	187	0.1	0.0	211	0.1	0.0	90	0.2	0.1	17	0.1	0.0	
Fasting blood glucose (mg/dL)	168	181.1	7.2	248	169.4	5.8	196	156.0	5.8	197	171.8	6.0	68	180.1	9.0	11	154.5	23.5	
ALT (U/L)	146	22.4	1.3	240	24.3	0.7	201	25.8	1.4	299	25.1	1.5	137	20.7	0.9	31	22.7	1.7	
AST (U/L)	154	23.7	0.8	246	26.3	0.7	183	32.3	2.6	244	26.8	1.3	79	21.9	1.1	21	23.0	1.8	
Alkaline phosphatase (U/L)	148	90.7	4.6	230	99.3	4.5	170	76.8	2.8	195	72.2	2.3	71	86.6	4.0	22	84.4	5.6	***
Total bilirubin (mg/dL)	148	0.6	0.0	219	0.6	0.0	167	0.6	0.0	205	0.6	0.0	62	0.5	0.0	21	0.5	0.1	*
Total cholesterol (mg/dL)	161	180.8	2.8	242	173.1	2.1	190	169.7	2.9	228	163.4	2.8	77	167.2	5.4	22	165.7	7.6	***
HDL (mg/dL)	156	65.1	1.4	233	64.9	1.3	174	65.5	1.4	227	64.9	1.5	74	62.5	2.9	20	62.0	4.1	
LDL (mg/dL)	138	98.9	2.5	229	94.2	1.7	177	88.4	2.2	218	83.2	2.1	69	85.1	3.8	20	86.0	7.6	***
Triglycerides (mg/dL)	161	55.2	2.9	242	57.6	2.6	191	55.2	2.3	228	53.0	2.0	76	53.2	3.5	22	41.5	5.4	
eGFR-CKD (mL/min/1.73m2)	176	86.1	1.9	250	85.1	1.5	217	84.6	1.6	325	87.0	1.3	146	86.5	2.1	33	86.1	4.8	

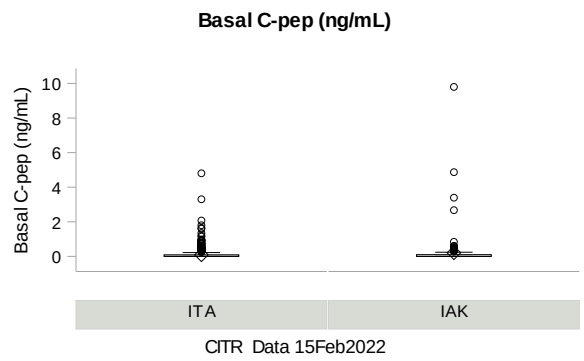
Exhibit 2 – 9 (continued)

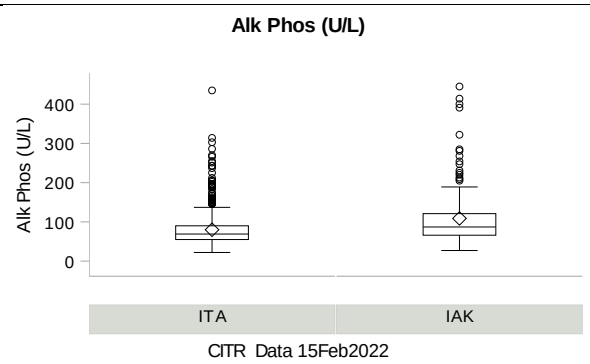
Recipient Laboratory Values at First Infusion

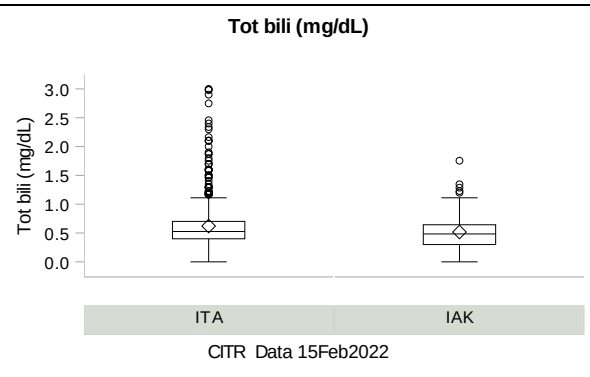
Significant trends in recipient laboratory values at first infusion from table above

By ITA or IAK

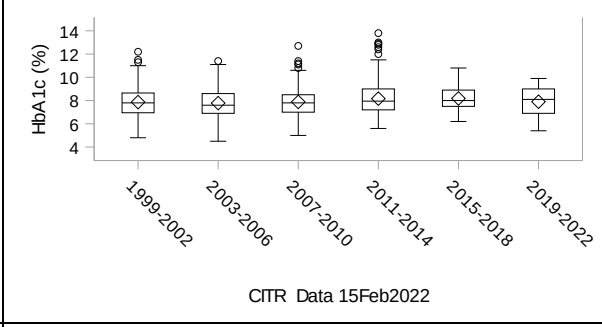


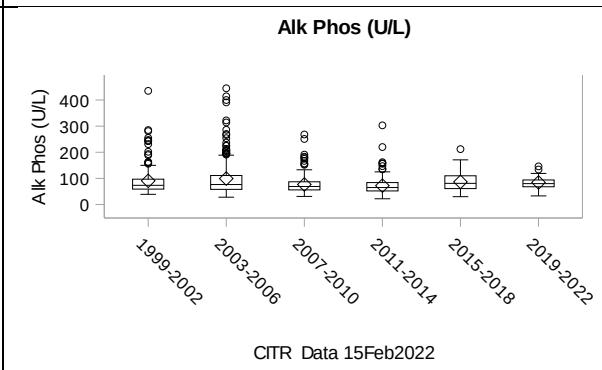






By Era





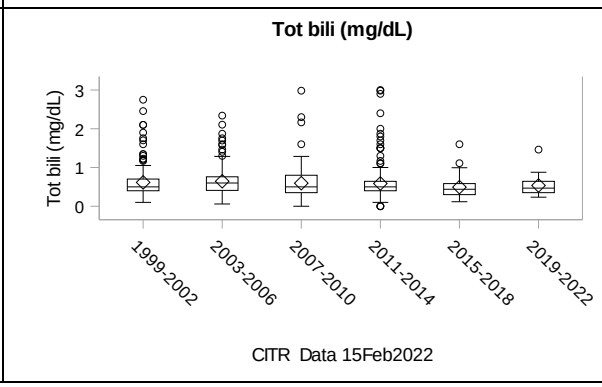


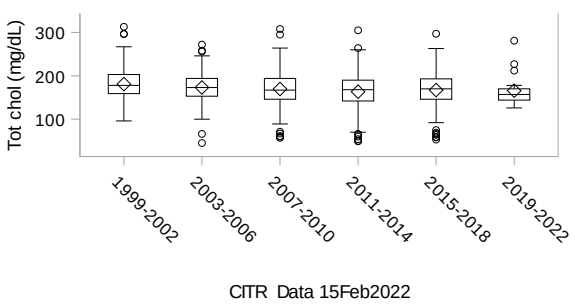
Exhibit 2 – 9 (continued)

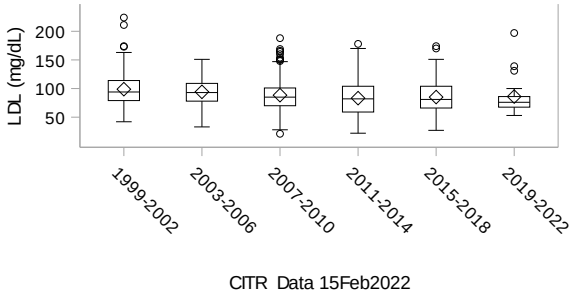
Recipient Laboratory Values at First Infusion

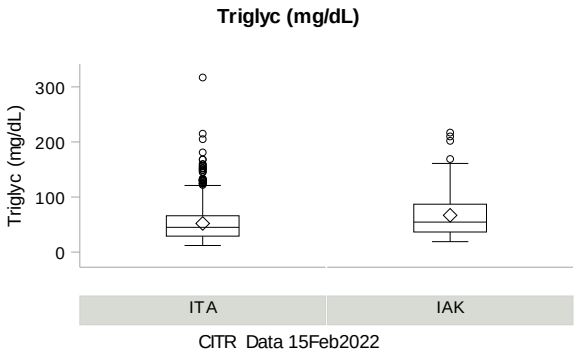
Significant trends in recipient laboratory values at first infusion from table above

By ITA or IAK

By Era







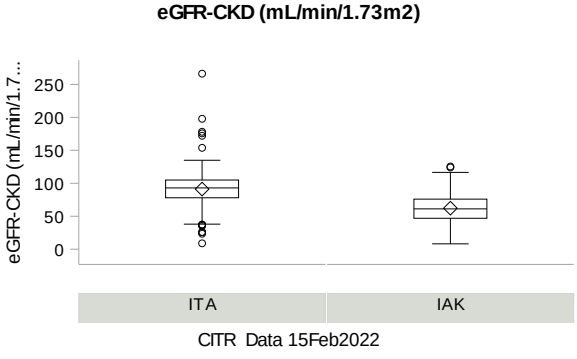


Exhibit 2 – 10
Donor Demographics (per Infusion)

	ITA			IAK			
	N	Mean	StdErr	N	Mean	StdErr	p
Age (yrs)	1075	44.5	0.4	214	45.5	0.8	

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			
	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	N	Mean	StdErr	p
Age (yrs)	289	43.7	0.7	398	43.5	0.6	276	45.7	0.7	208	46.0	0.8	102	46.6	1.3	16	42.1	2.2	**

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Gender	**Female**	743	39.9	127	35.3		135	37.1	192	39.0	177	38.6	236	38.8	111	42.9	19	45.2	
	Mixed	64	3.4	22	6.1	*	15	4.1	23	4.7	32	7.0	13	2.1	3	1.2		0.0	**
	Male	1057	56.7	211	58.6		214	58.8	277	56.3	250	54.5	359	59.0	145	56.0	23	54.8	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Gender	**Missing**	454	19.6	79	18.0		72	16.5	93	15.9	37	7.5	152	20.0	153	37.1	26	38.2	
	Available	1864	80.4	360	82.0		364	83.5	492	84.1	459	92.5	608	80.0	259	62.9	42	61.8	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Race	**White**	1067	89.1	141	89.2		227	91.5	247	86.4	225	89.6	311	87.6	163	91.6	35	92.1	
	Mixed	7	0.6		0.0			0.0	3	1.0	1	0.4	3	0.8		0.0		0.0	
	Non-white	124	10.4	17	10.8		21	8.5	36	12.6	25	10.0	41	11.5	15	8.4	3	7.9	

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

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

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Race	Missing	1120	48.3	281	64.0		188	43.1	299	51.1	245	49.4	405	53.3	234	56.8	30	44.1	
	Available	1198	51.7	158	36.0		248	56.9	286	48.9	251	50.6	355	46.7	178	43.2	38	55.9	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Ethnicity	**Non-Hispanic**	269	83.0	29	69.0	*	81	98.8	50	71.4	71	78.0	53	67.9	29	93.5	14	100.0	***
	Hispanic	55	17.0	13	31.0		1	1.2	20	28.6	20	22.0	25	32.1	2	6.5	0	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Ethnicity	Missing	1994	86.0	397	90.4		354	81.2	515	88.0	405	81.7	682	89.7	381	92.5	54	79.4	
	Available	324	14.0	42	9.6		82	18.8	70	12.0	91	18.3	78	10.3	31	7.5	14	20.6	

Exhibit 2 – 11
Donor Characteristics

	ITA			IAK				1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			
	N	Mean	SE	N	Mean	SE	p	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Donor age (yrs)	1075	44.5	0.4	214	45.5	0.8		289	43.7	0.7	398	43.5	0.6	276	45.7	0.7	208	46.0	0.8	102	46.6	1.3	16	42.1	2.2	**
Weight (kg)	1876	88.5	0.5	361	86.6	1.1		364	84.0	1.1	502	87.5	0.9	459	90.2	0.9	611	89.9	0.8	259	87.4	1.2	42	93.1	2.9	***
Height (cm)	1875	172.9	0.2	361	174.0	0.5		362	172.9	0.5	502	173.4	0.4	459	173.3	0.5	611	173.4	0.4	260	171.9	0.6	42	172.7	2.2	
Body Mass Index(kg/m2)	1874	29.6	0.1	361	28.6	0.3	**	362	28.1	0.3	502	29.1	0.3	459	30.0	0.3	611	29.9	0.2	259	29.6	0.4	42	31.9	1.6	***

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

Exhibit 2 – 11 (continued)
Donor Characteristics

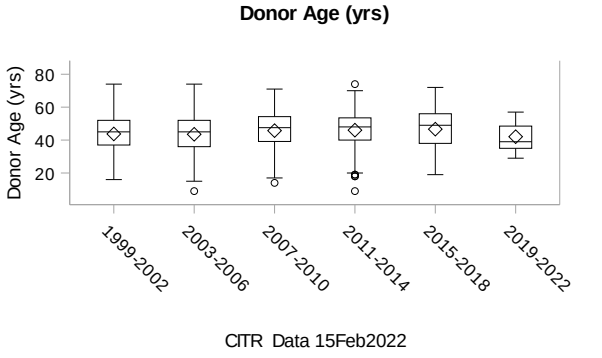
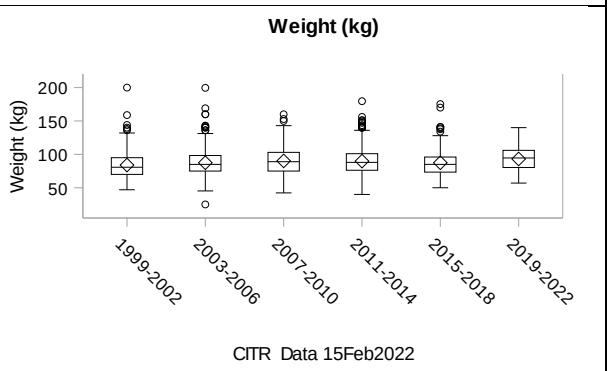
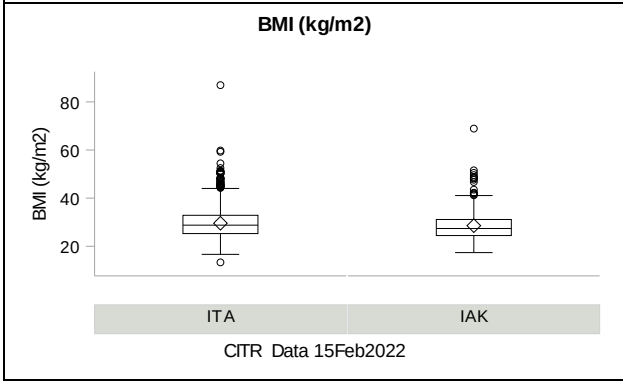
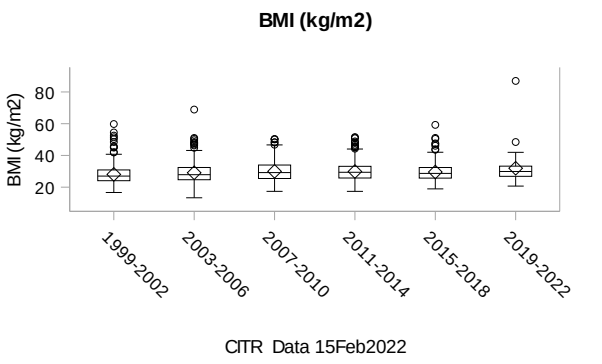
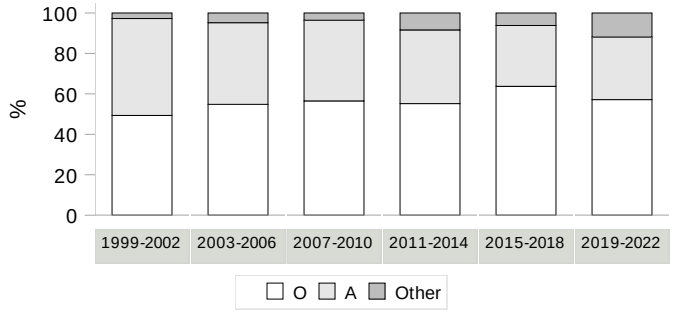
Significant trends in donor characteristics from table above	
By ITA or IAK	**By Era**
	
	
	

Exhibit 2 – 11 (continued)
Donor Characteristics

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Donor Blood Type	**O**	1025	55.1	206	57.2		180	49.3	274	54.8	252	56.5	336	55.2	165	63.7	24	57.1	*
	A	734	39.4	134	37.2		175	47.9	202	40.4	178	39.9	222	36.5	78	30.1	13	31.0	***
	Other	102	5.5	20	5.6		10	2.7	24	4.8	16	3.6	51	8.4	16	6.2	5	11.9	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Donor Blood Type	**Missing**	457	19.7	79	18.0		71	16.3	85	14.5	50	10.1	151	19.9	153	37.1	26	38.2	
	Available	1861	80.3	360	82.0		365	83.7	500	85.5	446	89.9	609	80.1	259	62.9	42	61.8	

Donor Blood Type



CITR Data 15Feb2022

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Hx Hypertension	**No**	1034	66.8	184	65.7		180	65.5	295	66.1	252	62.5	340	67.9	121	73.3	30	78.9	
	Yes	514	33.2	96	34.3		95	34.5	151	33.9	151	37.5	161	32.1	44	26.7	8	21.1	

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

Exhibit 2 – 11 (continued)
Donor Characteristics

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Hx Hypertension	Missing	770	33.2	159	36.2		161	36.9	139	23.8	93	18.8	259	34.1	247	60.0	30	44.1	
	Available	1548	66.8	280	63.8		275	63.1	446	76.2	403	81.3	501	65.9	165	40.0	38	55.9	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Hx Alcohol	**No**	1216	86.2	236	87.4		218	83.5	372	84.9	348	87.9	418	87.1	84	91.3	12	85.7	
	Yes	195	13.8	34	12.6		43	16.5	66	15.1	48	12.1	62	12.9	8	8.7	2	14.3	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Hx Alcohol	Missing	907	39.1	169	38.5		175	40.1	147	25.1	100	20.2	280	36.8	320	77.7	54	79.4	
	Available	1411	60.9	270	61.5		261	59.9	438	74.9	396	79.8	480	63.2	92	22.3	14	20.6	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Hx Diabetes	**No**	1591	99.5	282	99.6		324	99.7	457	99.8	402	100.0	487	99.0	166	99.4	37	97.4	
	Yes	8	0.5	1	0.4		1	0.3	1	0.2	0	0.0	5	1.0	1	0.6	1	2.6	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Hx Diabetes	Missing	719	31.0	156	35.5		111	25.5	127	21.7	94	19.0	268	35.3	245	59.5	30	44.1	
	Available	1599	69.0	283	64.5		325	74.5	458	78.3	402	81.0	492	64.7	167	40.5	38	55.9	

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

Exhibit 2 – 12

Characteristics of Hospitalization and Organ Procurement

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Time from admission to brain death (hrs)	959	56.6	3.3	186	54.4	3.9	
Time from cross clamp to pancreas recovery (hrs)	758	0.9	0.0	196	1.0	0.1	
Cold ischemia time (hrs)	1080	8.0	0.2	296	7.6	0.4	

	2011-2014			2003-2006			2007-2010			1999-2002			2015-2018			2019-2022			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Time from admission to brain death (hrs)	245	70.2	5.4	306	53.3	3.8	220	59.2	4.0	207	47.1	4.1	133	38.0	17.2	34	89.0	20.0	
Time from cross clamp to pancreas recovery (hrs)	169	1.0	0.1	359	0.9	0.1	175	1.0	0.1	179	0.6	0.0	59	0.8	0.1	13	0.9	0.2	*
Cold ischemia time (hrs)	193	9.2	0.5	472	7.4	0.1	278	8.0	0.5	356	7.3	0.2	65	10.3	1.2	12	10.7	4.3	***

		ITA		IAK		
		N	%	N	%	p
Cause of death	**CVA**	1061	59.8	205	64.9	
	Trauma	431	24.3	68	21.5	
	Other	281	15.8	43	13.6	

		2011-2014		2003-2006		2007-2010		1999-2002		2015-2018		2019-2022		
		N	%	N	%	N	%	N	%	N	%	N	%	p
Cause of death	**CVA**	329	59.2	285	59.9	261	61.1	200	59.0	163	65.2	28	68.3	
	Trauma	119	21.4	134	28.2	114	26.7	93	27.4	34	13.6	5	12.2	***
	Other	108	19.4	57	12.0	52	12.2	46	13.6	53	21.2	8	19.5	

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

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

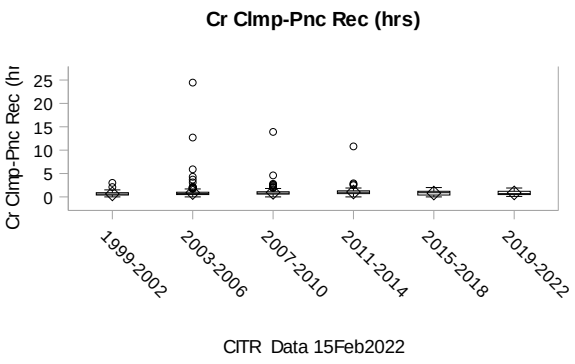
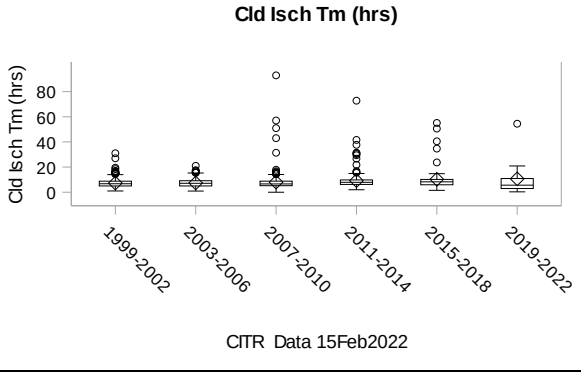
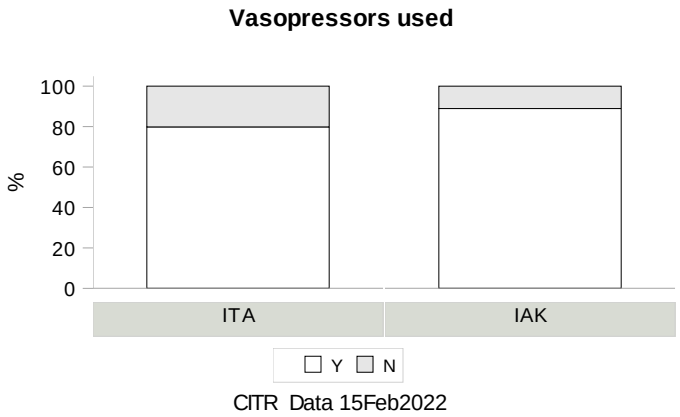
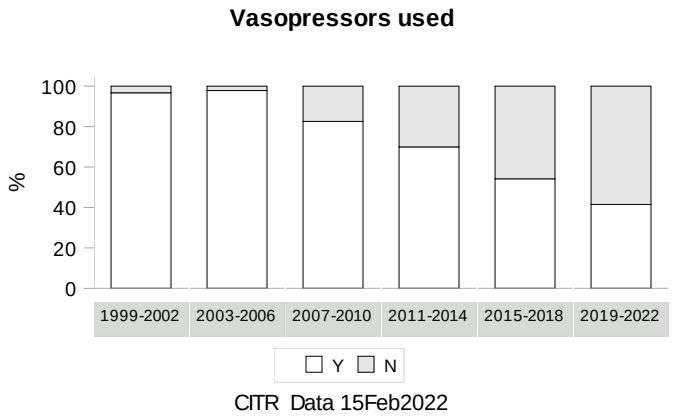
Significant trends in characteristics of hospitalization and organ procurement from table above	
By ITA or IAK	**By Era**
	
	

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

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Vasopressors used	**No**	326	20.2	31	11.1	***	10	3.3	10	2.2	67	17.4	147	30.1	99	45.8	24	58.5	***
	Yes	1290	79.8	249	88.9		295	96.7	451	97.8	317	82.6	342	69.9	117	54.2	17	41.5	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Vasopressors used	**Missing**	702	30.3	159	36.2		131	30.0	124	21.2	112	22.6	271	35.7	196	47.6	27	39.7	
	Available	1616	69.7	280	63.8		305	70.0	461	78.8	384	77.4	489	64.3	216	52.4	41	60.3	





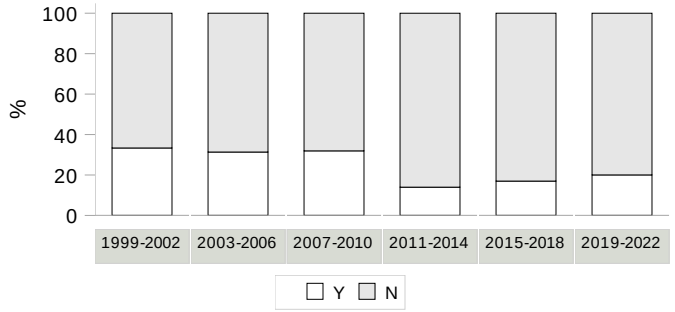
		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Transfusions during hospitalization	**No**	699	71.7	130	74.7		172	66.7	274	68.7	143	68.1	179	86.1	49	83.1	12	80.0	
	Yes	276	28.3	44	25.3		86	33.3	125	31.3	67	31.9	29	13.9	10	16.9	3	20.0	***

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

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

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Transfusions during hospitalization	Missing	1343	57.9	265	60.4		178	40.8	186	31.8	286	57.7	552	72.6	353	85.7	53	77.9	
	Available	975	42.1	174	39.6		258	59.2	399	68.2	210	42.3	208	27.4	59	14.3	15	22.1	

Transfus during hosp



CITR Data 15Feb2022

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Transfusions intraoperatively	**No**	674	94.0	122	94.6		201	91.4	318	94.6	151	96.2	87	94.6	28	93.3	11	100.0	
	Yes	43	6.0	7	5.4		19	8.6	18	5.4	6	3.8	5	5.4	2	6.7	0	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Transfusions intraoperatively	Missing	1601	69.1	310	70.6		216	49.5	249	42.6	339	68.3	668	87.9	382	92.7	57	83.8	
	Available	717	30.9	129	29.4		220	50.5	336	57.4	157	31.7	92	12.1	30	7.3	11	16.2	

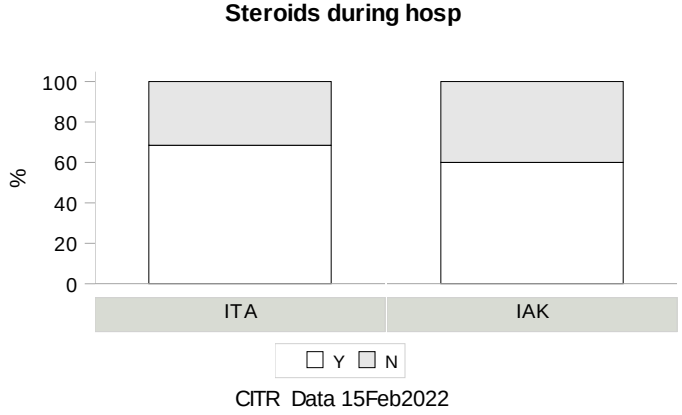
* p < 0.05 ** p < 0.01 *** p < 0.001

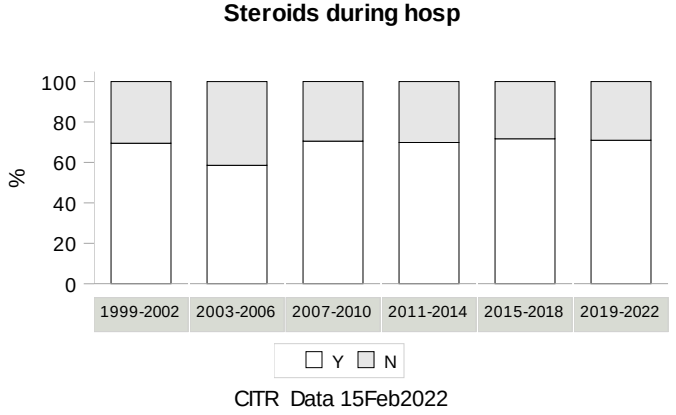
Exhibit 2 – 12 (continued)

Characteristics of Hospitalization and Organ Procurement

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Steroids given to donor during hospitalization	**No**	311	31.5	78	40.0	*	54	30.5	133	41.4	84	29.5	79	30.2	30	28.3	9	29.0	*
	Yes	676	68.5	117	60.0		123	69.5	188	58.6	201	70.5	183	69.8	76	71.7	22	71.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Steroids given to donor during hospitalization	**Missing**	1331	57.4	244	55.6		259	59.4	264	45.1	211	42.5	498	65.5	306	74.3	37	54.4	
	Available	987	42.6	195	44.4		177	40.6	321	54.9	285	57.5	262	34.5	106	25.7	31	45.6	





		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Insulin given to donor during hospitalization	**No**	666	52.0	113	46.9		172	65.9	234	55.1	141	38.4	177	47.3	45	55.6	10	66.7	***
	Yes	616	48.0	128	53.1		89	34.1	191	44.9	226	61.6	197	52.7	36	44.4	5	33.3	

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

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

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%
Insulin given to donor during hospitalization	Missing	1036	44.7	198	45.1		175	40.1	160	27.4	129	26.0	386	50.8	331	80.3	53	77.9
	Available	1282	55.3	241	54.9		261	59.9	425	72.6	367	74.0	374	49.2	81	19.7	15	22.1

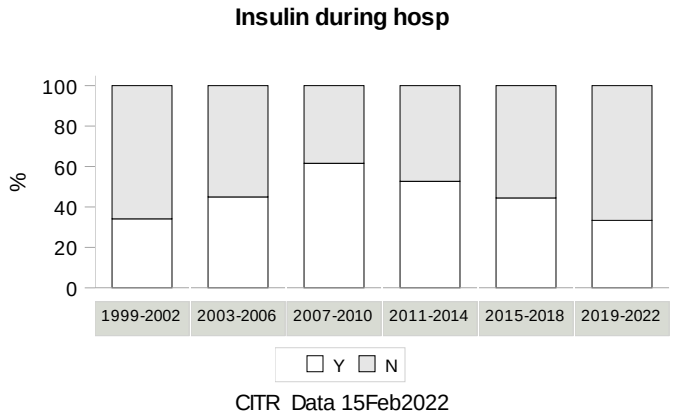


Exhibit 2 – 13
Donor Serology

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HIV	NEG	1626	100.0	302	100.0	334	100.0	468	100.0	418	100.0	503	100.0	167	100.0	38	100.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HIV	Missing	692	29.9	137	31.2	102	23.4	117	20.0	78	15.7	257	33.8	245	59.5	30	44.1
	Available	1626	70.1	302	68.8	334	76.6	468	80.0	418	84.3	503	66.2	167	40.5	38	55.9

Exhibit 2 – 13 (continued)
Donor Serology

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HTLV	**NEG**	1124	100.0	202	100.0	289	100.0	422	100.0	304	100.0	256	100.0	44	100.0	11	100.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HTLV	Missing	1194	51.5	237	54.0	147	33.7	163	27.9	192	38.7	504	66.3	368	89.3	57	83.8
	Available	1124	48.5	202	46.0	289	66.3	422	72.1	304	61.3	256	33.7	44	10.7	11	16.2

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
VDRL	**NEG**	1131	99.7	240	100.0	297	100.0	427	99.8	324	100.0	290	99.3	27	100.0	6	100.0
	POS	3	0.3	-	0.0	-	0.0	1	0.2	-	0.0	2	0.7	-	0.0	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
VDRL	Missing	1184	51.1	199	45.3	139	31.9	157	26.8	172	34.7	468	61.6	385	93.4	62	91.2
	Available	1134	48.9	240	54.7	297	68.1	428	73.2	324	65.3	292	38.4	27	6.6	6	8.8

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV	**NEG**	719	45.9	136	45.5	127	39.9	207	46.1	177	43.4	240	48.5	89	55.3	15	45.5
	POS	846	54.1	163	54.5	191	60.1	242	53.9	231	56.6	255	51.5	72	44.7	18	54.5

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
CMV	Missing	753	32.5	140	31.9	118	27.1	136	23.2	88	17.7	265	34.9	251	60.9	35	51.5
	Available	1565	67.5	299	68.1	318	72.9	449	76.8	408	82.3	495	65.1	161	39.1	33	48.5

Exhibit 2 – 13 (continued)
Donor Serology

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HBSag	NEG	1610	99.9	298	100.0	329	100.0	466	99.8	411	100.0	500	99.8	164	100.0	38	100.0
	POS	2	0.1	-	0.0	-	0.0	1	0.2	-	0.0	1	0.2	-	0.0	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HBSag	Missing	706	30.5	141	32.1	107	24.5	118	20.2	85	17.1	259	34.1	248	60.2	30	44.1
	Available	1612	69.5	298	67.9	329	75.5	467	79.8	411	82.9	501	65.9	164	39.8	38	55.9

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HBC	NEG	1526	99.2	278	99.6	304	98.7	462	99.6	385	98.7	463	100.0	159	99.4	31	96.9
	POS	12	0.8	1	0.4	4	1.3	2	0.4	5	1.3	-	0.0	1	0.6	1	3.1

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HBC	Missing	780	33.6	160	36.4	128	29.4	121	20.7	106	21.4	297	39.1	252	61.2	36	52.9
	Available	1538	66.4	279	63.6	308	70.6	464	79.3	390	78.6	463	60.9	160	38.8	32	47.1

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HCV	NEG	1475	99.9	264	99.6	324	99.7	454	100.0	385	99.7	401	100.0	143	100.0	32	100.0
	POS	1	0.1	1	0.4	1	0.3	-	0.0	1	0.3	-	0.0	-	0.0	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
HCV	Missing	842	36.3	174	39.6	111	25.5	131	22.4	110	22.2	359	47.2	269	65.3	36	52.9
	Available	1476	63.7	265	60.4	325	74.5	454	77.6	386	77.8	401	52.8	143	34.7	32	47.1

Exhibit 2 – 14

Donor Laboratory Data

	ITA			IAK			
	N	Mean	SE	N	Mean	SE	p
Serum creatinine (mg/dL)	1290	1.1	0.0	285	1.0	0.0	
BUN (mg/dL)	870	15.5	0.3	253	15.5	0.5	
Total bilirubin (mg/dL)	1083	0.9	0.0	257	0.8	0.0	
AST (U/L)	1238	76.1	5.5	271	70.2	9.5	
ALT (U/L)	1409	66.1	4.0	280	58.0	7.1	
Serum lipase (mKat/L)	1134	1.0	0.1	222	0.9	0.1	
Serum amylase (mKat/L)	1128	2.1	0.1	265	2.4	0.3	
Minimum pre-insulin blood glucose (mg/dL)	984	131.5	1.3	231	137.9	3.0	*
Maximum blood glucose (mg/dL)	1074	220.3	2.4	237	230.2	5.2	

	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Serum creatinine (mg/dL)	258	1.2	0.1	441	1.1	0.0	352	1.1	0.0	399	1.2	0.0	110	1.0	0.1	15	0.9	0.1	*
BUN (mg/dL)	196	15.3	0.7	330	14.7	0.5	250	16.2	0.6	267	16.0	0.6	65	15.3	1.0	15	16.3	2.1	
Total bilirubin (mg/dL)	210	0.8	0.0	363	0.9	0.0	337	0.8	0.0	347	0.8	0.0	68	0.8	0.1	15	0.9	0.2	
AST (U/L)	221	97.9	19.8	377	62.2	5.5	361	80.4	9.8	390	67.1	7.6	137	84.3	20.0	23	62.7	18.2	
ALT (U/L)	222	77.2	16.6	382	50.3	4.2	389	69.9	7.8	476	67.6	6.4	185	60.7	6.0	35	70.2	15.9	
Serum lipase (mKat/L)	243	0.9	0.1	362	1.1	0.1	303	1.1	0.1	347	1.0	0.1	90	0.8	0.2	11	0.4	0.0	
Serum amylase (mKat/L)	252	2.8	0.4	430	2.1	0.1	318	1.9	0.1	318	1.7	0.1	67	3.7	1.3	8	1.4	0.5	
Minimum pre-insulin blood glucose (mg/dL)	272	130.0	2.3	396	125.9	1.9	198	132.2	3.3	280	140.8	2.7	58	149.1	6.6	11	168.4	23.1	***
Maximum blood glucose (mg/dL)	240	244.3	6.3	418	226.3	3.9	264	218.5	4.2	315	207.7	3.9	63	200.8	7.4	11	194.6	20.3	***

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

Exhibit 2 – 14 (continued)
Donor Laboratory Data

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

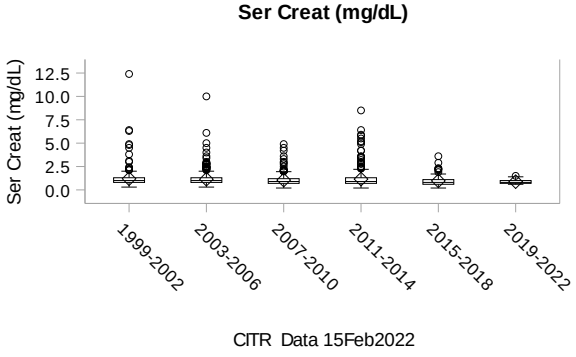
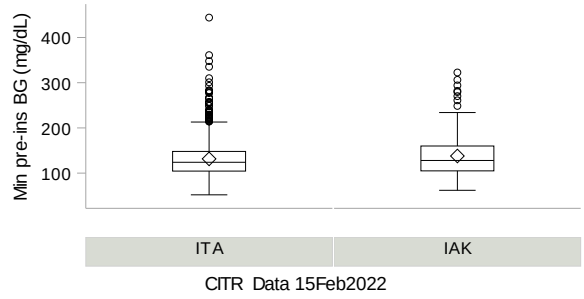
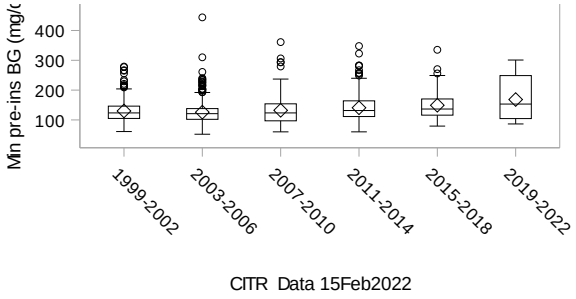
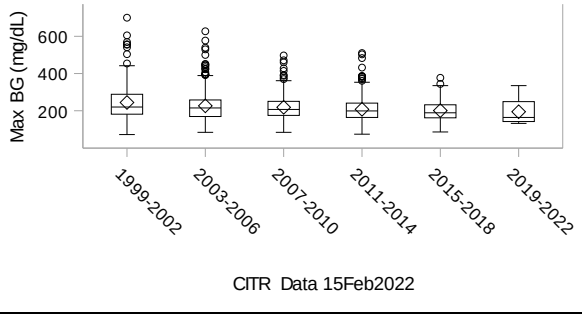
By ITA or IAK	By Era
	
	
	

Exhibit 2 – 15
Donor Laboratory Data

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Positive cross match	**No**	742	96.6	209	98.6		178	99.4	310	96.6	210	97.2	179	96.8	59	92.2	15	100.0	
	Yes	26	3.4	3	1.4		1	0.6	11	3.4	6	2.8	6	3.2	5	7.8		0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Positive cross match	**Missing**	1550	66.9	227	51.7		257	58.9	264	45.1	280	56.5	575	75.7	348	84.5	53	77.9	
	Available	768	33.1	212	48.3		179	41.1	321	54.9	216	43.5	185	24.3	64	15.5	15	22.1	

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

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 (1999-2002, 2003-2006, 2007-2010, 2011-2014, 2015-2018, and 2019-2022).

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

Over the duration of the Registry, the proportion of islet processing centers that were unrelated to the islet transplant center rose appreciably from 0% in 1999-2002 to 21% in 2015-2018 and has since declined, while the proportion of procurement teams unrelated to the islet transplant center has declined steadily from 31% in 1999-2002 to 14% in 2019-2022 (p. 3-4).

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

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

Islet preparations were cultured more frequently in the recent eras (97% in 2019-2022 vs. 37% in 1999-2002) and mean culture time has increased over the eras (Exhibit 3-2).

- Total cell volume infused has declined appreciably over the eras, while IEQ/Kg recipient has remained remarkably stable (Exhibit 3-4A).
- Endotoxin (both total and /kg) has declined sharply over the eras (Exhibit 3-4A).
- Stimulation index has declined over the eras (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

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Islet processing center	**Processing/transplant centers related**	1173	92.2	265	84.9	***	265	100.0	493	98.2	324	83.5	266	83.6	72	78.3	18	94.7	***
	Unrelated	95	7.5	46	14.7		0	0.0	9	1.8	62	16.0	50	15.7	19	20.7	1	5.3	
	Mixed	4	0.3	1	0.3		0	0.0	0	0.0	2	0.5	2	0.6	1	1.1	0	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Islet processing center	**Missing**	1012	44.3	128	29.1		65	19.7	72	12.5	91	19.0	428	57.4	393	81.0	91	82.7	
	Available	1272	55.7	312	70.9		265	80.3	502	87.5	388	81.0	318	42.6	92	19.0	19	17.3	

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

Exhibit 3 – 1A (continued)
Islet Processing Summary

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Procurement Team	**Unrelated**	355	25.5	58	19.9		81	30.6	157	32.5	88	25.7	59	16.8	21	10.9	7	13.7	
	Procurement/transplant centers related	975	70.0	221	75.7		170	64.2	302	62.5	239	69.9	276	78.6	167	87.0	42	82.4	***
	Mixed	27	1.9	4	1.4		7	2.6	14	2.9	8	2.3	1	0.3	1	0.5	-	0.0	
	Miss/unk	35	2.5	9	3.1		7	2.6	10	2.1	7	2.0	15	4.3	3	1.6	2	3.9	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Procurement Team	**Missing**	892	39.1	148	33.6		65	19.7	91	15.9	137	28.6	395	52.9	293	60.4	59	53.6	
	Available	1392	60.9	292	66.4		265	80.3	483	84.1	342	71.4	351	47.1	192	39.6	51	46.4	

		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%	p	N	%	N	%	N	%	N	%	N	%	N	%	p
Cultured	**Islets cultured >=6 hrs**	963	77.4	194	81.9		82	37.3	261	62.7	224	90.3	341	98.3	216	100.0	33	97.1	***
	None	281	22.6	43	18.1		138	62.7	155	37.3	24	9.7	6	1.7	-	0.0	1	2.9	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Cultured	**Missing**	1040	45.5	203	46.1		110	33.3	158	27.5	231	48.2	399	53.5	269	55.5	76	69.1	
	Available	1244	54.5	237	53.9		220	66.7	416	72.5	248	51.8	347	46.5	216	44.5	34	30.9	

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

Exhibit 3 – 1A
Islet Processing Summary (Continued)

		ITA		IAK		p	1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		p
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Gradient type	**Continuous**	1063	90.3	225	89.6		176	79.3	379	82.8	291	96.0	336	99.7	87	97.8	19	100.0	
	Discontinuous	34	2.9	17	6.8		20	9.0	28	6.1	1	0.3	1	0.3	1	1.1	-	0.0	
	Both	65	5.5	6	2.4	*	24	10.8	39	8.5	7	2.3	-	0.0	1	1.1	-	0.0	***
	None	1	0.1	-	0.0		-	0.0	1	0.2	-	0.0	-	0.0	-	0.0	-	0.0	
	Mixed	14	1.2	3	1.2		2	0.9	11	2.4	4	1.3	-	0.0	-	0.0	-	0.0	

Data completeness		ITA		IAK			1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022		
		N	%	N	%		N	%	N	%	N	%	N	%	N	%	N	%	
Gradient type	**Missing**	1107	48.5	189	43.0		108	32.7	116	20.2	176	36.7	409	54.8	396	81.6	91	82.7	
	Available	1177	51.5	251	57.0		222	67.3	458	79.8	303	63.3	337	45.2	89	18.4	19	17.3	

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

Exhibit 3 – 1B
Final Islet Preparation Microbiology (Continued)

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Aerobic culture	**Negative**	1220	98.3	242	98.0	220	97.3	441	99.3	294	97.7	344	97.7	144	99.3	19	95.0
	Positive	21	1.7	5	2.0	6	2.7	3	0.7	7	2.3	8	2.3	1	0.7	1	5.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Aerobic culture	Missing	1043	45.7	193	43.9	104	31.5	130	22.6	178	37.2	394	52.8	340	70.1	90	81.8
	Available	1241	54.3	247	56.1	226	68.5	444	77.4	301	62.8	352	47.2	145	29.9	20	18.2

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anaerobic culture	**Negative**	1109	98.9	220	100.0	170	97.7	356	99.7	291	99.7	349	98.9	143	98.6	20	100.0
	Positive	12	1.1	-	0.0	4	2.3	1	0.3	1	0.3	4	1.1	2	1.4	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Anaerobic culture	Missing	1163	50.9	220	50.0	156	47.3	217	37.8	187	39.0	393	52.7	340	70.1	90	81.8
	Available	1121	49.1	220	50.0	174	52.7	357	62.2	292	61.0	353	47.3	145	29.9	20	18.2

Exhibit 3 – 1B
Final Islet Preparation Microbiology (Continued)

		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Fungal Culture	**Negative**	1152	98.8	206	98.6	221	100.0	448	99.1	271	99.6	299	96.5	112	100.0	7	87.5
	Positive	14	1.2	3	1.4	-	0.0	4	0.9	1	0.4	11	3.5	-	0.0	1	12.5

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Fungal Culture	**Missing**	1118	48.9	231	52.5	109	33.0	122	21.3	207	43.2	436	58.4	373	76.9	102	92.7
	Available	1166	51.1	209	47.5	221	67.0	452	78.7	272	56.8	310	41.6	112	23.1	8	7.3

		ITA		IAK		1999-2002		2003-2006		2007-2010		2015-2018		2011-2014		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mycoplasma	**Negative**	707	99.9	66	100.0	170	99.4	247	100.0	121	100.0	64	100.0	169	100.0	2	100.0
	Positive	1	0.1	-	0.0	1	0.6	-	0.0	-	0.0	-	0.0	-	0.0	-	0.0

Data completeness		ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
		N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Mycoplasma	**Missing**	1576	69.0	374	85.0	159	48.2	327	57.0	358	74.7	577	77.3	421	86.8	108	98.2
	Available	708	31.0	66	15.0	171	51.8	247	43.0	121	25.3	169	22.7	64	13.2	2	1.8

Exhibit 3 – 2
Cold Ischemia Information

	Transplant type							Era																	
	ITA			IAK				1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			
	N	Mean	SD	N	Mean	SD	p	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	N	Mean	SD	p
Time from cross clamp to pancreas recovery (hrs)	758	0.9	1.2	196	1.0	0.9		137	0.6	0.4	351	0.9	1.5	191	0.9	1.1	185	1.0	0.8	73	0.9	0.5	17	0.7	0.5	*
Duration of cold ischemia (hrs)	1080	8.0	5.5	296	7.6	6.5		279	7.2	3.5	482	7.3	3.1	312	8.2	7.3	200	8.6	6.6	86	10.6	9.5	17	10.0	12.6	***
Time from brain death to pancreas recovery (hrs)	703	20.1	9.0	181	17.3	9.1	***	128	17.0	7.0	315	19.5	8.9	175	20.6	9.2	180	19.9	9.0	73	19.6	11.4	13	25.5	10.0	**
Culture time (hrs)	1243	21.0	16.5	237	25.6	18.6	***	220	11.6	17.7	416	17.7	17.9	248	25.7	16.3	346	28.6	14.7	216	24.1	11.6	34	22.4	10.5	***

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

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

Infusions	Transplant type							Era																
	ITA			IAK			p	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			p
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	695	7.1	0.2	127	6.9	0.4		140	8.4	0.4	202	8.2	0.3	145	6.8	0.4	212	5.8	0.2	103	6.0	0.4	20	5.6	0.8	***
Total islet particles (final preparation)	560	820.2	19.0	111	805.3	40.4		127	927.2	44.4	185	864.6	29.3	115	732.8	39.1	159	805.3	34.8	73	732.9	52.9	12	432.5	110.6	***
Embedded islets (%)	484	15.4	0.6	71	14.6	1.6		92	13.9	1.4	140	16.1	1.2	95	16.6	1.5	157	16.2	1.1	67	12.1	1.5	4	11.0	3.5	
Islet equivalents (1000s)	765	855.4	15.3	153	928.9	39.7		136	895.6	38.4	189	881.7	29.3	162	898.4	37.3	294	897.4	26.2	114	733.2	34.7	23	657.2	63.5	**
Islet equivalents(1000s)/kg recipient	726	12.6	0.2	176	13.3	0.5		163	13.9	0.5	219	13.6	0.4	192	12.3	0.4	230	12.1	0.4	79	12.0	0.6	19	9.3	0.9	***
Beta cells (x10^6)	207	417.3	22.3	22	426.5	76.9		61	445.6	41.6	81	436.9	37.4	26	469.8	66.5	61	344.0	37.5	0	-	-	0	-	-	
Beta cells/kg recipient weight	168	6.3	0.4	15	8.5	1.8		58	6.7	0.6	74	6.7	0.7	16	5.5	0.9	35	6.0	0.8	0	-	-	0	-	-	
Insulin content (1000s micrograms)	169	6.2	0.3	16	5.3	0.8		66	6.3	0.5	91	6.0	0.4	7	5.1	1.1	6	6.4	1.3	8	6.9	1.7	7	4.7	1.2	
Total Endotoxin units	544	30.9	3.6	127	49.7	7.5	*	120	46.1	7.3	190	52.2	8.8	169	16.2	3.6	144	25.3	4.9	39	32.9	10.1	9	3.0	0.9	**
Endotoxin units/kg recipient weight	508	0.5	0.1	115	0.8	0.1	*	114	0.8	0.1	181	0.8	0.1	155	0.2	0.1	131	0.4	0.1	33	0.6	0.2	9	0.0	0.0	***
Islet potency: Stimulation index	594	3.1	0.1	144	3.5	0.2		144	3.7	0.3	193	3.2	0.2	131	2.9	0.2	180	3.0	0.2	80	2.8	0.2	10	3.7	0.7	**
Islet viability	759	89.4	0.2	141	91.6	0.5	***	137	91.0	0.5	216	91.2	0.3	154	90.7	0.5	239	88.9	0.4	130	87.1	0.5	24	87.2	1.6	***
Purity	576	61.2	0.6	153	60.6	1.1		145	60.0	1.2	223	60.9	1.0	129	64.0	1.3	152	61.4	1.0	76	58.4	1.5	4	53.3	5.3	
Total DNA	253	19.6	1.1	26	16.9	2.6		65	17.4	1.8	97	20.7	1.9	32	20.3	3.1	70	20.8	2.1	8	10.9	3.2	7	10.2	4.0	

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

Exhibit 3 – 4A

Islet Product Characteristics (Per Infusion)

Infusions	Transplant type							Era																	
	ITA			IAK			p	1999-2002			2003-2006			2007-2010			2011-2014			2015-2018			2019-2022			p
	N	Mean	SE	N	Mean	SE		N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	
Total cell volume	1362	3.6	0.1	230	3.8	0.2		227	4.0	0.1	426	3.9	0.1	276	3.7	0.1	398	3.3	0.1	219	3.3	0.1	46	3.7	0.3	***
Total islet particles (final preparation)	1173	391.2	4.9	213	419.7	12.8	*	205	414.9	12.4	386	410.1	8.8	244	363.1	9.5	315	391.3	9.6	200	406.2	12.6	36	327.4	30.8	
Embedded islets (%)	992	15.1	0.5	114	14.0	1.3		137	13.5	1.5	274	16.6	1.2	200	17.6	1.2	291	15.8	0.9	183	10.8	1.0	21	7.0	1.6	**
Islet equivalents (1000s)	1491	438.4	4.3	282	504.0	15.1	***	219	418.4	10.4	391	411.0	7.8	303	463.4	11.2	553	485.3	8.8	258	448.5	10.3	49	387.5	20.1	***
Islet equivalents(1000s)/kg recipient	1446	6.3	0.1	310	7.6	0.2	***	257	6.6	0.2	469	6.5	0.1	360	6.6	0.1	451	6.6	0.1	178	6.4	0.2	41	6.6	0.4	
Beta cells (x10^6)	363	237.8	10.6	33	284.3	32.3		91	191.4	18.4	140	240.0	16.1	60	293.7	28.2	105	257.7	21.2	0	-	-	0	-	-	**
Beta cells/kg recipient weight	299	3.5	0.2	24	5.3	0.6	**	85	2.9	0.3	127	3.7	0.3	46	3.9	0.4	65	4.4	0.4	0	-	-	0	-	-	**
Insulin content (1000s micrograms)	303	3.4	0.1	29	2.9	0.4		105	3.4	0.2	170	3.6	0.2	17	2.2	0.3	10	2.8	0.5	17	3.8	0.7	13	2.7	0.5	
Total Endotoxin units	1003	16.8	1.5	218	29.0	3.6	***	161	27.8	4.6	390	27.5	3.1	309	6.8	1.3	253	15.0	2.4	90	21.9	4.6	18	2.4	0.7	***
Endotoxin units/kg recipient weight	942	0.3	0.0	198	0.4	0.1	***	153	0.5	0.1	371	0.4	0.0	286	0.1	0.0	231	0.2	0.0	81	0.3	0.1	18	0.0	0.0	***
Islet potency: Stimulation index	1165	3.0	0.1	237	3.4	0.2		224	3.8	0.3	392	3.2	0.2	250	2.6	0.1	315	3.1	0.2	195	2.7	0.1	26	2.8	0.4	***
Islet viability	1493	89.3	0.2	272	91.3	0.4	***	182	91.2	0.5	469	91.4	0.3	306	90.0	0.4	447	88.6	0.3	298	87.2	0.4	63	87.8	1.0	***
Purity	1135	61.0	0.5	292	60.3	1.0		194	59.8	1.3	485	61.3	0.8	254	63.4	1.0	276	61.4	0.9	197	57.1	1.0	21	54.7	2.6	*
Total DNA	472	10.4	0.5	42	10.5	1.4	***	97	6.1	0.7	184	10.1	0.9	80	12.0	1.1	126	13.9	1.0	16	5.4	0.9	11	7.8	2.3	***

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

Exhibit 3 – 4B

Islet Product Characteristics by Infusion Sequence

Transplant type ITA

	Infusion Number									
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Total cell volume	651	3.7	0.1	495	3.5	0.1	216	3.4	0.1	*
Total islet particles (final preparation)	530	394.7	7.7	422	390.0	8.1	221	385.1	9.8	
Embedded islets (%)	443	15.5	0.8	354	15.8	1.0	195	13.1	1.1	
Islet equivalents (1000s)	715	444.7	6.5	561	436.0	6.8	215	424.0	9.6	
Islet equivalents(1000s)/kg recipient	713	6.6	0.1	519	6.2	0.1	214	5.9	0.2	***
Beta cells (x10^6)	171	232.8	16.0	137	231.7	16.5	55	268.3	27.2	
Beta cells/kg recipient weight	135	3.4	0.3	115	3.5	0.3	49	3.8	0.4	
Insulin content (1000s micrograms)	154	3.6	0.2	116	3.1	0.2	33	3.8	0.4	
Total Endotoxin units	502	14.3	1.5	359	19.4	2.9	142	18.7	4.8	
Endotoxin units/kg recipient weight	469	0.2	0.0	340	0.3	0.0	133	0.3	0.1	
Islet potency: Stimulation index	554	3.1	0.1	410	3.2	0.2	201	2.6	0.2	
Islet viability	704	89.7	0.2	548	89.1	0.3	241	88.6	0.5	
Purity	519	61.5	0.7	408	61.1	0.8	208	59.4	1.1	
Total DNA	220	10.6	0.8	177	9.6	0.7	75	11.6	1.3	

Transplant type IAK

	Infusion Number									
	1			2			>=3			
	N	Mean	SE	N	Mean	SE	N	Mean	SE	p
Total cell volume	118	4.0	0.2	92	3.5	0.2	20	4.1	0.4	
Total islet particles (final preparation)	102	440.2	20.5	79	393.1	18.0	32	420.2	30.7	
Embedded islets (%)	57	15.4	2.0	43	13.0	2.1	14	11.6	3.3	
Islet equivalents (1000s)	144	546.4	22.5	104	476.1	22.8	34	409.6	34.2	***
Islet equivalents(1000s)/kg recipient	170	8.3	0.3	114	6.9	0.3	26	5.7	0.5	***
Beta cells (x10^6)	17	292.9	47.5	12	272.5	47.9	4	283.5	123.5	
Beta cells/kg recipient weight	11	5.0	0.9	9	6.0	0.9	4	4.5	2.0	
Insulin content (1000s micrograms)	11	3.1	0.5	12	3.1	0.7	6	2.2	0.5	
Total Endotoxin units	118	31.6	5.0	81	28.9	6.0	19	12.6	9.0	
Endotoxin units/kg recipient weight	107	0.5	0.1	73	0.4	0.1	18	0.2	0.1	
Islet potency: Stimulation index	128	3.7	0.3	83	3.1	0.3	26	2.5	0.3	*
Islet viability	132	91.8	0.5	106	91.2	0.6	34	89.9	1.0	
Purity	148	60.9	1.3	113	60.1	1.5	31	58.2	3.9	
Total DNA	21	10.2	1.8	16	11.9	2.9	5	6.9	2.6	

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

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

p<0.05 (regression coefficient)	Islet characteristics													
	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg recipient	Total beta cells	Beta cells/kg recipient	Insulin content	Total endotoxin	Endotoxin /kg recipient	Stimulation index	Viability	Purity	DNA content
Islet predictors		0.03 (28.5)		<.0001 (74.9)	<.0001 (1.24)		0.008 (1.75)		0.0006 (12.2)	0.0009 (0.189)		<.0001 (2.05)		
ITA vs IAK														
Year	<.0001 (-0.051)		0.003 (-0.286)	0.0002 (2.99)		0.006 (6.24)	0.006 (0.109)	<.0001 (-1.20)		<.0001 (-0.0201)	0.0004 (-0.0507)	<.0001 (-0.288)	0.03 (-0.191)	<.0001 (0.375)
Donor gender		<.0001 (37.1)		<.0001 (47.0)	0.0002 (0.530)						0.049 (0.313)			
Donor blood type A	0.003 (-0.333)		0.02 (-2.50)					0.02 (-0.589)						
Donor CMV			0.02 (2.86)									0.004 (1.05)		
Donor Hx HPT		0.008 (29.0)	0.0007 (-4.15)						0.01 (7.49)	0.02 (0.114)				
Donor Hx ETOH														
Donor hospital transfusion												0.01 (1.22)		
Donor intra-op transfusion														
Donor given steroid				<.0001 (78.0)	<.0001 (1.05)	0.006 (112)	0.03 (1.53)		0.005 (12.2)	0.01 (0.171)			<.0001 (7.16)	
Donor given insulin				0.001 (31.7)	0.02 (0.36)	0.0002 (78.0)	0.007 (1.01)		0.03 (6.72)	0.04 (0.101)			0.03 (2.19)	0.002 (3.04)
Procurement team related				0.03 (-9.81)										
Gradient type	0.02 (-0.402)			0.04 (30.1)		0.004 (-109)	0.0004 (-2.27)							<.0001 (-6.96)

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

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg donor	Total beta cells	Beta cells/kg donor	Insulin content	Total endotoxin	Endotoxin/ kg donor	Stimulation index
Mean donor age (yrs)	-0.09457 0.0019 1078	0.07131 0.0268 964	-0.17067 <.0001 748	-0.05344 0.0847 1042	-0.06008 0.0507 1058	-0.02241 0.7149 268	-0.05220 0.4179 243	0.04749 0.4085 305	0.01760 0.5867 957	0.00584 0.8613 899	-0.12055 0.0001 1005
Donor Weight (kg)	0.07745 0.0037 1400	0.07605 0.0047 1382	0.01188 0.6937 1102	0.33469 <.0001 1769	0.28535 <.0001 1544	0.04249 0.4003 394	0.01133 0.8398 321	0.01194 0.8289 330	0.04037 0.1593 1217	0.02902 0.3285 1136	0.06500 0.0153 1392
Donor height	0.02596 0.3320 1399	0.11014 <.0001 1381	0.01578 0.6009 1101	0.18116 <.0001 1767	0.18060 <.0001 1542	-0.06036 0.2325 393	-0.07137 0.2029 320	0.09246 0.0941 329	-0.01507 0.5995 1217	-0.02538 0.3927 1136	0.04023 0.1335 1392
Donor Body Mass Index (kg/m2)	0.06051 0.0237 1398	0.02682 0.3195 1380	-0.00193 0.9491 1100	0.27047 <.0001 1767	0.21788 <.0001 1542	0.06795 0.1788 393	0.04484 0.4241 320	-0.02452 0.6576 329	0.05202 0.0697 1217	0.04521 0.1278 1136	0.05642 0.0354 1391
Pre-ins donor glucose	-0.03109 0.3383 951	-0.06592 0.0453 923	0.07148 0.0598 694	0.00652 0.8329 1048	0.01121 0.7136 1074	-0.02183 0.7069 299	0.00013 0.9984 256	0.00238 0.9680 286	0.09171 0.0046 955	0.09101 0.0063 900	0.06040 0.0599 971
Max donor glucose	0.03271 0.2962 1022	-0.03552 0.2632 994	-0.00254 0.9447 749	0.08487 0.0043 1128	0.08143 0.0059 1140	0.10553 0.0601 318	0.13892 0.0248 261	-0.06249 0.3271 248	0.05034 0.1092 1014	0.04878 0.1342 944	0.01840 0.5556 1029
Donor creatinine	0.09956 0.0007 1149	0.02481 0.3979 1163	-0.01377 0.6767 919	0.13701 <.0001 1336	0.12933 <.0001 1275	-0.06225 0.2691 317	-0.06143 0.3344 249	0.03852 0.5535 239	-0.02686 0.3722 1106	-0.02764 0.3750 1032	0.05326 0.0662 1190
Donor BUN	0.11735 0.0007 830	0.00534 0.8819 778	-0.03367 0.4414 525	0.15115 <.0001 925	0.11911 0.0002 962	-0.04689 0.5662 152	-0.08686 0.3714 108	-0.01546 0.8377 178	-0.00337 0.9174 947	-0.00878 0.7952 877	0.10655 0.0016 874

Exhibit 3 – 6
Correlation of Islet Characteristics with Donor, Recovery, and Processing Characteristics (Continued)

Spearman Correlation Coefficients Prob > |r| under H0: Rho=0 Number of Observations	Packed cell volume	Total particle count	Trapped islets	Total IEQs infused	IEQs/kg donor	Total beta cells	Beta cells/kg donor	Insulin content	Total endotoxin	Endotoxin/ kg donor	Stimulation index
Donor AST	0.01887 0.5427 1043	-0.00411 0.8952 1031	0.00874 0.8072 783	-0.00292 0.9202 1180	-0.00246 0.9340 1136	-0.05751 0.3721 243	-0.05006 0.5021 182	0.07048 0.3365 188	-0.03331 0.2839 1037	-0.03462 0.2827 965	0.03330 0.2706 1096
Donor ALT	0.06307 0.0402 1058	0.02065 0.5053 1043	0.00656 0.8533 796	0.08078 0.0033 1324	0.07344 0.0118 1174	-0.03123 0.6238 249	-0.04199 0.5683 187	0.04957 0.4925 194	-0.02898 0.3423 1076	-0.02844 0.3682 1003	0.04236 0.1582 1111
Donor lipase	0.03346 0.2998 962	0.02230 0.4844 985	-0.02775 0.4372 786	0.05204 0.0800 1133	0.05435 0.0716 1100	-0.05472 0.3548 288	-0.04953 0.4528 232	0.00802 0.9033 232	-0.01606 0.6147 985	-0.02291 0.4860 927	0.02048 0.5060 1057
Donor serum amylase	0.04583 0.1436 1020	0.04908 0.1200 1005	0.02600 0.4683 780	-0.01878 0.5225 1162	-0.01151 0.6959 1156	-0.10061 0.0923 281	-0.12282 0.0690 220	0.11510 0.0850 225	-0.01905 0.5462 1006	-0.01669 0.6088 943	0.02890 0.3502 1047
Time from cross clamp to pancreas recovery (hrs)	-0.07563 0.0307 816	0.03261 0.3656 772	-0.03900 0.3526 570	-0.07122 0.0387 843	-0.05584 0.1129 807	-0.07467 0.2563 233	-0.01981 0.7901 183	-0.02792 0.6784 223	-0.22497 <.0001 763	-0.23820 <.0001 696	0.01313 0.7152 775
Time from brain death to pancreas recovery (hrs)	0.00258 0.9436 754	-0.04254 0.2590 706	0.04037 0.3568 523	0.03455 0.3355 779	-0.00307 0.9334 744	0.12935 0.0571 217	0.07290 0.3419 172	-0.06710 0.3321 211	-0.01501 0.6858 729	-0.01244 0.7491 664	0.04667 0.2057 737
Cold ischemic time (hrs)	-0.06181 0.0432 1070	0.08562 0.0063 1018	-0.12843 0.0004 753	0.03804 0.2087 1094	-0.00000 0.9999 1161	-0.01964 0.7426 282	-0.02568 0.6843 253	0.05990 0.2839 322	-0.00383 0.9023 1030	-0.01472 0.6492 957	-0.04672 0.1323 1039
Culture time (hrs)	-0.11901 <.0001 1201	0.04683 0.0966 1260	-0.03291 0.2913 1030	0.17526 <.0001 1288	0.07099 0.0153 1167	0.23835 <.0001 382	0.24341 <.0001 309	-0.03274 0.5614 317	0.16688 <.0001 974	0.17069 <.0001 902	0.05925 0.0379 1228

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

	ITA									IAK								
	1			2			>=3			1			2			>=3		
	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE	N	Mean	SE
Islet equivalents infused (1000s)	793	438.4	6.1	572	420.8	6.7	234	405.8	9.0	188	540.5	18.7	126	461.5	20.1	29	430.9	49.9
Islet equivalents infused(1000s)/donor kg	713	6.6	0.1	519	6.2	0.1	214	5.9	0.2	170	8.3	0.3	114	6.9	0.3	26	5.7	0.5
Embedded islets (%)	443	15.5	0.8	354	15.8	1.0	195	13.1	1.1	57	15.4	2.0	43	13.0	2.1	14	11.6	3.3
Cell volume (mL)	651	3.7	0.1	495	3.5	0.1	216	3.4	0.1	118	4.0	0.2	92	3.5	0.2	20	4.1	0.4
Time since first infusion (weeks)	825	31.3	1.6	825	31.3	1.6	351	21.7	1.7	159	35.4	4.3	159	35.4	4.3	45	28.3	9.2
Time since second infusion (weeks)	290	99.4	7.7	290	99.4	7.7	351	105.4	7.2	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

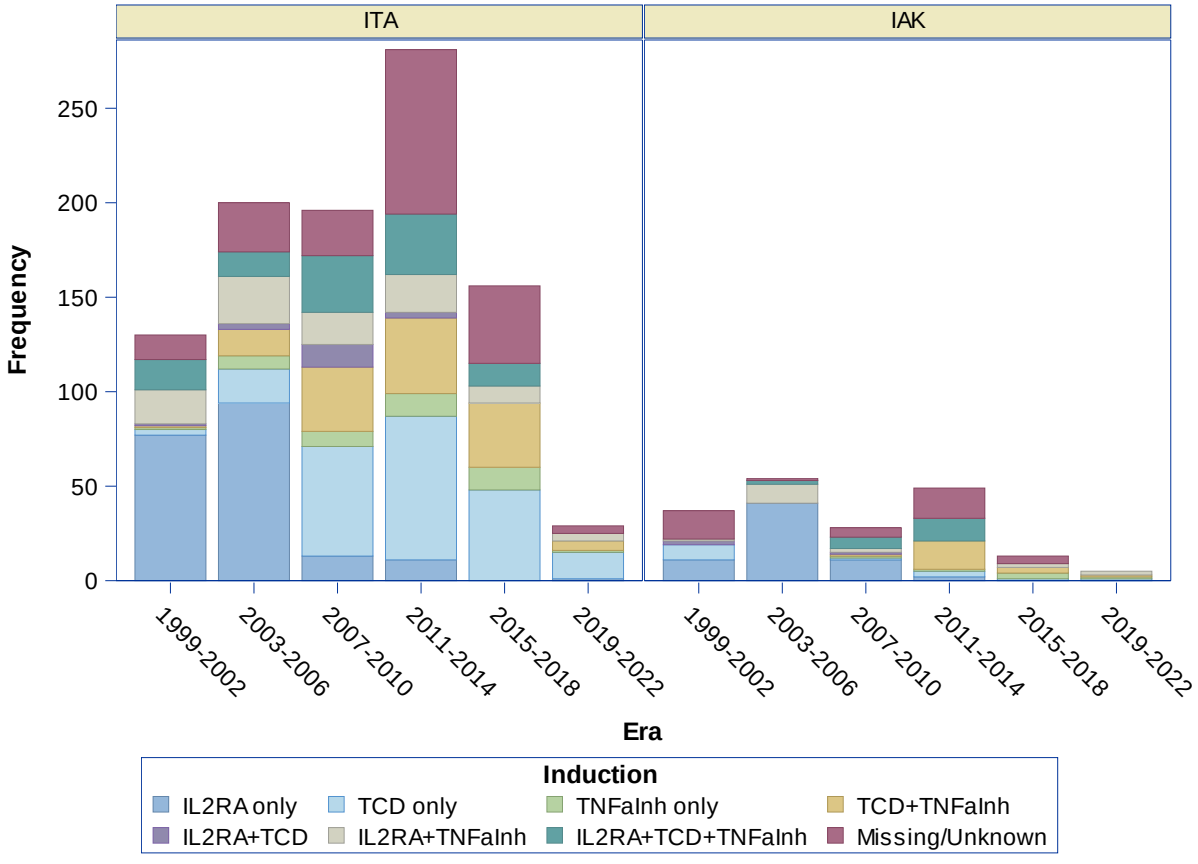
The following table classifies the induction and maintenance therapies used in CITR allograft recipients.

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

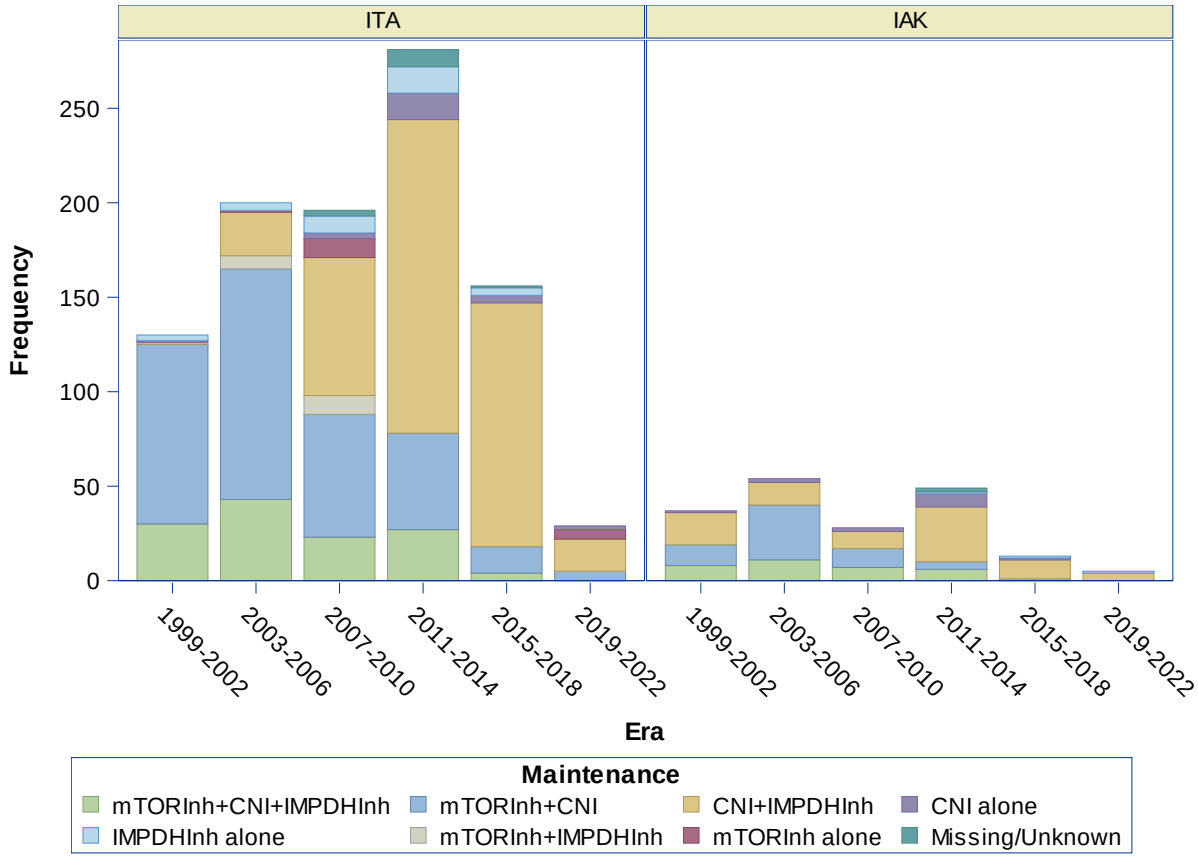


CITR Data 15Feb2022

	Type of transplant				Era											
	ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Induction																
IL2RA only	196	19.8	65	34.9	88	52.7	135	53.1	24	10.7	13	3.9	.	.	1	2.9
TCD only	217	21.9	14	7.5	11	6.6	18	7.1	59	26.3	79	23.9	49	29.0	15	44.1
TNFaInh only	41	4.1	6	3.2	1	0.6	7	2.8	9	4.0	13	3.9	15	8.9	2	5.9
TCD+TNFaInh	128	12.9	20	10.8	1	0.6	14	5.5	35	15.6	55	16.7	37	21.9	6	17.6
IL2RA+TCD	19	1.9	3	1.6	3	1.8	3	1.2	13	5.8	3	0.9	.	.	.	.
IL2RA+TNFaInh	93	9.4	17	9.1	19	11.4	35	13.8	19	8.5	20	6.1	11	6.5	6	17.6
IL2RA+TCD+TNFaInh	103	10.4	20	10.8	16	9.6	15	5.9	36	16.1	44	13.3	12	7.1	.	.
Missing/Unknown	195	19.7	41	22.0	28	16.8	27	10.6	29	12.9	103	31.2	45	26.6	4	11.8
TOTAL	992	100.0	186	100.0	167	100.0	254	100.0	224	100.0	330	100.0	169	100.0	34	100.0

Exhibit 4 – 2

Maintenance Immunosuppression by Transplant Type and Era



CITR Data 15Feb2022

	Type of transplant				Era											
	ITA		IAK		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Maintenance																
mTORInh+CNI+IMPDHInh	127	12.8	32	17.2	38	22.8	54	21.3	30	13.4	33	10.0	4	2.4	.	.
mTORInh+CNI	352	35.5	55	29.6	106	63.5	151	59.4	75	33.5	55	16.7	15	8.9	5	14.7
mTORInh+IMPDHInh	17	1.7	.	.	.	.	7	2.8	10	4.5	.	.	.	.	.	.
CNI+IMPDHInh	409	41.2	81	43.5	18	10.8	35	13.8	82	36.6	195	59.1	139	82.2	21	61.8
mTORInh alone	16	1.6	.	.	.	.	1	0.4	10	4.5	.	.	.	.	5	14.7
CNI alone	24	2.4	13	7.0	2	1.2	2	0.8	5	2.2	21	6.4	5	3.0	2	5.9
IMPDHInh alone	34	3.4	3	1.6	3	1.8	4	1.6	9	4.0	15	4.5	5	3.0	1	2.9
Missing/Unknown	13	1.3	2	1.1	.	.	.	.	3	1.3	11	3.3	1	0.6	.	.
TOTAL	992	100.0	186	100.0	167	100.0	254	100.0	224	100.0	330	100.0	169	100.0	34	100.0

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 5-10). 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 5-12 and 5-5). 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 0.3-0.5 ng/mL, is associated with lowered insulin use, improved HbA1c, greater glycemic control, and lower levels of severe hypoglycemia, which is drastically reduced over all follow-up even with C-peptide <0.3 ng/mL. While these strong associations among the co-primary outcomes are highly significant, any causal relationships cannot be deduced just from the associations; a temporal analysis is a separate focus topic.

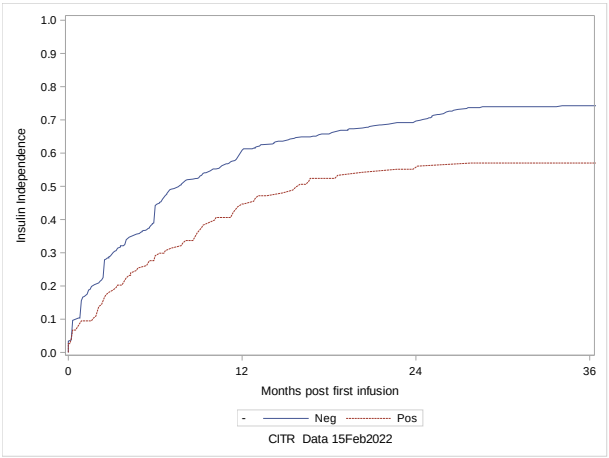
Re-infusion

Re-infusion may have been conducted without (1011/1931=52.4%) or after (308/649=47.5%) 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=0.2). A number of re-infusions were conducted while the patient was not only C-peptide positive but also insulin independent (Exhibit 5-14B, 137/425=32.2%, for all infusions): re-infusion was much more likely when the patient had not yet achieved insulin independence (p<0.0001, Exhibit 5-14B). Second infusion rates have been remarkably constant over the whole history of the CITR (p=0.4, Exhibit 5-14C) and do not differ significantly by transplant type (p=0.6, Exhibit 5-14D).

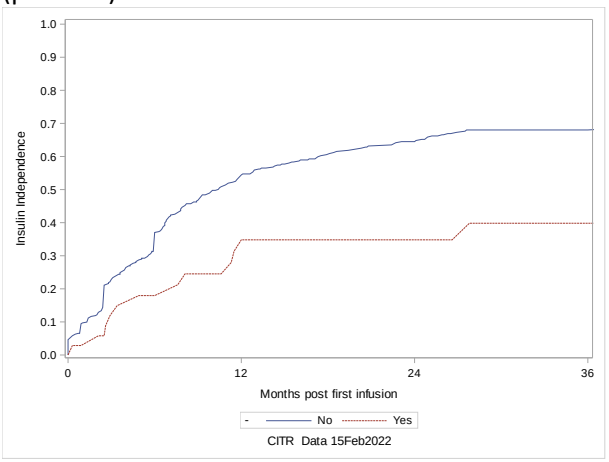
Exhibit 5 – 1A

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

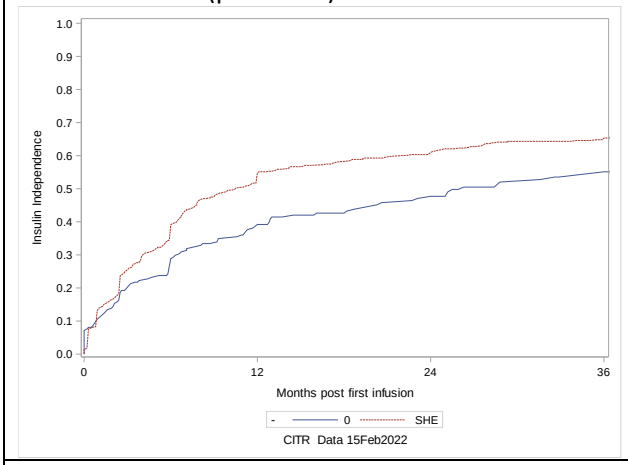
A. Baseline IA-2 autoantibody (p<0.0001)



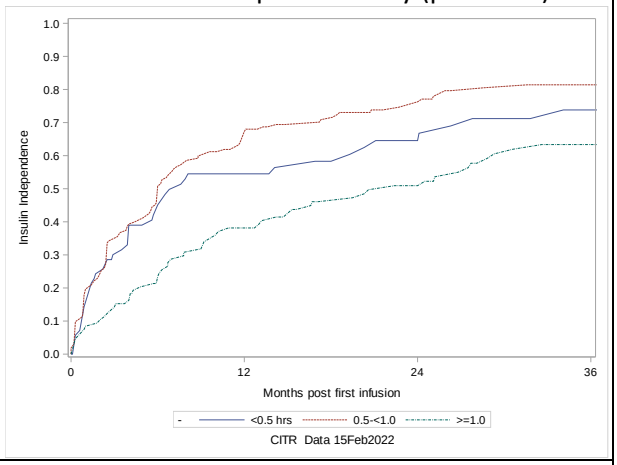
B. Baseline antihyperglycemia medication (p=0.004)



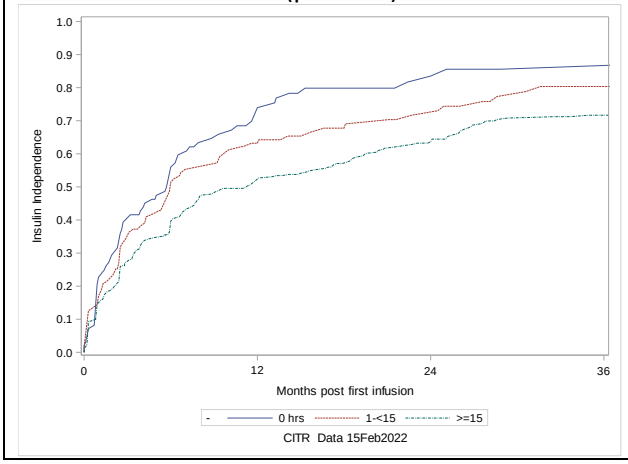
C. Baseline SHE (p=0.0009)



D. Hours: cross-clamp to recovery (p<0.0001)



E. Hours: culture time (p=0.001)



F. Islets Cultured >=6 hrs (p=0.0002)

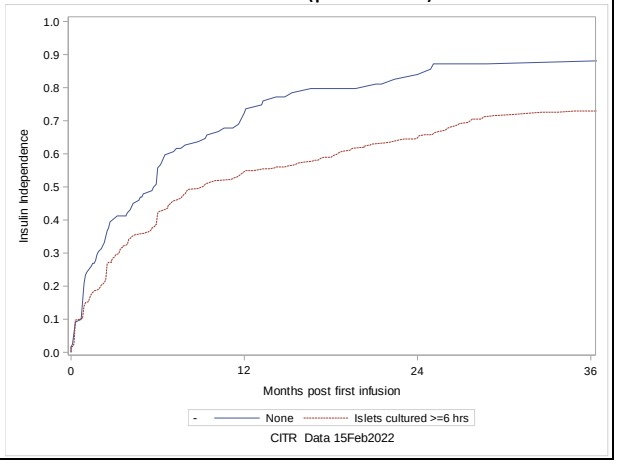
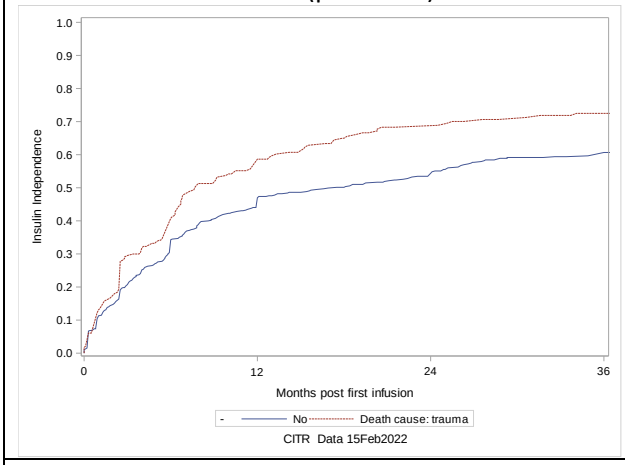
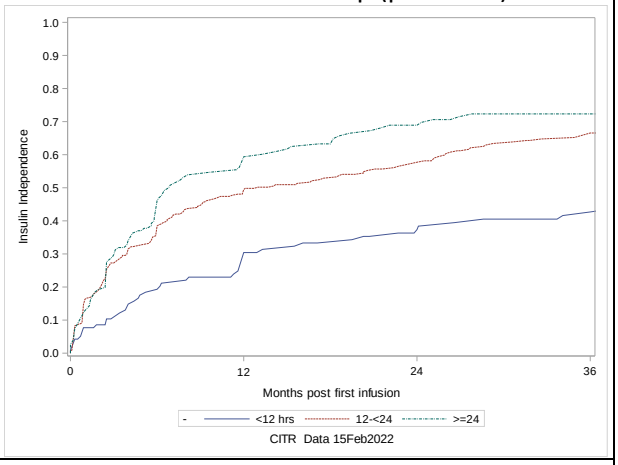


Exhibit 5 – 1A (continued)
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

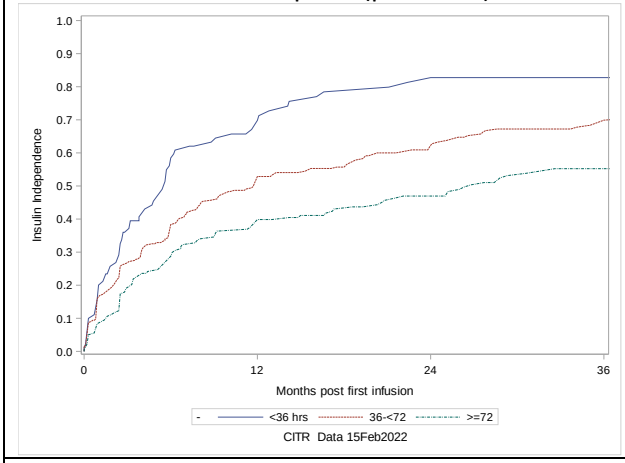
G. Donor Trauma death (p=0.0004)



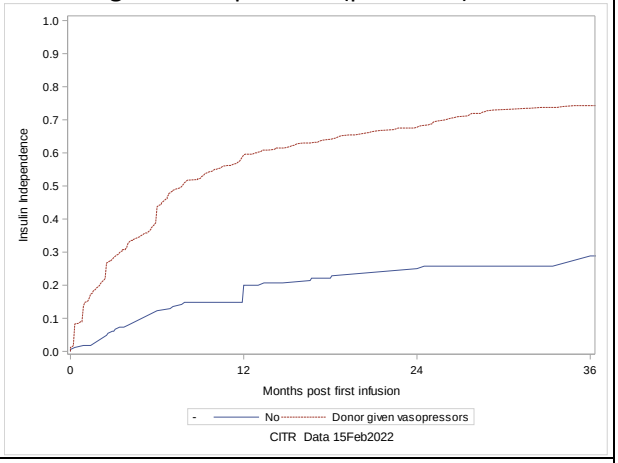
H. Hours: death to cross-clamp (p<0.0001)



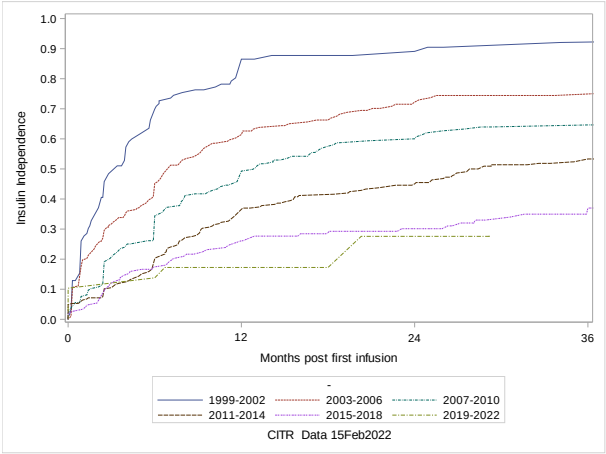
I. Hours: death to transplant (p<0.0001)



J. Donor given vasopressors (p<0.0001)



K. Era (p<0.0001)



L. Induction Immunosuppression Regimen (p<0.0001)

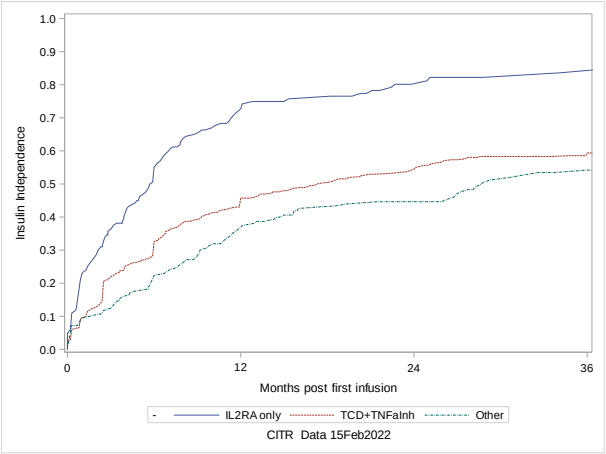
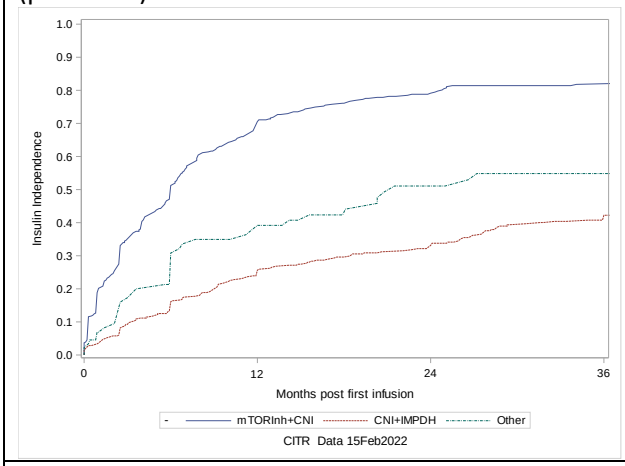
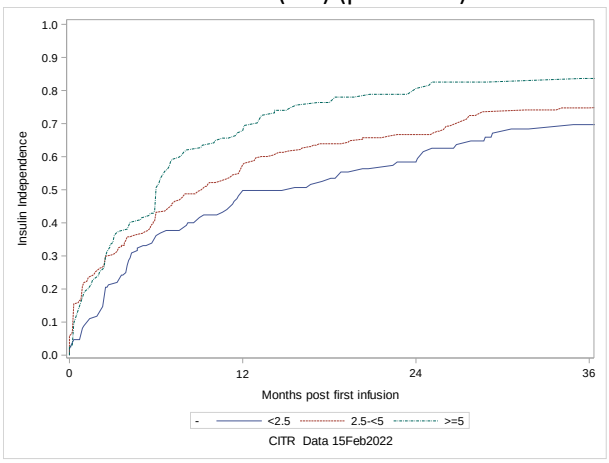


Exhibit 5 – 1A (continued)
Univariate Effects of Individual Variables (p<0.01) on First Achievement of Insulin Independence Post First Infusion among ITA Recipients

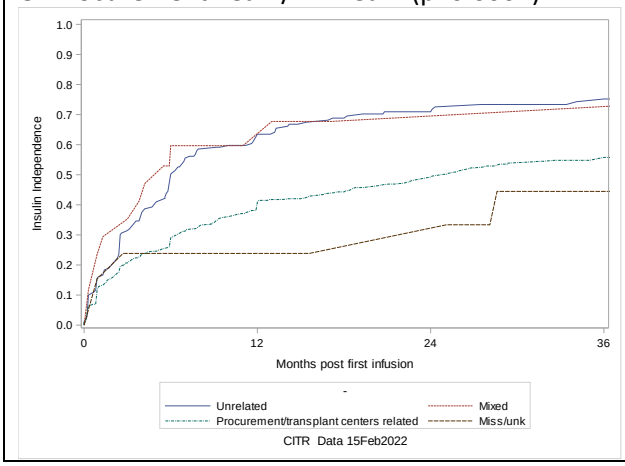
M. Maintenance Immunosuppression Regimen (p<0.0001)



N. Packed cell volume (mL) (p=0.0009)



O. Procurement Team/ Inf Team (p<0.0001)



P. Hours: recovery to transplant (p<0.0001)

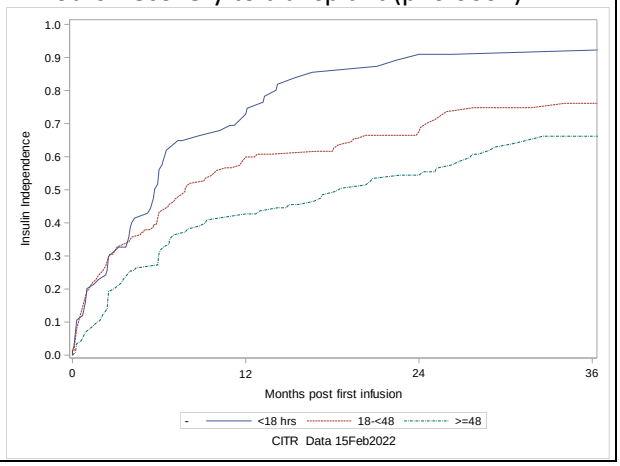


Exhibit 5 – 1B

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

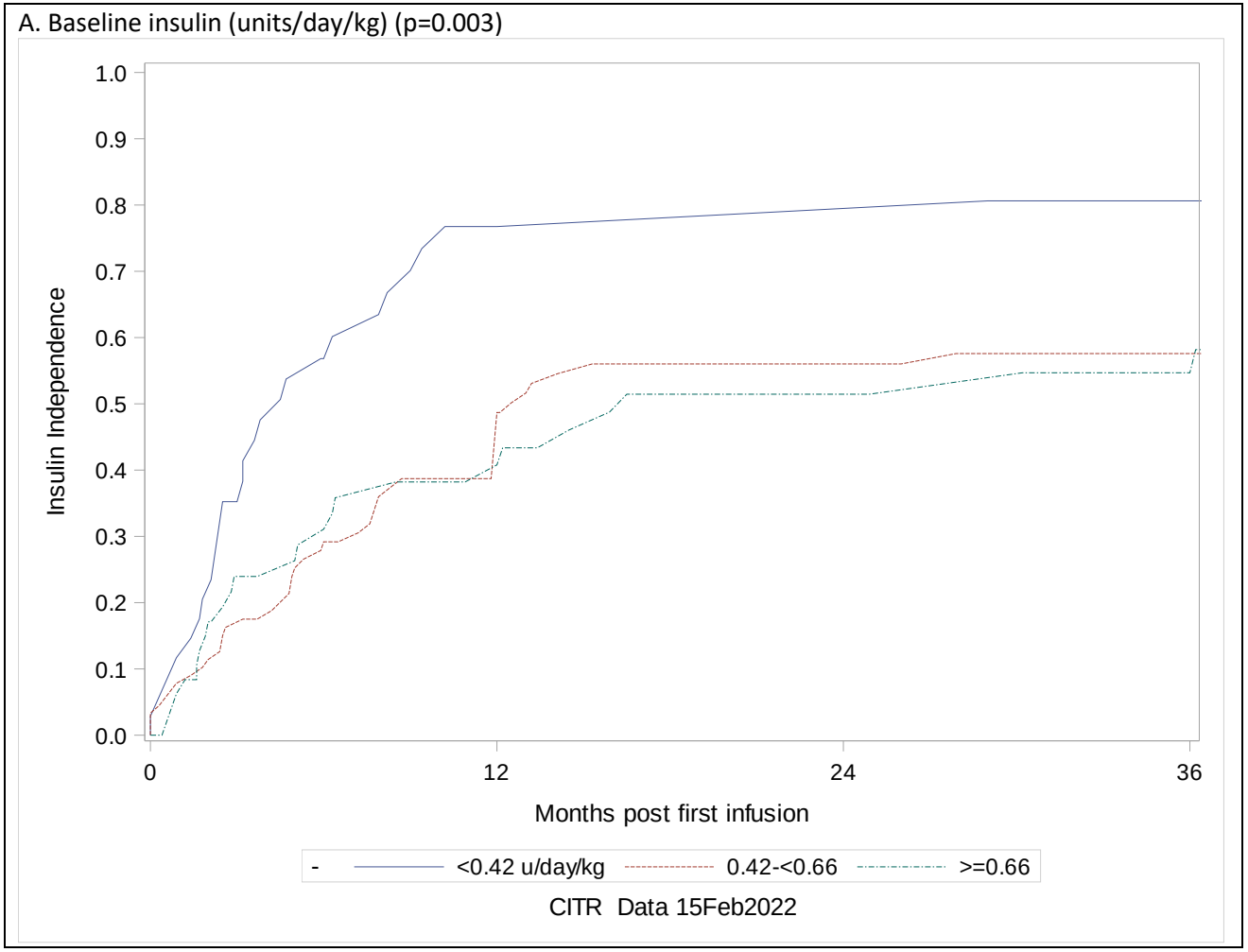


Exhibit 5 – 2A

Unadjusted Prevalence of Insulin Independence Post Last Infusion

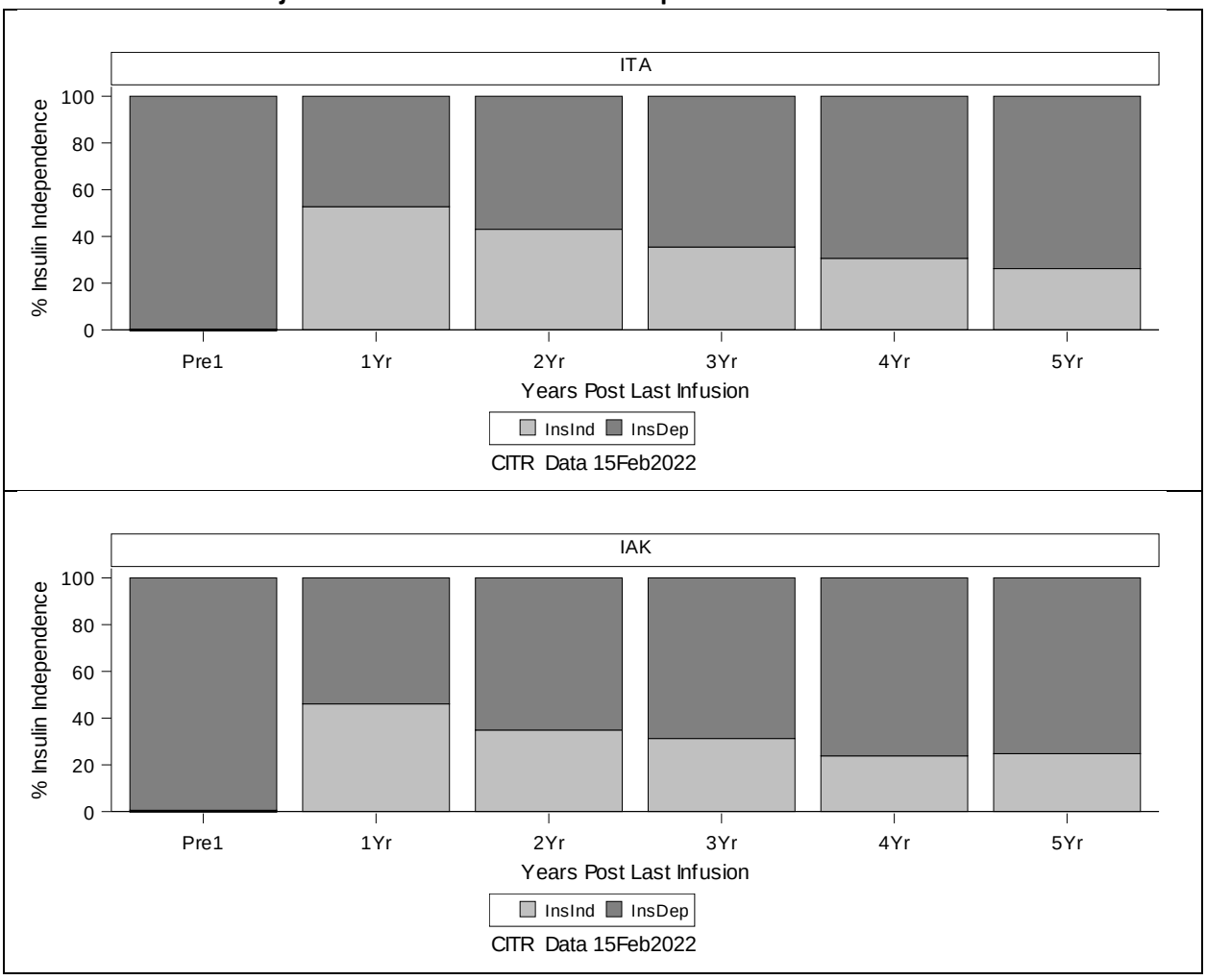


Exhibit 5 – 2B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

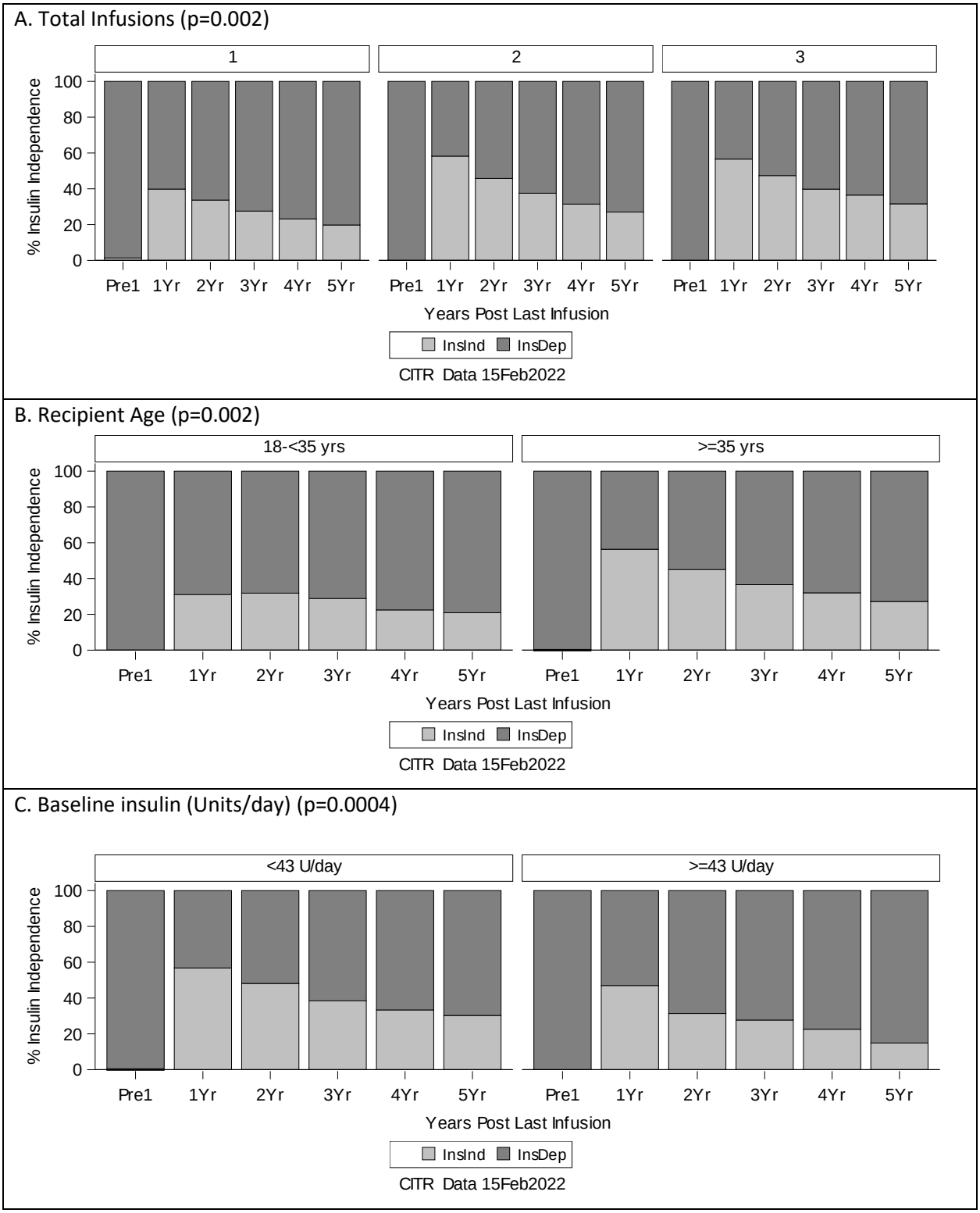
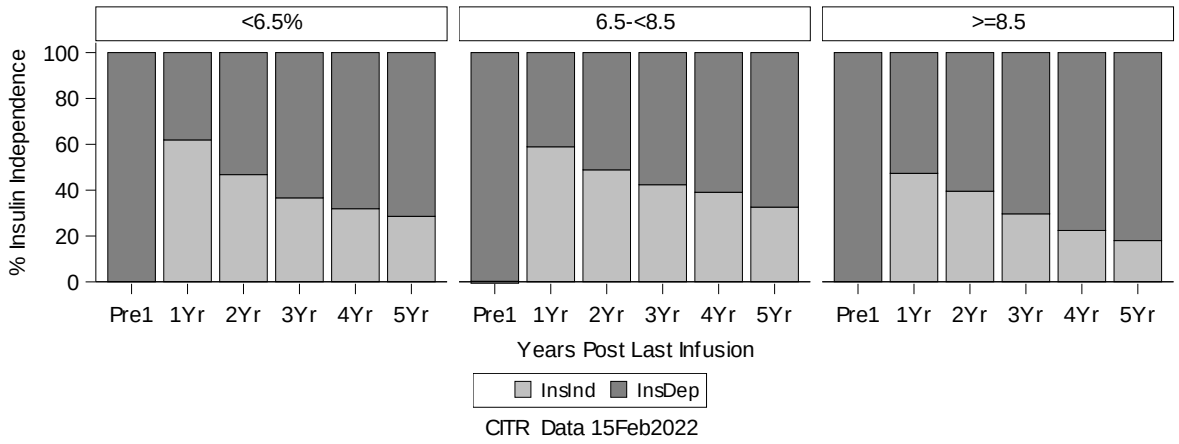
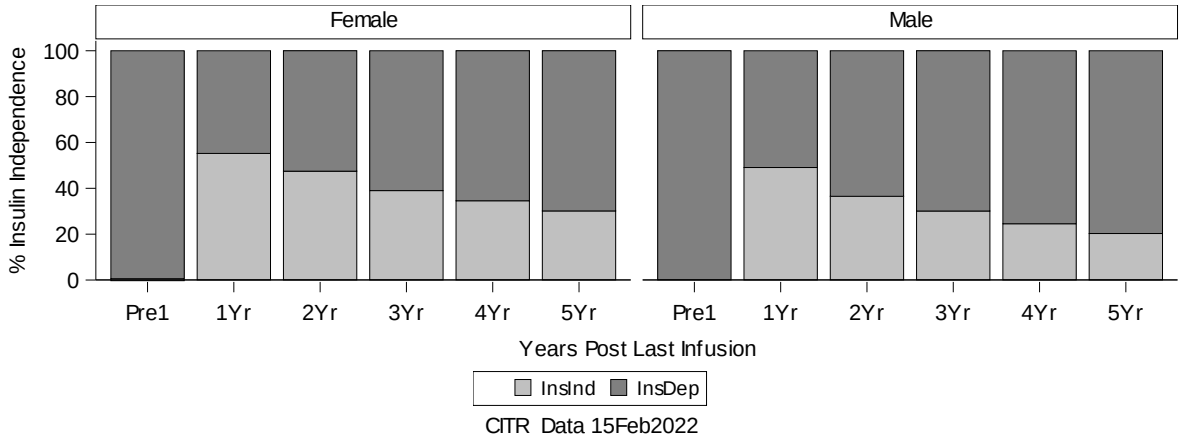


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

D. Baseline HbA1c (p=0.003)



E. Recipient Sex (p=0.005)



F. Baseline IA-2 autoantibody (p=0.001)

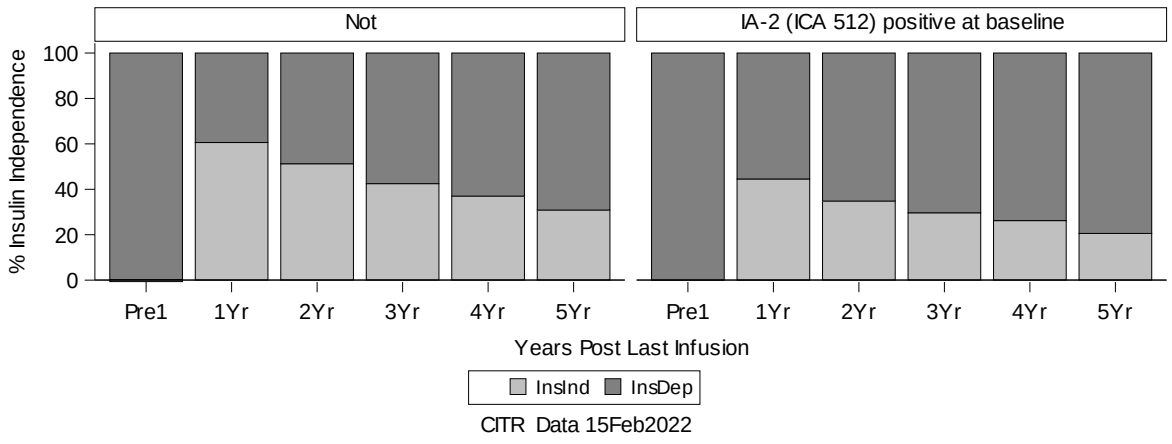
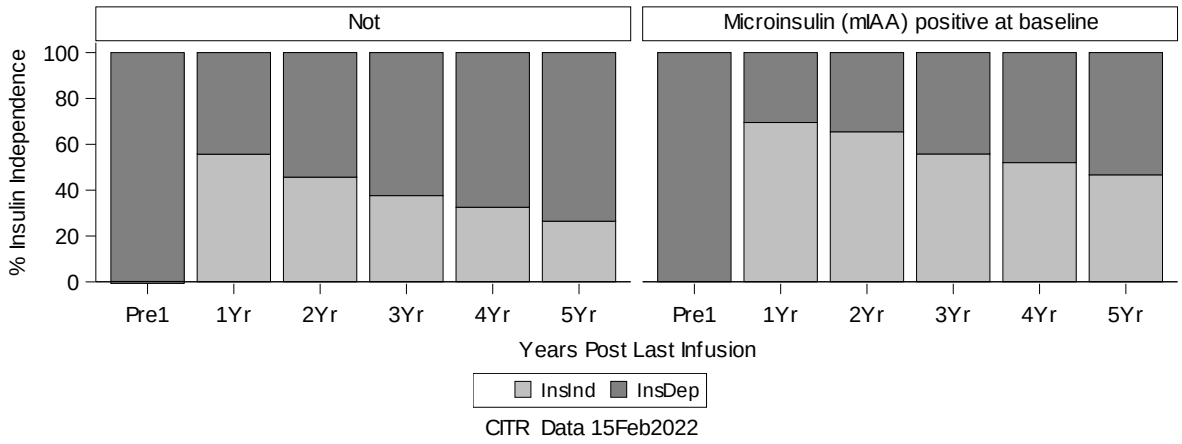
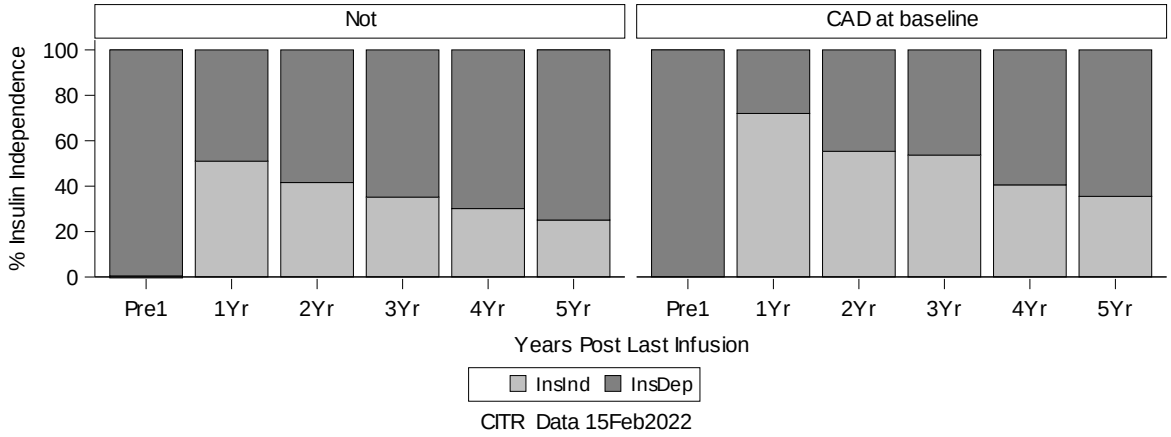


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

G. Baseline microinsulin autoantibody (p=0.001)



H. Baseline CAD (p=0.002)



I. Baseline triglycerides (p=0.007)

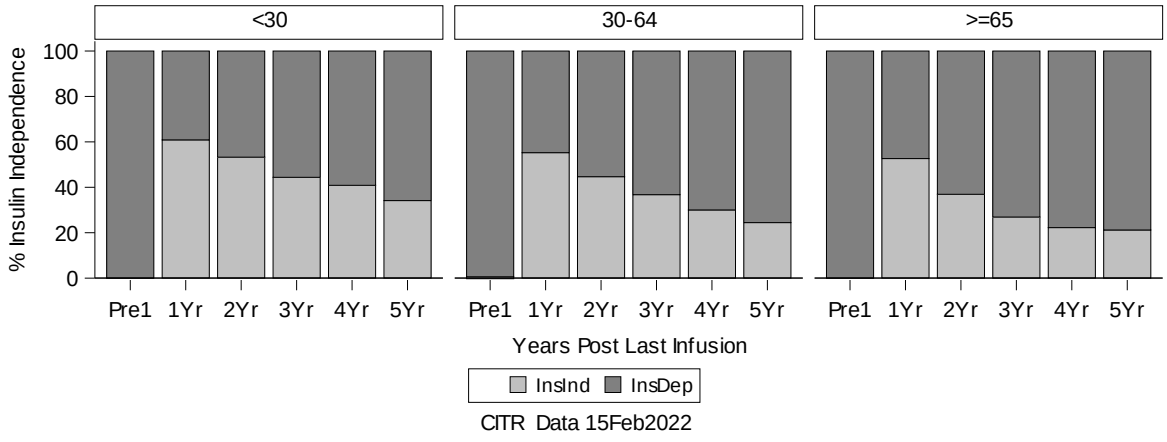
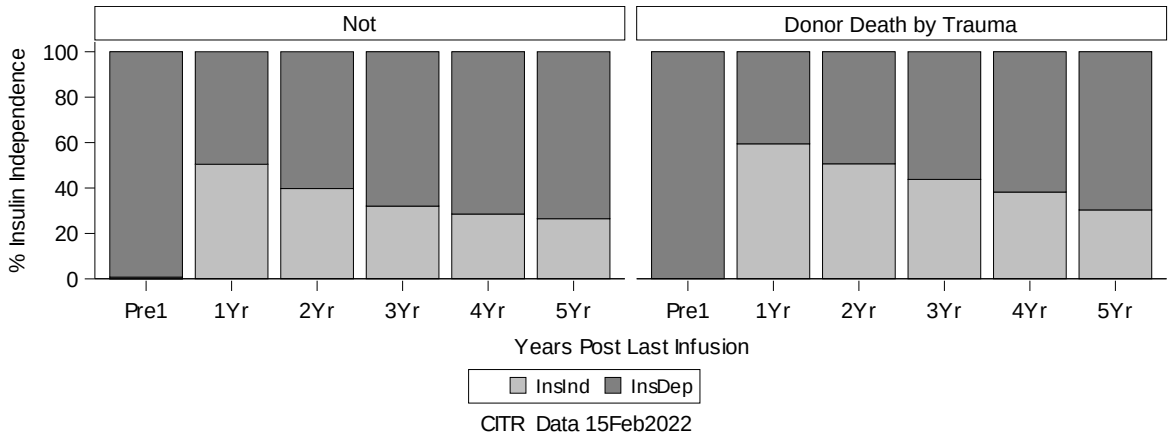
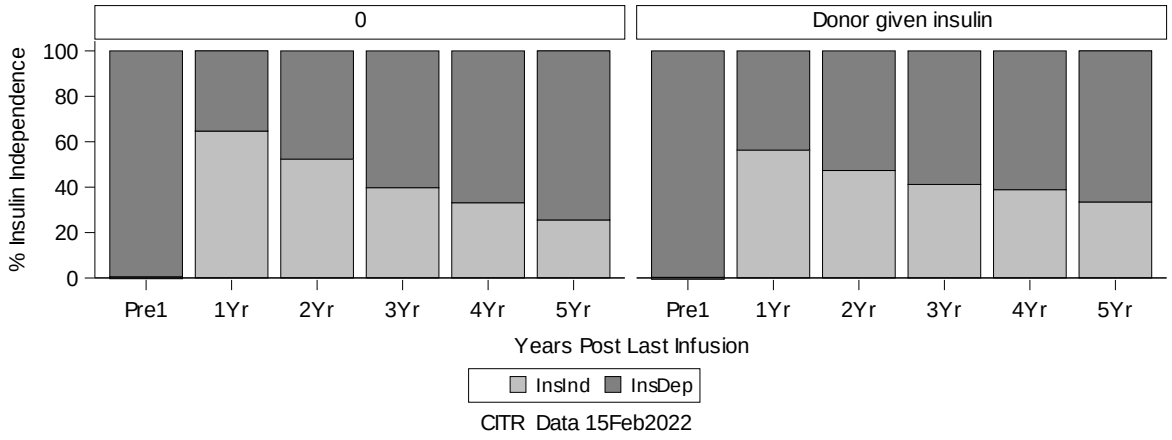


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

J. Donor Death Trauma (p=0.003)



K. Donor given insulin during hospital stay (p=0.004)



L. Donor given vasopressors (p<0.0001)

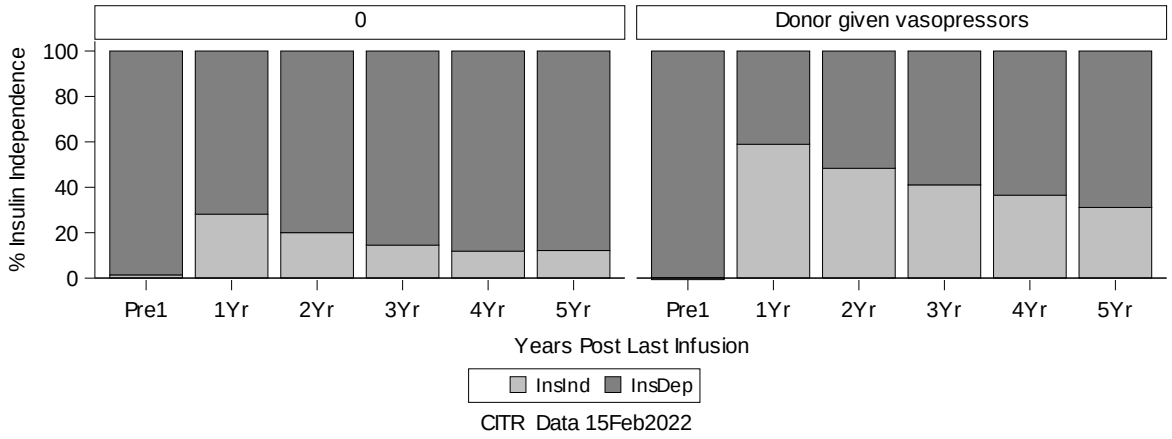
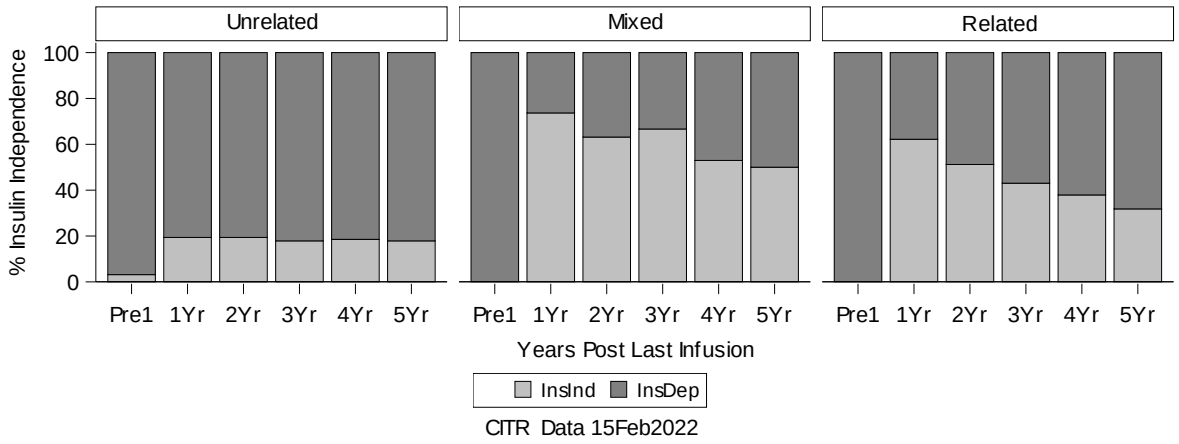
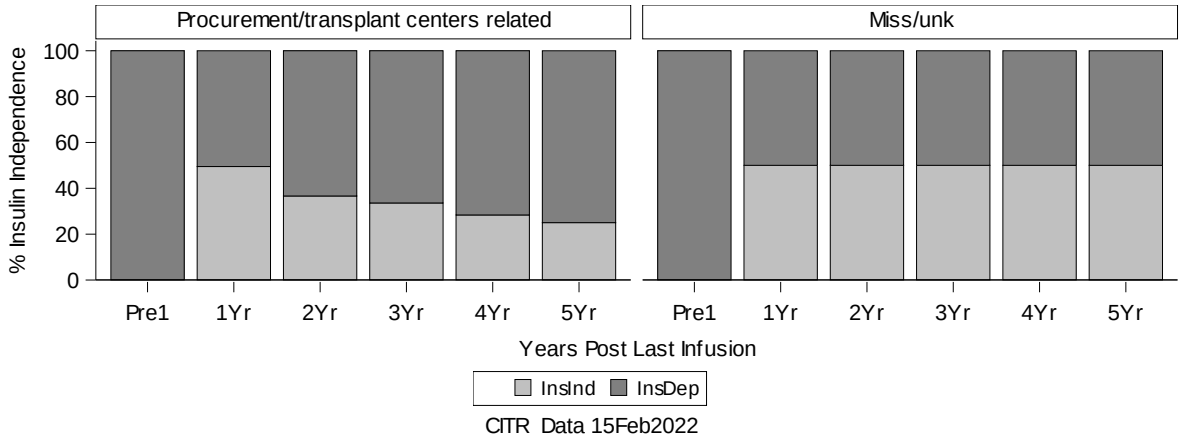


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

M. Processing Center/ Inf Center Related (p=0.004)



N. Procurement Team/ Inf Team Related (p=0.004)



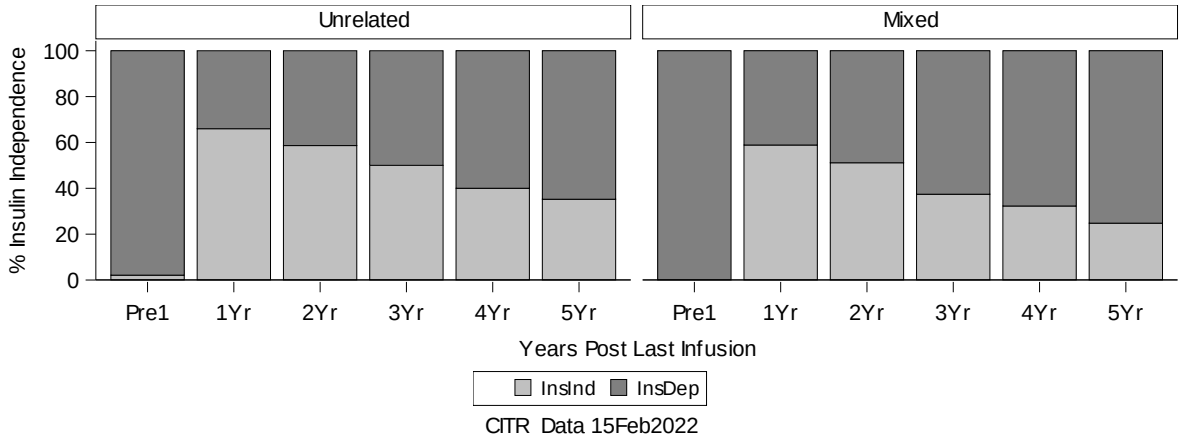
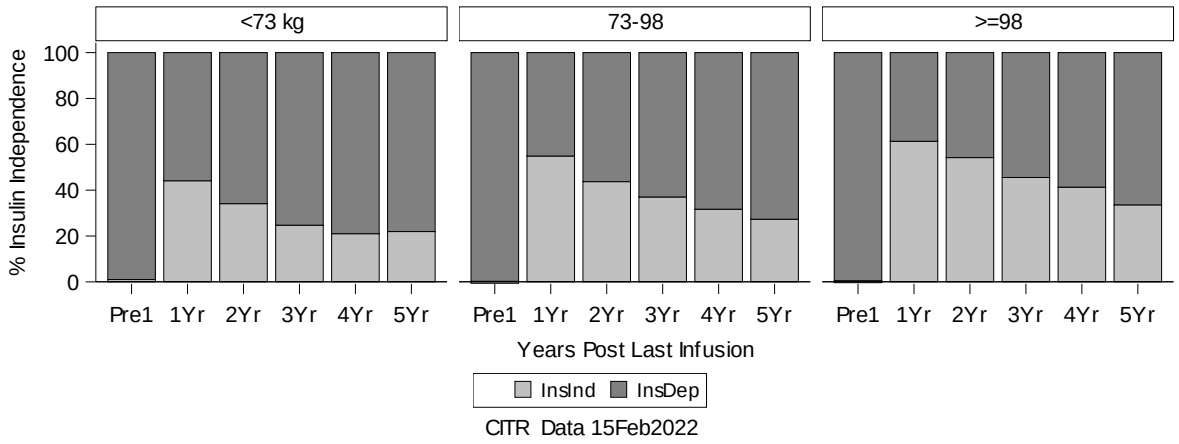
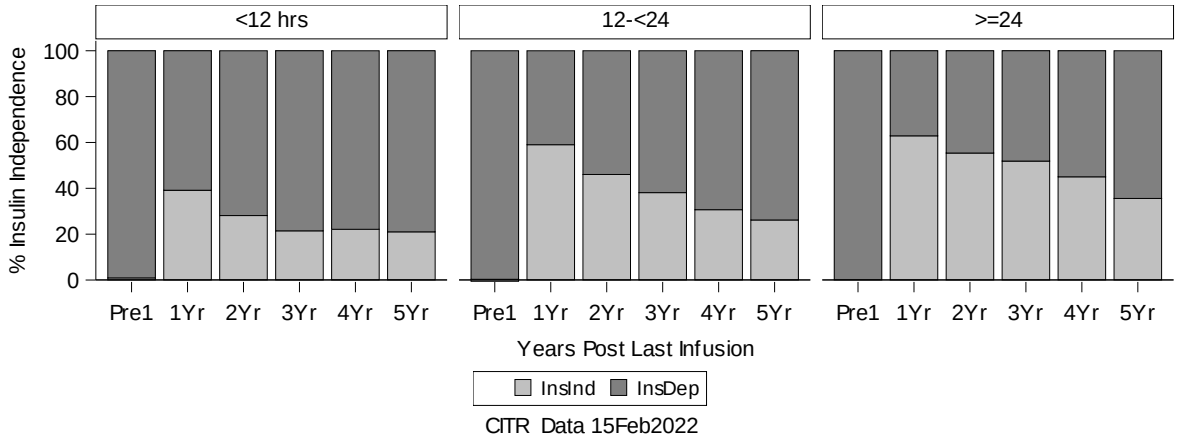


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

O. Donor Weight (p=0.003)



P. Hours: death to cross-clamp (p=0.0003)



Q. IEQ/islet particle ratio (p=0.008)

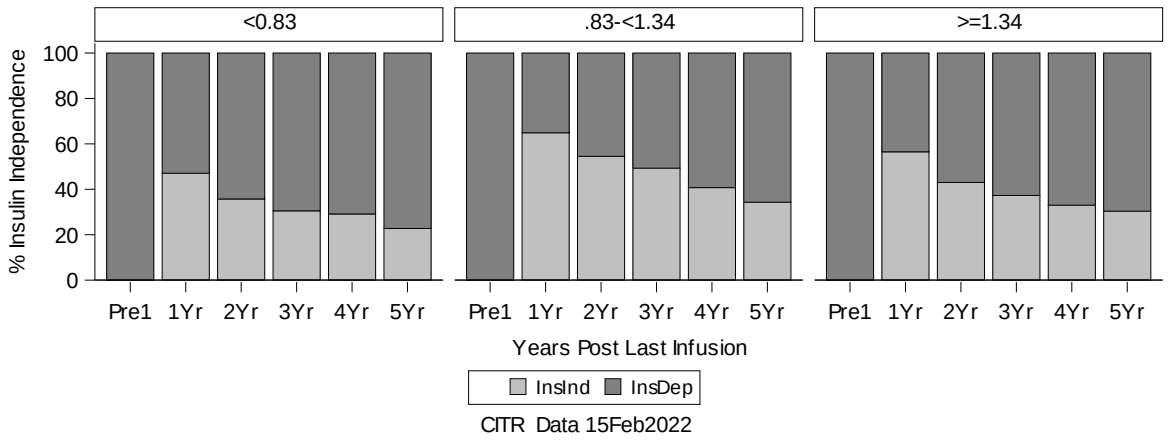
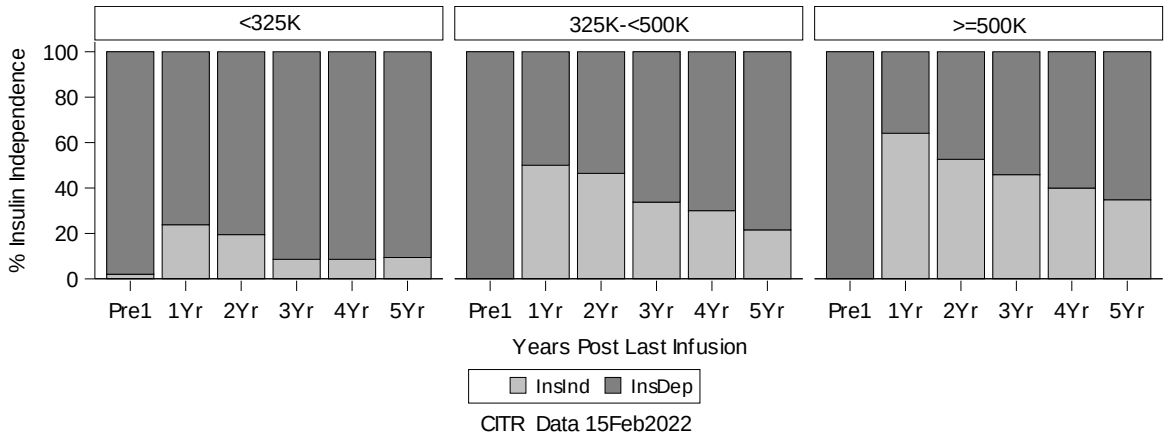
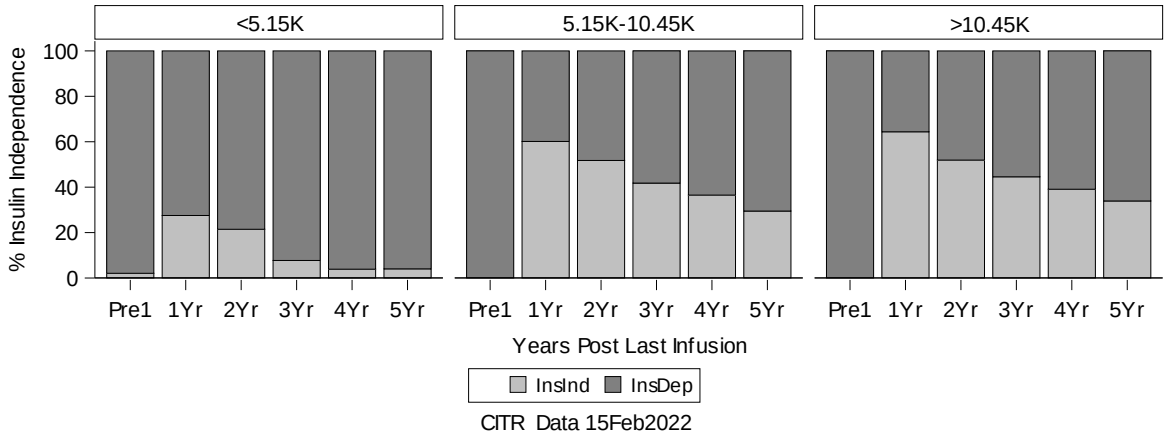


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

R. IEQs infused (1000s) (p<0.0001)



S. Total IEQs Infused/kg recipient (p=0.0007)



T. Immunosuppression: IL2RA (p=0.0002)

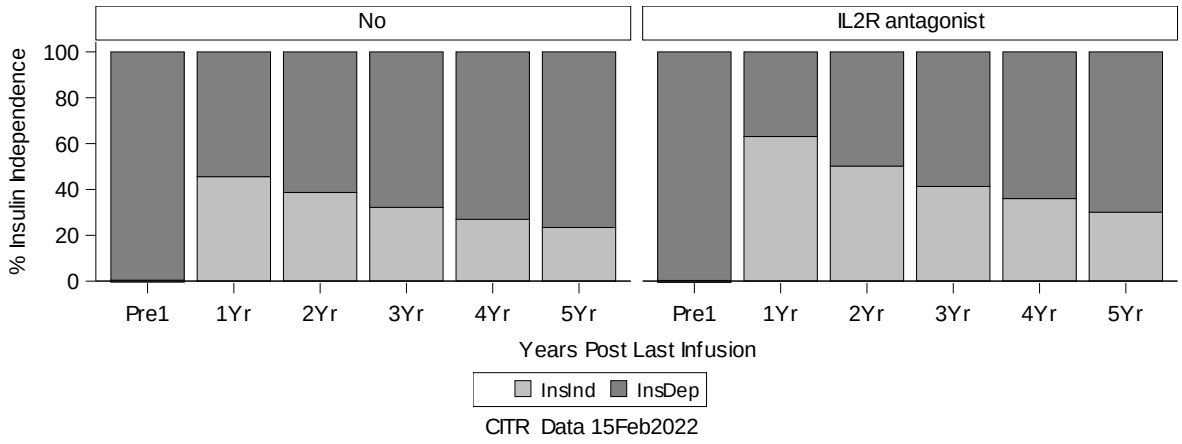
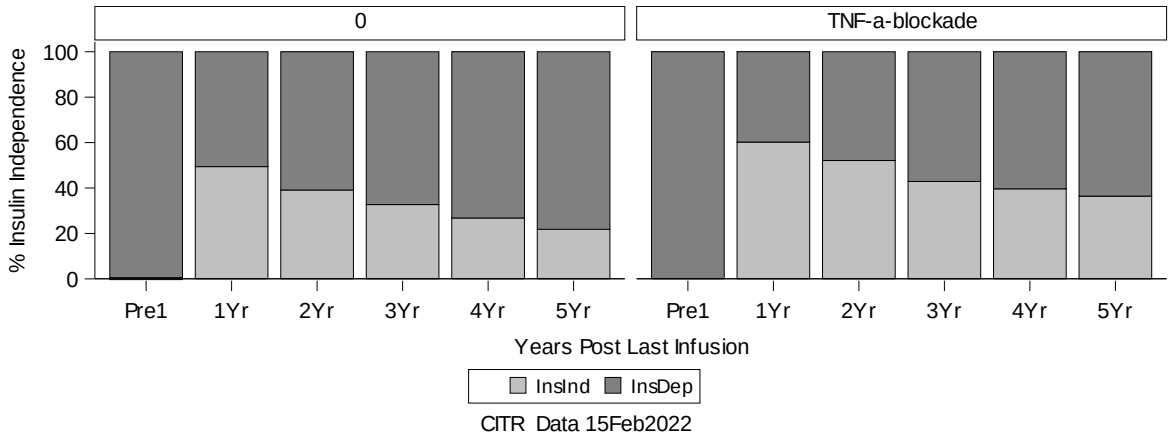
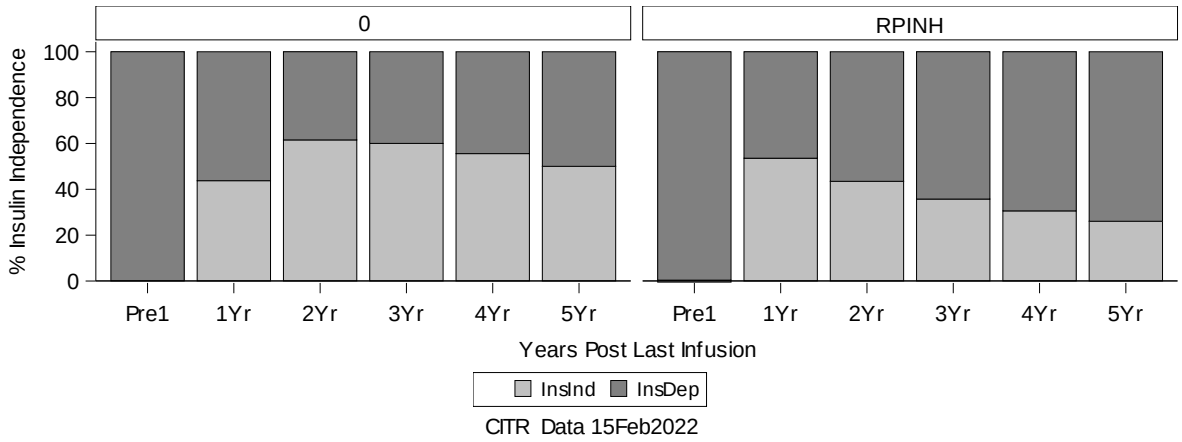


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

U. Immunosuppression: TNFa (p=0.0001)



V. Immunosuppression: RPINH (p<0.0001)



W. Immunosuppression: mTOR (p<0.0001)

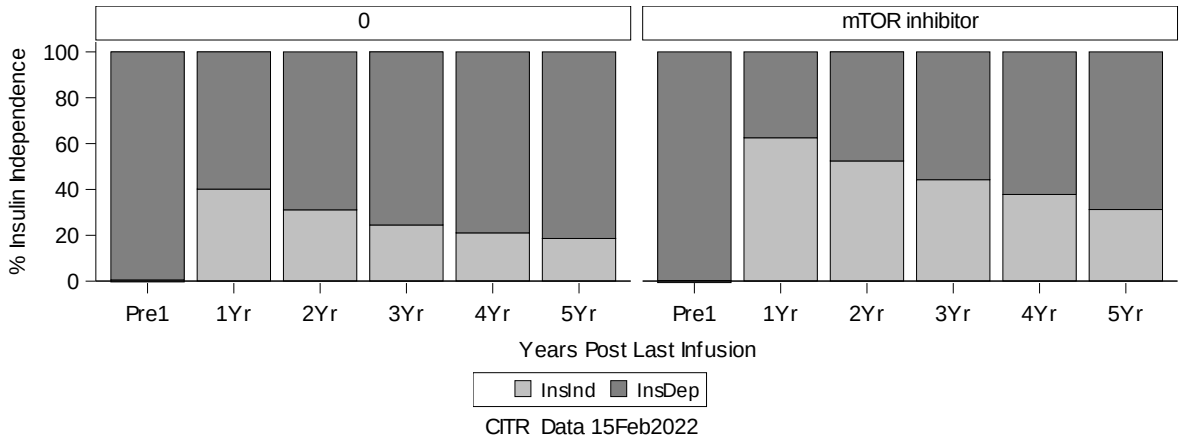
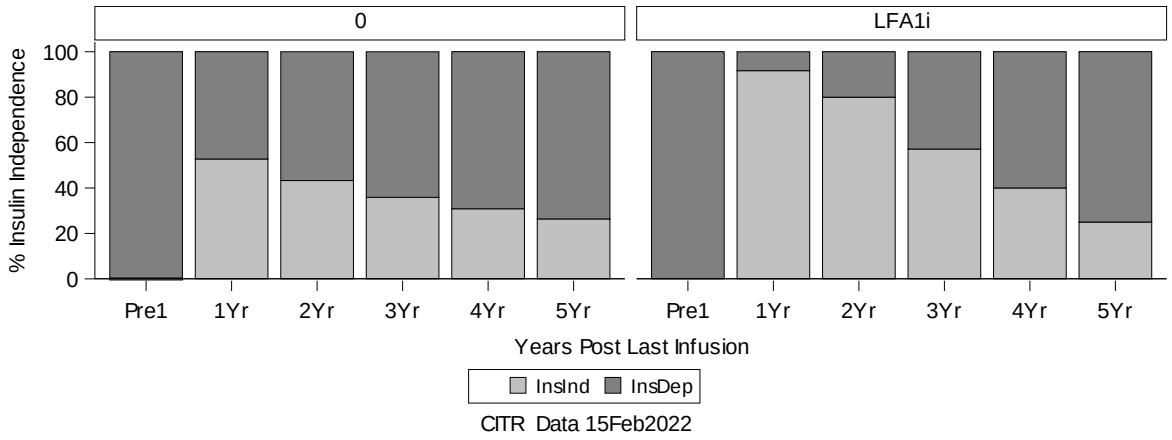
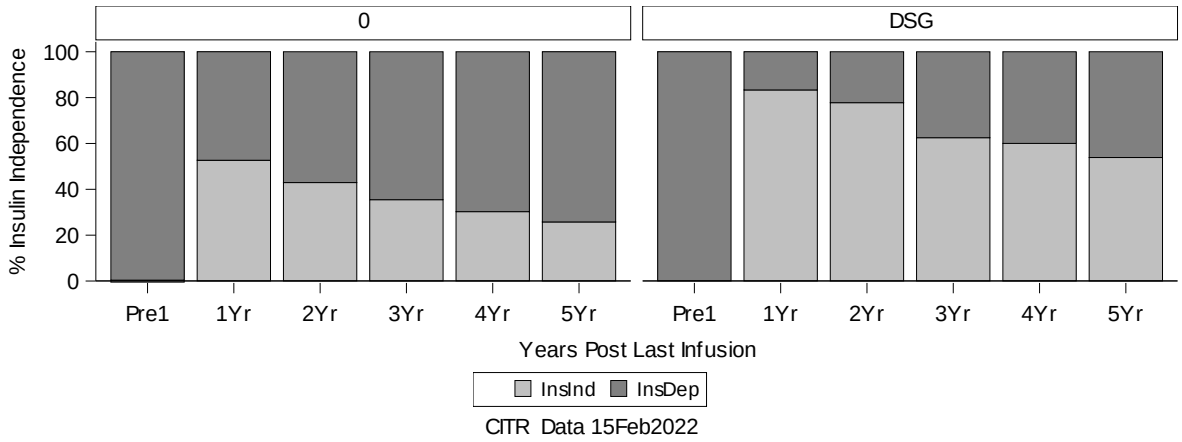


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

X. Immunosuppression: LFA1i (p=0.0001)



Y. Immunosuppression: DSG (p=0.0001)



Z. Immunosuppression: Efalizumab (p=0.0001)

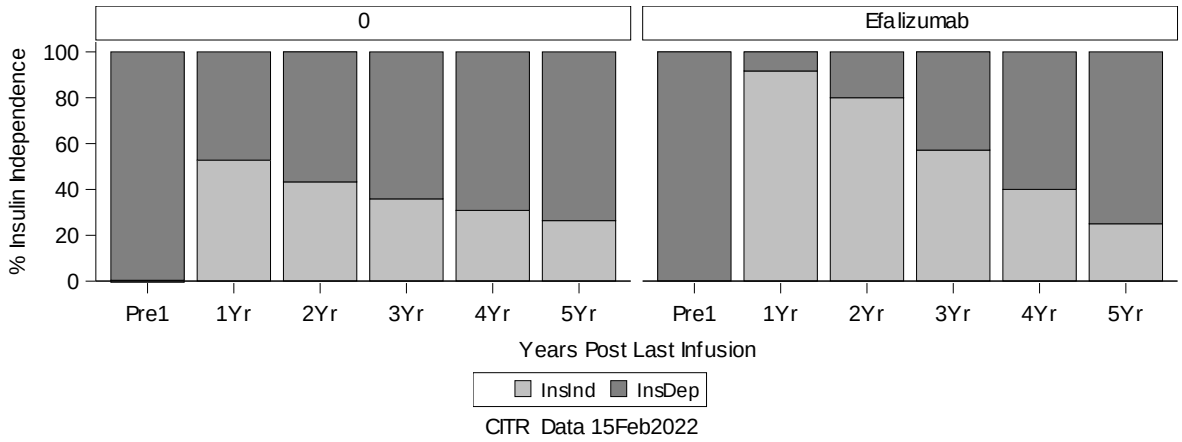
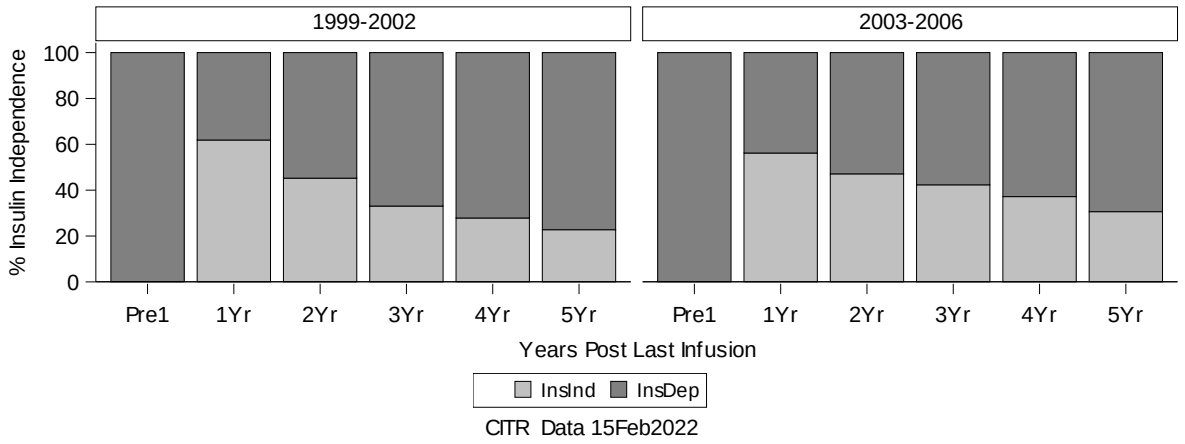
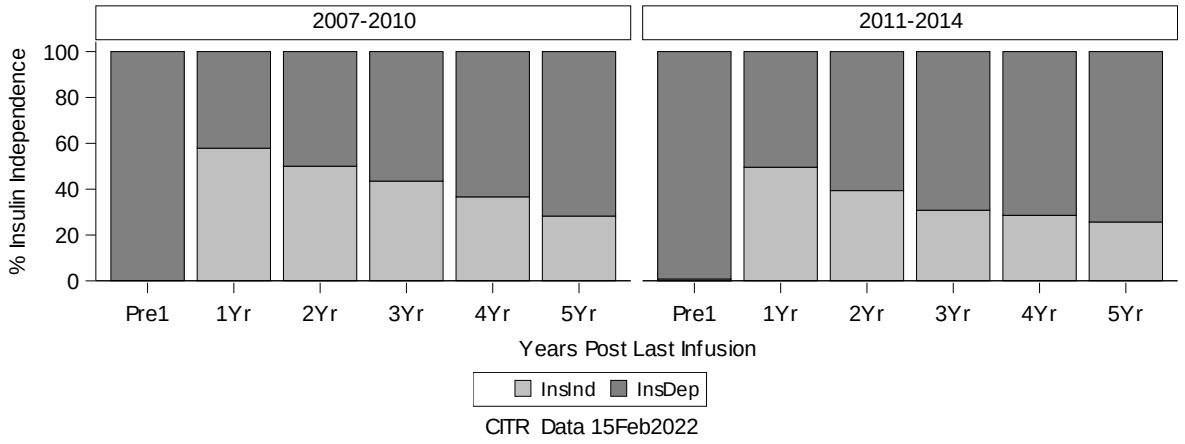


Exhibit 5 – 2B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among ITA Recipients

AA. Era (p=0.004)





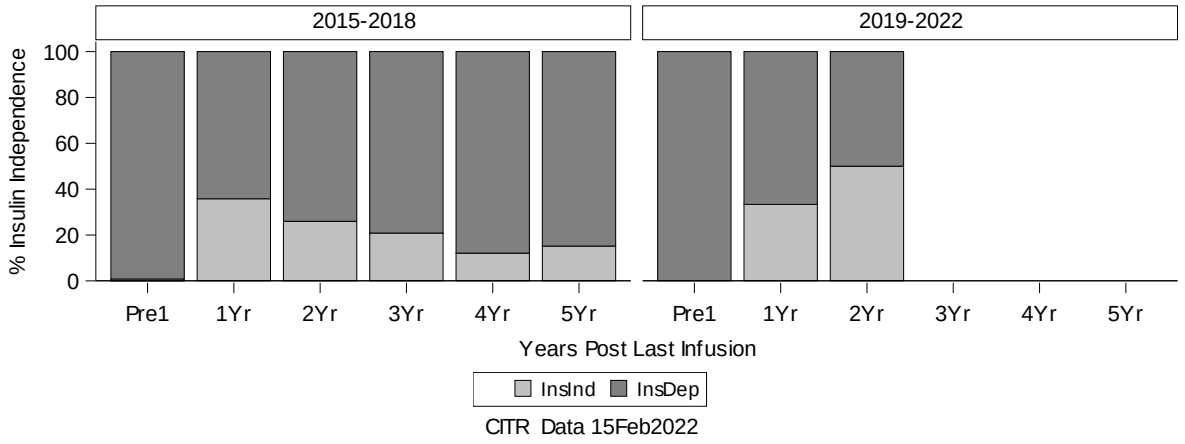
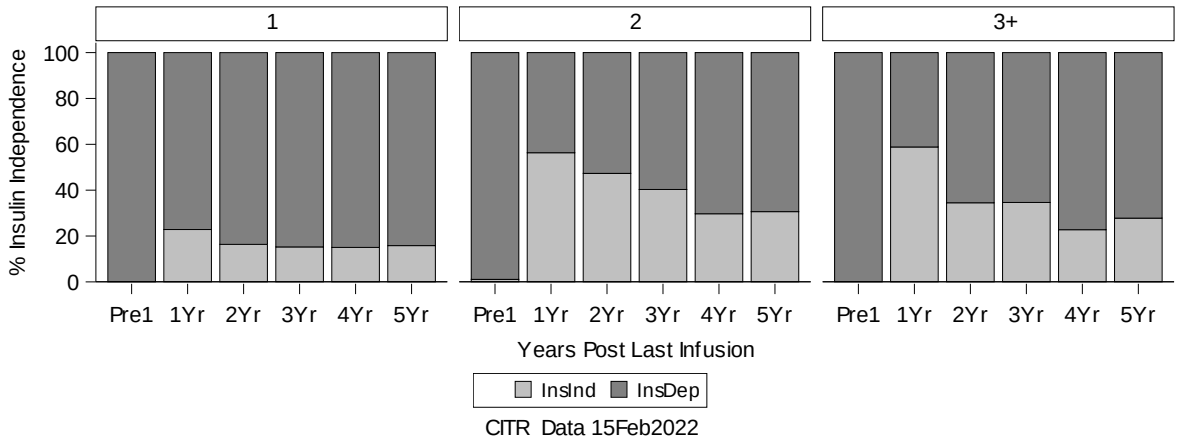
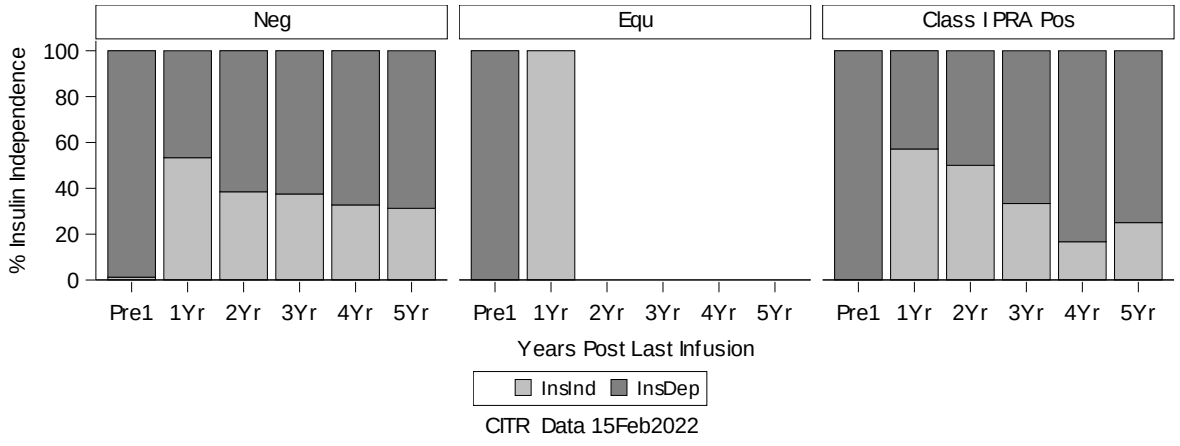


Exhibit 5 – 2C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

A. Total infusions (p=0.005)



B. Baseline Class 1 PRA (p<0.0001)



C. Baseline Class 2 PRA (p=0.001)

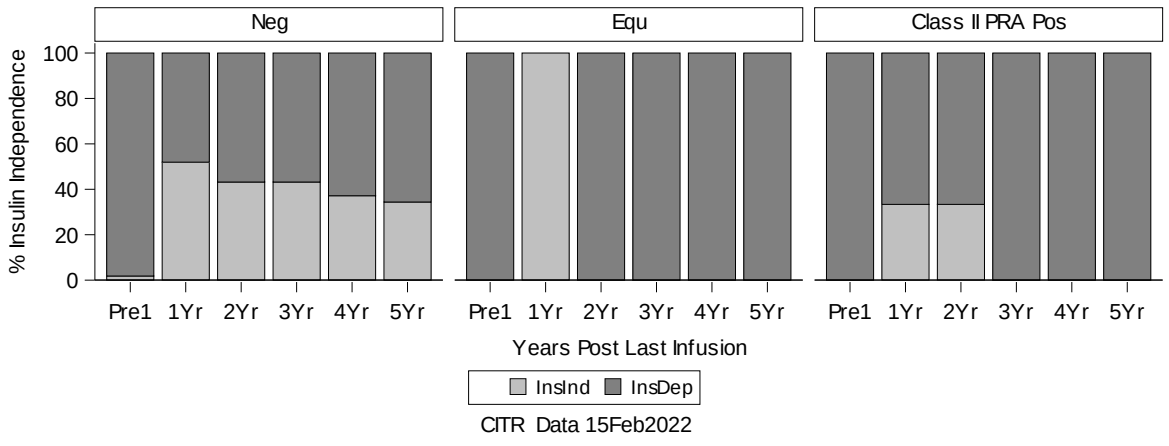
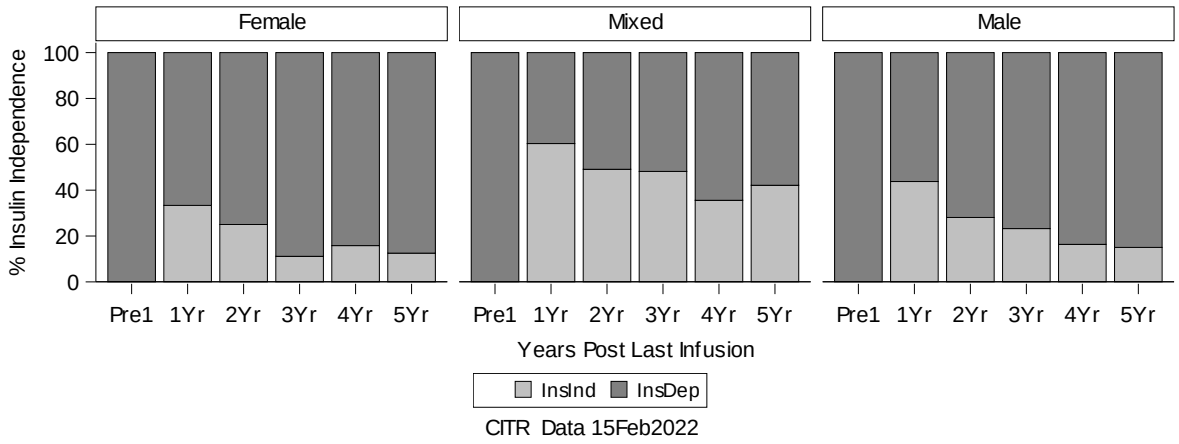
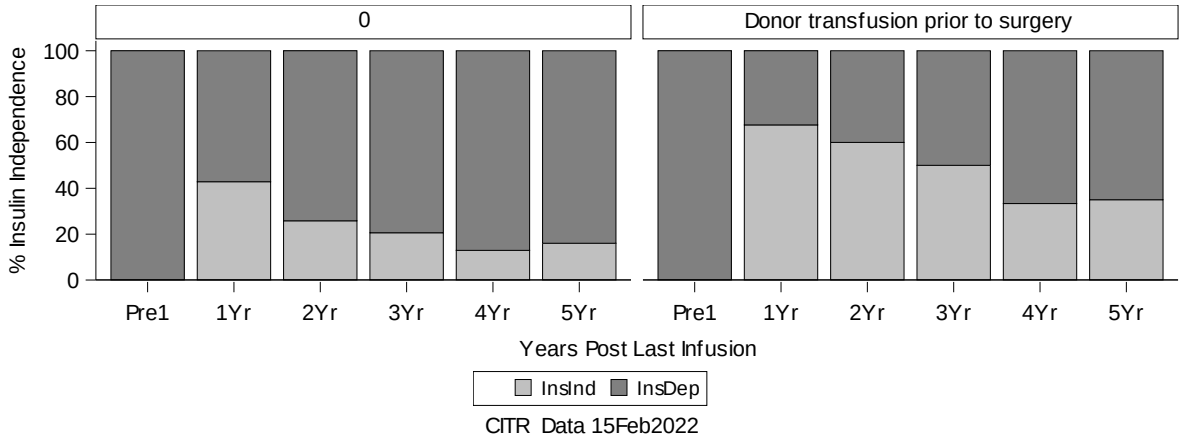


Exhibit 5 – 2C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

D. Donor Sex (p=0.006)



E. Donor given transfusions prior to surgery (p=0.009)



F. Processing Center/ Inf Center Related (p<0.0001)

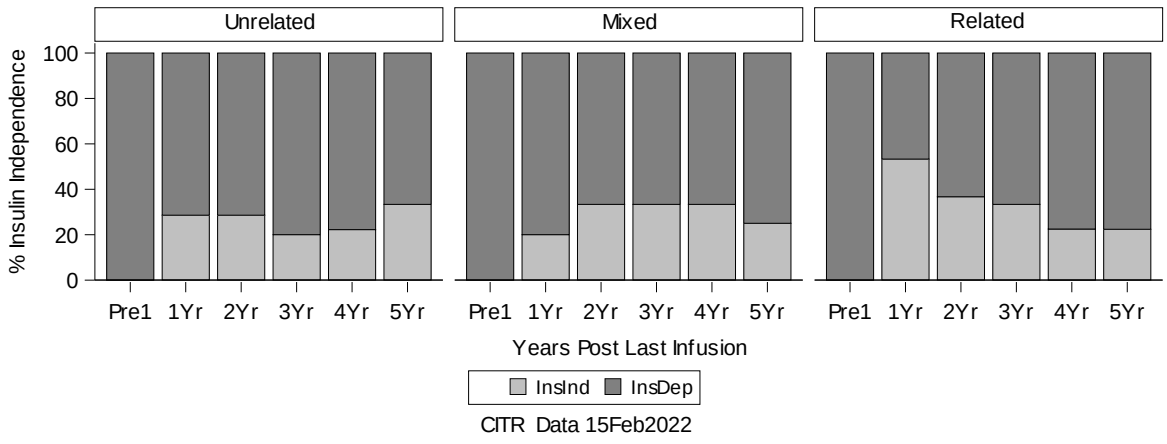
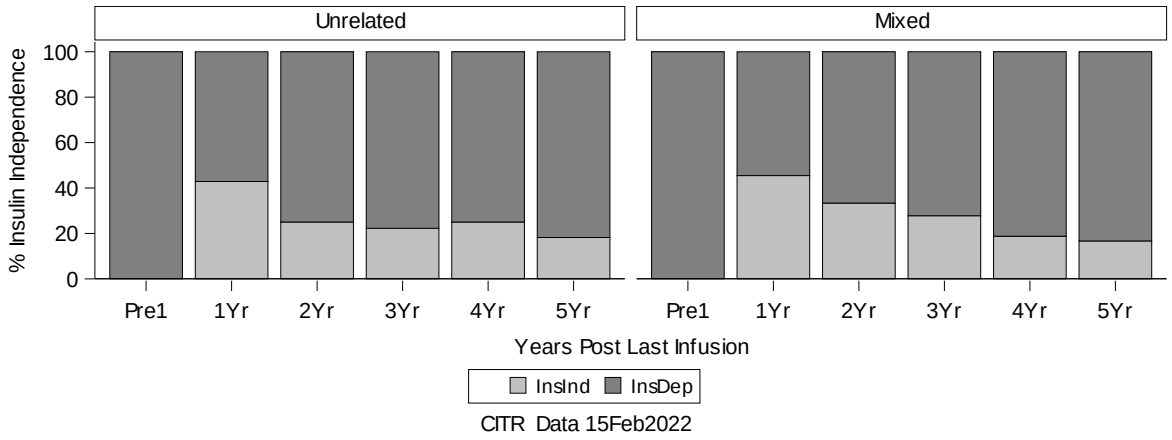
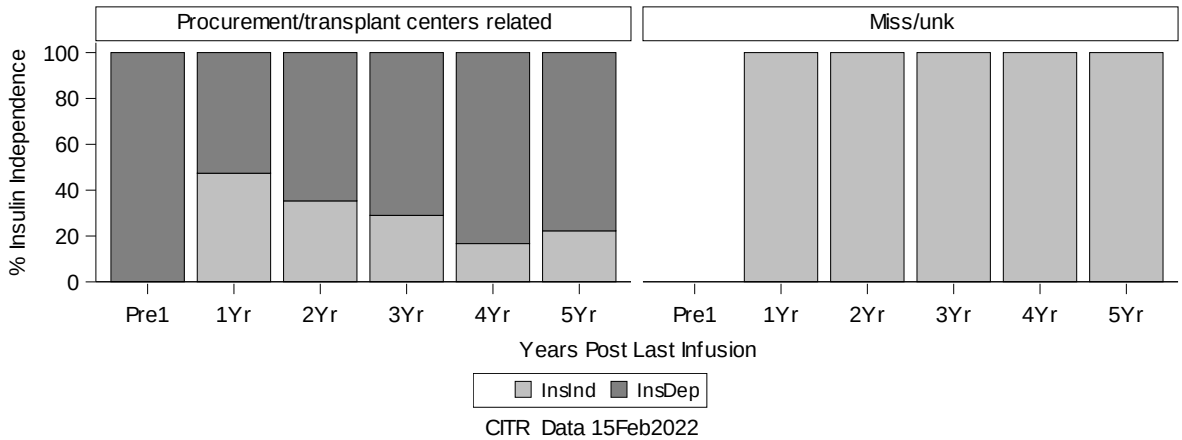


Exhibit 5 – 2C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

G. Procurement Team/ Inf Team Related (p<0.0001)





H. Hours: death to recovery (p=0.0007)

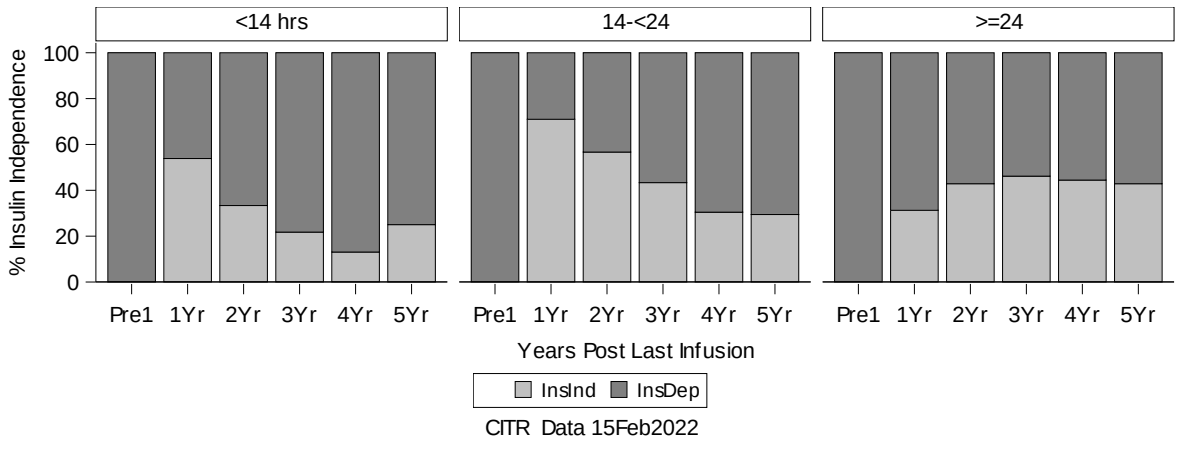
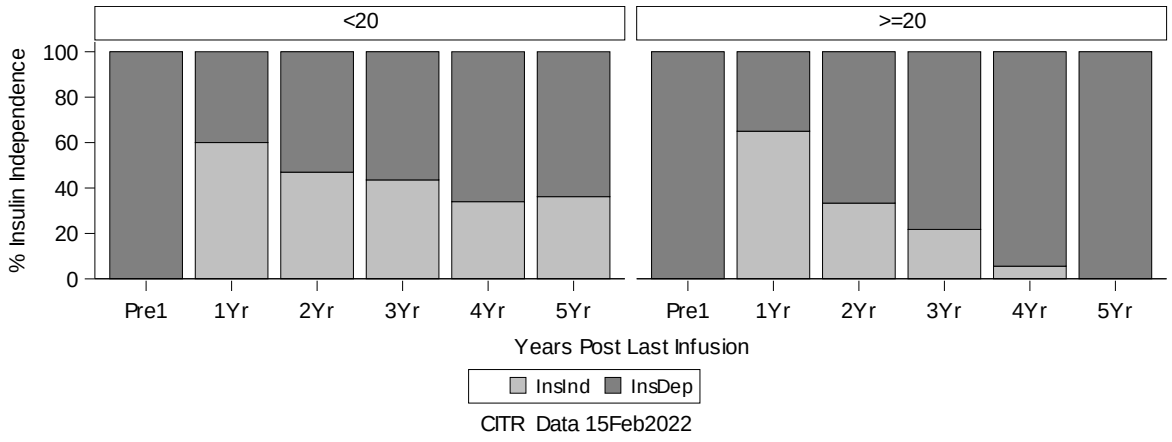


Exhibit 5 – 2C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Insulin Independence Post Last Infusion among IAK Recipients

I. Endotoxin (p=0.001)



J. Endotoxin/kg recipient (p=0.0095)

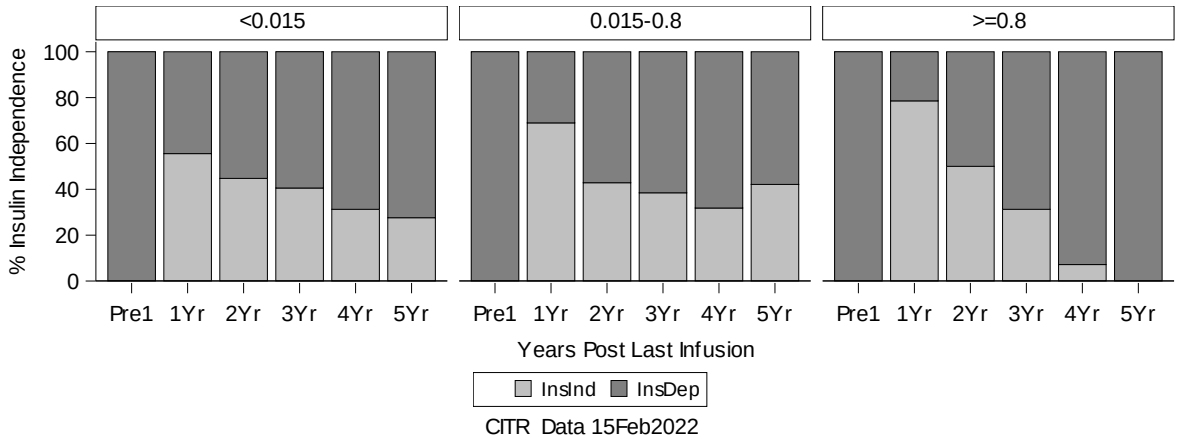


Exhibit 5 – 3A
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

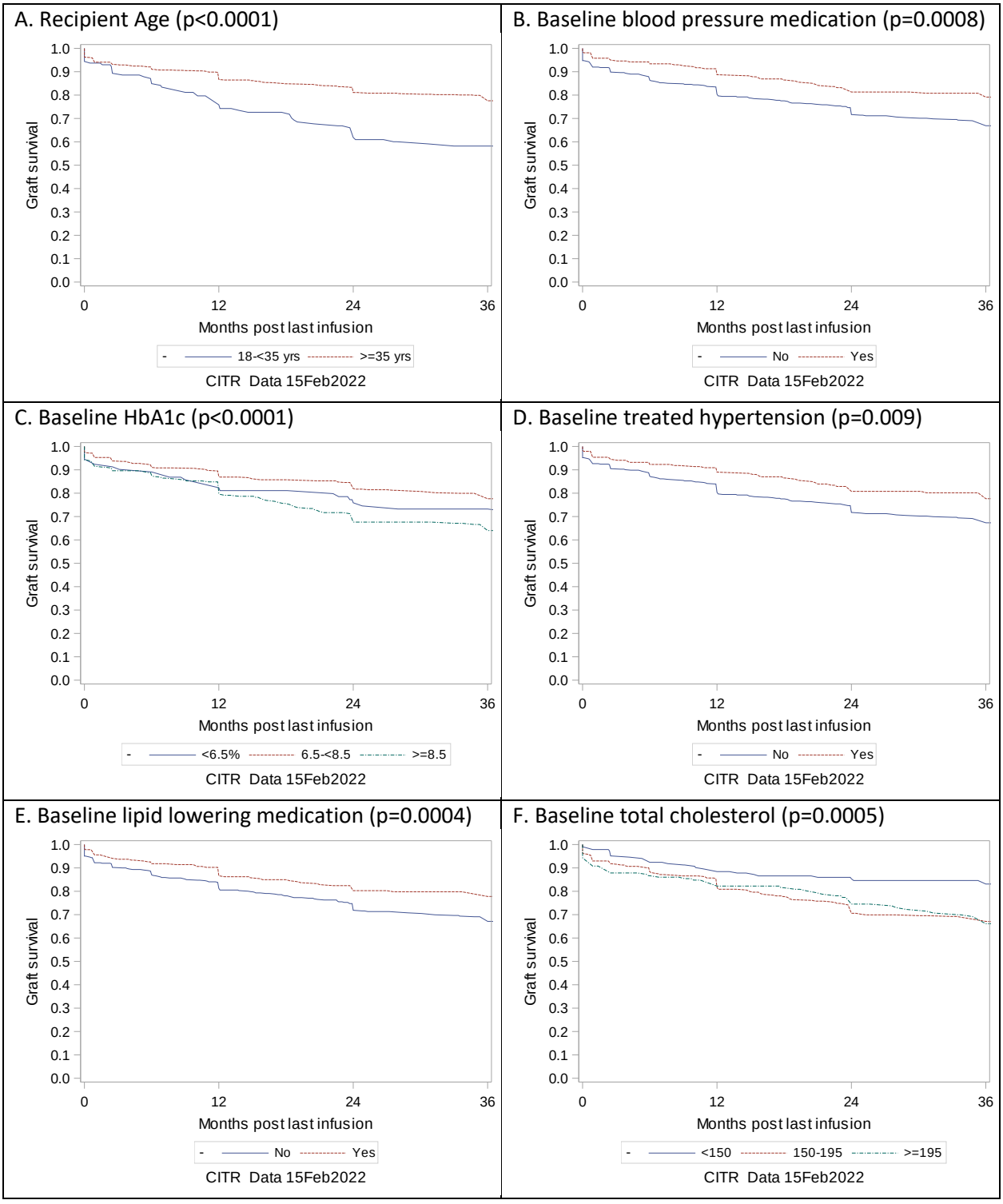
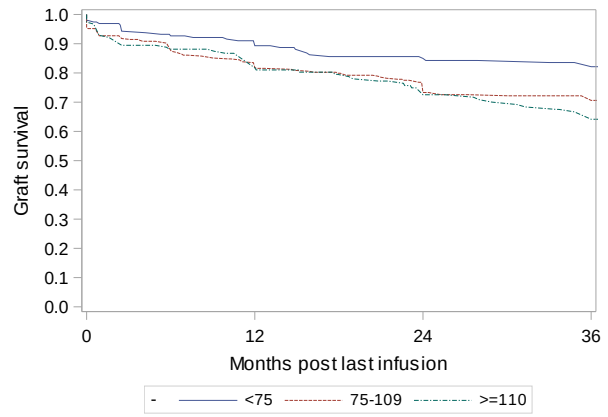
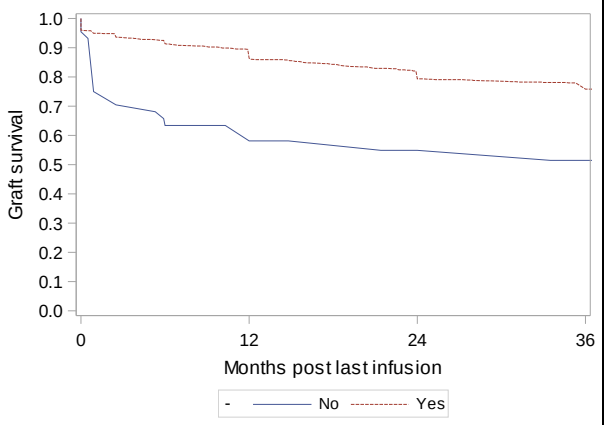


Exhibit 5 – 3A (continued)
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

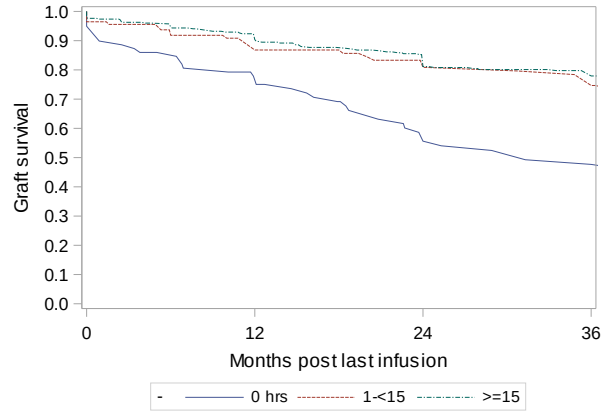
G. Baseline LDL (p=0.0008)



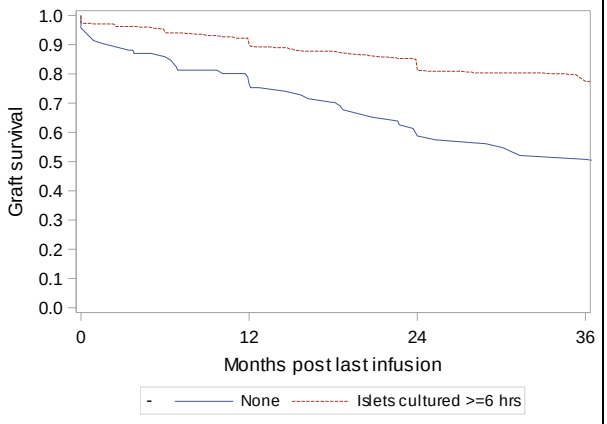
H. Immunosuppression: Calcineurin Inh. (p<0.0001)



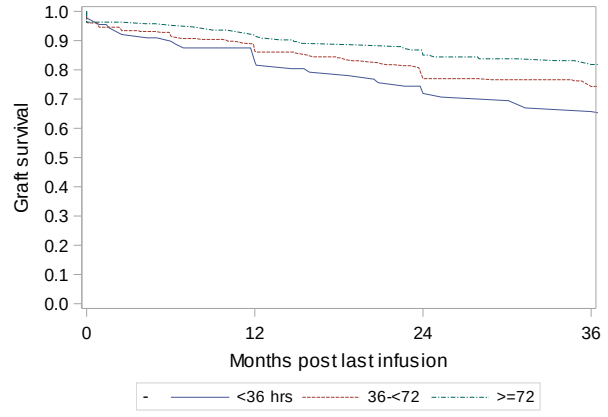
I. Hours: culture time (p<0.0001)



J. Islets Cultured >=6 hrs (p<0.0001)



K. Hours: death-transplant (p=0.003)



L. Diabetes duration (yrs) (p=0.0002)

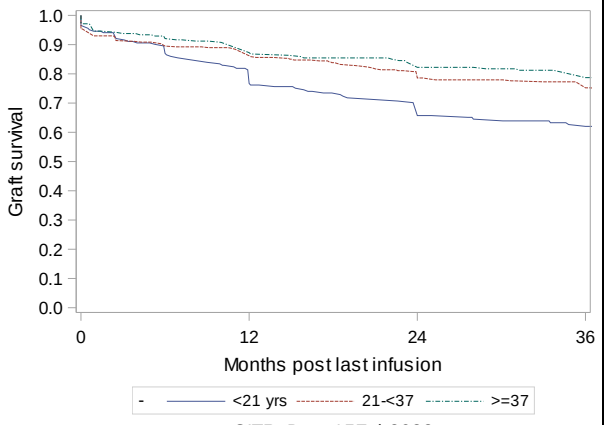
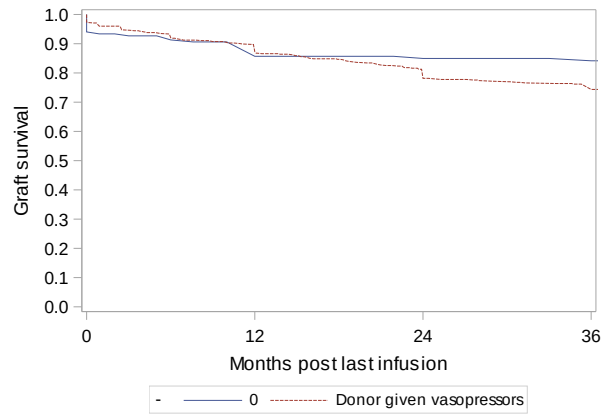
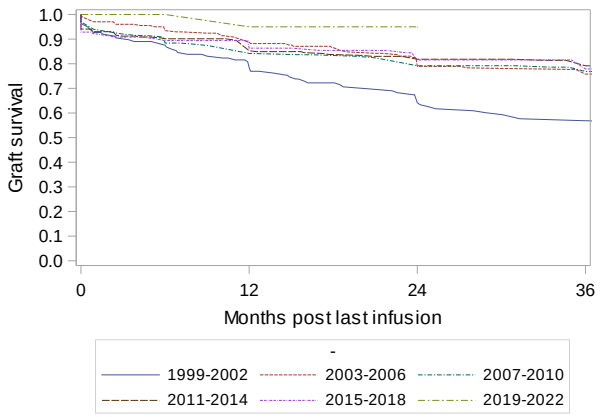


Exhibit 5 – 3A (continued)
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

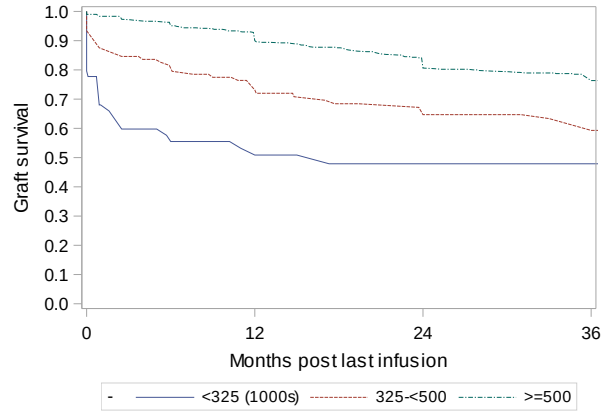
M. Donor given vasopressors (p=0.008)



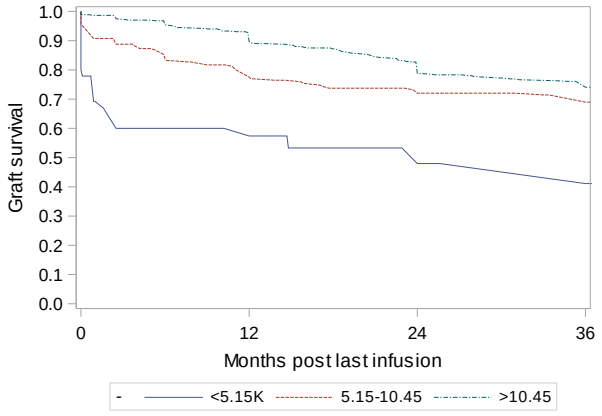
N. Era (p<0.0001)



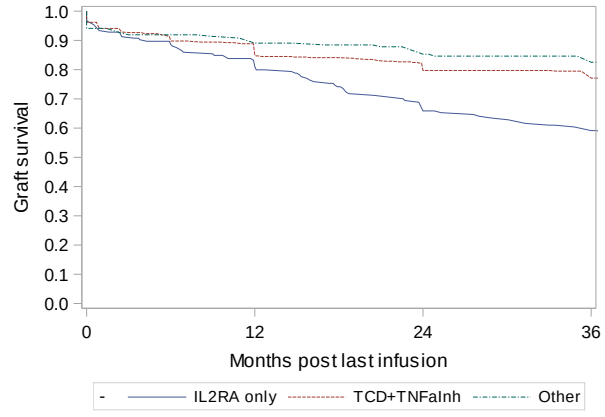
O. IEQs Infused (1000s) (p<0.0001)



P. IEQs Infused/kg Recipient (1000s) (p<0.0001)



Q. Induction Immunosuppression Regimen (p<0.0001)



R. Immunosuppression: mTOR Inihibitor (p=0.0002)

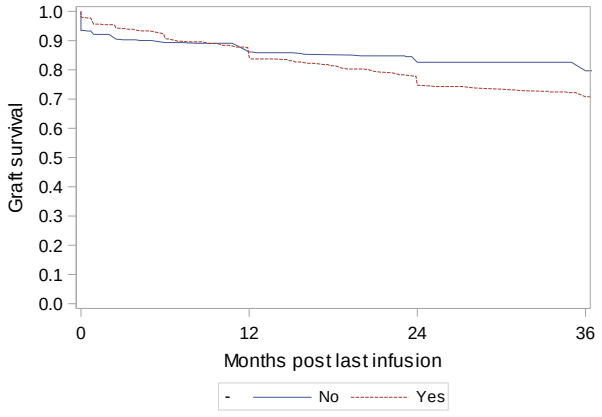


Exhibit 5 – 3A (continued)
Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

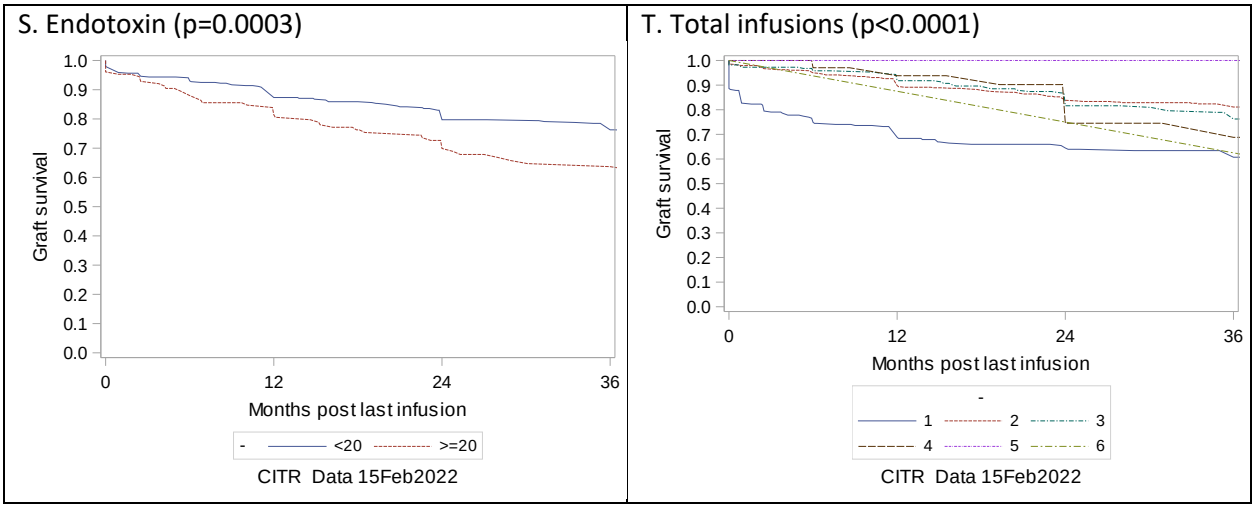
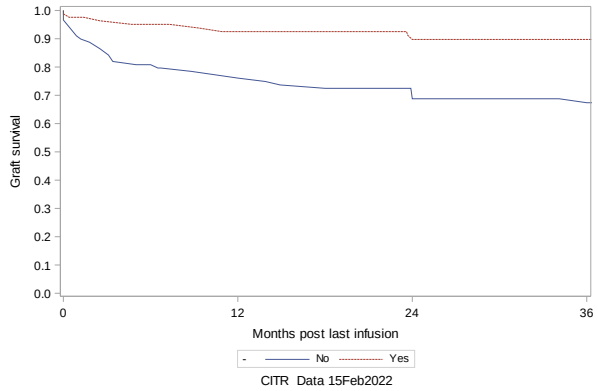


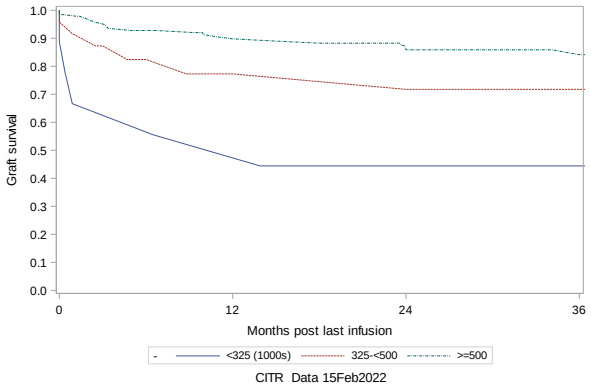
Exhibit 5 – 3B

Univariate Effects of Individual Variables (p<0.01) on Retention of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

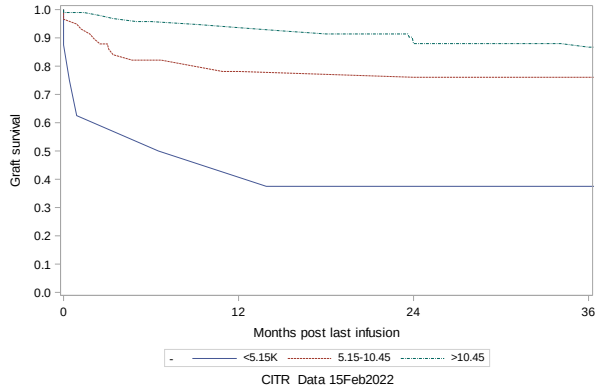
A. Baseline lipid lowering medication (p=0.002)



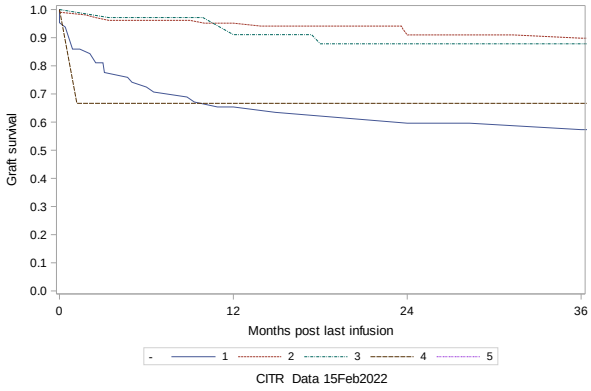
B. IEQs Infused (p=0.004)



C. IEQs Infused/kg Recipient (p=0.001)



D. Total infusions (p=0.0004).



E. Baseline GAD 65 autoantibody (p=0.003)

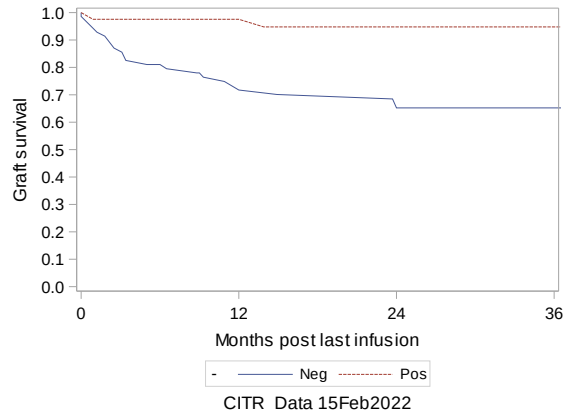


Exhibit 5 – 4A

Unadjusted Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion

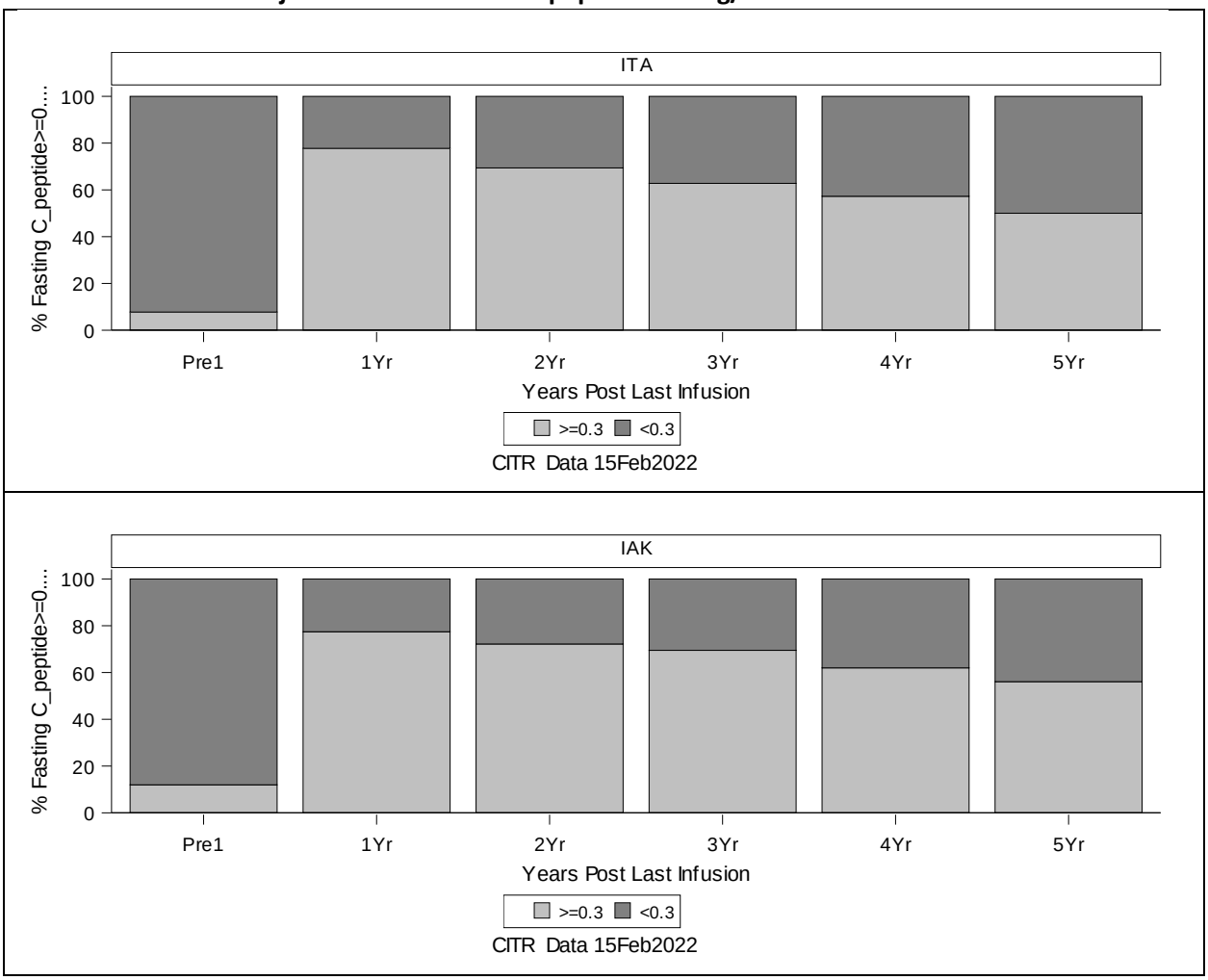
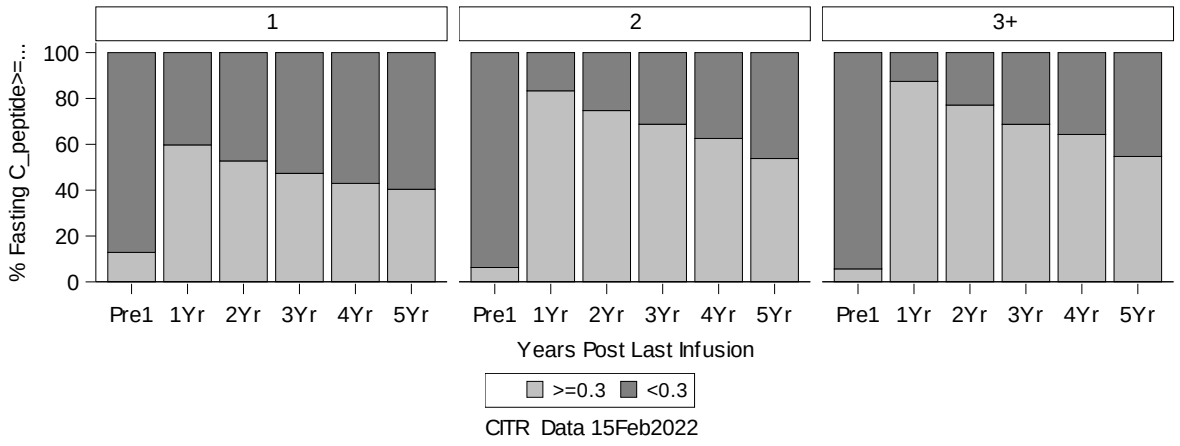


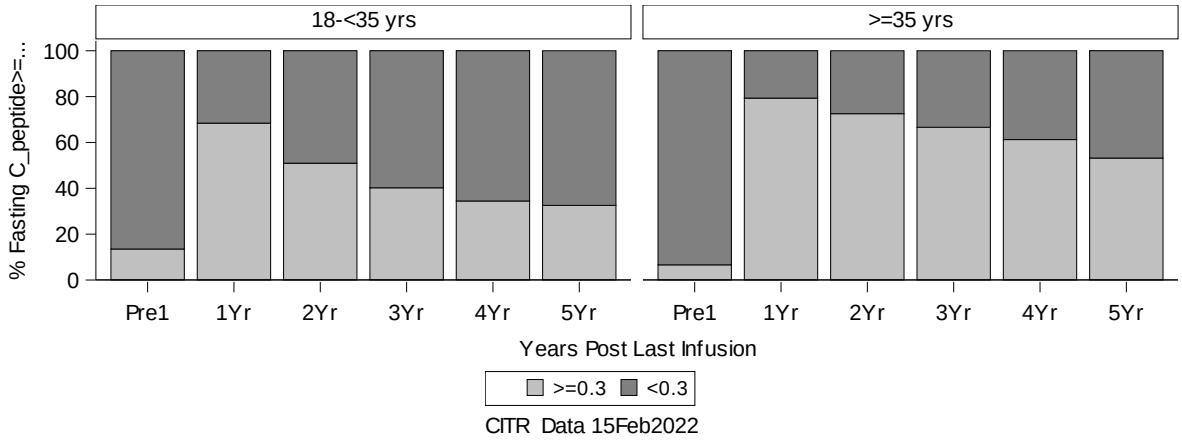
Exhibit 5 – 4B

Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

A. Total infusions (p<0.0001)



B. Recipient Age (p<0.0001)



C. Diabetes duration (yrs) (p=0.006)

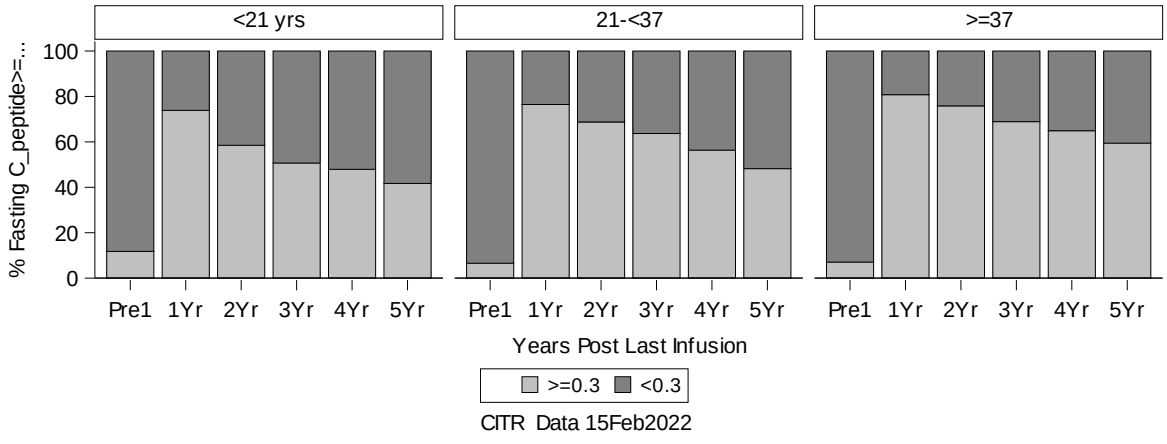
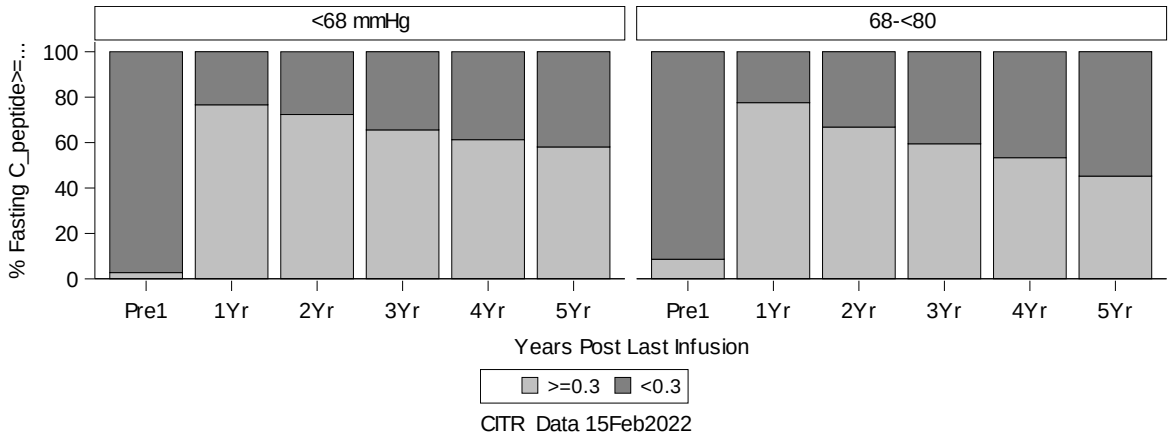
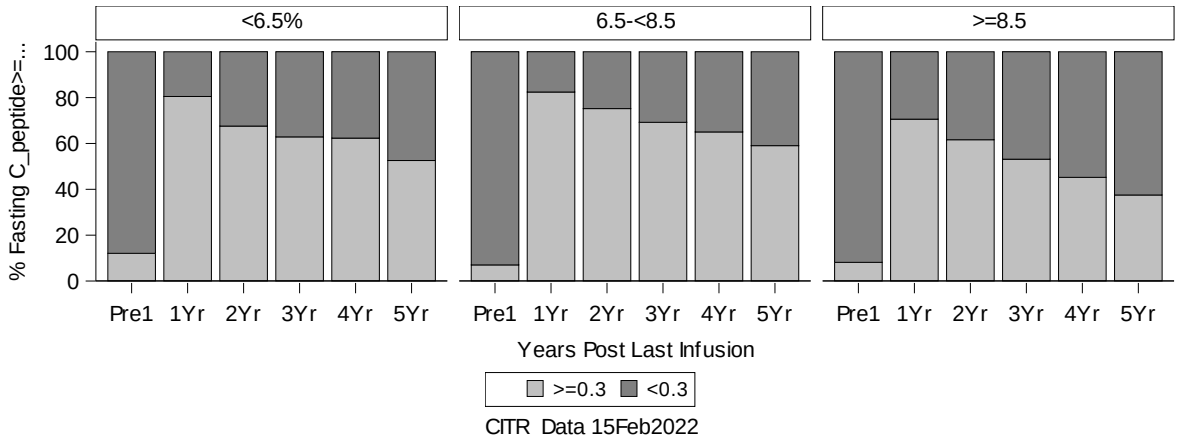


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

D. Baseline DBP (p=0.004)



E. Baseline HbA1c (p=0.0002)



F. Baseline microinsulin autoantibody (p=0.002)

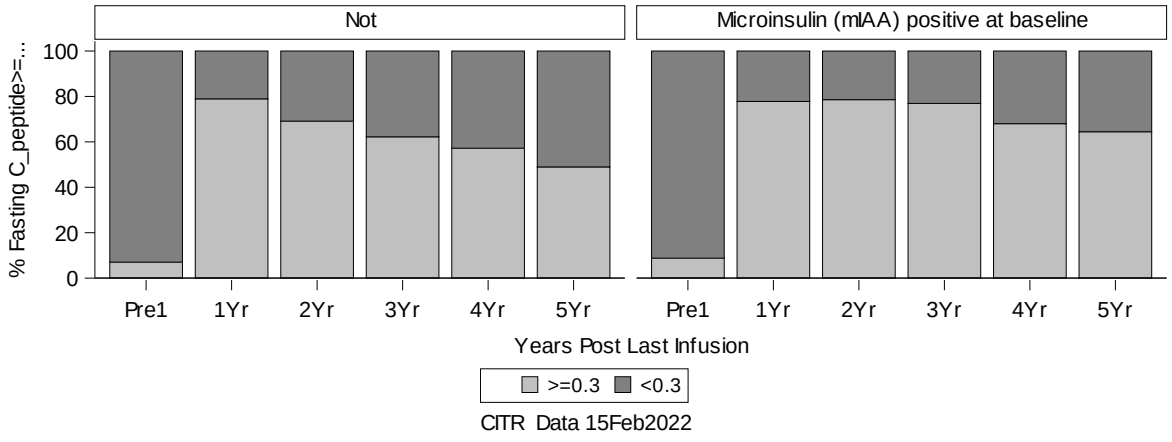
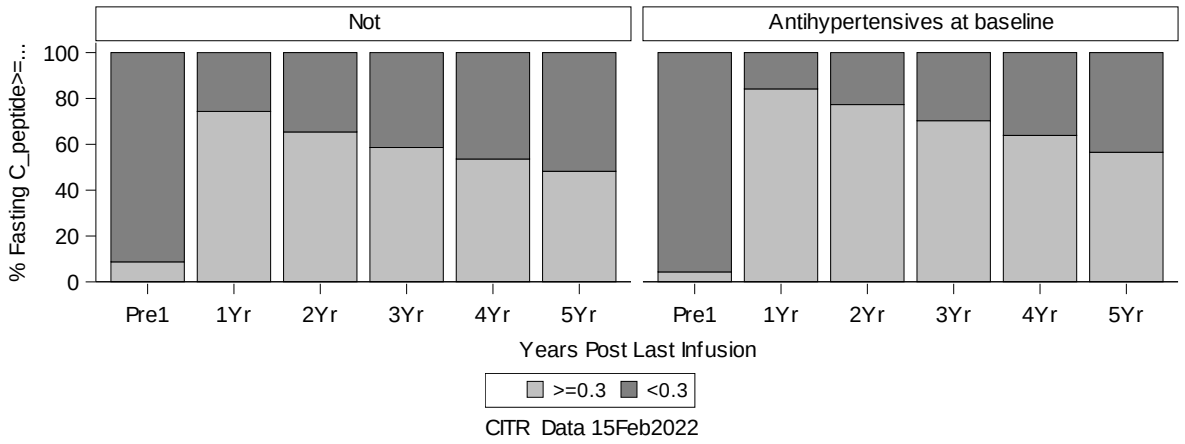
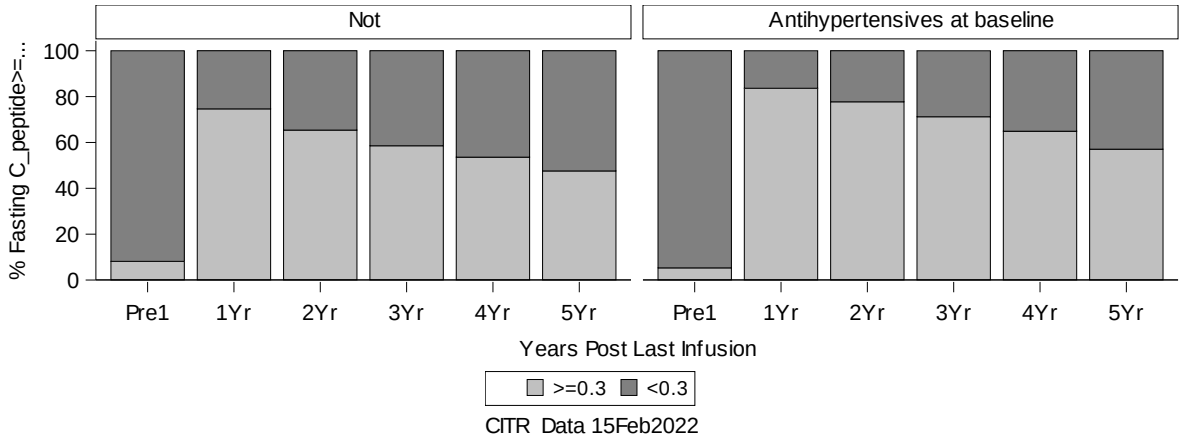


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

G. Baseline treated hypertension (p=0.003)



H. Baseline blood pressure medication (p=0.002)



I. Baseline lipid lowering medication (p=0.0008)

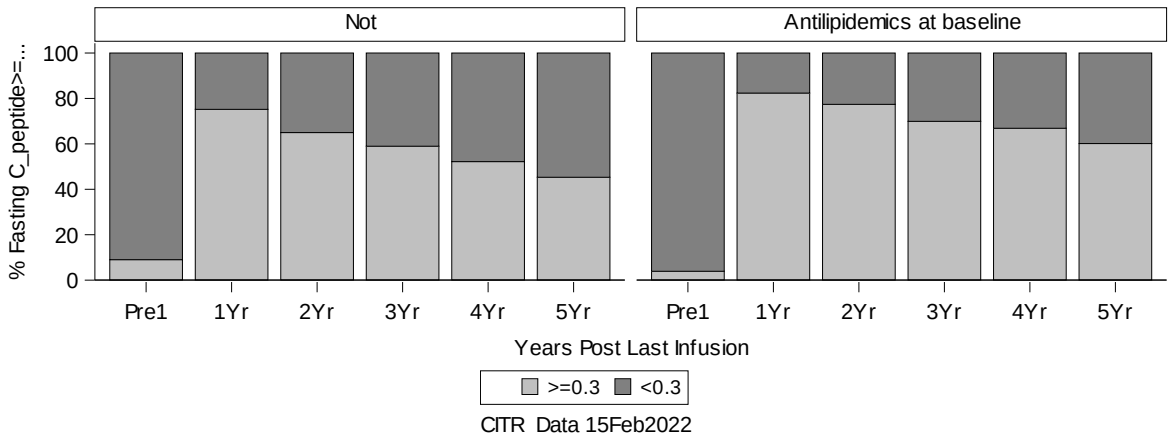
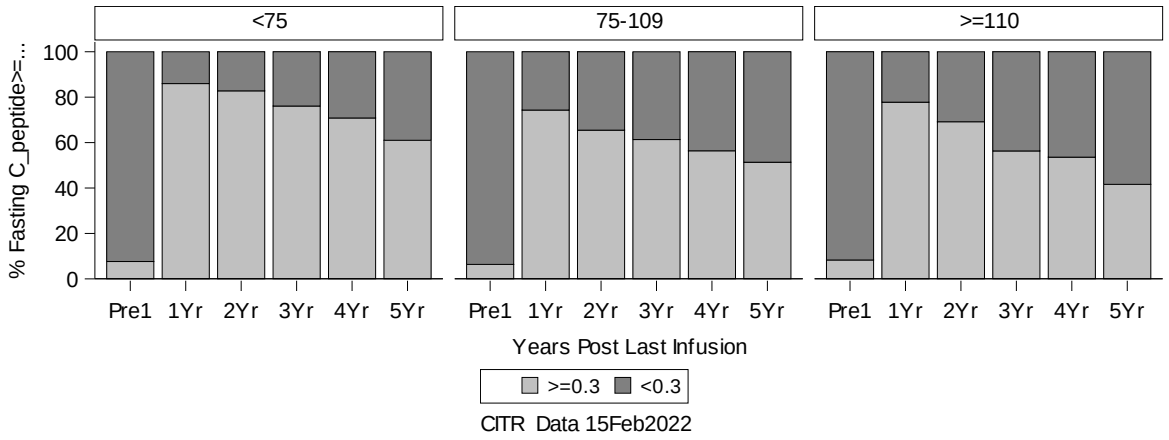
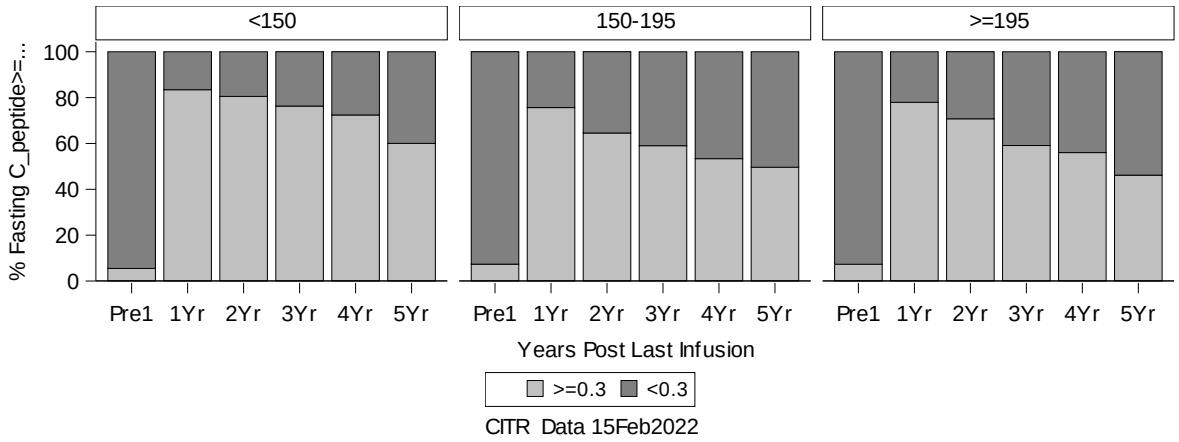


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

J. Baseline LDL (p=0.0005)



K. Baseline chol (p=0.001)



L. Donor Race (p=0.0007)

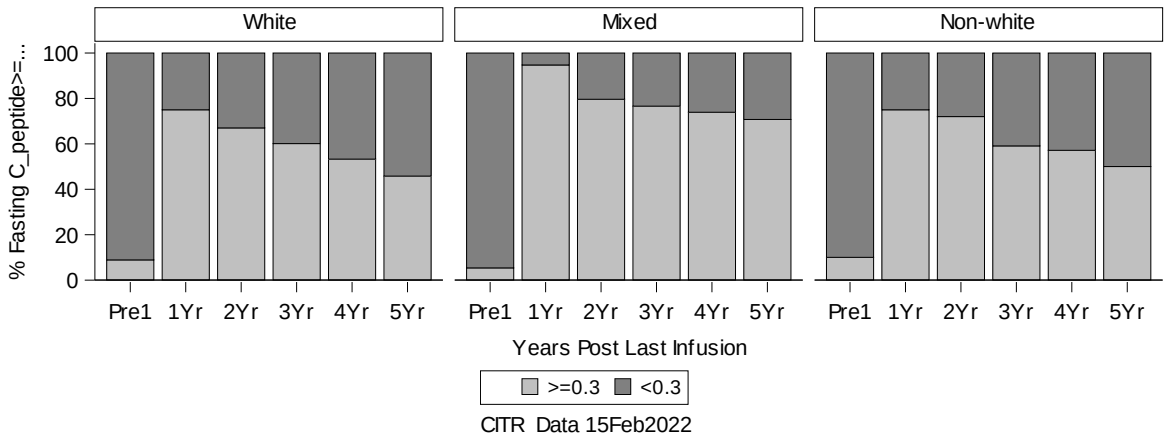
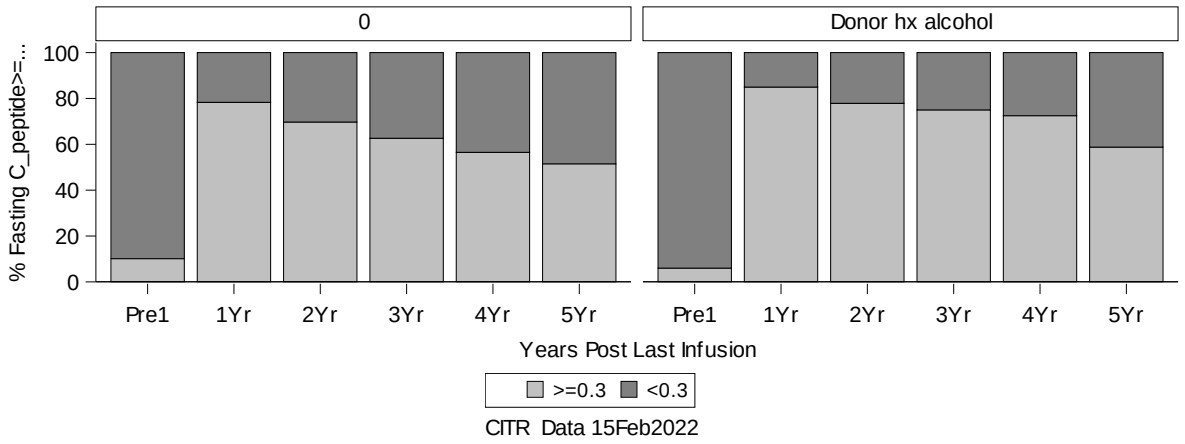
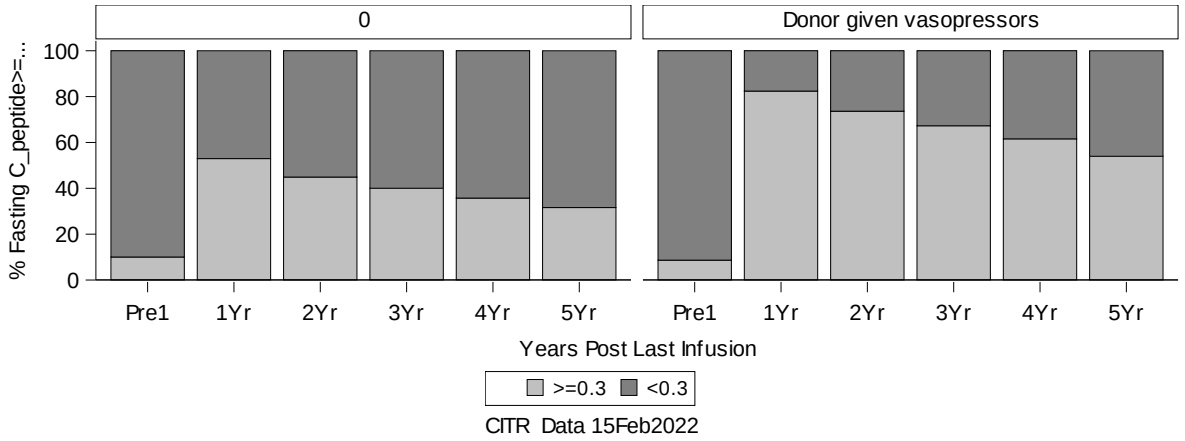


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

M. Donor History of alcohol abuse (p=0.009)



N. Vasopressors used (p=0.001)



O. Donor given transfusions prior to surgery (p=0.003)

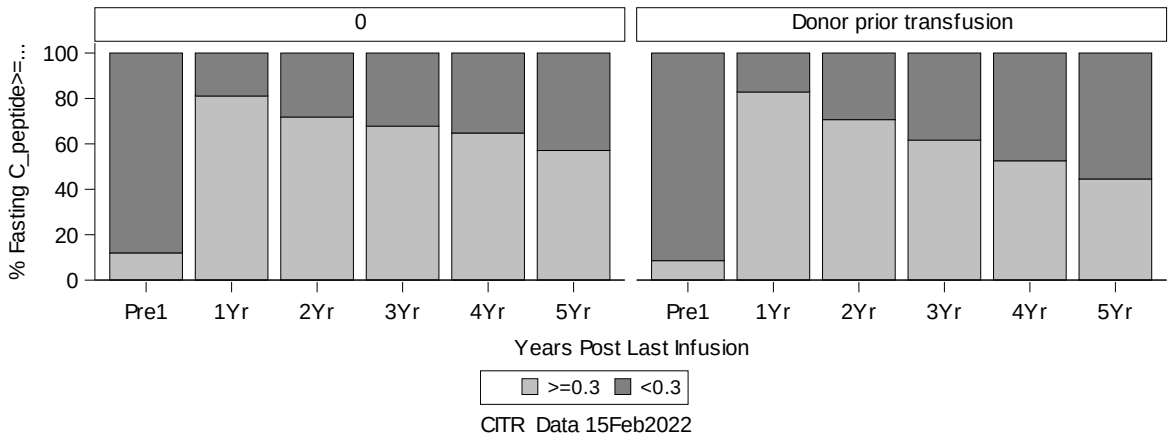
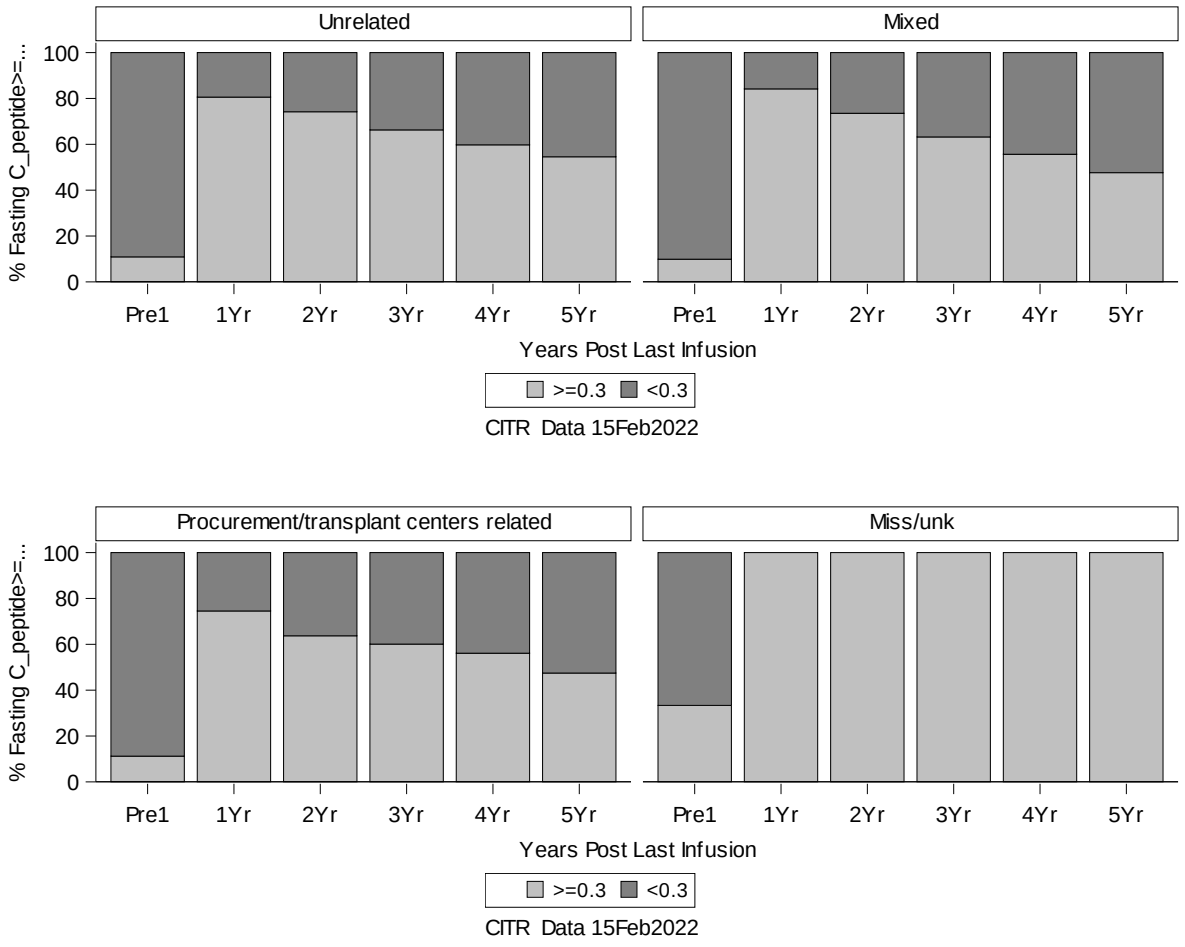


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

P. Procurement Team/ Inf Team Related (p<0.0001)



Q. Islets Cultured ≥6 hrs (p<0.0001)

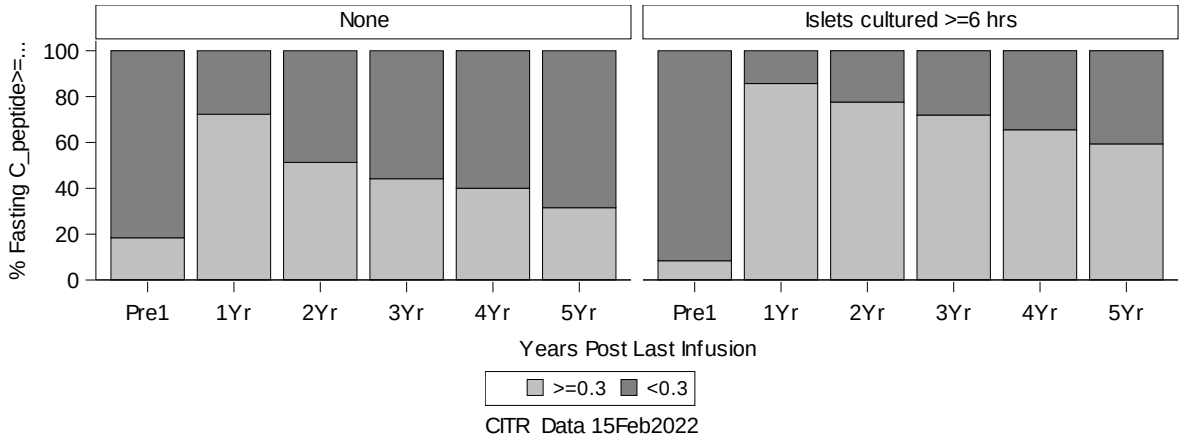
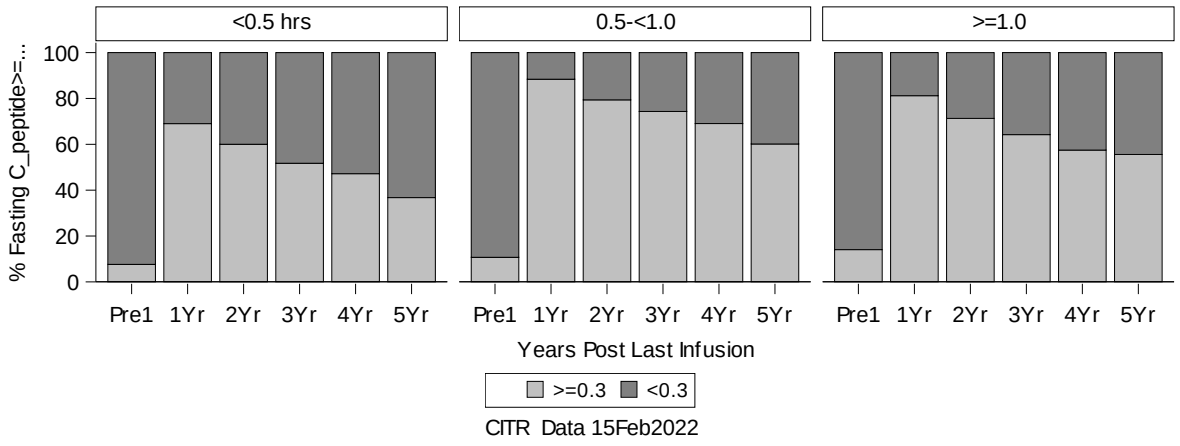


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

R. Hours: cross-clamp to recovery (p=0.004)



S. Hours culture time (p=0.0004)

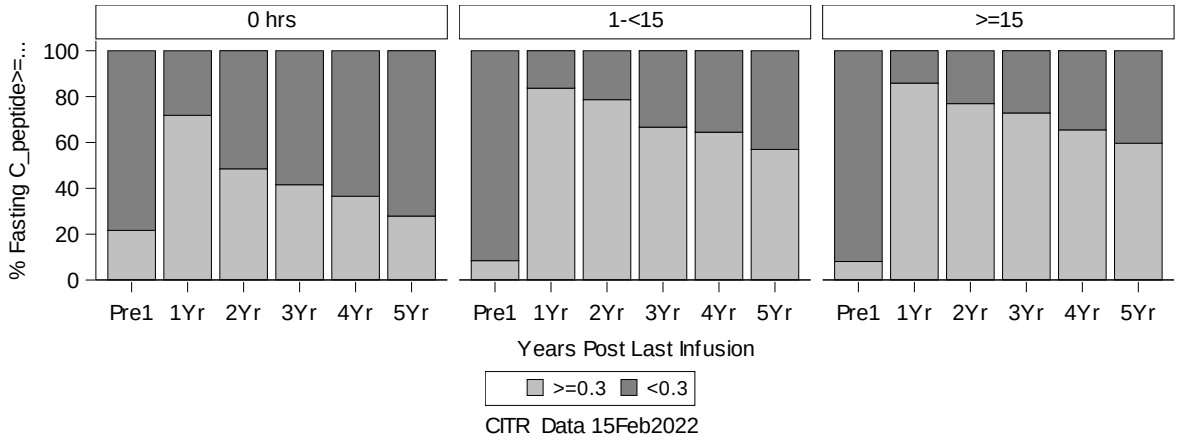
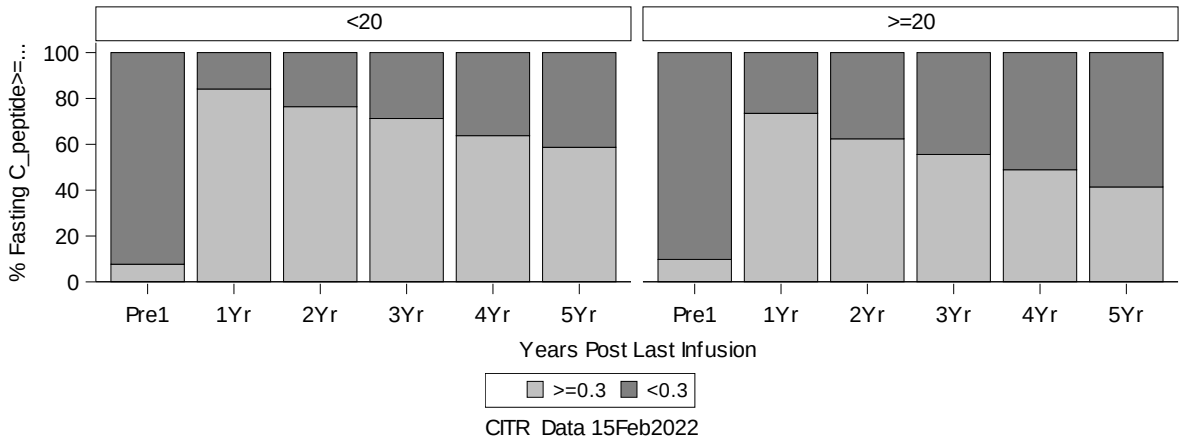
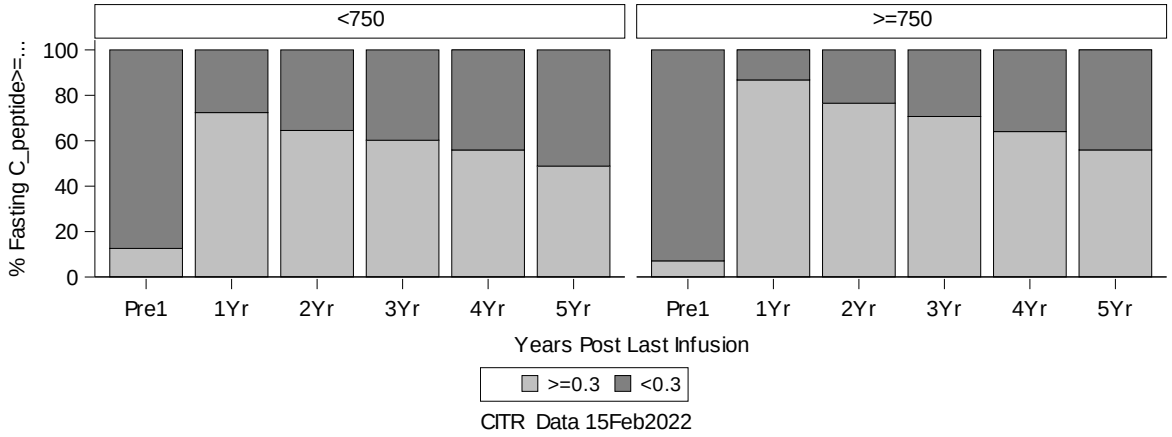


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

U. Endotoxin (p=0.005)



V. IEQs(1000s,particle count) (p=0.005)



W. IEQs infused (1000s) (p<0.0001)

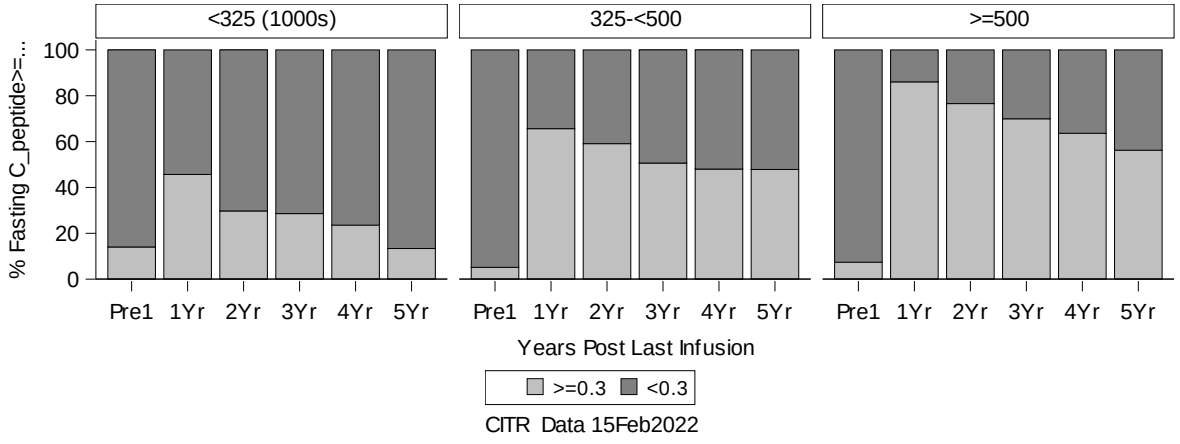
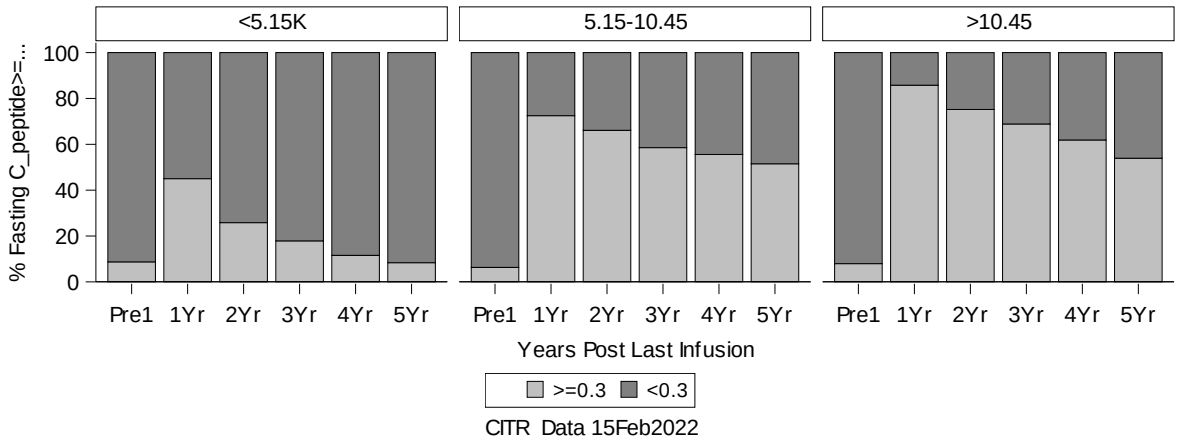
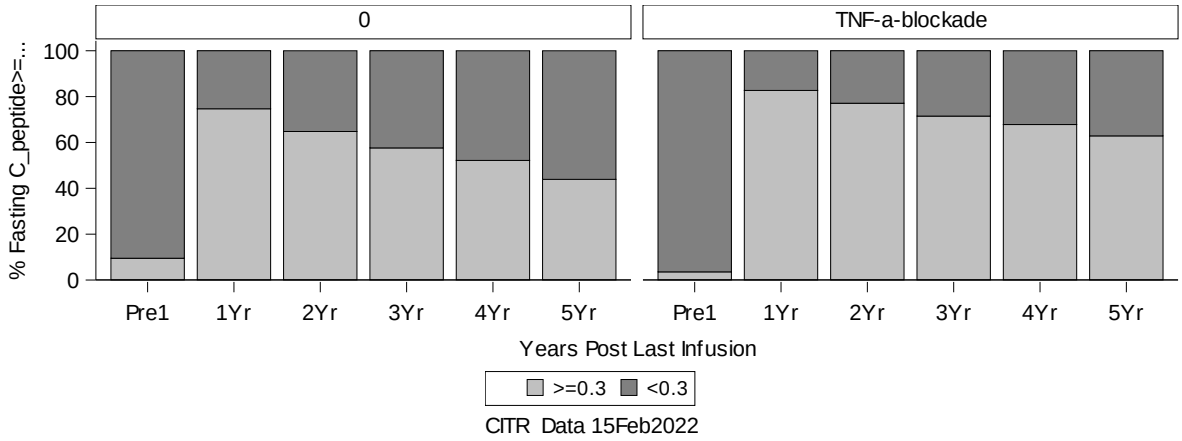


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

X. Total IEQs Infused/kg recipient (1000s) (p<0.0001)



Y. Immunosuppression: TNFa (p<0.0001)



Z. Immunosuppression: Calcineurin inhibitor (p=0.001)

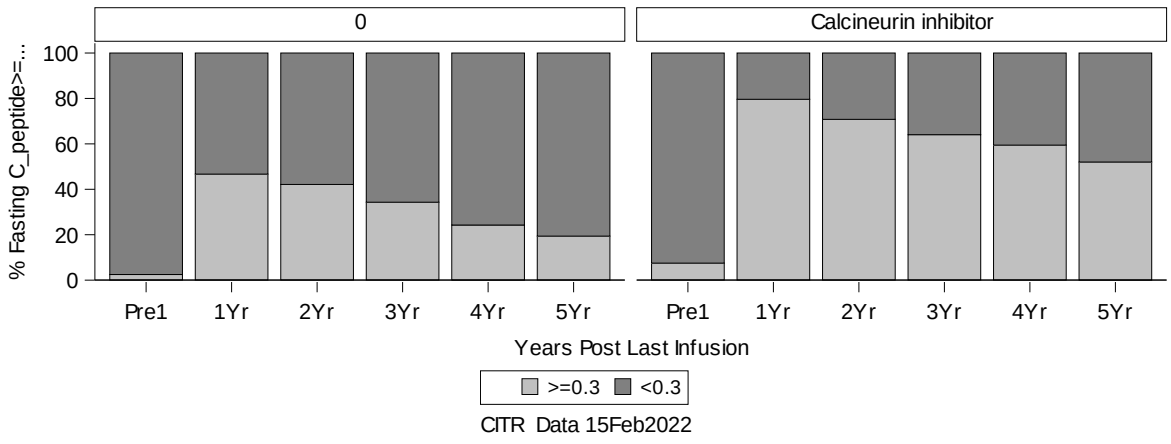


Exhibit 5 – 4B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among ITA Recipients

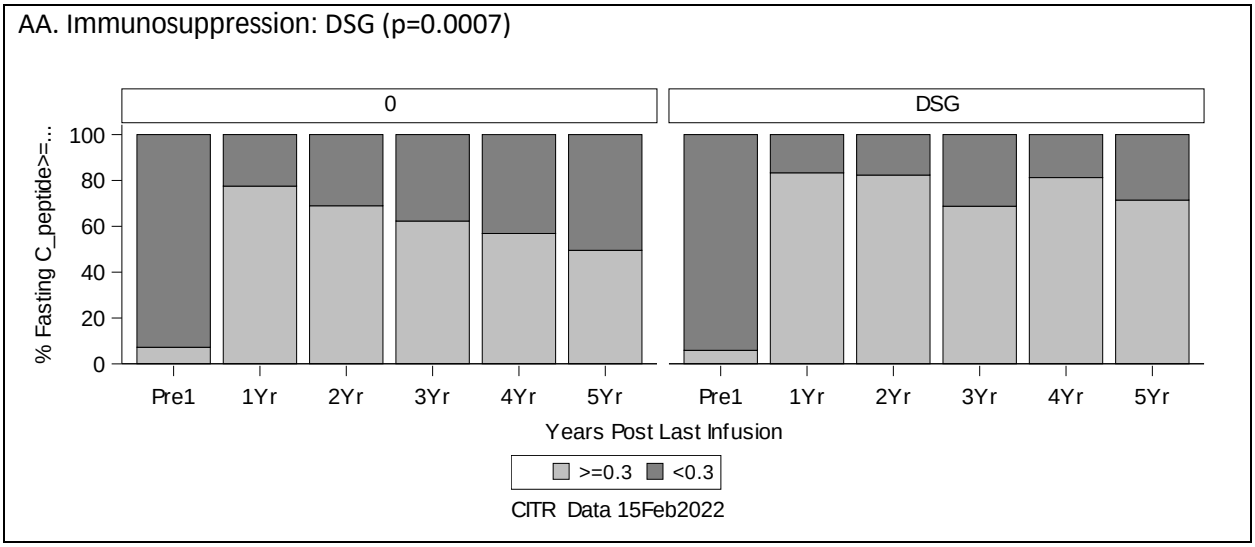
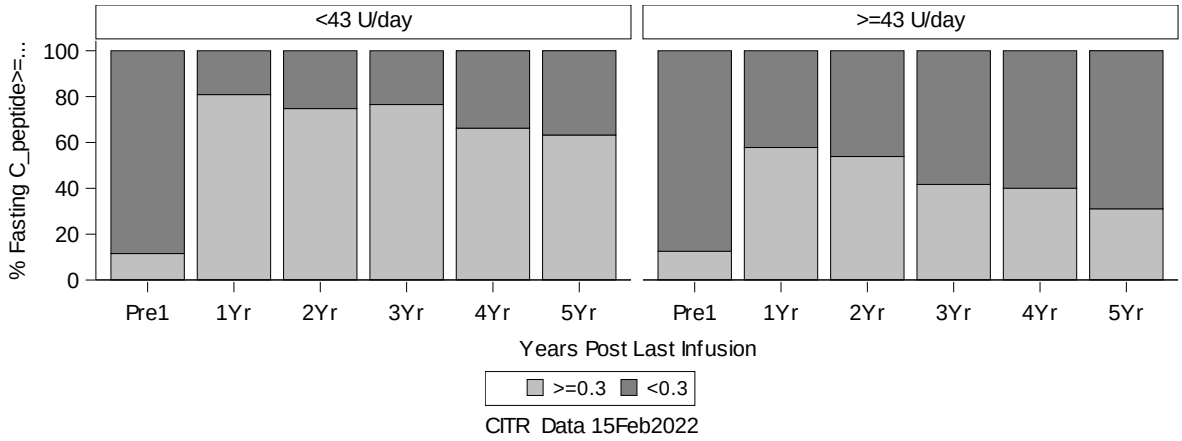


Exhibit 5 – 4C

Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

A. Total infusions (p=0.0001)

B. Baseline insulin (Units/day) (p=0.005)



C. Baseline GAD 65 autoantibody (p=0.002)

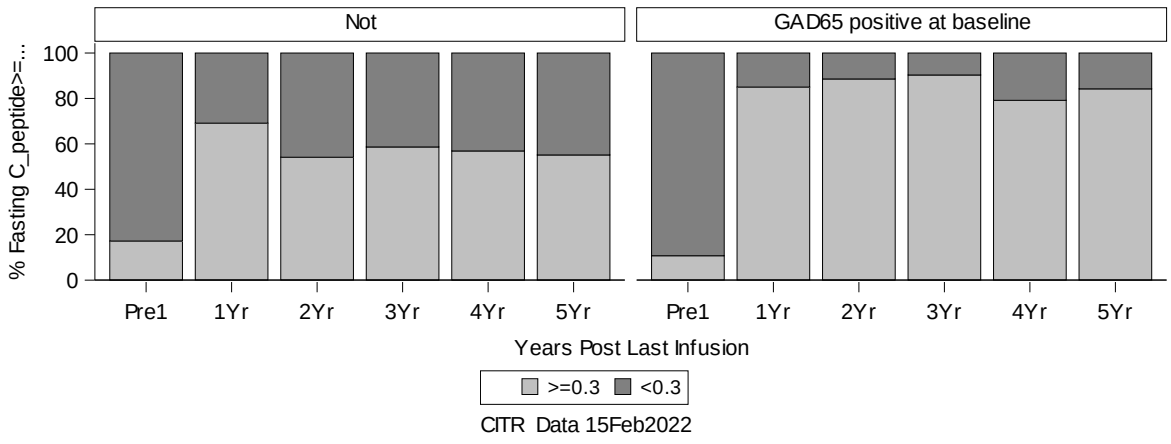
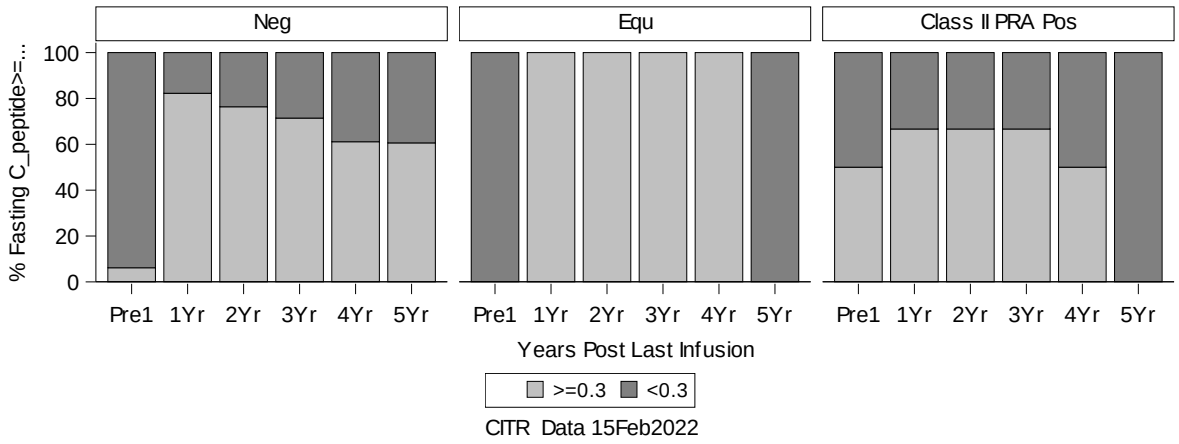
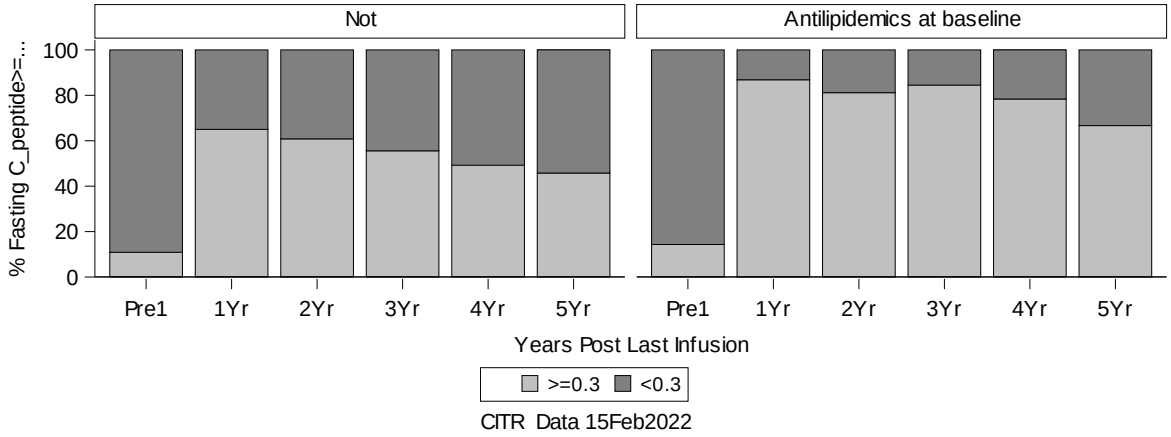


Exhibit 5 – 4C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

D. Baseline Class 2 PRA (p<0.0001)



E. Baseline lipid lowering medication (p=0.0009)



F. Baseline retinopathy (p=0.0009)

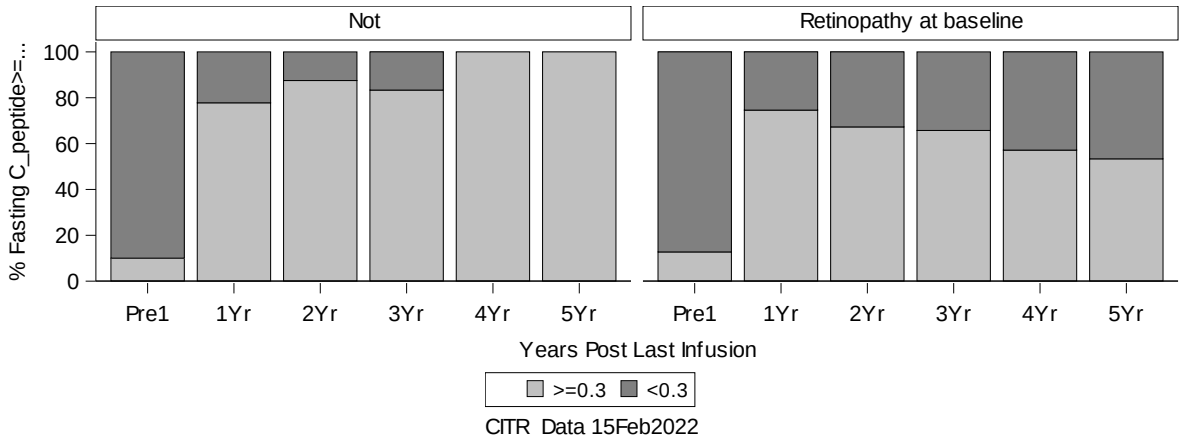
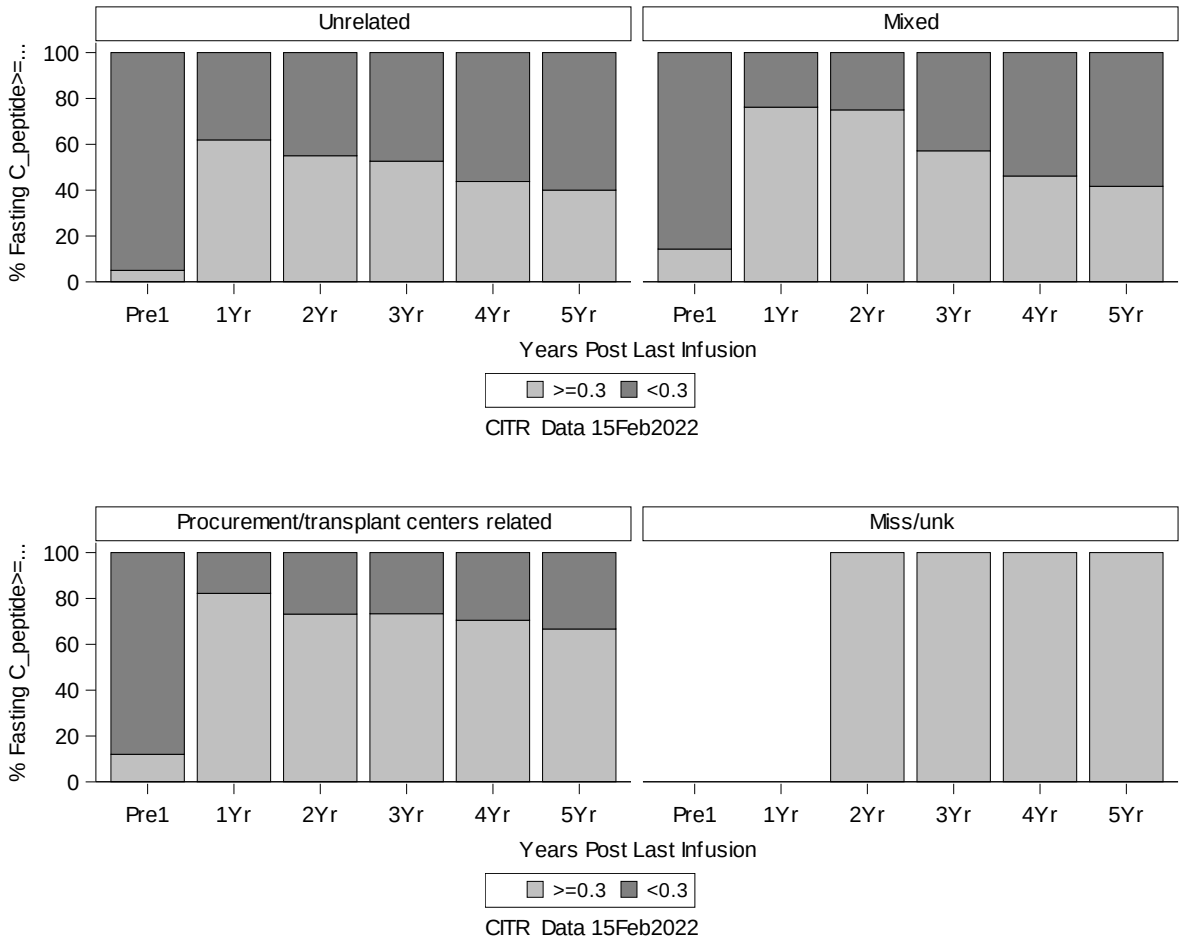


Exhibit 5 – 4C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

G. Procurement Team/ Inf Team Related (p<0.0001)



H. Donor serum creatinine (p=0.006)

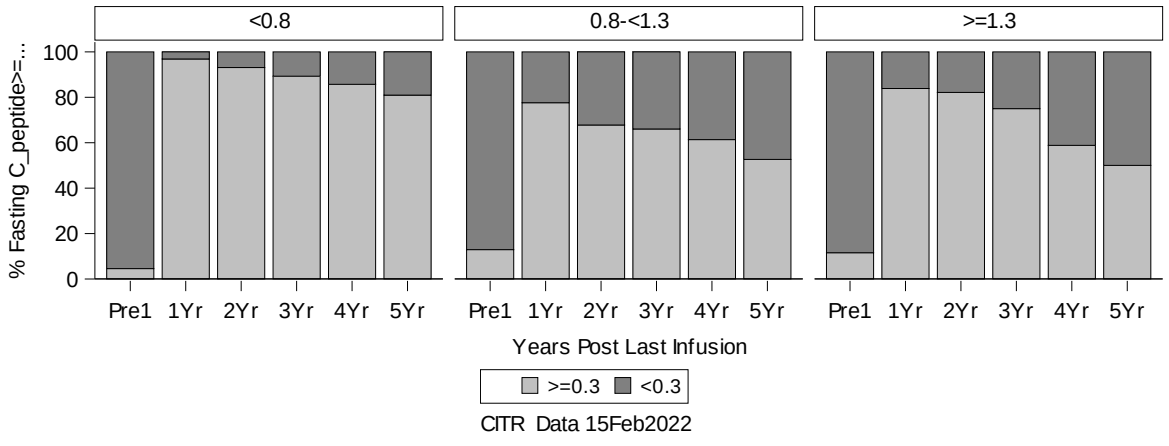
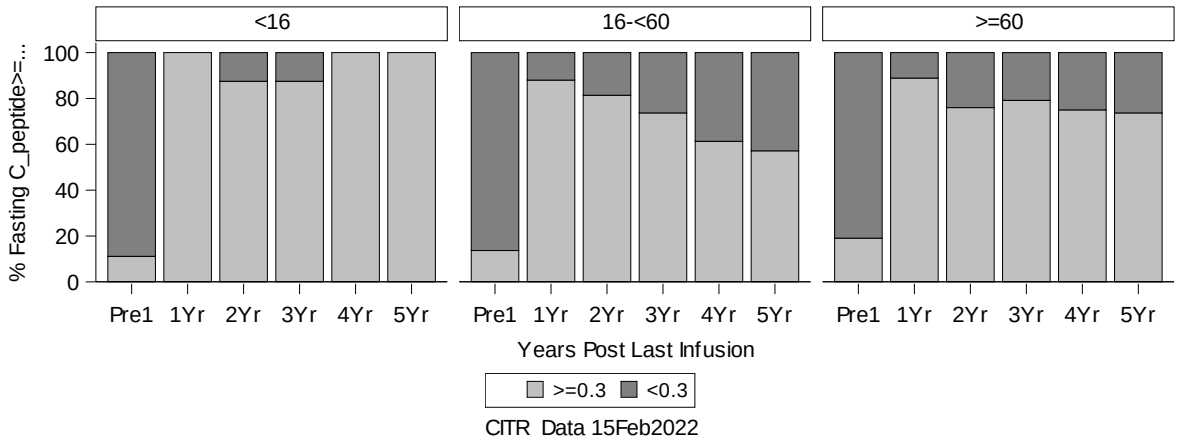
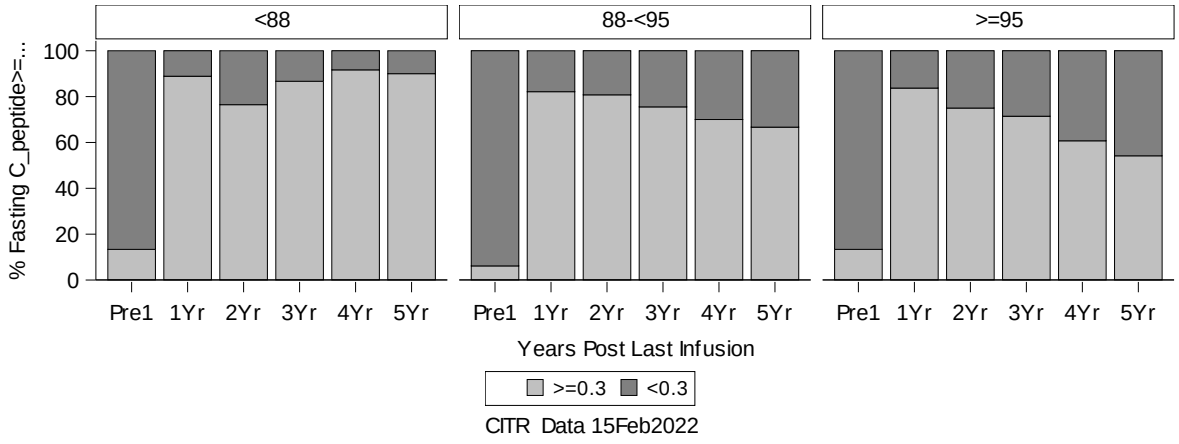


Exhibit 5 – 4C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

I. Hours: admission to brain death (p=0.002)



J. Islet viability (p=0.007)



K. Immunosuppression: mTOR Inhibitor (p=0.006)

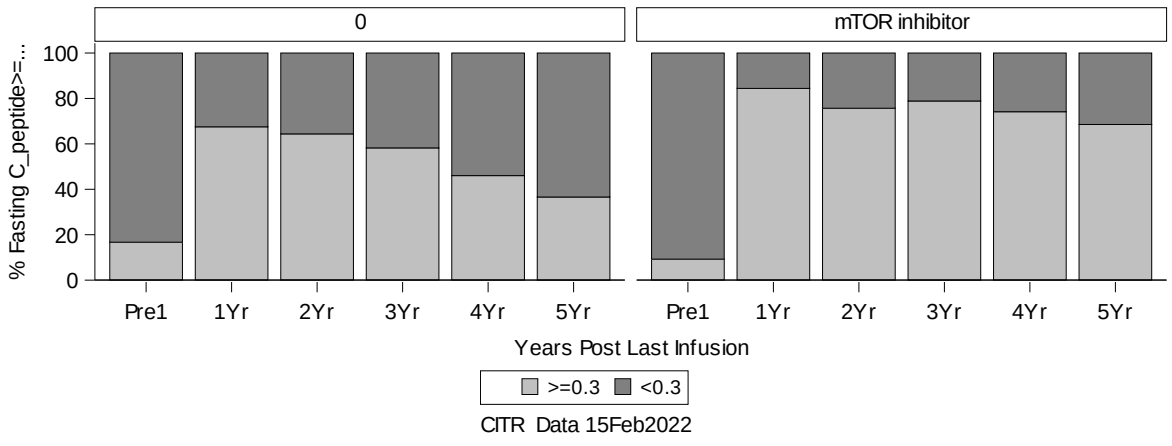


Exhibit 5 – 4C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of C-peptide ≥0.3 ng/mL Post Last Infusion among IAK Recipients

L. Immunosuppression: Steroid (p=0.007)

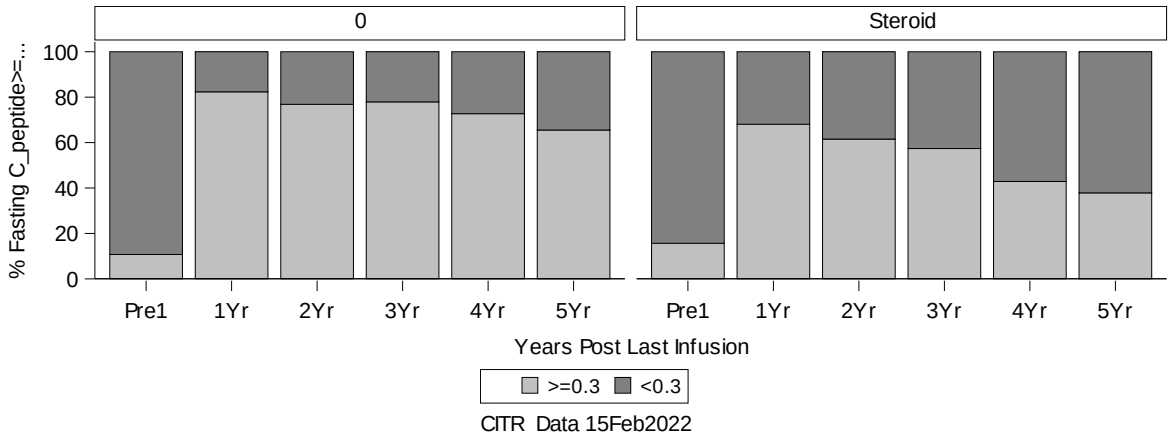


Exhibit 5 – 5A

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

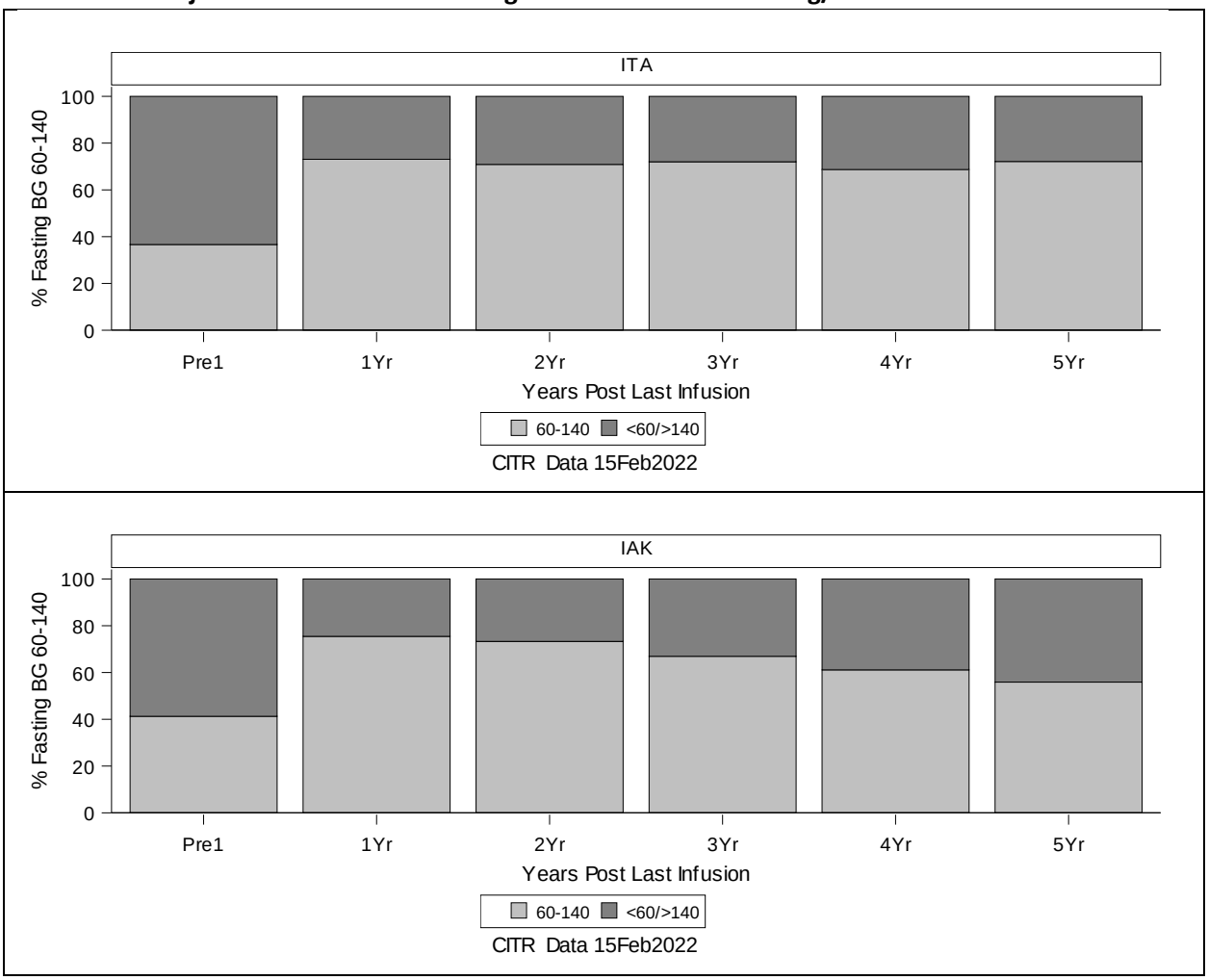
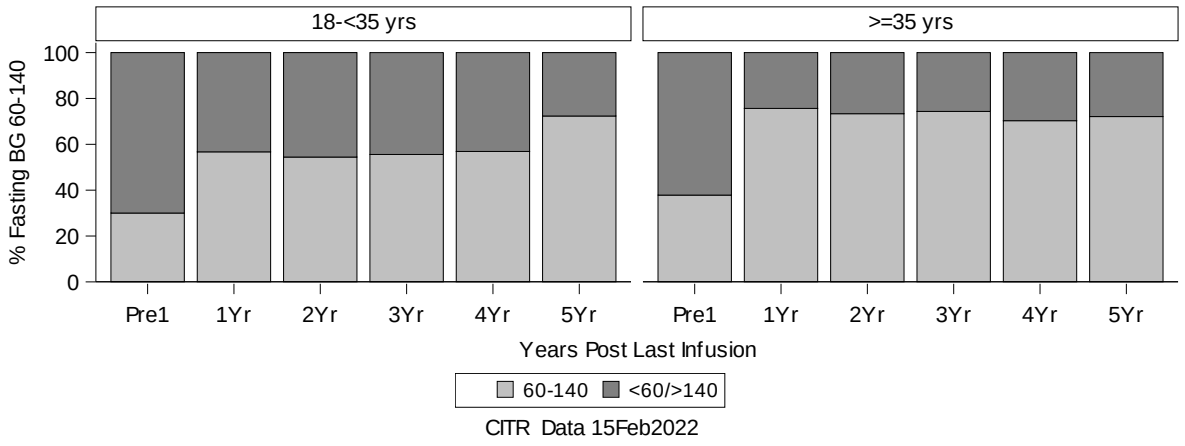


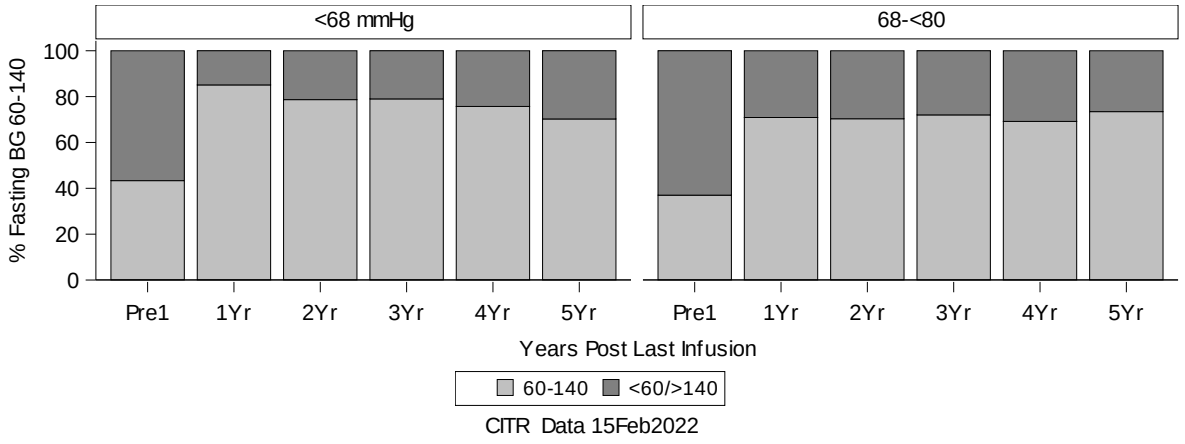
Exhibit 5 – 5B

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

A. Recipient Age (p=0.0006)



B. Baseline DBP (p=0.009)



C. Baseline insulin (Units/day) (p<0.0001)

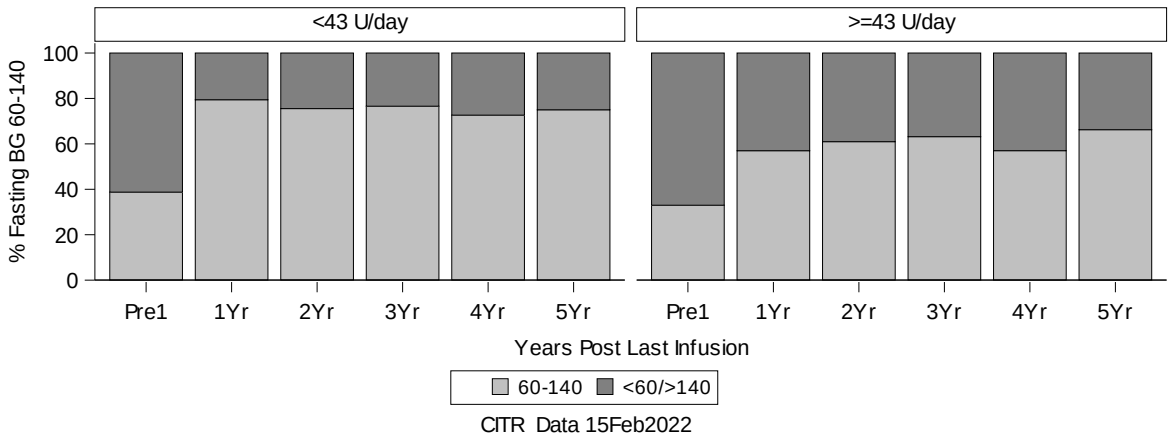
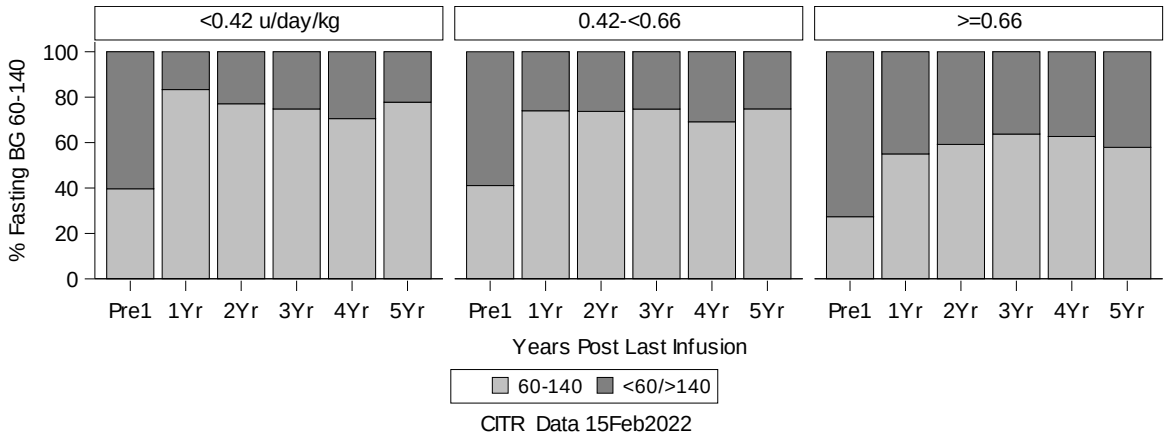
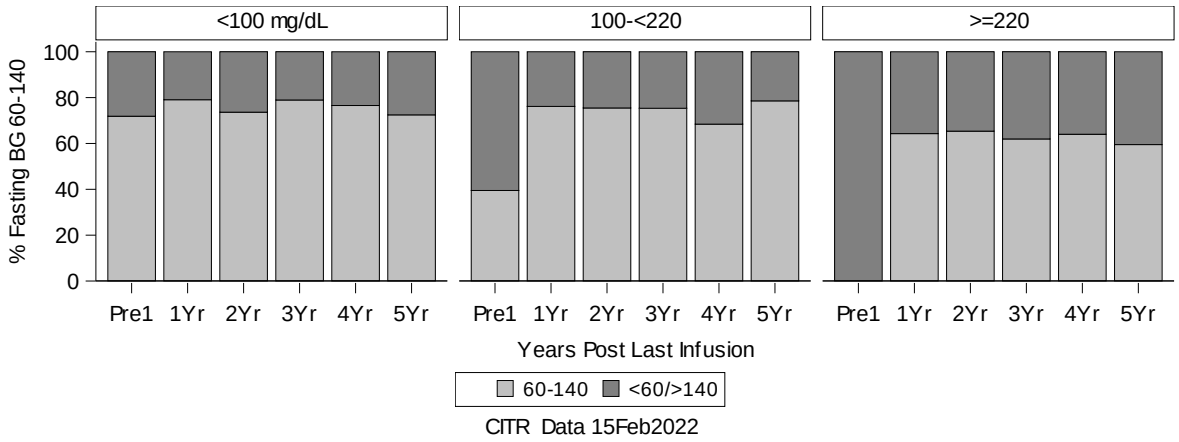


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

D. Baseline insulin (units/day/kg) (p=0.0004)



E. Baseline fasting BG (p=0.005)



F. Baseline HbA1c (p=0.0002)

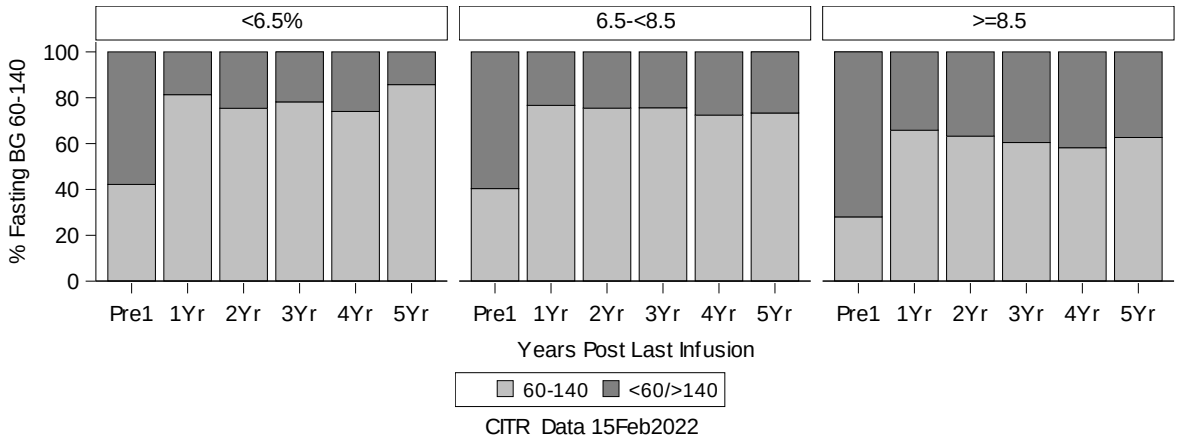
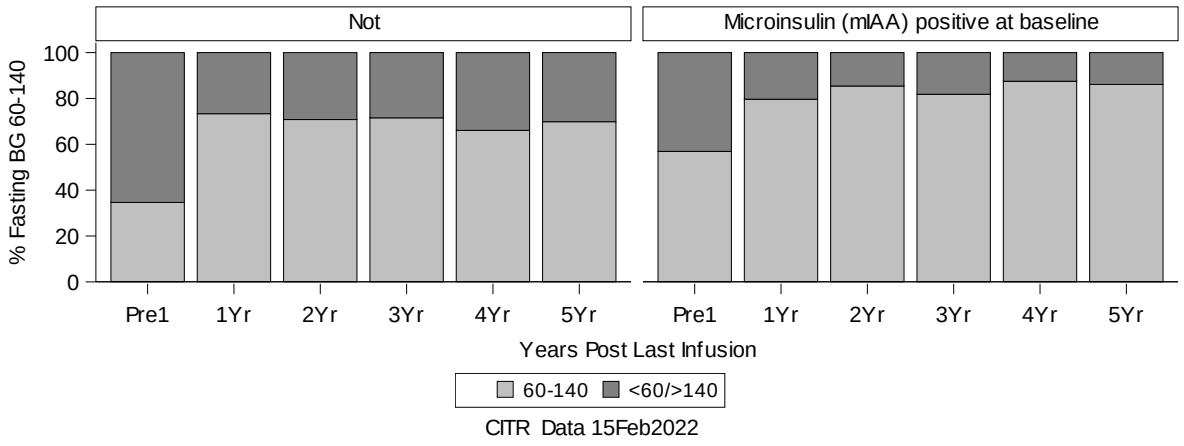
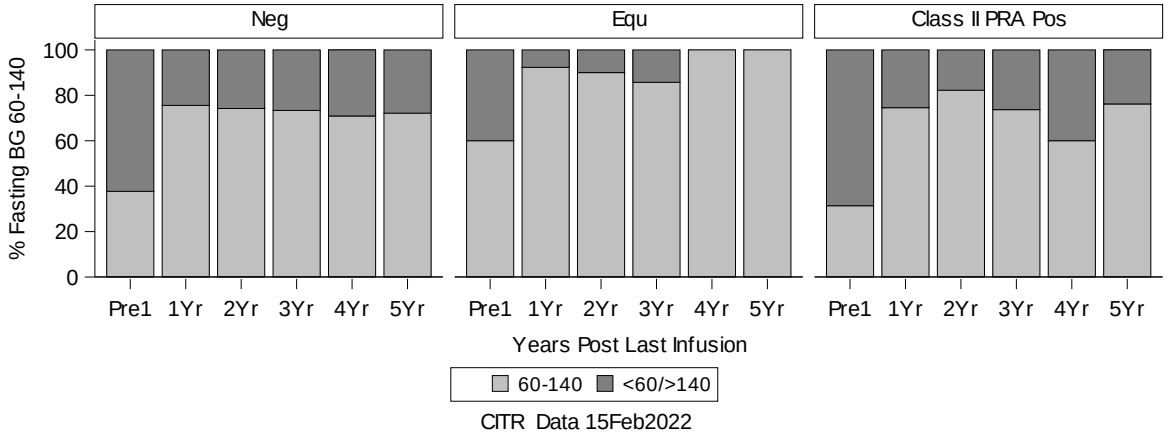


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

G. Baseline microinsulin autoantibody (p=0.0002)



H. Baseline Class 2 PRA (p<0.0001)



I. Baseline autonomic neuropathy (p=0.006)

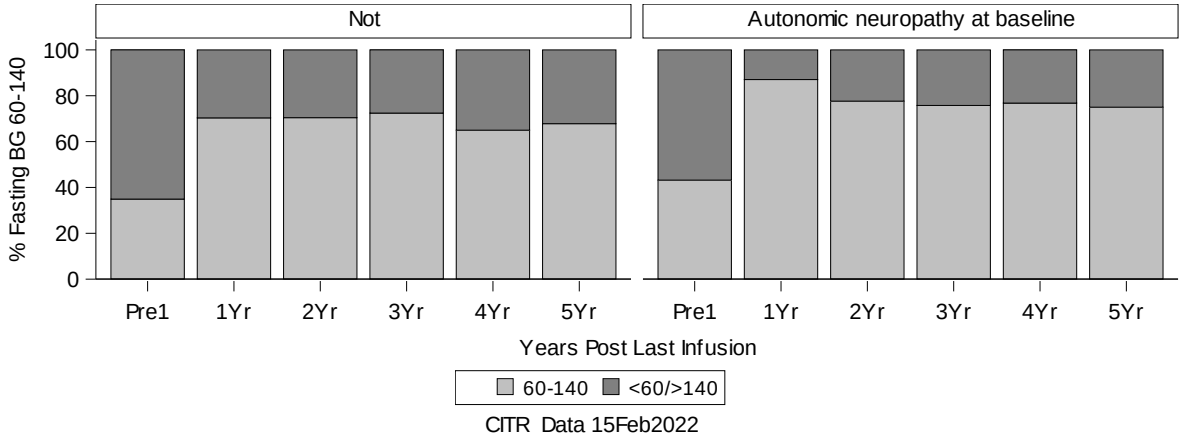
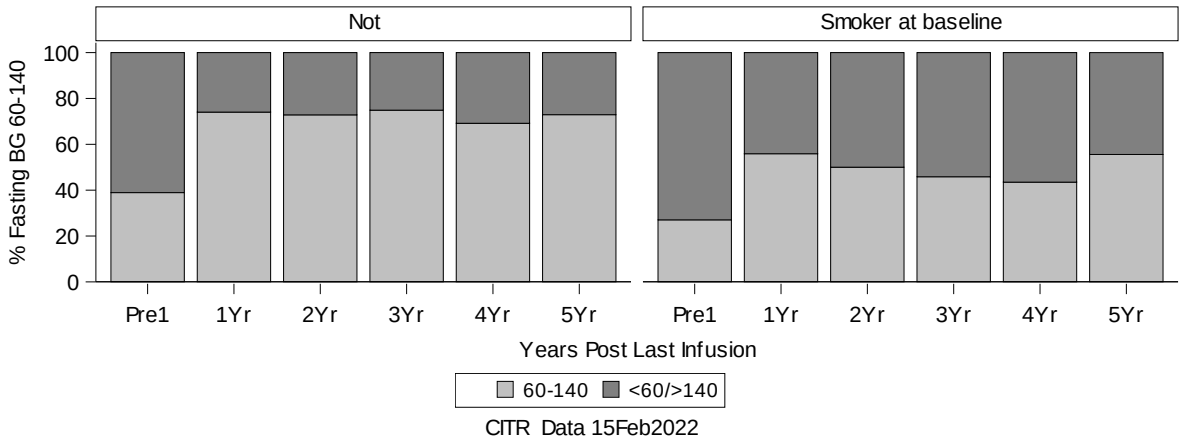
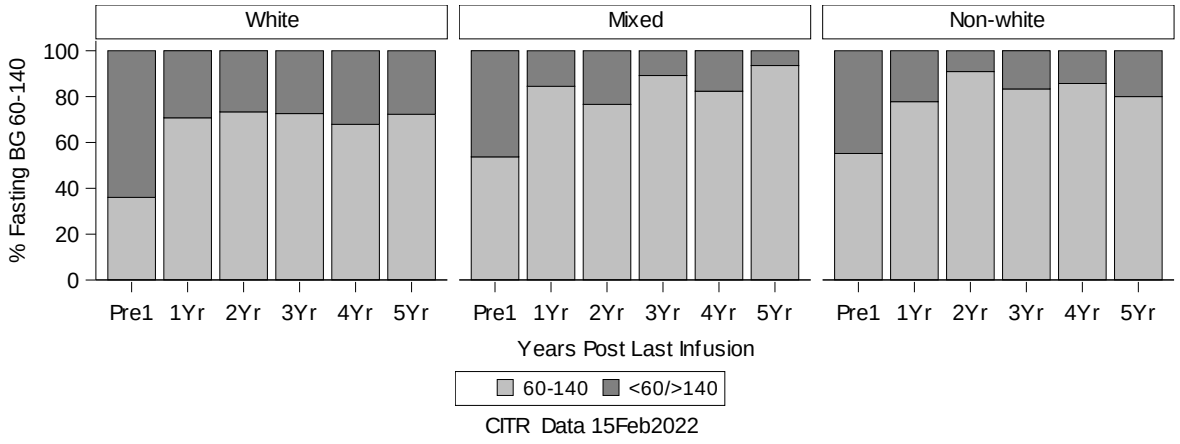


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

J. Baseline smoking (p=0.008)



K. Donor Race (p=0.0004)



L. Donor ethnicity (p<0.0001)

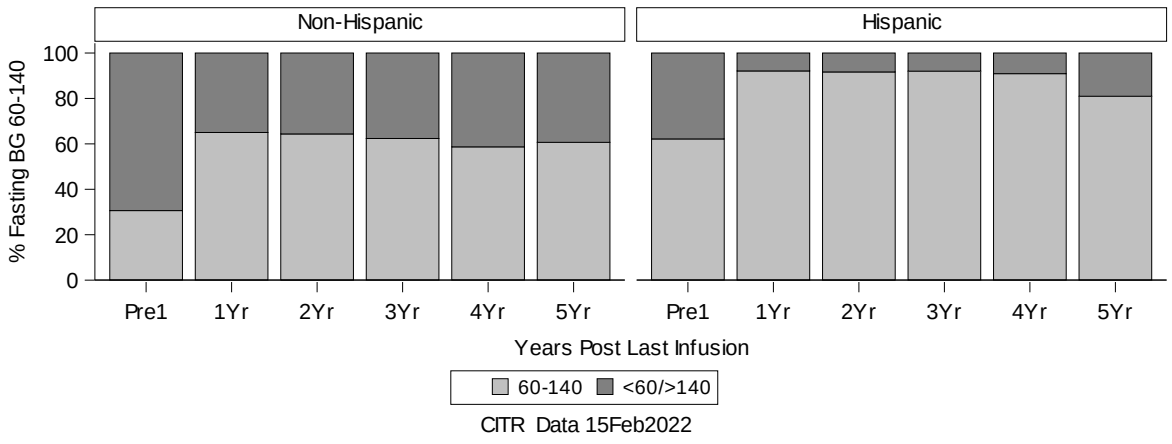
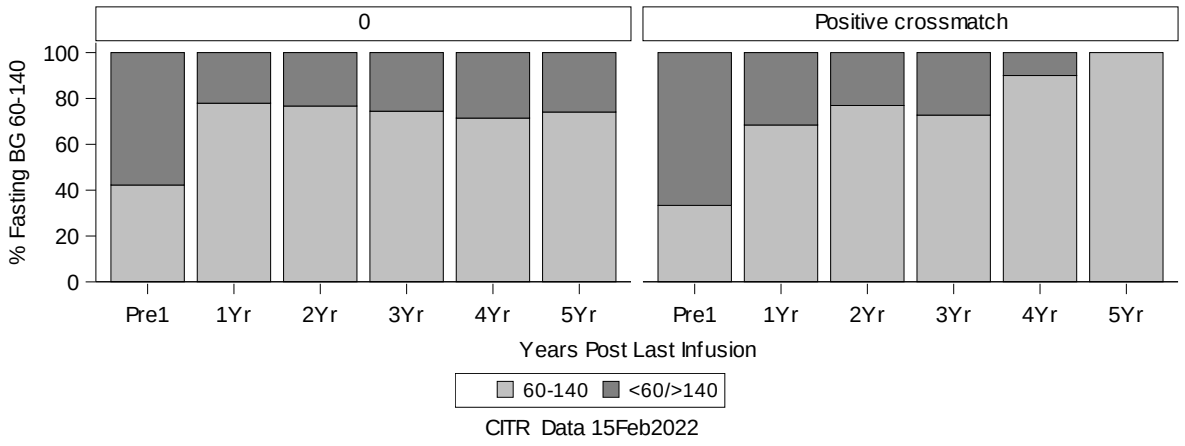
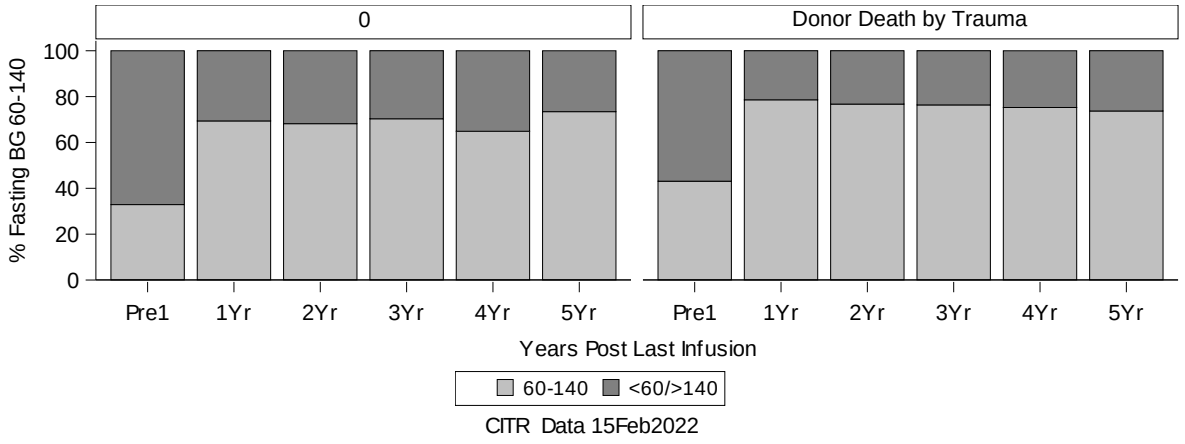


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

M. Any positive crossmatch (p=0.006)



N. Donor trauma death (p=0.006)



O. Donor CVA death (p=0.003)

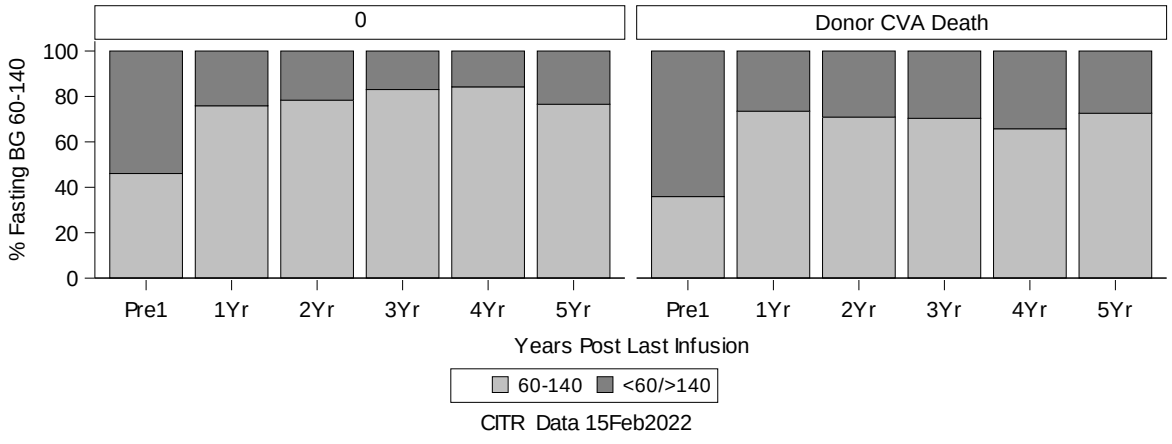
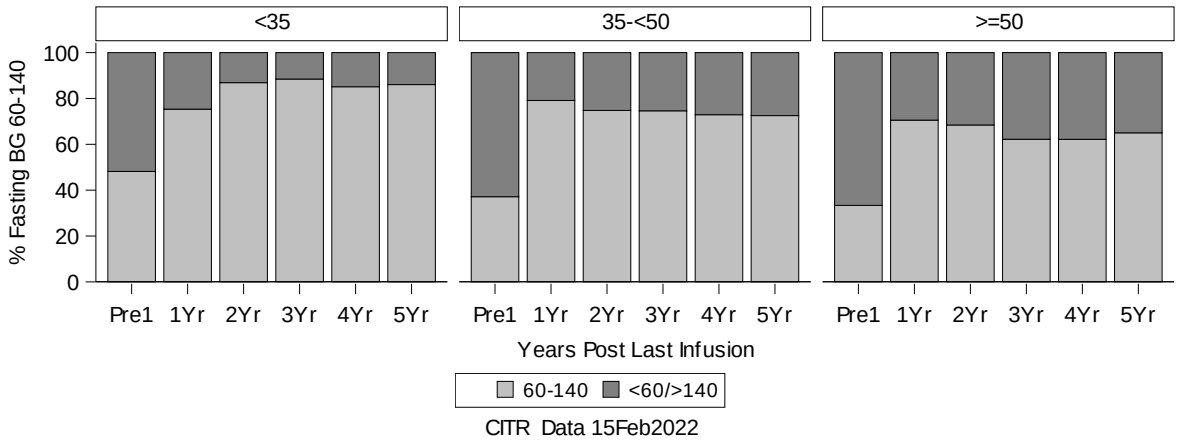
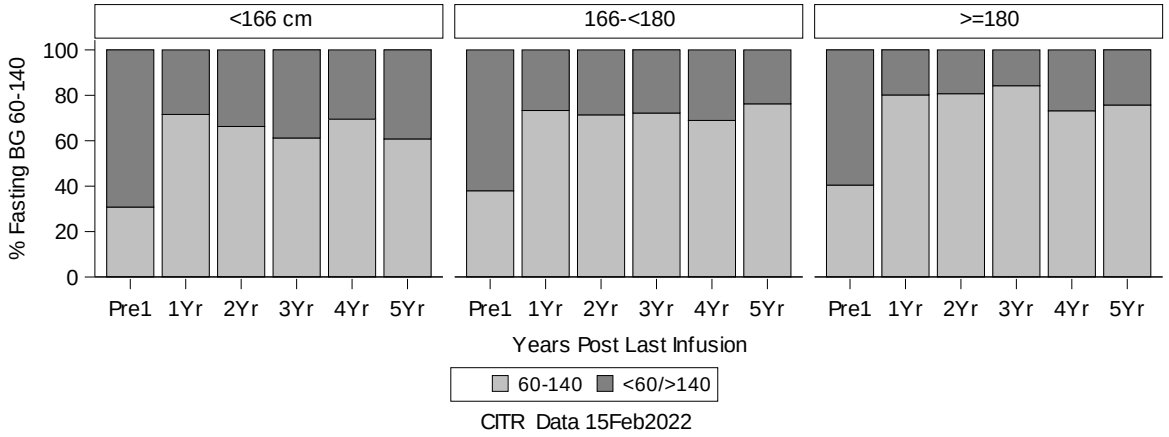


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

P. Donor age (yrs) (p=0.003)



Q. Donor height (p=0.008)



R. Donor weight (p<0.0001)

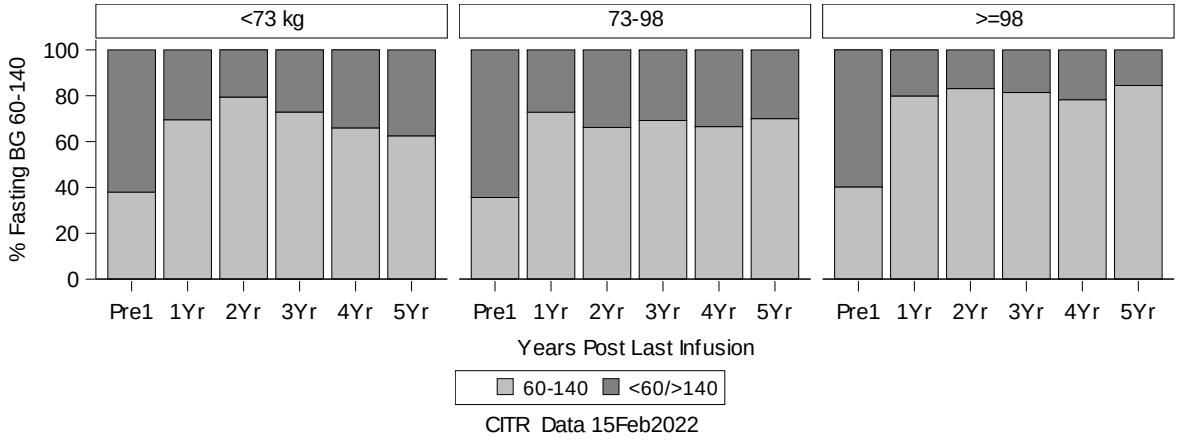
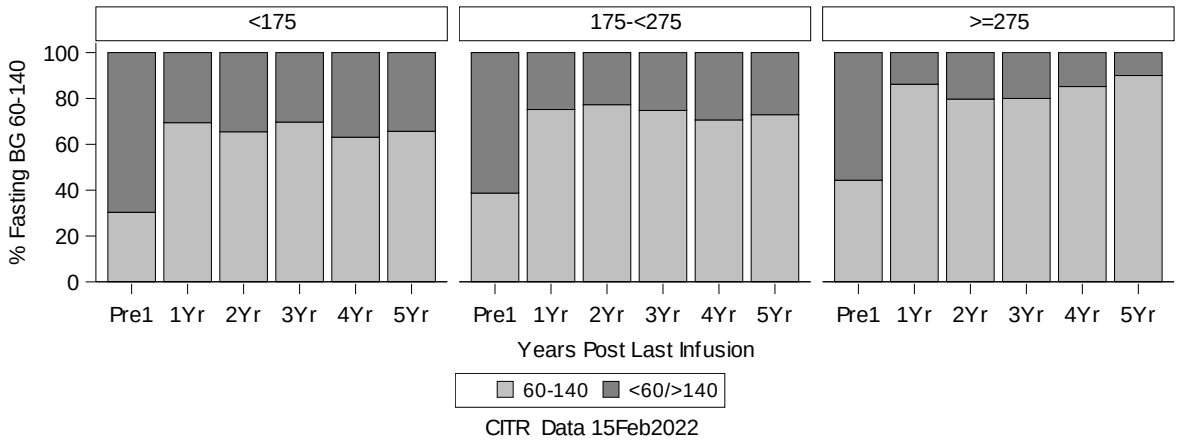
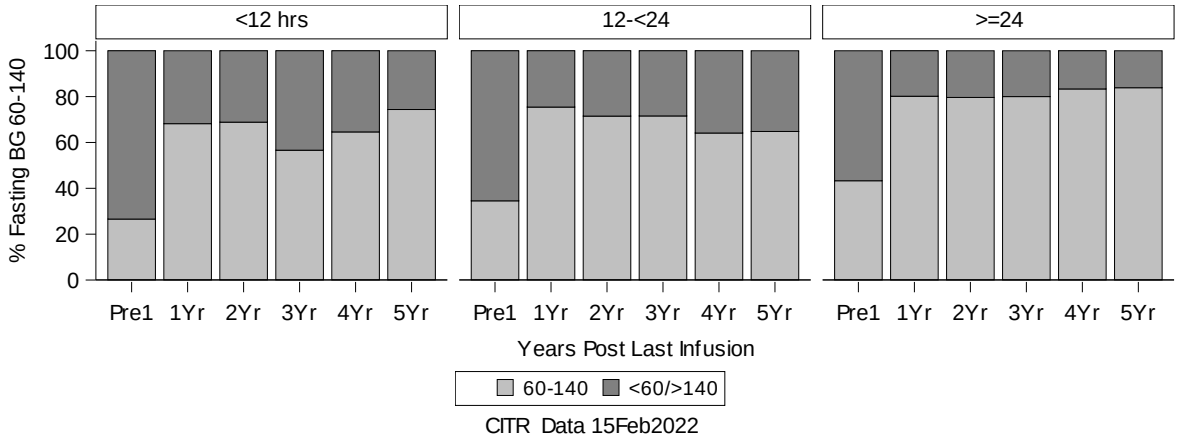


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

S. Max donor glucose (p=0.0003)



T. Hours: death to cross-clamp (p=0.0009)



U. Islet viability (p=0.004)

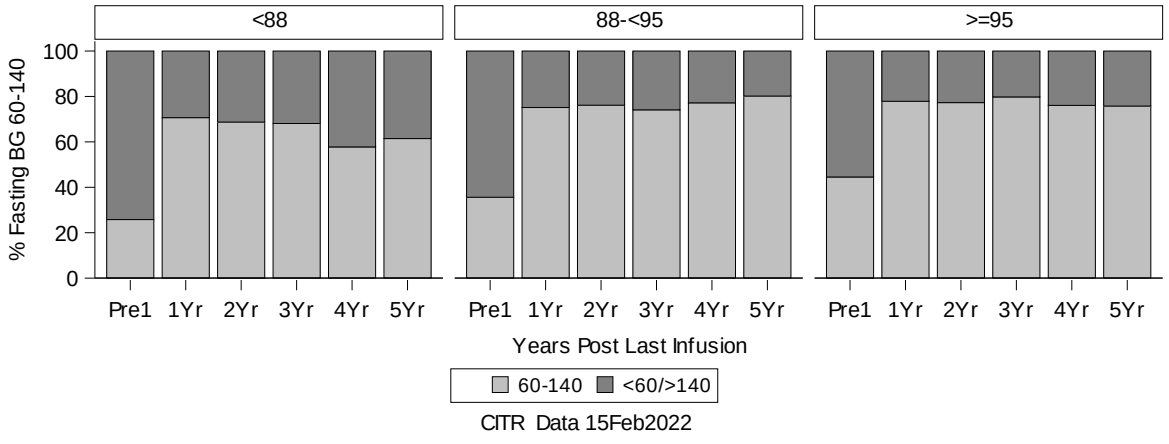
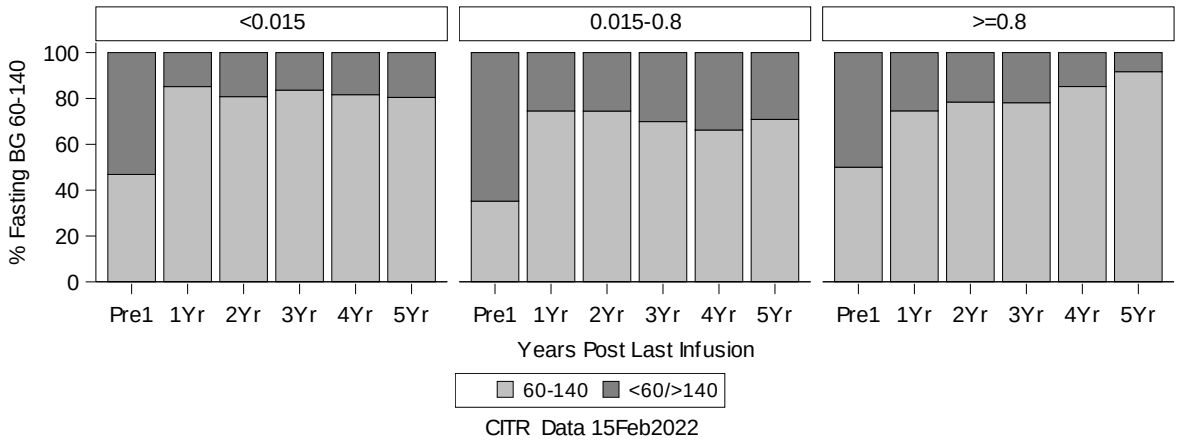
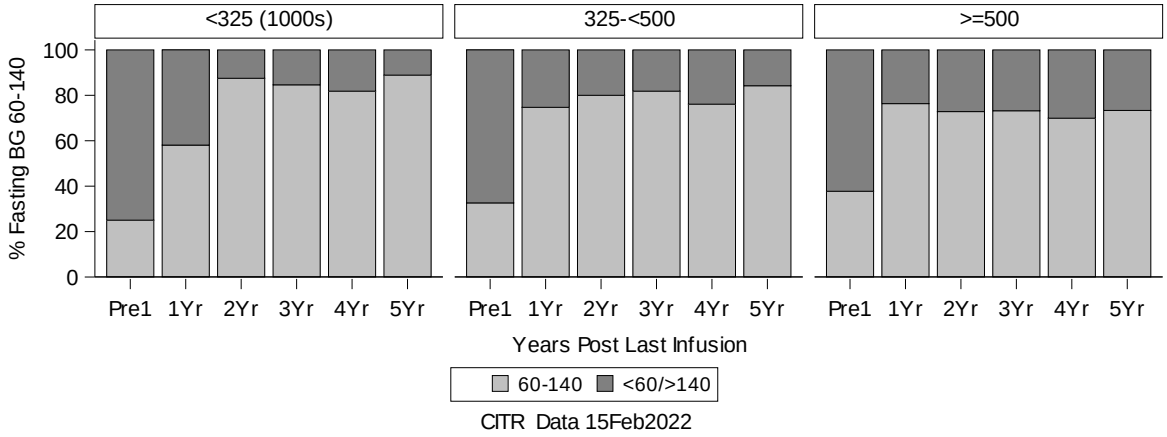


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

V. Endotoxin/kg recipient (p=0.003)



W. IEQs infused (1000s) (p=0.009)



X. Immunosuppression: IL2RA (p=0.0006)

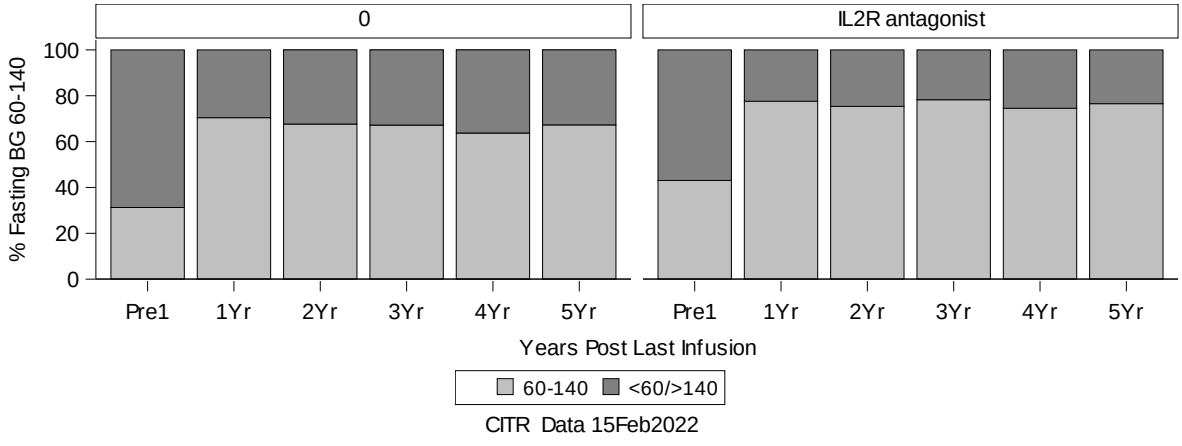
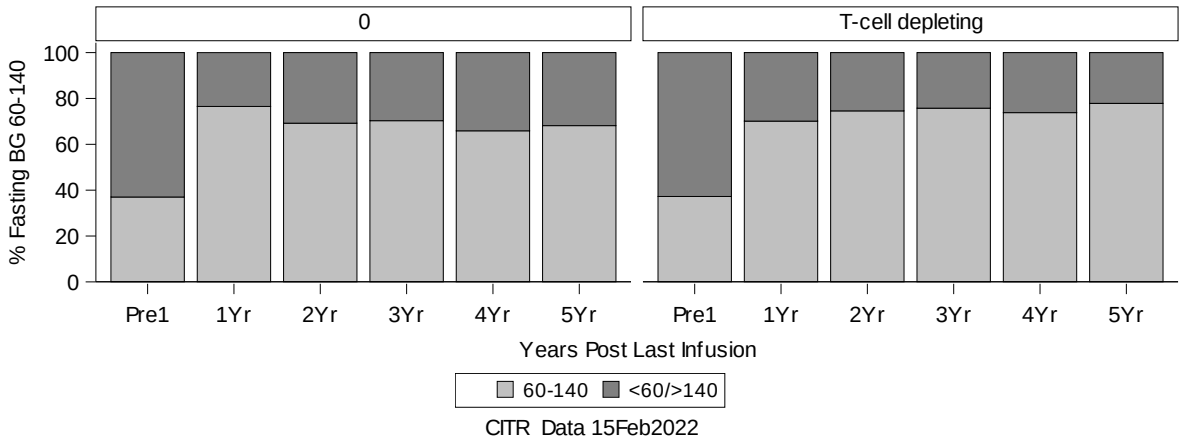
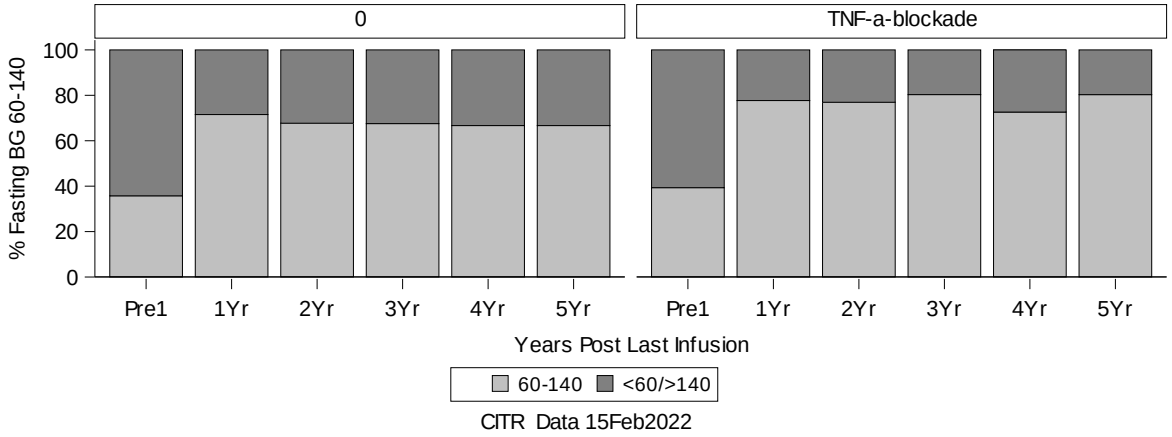


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

Y. Immunosuppression: TCD (p=0.002)



Z. Immunosupression: TNFa (p=0.0004)



AA. Immunosuppression: mTOR Inhibitor (p<0.0001)

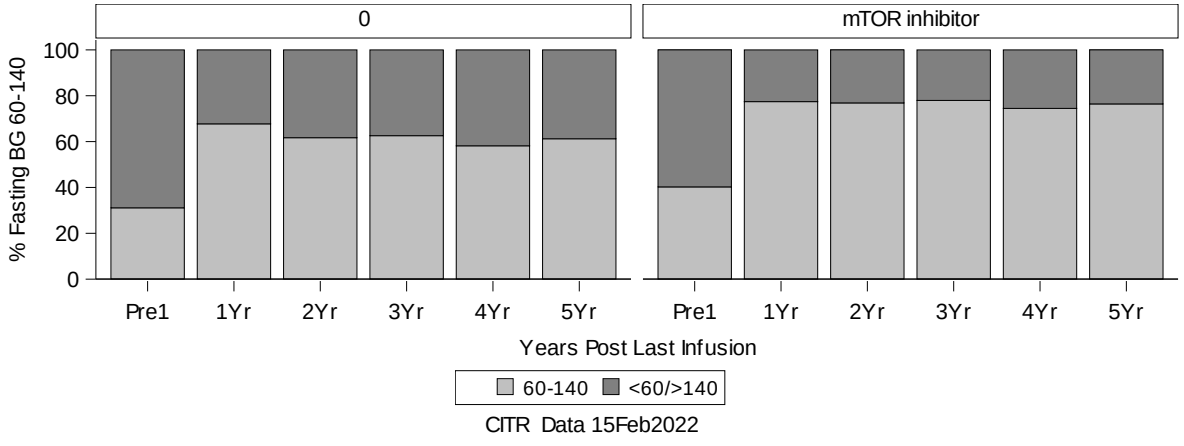
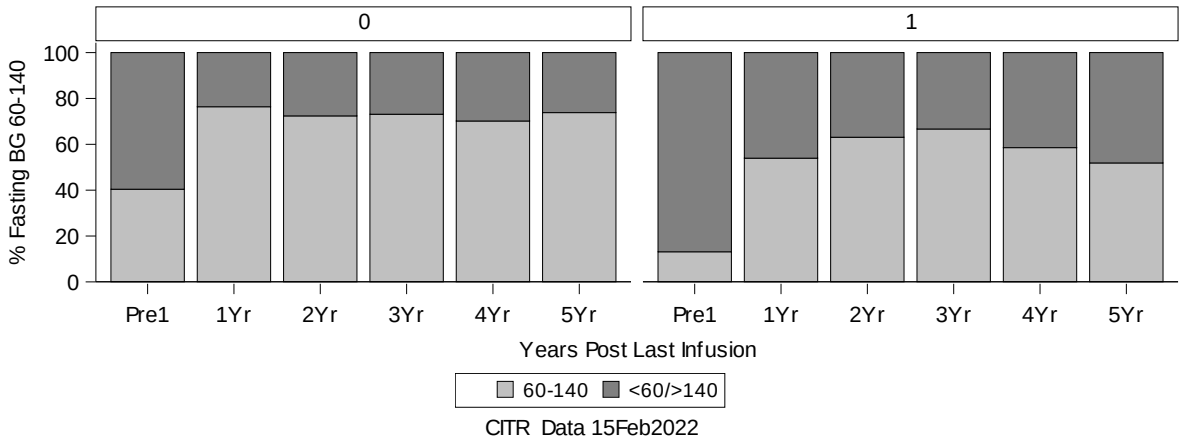


Exhibit 5 – 5B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among ITA Recipients

BB. Immunosuppression: IL1R (p=0.002)



CC. Immunosuppression Steroid (p=0.004)

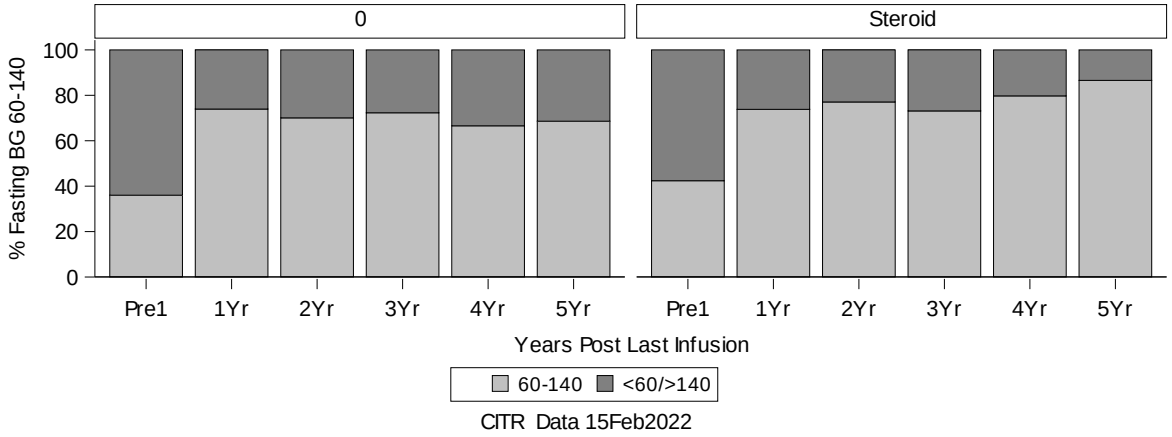
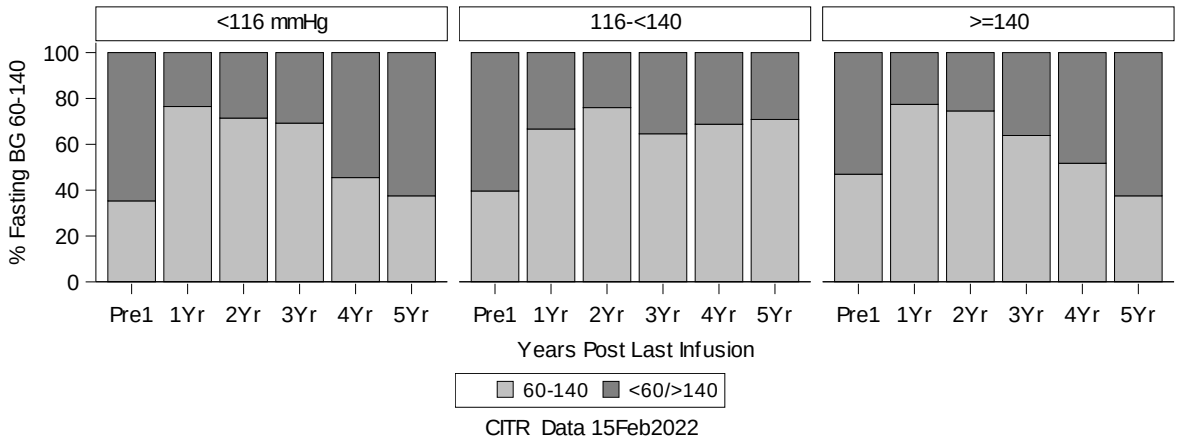
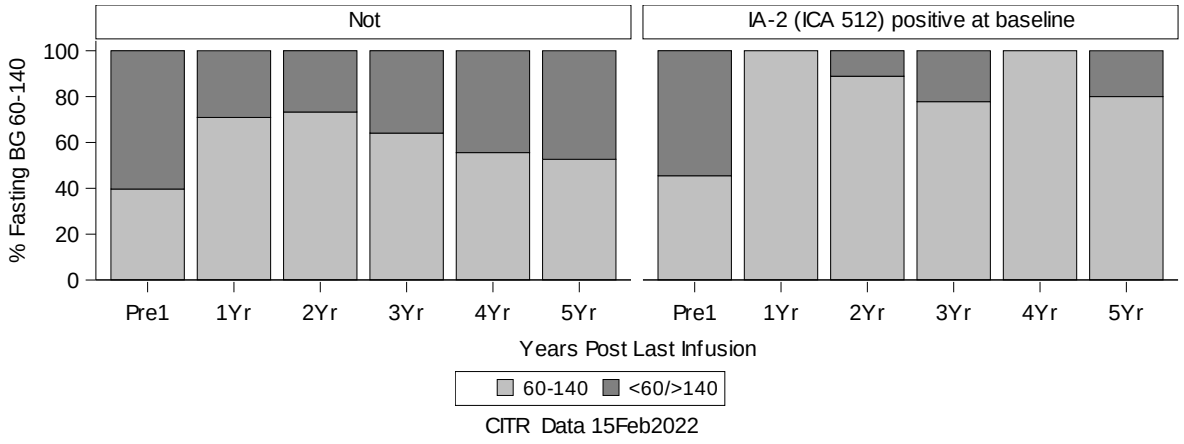


Exhibit 5 – 5C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

A. Baseline SBP (p=0.002)



B. Baseline IA-2 autoantibody (p<0.0001)



C. Baseline microinsulin autoantibody (p<0.0001)

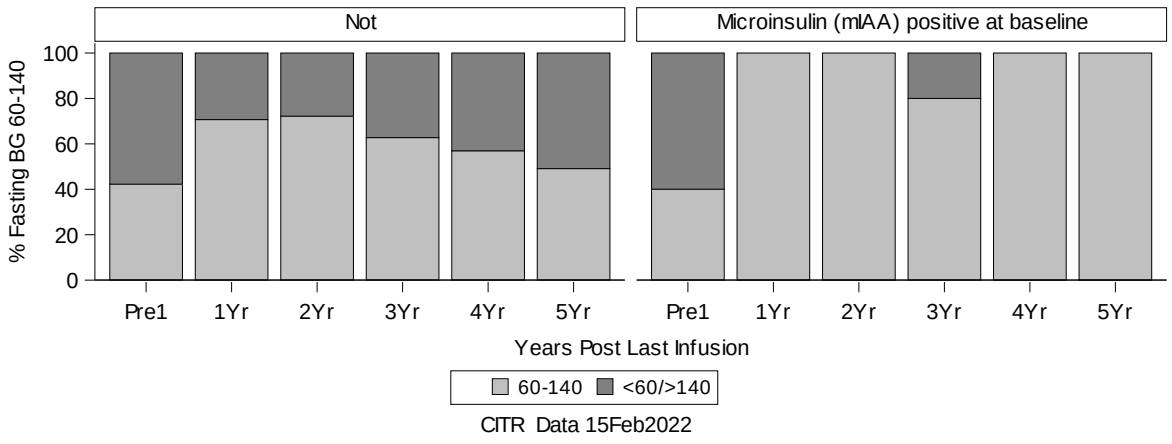
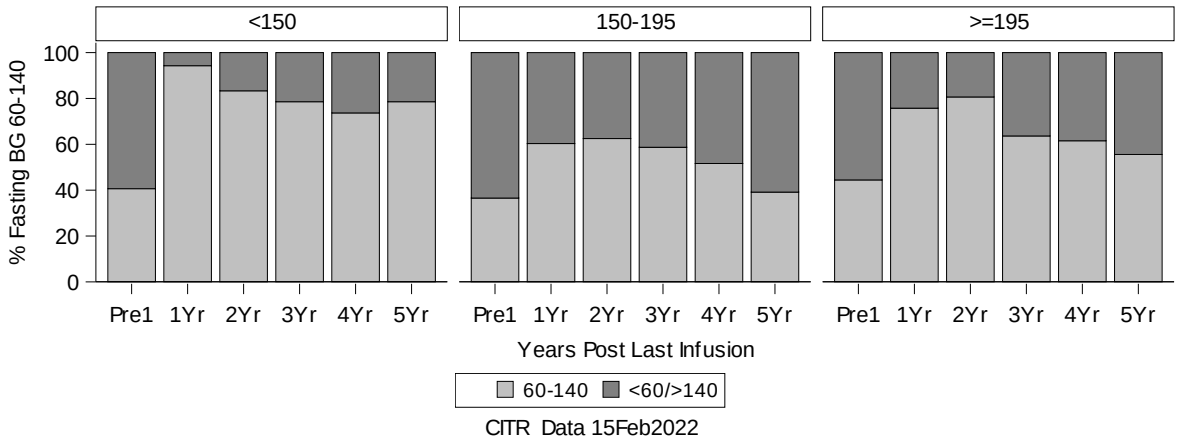
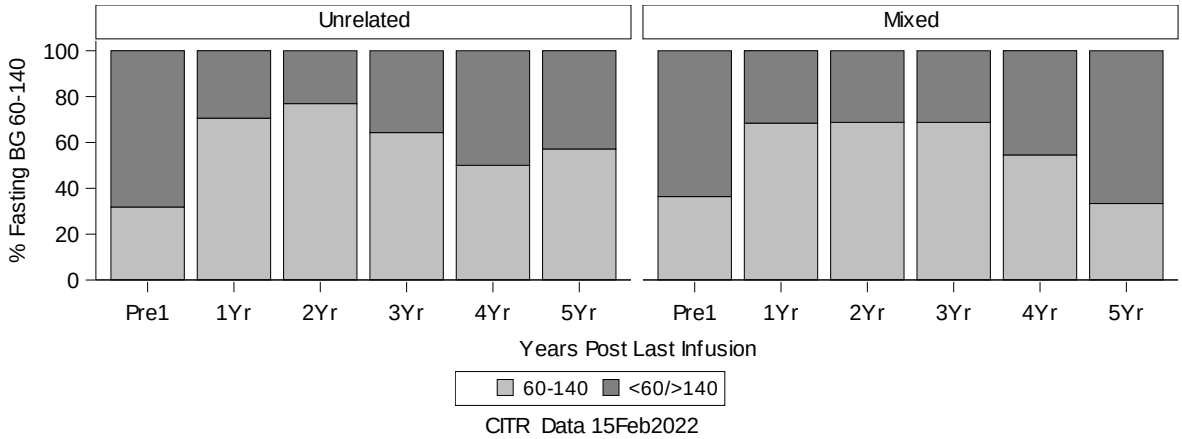


Exhibit 5 – 5C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

D. Baseline cholesterol (p=0.0002)



E. Procurement Team/ Inf Team Related (p<0.0001)



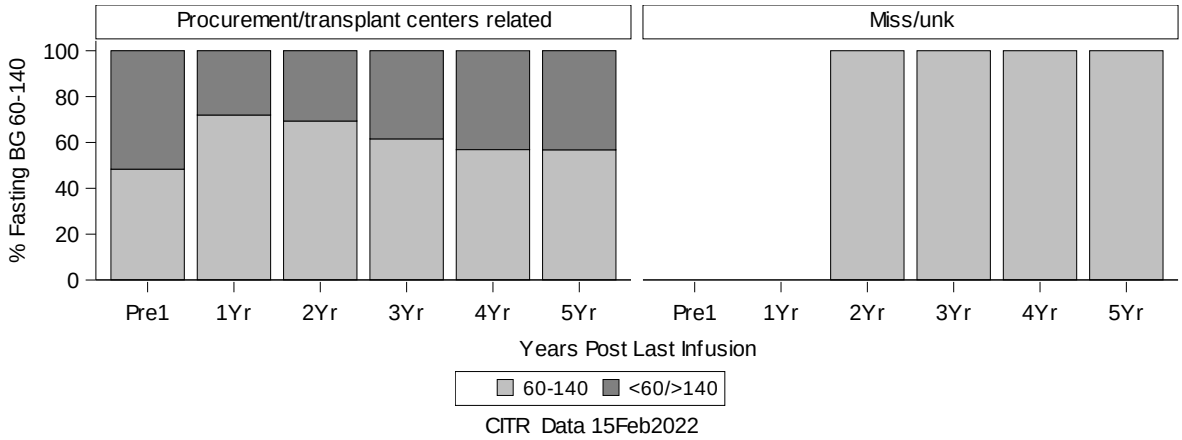
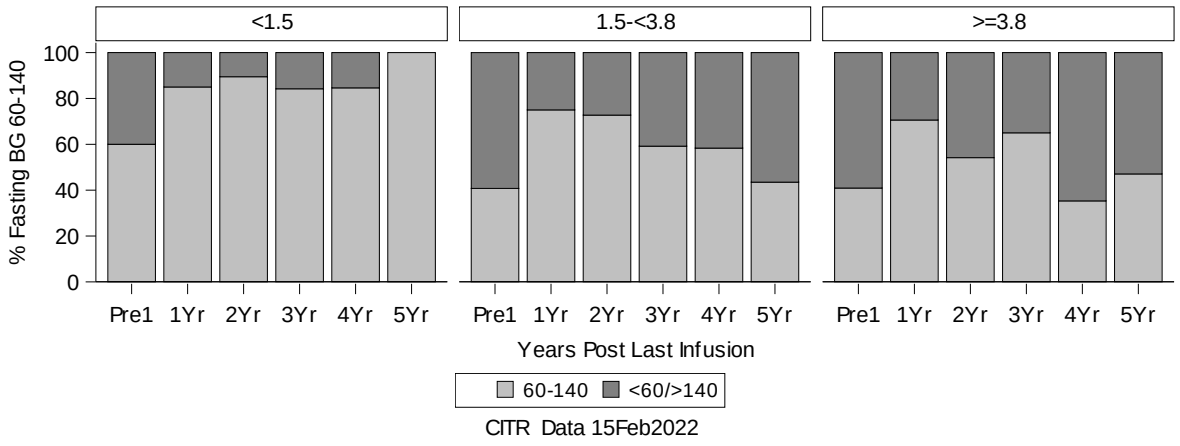


Exhibit 5 – 5C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Fasting Blood Glucose 60-140 mg/mL Post Last Infusion among IAK Recipients

F. Stimulation index (p<0.0001)



G. Immunosuppression: TNFa (p=0.005)

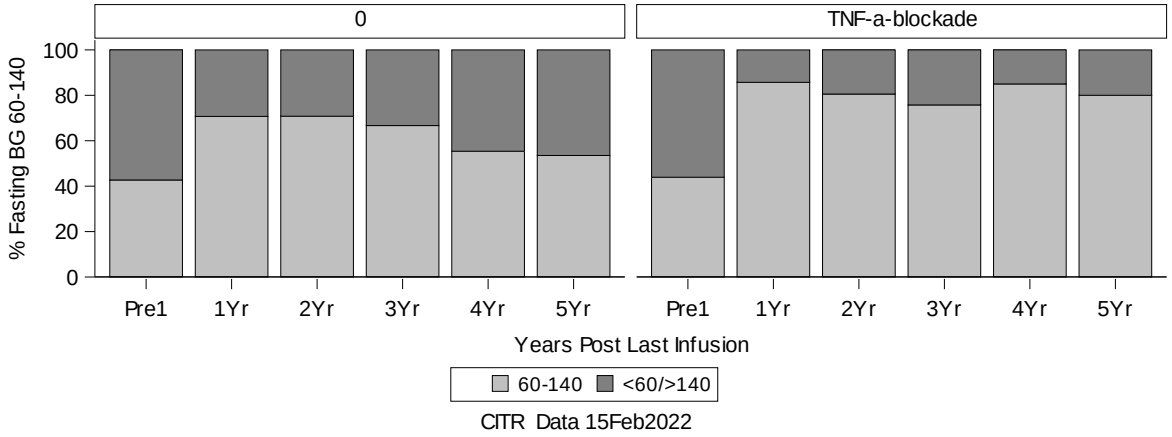


Exhibit 5 – 6A
Unadjusted Prevalence of HbA1c<7.0% Post Last Infusion

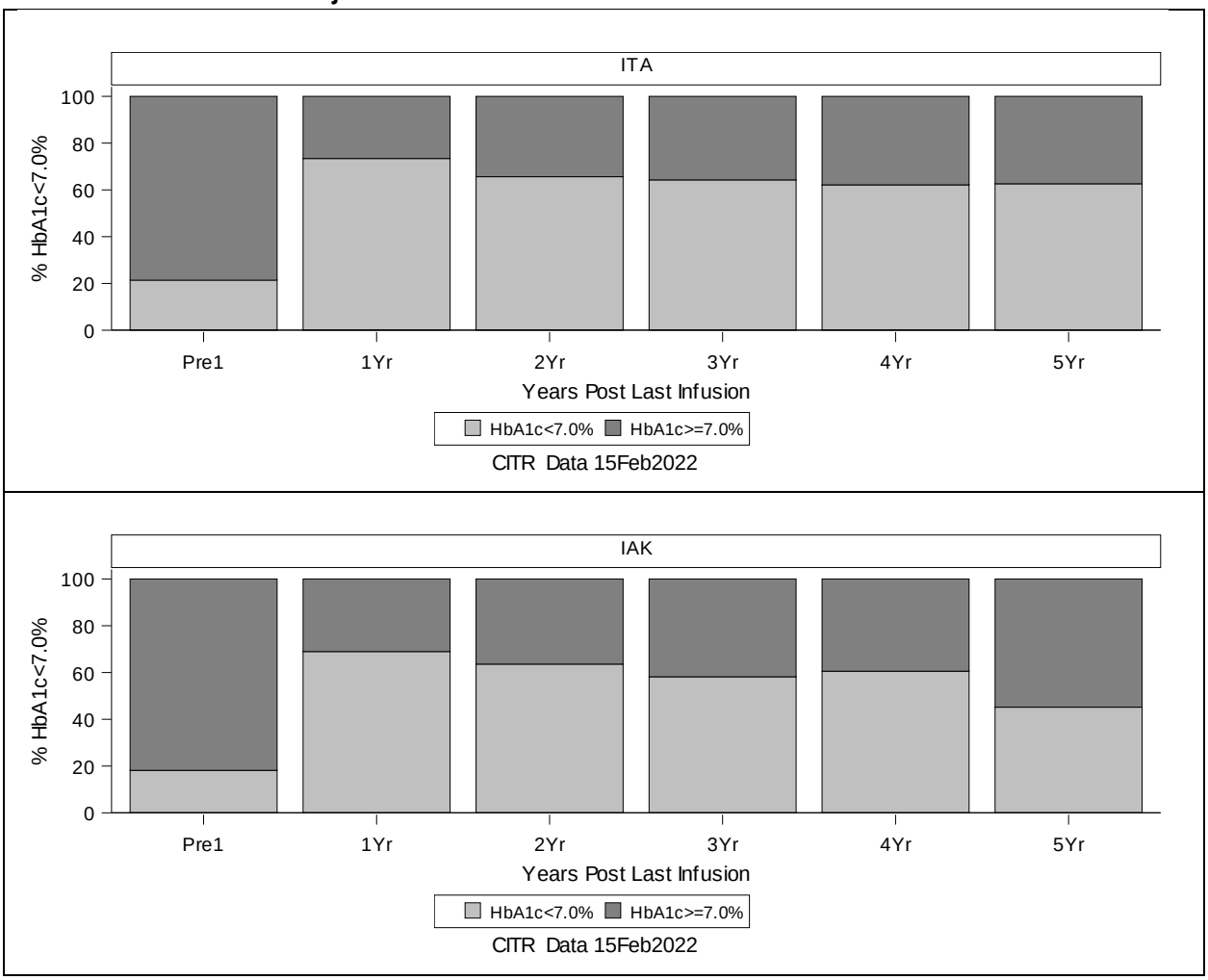
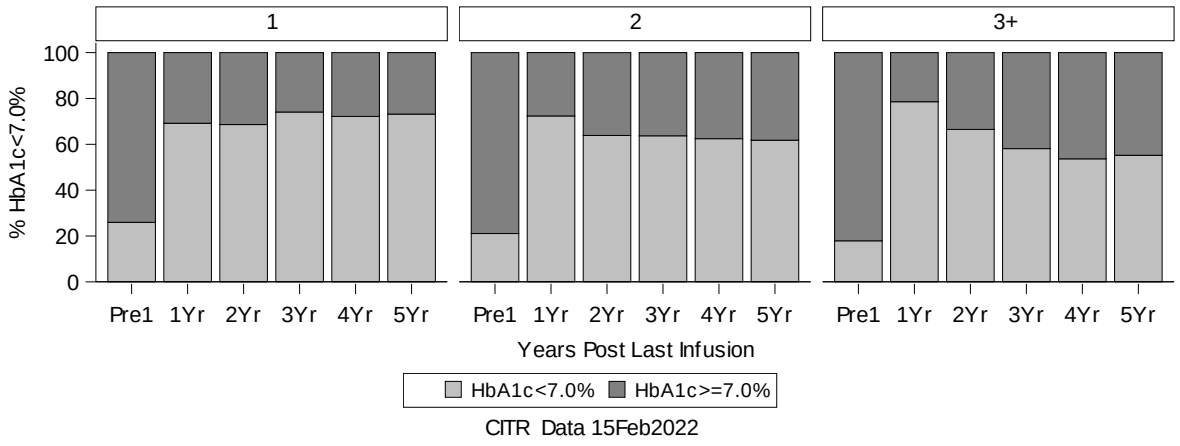
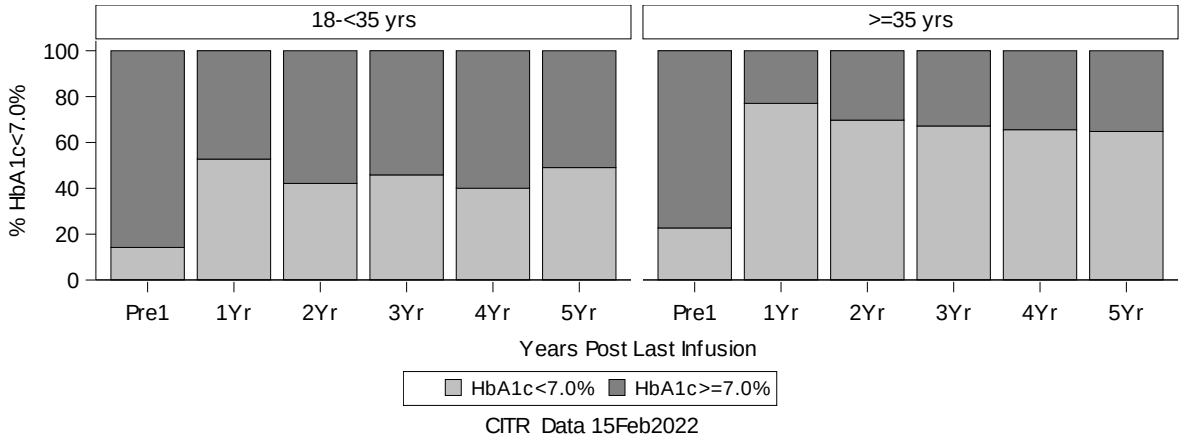


Exhibit 5 – 6B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

A. Total infusions (p=0.0001)



B. Recipient age (p<0.0001)



C. Diabetes duration (p=0.0001)

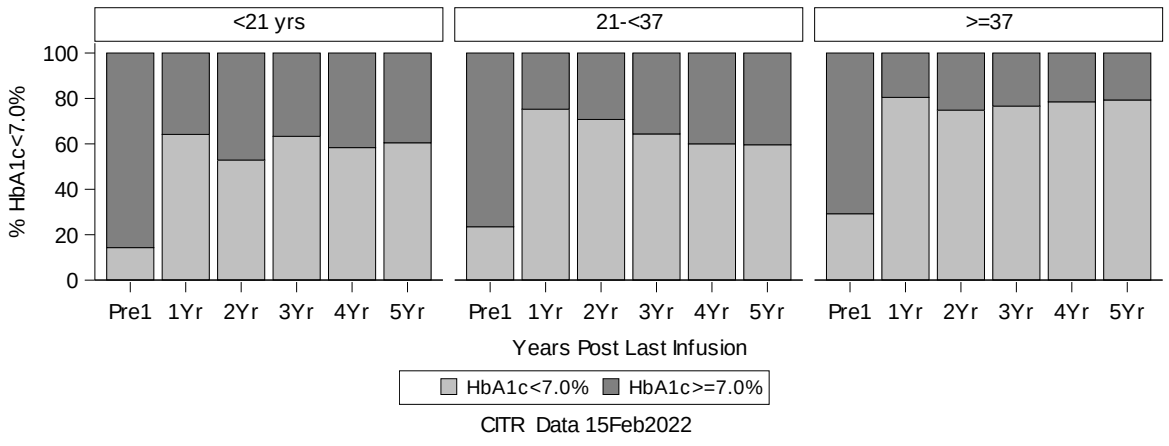
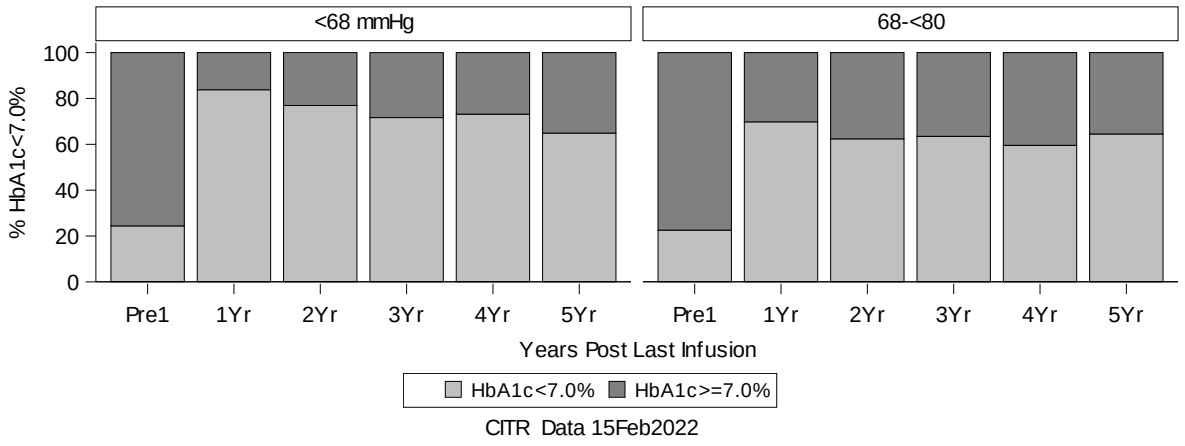
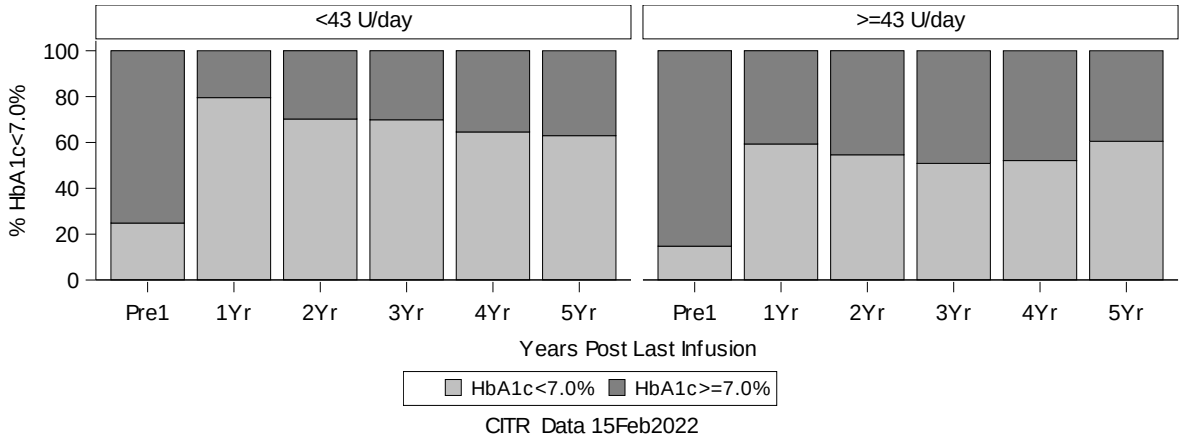


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

D. Baseline DBP (p=0.0008)



E. Baseline insulin (Units/day) (p=0.0002)



F. Baseline insulin (units/day/kg) (p=0.001)

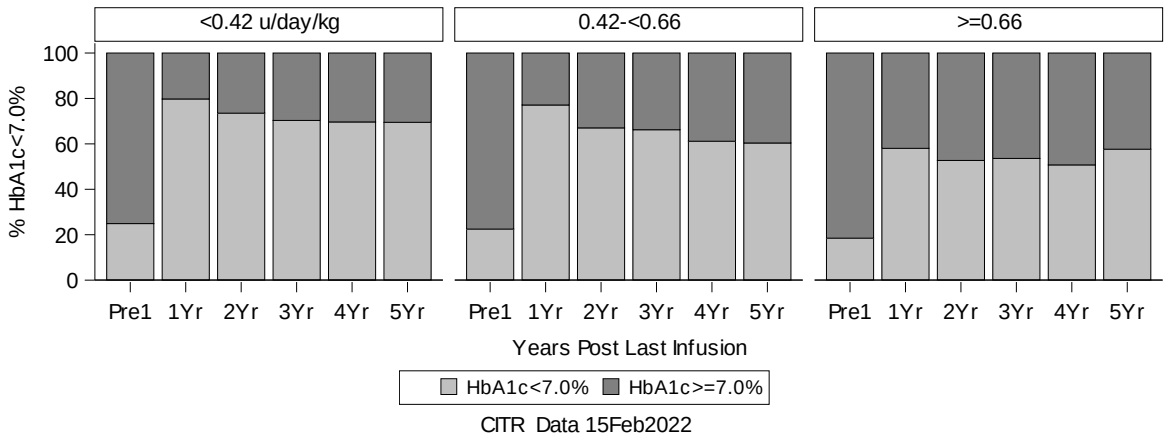
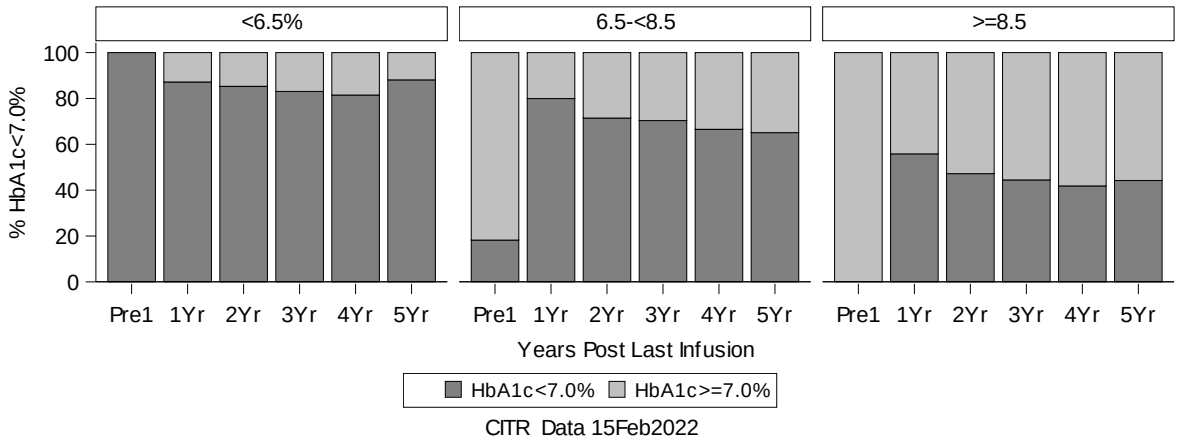
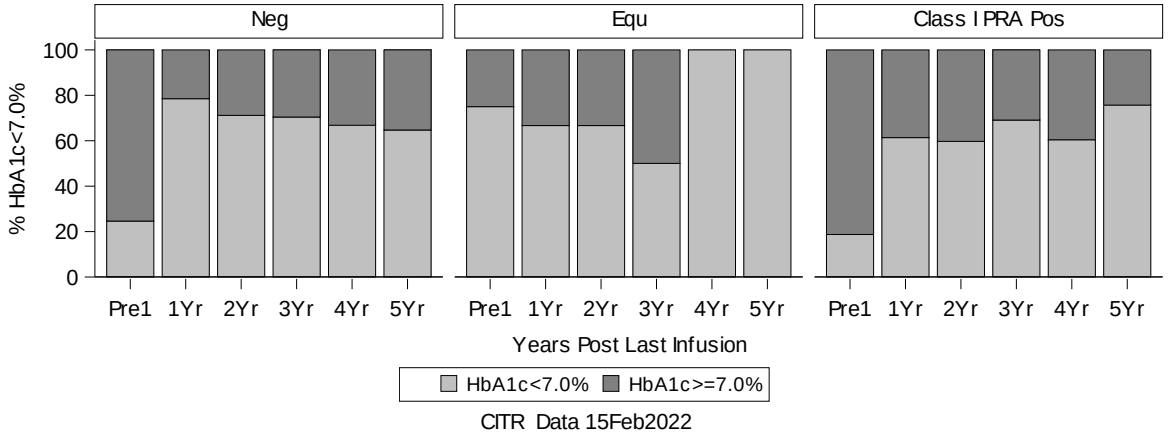


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

G. Baseline HbA1c (p<0.0001)



H. Baseline Class 1 PRA (p=0.009)



I. Baseline CVA (p<0.0001)

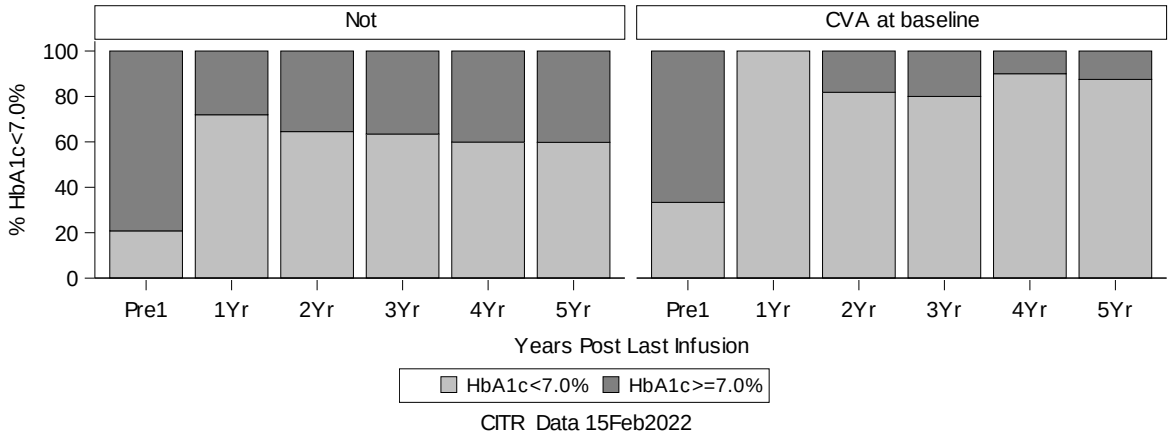
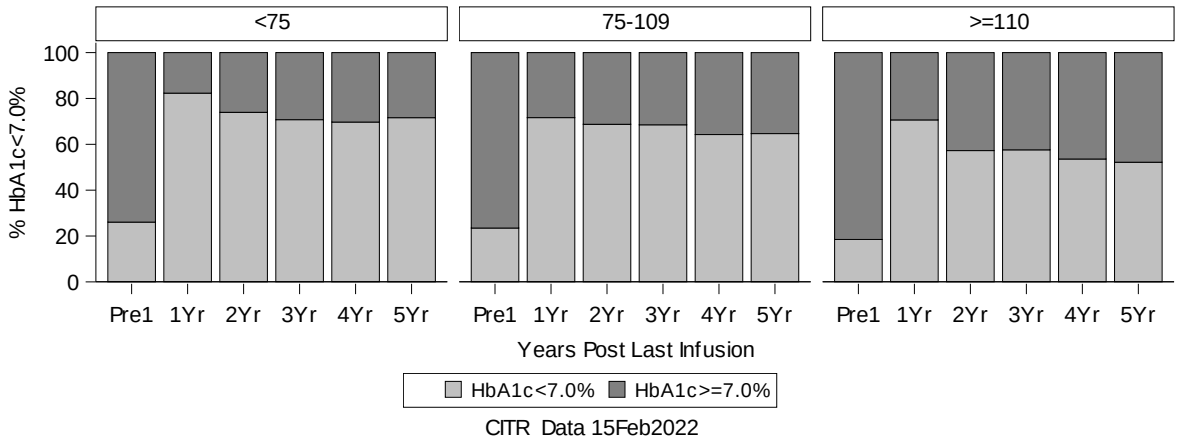
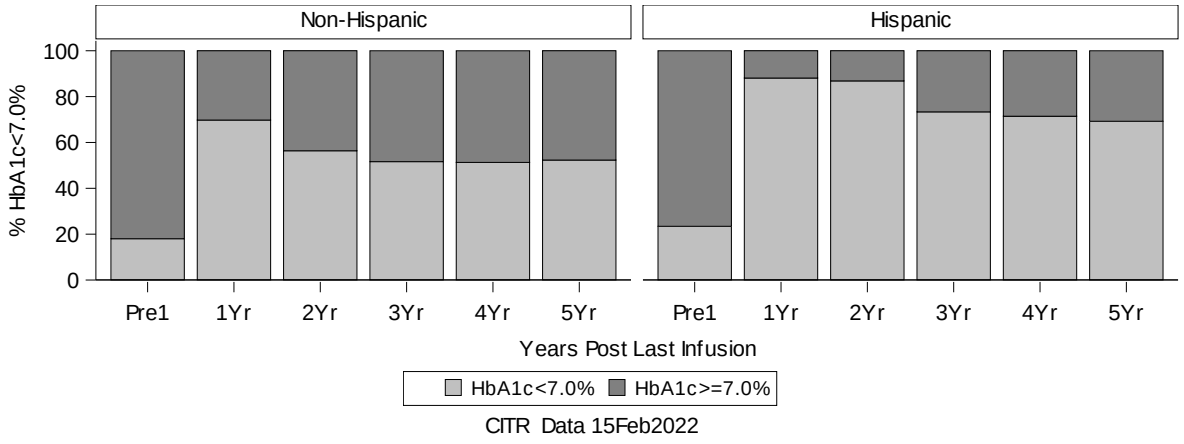


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

J. Baseline LDL (p=0.006)



K. Donor Ethnicity (p=0.0004)



L. Any positive crossmatch (p=0.0008)

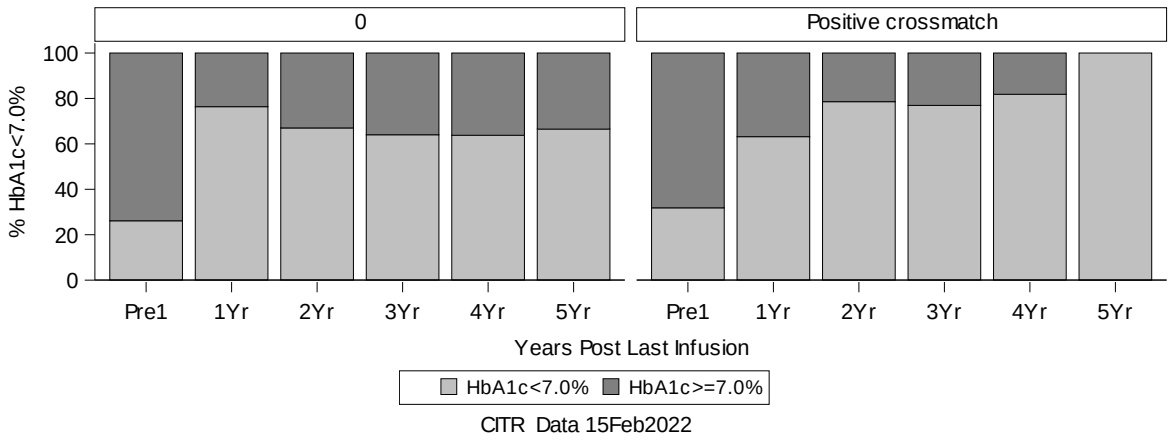


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

M. Donor CVA death (p=0.005)

N. Donor History of hypertension (p=0.0004)

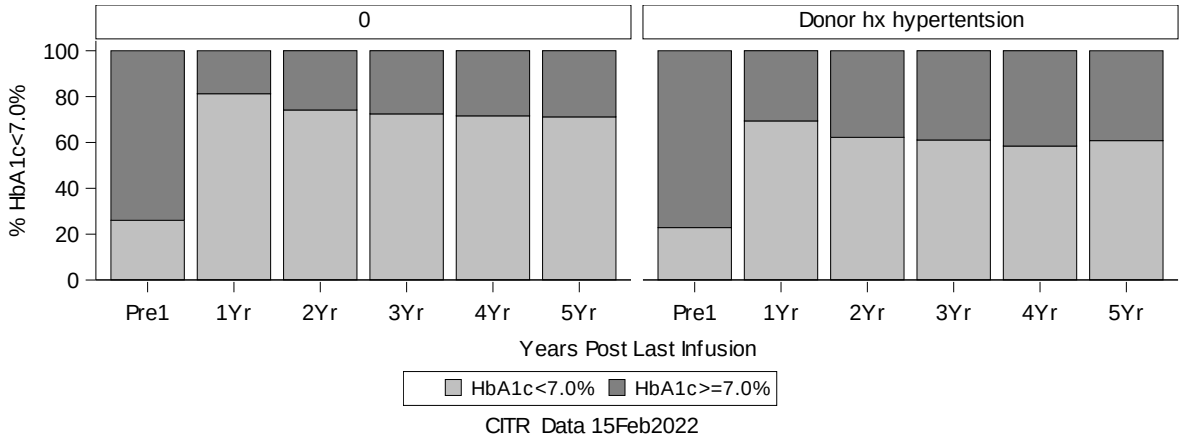
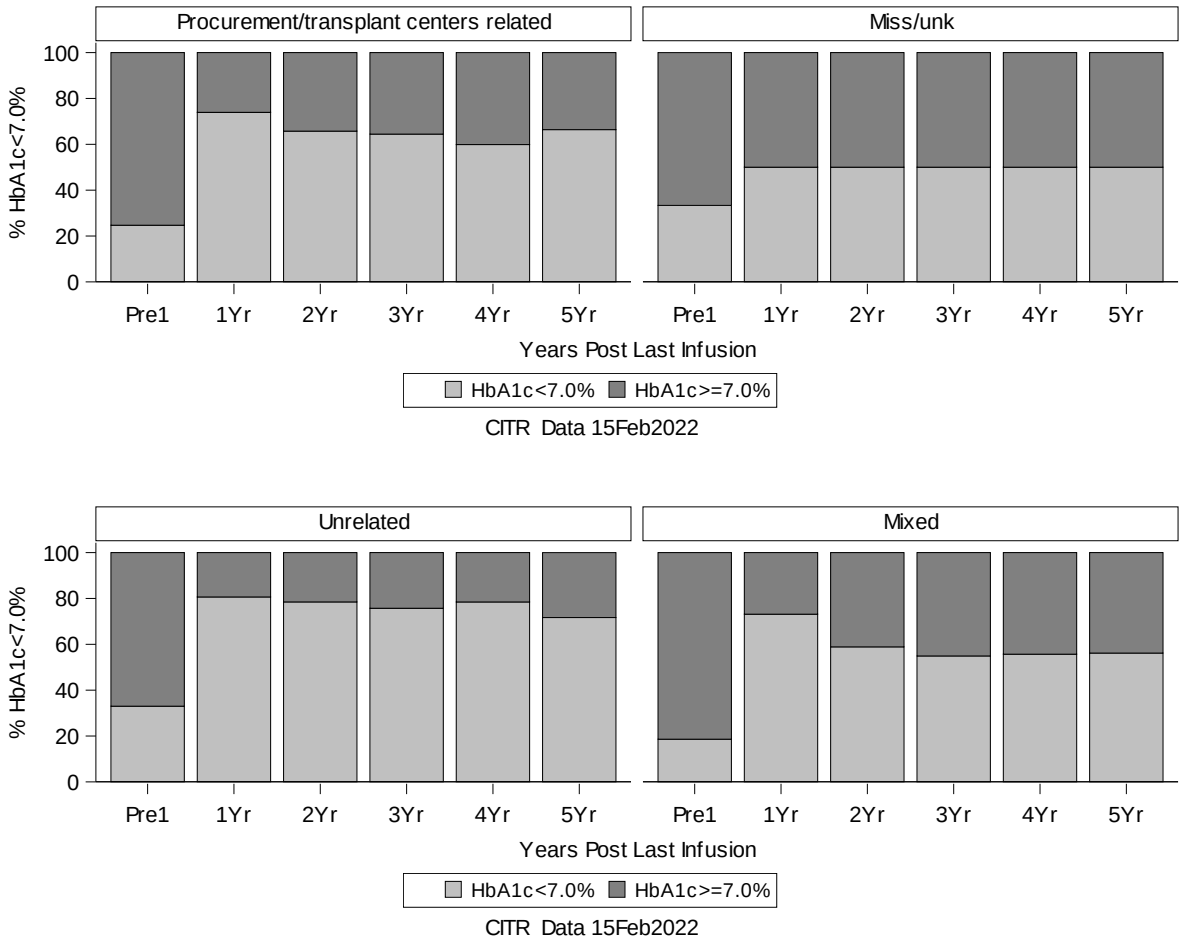


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

O. Procurement Team/ Inf Team Related (p=0.007)



P. Donor Age (yrs) (p=0.0008)

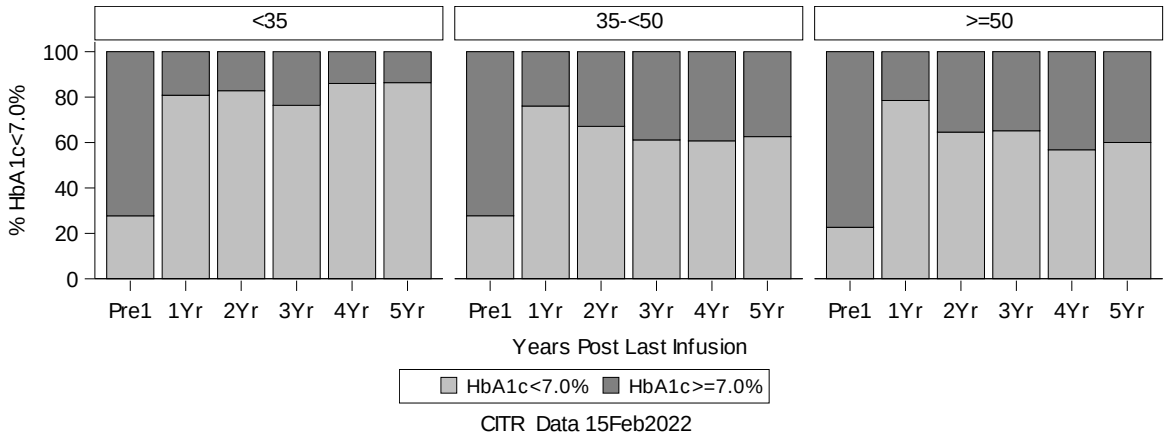
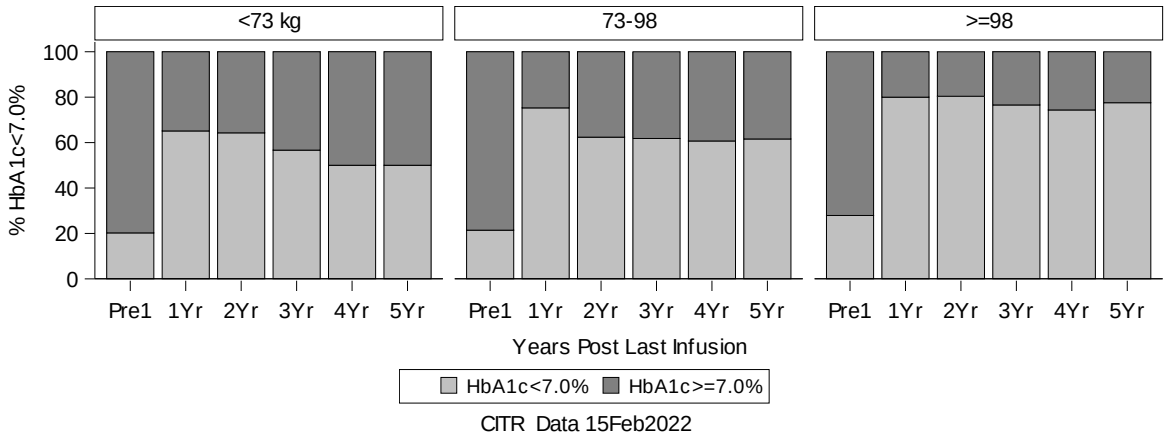
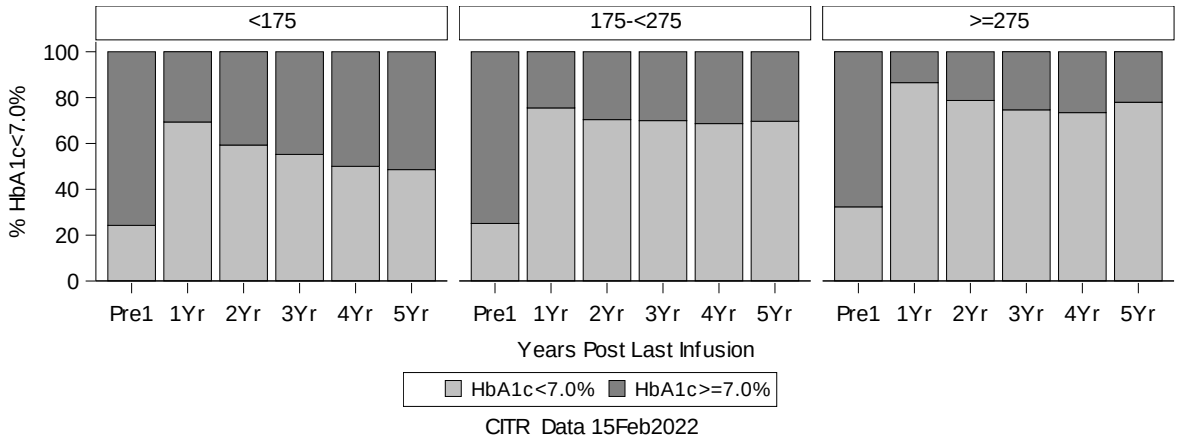


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Q. Donor Weight (p<0.0001)



R. Max donor glucose (p=0.0006)



S. Hours: death to cross-clamp (p=0.003)

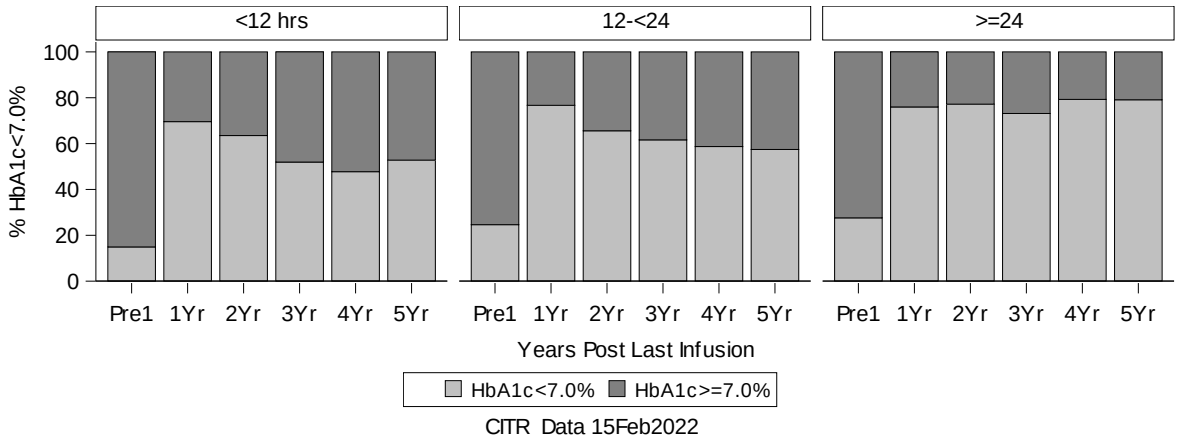
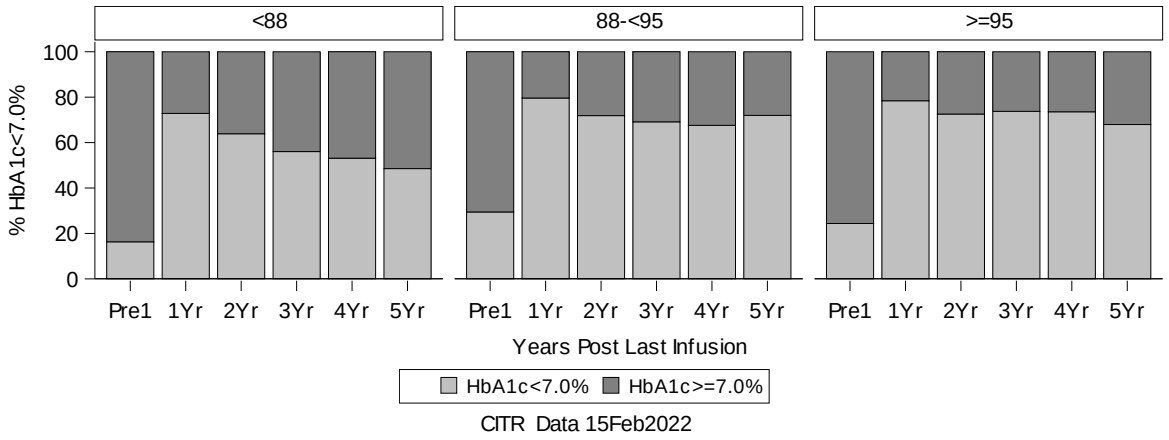
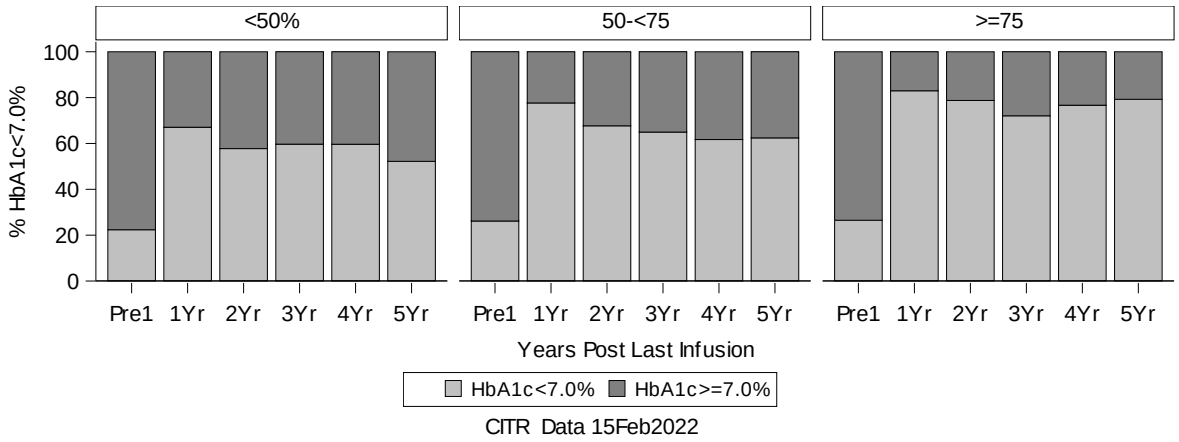


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

T. Islet viability (p=0.007)



U. Purity (p=0.005)



V. Beta cells/kg recipient (p=0.004)

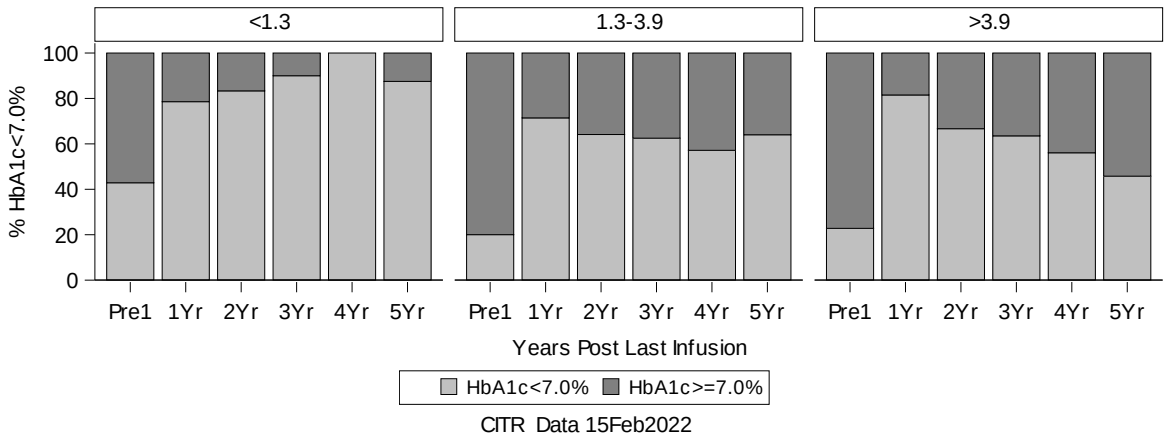
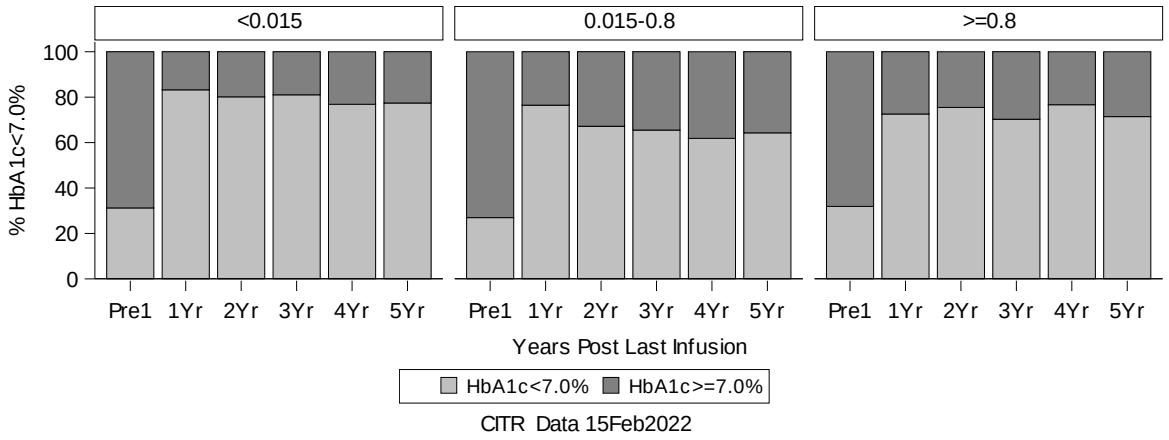
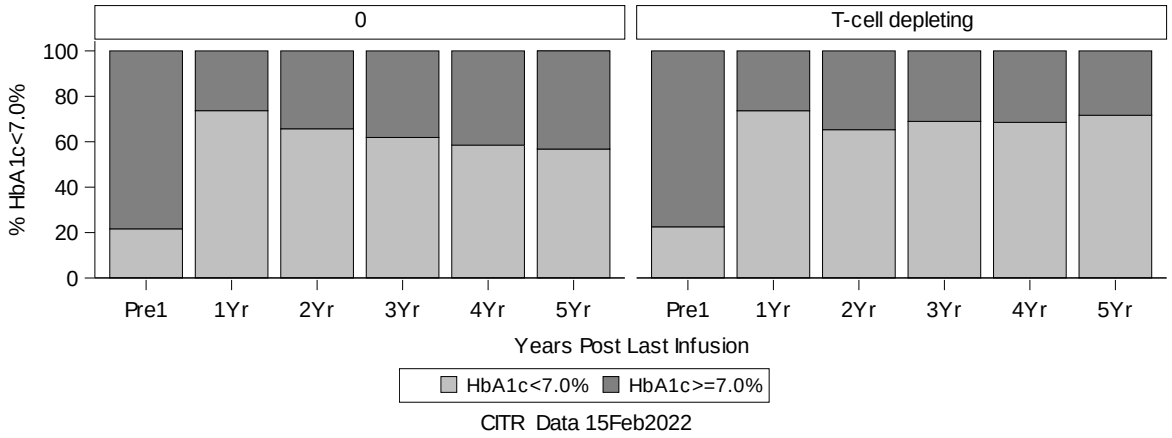


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

W. Endotoxin/kg recipient (p=0.005)



X. Immunosuppression: TCD (p=0.003)



Y. Immunosuppression: TNFa (p<0.0001)

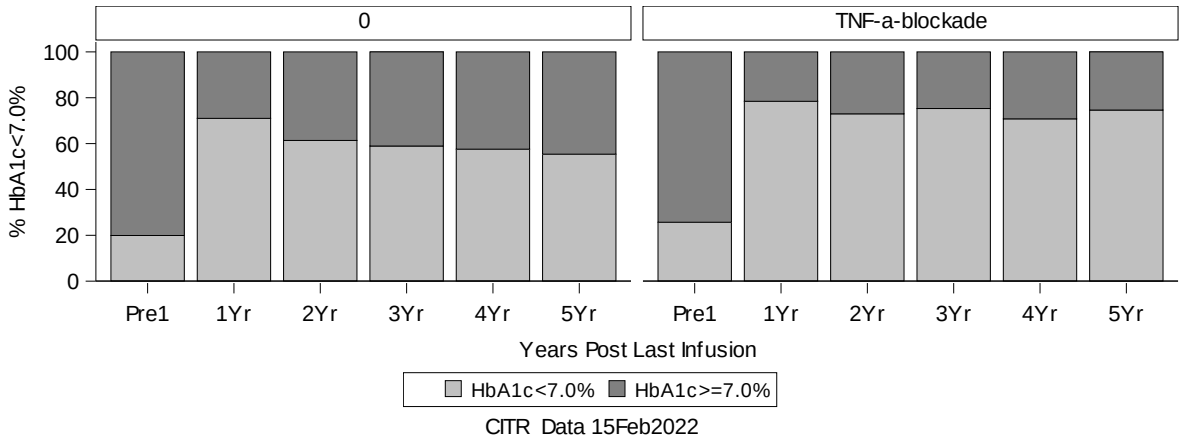
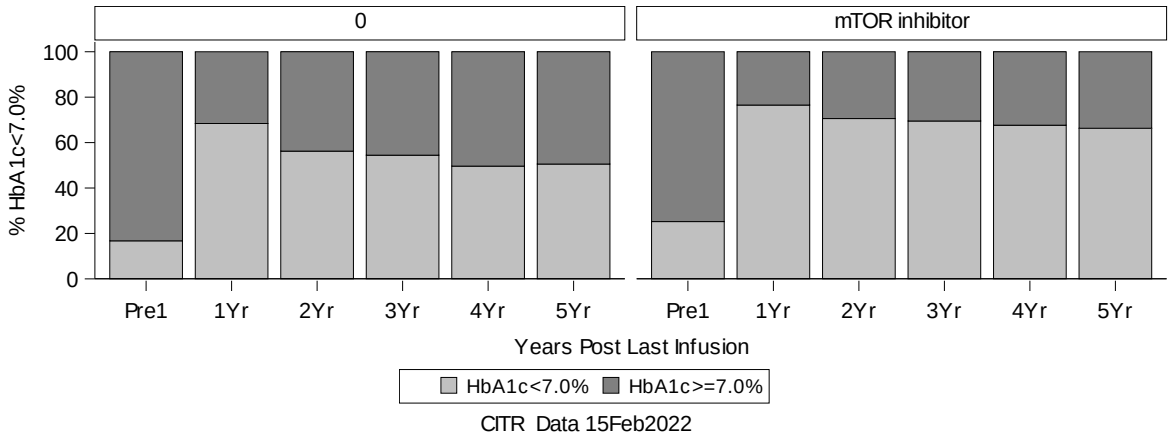
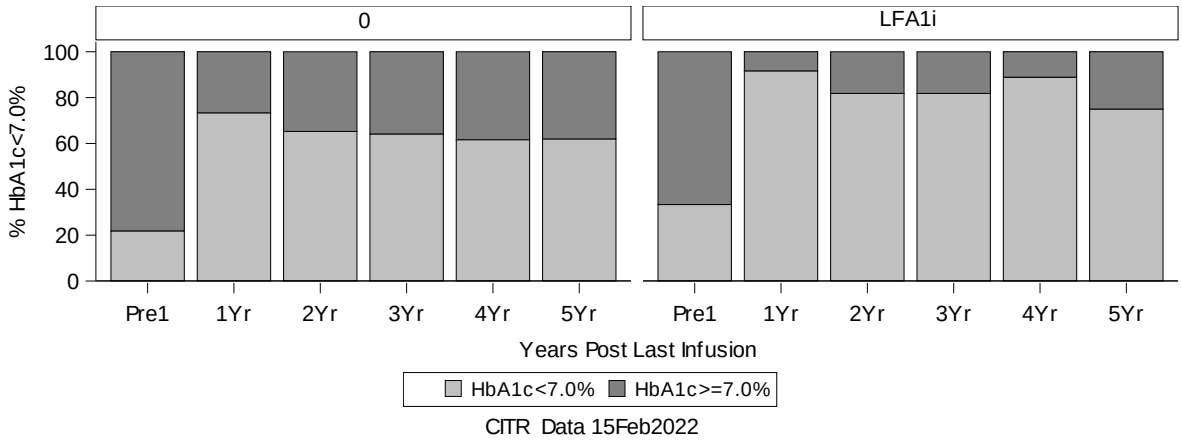


Exhibit 5 – 6B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among ITA Recipients

Z. Immunosuppression: mTOR Inhibitor (p<0.0001)



AA. Immunosuppression: LFA1i (p=0.0004)



BB. Immunosuppression: Efalizumab (p=0.0004)

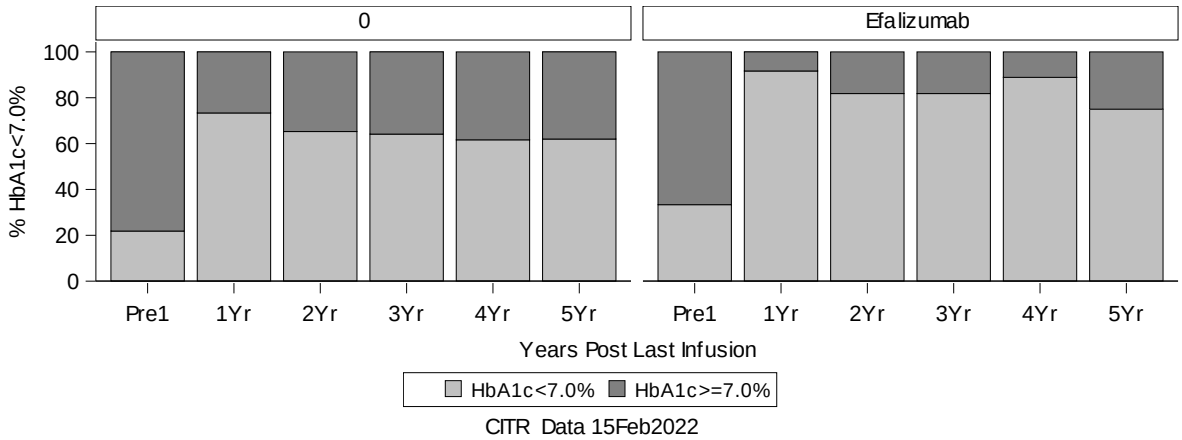
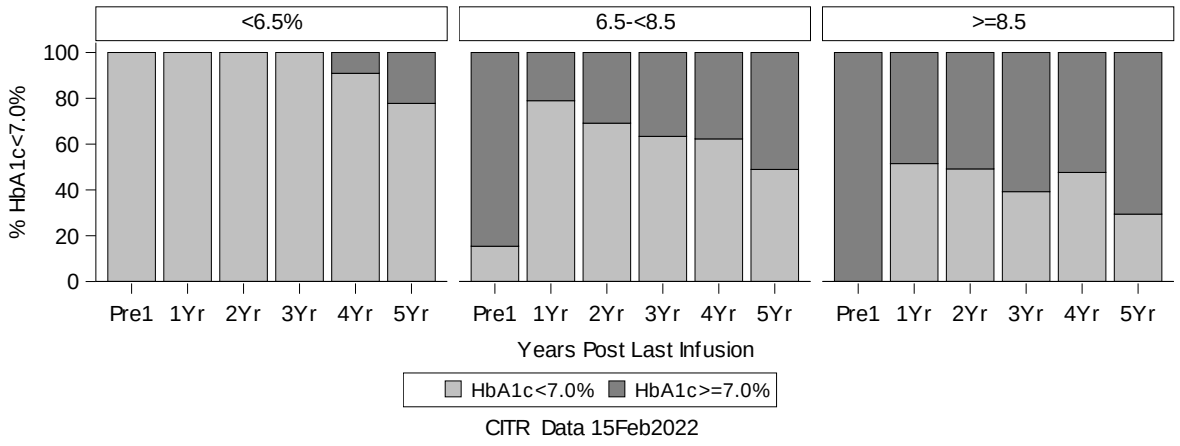


Exhibit 5 – 6C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

A. Baseline HbA1c (p<0.0001)



B. Baseline microinsulin autoantibody (p=0.007)

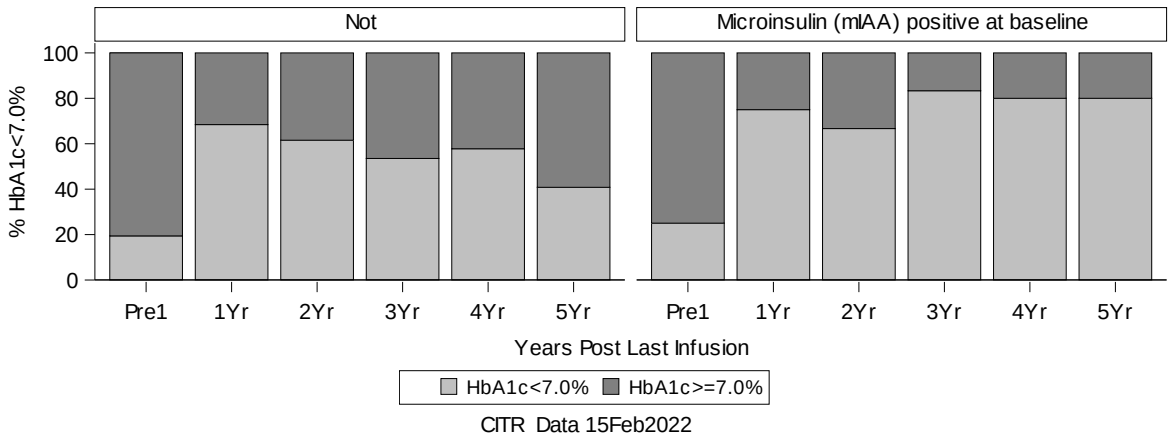
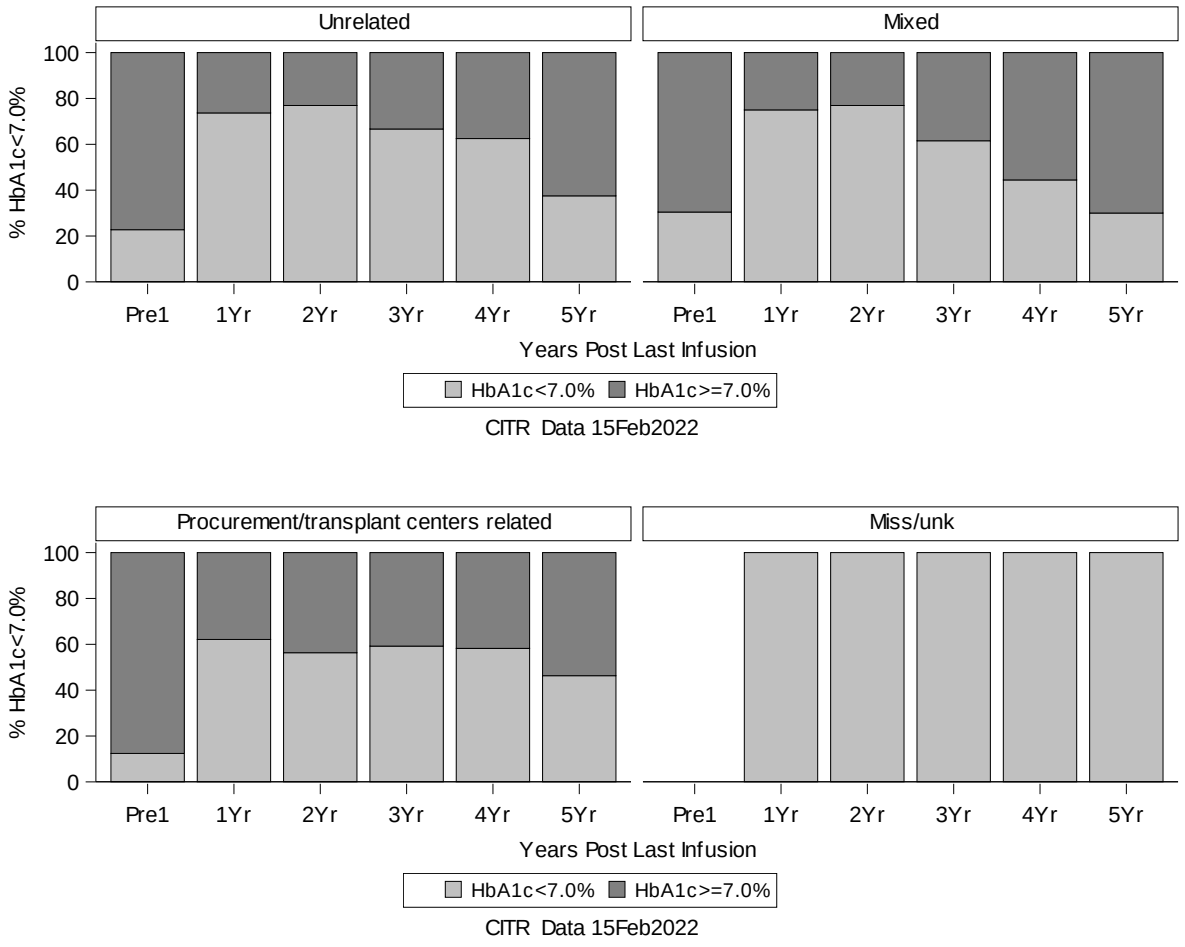


Exhibit 5 – 6C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

C. Procurement Team/ Inf Team Related (p<0.0001)



D. Donor serum creatinine (p=0.004)

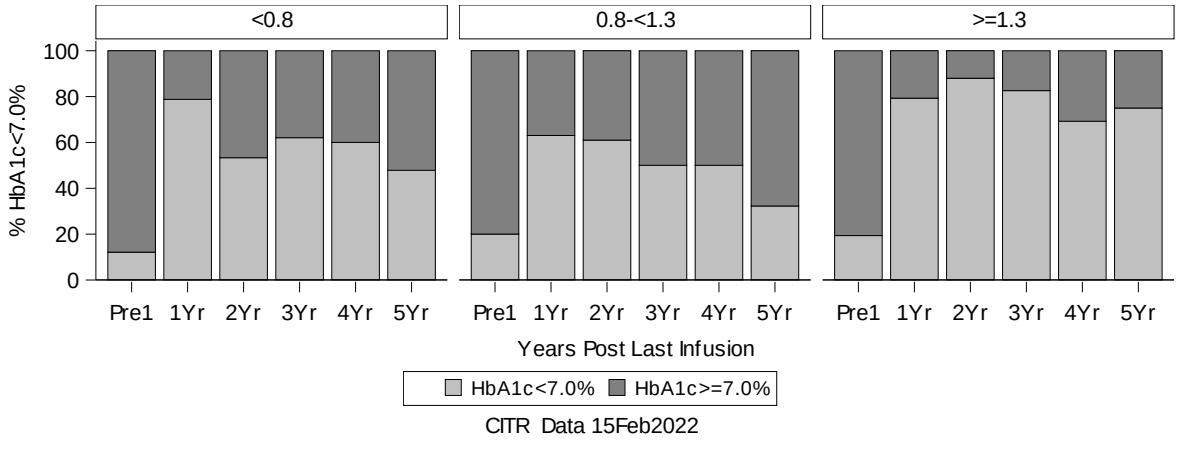


Exhibit 5 – 6C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% Post Last Infusion among IAK Recipients

E. Era (p<0.0001)

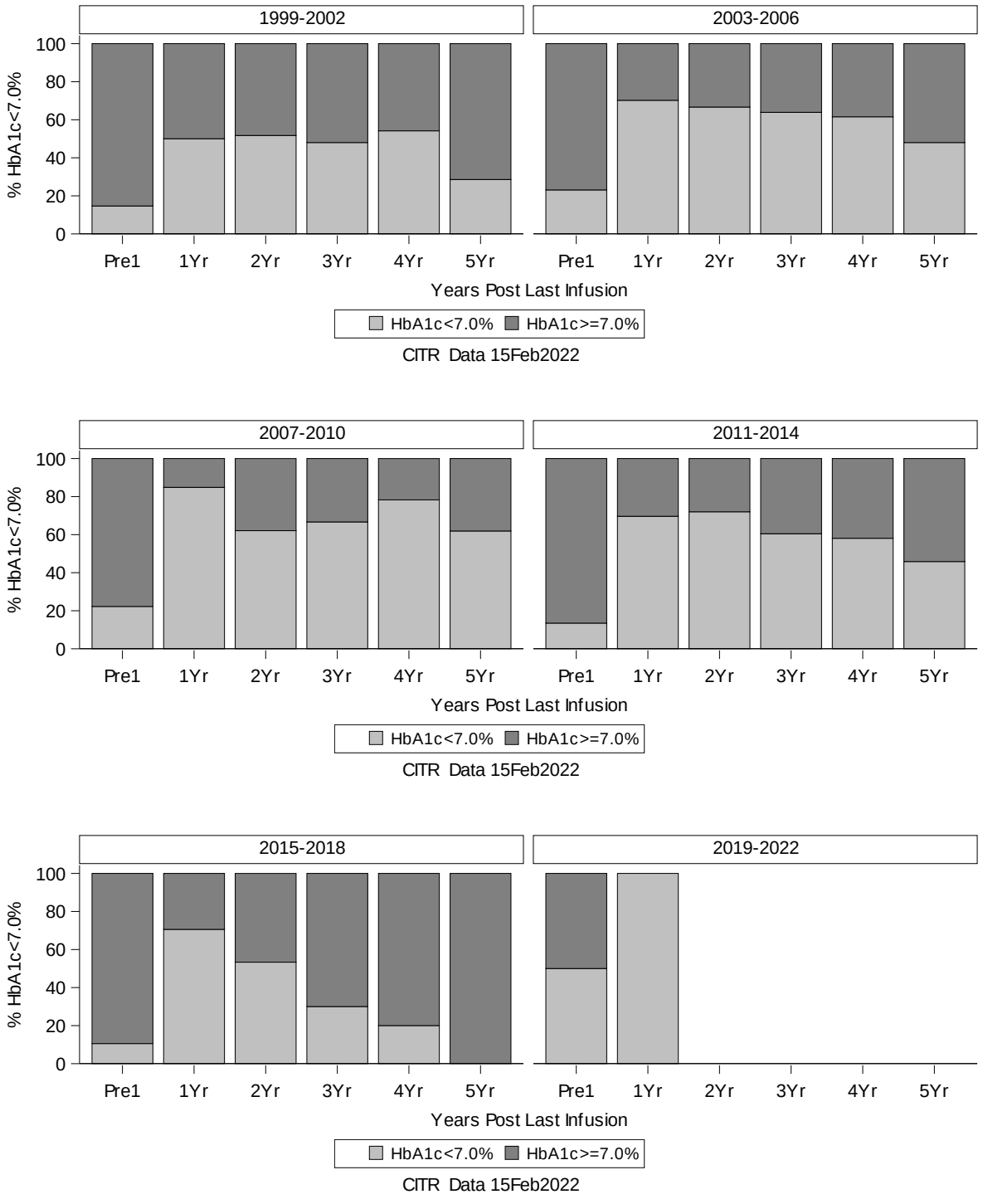


Exhibit 5 – 7A

Unadjusted Prevalence of Absence of Severe Hypoglycemia Events Post Last Infusion

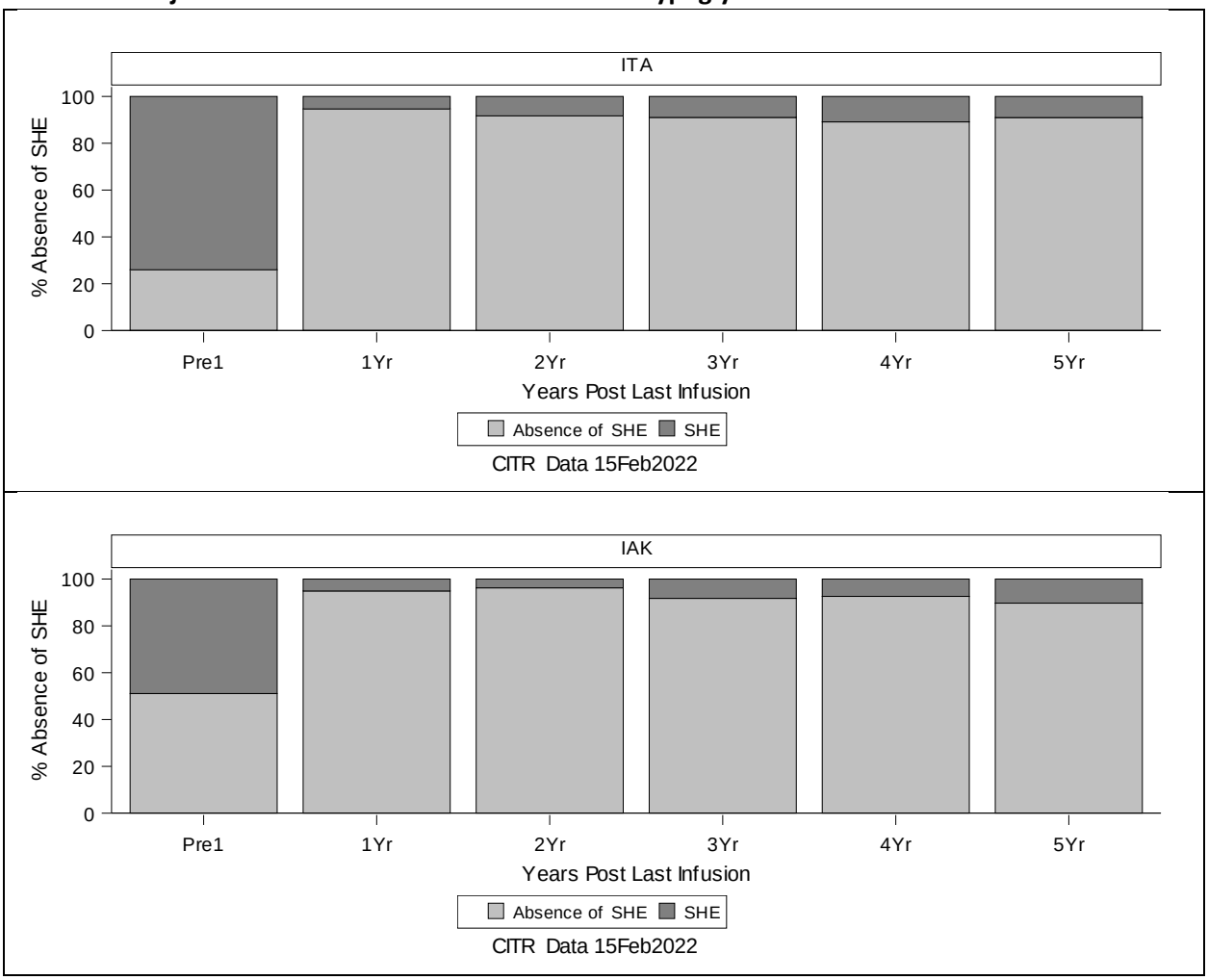
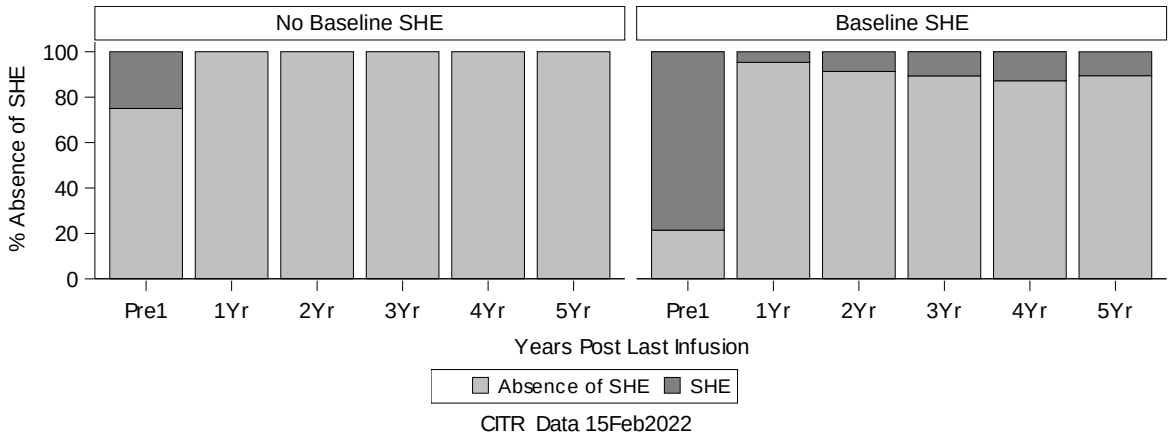
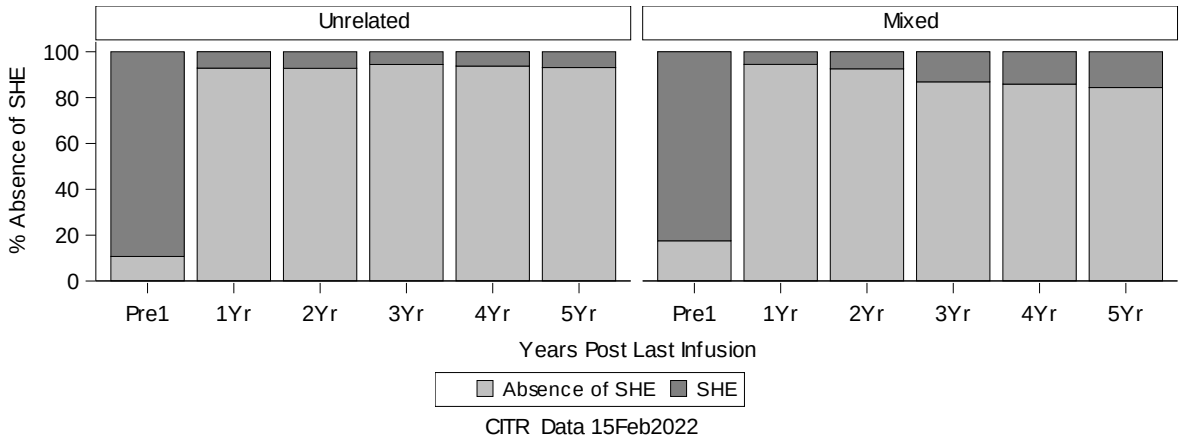


Exhibit 5 – 7B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipient

A. Baseline hypoglycemia status (p<0.0001)



B. Procurement Team/ Inf Team Related (p<0.0001)



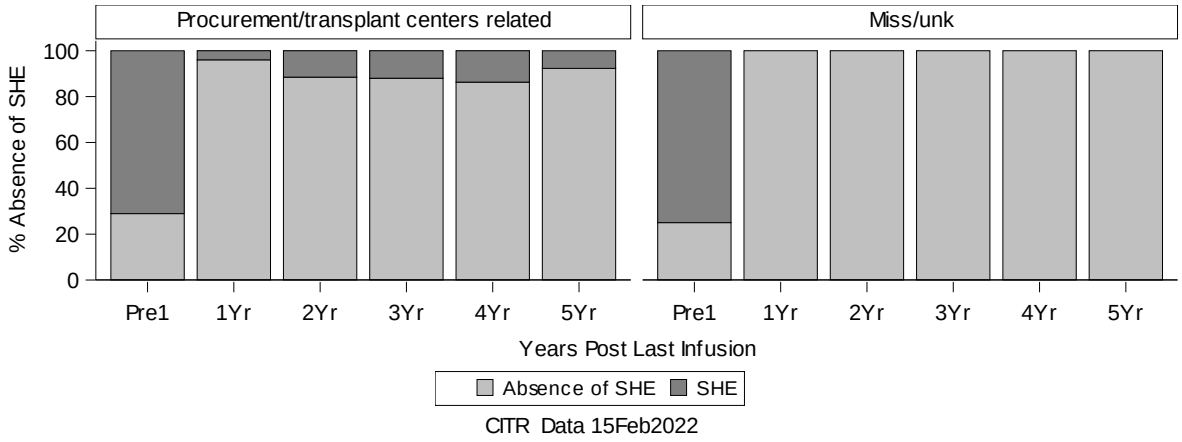
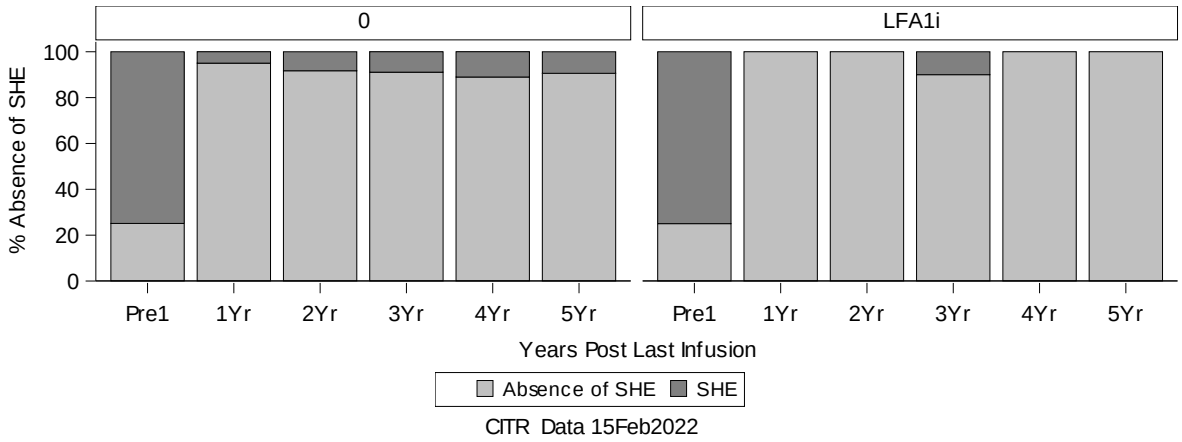


Exhibit 5 – 7B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipient

C. Donor serum creatinine (p=0.008)

D. Immunosuppression: LFA1i (p=0.003)



E. Immunosuppression: Efalizumab (p=0.003)

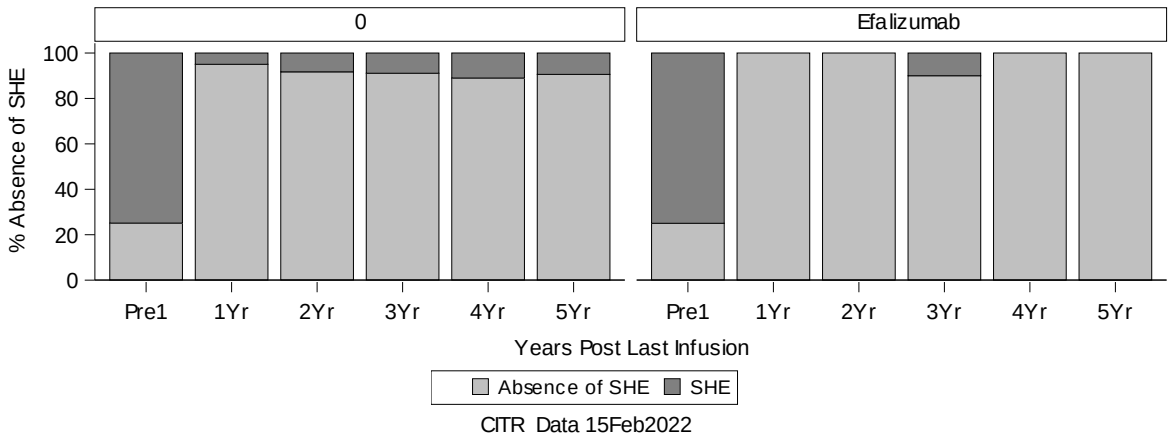
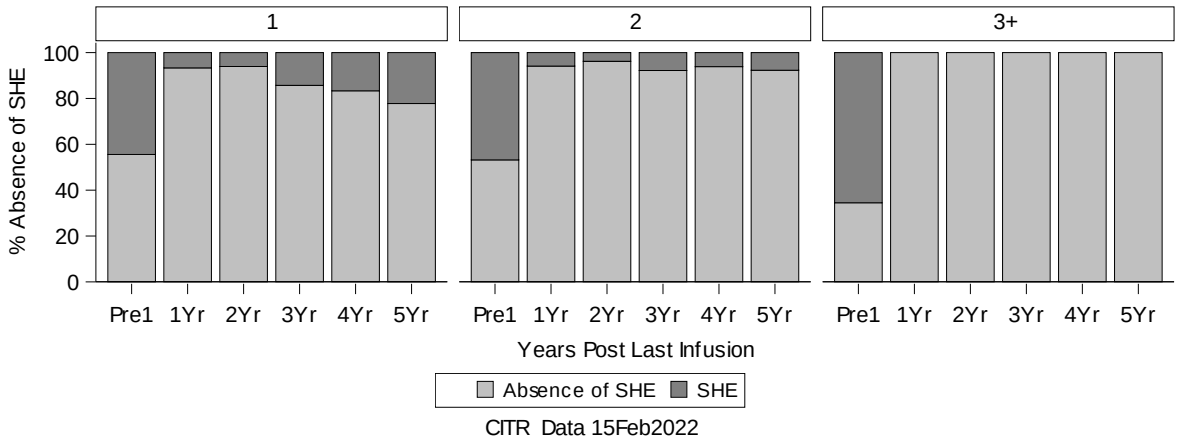
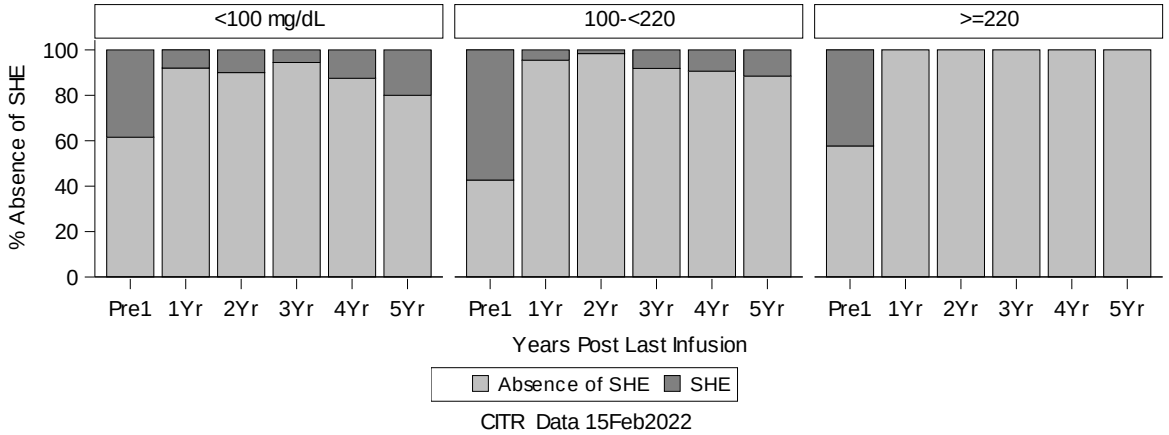


Exhibit 5 – 7C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipient

A. Total infusions (p=0.0003)



B. Baseline fasting BG (p=0.002)



C. Microinsulin (mIAA) positive at baseline (p=0.0001)

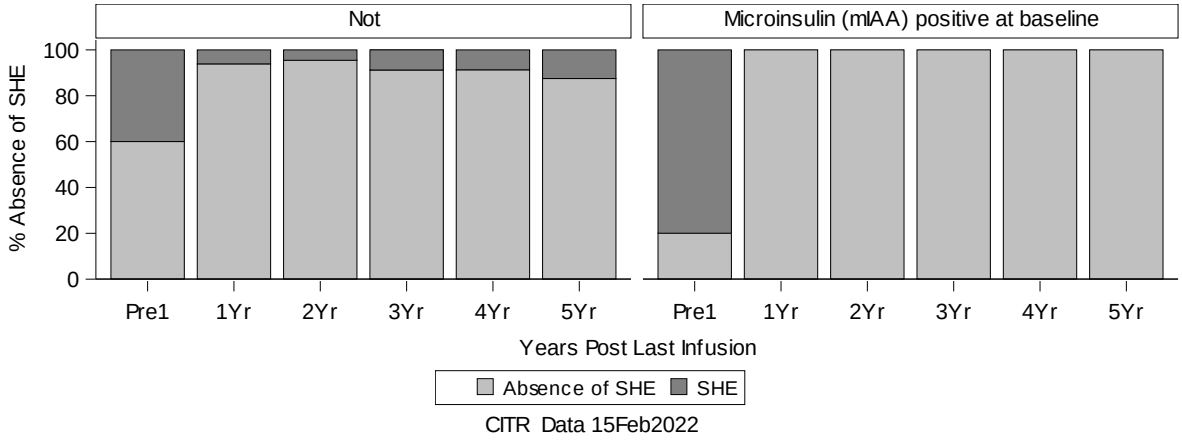
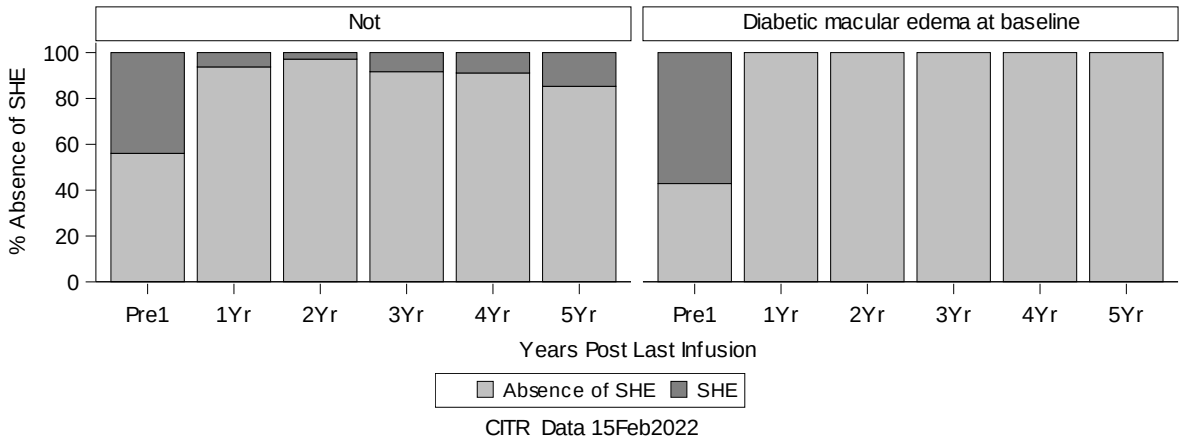
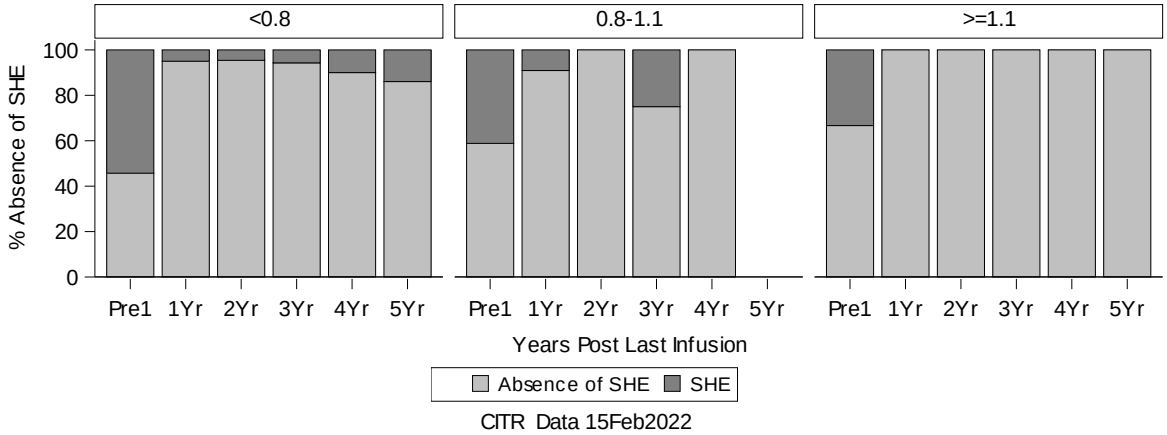


Exhibit 5 – 7C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipient

D. Baseline diabetic macular edema (p=0.003)



E. Baseline total bilirubin (p=0.006)



F. Processing Center/ Inf Center Related (p=0.0009)

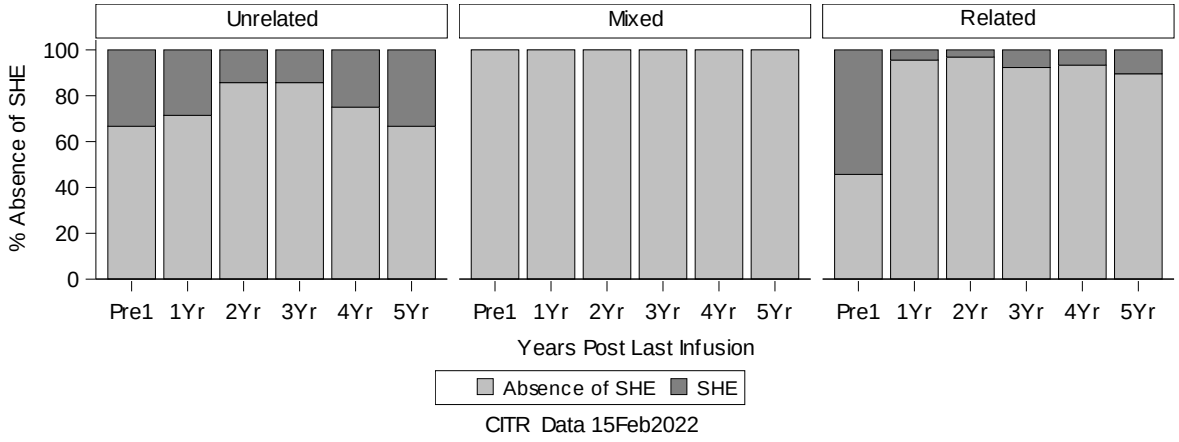


Exhibit 5 – 7C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipient

G. Procurement Team/ Inf Team Related (p=0.003)

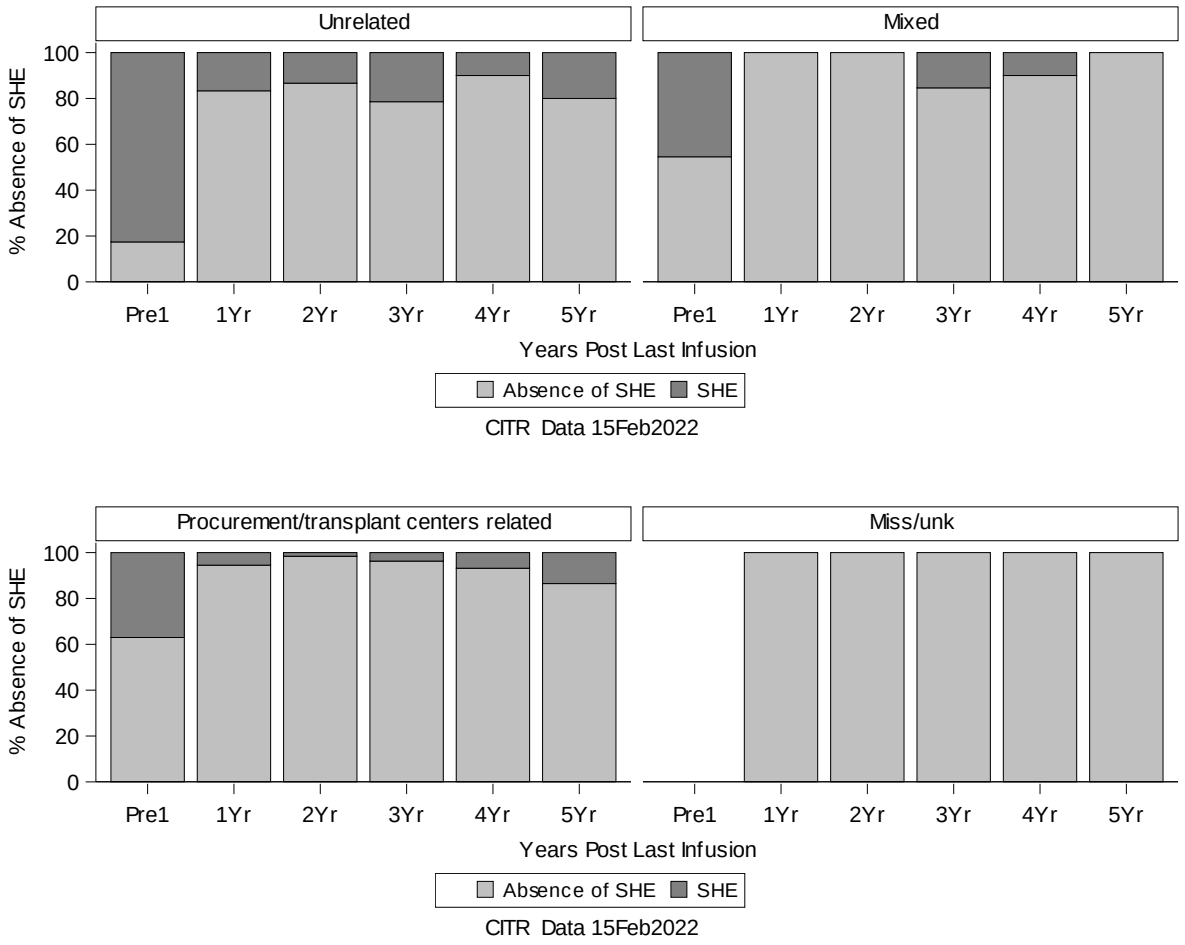


Exhibit 5 – 8A

Unadjusted Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion

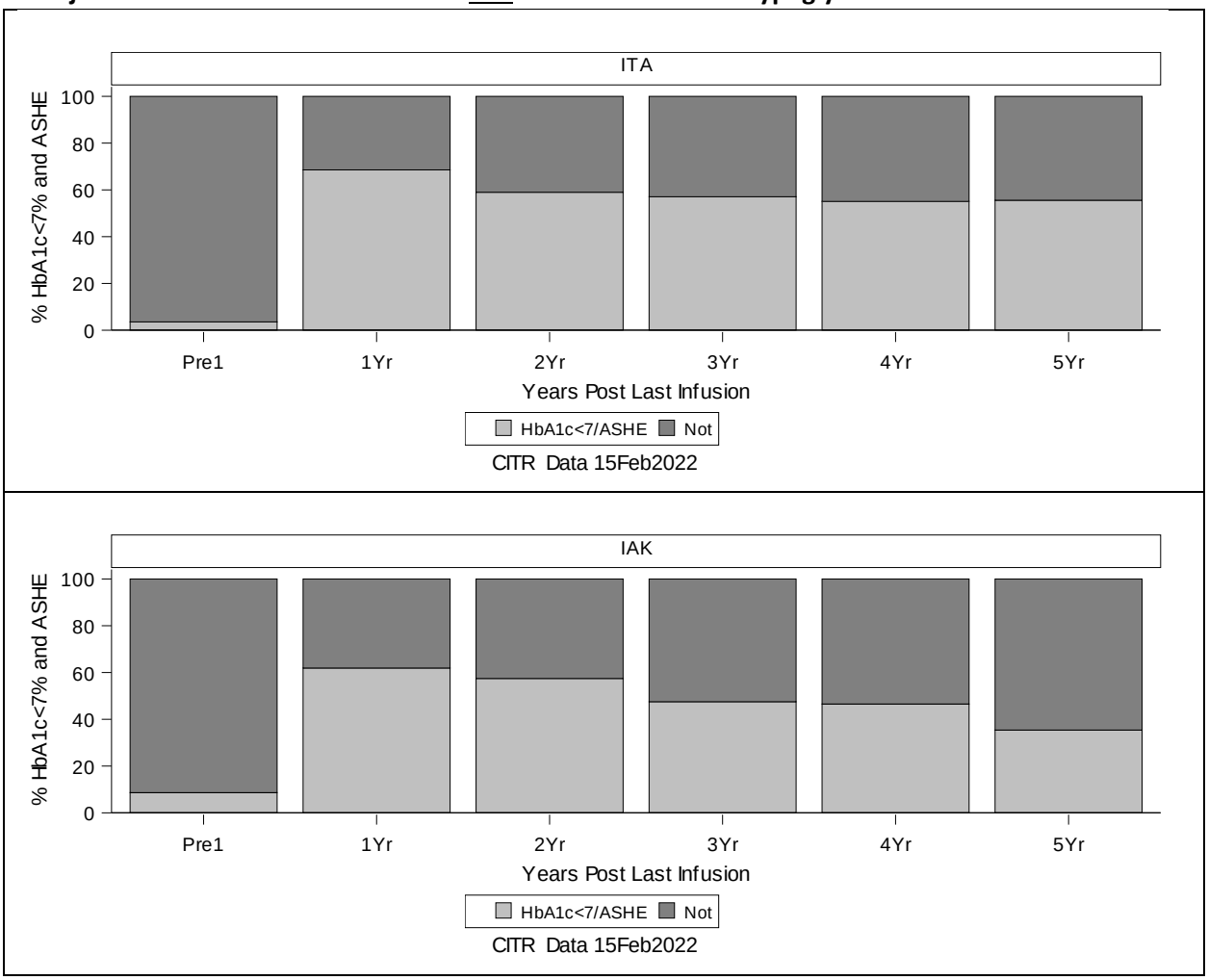
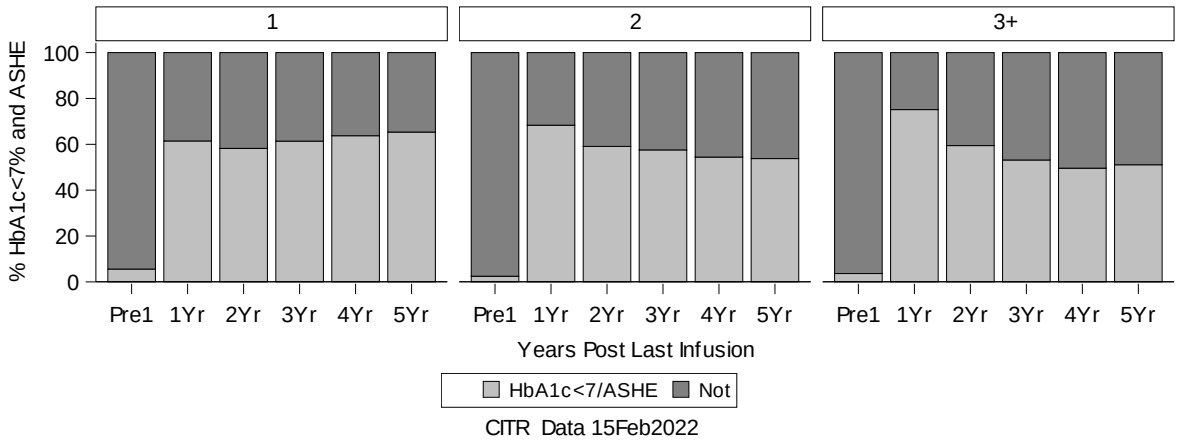
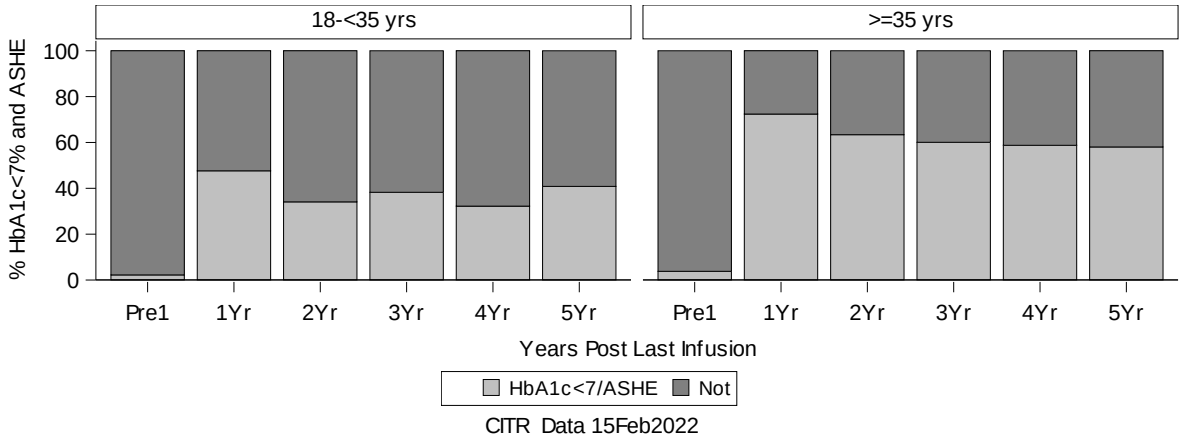


Exhibit 5 – 8B
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

A. Total infusions (p=0.0003)



B. Recipient Age (p<0.0001)



C. Diabetes Duration (p=0.0001)

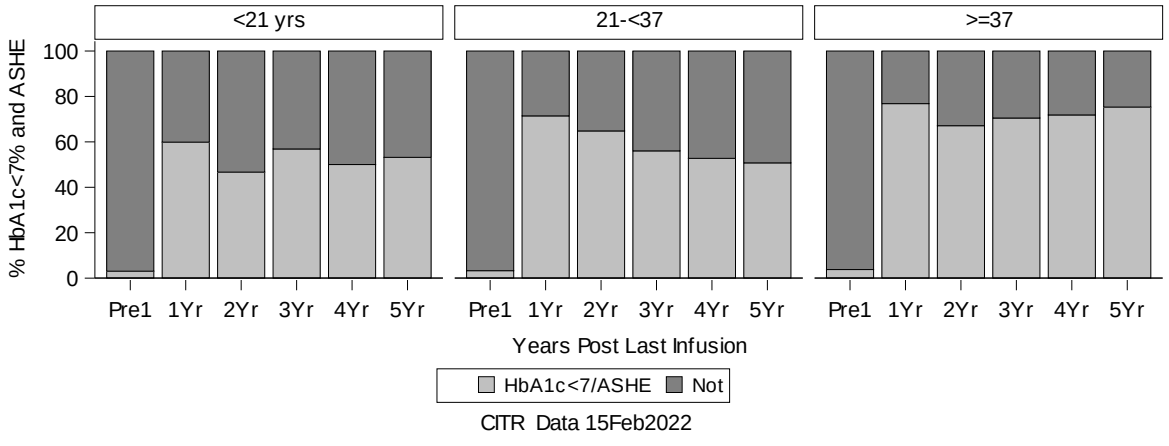
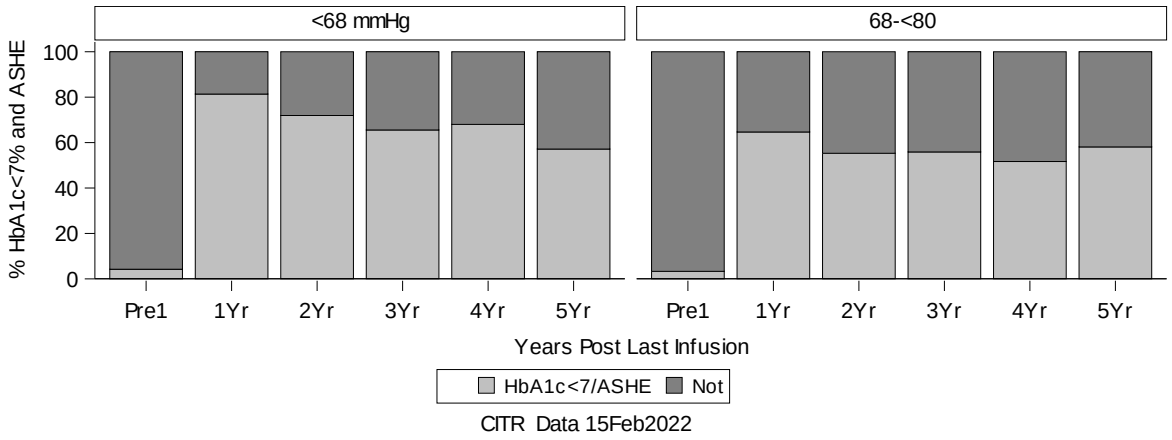
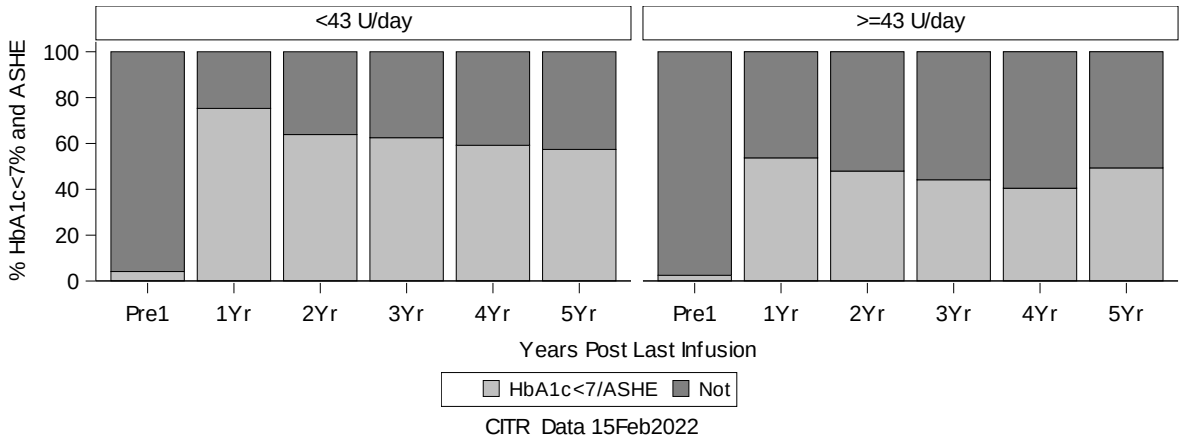


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

D. Baseline DBP (p=0.0004)



E. Baseline insulin (Units/day) (p<0.0001)



F. Baseline insulin (units/day/kg) (p=0.001)

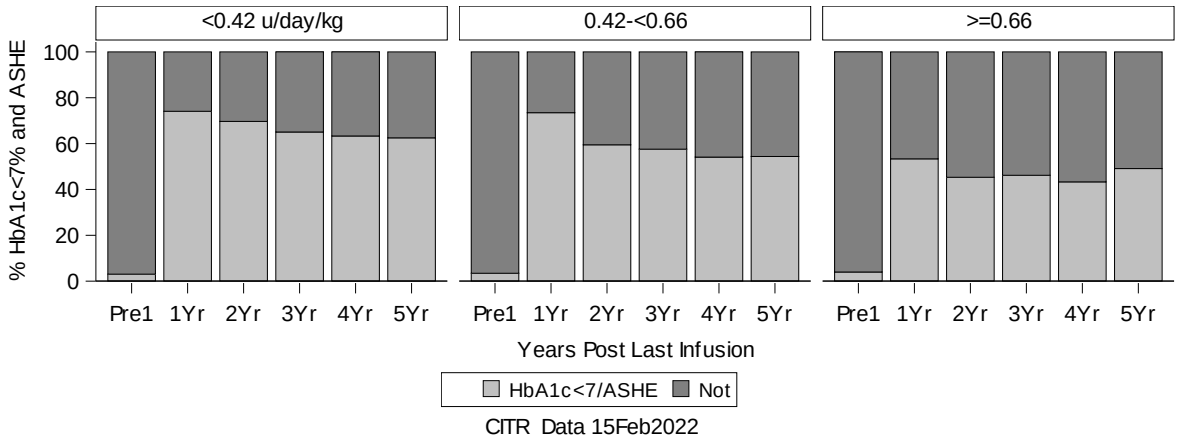
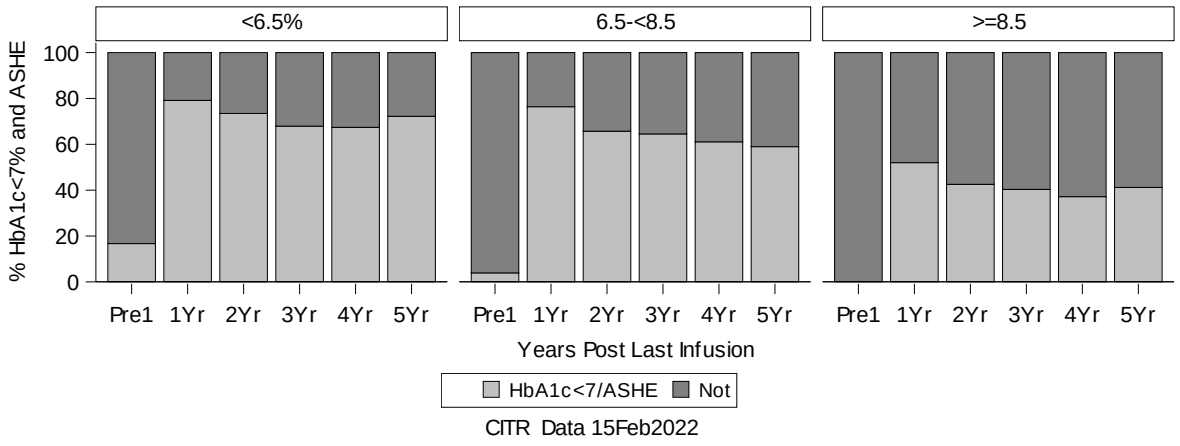
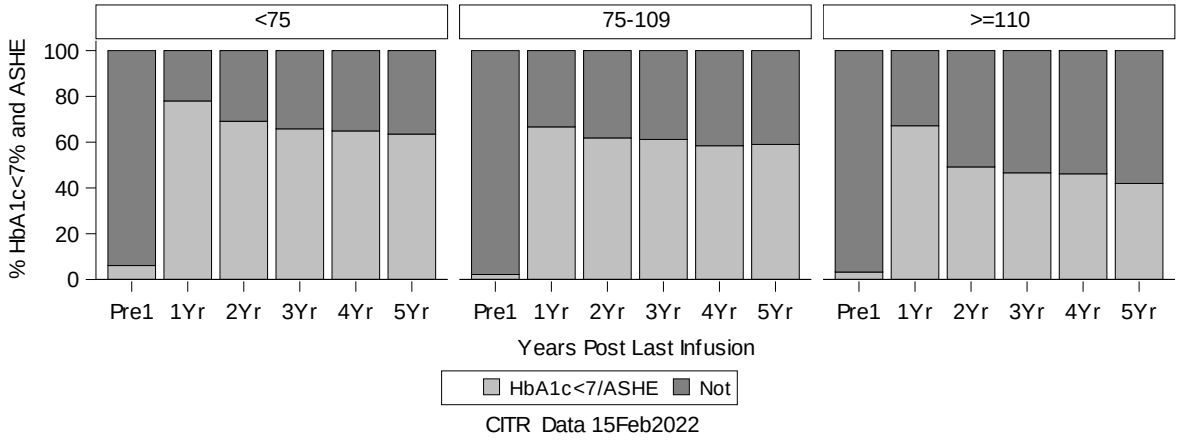


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

G. Baseline HbA1c (p<0.0001)



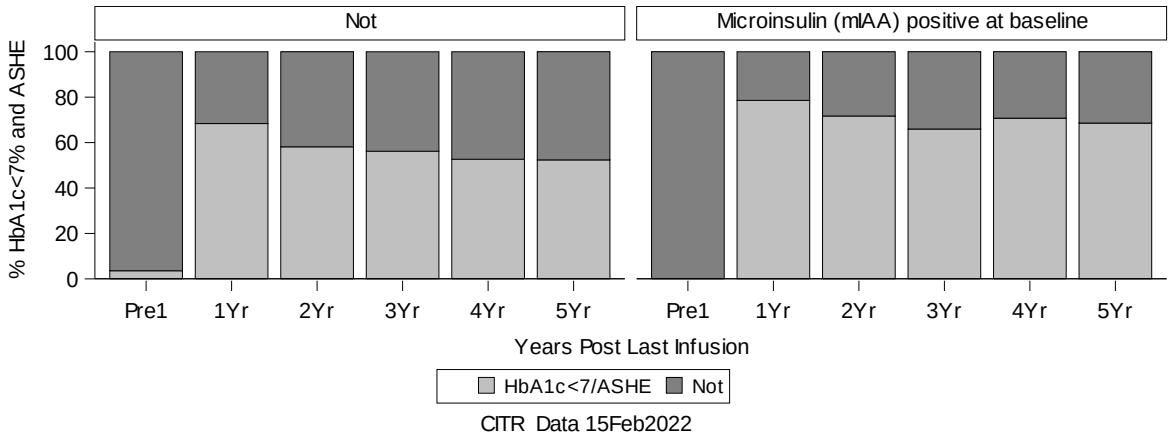
H. Baseline LDL (p=0.003)



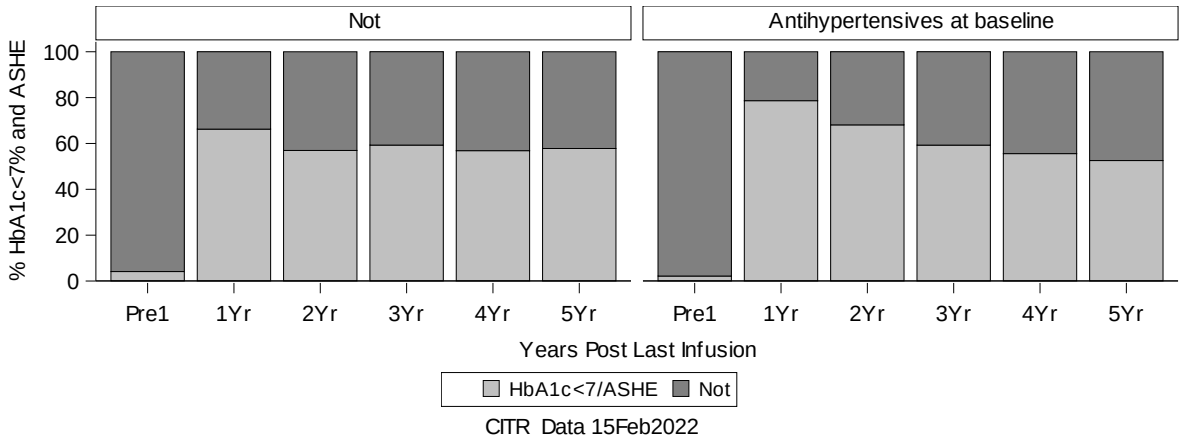
I. Baseline IA-2 autoantibody (p=0.004)

Exhibit 5 – 8B (continued)
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

J. Baseline microinsulin autoantibody (p=0.007)



K. Baseline treated hypertension (p=0.008)



L. Baseline CVA (p=0.008)

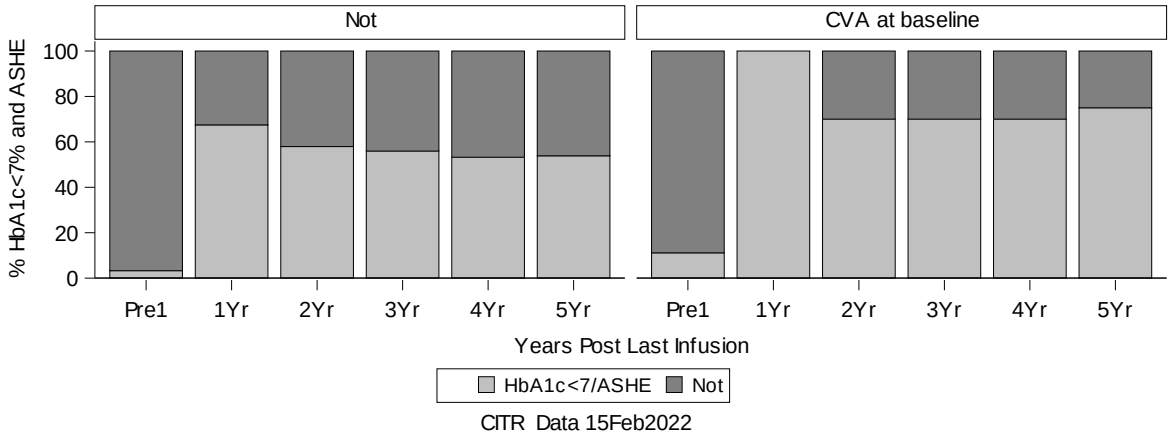
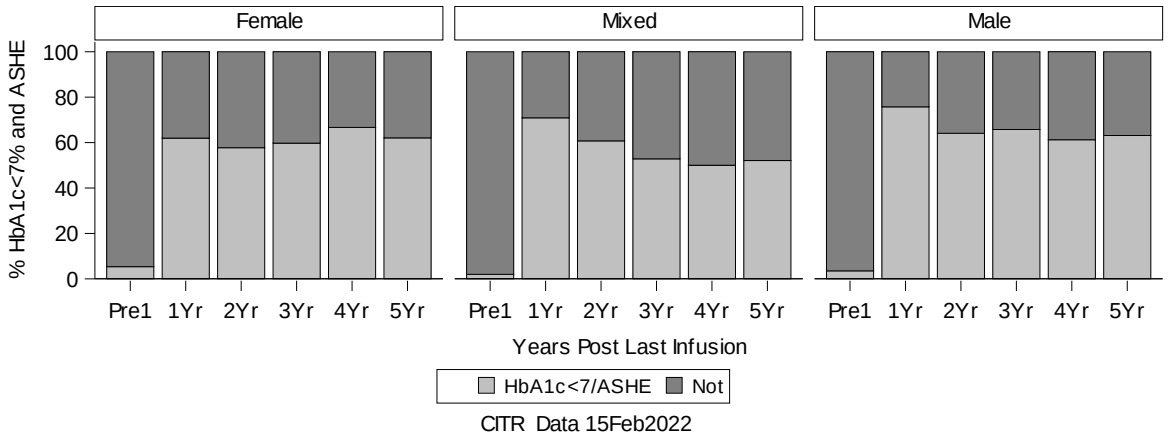
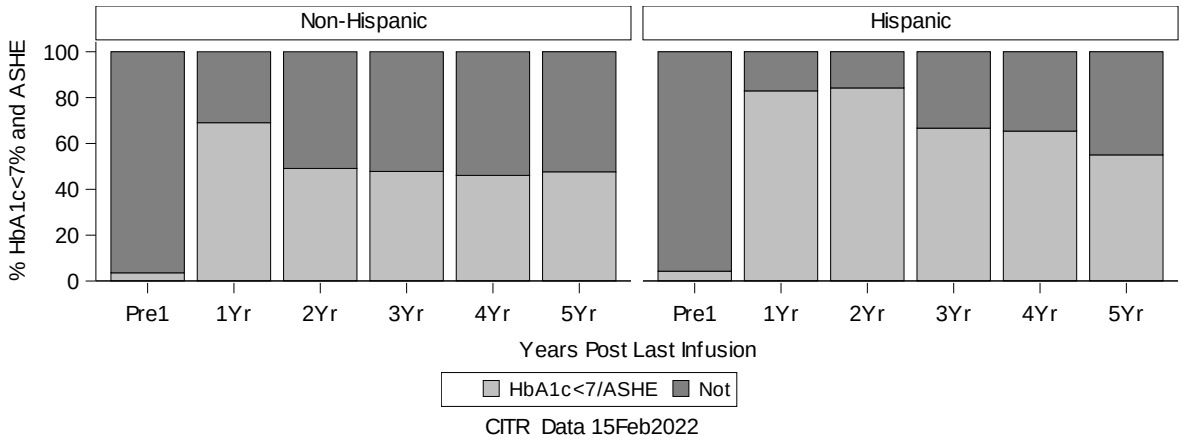


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

M. Donor Sex (p=0.003)



N. Donor ethnicity (p=0.002)



O. Any positive crossmatch (p=0.005)

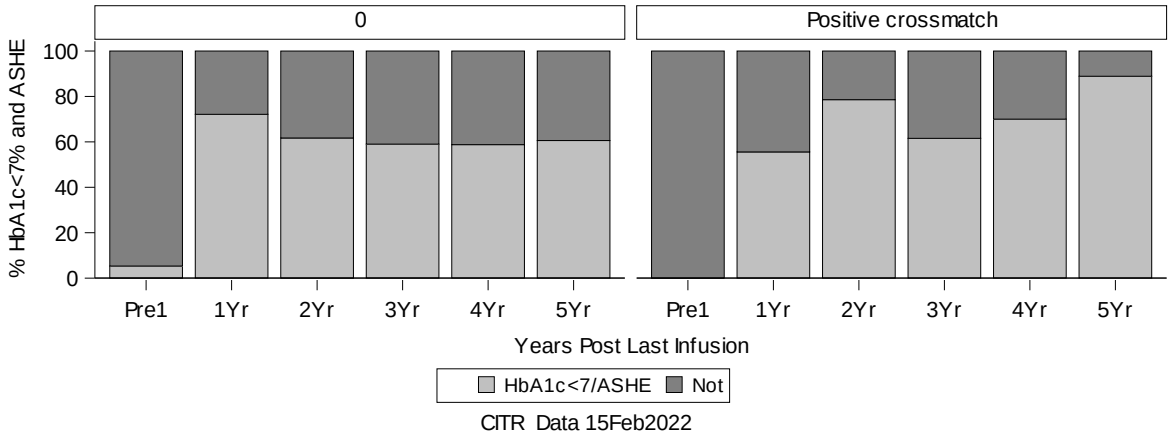
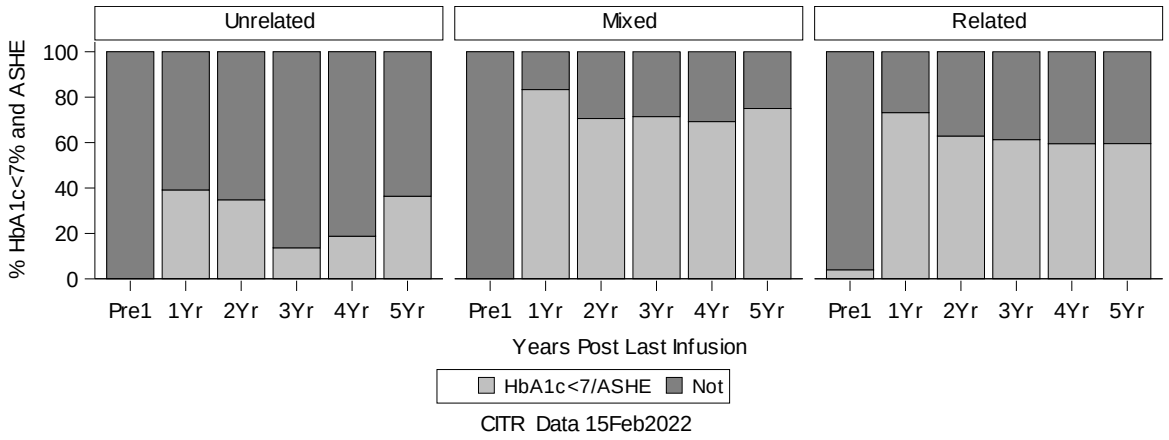
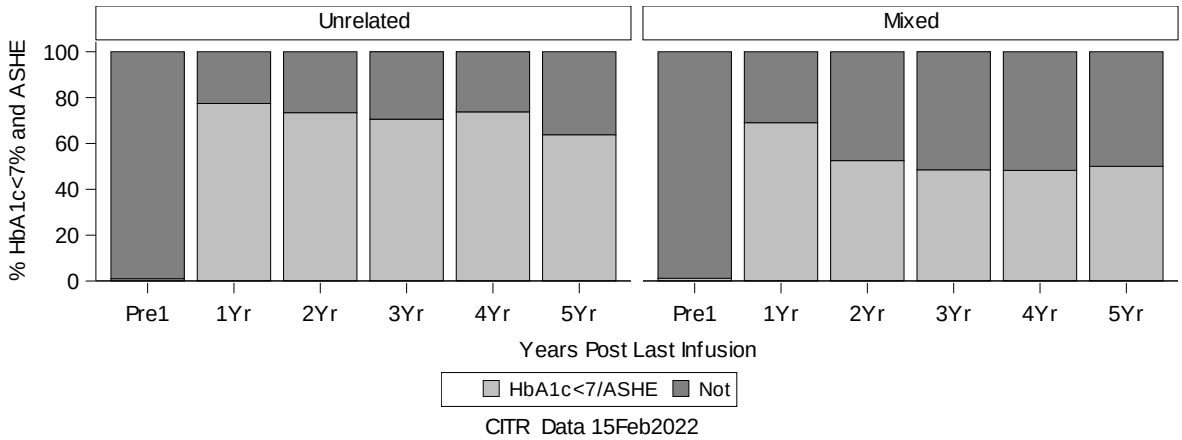


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

P. Processing Center/ Inf Center Related (p=0.007)



Q. Procurement Team/ Inf Team Related (p=0.004)



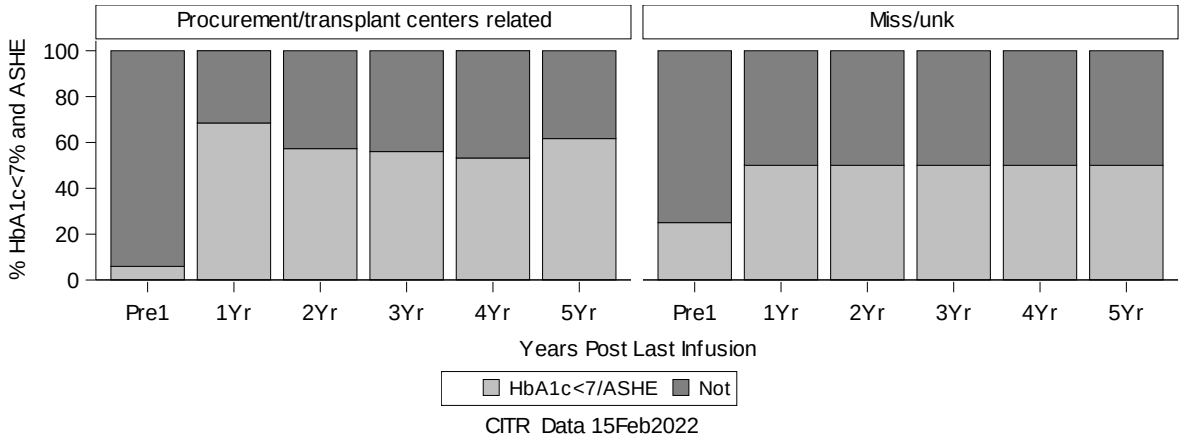
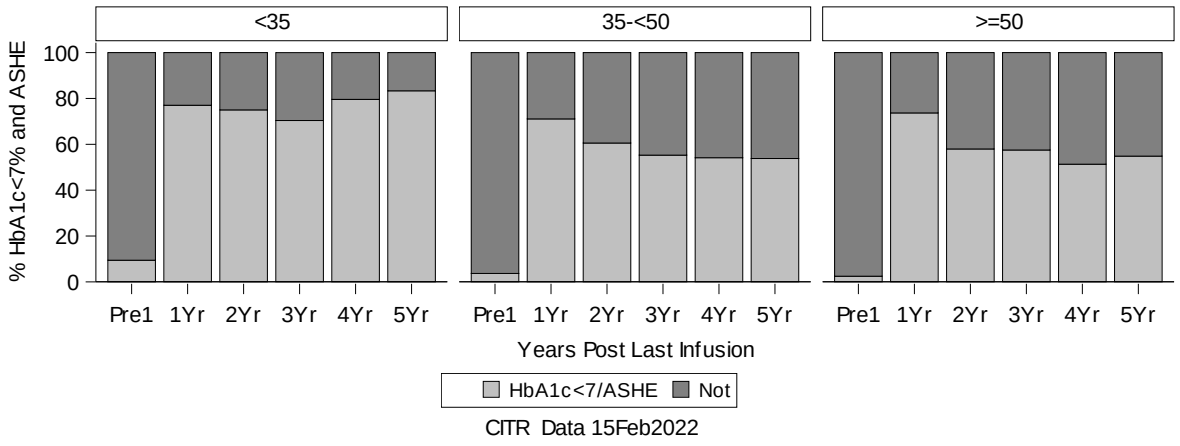
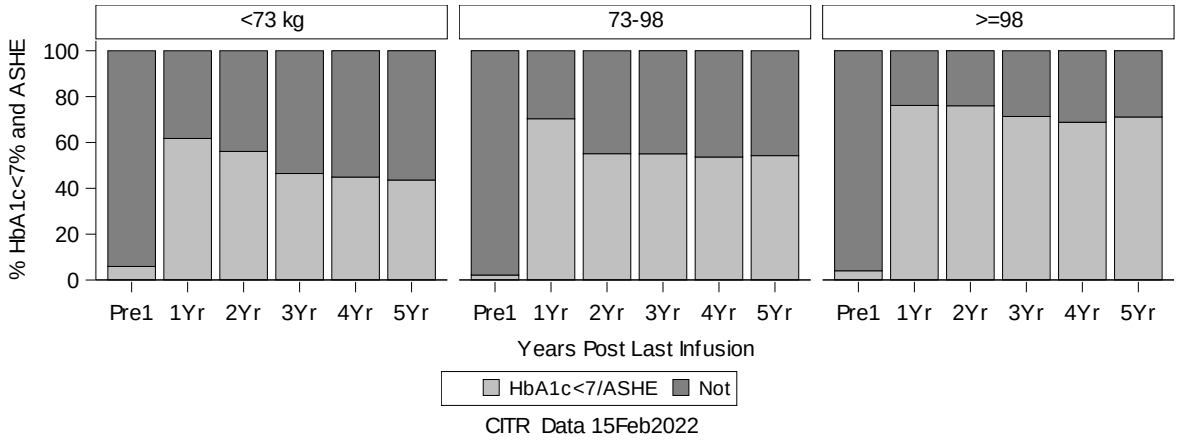


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

R. Donor age (yrs) (p=0.001)



S. Donor weight (p<0.0001)



T. Max donor glucose (p=0.0005)

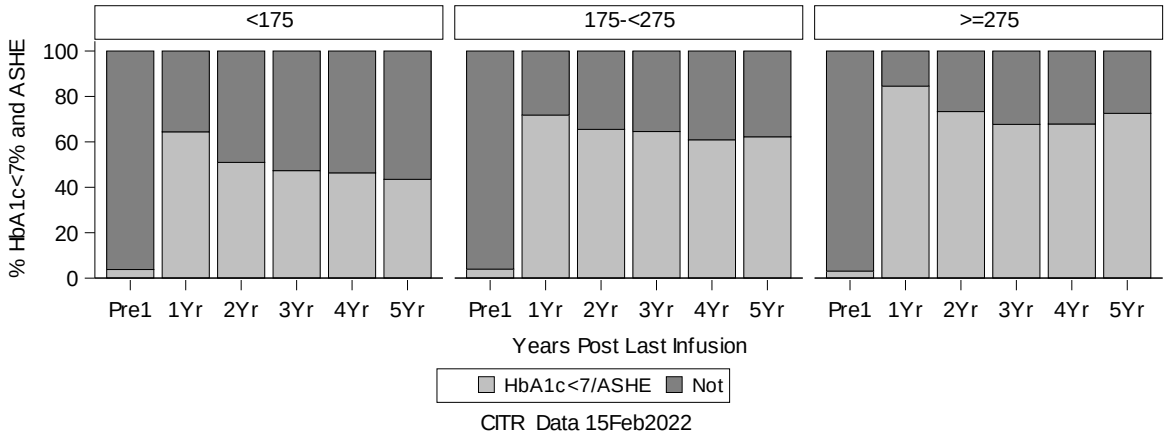
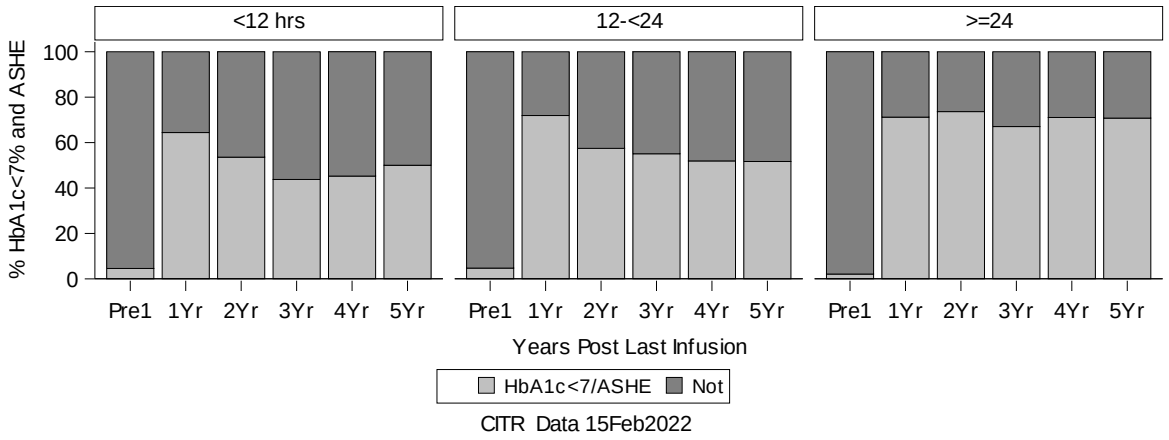
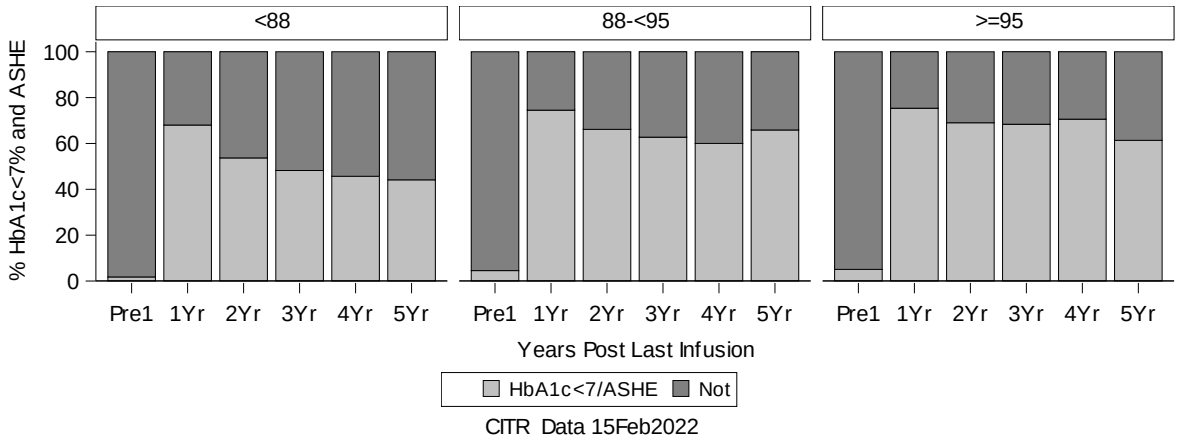


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

U. Hours: death to cross-clamp (p=0.003)



V. Islet viability (p=0.002)



W. Immunosuppression: TCD (p=0.005)

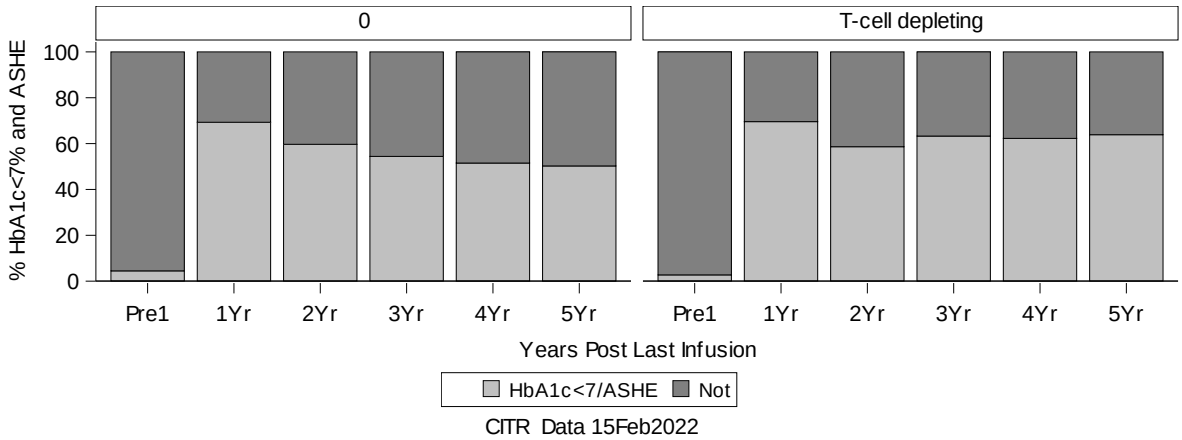
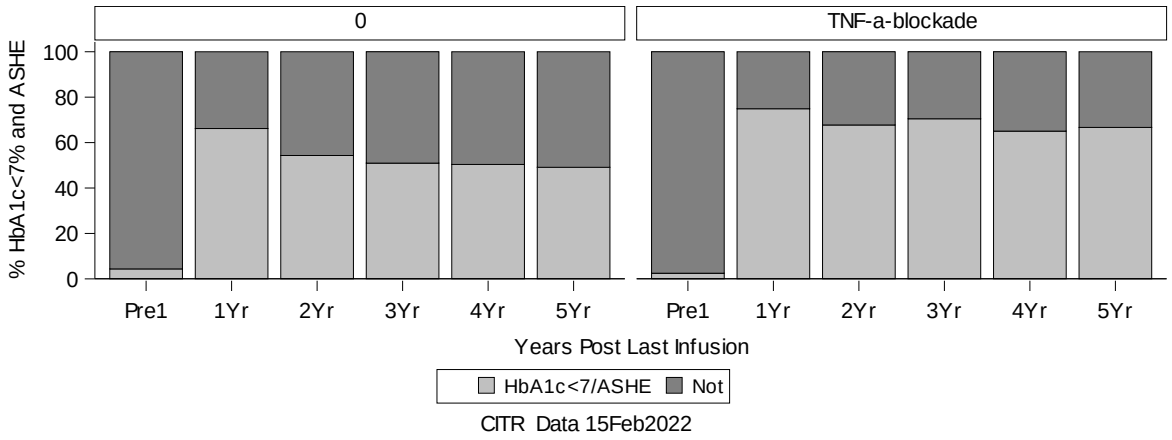
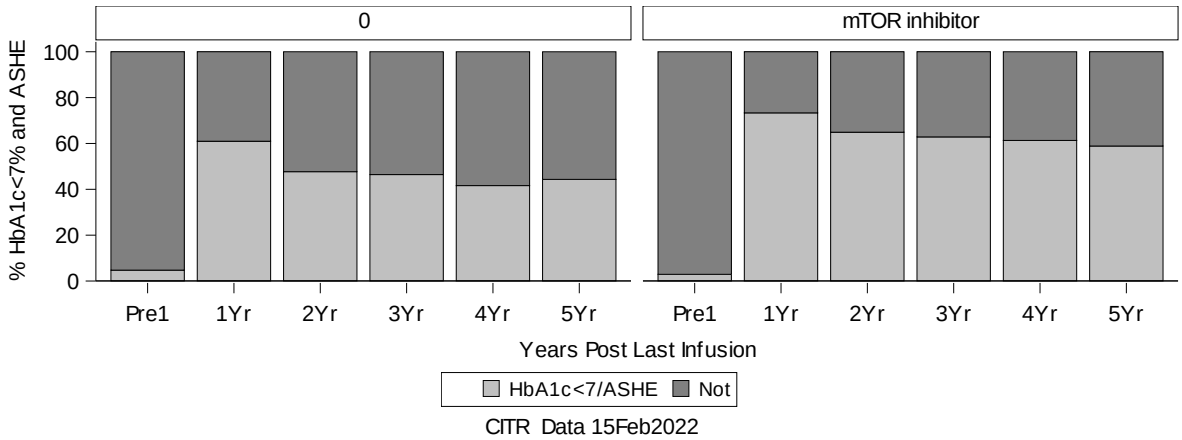


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

X. Immunosuppression: TNFa (p<0.0001)



Y. Immunosuppression: mTOR Inhibitor (p<0.0001)



Z. Immunosuppression: LFA1i (p<0.0001)

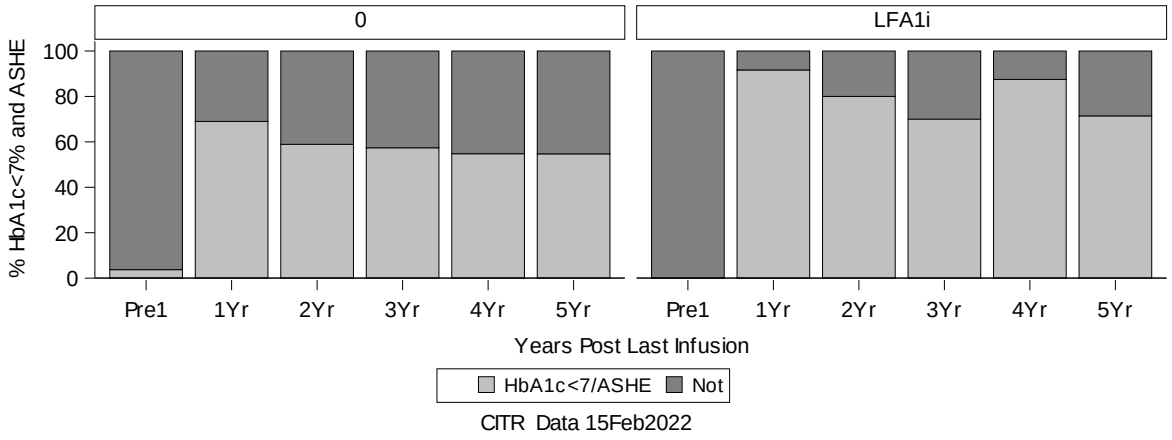


Exhibit 5 – 8B (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among ITA Recipients

AA. Immunosuppression: Efalizumab (p<0.0001)

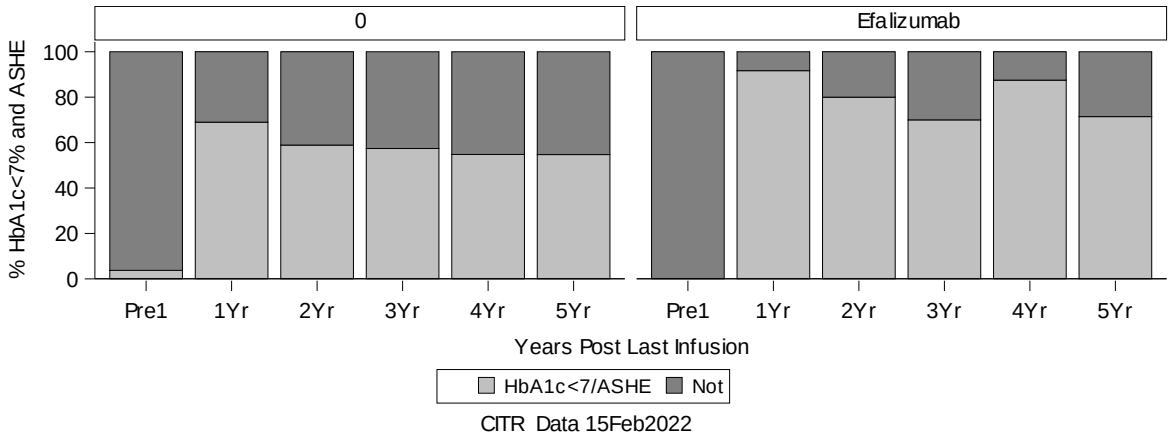
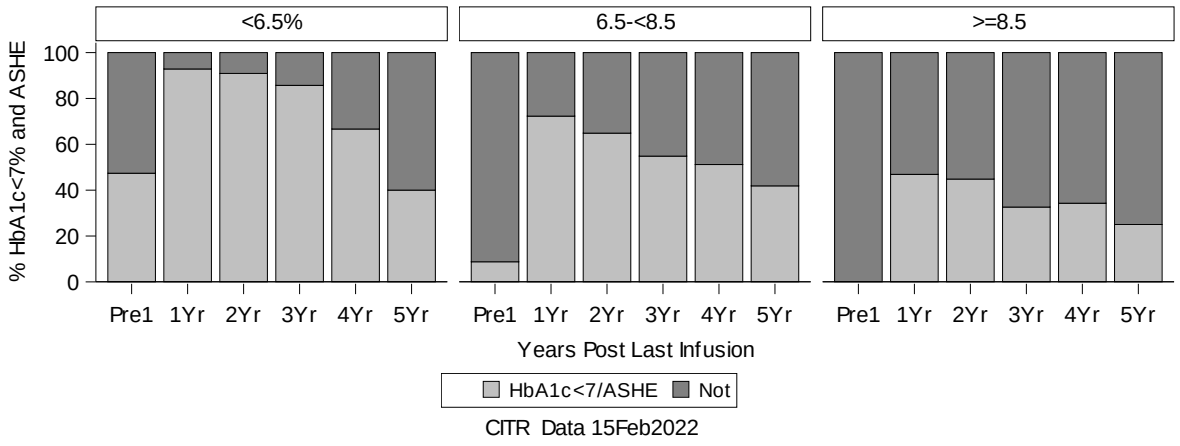
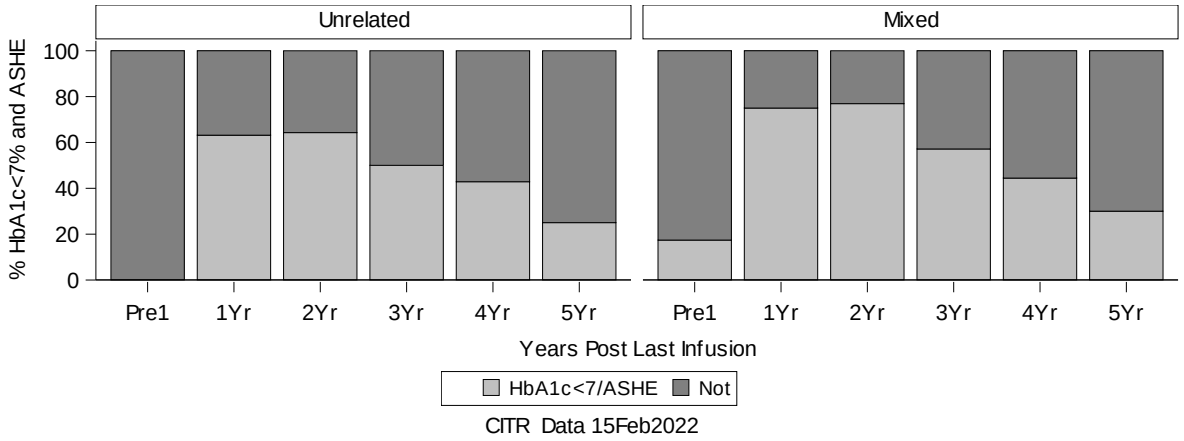


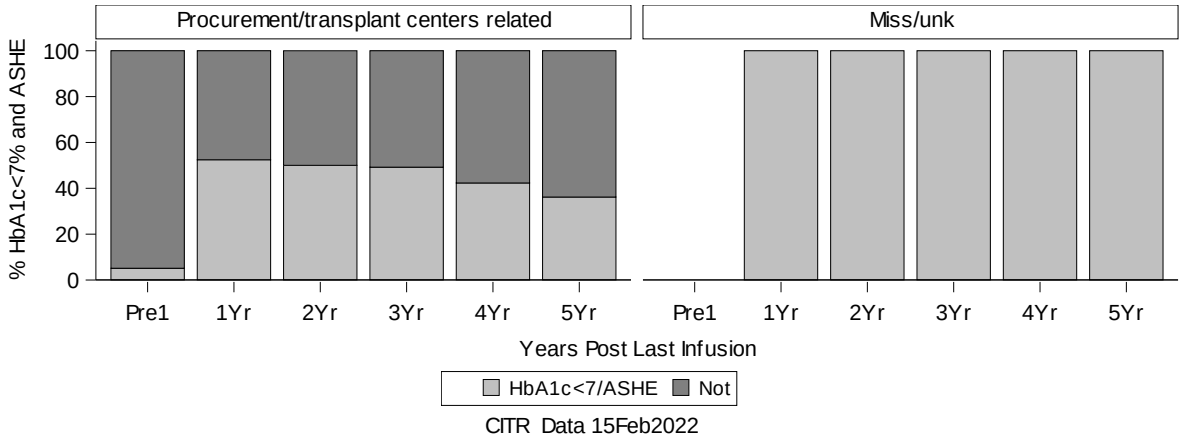
Exhibit 5 – 8C
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

A. Baseline HbA1c (p=0.0003)



B. Procurement Team/ Inf Team Related (p<0.0001)

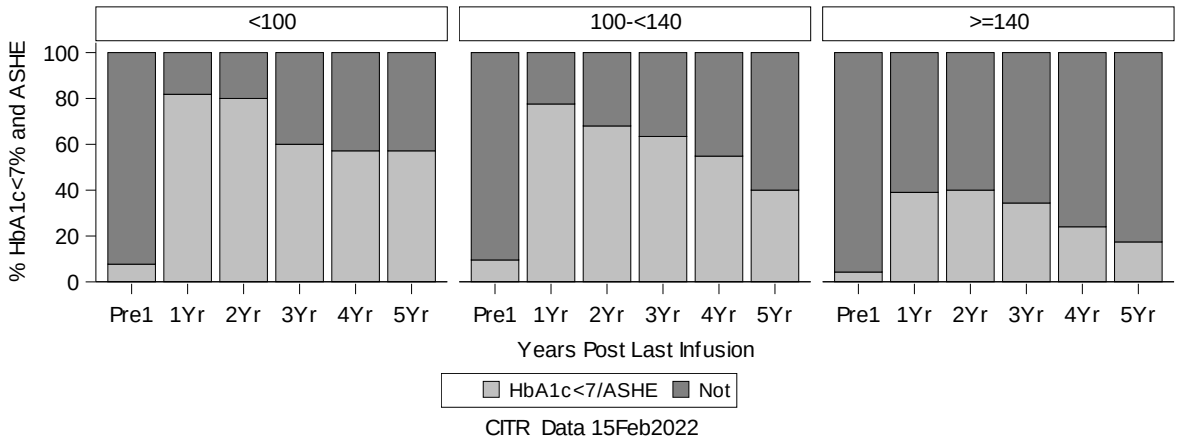




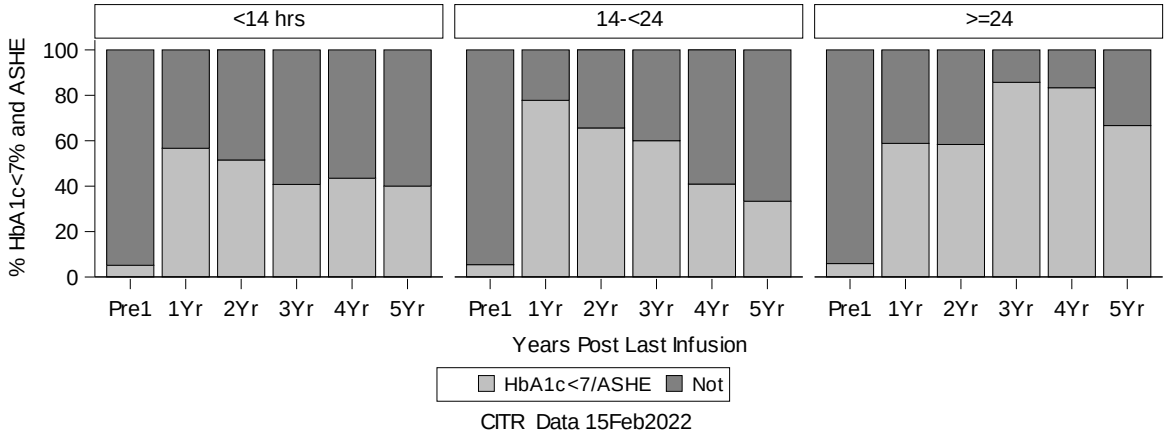
5 – 8C (continued)

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

C. Pre-Ins donor glucose (p=0.004)



D. Hours: death to recovery (p=0.007)



E. Endotoxin (p=0.005)

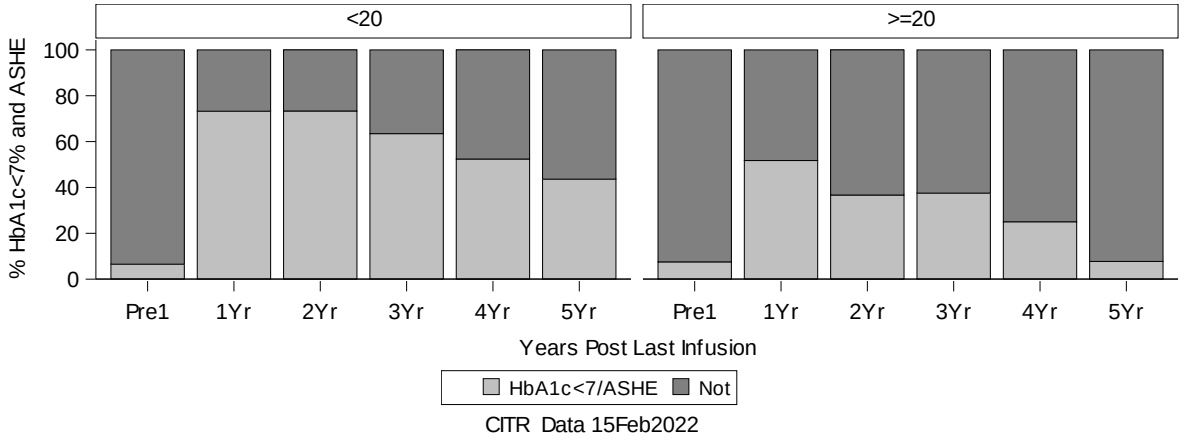


Exhibit 5 – 8C (continued)
Univariate Effects of Individual Variables (p<0.01) on Prevalence of HbA1c<7.0% and Absence of Severe Hypoglycemic Events Post Last Infusion among IAK Recipients

F. Endotoxin/kg recipient (p=0.0096)

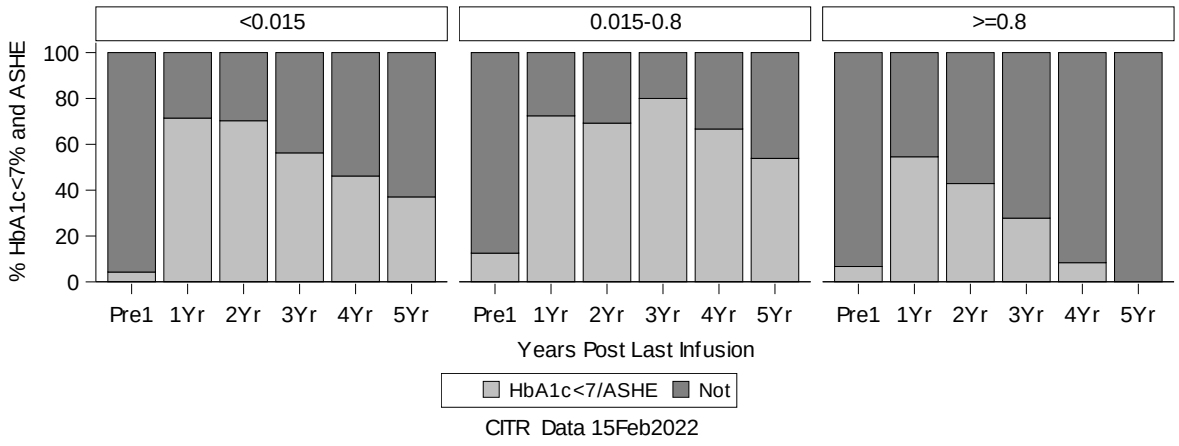


Exhibit 5 – 9

Insulin Dose (U/day) Post Last Infusion

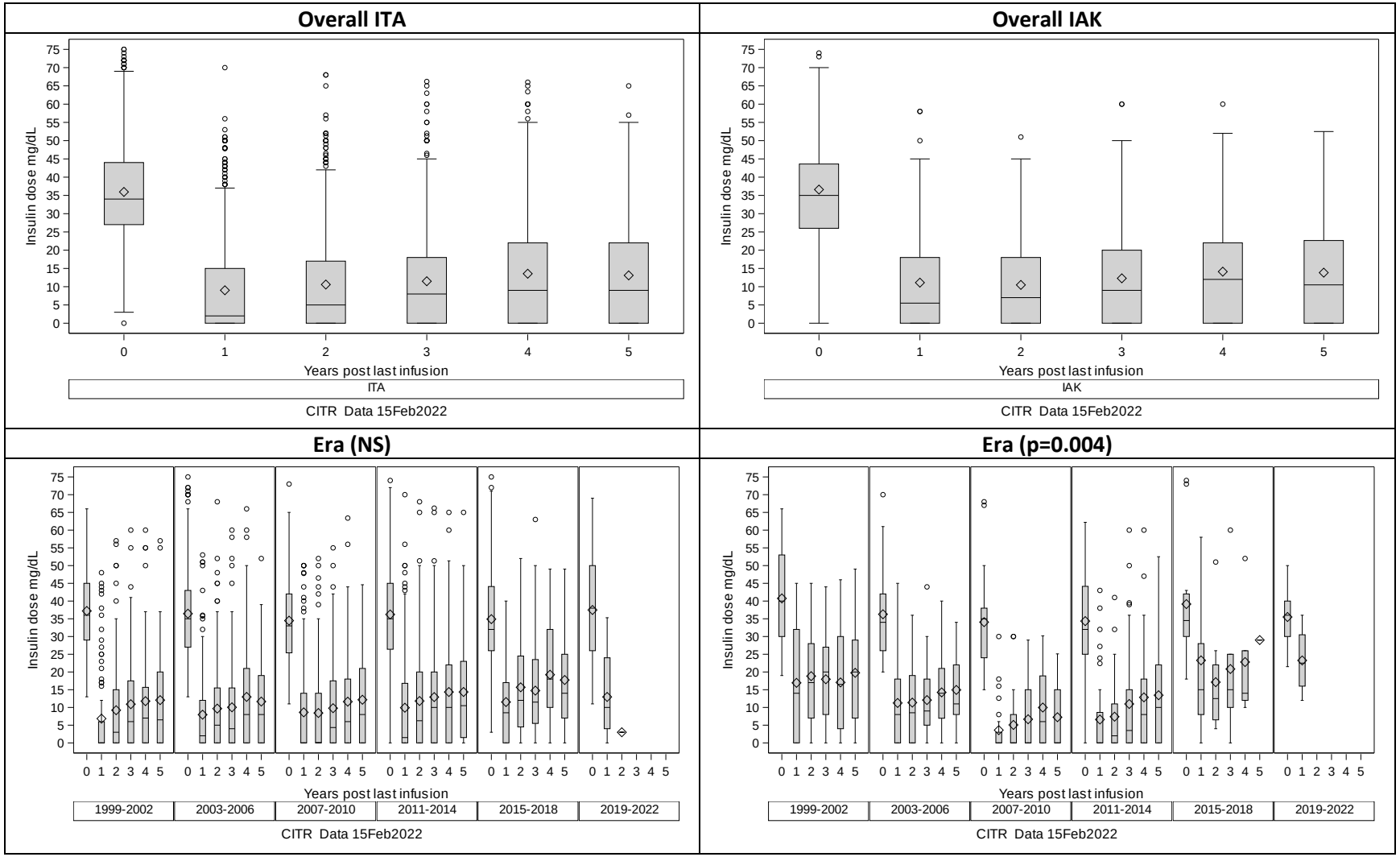


Exhibit 5 – 9 (continued)

Insulin Dose (U/day) Post Last Infusion

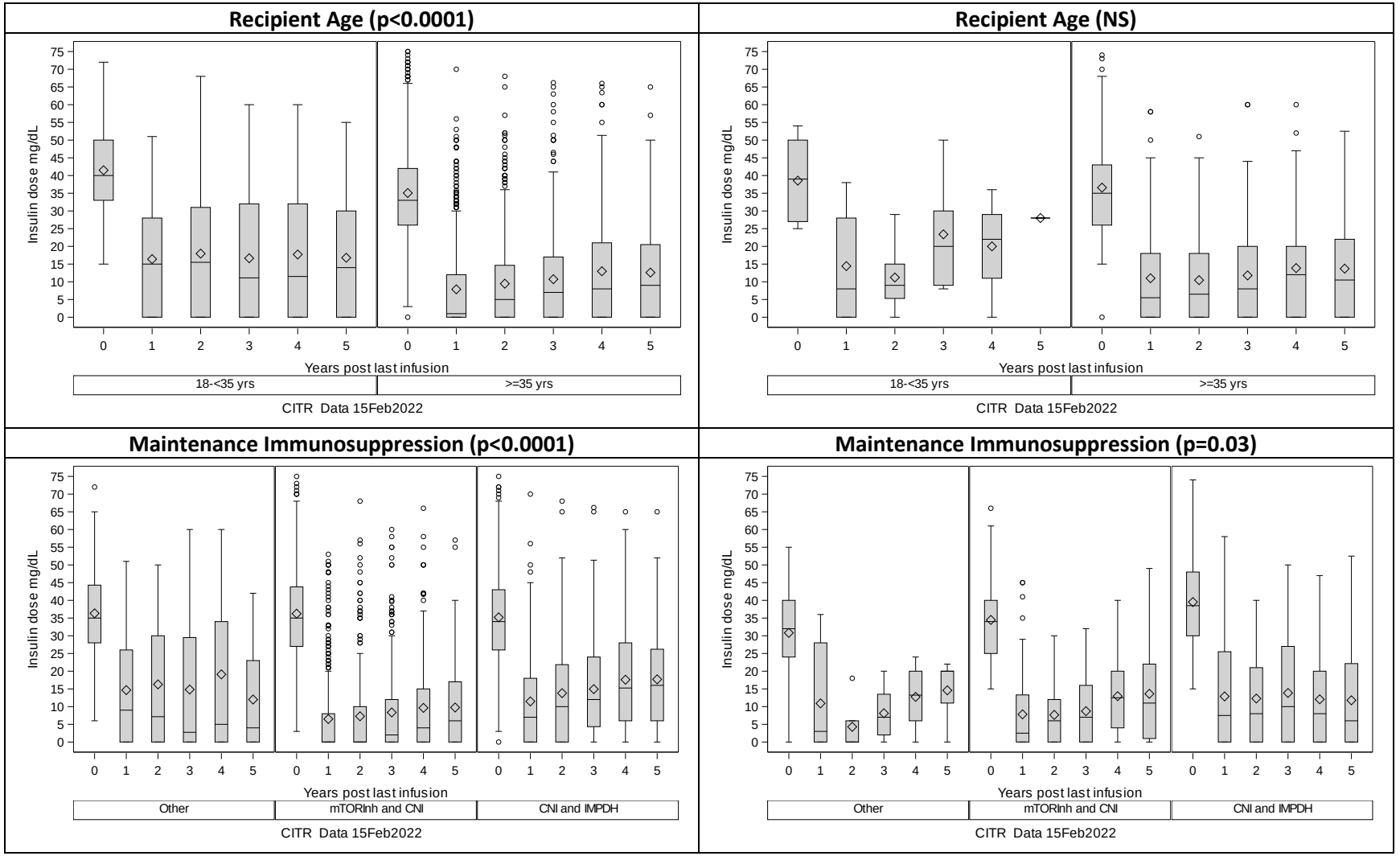


Exhibit 5 – 10

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

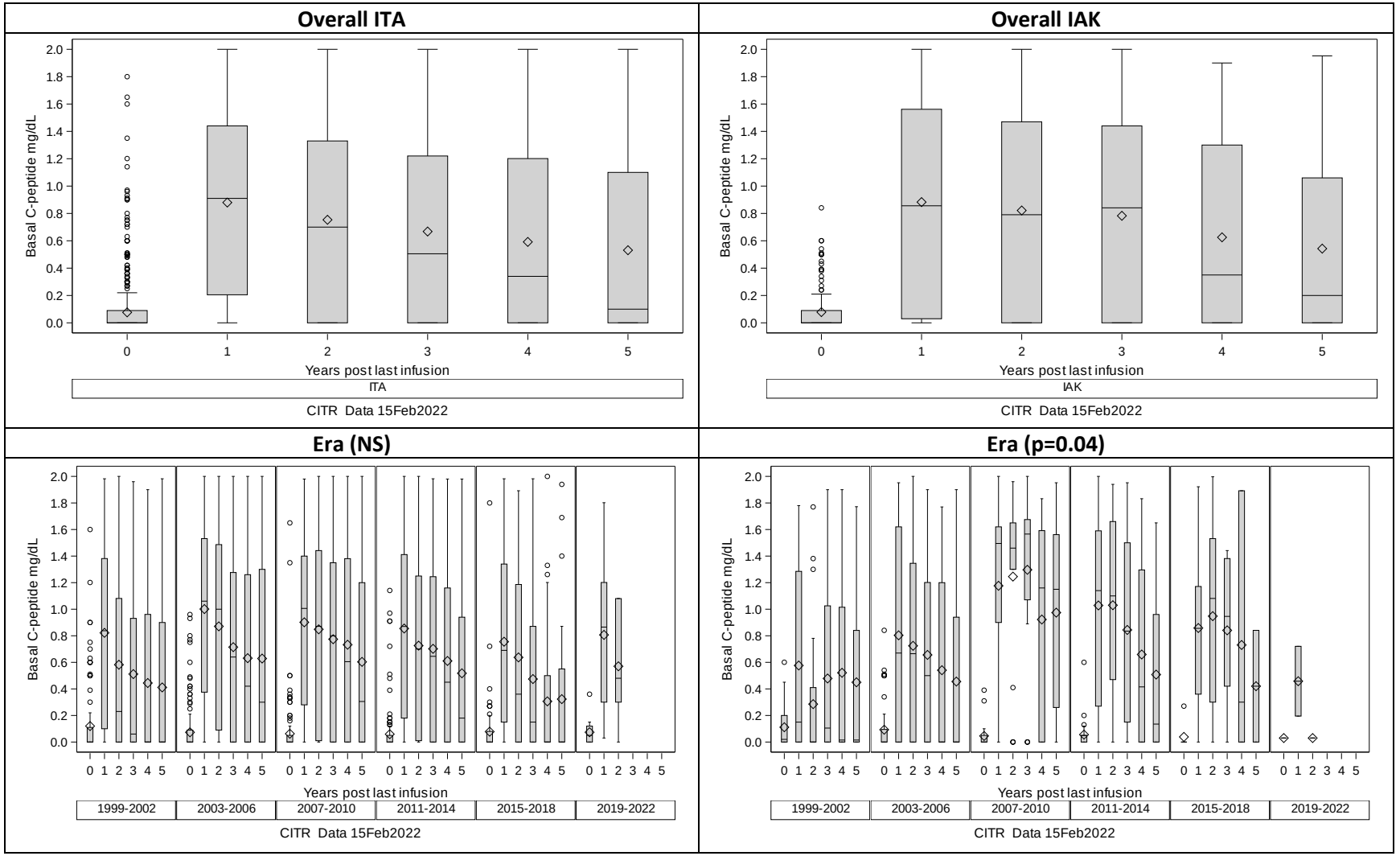


Exhibit 5 – 10 (continued)

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

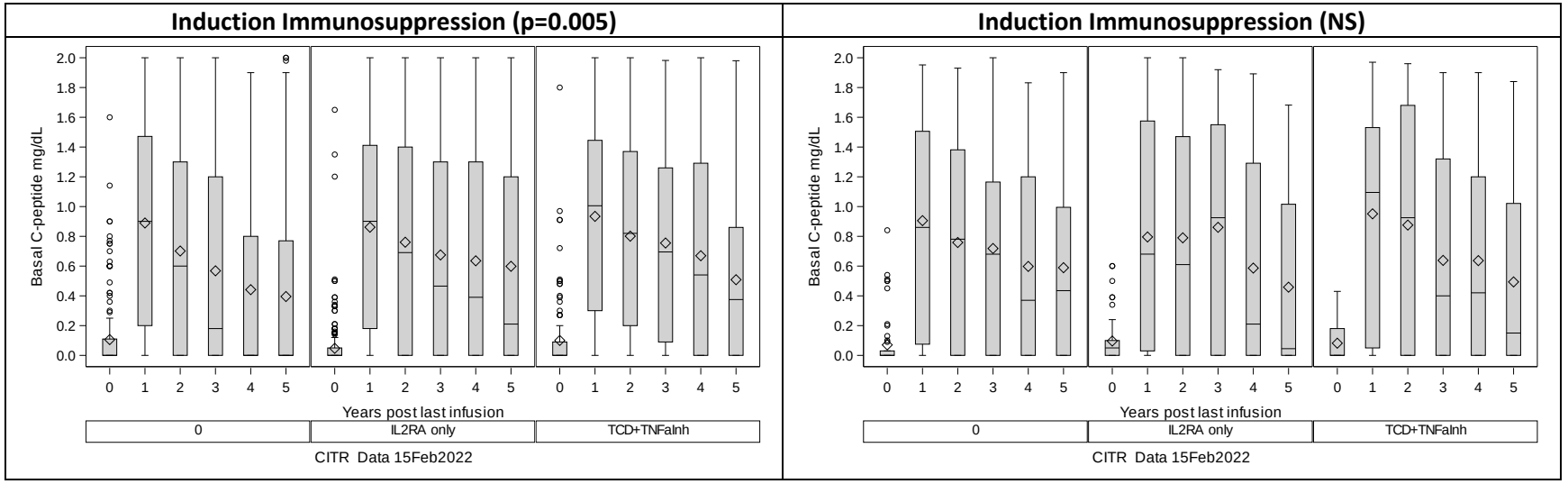


Exhibit 5 – 11

HbA1c (%) Post Last Infusion

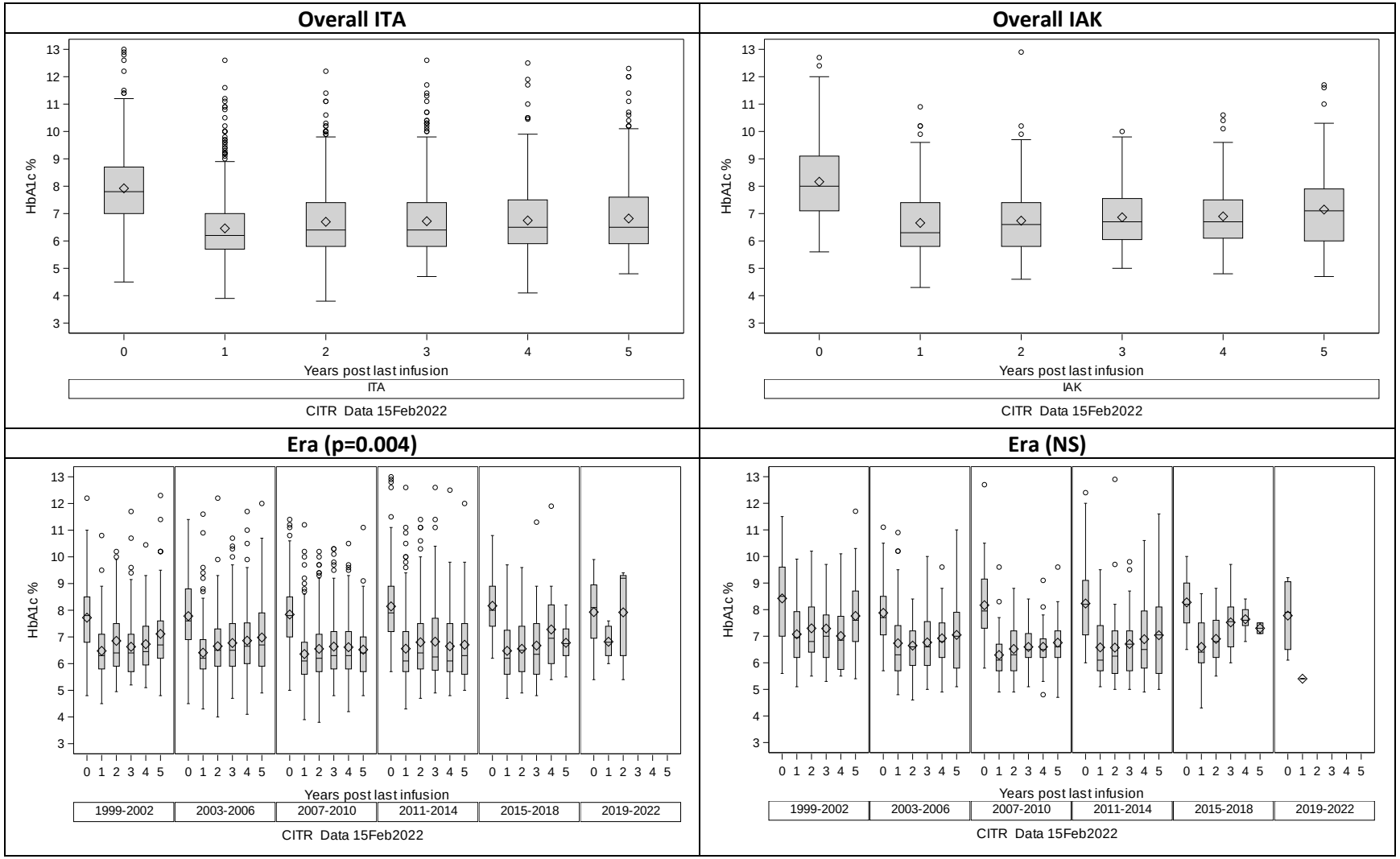
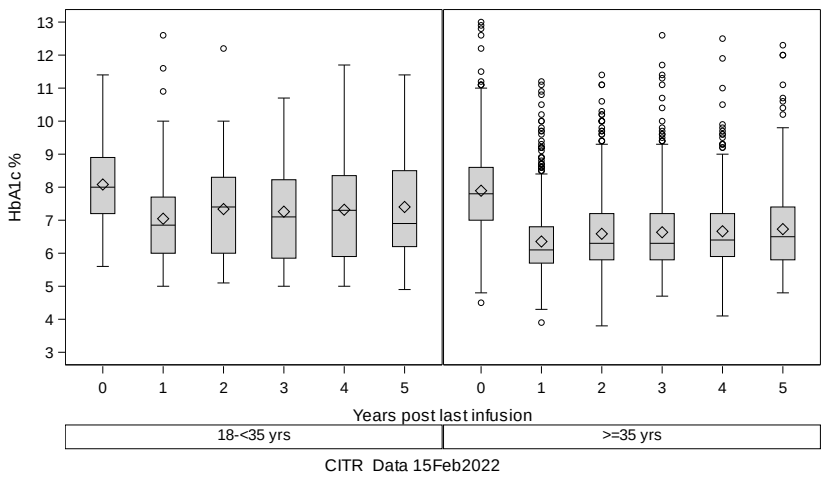
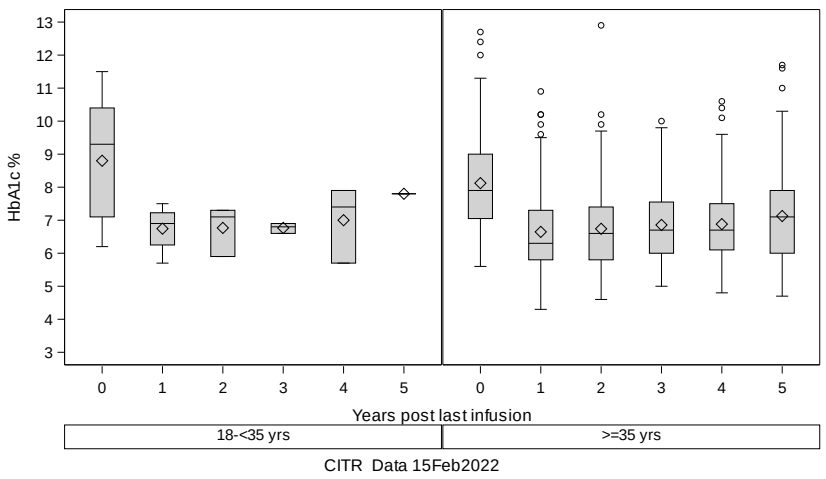


Exhibit 5 – 11 (continued)
HbA1c (%) Post Last Infusion

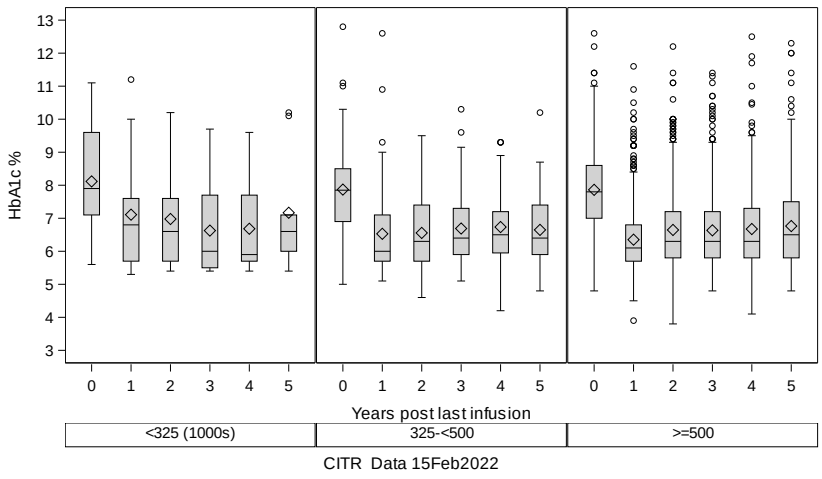
Recipient Age (p<0.0001)



Recipient Age (NS)



IEQs Infused (p=0.001)



IEQs Infused (NS)

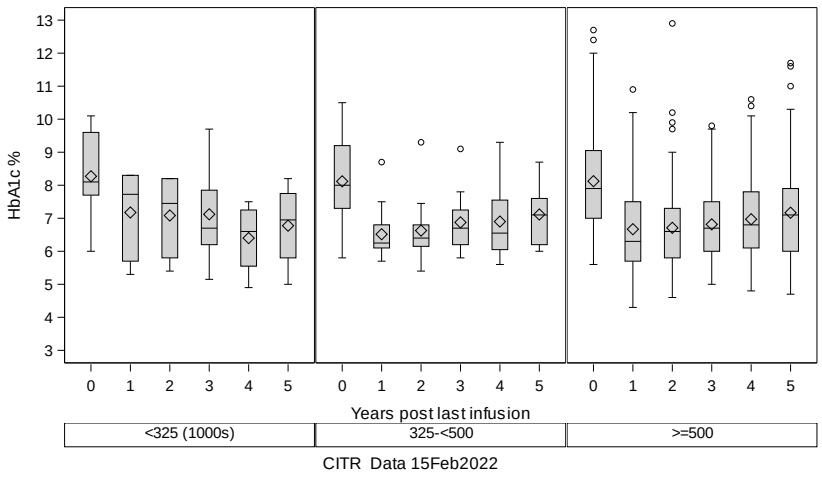


Exhibit 5 – 11 (continued)

HbA1c (%) Post Last Infusion

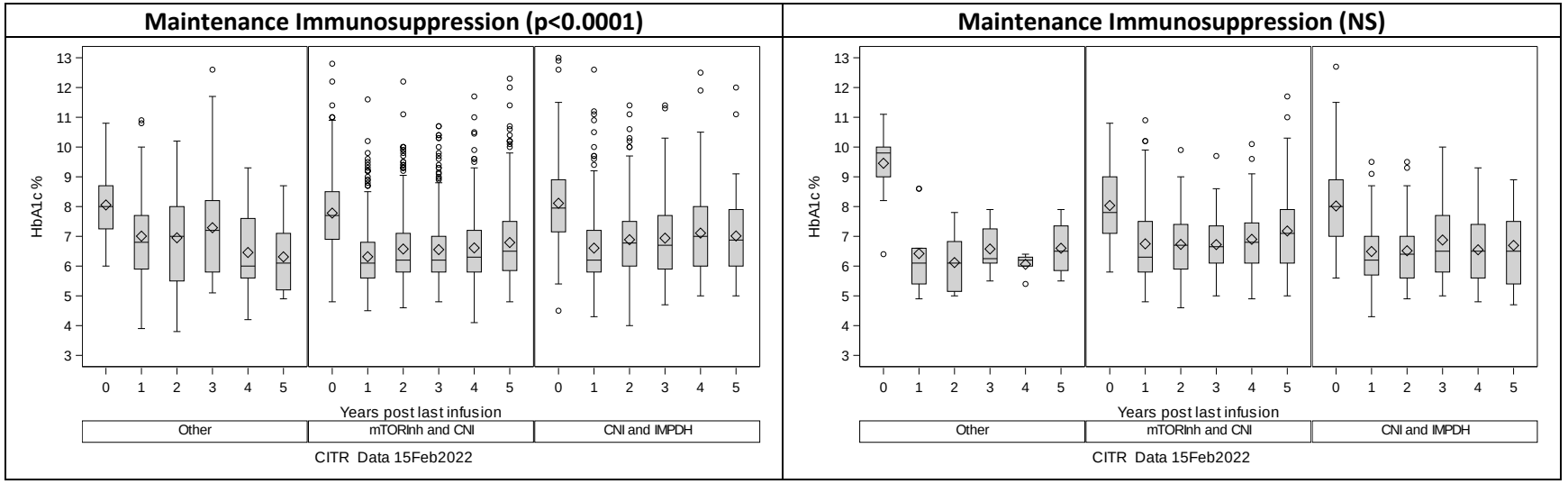


Exhibit 5 – 12

Fasting Blood Glucose (mg/dL) Post Last Infusion

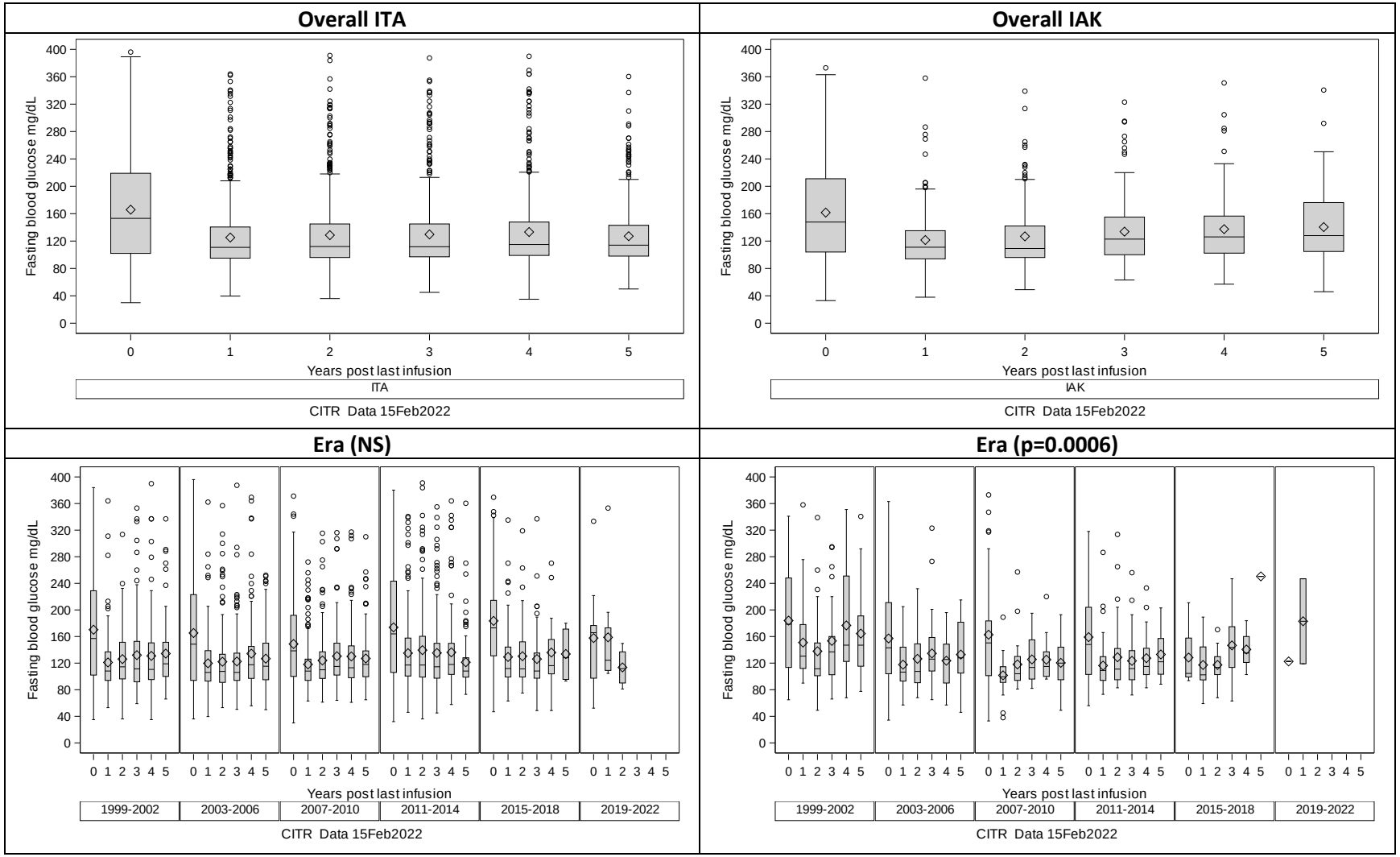


Exhibit 5 – 12 (continued)

Fasting Blood Glucose (mg/dL) Post Last Infusion

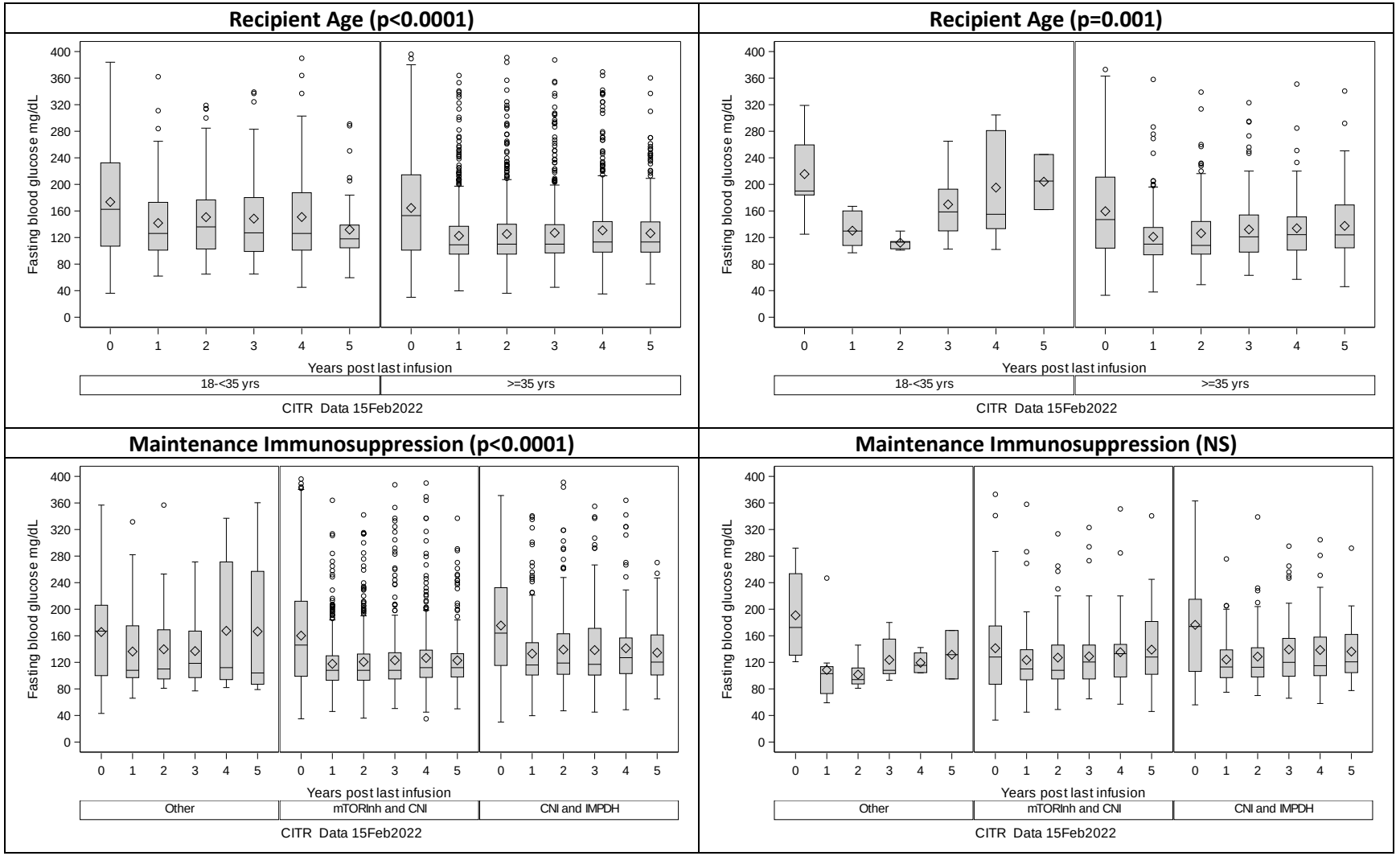


Exhibit 5 – 13
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion

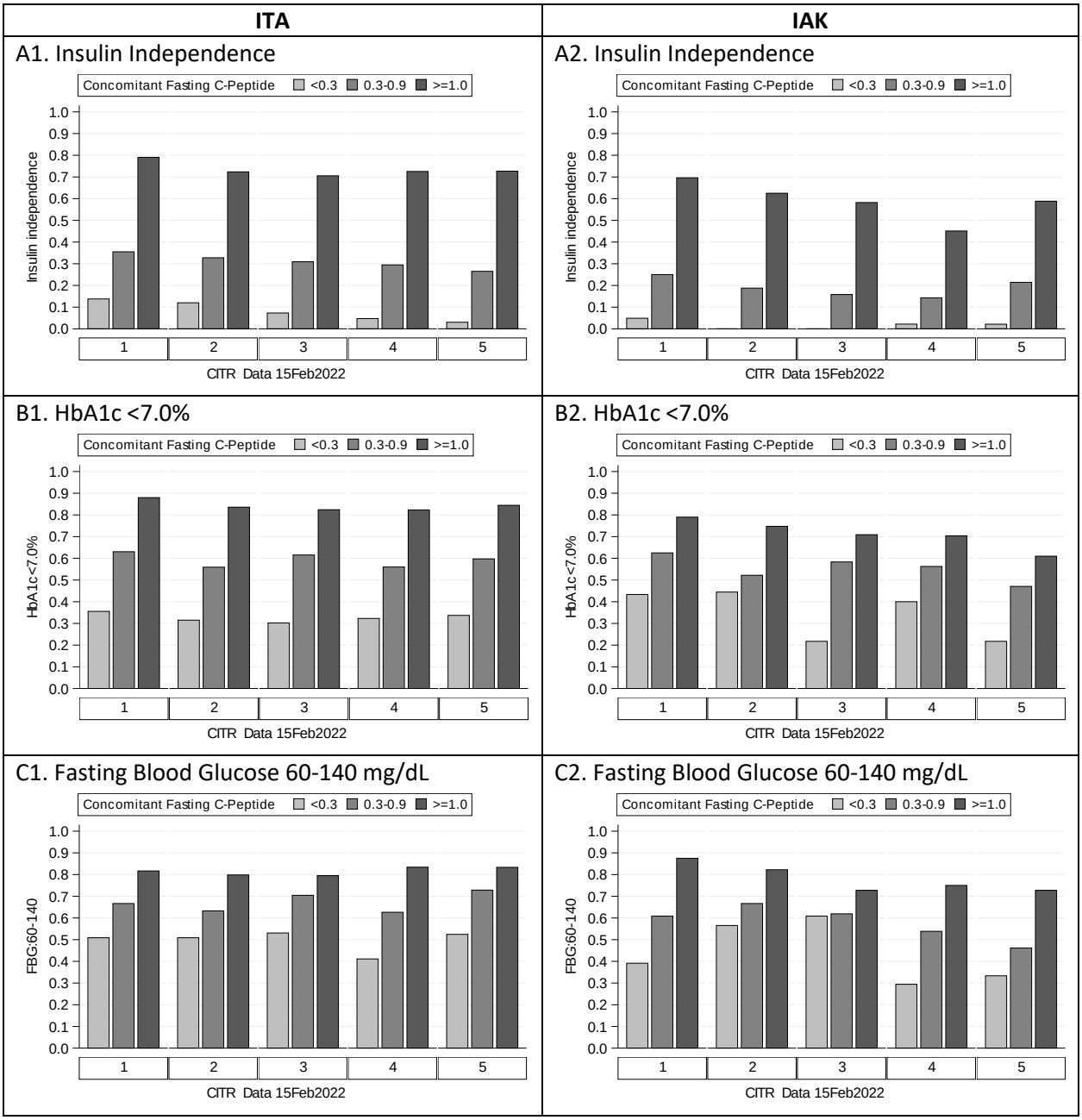
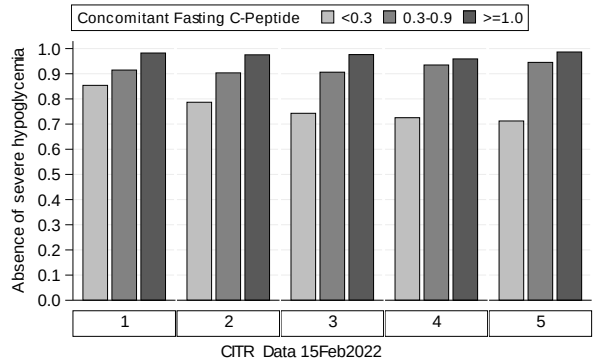
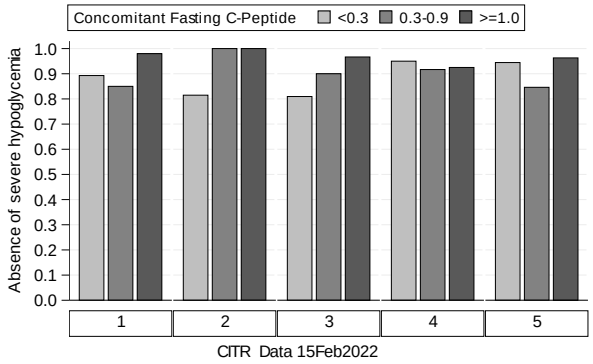


Exhibit 5 – 13 (continued)
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years 1-5 Post Last Infusion

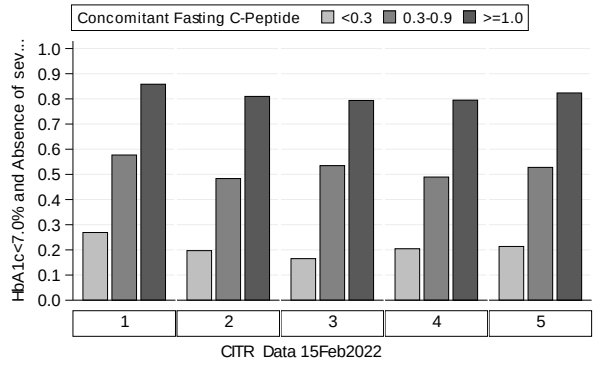
D1. Absence of Severe Hypoglycemic Events



D2. Absence of Severe Hypoglycemic Events



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



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

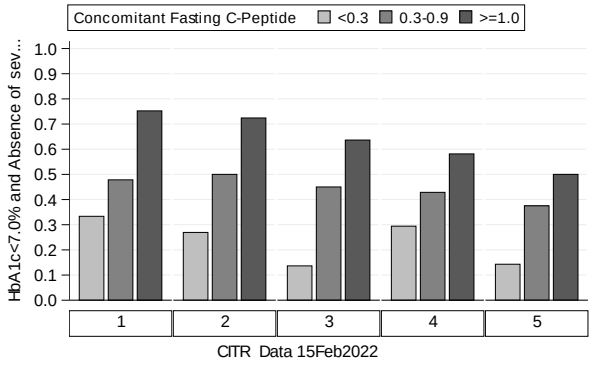
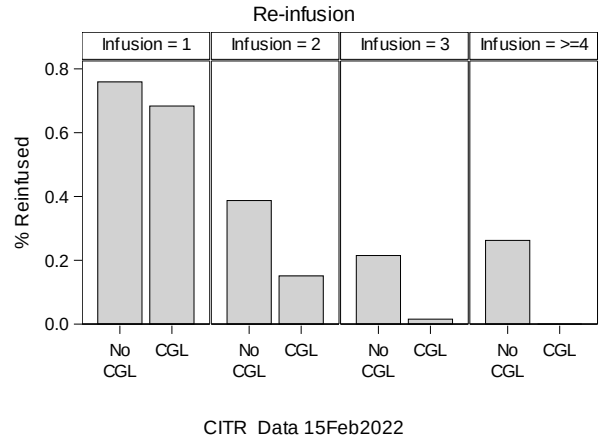


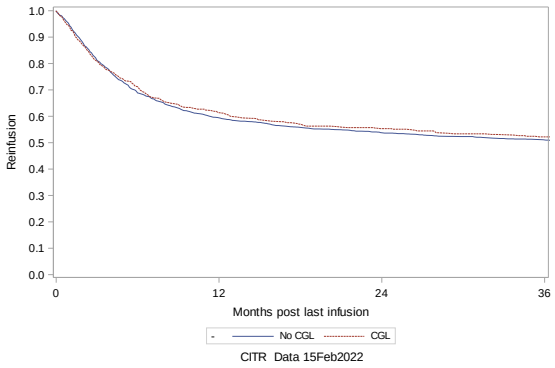
Exhibit 5 – 14

Re-Infusion

(after each infusion sequence)

A. By previous complete graft loss (CGL) (p=0.2)

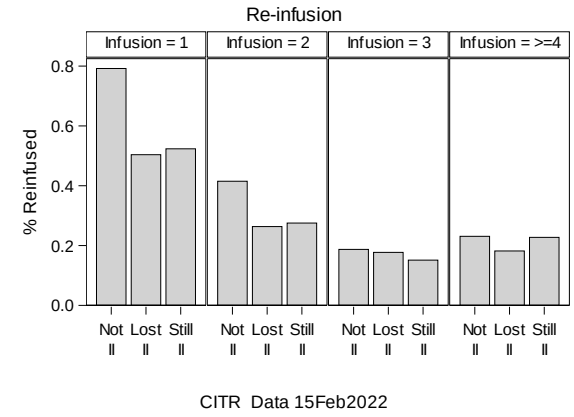


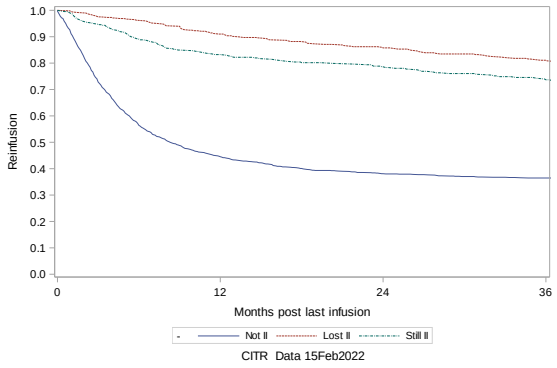


	Reinfusion		
	No	*Yes*	*Total*
	N	*N*	*N*
Infusion 1	335	926	1261
Infusion 2	605	321	926
Infusion 3	265	56	321
Infusion ≥4	56	16	72
All	1261	1319	2580

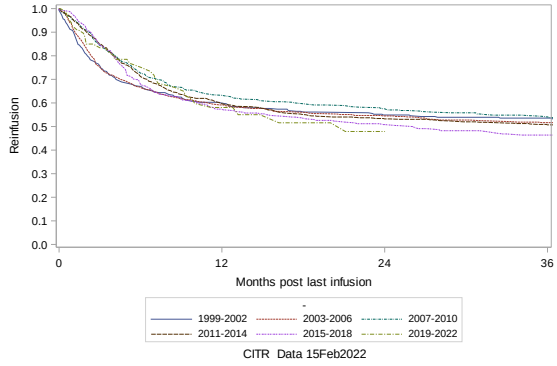
Exhibit 5 – 14 (continued)
Re-Infusion
(after each infusion sequence)

B. By concurrent insulin independence (p<0.0001)

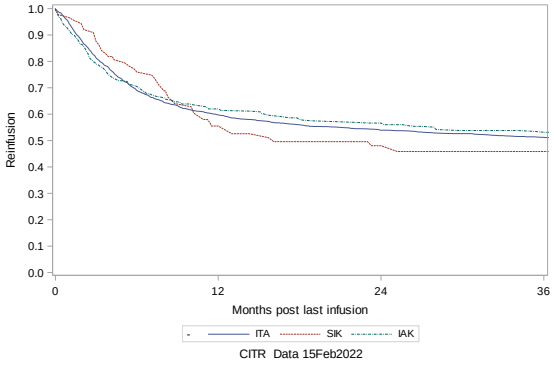




C. By Era (p=0.4)



D. By Transplant Type (p=0.6)



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 typically rises after islet transplantation and then levels off (Exhibit 6-1A). ALT remained elevated over 5 years post-last infusion in recipients who received induction immunosuppression with IL2A-alone while recipients who received other regimens gradually returned to baseline levels ($p=0.0002$). Also, ALT levels decreased over 5 years post-last infusion among recipients who received maintenance immunosuppression with CNI+IMPDH, but remained elevated among those who received other regimens ($p=0.0005$).

Similar trends with respect to rise after islet transplantation and importance of immunosuppression regimens are observed for AST (Exhibit 6-1B). AST was significantly higher in IAK than ITA ($p=0.008$).

There is very little change in alkaline phosphatase in follow-up after islet transplantation (Exhibit 6-2); however, across eras there has been a significant decline in initial – and hence follow-up – levels ($p<0.0001$). Initial levels are higher in IAK compared to ITA, and these levels persist relatively unchanged 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). None of the factors analyzed showed a significant effect on total bilirubin.

There is a mild, not statistically significant, decline in HDL cholesterol over the years following islet transplantation in both ITA and IAK, which was consistent across the eras (Exihibit 6-4). The decline over follow-up time was less pronounced in subjects who received induction immunosuppression with TCD+TNFaInh ($p=0.0002$).

In the early eras, a decline in LDL cholesterol in follow-up was noted (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 4 and 5 years post-last infusion ($p<0.0001$). 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 ($p=0.002$).

Triglycerides rose somewhat following islet transplantation (Exhibit 6-6). Initial levels were lower in ITA than IAK, but rose such that levels were similar between transplant types post transplant. There were no net effects of age or IEQ infused, but levels were higher among recipients managed with both mTOR inhibitors and calcineurin inhibitors compared to other maintenance immunosuppression regimens (p=0.0001), and for induction with IL2RA alone or TCD+TNFa inhibition compared to other induction immunosuppression regimens (p=0.001).

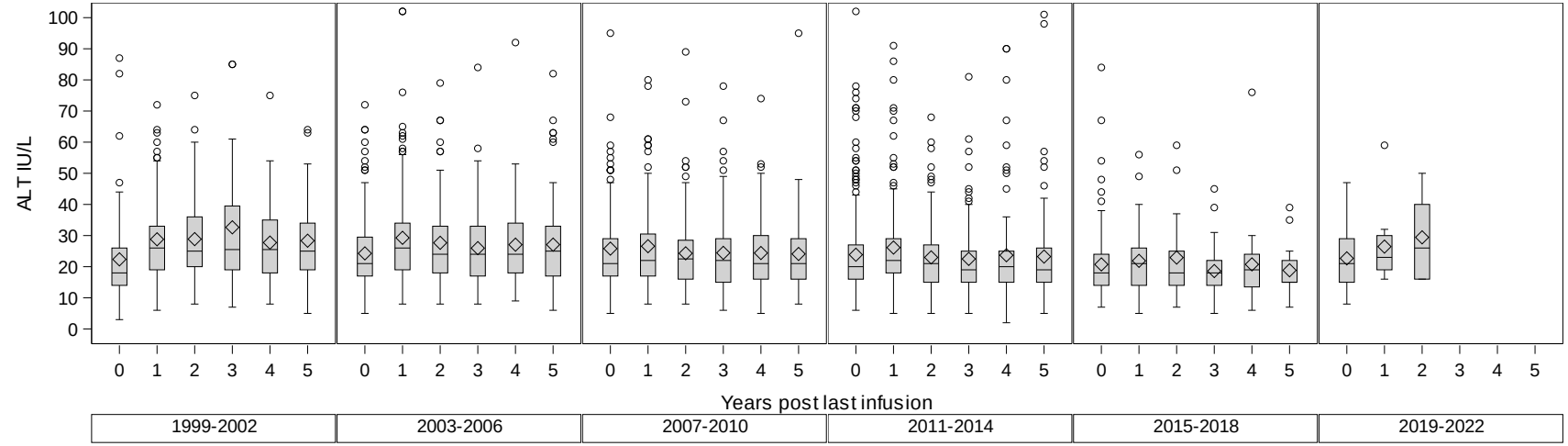
Total cholesterol was generally higher at baseline and declined in follow-up after islet transplantation in early eras, but in recent eras has increased over follow-up (Exhibit 6-7). Induction with TCD+TNFa inhibition was associated with significantly less decline over follow-up time (p<0.0001).

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=0.0005). Recipients who received the fewest IEQ's infused showed the greatest increase (p=0.0001).

The decline in CKD-Epi eGFR after islet transplantation is both statistically significant and clinically important (Exhibit 6-9). IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate (p<0.0001). Initial levels were also lower in recipients age ≥ 35 and declined at 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=0.002).

Exhibit 6 – 1A
ALT (IU/L)

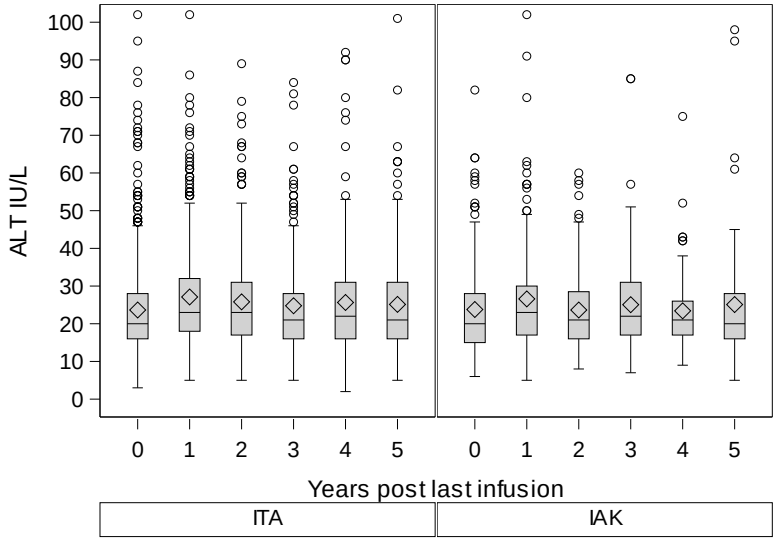
A. Era (p=0.002)



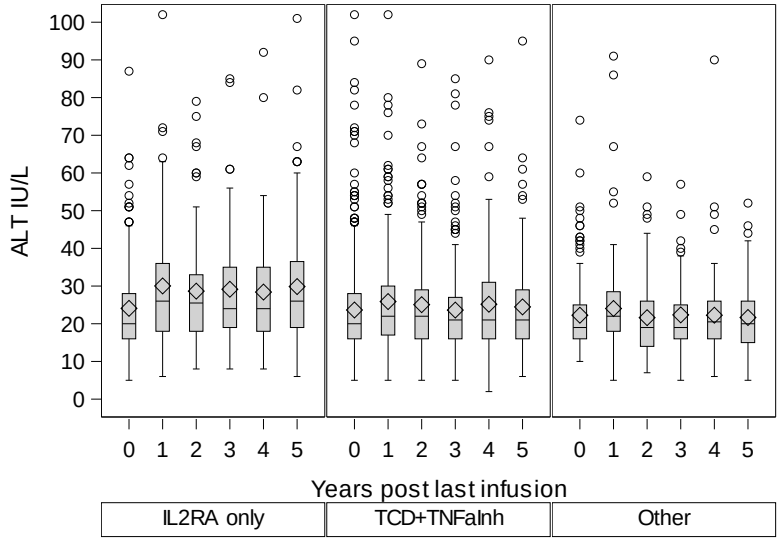
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**
Means																																
22	29	29	33	28	28	24	29	28	26	27	27	26	27	24	24	24	24	24	26	23	22	24	23	21	22	23	19	21	19	23	26	29
S.E.																																
1	1	2	3	2	2	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	2	2	1	1	3	1	3	3	2	4	5

Exhibit 6 – 1A (continued)
ALT (IU/L)

B. Transplant Type (p=NS)



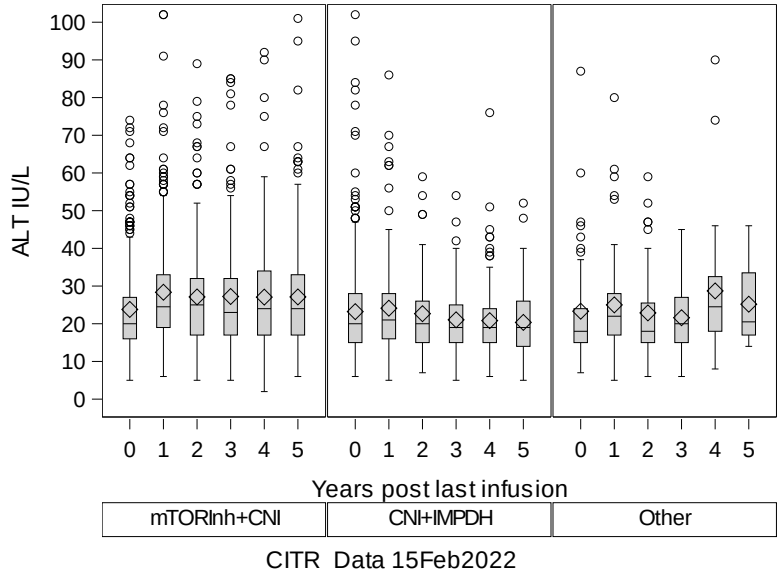
C. Induction Immunosuppression (p=0.0002)



ITA						IAK						IL2RA only						TCD+TNFaInh						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																													
24	27	26	25	26	25	24	27	24	25	23	25	24	30	29	29	28	30	24	26	25	24	25	24	22	24	22	22	22	22
S.E.																													
0	1	1	1	1	1	1	1	1	1	1	2	1	1	2	2	2	2	1	1	1	1	1	1	1	1	1	1	1	1

Exhibit 6 – 1A (continued)
ALT (IU/L)

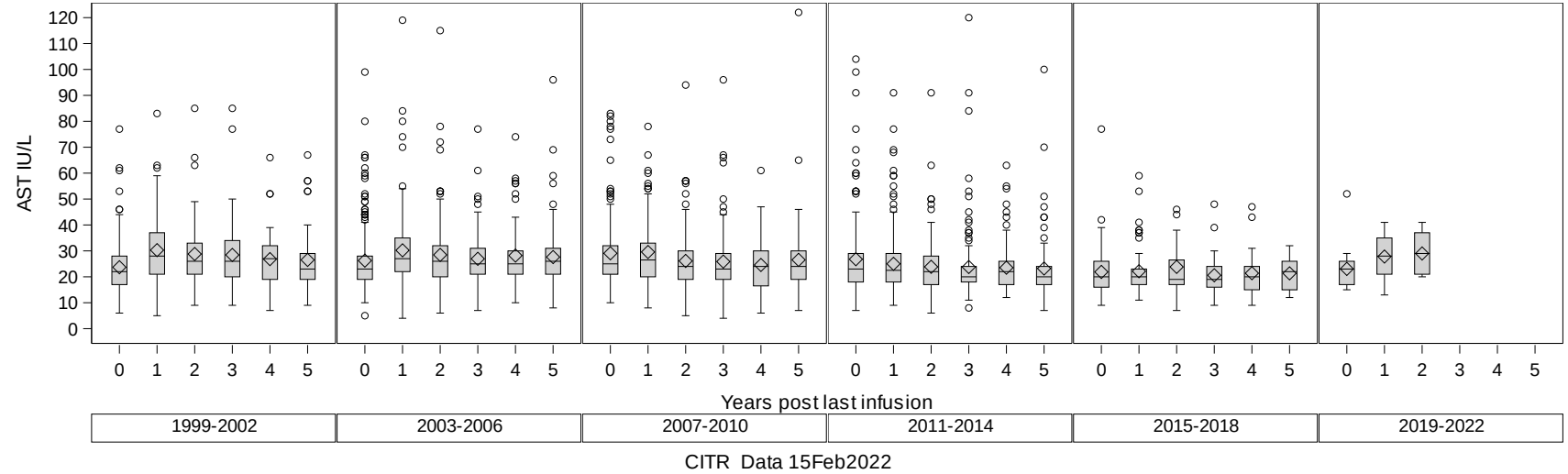
D. Maintenance Immunosuppression (p=0.0005)



mTORInh+CNI						CNI+IMPDH						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																	
24	28	27	27	27	27	23	24	23	21	21	20	23	25	23	22	29	25
S.E.																	
1	1	1	1	1	1	1	1	1	1	1	1	2	2	2	1	4	3

Exhibit 6 – 1B
AST (IU/L)

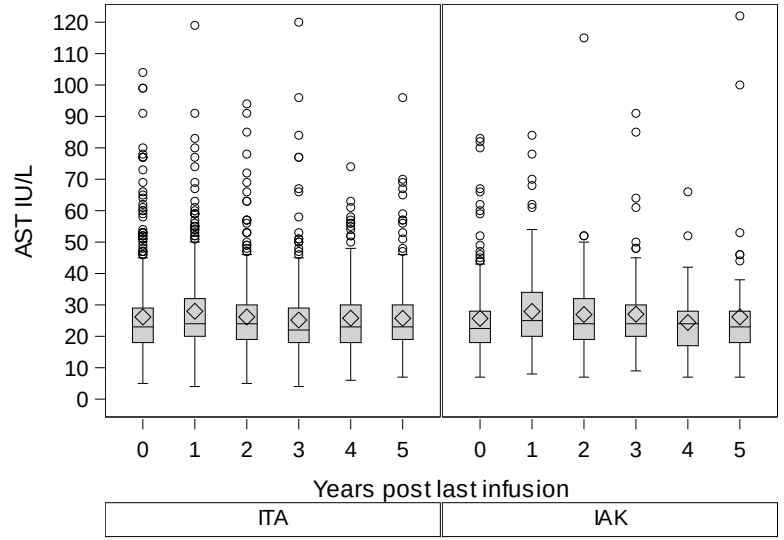
A. Era (p=0.001)



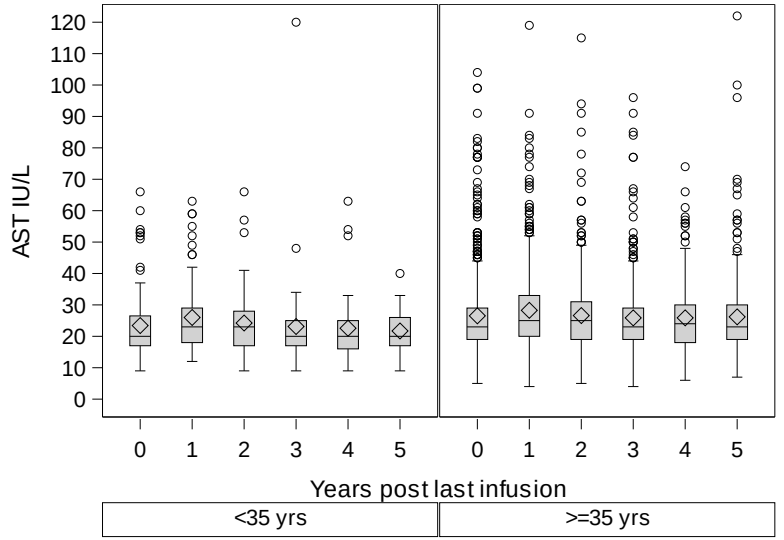
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Means																																
24	30	29	28	27	27	26	30	28	27	28	28	29	30	26	26	25	27	27	25	24	24	24	23	22	22	24	21	21	21	23	28	29
S.E.																																
1	1	1	2	1	2	1	1	1	1	2	1	1	2	1	1	1	2	1	1	1	1	1	1	1	1	2	1	2	2	2	2	3

Exhibit 6 – 1B (continued)
AST (IU/L)

B. Transplant Type (p=NS)



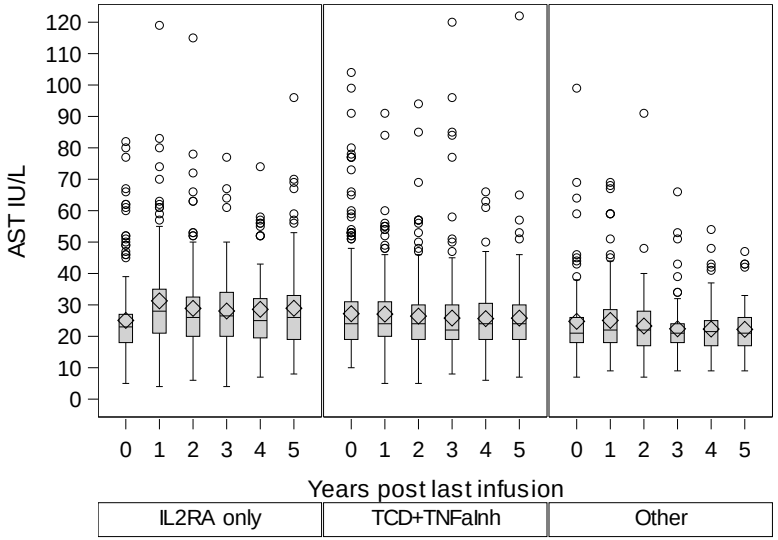
C. Recipient Age (p=0.009)



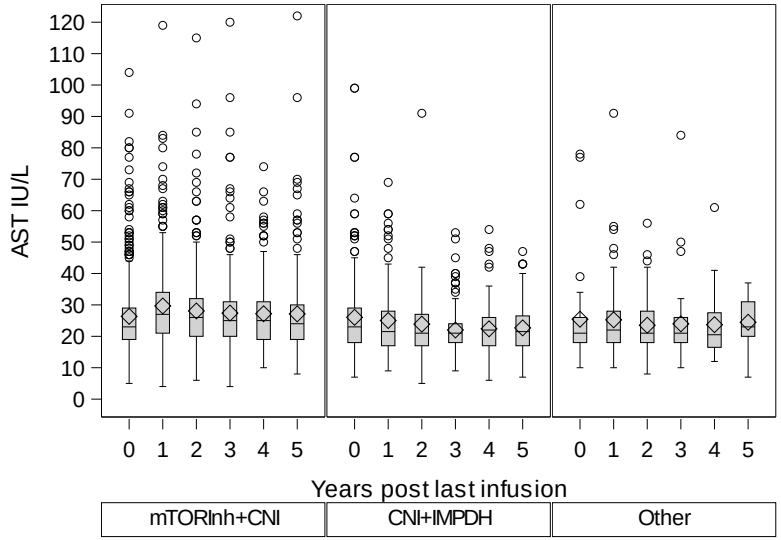
ITA						IAK						<35 Years						≥35 Years					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Means																							
26	28	26	25	26	26	26	28	27	27	24	26	23	26	24	23	23	22	27	28	27	26	26	26	23	26	24	23	23	22
S.E.																							
1	1	1	1	1	1	1	1	1	1	1	2	1	1	1	2	2	1	1	1	1	1	1	1	1	1	1	2	2	1

Exhibit 6 – 1B (continued)
AST (IU/L)

D. Induction Immunosuppression (p=0.0002)



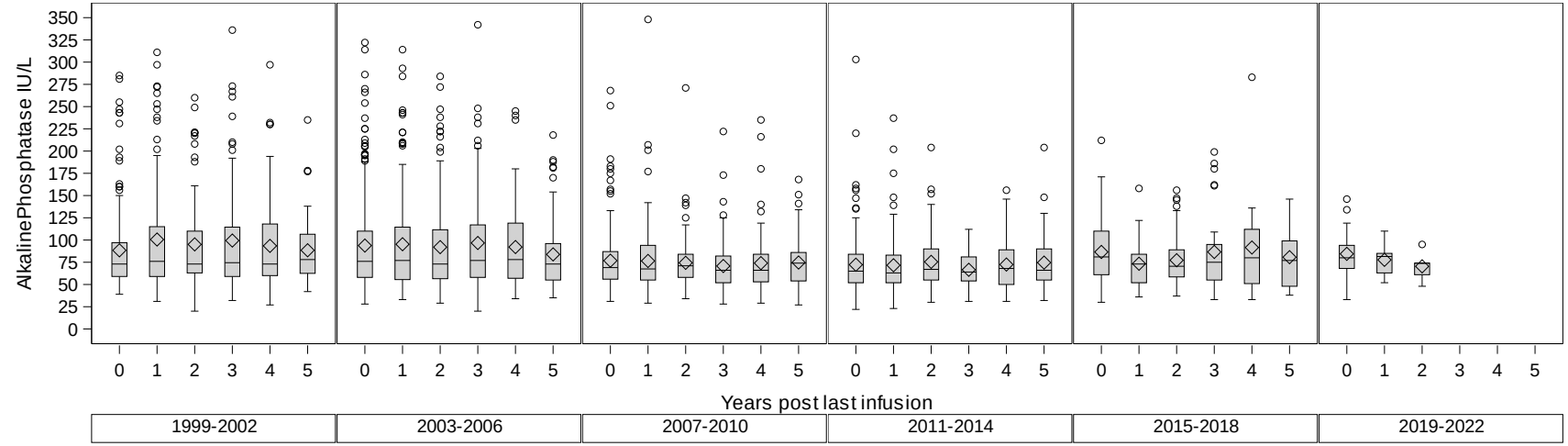
E. Maintenance Immunosuppression (p=0.0002)



IL2RA only						TCD+TNFaInh						Other						mTORInh+CNI						CNI+IMPDH						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																																			
25	31	29	28	29	29	27	27	26	26	26	26	25	25	23	22	22	22	26	30	28	27	27	27	26	25	24	22	22	23	25	25	24	24	24	24
S.E.																																			
1	1	1	1	2	2	1	1	1	1	1	1	2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	2	2	1	2	2	2

Exhibit 6 – 2
Alkaline Phosphatase (IU/L)

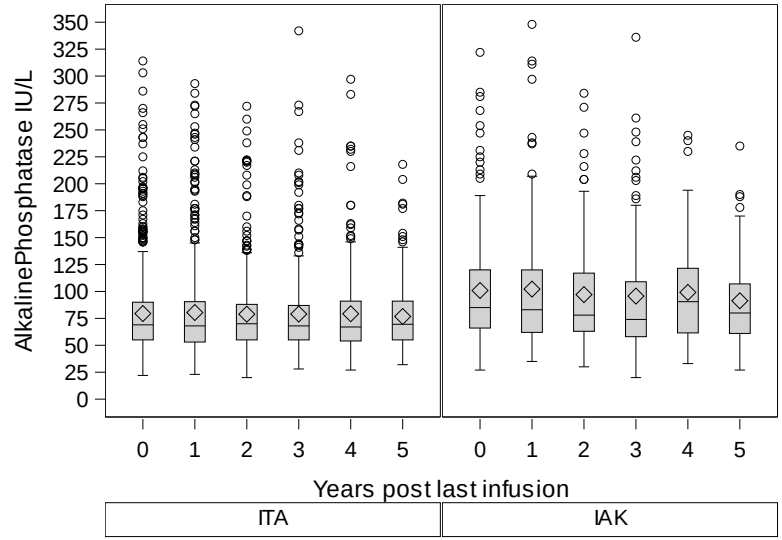
A. Era (p<0.0001)



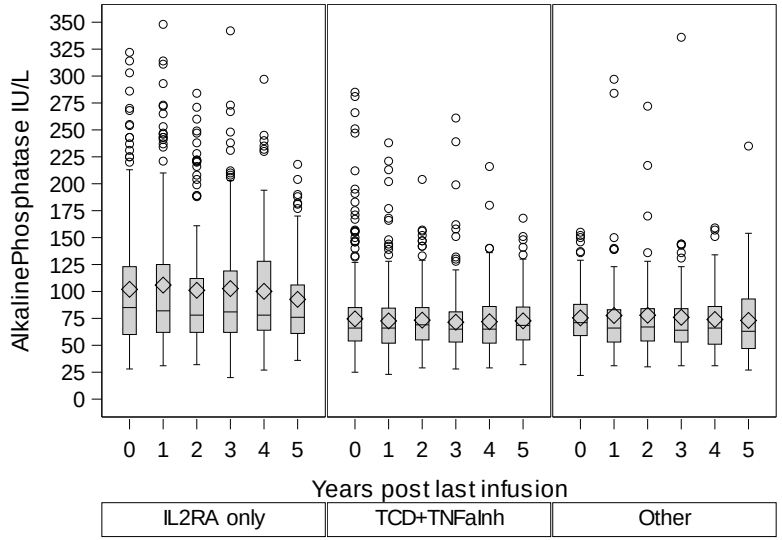
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Means																																
88	101	95	99	93	88	94	95	92	97	92	84	77	76	74	71	74	75	72	72	75	67	72	75	87	73	77	87	92	81	84	78	70
S.E.																																
4	6	7	8	7	6	4	4	5	5	5	5	3	3	3	3	4	4	2	3	3	2	3	4	4	3	4	8	13	12	6	5	8

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

B. Transplant Type (p<0.0001)



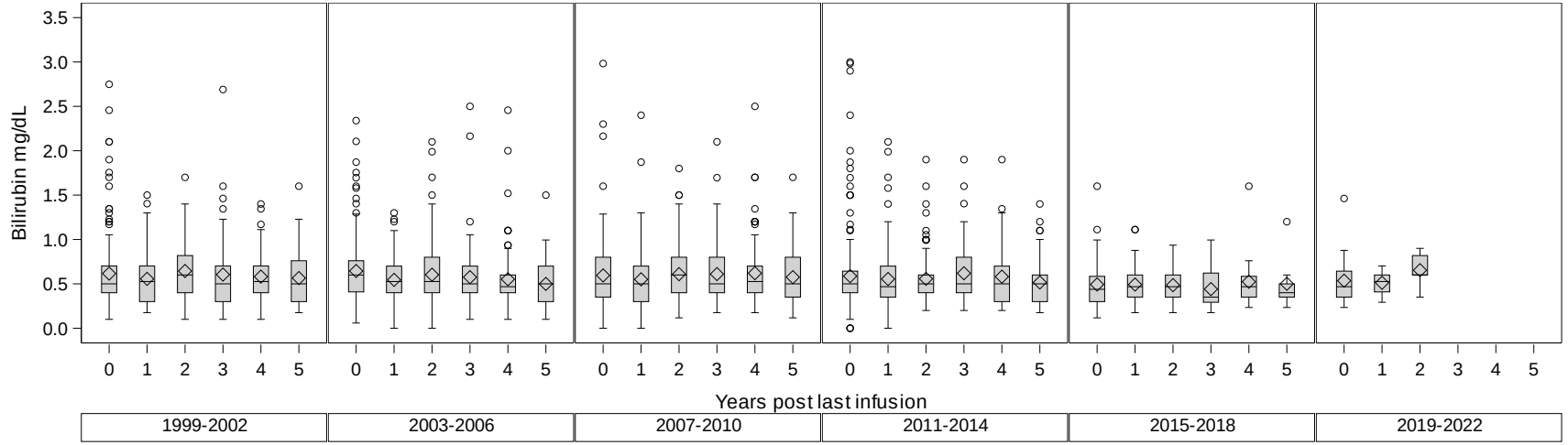
C. Induction Immunosuppression (p<0.0001)



ITA						IAK						IL2RA only						TCD+TNFaInh						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																													
79	80	79	79	79	77	101	102	97	96	99	91	102	106	101	103	100	93	75	73	73	71	72	73	75	78	78	76	74	73
S.E.																													
2	2	2	2	3	2	4	5	5	6	6	6	4	5	5	6	6	6	2	2	2	2	2	2	3	5	6	6	5	8

Exhibit 6 – 3
Total Bilirubin

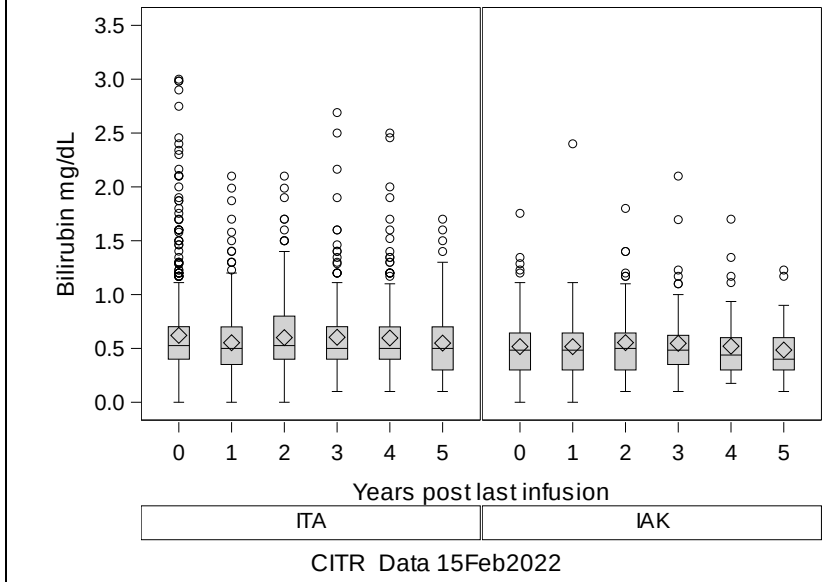
A. Era (p=NS)



1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Means																																
0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.6	0.6	0.6	0.5	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.5	0.4	0.5	0.5	0.5	0.5	0.7
S.E.																																
0.0	0.0	0.0	0.1	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.1

Exhibit 6 – 3 (continued)
Total Bilirubin

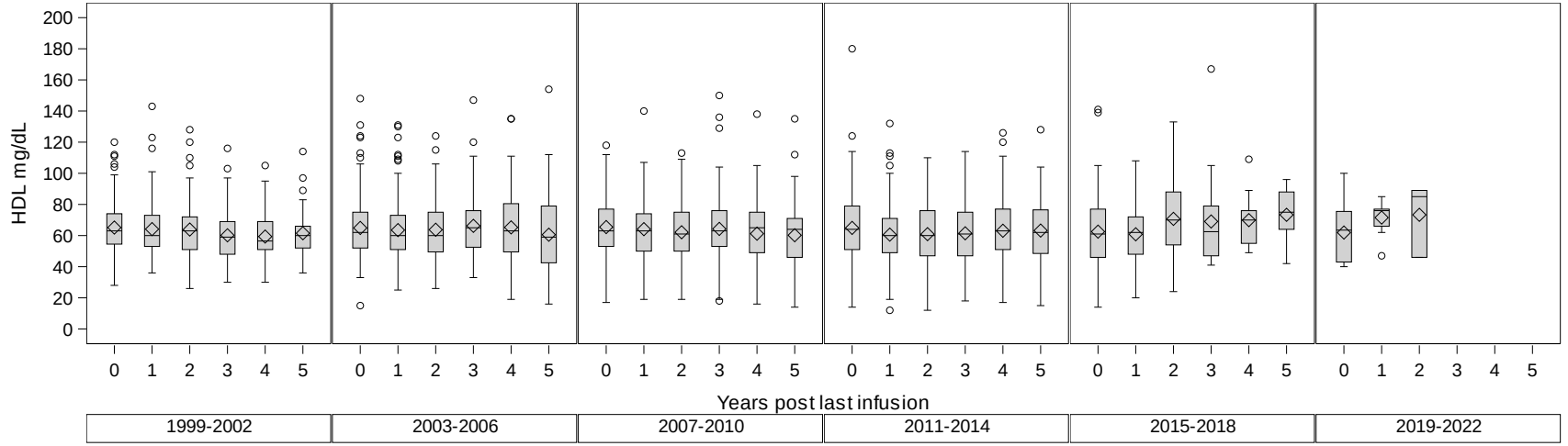
B. Transplant Type (p=NS)



ITA						IAK					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means											
0.6	0.6	0.6	0.6	0.6	0.5	0.5	0.5	0.6	0.5	0.5	0.5
S.E.											
0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Exhibit 6 – 4
HDL Cholesterol (mg/dL)

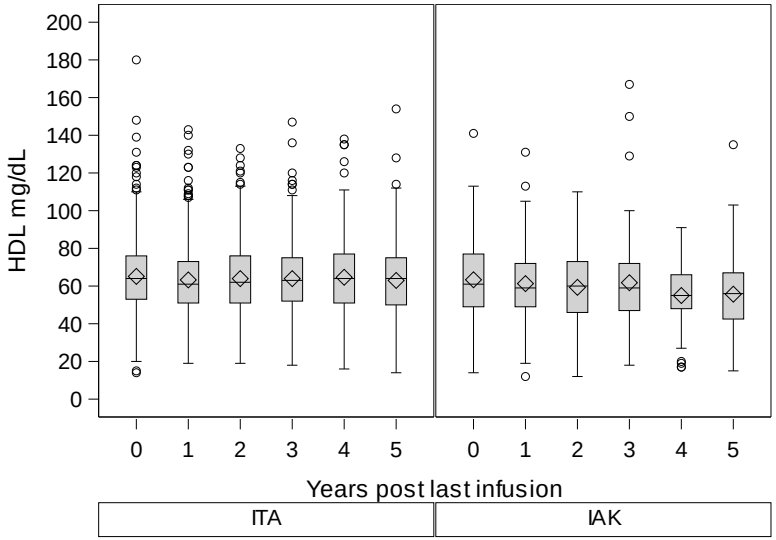
A. Era (p=NS)



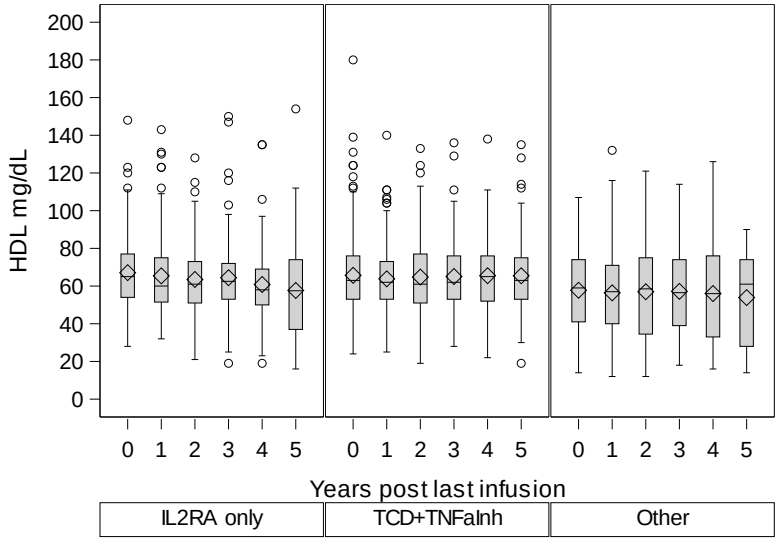
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**
Means																																
65	64	64	60	59	61	65	64	64	66	65	61	65	64	62	64	61	60	65	61	61	61	63	63	63	61	71	69	70	73	62	72	73
S.E.																																
1	2	2	2	2	2	1	2	2	2	3	3	1	2	2	2	2	3	1	2	2	2	2	3	3	3	4	7	5	8	4	4	14

Exhibit 6 – 4 (continued)
HDL Cholesterol (mg/dL)

B. Transplant Type (p=NS)



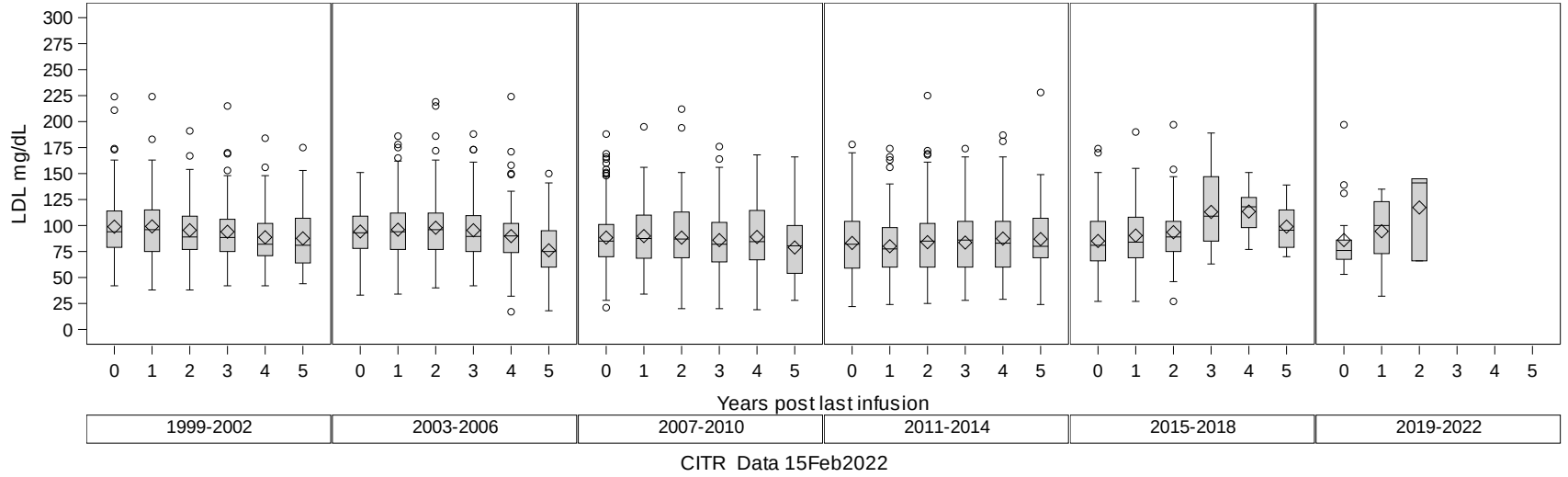
C. Induction Immunosuppression (p=0.0002)



ITA						IAK						IL2RA only						TCD+TNFaInh						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																													
65	63	64	64	65	63	63	61	59	62	55	56	67	65	63	64	61	58	66	64	65	65	65	65	58	56	57	57	56	54
S.E.																													
1	1	1	1	1	1	2	2	2	3	2	3	1	2	2	2	2	3	1	1	1	1	1	2	2	3	3	3	3	4

Exhibit 6 – 5
LDL Cholesterol (mg/dL)

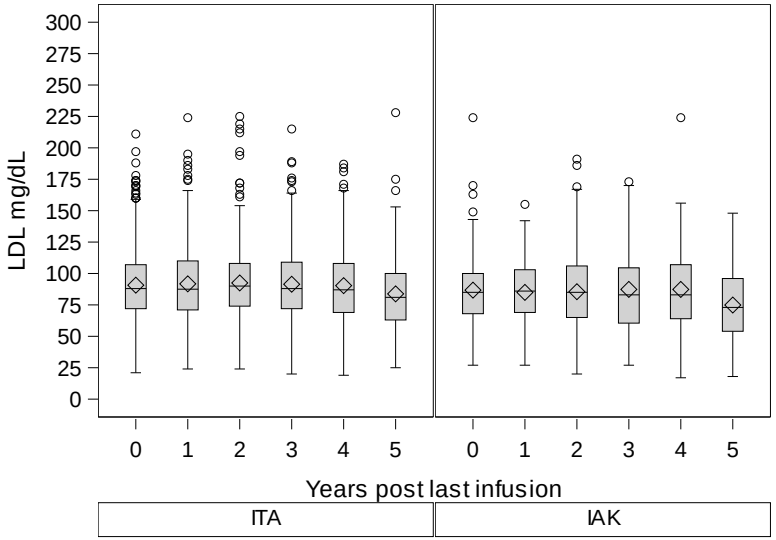
A. Era (p<0.0001)



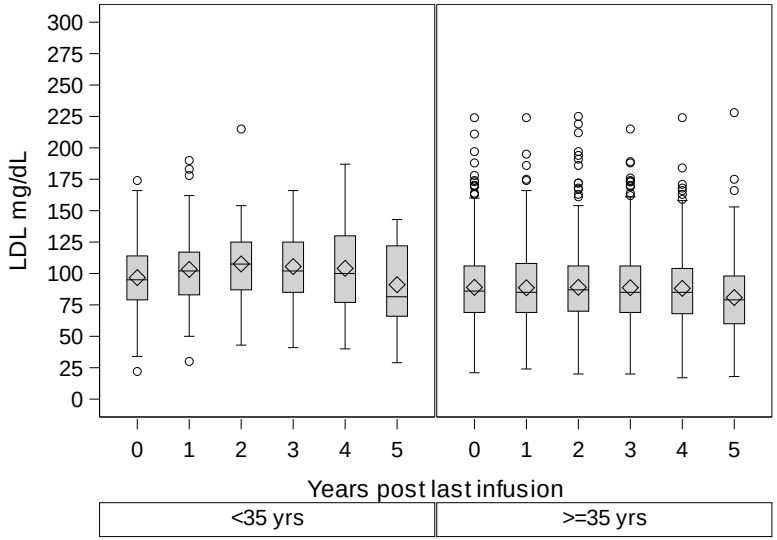
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Mean																																
99	99	96	94	89	88	94	96	98	95	90	76	88	90	88	86	89	79	83	80	84	84	87	87	85	90	94	113	113	99	86	94	117
S.E.																																
3	3	3	3	4	4	2	2	3	3	3	3	2	2	3	3	4	4	2	2	3	3	4	4	4	5	6	8	6	10	8	12	26

Exhibit 6 – 5 (continued)
LDL Cholesterol (mg/dL)

B. Transplant Type (p=NS)



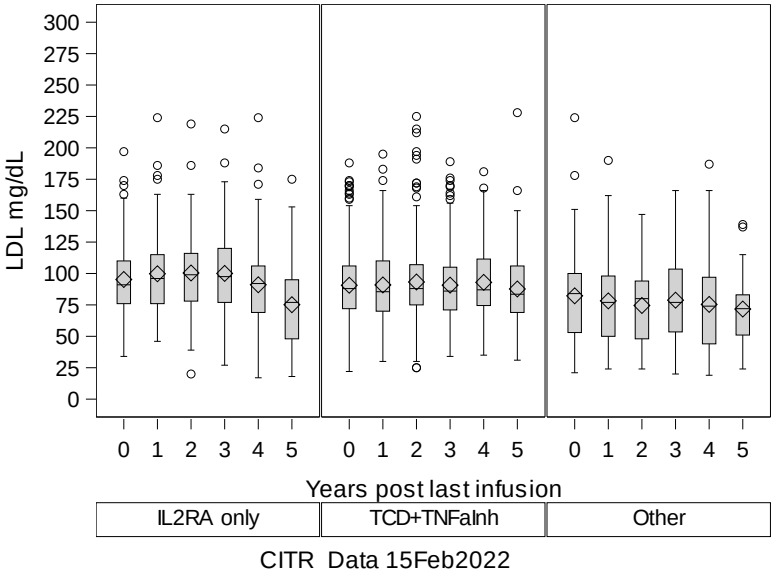
C. Recipient Age (p<0.0001)



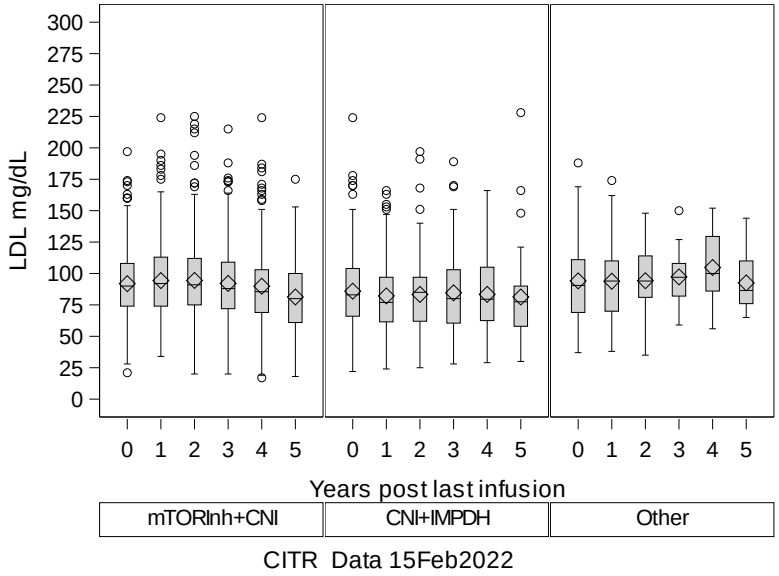
ITA						IAK						<35 years						≥35 years					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																							
91	92	92	91	90	84	87	85	86	87	87	75	97	103	108	106	104	91	89	89	89	89	88	81
S.E.																							
1	1	2	2	2	2	2	3	3	4	5	4	3	3	4	5	7	6	1	1	1	2	2	2

Exhibit 6 – 5 (continued)
LDL Cholesterol (mg/dL)

D. Induction Immunosuppression (p<0.0001)



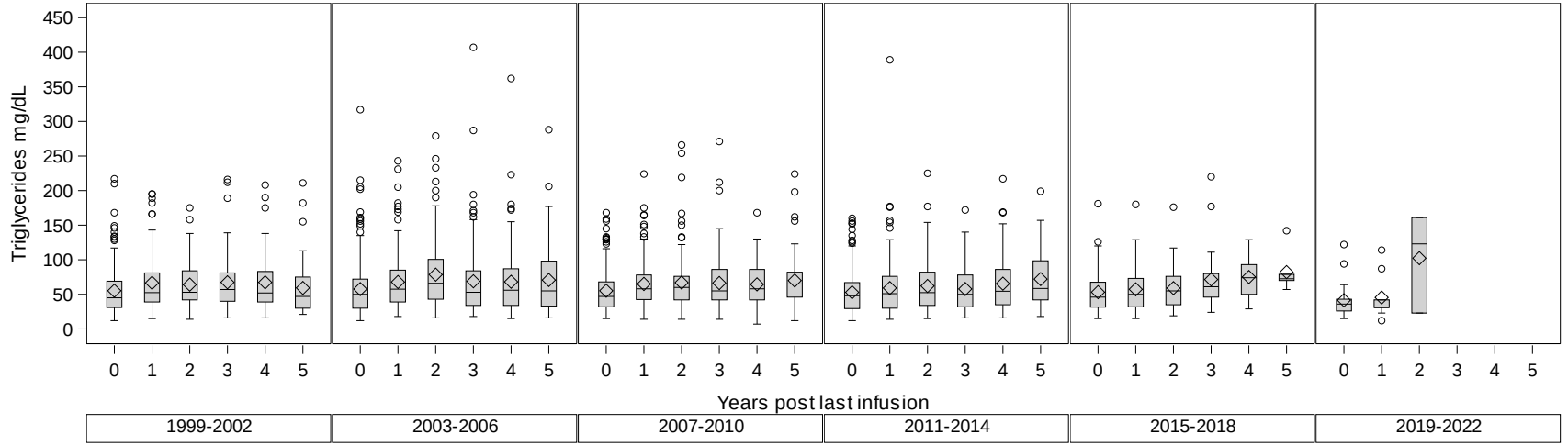
E. Maintenance Immunosuppression (p=0.002)



IL2RA only						TCD+TNFaInh						Other						mTORinh+CNI						CNI+IMPDH						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																																			
95	100	100	100	91	75	91	91	93	91	93	88	82	78	75	79	75	72	92	94	94	92	90	81	86	82	83	85	83	81	94	94	94	97	105	93
S.E.																																			
2	2	3	3	4	4	1	2	2	2	2	2	3	4	3	4	5	4	1	2	2	2	2	2	2	3	3	4	4	5	3	4	4	4	9	8

Exhibit 6 – 6
Triglycerides (mg/dL)

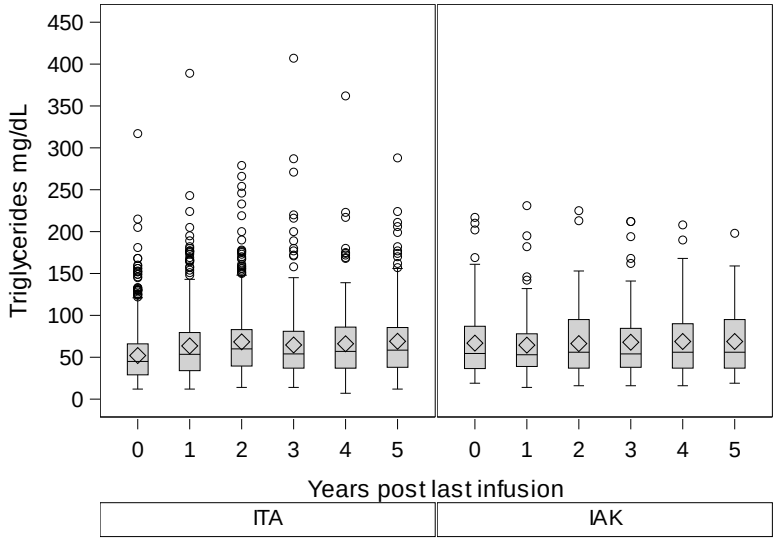
A. Era (p=NS)



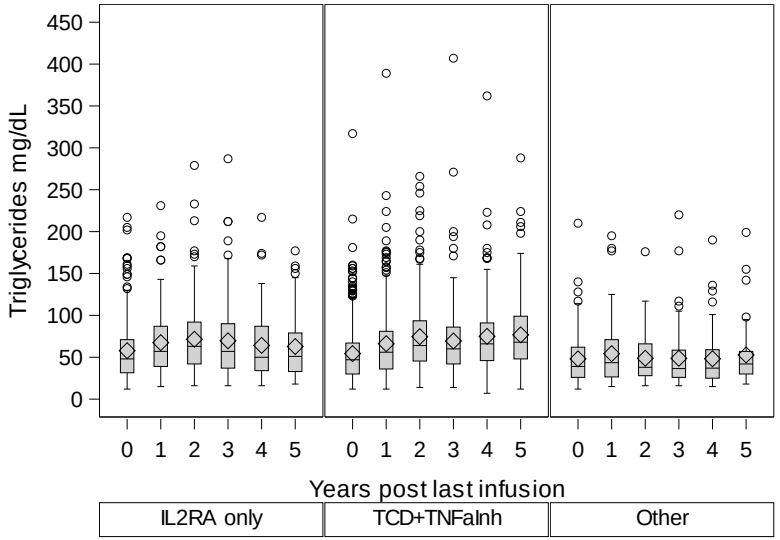
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Means																																
55	67	64	67	67	59	58	68	79	69	68	71	55	65	67	66	64	70	53	59	62	58	65	72	53	57	59	71	75	82	42	45	102
S.E.																																
3	4	4	5	6	6	3	3	4	5	5	5	2	3	3	4	3	5	2	3	3	3	5	5	3	5	6	10	9	12	5	11	41

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

B. Transplant Type (p<0.0001)



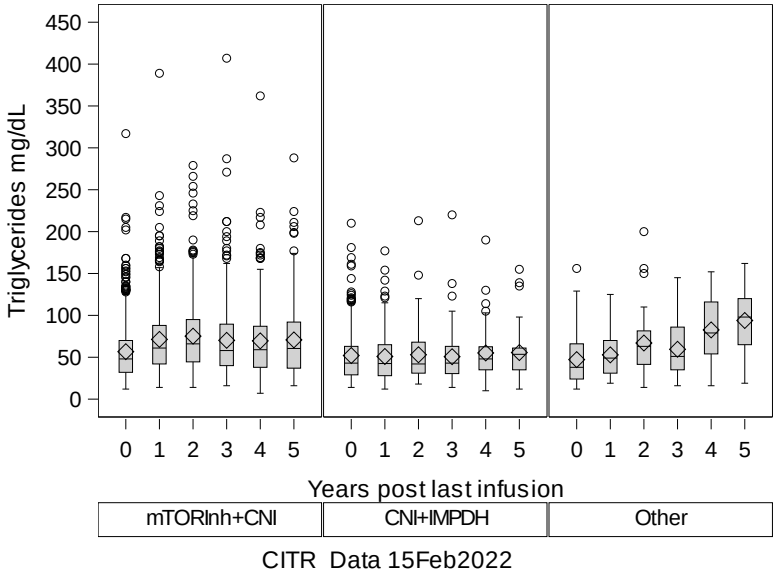
C. Induction Immunosuppression (p=0.001)



ITA						IAK						IL2RA only						TCD+TNFaInh						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																													
52	64	68	65	66	69	67	64	66	68	69	69	58	67	71	70	64	63	54	66	75	69	75	77	48	54	49	49	48	53
S.E.																													
1	2	2	2	3	3	3	3	4	5	5	5	2	3	4	4	4	5	2	2	3	3	3	4	2	4	3	4	4	5

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

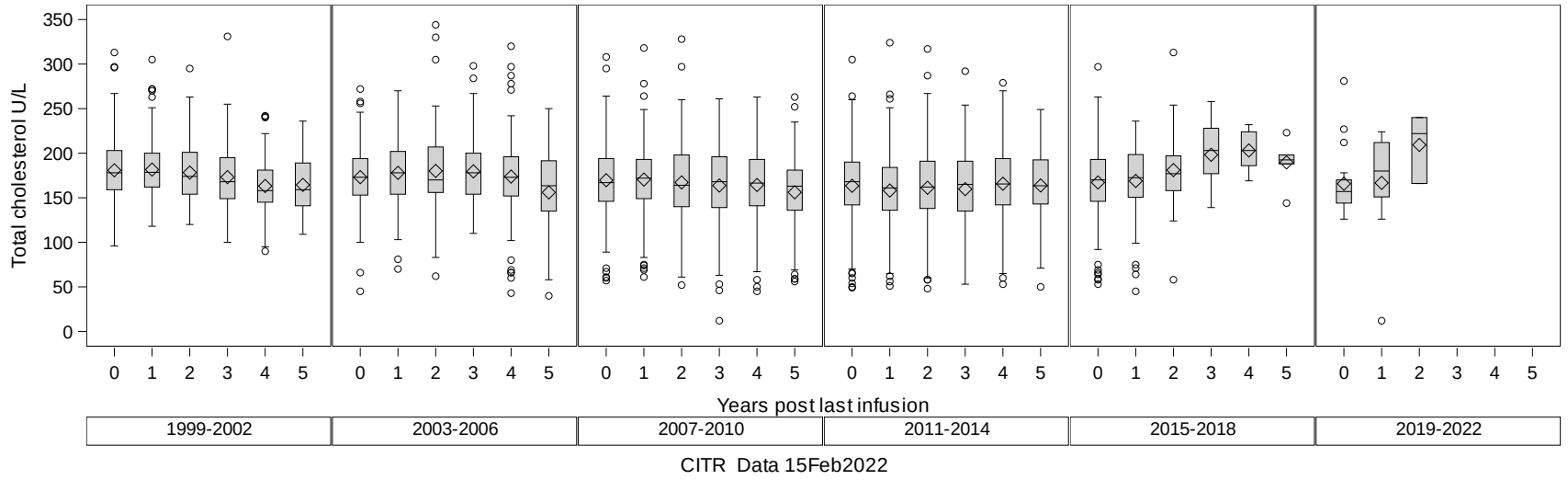
D. Maintenance Immunosuppression (p=0.0001)



mTORinh+CNI						CNI+IMPDH						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																	
57	71	75	70	70	71	52	51	53	51	55	56	47	53	67	60	83	94
S.E.																	
2	2	2	3	3	3	2	3	3	3	4	4	3	4	5	6	11	14

Exhibit 6 – 7
Total Cholesterol (mg/dL)

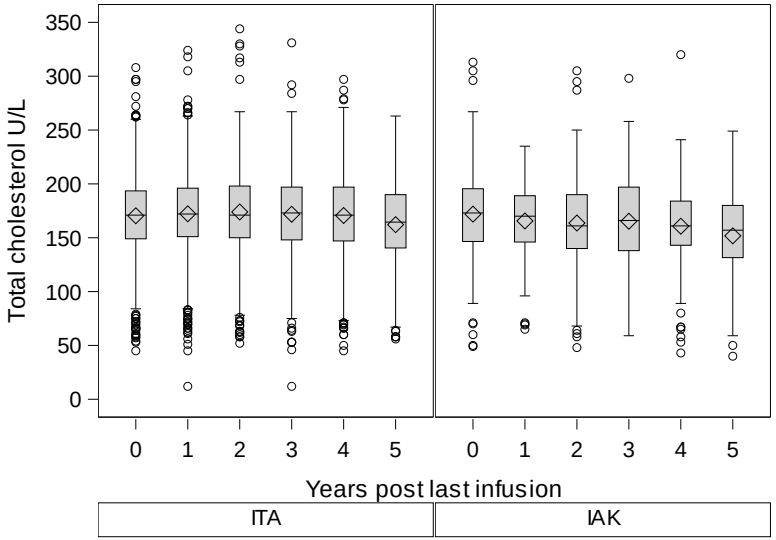
A. Era (p=0.0001)



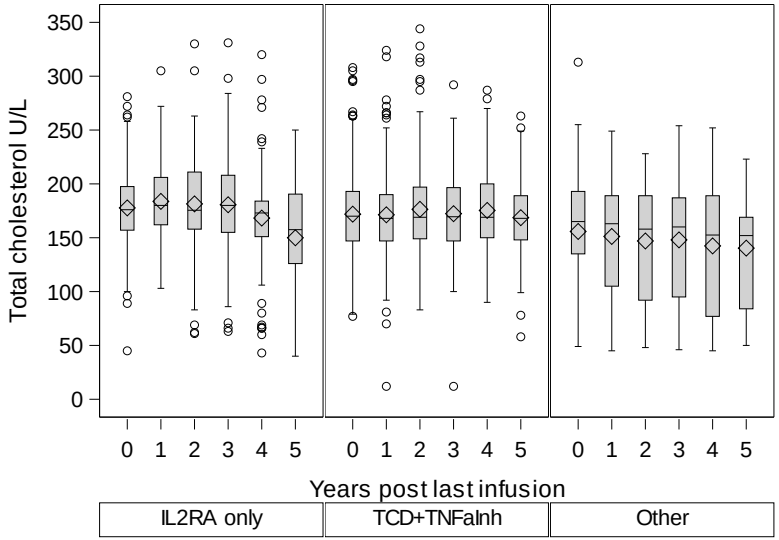
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Means																																
181	182	178	173	163	164	173	178	180	180	174	156	170	170	167	164	164	156	163	158	161	160	166	164	167	169	181	198	203	190	166	167	209
S.E.																																
3	3	4	4	5	4	2	3	3	3	5	5	3	3	4	5	5	5	3	3	4	5	5	5	5	6	8	7	6	11	8	22	22

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

B. Transplant Type (p=NS)



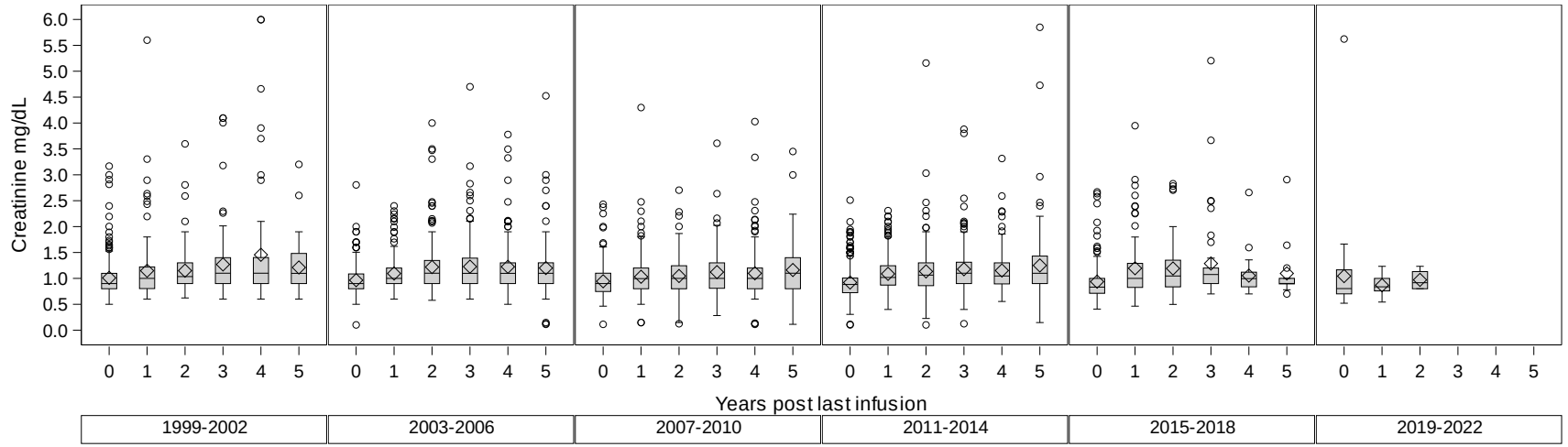
C. Induction Immunosuppression (p<0.0001)



ITA						IAK						IL2RA only						TCD+TNFaInh						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																													
170	172	174	172	171	162	172	166	164	165	161	152	178	184	181	181	168	150	172	171	176	172	175	169	156	151	147	148	142	140
S.E.																													
1	2	2	2	3	3	3	3	5	5	6	6	2	3	4	4	5	6	2	2	2	3	3	3	4	5	6	6	7	7

Exhibit 6 – 8
Serum Creatinine (mg/dL)

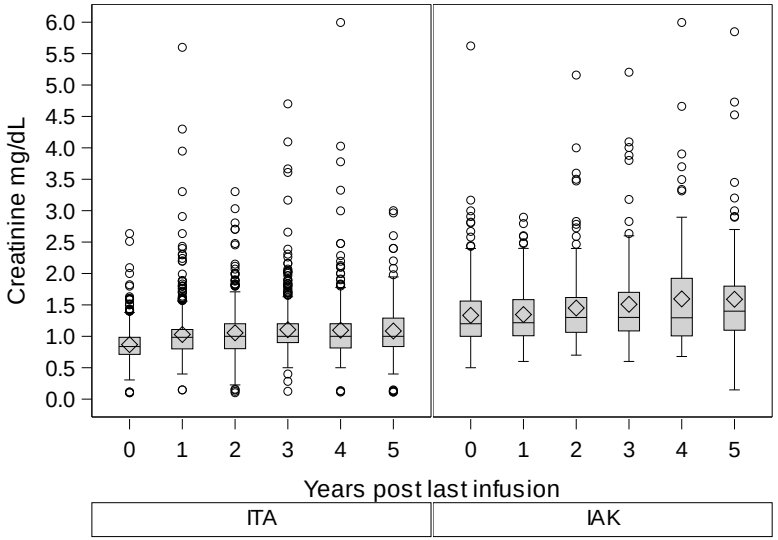
A. Era (p=NS)



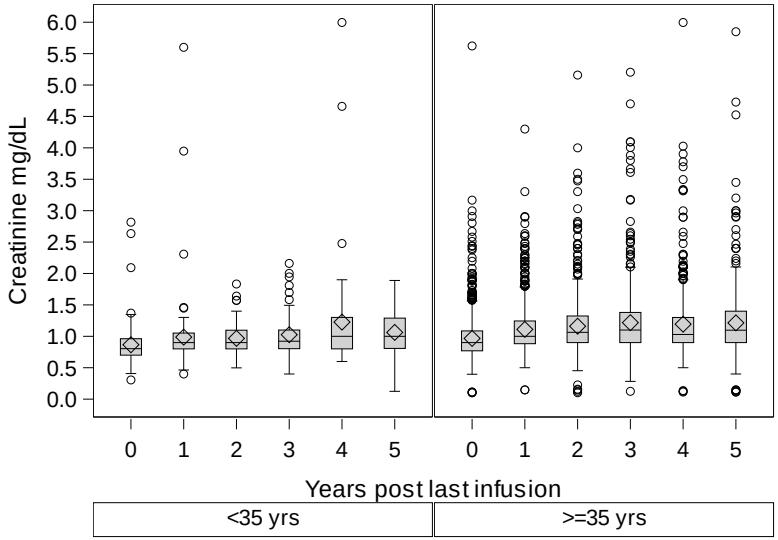
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5	0	1	2
Means																																
1.0	1.1	1.1	1.3	1.5	1.2	1.0	1.1	1.2	1.2	1.2	1.2	0.9	1.0	1.0	1.1	1.1	1.2	0.9	1.1	1.1	1.2	1.2	1.2	0.9	1.2	1.2	1.3	1.1	1.1	1.0	0.9	1.0
S.E.																																
0.0	0.1	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.1	0.0	0.1	0.1	0.1	0.1	0.2	0.2	0.1	0.1

Exhibit 6 – 8 (continued)
Serum Creatinine (mg/dL)

B. Transplant Type (p<0.0001)



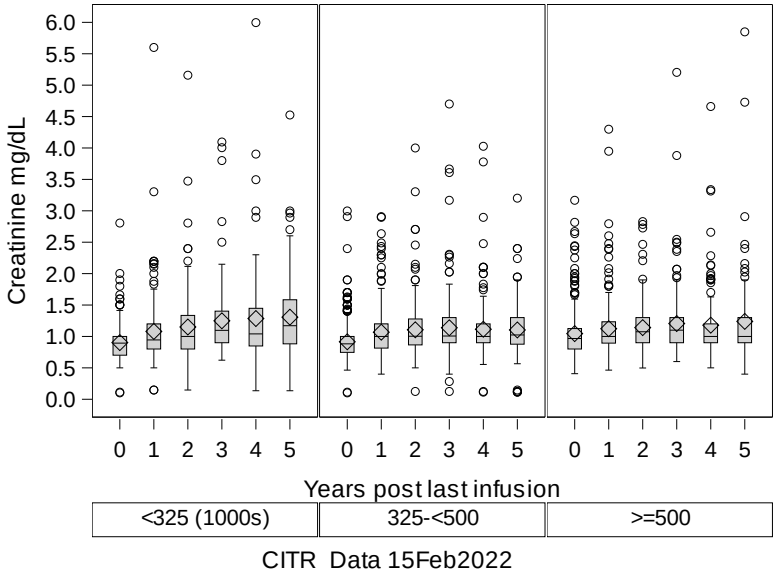
C. Recipient Age (p=0.0005)



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

Exhibit 6 – 8 (continued)
Serum Creatinine (mg/dL)

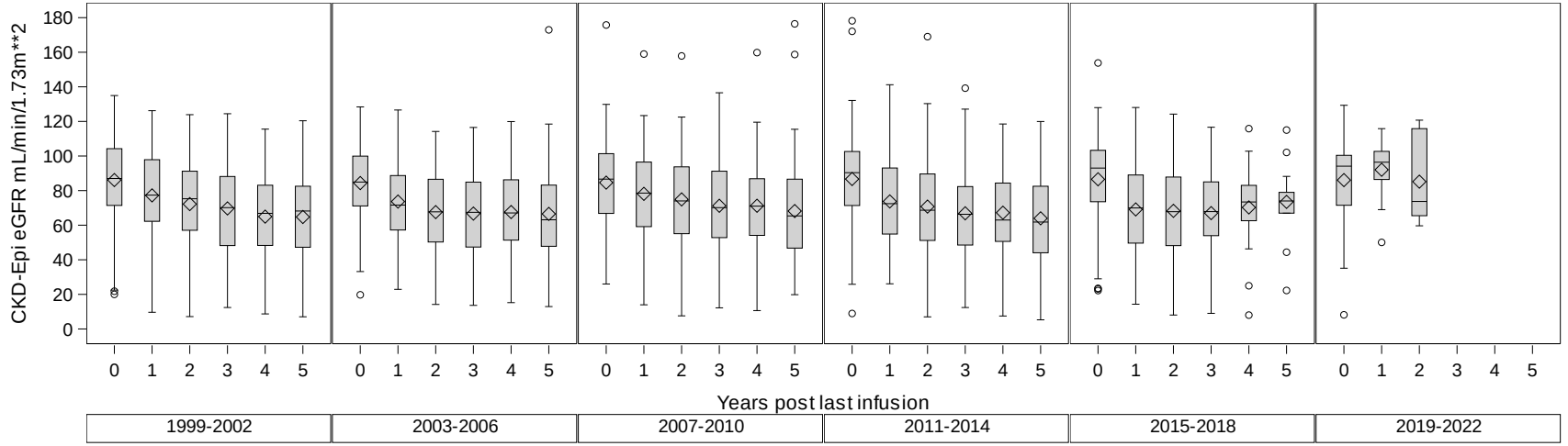
D. IEQs Infused (p=0.0001)



<325k IEQs						325k-<500k IEQs						≥500k IEQs					
0	1	2	3	4	5	0	1	2	3	4	5	0	1	2	3	4	5
Means																	
0.9	1.1	1.2	1.2	1.3	1.3	0.9	1.1	1.1	1.1	1.1	1.1	1.0	1.1	1.1	1.2	1.2	1.2
S.E.																	
0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.1	0.1

Exhibit 6 – 9
CKD-EPI eGFR

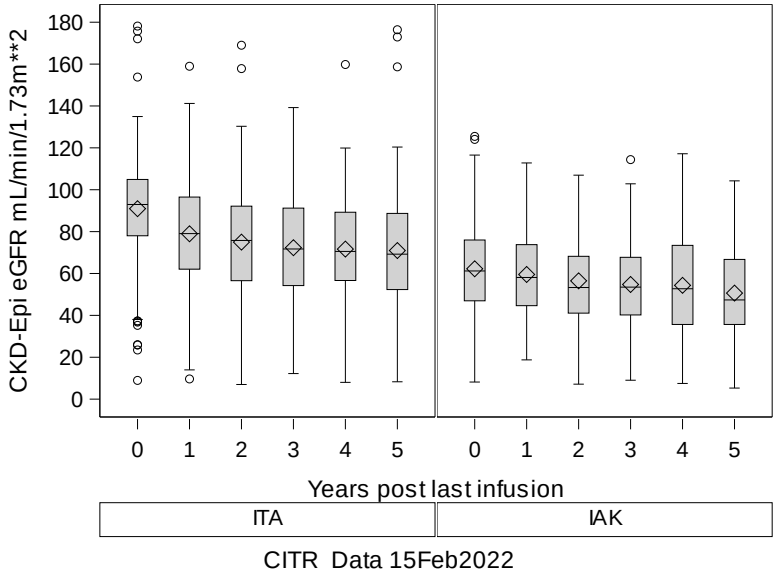
A. Era (p=NS)



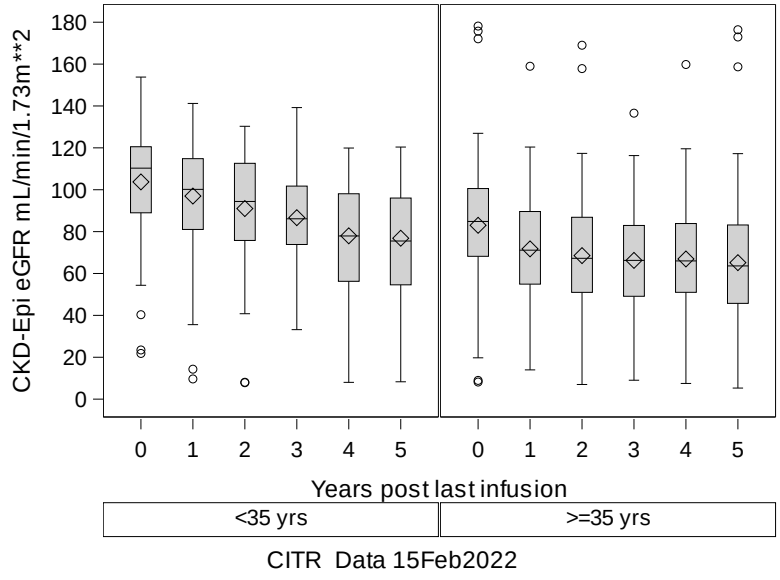
1999-2002						2003-2006						2007-2010						2011-2014						2015-2018						2019-2022		
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**
Means																																
86	77	72	70	65	65	84	74	68	67	68	67	85	78	75	71	71	68	87	74	71	67	67	64	87	69	68	67	70	73	86	92	85
S.E.																																
2	2	3	3	3	3	1	2	2	2	2	3	2	2	2	2	2	3	1	2	2	2	2	3	2	3	3	4	4	6	5	6	9

Exhibit 6 – 9 (continued)
CKD-EPI eGFR

B. Transplant Type (p<0.0001)



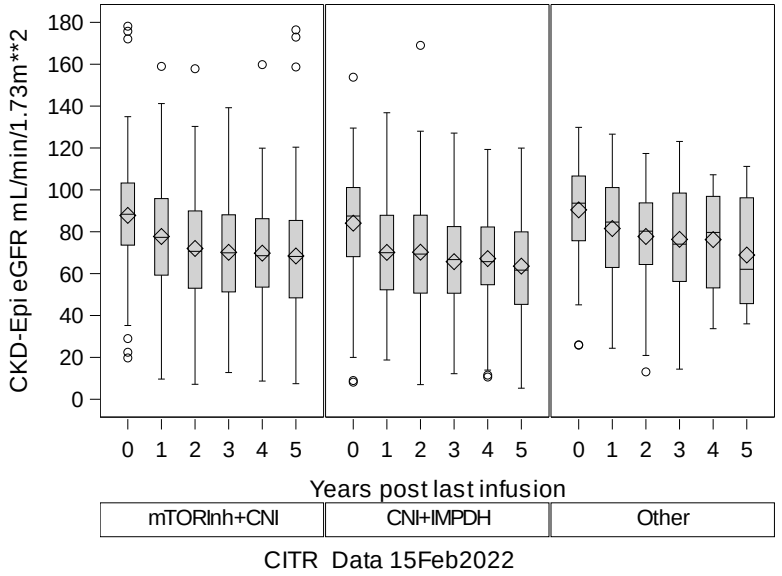
C. Recipient Age (p<0.0001)



ITA						IAK						<35 years						≥35 years					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																							
91	79	75	72	72	71	62	60	56	55	54	51	104	97	91	87	78	77	83	72	69	66	67	65
S.E.																							
1	1	1	1	1	1	2	2	2	2	3	3	2	2	3	3	4	5	1	1	1	1	1	1

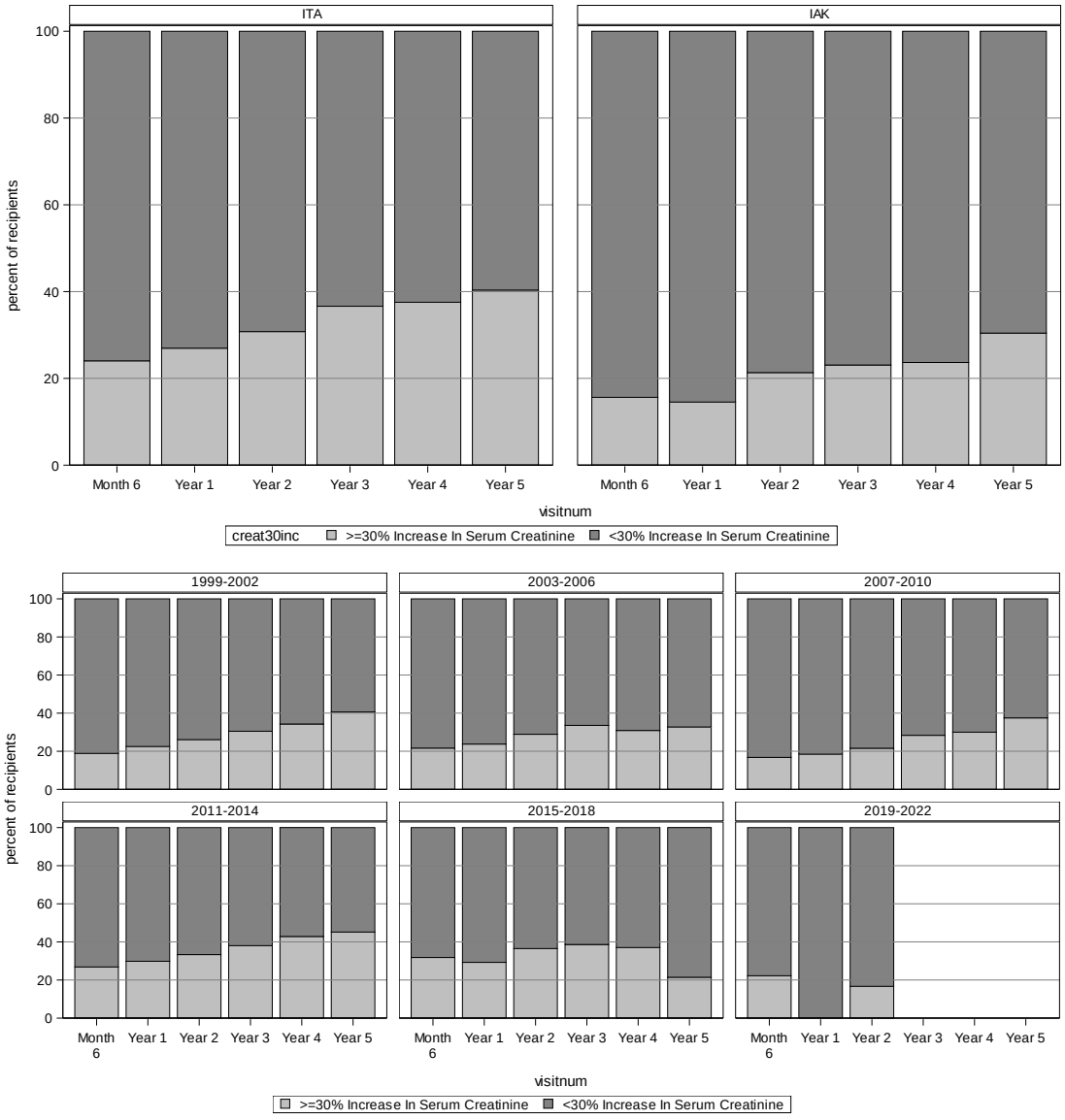
Exhibit 6 – 9 (continued)
CKD-EPI eGFR

D. Maintenance Immunosuppression (p=0.002)



mTORinh+CNI						CNI+IMPDH						Other					
0	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**	**0**	**1**	**2**	**3**	**4**	**5**
Means																	
88	78	72	70	70	68	84	70	70	66	67	64	90	82	78	76	76	69
S.E.																	
1	1	1	1	1	2	1	1	2	2	2	2	2	3	3	4	5	6

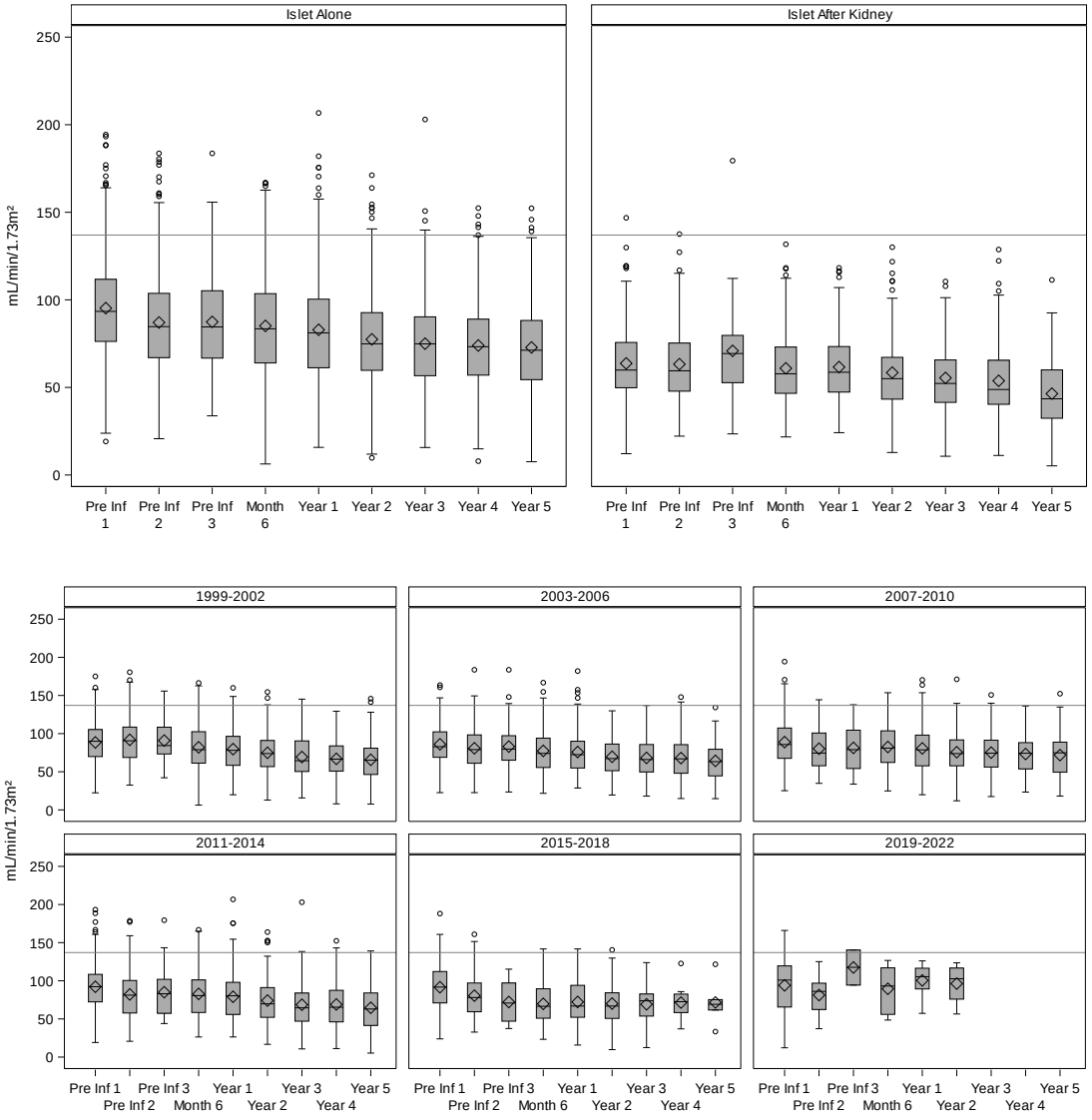
Exhibit 6 – 10
Percent of Recipients with a 30% increase in Serum Creatinine at each Follow-up Time Point by Infusion Type and Era



	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	624	638	523	415	349	285
Islet After Kidney	160	172	150	130	93	92
1999-2002	122	129	92	82	70	64
2003-2006	194	202	173	143	123	110
2007-2010	179	168	153	134	110	96
2011-2014	205	218	186	142	112	93
2015-2018	66	82	63	44	27	14
2019-2022	18	11	6	0	0	0

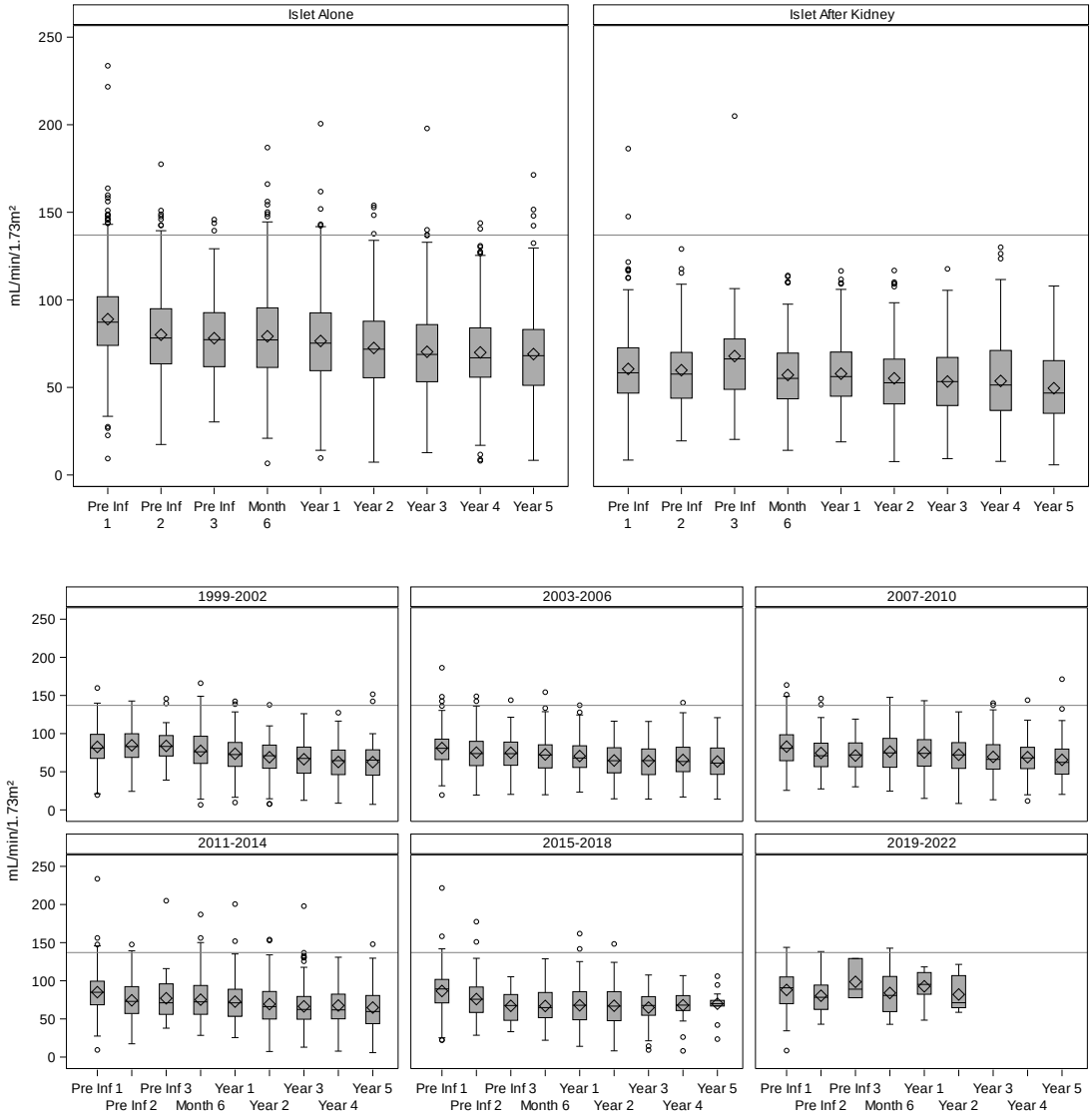
Exhibit 6 – 11

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



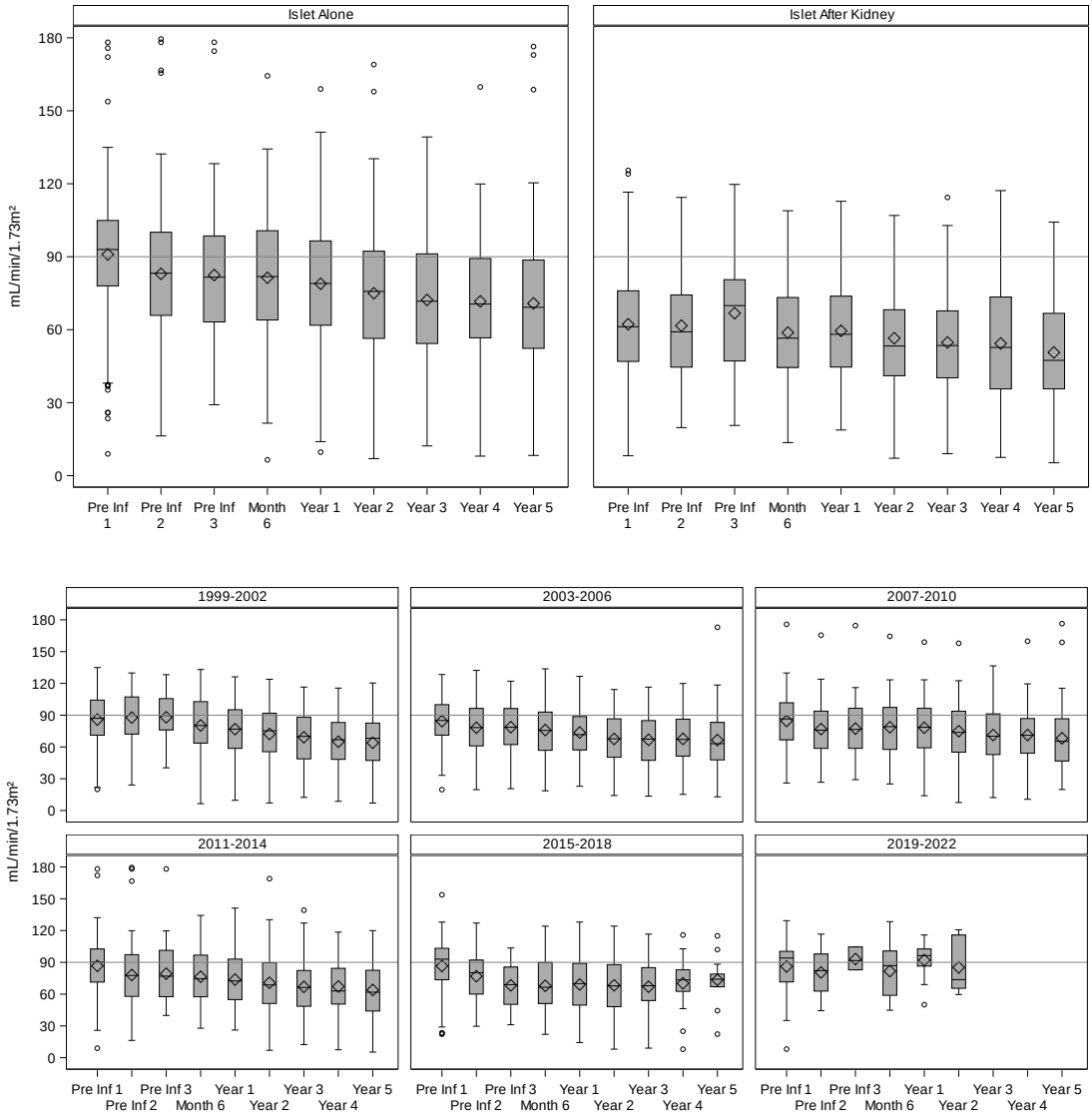
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	897	549	153	587	559	449	340	276	212
Islet After Kidney	197	119	25	146	151	128	109	77	63
1999-2002	169	111	44	120	120	87	79	66	52
2003-2006	242	187	65	180	180	152	120	94	74
2007-2010	209	117	26	174	160	143	110	91	71
2011-2014	306	155	29	181	174	142	113	86	71
2015-2018	135	82	11	62	66	49	27	16	7
2019-2022	33	16	3	16	10	4	0	0	0

Exhibit 6 – 12
MDRD Estimated Cockgroft-Gault (mL/min/1.73m²) by Infusion Type and Era



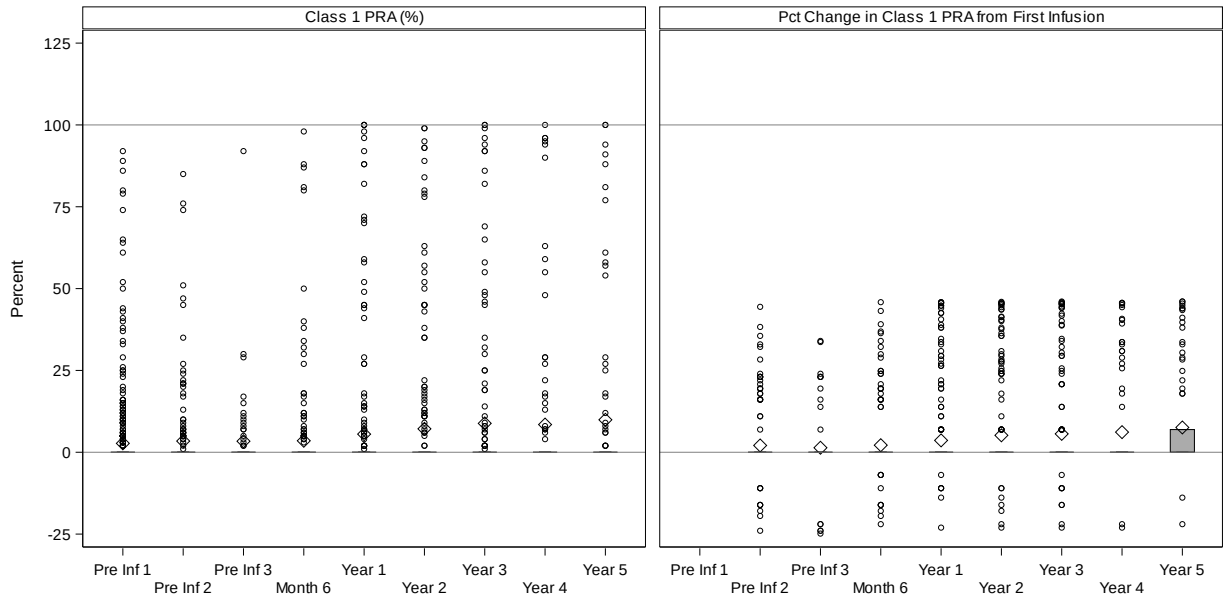
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	929	593	175	645	670	555	445	369	301
Islet After Kidney	211	123	27	162	174	149	129	92	91
1999-2002	170	113	44	123	130	92	84	71	66
2003-2006	250	195	72	195	201	172	141	121	107
2007-2010	216	129	31	188	179	167	147	119	105
2011-2014	325	177	41	215	238	201	157	122	100
2015-2018	146	86	11	68	85	65	45	28	14
2019-2022	33	16	3	18	11	7	0	0	0

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



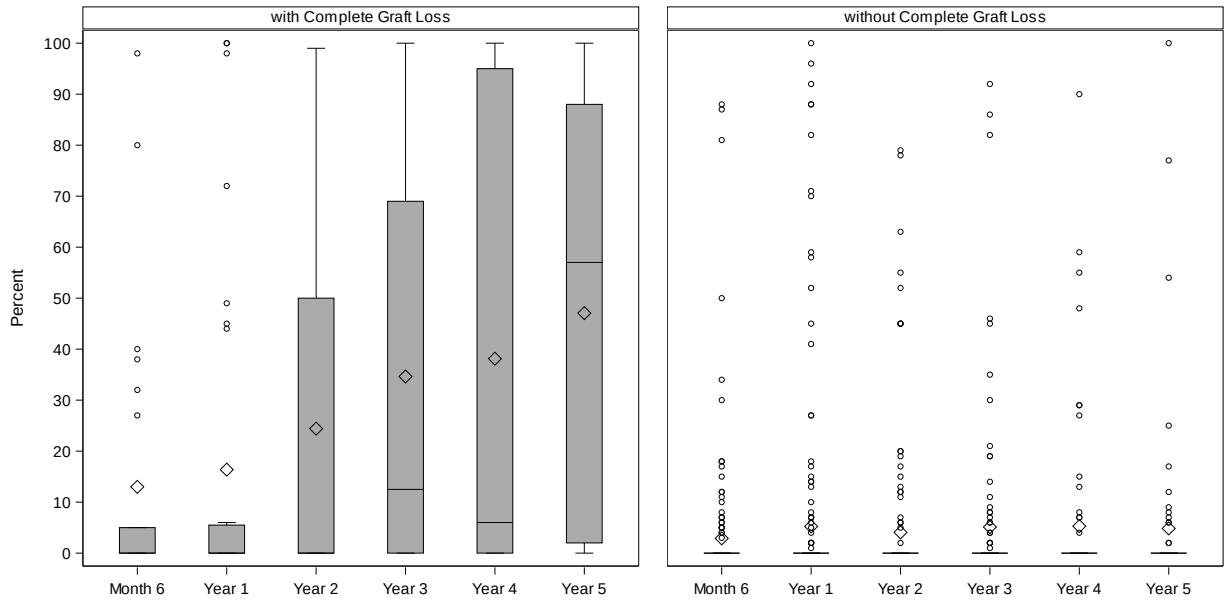
	Pre Inf 1	Pre Inf 2	Pre Inf 3	Month 6	Year 1	Year 2	Year 3	Year 4	Year 5
Islet Alone	929	593	175	645	670	555	445	369	301
Islet After Kidney	211	123	27	162	174	149	129	92	91
1999-2002	170	113	44	123	130	92	84	71	66
2003-2006	250	195	72	195	201	172	141	121	107
2007-2010	216	129	31	188	179	167	147	119	105
2011-2014	325	177	41	215	238	201	157	122	100
2015-2018	146	86	11	68	85	65	45	28	14
2019-2022	33	16	3	18	11	7	0	0	0

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 (%)	666	225	78	251	312	250	178	118	104
Percent Change in Class 1 PRA from First Infusion	0	204	74	223	276	214	161	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	25	32	34	22	15	15
without Complete Graft Loss	188	220	154	110	74	67

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.

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).

About 11% ITA and 14% 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 15% or more of patients experiencing SAEs in early eras compared to ~5% in 2011-2014 and 2015-2018. There is likely some lag in reporting for 2019-2022.

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 (31%) than ITA (23%) and there was a significant decline post-2010 (>25% pre vs. <15% post). 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.

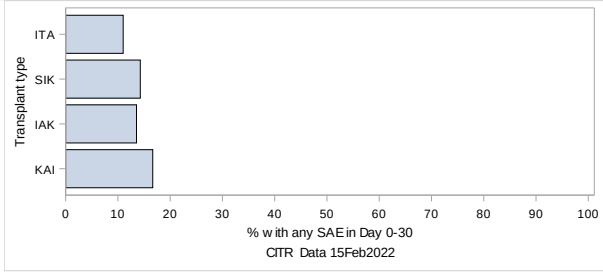
The total cohort of 1373 allo-islet recipients were followed for a mean of 5.8±3.8 SD years, comprising 7,963 person-years of follow-up from first infusion (7-6A). A total of 189 events in 101 recipients were classified “Neoplasm”. Of the total 189 events, 61% were deemed possibly related to immunosuppression, and 12% definitely related. Of the total events, 69% recovered, 10% did not recover, 5% recovered with sequelae, and 3% resulted in fatality. There were 41 instances in 23 patients of basal carcinoma of the skin and 86 instances in 38 patients of squamous carcinoma of the skin (Exhibit 7-6B). There were 56 instances in 39 recipients of non-skin cancers. Eleven deaths due to cancer occurred (see Exhibit 7-7B for details).

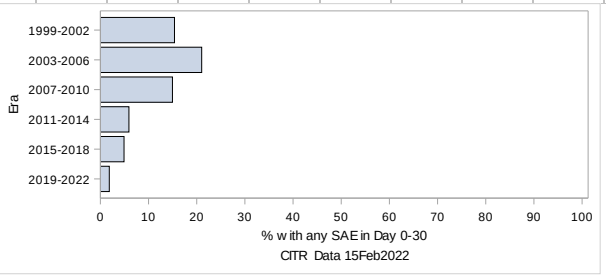
There have been 77 or 5.5% deaths; cumulative mortality rates differed significantly by transplant type ($p<0.0001$) but not by era (Exhibit 7-7A). SIK transplant recipients were disproportionately represented among fatalities comprising only 3.5% of the allo-islet recipient population, but 15.6% percent of deaths. Of the reported deaths, ten were deemed possibly related or definitely related to islet transplantation or immunosuppression (Exhibit 7-7B).

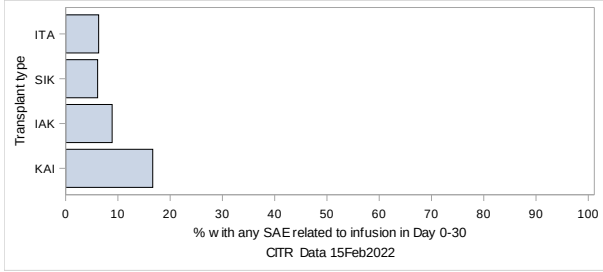
Life-threatening events have occurred in 13.4% of islet-alone, in 16.5% of IAK recipients, and in 20.4% of SIK recipients (p=NS, Exhibit 7-8A). Recent eras have seen a substantial decline in the incidence of life-threatening events (p<0.0001). The most common life-threatening events reported were abnormal granulocytes (24 events) followed by abnormal liver function (23 events) and hypoglycaemia (14 events). About 75% of patients who experienced a life-threatening event recovered fully, 12% recovered with sequelae, 5% did not recover, and 9% died as a result of the event.

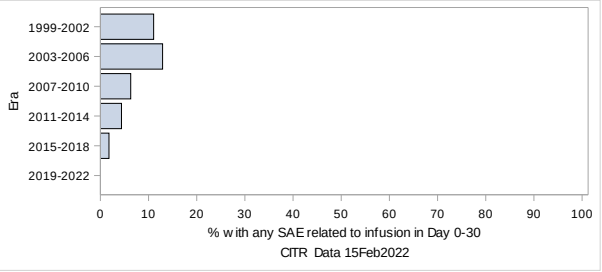
Exhibit 7 – 1
Serious Adverse Events (SAEs) in Days 0-30 Post 1st Infusion

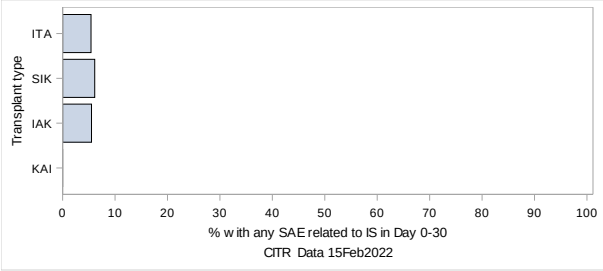
Percent of Recipients with:	Type								Era											
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE in Day 0-30	122	11.0	7	14.3	32	13.6	1	16.7	32	15.4	57	21.0	38	15.0	23	5.9	11	4.9	1	1.9
Any SAE related to infusion in Day 0-30	70	6.3	3	6.1	21	8.9	1	16.7	23	11.1	35	12.9	16	6.3	17	4.4	4	1.8	0	0.0
Any SAE related to IS in Day 0-30	60	5.4	3	6.1	13	5.5	0	0.0	7	3.4	28	10.3	27	10.6	11	2.8	3	1.3	0	0.0
Any SAE related to both in Day 0-30	16	1.4	1	2.0	4	1.7	0	0.0	2	1.0	5	1.8	8	3.1	6	1.5	0	0.0	0	0.0
Any SAE related to neither in Day 0-30	20	1.8	4	8.2	5	2.1	0	0.0	5	2.4	7	2.6	6	2.4	6	1.5	4	1.8	1	1.9











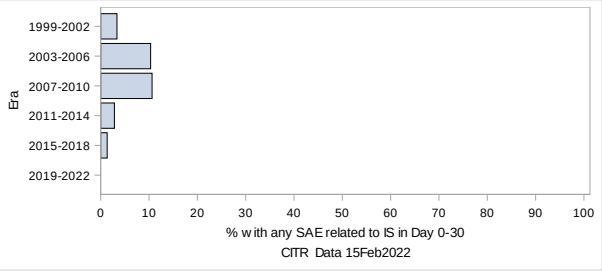


Exhibit 7 – 1 (continued)

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

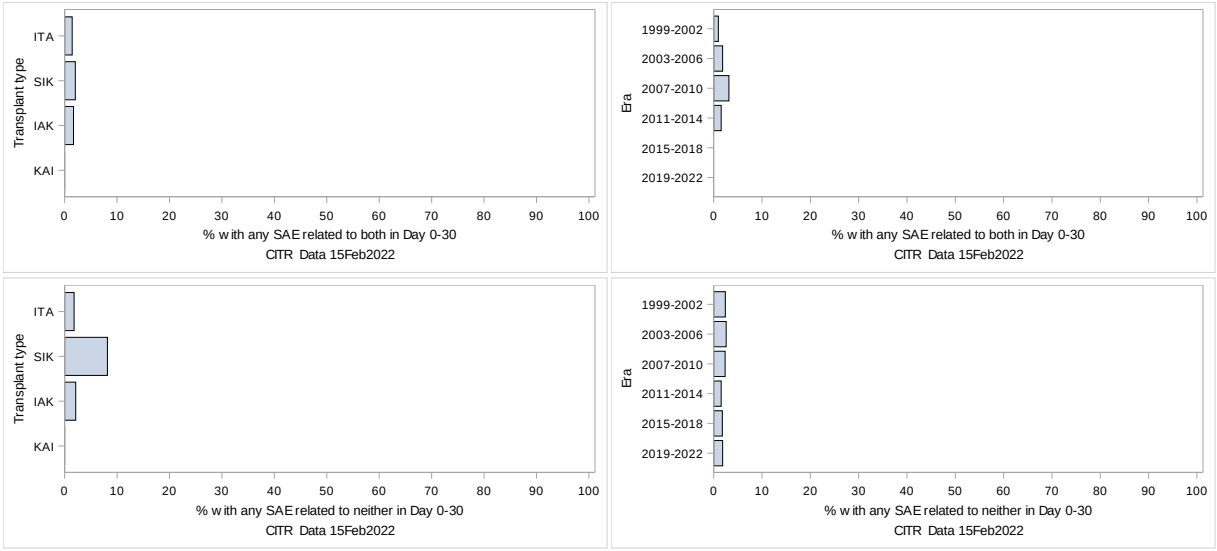


Exhibit 7 – 2

Serious Adverse Events (SAEs) in Year 1 Post 1st Infusion

Percent of Recipients with:	Type								Era											
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE in 1-year	254	22.9	13	26.5	72	30.5	3	50.0	78	37.5	106	39.1	70	27.6	58	14.9	26	11.6	4	7.4
Any SAE related to infusion in 1-year	117	10.6	3	6.1	35	14.8	2	33.3	37	17.8	55	20.3	30	11.8	28	7.2	5	2.2	2	3.7
Any SAE related to IS in 1-year	147	13.3	7	14.3	35	14.8	2	33.3	40	19.2	66	24.4	48	18.9	26	6.7	9	4.0	2	3.7
Any SAE related to both in 1-year	32	2.9	1	2.0	7	3.0	0	0.0	7	3.4	9	3.3	12	4.7	11	2.8	0	0.0	1	1.9
Any SAE related to neither in 1-year	78	7.0	8	16.3	26	11.0	1	16.7	26	12.5	24	8.9	21	8.3	25	6.4	16	7.1	1	1.9

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

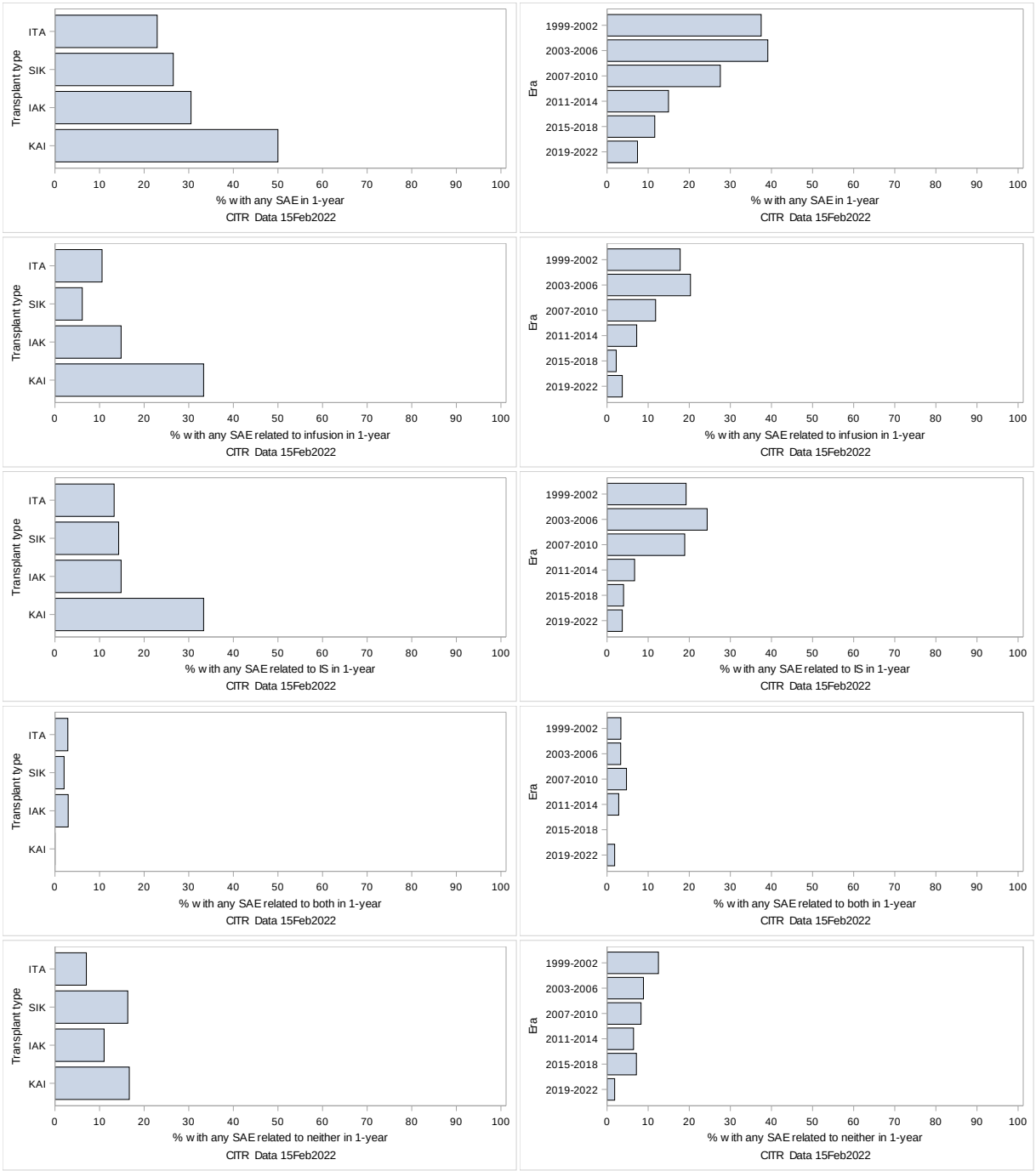
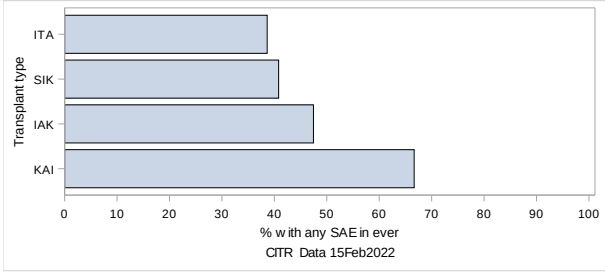
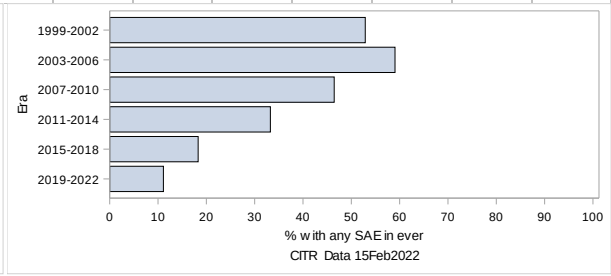


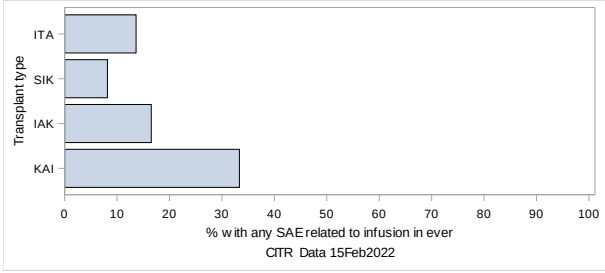
Exhibit 7 –3

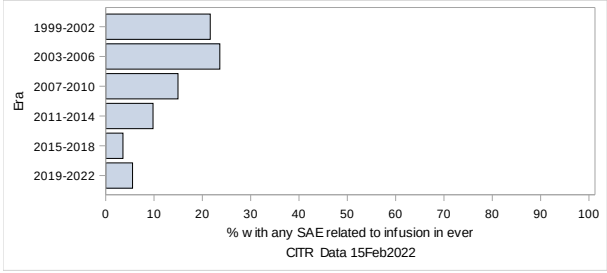
Recipients with a Serious Adverse Event (SAE) Any Time Post Islet Transplant

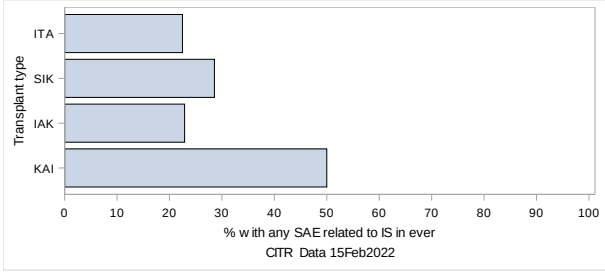
Percent of Recipients with:	Type								Era											
	ITA		SIK		IAK		KAI		1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%	N	%
Any SAE ever	428	38.6	20	40.8	112	47.5	4	66.7	110	52.9	160	59.0	118	46.5	129	33.2	41	18.3	6	11.1
Any SAE related to infusion ever	151	13.6	4	8.2	39	16.5	2	33.3	45	21.6	64	23.6	38	15.0	38	9.8	8	3.6	3	5.6
Any SAE related to IS ever	249	22.5	14	28.6	54	22.9	3	50.0	61	29.3	107	39.5	77	30.3	53	13.7	19	8.5	3	5.6
Any SAE related to both ever	49	4.4	1	2.0	9	3.8	0	0.0	9	4.3	15	5.5	18	7.1	14	3.6	2	0.9	1	1.9
Any SAE related to neither ever	242	21.8	13	26.5	76	32.2	2	33.3	65	31.3	85	31.4	74	29.1	87	22.4	21	9.4	1	1.9











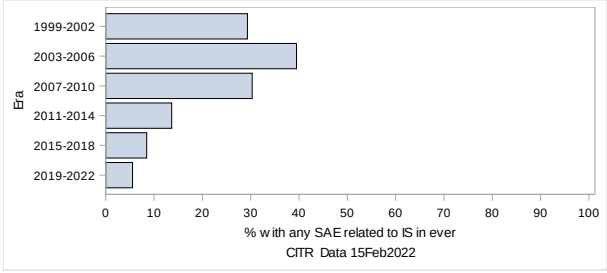


Exhibit 7 –3 (continued)
Recipients with a Serious Adverse Event (SAE) Any Time Post Islet Transplant

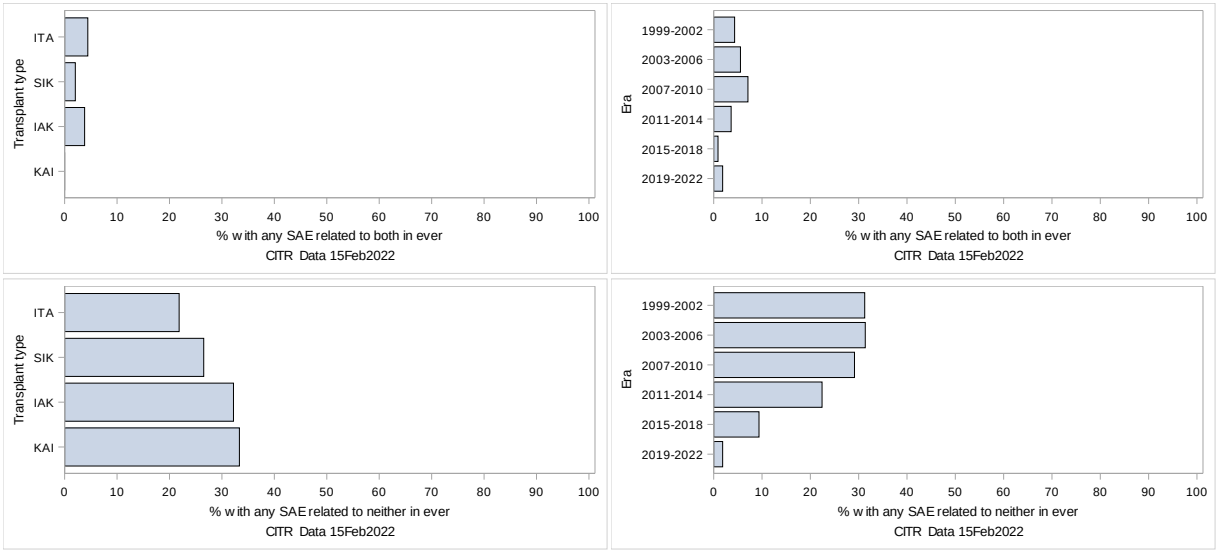


Exhibit 7 –4
SAE Criteria

	Transplant type							
	ITA		SIK		IAK		KAI	
	N	%	N	%	N	%	N	%
Total recipients (N)	1108	100.0	49	100.0	236	100.0	6	100.0
Death	35	3.2	12	24.5	28	11.9	1	16.7
Life Threatening	146	13.2	9	18.4	37	15.7	1	16.7
Hospitalization	317	28.6	17	34.7	82	34.7	4	66.7
Congenital abnormality	2	0.2	1	2.0	0	0.0	0	0.0
Long term disability	32	2.9	2	4.1	14	5.9	0	0.0
PI Indicated Serious	72	6.5	3	6.1	21	8.9	0	0.0

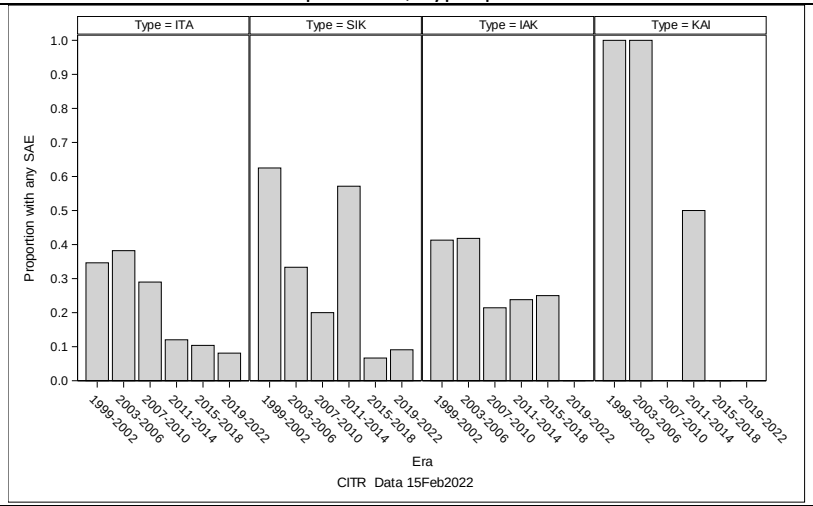
	Era											
	1999-2002		2003-2006		2007-2010		2011-2014		2015-2018		2019-2022	
	N	%	N	%	N	%	N	%	N	%	N	%
Total recipients (N)	208	100.0	271	100.0	254	100.0	388	100.0	224	100.0	54	100.0
Death	24	11.5	17	6.3	17	6.7	15	3.9	2	0.9	1	1.9
Life Threatening	50	24.0	83	30.6	23	9.1	24	6.2	11	4.9	2	3.7
Hospitalization	95	45.7	134	49.4	73	28.7	79	20.4	37	16.5	2	3.7
Congenital abnormality	1	0.5	1	0.4	0	0.0	1	0.3	0	0.0	0	0.0
Long term disability	11	5.3	12	4.4	14	5.5	10	2.6	1	0.4	0	0.0
PI Indicated Serious	19	9.1	36	13.3	26	10.2	7	1.8	3	1.3	5	9.3

Exhibit 7 –5

Incidence of SAEs per Recipient by Type of Transplant and Era

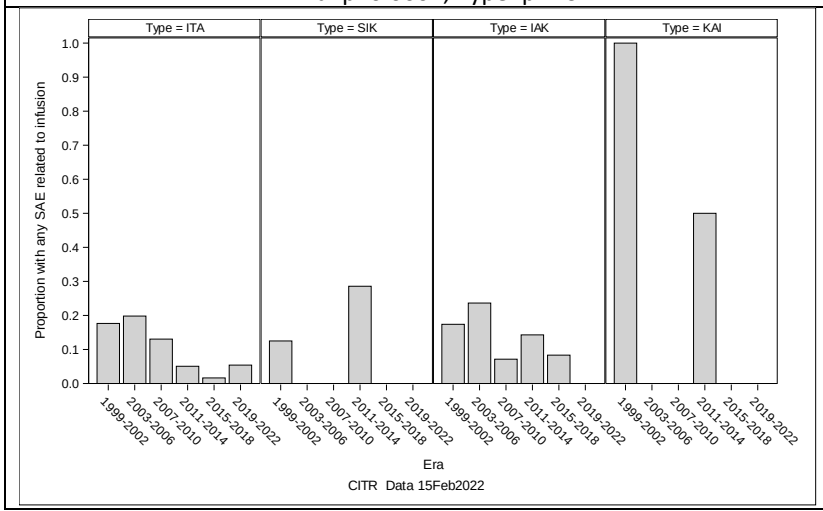
Any SAE in First Year Post Transplant

Era: p<0.0001, Type: p=0.02



Any SAE in First Year Post Transplant Related to Infusion

Era: p<0.0001, Type: p=NS



Any AE in First Year Post Transplant Related to Immunosuppression

Era: p<0.0001, Type: p=NS

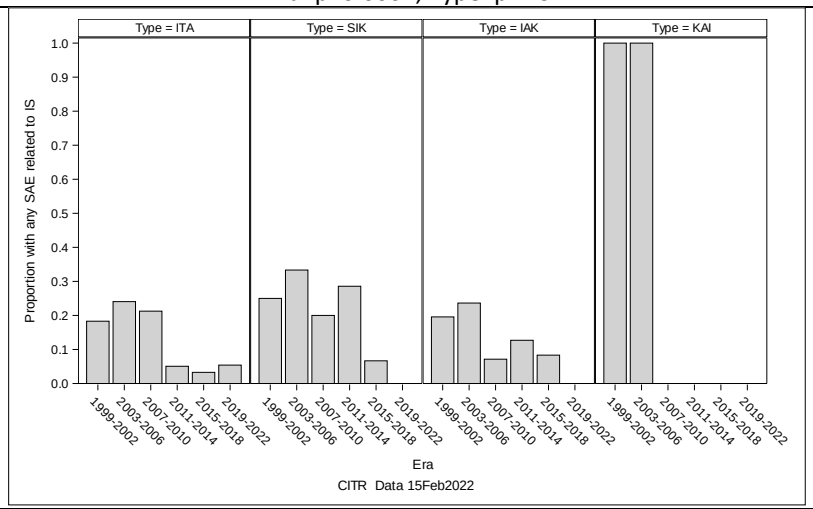


Exhibit 7 –6A
Total years of follow-up

	N	Mean	Std
Total years of follow-up	1373	5.8	3.8

Exhibit 7 –6B
All Neoplasms

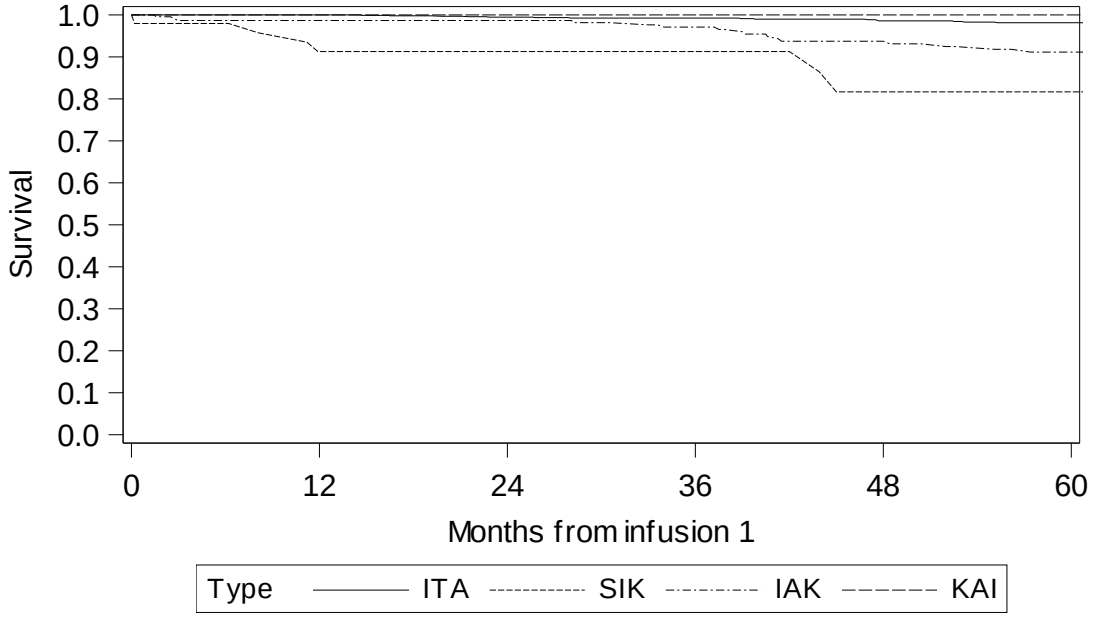
		Relatedness to Immunosuppression					Outcome					
	Total	Unk.	Not related	Unlikely related	Possibly related	Related	Unk.	Not recovered	Recovering	Recovered	Recovered with sequelae	Fatal
	N	%	%	%	%	%	%	%	%	%	%	%
Total Events	**189**	18.5	5.3	3.2	60.8	12.2	9.0	10.1	4.2	68.8	4.8	3.2
Other	**30**	20.0	10.0	10.0	60.0	0.0	0.0	20.0	16.7	56.7	3.3	3.3
Basal cell carcinoma	**41**	12.2	0.0	0.0	68.3	19.5	9.8	0.0	0.0	80.5	9.8	0.0
Ductal carcinoma	**5**	0.0	20.0	40.0	40.0	0.0	0.0	40.0	0.0	60.0	0.0	0.0
Lung carcinoma	**3**	33.3	0.0	33.3	33.3	0.0	33.3	33.3	0.0	0.0	0.0	33.3
Metastasis	**3**	33.3	0.0	0.0	66.7	0.0	0.0	33.3	0.0	0.0	33.3	33.3
Papillary	**5**	20.0	20.0	0.0	60.0	0.0	0.0	0.0	20.0	80.0	0.0	0.0
Post-transplant lymphoproliferative	**9**	22.2	44.4	0.0	33.3	0.0	0.0	55.6	11.1	33.3	0.0	0.0
Pulmonary nodules	**1**	0.0	0.0	0.0	100	0.0	0.0	100	0.0	0.0	0.0	0.0
Skin, type other or not reported	**6**	50.0	0.0	0.0	50.0	0.0	33.3	0.0	0.0	50.0	16.7	0.0
Squamous cell	**86**	18.6	1.2	0.0	62.8	17.4	11.6	3.5	1.2	77.9	2.3	3.5

Exhibit 7 –6C

First Neoplasm in Patient

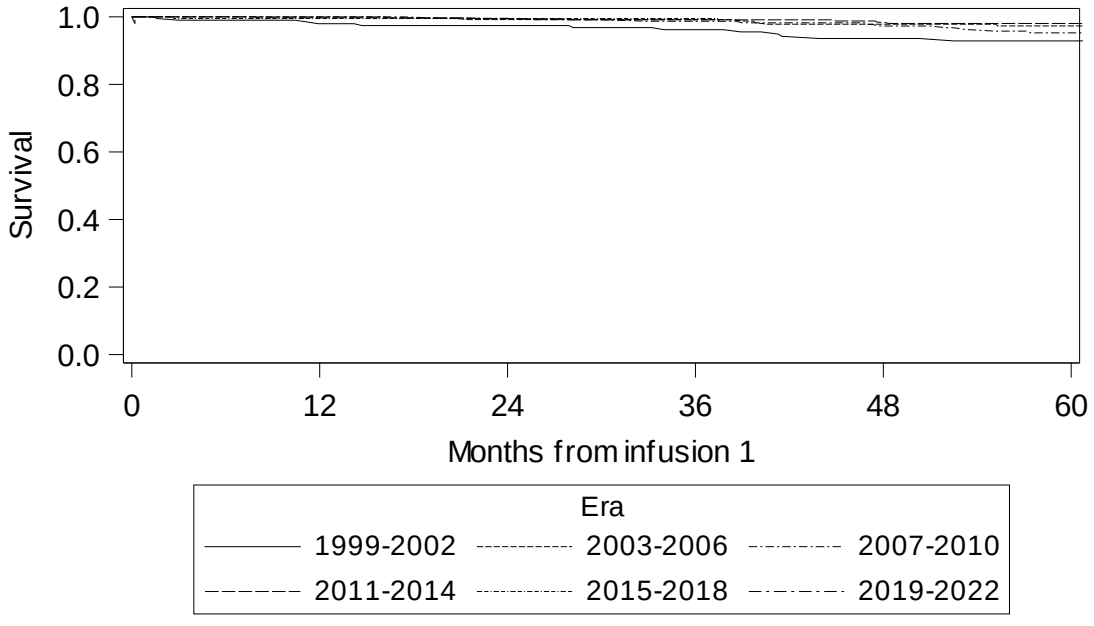
		Relatedness to Immunosuppression					Outcome					
	Total	Unk.	Not related	Unlikely related	Possibly related	Related	Unk.	Not recovered	Recovering	Recovered	Recovered with sequelae	Fatal
	N	%	%	%	%	%	%	%	%	%	%	%
Total Events	**101**	19.8	5.9	3.0	67.3	4.0	6.9	12.9	5.0	65.3	6.9	3.0
Other	**19**	21.1	10.5	5.3	63.2	0.0	0.0	21.1	15.8	52.6	5.3	5.3
Basal cell carcinoma	**23**	13.0	0.0	0.0	82.6	4.3	4.3	0.0	0.0	82.6	13.0	0.0
Ductal carcinoma	**4**	0.0	25.0	50.0	25.0	0.0	0.0	50.0	0.0	50.0	0.0	0.0
Lung carcinoma	**2**	50.0	0.0	0.0	50.0	0.0	50.0	50.0	0.0	0.0	0.0	0.0
Metastasis	**3**	33.3	0.0	0.0	66.7	0.0	0.0	33.3	0.0	0.0	33.3	33.3
Papillary	**5**	20.0	20.0	0.0	60.0	0.0	0.0	0.0	20.0	80.0	0.0	0.0
Post-transplant lymphoproliferative	**5**	20.0	20.0	0.0	60.0	0.0	0.0	60.0	20.0	20.0	0.0	0.0
Pulmonary nodules	**1**	0.0	0.0	0.0	100	0.0	0.0	100	0.0	0.0	0.0	0.0
Skin, type other or not reported	**1**	0.0	0.0	0.0	100	0.0	0.0	0.0	0.0	100	0.0	0.0
Squamous cell	**38**	23.7	2.6	0.0	65.8	7.9	13.2	2.6	0.0	76.3	5.3	2.6

Exhibit 7 –7A
Deaths



CITR Data 15Feb2022

	ITA	SIK	IAK	KAI
Deaths/N	32/1,108	12/49	28/236	1/6



CITR Data 15Feb2022

	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
Deaths/N	23/208	17/271	17/254	13/388	2/224	1/54

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	MedDRA Primary Cause of Death	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immunosuppression
1	ITA	Unknown	2002	Unknown	Tumor on head	Missing Information	Missing Information	.	Yes
2	ITA	Unknown	2008	Unknown	Lung cancer	Unrelated	Unlikely Related	.	Yes
3	ITA	Unknown	2012	Unknown	Renal failure	Unrelated	Unlikely Related	.	Yes
4	ITA	Unknown	2012	Unknown	Liver cancer	Unrelated	Possibly Related	.	Yes
5	ITA	1.2	2002	44	Unknown	Missing Information	Missing Information	.	
6	ITA	1.4	2005	46	Atherosclerotic Coronary Artery Disease	Unrelated	Unrelated	.	Yes
7	ITA	1.7	2008	63	Multiorgan failure infxn unk orig	Unrelated	Related	.	Yes
8	ITA	1.8	2003	43	Acute Methadone and Diphenhydramine Toxicity	Unrelated	Unrelated	>0	Yes
9	ITA	1.9	2012	59	myocardial infarction	Unrelated	Unrelated	.	Yes
10	ITA	2.1	2009	45	Unknown	Missing Information	Missing Information	.	Yes
11	ITA	2.3	2014	67	Unknown	Missing Information	Missing Information	.	Yes
12	ITA	3.2	2002	45	viral meningitis	Unrelated	Possibly Related	.	Yes
13	ITA	3.3	2006	58	Unknown	Missing Information	Missing Information	.	Yes
14	ITA	3.9	2010	66	Unknown	Missing Information	Missing Information	.	
15	ITA	4	2010	50	Unknown	Missing Information	Missing Information	.	
16	ITA	4	2012	48	Nocturnal hypoglycemia	Missing Information	Missing Information	.	
17	ITA	4.4	2001	40	Unknown	Unrelated	Unlikely Related	.	Yes
18	ITA	4.4	2007	62	Unknown	Missing Information	Missing Information	.	
19	ITA	4.6	2006	71	Cardiac failure	Related	Unrelated	>0	Yes
20	ITA	5.3	2003	30	Infection	Unrelated	Unlikely Related	>0	
21	ITA	5.9	2013	69	Unknown	Missing Information	Missing Information	.	Yes
22	ITA	5.9	2014	63	Lung Cancer	Missing Information	Missing Information	.	Yes
23	ITA	6.5	2000	46	Diabetic Ketoacidosis due to Diabetes Mellitus	Unrelated	Unrelated	.	Yes
24	ITA	7.7	2005	68	Unknown	Missing Information	Missing Information	.	Yes
25	ITA	8.2	2000	40	Pneumonia	Unrelated	Unrelated	>0	Yes
26	ITA	8.8	2010	63	Unknown	Missing Information	Missing Information	.	Yes
27	ITA	9.8	2009	70	advanced dementia	Unrelated	Possibly Related	.	Yes
28	ITA	10	2006	77	Sepsis	Missing Information	Missing Information	.	Yes
29	ITA	10	2010	66	Respiratory failure related to Pneumocystis Pneumo	Missing Information	Missing Information	.	Yes

Exhibit 7 –7B (continued)

Deaths by Cause and Relatedness to Procedure or Immunosuppression

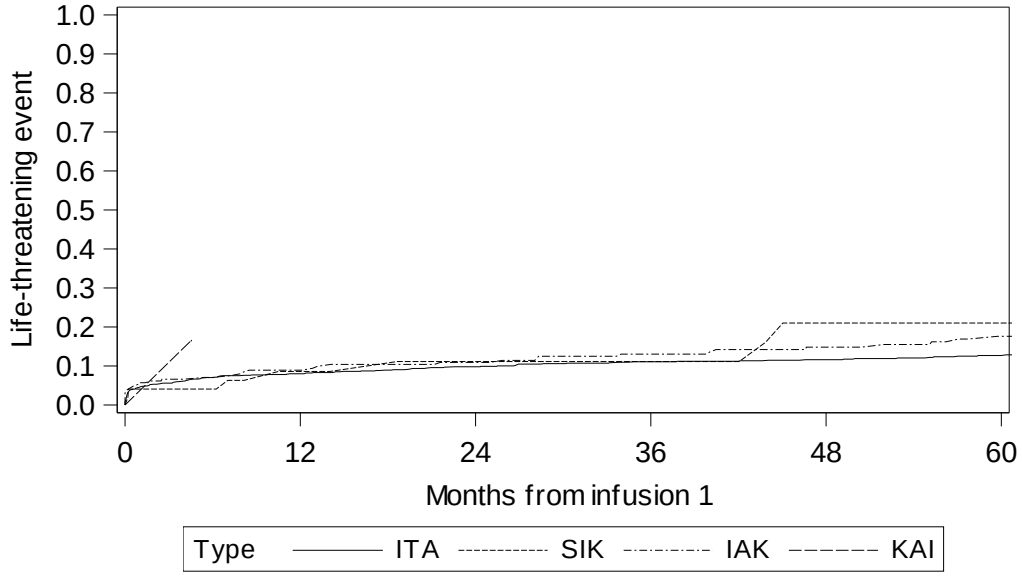
	Type of Transplant	Years post infusion 1	Year of Transplant	Age at Death	MedDRA Primary Cause of Death	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immunosuppression
30	ITA	10.7	2005	55	Diabetes complications	Missing Information	Missing Information	.	Yes
31	ITA	10.7	2007	69	CARDIAC CATH	Unrelated	Unrelated	.	Yes
32	ITA	12.8	2002	57	Unknown	Missing Information	Missing Information	.	Yes
33	ITA	13	2004	50	Unknown	Missing Information	Missing Information	.	Yes
34	ITA	14.7	2004	59	Tumor on head	Missing Information	Missing Information	.	Yes
35	ITA	19.8	2000	51	subarachnoid hemorrhage	Missing Information	Missing Information	.	Yes
36	ITA	20.8	2000	56	Cancer	Unrelated	Unrelated	.	Yes
1	SIK	0	2019	67	state of shock	Unrelated	Unrelated	.	
2	SIK	0.7	2012	47	Acute myocardial infarction	Unrelated	Unrelated	.	Yes
3	SIK	0.9	2001	51	respiratory arrest after therapy withdrawal	Unrelated	Related	.	Yes
4	SIK	1	2000	34	Unknown	Unrelated	Unlikely Related	.	Yes
5	SIK	3.7	2002	62	Subarachnoid hemorrhage mesencephalic	Unrelated	Unrelated	.	Yes
6	SIK	3.8	2014	66	Metastatic SCC	Unrelated	Unlikely Related	>0	Yes
7	SIK	6.2	2000	56	Unknown	Unrelated	Unlikely Related	.	Yes
8	SIK	6.7	2012	61	Septic choc	Unrelated	Unrelated	.	Yes
9	SIK	8.8	1999	63	Lung Carcinoma Non-small cell poorly differentiate	Unrelated	Unlikely Related	>0	Yes
10	SIK	8.9	2011	54	Unknown	Missing Information	Missing Information	.	Yes
11	SIK	14.2	2003	72	Myocardial infarction	Missing Information	Missing Information	.	Yes
12	SIK	15.8	2000	70	necrosis of the foot surinfected	Missing Information	Missing Information	.	Yes
1	IAK	0.1	2002	52	Infectious pneumopathy	Missing Information	Related	.	Yes
2	IAK	0.2	2018	47	Ischemic coronary disease	Missing Information	Missing Information	.	
3	IAK	0.3	2001	35	CARDIO RESPIRATORY ARREST	Unlikely Related	Unlikely Related	.	Yes
4	IAK	2.3	1999	53	Congestive heart failure	Unrelated	Unrelated	.	
5	IAK	2.7	2010	61	Cerebrovascular accident	Missing Information	Missing Information	.	
6	IAK	2.8	2000	36	Respiratory arrest	Missing Information	Missing Information	.	
7	IAK	3.1	2017	73	Unknown	Missing Information	Missing Information	.	
8	IAK	3.2	2008	55	Unknown	Missing Information	Missing Information	.	
9	IAK	3.3	2004	46	Brain hemorrhage	Unrelated	Unrelated	>0	Yes
10	IAK	3.4	2004	54	Digestive cancer	Unrelated	Possibly Related	.	Yes

Exhibit 7 –7B (continued)

Deaths by Cause and Relatedness to Procedure or Immunosuppression

	Type of Transplant	Years post infusion 1	Year of Transplant	Age at Death	Primary Cause of Death	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	Complete Graft Failure	Active Immunosuppression
11	IAK	3.4	2000	52	cerebrovascular event	Unrelated	Unrelated	>0	Yes
12	IAK	3.5	2001	52	massive Hemorrhagic Infarct	Unrelated	Unrelated	.	Yes
13	IAK	4	2012	40	Unknown	Missing Information	Missing Information	.	Yes
14	IAK	4.3	2008	51	Squamous cell	Unlikely Related	Possibly Related	>0	Yes
15	IAK	4.6	2007	56	severe chronic cardiovascular complications	Unrelated	Unrelated	>0	Yes
16	IAK	4.8	2010	63	pneumonia	Missing Information	Missing Information	.	
17	IAK	5.5	2012	60	Cardiac arrest	Unrelated	Unrelated	.	Yes
18	IAK	5.5	2010	65	ischemic cardiomyopathy	Missing Information	Missing Information	.	
19	IAK	5.7	2000	40	Acute myocardial infarction	Unrelated	Unrelated	.	
20	IAK	5.9	2011	60	cardiac arrest	Missing Information	Missing Information	.	
21	IAK	6.3	2003	62	pneumonia	Unrelated	Unrelated	.	Yes
22	IAK	6.5	2011	48	Unknown	Missing Information	Missing Information	.	
23	IAK	8.9	2009	64	Unknown	Missing Information	Missing Information	.	Yes
24	IAK	10.2	2003	55	Cardiac decomposition	Missing Information	Missing Information	.	Yes
25	IAK	10.7	2007	62	Unknown	Missing Information	Missing Information	.	Yes
26	IAK	11	1999	60	Acute myocardial infarction	Missing Information	Missing Information	.	Yes
27	IAK	11.3	2006	62	Unknown	Unlikely Related	Unlikely Related	.	Yes
28	IAK	11.8	2006	56	Lung carcinoma	Unrelated	Possibly Related	.	Yes
1	KAI	16.9	1999	71	Unknown	Missing Information	Missing Information	.	Yes

Exhibit 7 –8A
Life-Threatening Events



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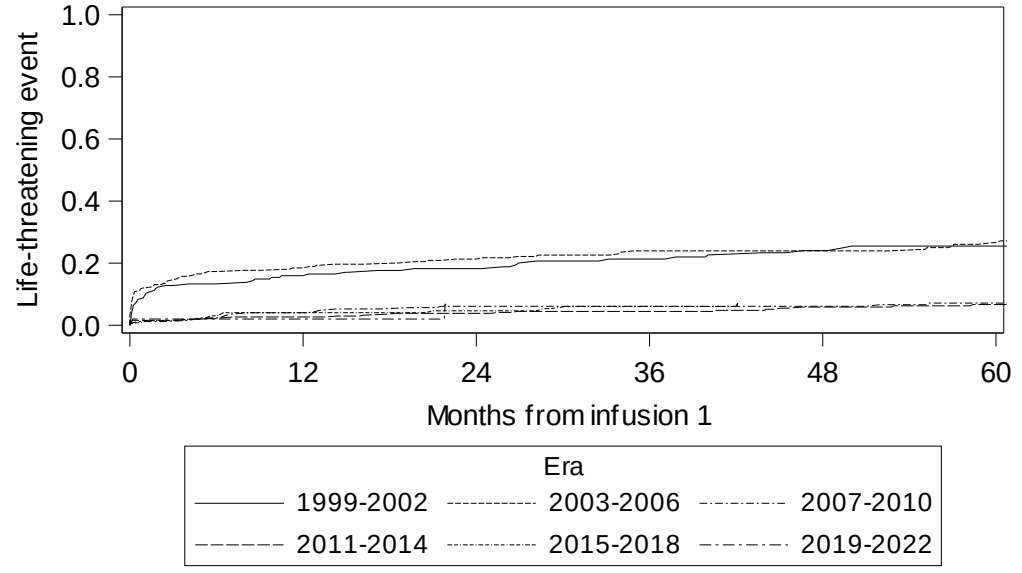
	ITA	SIK	IAK	KAI
Life-threatening events/N	148/1,108	10/49	39/236	1/6



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	1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
Life-threatening events/N	51/208	84/271	24/254	24/388	13/234	2/54

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	Possibly Related	Possibly Related	Blood and lymphatic system disorders	Neutropenia	1999-2002	0.2
		Unlikely Related	Investigations	Haemoglobin	2003-2006	0.9
	Related	Unlikely Related	Gastrointestinal disorders	Gastrointestinal haemorrhage	2003-2006	0.0
			Vascular disorders	Haemorrhage	2003-2006	5.4
			Vascular disorders	Haemorrhage	1999-2002	0.0
		Unrelated	Gastrointestinal disorders	Pancreatic haemorrhage	2003-2006	0.0
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	0.0
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	1.8
			Hepatobiliary disorders	Hepatic haematoma	2011-2014	0.0
			Vascular disorders	Haematoma	2003-2006	0.0
			Vascular disorders	Haemorrhage	2011-2014	0.0
			Vascular disorders	Shock haemorrhagic	2015-2018	0.0
	Unlikely Related	Possibly Related	Immune system disorders	Hypersensitivity	2003-2006	34.0
			Infections and infestations	Infection	2003-2006	14.1
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Squamous cell carcinoma	2007-2010	52.0
			Renal and urinary disorders	Renal failure	1999-2002	8.1
		Unlikely Related	Cardiac disorders	Cardio-respiratory arrest	2003-2006	55.2
			Cardiac disorders	Myocardial ischaemia	1999-2002	40.0
		Unrelated	Nervous system disorders	Cerebral ischaemia	1999-2002	66.6
	Unrelated	Possibly Related	Blood and lymphatic system disorders	Neutropenia	2003-2006	0.4
			Infections and infestations	Opportunistic infection	2007-2010	12.8
			Investigations	Granulocytes abnormal	2003-2006	2.5
			Investigations	Granulocytes abnormal	2003-2006	7.9
			Investigations	Haemoglobin	1999-2002	46.6
			Renal and urinary disorders	Proteinuria	2003-2006	28.3
		Related	Respiratory, thoracic and mediastinal disorders	Pneumonitis	1999-2002	0.6
		Unlikely Related	Blood and lymphatic system disorders	Blood disorder	1999-2002	8.5
			General disorders and administration site conditions	Generalised oedema	2011-2014	40.5
			Infections and infestations	Gangrene	2007-2010	21.6

Exhibit 7 –8B (continued)

Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
IAK	Unrelated	Unrelated	Cardiac disorders	Cardio-respiratory arrest	1999-2002	28.2
			Cardiac disorders	Myocardial ischaemia	2003-2006	59.8
			Investigations	Troponin I	2003-2006	57.1
			Nervous system disorders	Cerebral ischaemia	2007-2010	13.2
			Vascular disorders	Haematoma	1999-2002	25.8
ITA	Possibly Related	Possibly Related	Blood and lymphatic system disorders	Lymphadenopathy	2007-2010	114.6
			Cardiac disorders	Myocardial ischaemia	2003-2006	0.0
			Investigations	Liver function test abnormal	2003-2006	0.2
			Investigations	Liver function test abnormal	2003-2006	0.1
			Respiratory, thoracic and mediastinal disorders	Aspiration	2007-2010	0.1
		Related	Blood and lymphatic system disorders	Lymphopenia	2007-2010	0.0
		Unlikely Related	Hepatobiliary disorders	Cholecystitis	1999-2002	12.4
			Investigations	Blood alkaline phosphatase	1999-2002	0.2
			Investigations	Blood alkaline phosphatase	2003-2006	0.1
			Investigations	Blood alkaline phosphatase	2003-2006	0.1
			Investigations	Liver function test abnormal	1999-2002	0.3
			Investigations	Liver function test abnormal	1999-2002	0.2
			Investigations	Liver function test abnormal	1999-2002	0.2
			Investigations	Liver function test abnormal	2003-2006	0.0
			Investigations	Liver function test abnormal	2003-2006	0.3
			Investigations	Liver function test abnormal	1999-2002	0.2
			Investigations	Liver function test abnormal	1999-2002	0.1
			Investigations	Liver function test abnormal	1999-2002	0.0
			Investigations	Liver function test abnormal	1999-2002	0.1
			Investigations	Liver function test abnormal	1999-2002	0.1
			Investigations	Liver function test abnormal	2003-2006	12.9
			Investigations	Liver function test abnormal	2003-2006	0.1
			Investigations	Liver function test abnormal	2003-2006	0.1
			Investigations	Liver function test abnormal	2003-2006	0.1
			Investigations	Liver function test abnormal	2003-2006	0.3

Exhibit 7 –8B (continued)

Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
ITA	Possibly Related	Unlikely Related	Investigations	Liver function test abnormal	2003-2006	0.3
			Investigations	Liver function test abnormal	2003-2006	0.2
			Investigations	Liver function test abnormal	2003-2006	0.0
			Investigations	Liver function test abnormal	2003-2006	0.0
			Metabolism and nutrition disorders	Ketoacidosis	2007-2010	4.5
		Unrelated	Gastrointestinal disorders	Gastrointestinal disorder	2015-2018	5.3
	Related	Possibly Related	Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	1.1
		Related	Investigations	Granulocytes abnormal	2003-2006	0.1
			Investigations	Liver function test abnormal	1999-2002	1.1
			Nervous system disorders	Neuroleptic malignant syndrome	2011-2014	0.0
		Unlikely Related	Gastrointestinal disorders	Haemoperitoneum	2007-2010	6.4
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	1.0
			Gastrointestinal disorders	Peritoneal haemorrhage	2007-2010	6.7
			Hepatobiliary disorders	Portal vein thrombosis	2019-2022	21.8
		Unrelated	Cardiac disorders	Cardio-respiratory arrest	2011-2014	0.0
			Gastrointestinal disorders	Gastrointestinal obstruction	2003-2006	1.6
			Gastrointestinal disorders	Peritoneal haemorrhage	2003-2006	0.0
			Gastrointestinal disorders	Peritoneal haemorrhage	1999-2002	17.2
			Gastrointestinal disorders	Peritoneal haemorrhage	2007-2010	8.2
			Gastrointestinal disorders	Peritoneal haemorrhage	2011-2014	16.2
			General disorders and administration site conditions	Death	2003-2006	55.1
			Hepatobiliary disorders	Portal vein thrombosis	2003-2006	3.3
			Hepatobiliary disorders	Portal vein thrombosis	2003-2006	0.0
			Hepatobiliary disorders	Subcapsular hepatic haematoma	2011-2014	0.1
			Hepatobiliary disorders	Subcapsular hepatic haematoma	2015-2018	42.1
			Infections and infestations	Infection	2003-2006	1.6
			Investigations	Liver function test abnormal	1999-2002	0.1
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	2.6
	Unlikely Related	Possibly Related	Gastrointestinal disorders	Abdominal pain	2011-2014	0.2
			Infections and infestations	Infection	1999-2002	33.2

Exhibit 7 –8B (continued)

Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
ITA	Unlikely Related	Possibly Related	Investigations	Granulocytes abnormal	1999-2002	0.9
			Investigations	Granulocytes abnormal	2003-2006	19.7
			Investigations	Granulocytes abnormal	2003-2006	0.1
			Investigations	Granulocytes abnormal	2003-2006	0.7
			Investigations	Granulocytes abnormal	2003-2006	0.3
			Renal and urinary disorders	Renal failure	2003-2006	3.3
		Related	Infections and infestations	Pneumonia cytomegaloviral	2003-2006	60.3
			Investigations	Granulocytes abnormal	2003-2006	0.1
			Investigations	Granulocytes abnormal	2007-2010	4.8
		Unlikely Related	Infections and infestations	Infection	2007-2010	14.3
			Nervous system disorders	Serotonin syndrome	2003-2006	77.5
		Unrelated	Vascular disorders	Hypotension	2015-2018	6.5
	Unrelated	Possibly Related	Blood and lymphatic system disorders	Neutropenia	1999-2002	26.7
			Infections and infestations	Infection	2003-2006	20.7
			Infections and infestations	Infection	2003-2006	33.9
			Infections and infestations	Pyelonephritis	2015-2018	6.1
			Investigations	Granulocytes abnormal	1999-2002	1.9
			Investigations	Granulocytes abnormal	1999-2002	2.5
			Investigations	Granulocytes abnormal	1999-2002	1.4
			Investigations	Granulocytes abnormal	1999-2002	4.1
			Investigations	Granulocytes abnormal	1999-2002	1.7
			Investigations	Granulocytes abnormal	1999-2002	49.2
			Investigations	Granulocytes abnormal	1999-2002	0.5
			Investigations	Granulocytes abnormal	2003-2006	3.4
			Investigations	Haemoglobin decreased	2003-2006	1.7
			Investigations	Neutrophil count decreased	2007-2010	110.6
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	11.3
			Metabolism and nutrition disorders	Hypoglycaemia unawareness	2007-2010	125.2
			Metabolism and nutrition disorders	Hypophosphataemia	2003-2006	2.3

Exhibit 7 –8B (continued)

Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
ITA	Unrelated	Possibly Related	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	2003-2006	22.6
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant pleural effusion	1999-2002	228.3
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1999-2002	26.9
			Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	2015-2018	30.3
			Vascular disorders	Hypertension	1999-2002	50.0
		Related	Blood and lymphatic system disorders	Lymphopenia	2003-2006	0.0
			Blood and lymphatic system disorders	Lymphopenia	2003-2006	0.0
			Blood and lymphatic system disorders	Lymphopenia	2003-2006	-1.2
			Blood and lymphatic system disorders	Lymphopenia	2003-2006	0.0
			Blood and lymphatic system disorders	Lymphopenia	2011-2014	18.4
			Blood and lymphatic system disorders	Pancytopenia	2011-2014	6.3
			General disorders and administration site conditions	Multiple organ dysfunction syndrome	2007-2010	19.4
			Infections and infestations	Cytomegalovirus viraemia	2015-2018	21.0
			Investigations	Granulocytes abnormal	1999-2002	37.8
			Investigations	Granulocytes abnormal	1999-2002	9.8
			Investigations	Granulocytes abnormal	2003-2006	0.2
			Investigations	Granulocytes abnormal	2003-2006	0.7
			Investigations	Granulocytes abnormal	2003-2006	5.2
			Investigations	Granulocytes abnormal	2003-2006	3.6
			Psychiatric disorders	Insomnia	1999-2002	19.7
			Renal and urinary disorders	Proteinuria	2003-2006	24.3
		Unlikely Related	Cardiac disorders	Acute myocardial infarction	2011-2014	65.9
			Cardiac disorders	Myocardial ischaemia	2007-2010	4.1
			General disorders and administration site conditions	Pyrexia	2011-2014	25.5
		Unrelated	Cardiac disorders	Coronary artery disease	2003-2006	131.0
			Cardiac disorders	Myocardial ischaemia	2003-2006	87.5
			Cardiac disorders	Myocardial ischaemia	2007-2010	0.7

Exhibit 7 –8B (continued)
Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
ITA	Unrelated	Unrelated	Infections and infestations	Infection	1999-2002	106.8
			Infections and infestations	Urosepsis	2003-2006	96.6
			Injury, poisoning and procedural complications	Subdural haemorrhage	2007-2010	113.5
			Metabolism and nutrition disorders	Diabetic ketoacidosis	2011-2014	5.2
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	26.9
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2002	8.7
			Metabolism and nutrition disorders	Hypoglycaemia	1999-2002	14.9
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	11.1
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	34.9
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	12.4
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	-8.1
			Metabolism and nutrition disorders	Hypoglycaemia	2003-2006	-9.8
			Metabolism and nutrition disorders	Hypoglycaemia	2011-2014	58.4
			Metabolism and nutrition disorders	Hypoglycaemia	2015-2018	28.7
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	2003-2006	105.9
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	2003-2006	4.4
			Nervous system disorders	Cerebellar ischaemia	2007-2010	55.4
			Nervous system disorders	Hypoglycaemic coma	2011-2014	46.6
			Nervous system disorders	Hypoglycaemic coma	2011-2014	14.4
KAI	Unrelated	Unrelated	Reproductive system and breast disorders	Ovarian cyst ruptured	2003-2006	4.6
SIK	Related	Possibly Related	Immune system disorders	Transplant rejection	2007-2010	7.0
	Unlikely Related	Possibly Related	Blood and lymphatic system disorders	Lymphopenia	2003-2006	18.6
		Unlikely Related	Nervous system disorders	Cerebral ischaemia	1999-2002	0.2
	Unrelated	Possibly Related	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	B-cell lymphoma	2011-2014	79.1
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Neoplasm malignant	1999-2002	105.0
			Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Papillary thyroid cancer	2003-2006	79.0

Exhibit 7 –8B (continued)

Life-Threatening Events (By Relatedness to Infusion or Immunosuppression)

Type of Transplant	Related to Infusion Procedure?	Related to Immunosuppression Therapy?	System/Organ Class	MedDRA Preferred Term	Era	Months post infusion 1
SIK	Unrelated	Unlikely Related	General disorders and administration site conditions	Death	2011-2014	45.0
			Immune system disorders	Hypersensitivity	1999-2002	10.5
		Unrelated	General disorders and administration site conditions	Adverse event	2019-2022	0.2
			General disorders and administration site conditions	Death	1999-2002	43.9

Exhibit 7 –8C

Life-Threatening Events (Outcome by System/Organ Class)

		Total	AE Outcome					
			Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	%	%	%	%	%	%
Total		194	4.6	3.6	79.4	8.8	3.1	0.5
System/Organ Class	**Preferred Term**							
Blood and lymphatic system disorders	**Blood disorder**	1	.	.	100.0	.	.	.
	Lymphadenopathy	1	.	.	100.0	.	.	.
	Lymphopenia	7	.	.		.	.	.
	Neutropenia	3	.	.	100.0	.	.	.
	Pancytopenia	1	.	.	100.0	.	.	.
Cardiac disorders	**Acute myocardial infarction**	1	.	.	100.0	100.0	.	.
	Cardio-respiratory arrest	2	50.0	.	100.0	.	.	.
	Coronary artery disease	1	.	.	.	100.0	.	.
	Myocardial ischaemia	7	.	.	50.0	14.3	.	.

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

			AE Outcome					
		Total	Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	%	%	%	%	%	%
Gastrointestinal disorders	Abdominal pain	1	.	.	.	.	.	.
	Gastrointestinal disorder	1	.	.	85.7	.	.	.
	Gastrointestinal haemorrhage	1	.	.	100.0	.	.	.
	Gastrointestinal obstruction	1	.	.	100.0	.	.	.
	Haemoperitoneum	1	.	.	100.0	100.0	.	.
	Peritoneal haemorrhage	9	.	.	100.0	.	.	.
General disorders and administration site conditions	Adverse event	1	100.0	.	.	.	.	.
	Death	4	100.0	.	100.0	.	.	.
	Generalised oedema	1	.	.	.	100.0	.	.
	Multiple organ dysfunction syndrome	1	100.0	.	.	.	.	.
	Pyrexia	1	.	.	.	.	.	.
	Unevaluable event	1	.	.	.	100.0	.	.
Hepatobiliary disorders	Cholecystitis	1	.	.	100.0	.	.	.
	Cholecystitis acute	1	.	.	.	.	.	.
	Hepatic haematoma	1	.	.	100.0	.	.	.
	Portal vein thrombosis	4	.	.	100.0	.	25.0	.
	Subcapsular hepatic haematoma	2	.	.	100.0	.	50.0	.
Immune system disorders	Hypersensitivity	3	.	.	75.0	33.3	.	33.3
	Transplant rejection	1	.	.	50.0	.	.	.

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

			AE Outcome					
		Total	Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	%	%	%	%	%	%
Infections and infestations	BK virus infection	1	.	.	33.3	.	.	.
	Cytomegalovirus viraemia	1	.	.	100.0	.	.	.
	Gangrene	1	.	.	100.0	.	.	.
	Infection	7	.	.	100.0	42.9	.	.
	Opportunistic infection	1	.	.	100.0	.	.	.
	Pneumonia cytomegaloviral	1	.	.	57.1	.	.	.
	Urosepsis	1	.	.	100.0	.	.	.
Injury, poisoning and procedural complications	Concussion	1	.	.	100.0	.	.	.
	Overdose	1	.	.	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	2	.	.	100.0	.	.	.
	Haemoglobin decreased	1	.	.	100.0	.	.	.
	Liver function test abnormal	23	.	.	100.0	4.3	.	.
	Neutrophil count decreased	1	.	.	100.0	.	.	.
	Troponin I	1	.	.	95.7	.	.	.
Metabolism and nutrition disorders	Diabetic ketoacidosis	1	.	.	100.0	.	.	.
	Hypoglycaemia	14	.	.	100.0	.	.	.
	Hypoglycaemia unawareness	1	.	100.0	100.0	.	.	.
	Hypophosphataemia	1	.	.	100.0	.	.	.
	Ketoacidosis	1	.	.	.	.	.	.

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

			AE Outcome					
		Total	Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	%	%	%	%	%	%
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	B-cell lymphoma	1	.	100.0	100.0	.	.	.
	Basal cell carcinoma	1	.	.	100.0	100.0	.	.
	Breast cancer	2	.	.	.	50.0	50.0	.
	Malignant melanoma	1	.	.	.	.	.	.
	Malignant pleural effusion	1	.	100.0	.	.	.	.
	Neoplasm malignant	3	.	66.7	100.0	.	.	.
	Papillary thyroid cancer	1	.	.	.	.	100.0	.
	Polycythaemia vera	1	.	.	33.3	.	100.0	.
	Squamous cell carcinoma	3	33.3	.	.	.	.	.
	Transitional cell carcinoma	1	.	.	.	.	.	.
Nervous system disorders	Cerebellar ischaemia	1	.	.	66.7	100.0	.	.
	Cerebral ischaemia	3	.	33.3	100.0	66.7	.	.
	Hypoglycaemic coma	2	.	.	.	.	.	.
	Neuroleptic malignant syndrome	1	.	.	.	.	.	.
	Serotonin syndrome	1	.	.	100.0	.	.	.
Psychiatric disorders	Insomnia	1	.	.	100.0	.	.	.
Renal and urinary disorders	Proteinuria	2	.	50.0	100.0	.	.	.
	Renal failure	3	.	.	100.0	33.3	33.3	.
Reproductive system and breast disorders	Ovarian cyst ruptured	1	.	.	50.0	.	.	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory failure	1	.	.	33.3	.	.	.
	Aspiration	1	.	.	100.0	.	.	.
	Asthma	1	.	.	100.0	.	.	.
	Pneumonitis	1	100.0	.	100.0	.	.	.

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

		Total	AE Outcome					
			Fatal	Not recovered	Recovered	Recovered with sequelae	Recovering	Unknown
		N	%	%	%	%	%	%
Skin and subcutaneous tissue disorders	**Skin lesion**	1	.	.	100.0	.	.	.
Vascular disorders	**Haematoma**	2	.	.	.	.	.	.
	Haemorrhage	3	.	.	100.0	.	.	.
	Hypertension	1	.	.	100.0	.	.	.
	Hypotension	1	.	.	100.0	.	.	.
	Peripheral ischaemia	1	.	.	100.0	.	.	.
	Shock haemorrhagic	1	.	.	100.0	.	.	.

Exhibit 7 –9

All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
System/Organ Class	Preferred term					
Blood and lymphatic system disorders	Agranulocytosis	1	.	1	.	.
	Anaemia	10	7	1	2	.
	Blood disorder	4	3	.	1	.
	Bone marrow disorder	2	2	.	.	.
	Febrile neutropenia	8	8	.	.	.
	Haemolysis	1	1	.	.	.
	Hypochromic anaemia	2	2	.	.	.
	Leukopenia	6	2	1	3	.
	Lymphadenopathy	2	2	.	.	.
	Lymphopenia	14	11	2	1	.
	Myelosuppression	2	2	.	.	.
	Neutropenia	35	28	1	6	.
	Pancytopenia	1	1	.	.	.
	Platelet disorder	1	1	.	.	.
	Thrombocytopenia	7	7	.	.	.
Cardiac disorders	Acute coronary syndrome	1	1	.	.	.
	Acute myocardial infarction	6	4	1	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	4	2	1	1	.
	Myocardial ischaemia	19	11	2	6	.
	Myocarditis	2	2	.	.	.
	Pericardial effusion	2	.	.	2	.
	Pericarditis	1	1	.	.	.
Endocrine disorders	Endocrine disorder	4	2	.	2	.
	Hypoglycaemia	1	1	.	.	.
	Thyroiditis subacute	1	1	.	.	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

		Overall	Transplant type			
			ITA	SIK	IAK	KAI
		N	N	N	N	N
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	51	45	2	4	.
	Food poisoning	1	1	.	.	.
	Gastritis	1	.	.	1	.
	Gastrointestinal disorder	22	14	2	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	.
	Pancreatic haemorrhage	1	.	.	1	.
	Pancreatitis	1	1	.	.	.
	Peritoneal haemorrhage	44	32	2	10	.
	Small intestinal obstruction	9	9	.	.	.
	Umbilical hernia	1	1	.	.	.
	Vomiting	50	42	.	8	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
General disorders and administration site conditions	Adverse event	5	2	2	1	.
	Asthenia	1	1	.	.	.
	Chest pain	3	3	.	.	.
	Chills	1	1	.	.	.
	Death	19	7	7	5	.
	Fatigue	4	4	.	.	.
	Generalised oedema	1	.	.	1	.
	Impaired healing	1	.	.	1	.
	Influenza like illness	1	1	.	.	.
	Mucosal inflammation	8	6	.	1	1
	Multiple organ dysfunction syndrome	1	1	.	.	.
	Oedema peripheral	6	4	.	2	.
	Pain	29	25	.	3	1
	Pyrexia	8	8	.	.	.
	Systemic inflammatory response syndrome	4	1	.	3	.
	Ulcer	1	.	.	1	.
	Unevaluable event	4	4	.	.	.
Hepatobiliary disorders	Biliary tract disorder	1	1	.	.	.
	Cholecystitis	10	7	1	2	.
	Cholecystitis acute	1	1	.	.	.
	Hepatic artery stenosis	1	.	1	.	.
	Hepatic haematoma	5	3	1	1	.
	Hepatic haemorrhage	3	3	.	.	.
	Hepatitis cholestatic	1	1	.	.	.
	Hepatobiliary disease	2	2	.	.	.
	Portal vein thrombosis	13	12	.	1	.
	Subcapsular hepatic haematoma	8	7	.	1	.
Immune system disorders	Autoimmune disorder	1	1	.	.	.
	Cytokine release syndrome	1	1	.	.	.
	Graft versus host disease	2	2	.	.	.
	Hypersensitivity	21	17	2	2	.
	Pancreas transplant rejection	2	1	.	1	.
	Sensitisation	2	1	.	1	.
	Serum sickness	3	3	.	.	.
	Transplant rejection	3	3	.	.	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

		Overall	Transplant type			
			ITA	SIK	IAK	KAI
		N	N	N	N	N
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	1	.	1	.	.
	COVID-19 pneumonia	1	1	.	.	.
	Clostridium difficile colitis	2	2	.	.	.
	Clostridium difficile infection	2	2	.	.	.
	Coccidioidomycosis	1	1	.	.	.
	Coronavirus infection	1	.	1	.	.
	Cytomegalovirus hepatitis	1	.	.	1	.
	Cytomegalovirus infection	2	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	.
	Herpes simplex	1	1	.	.	.
	Infection	100	59	13	27	1
	Joint abscess	1	1	.	.	.
	Kidney infection	2	2	.	.	.
	Klebsiella sepsis	1	1	.	.	.
	Large intestine infection	2	2	.	.	.
	Localised infection	1	1	.	.	.
	Metapneumovirus infection	1	1	.	.	.
	Norovirus infection	4	4	.	.	.
	Oesophageal candidiasis	1	1	.	.	.
	Opportunistic infection	2	1	.	1	.
	Oral herpes	1	1	.	.	.
	Osteomyelitis	1	1	.	.	.
	Pneumocystis jirovecii pneumonia	2	.	2	.	.
	Pneumonia	27	15	4	7	1
	Pneumonia cytomegaloviral	2	1	1	.	.
	Pneumonia legionella	1	1	.	.	.
	Pneumonia pseudomonal	2	.	1	.	1
	Polyomavirus viraemia	1	.	.	1	.
	Polyomavirus-associated nephropathy	2	.	2	.	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
Infections and infestations	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	19	6	.	13	.
	Urosepsis	2	1	1	.	.
	Vestibular neuronitis	1	1	.	.	.
	Viral infection	1	1	.	.	.
Injury, poisoning and procedural complications	Combined tibia-fibula fracture	1	1	.	.	.
	Foot fracture	1	1	.	.	.
	Fracture	9	8	.	1	.
	Hip fracture	9	9	.	.	.
	Incision site pain	1	1	.	.	.
	Injury	3	2	.	1	.
	Limb injury	1	1	.	.	.
	Lower limb fracture	1	1	.	.	.
	Overdose	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	12	8	1	3	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
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	.	.	.
	Glomerular filtration rate	1	.	.	1	.
	Glomerular filtration rate decreased	1	.	.	1	.
	Granulocytes abnormal	56	50	.	6	.
	Haemoglobin	17	13	.	3	1
	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	80	54	.	26	.
	Hypoglycaemia unawareness	1	1	.	.	.
	Hypokalaemia	1	1	.	.	.
	Hypomagnesaemia	1	1	.	.	.
	Hyponatraemia	7	7	.	.	.
	Hypophosphataemia	1	1	.	.	.
	Hypovolaemia	2	.	.	2	.
	Ketoacidosis	17	14	.	3	.
	Malnutrition	1	.	.	1	.
	Metabolic disorder	1	.	.	1	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

		Overall	Transplant type			
			ITA	SIK	IAK	KAI
		N	N	N	N	N
Musculoskeletal and connective tissue disorders	Arthralgia	2	2	.	.	.
	Arthritis	2	2	.	.	.
	Arthritis reactive	1	1	.	.	.
	Arthropathy	1	1	.	.	.
	Hip fracture	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	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma	2	.	.	2	.
	B-cell lymphoma	1	.	1	.	.
	Basal cell carcinoma	15	14	.	1	.
	Basosquamous carcinoma	2	1	.	1	.
	Breast cancer	5	5	.	.	.
	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 pancreas	1	1	.	.	.
	Intraductal proliferative breast lesion	1	1	.	.	.
	Invasive ductal breast carcinoma	1	1	.	.	.
	Lung carcinoma cell type unspecified stage III	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	17	12	1	4	.
	Ovarian adenoma	1	1	.	.	.
	Papillary thyroid cancer	2	1	1	.	.
	Plasma cell myeloma	1	1	.	.	.
	Polycythaemia vera	1	1	.	.	.
	Post transplant lymphoproliferative disorder	6	2	.	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	.	.	.
	Transitional cell carcinoma	2	2	.	.	.
	Uterine leiomyoma	1	1	.	.	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
Nervous system disorders	Amnesia	1	1	.	.	.
	Cerebellar ischaemia	1	1	.	.	.
	Cerebellar stroke	3	3	.	.	.
	Cerebral ischaemia	10	.	1	9	.
	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	.	.	.
	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	.	.	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
Renal and urinary disorders	Acute kidney injury	6	3	.	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	28	15	3	10	.
	Renal infarct	1	1	.	.	.
	Tubulointerstitial nephritis	1	1	.	.	.
	Urinary bladder haemorrhage	3	1	.	2	.
	Urinary retention	1	1	.	.	.
Reproductive system and breast disorders	Cervical dysplasia	1	1	.	.	.
	Lactation disorder	1	1	.	.	.
	Ovarian cyst	1	.	.	.	1
	Ovarian cyst ruptured	1	.	.	.	1
	Rectocele	1	1	.	.	.
	Sexual dysfunction	7	6	.	1	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	2	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	1	1	.	.	.
	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	.	.	.

Exhibit 7 –9 (continued)
All SAEs Classified by Transplant Type

			Transplant type			
		Overall	ITA	SIK	IAK	KAI
		N	N	N	N	N
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	.	.	.
	Skin neoplasm excision	2	2	.	.	.
	Surgery	6	3	.	3	.
	Thymectomy	1	.	1	.	.
	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	4	1	2	1	.
	Shock haemorrhagic	1	.	.	1	.
	Thrombosis	2	.	1	1	.
	Vascular occlusion	1	1	.	.	.

Exhibit 7 –10
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
System/Organ Class	Preferred term						
Blood and lymphatic system disorders	Agranulocytosis	.	1	.	.	.	.
	Anaemia	.	1	4	4	1	.
	Blood disorder	1	.	1	.	1	1
	Bone marrow disorder	.	.	.	2	.	.
	Febrile neutropenia	.	1	5	2	.	.
	Haemolysis	.	1	.	.	.	.
	Hypochromic anaemia	.	.	2	.	.	.
	Leukopenia	.	.	.	4	2	.
	Lymphadenopathy	.	.	1	1	.	.
	Lymphopenia	1	7	5	1	.	.
	Myelosuppression	.	.	.	2	.	.
	Neutropenia	2	1	4	25	3	.
	Pancytopenia	.	.	.	1	.	.
	Platelet disorder	.	1	.	.	.	.
	Thrombocytopenia	.	.	7	.	.	.
Cardiac disorders	Acute coronary syndrome	.	.	1	.	.	.
	Acute myocardial infarction	1	.	1	4	.	.
	Arrhythmia	.	1	.	.	.	.
	Atrial fibrillation	.	.	2	.	.	.
	Atrial flutter	.	.	1	.	.	.
	Atrioventricular block	.	1	.	.	.	.
	Bradycardia	.	.	.	1	.	.
	Brugada syndrome	.	1	.	.	.	.
	Cardiac arrest	.	.	.	1	.	.
	Cardiac disorder	1	.	1	.	.	.
	Cardiac failure congestive	.	.	2	.	.	.
	Cardio-respiratory arrest	1	1	.	1	.	.
	Coronary artery disease	.	2	.	2	.	.
	Left ventricular dysfunction	.	.	1	.	.	.
	Mitral valve incompetence	.	.	1	.	.	.
	Myocardial infarction	.	2	.	2	.	.
	Myocardial ischaemia	5	7	5	1	1	.
	Myocarditis	1	1	.	.	.	.
	Pericardial effusion	1	1	.	.	.	.
	Pericarditis	.	1	.	.	.	.
Endocrine disorders	Endocrine disorder	1	1	2	.	.	.
	Hypoglycaemia	.	.	.	1	.	.
	Thyroiditis subacute	1	.	.	.	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Eye disorders	Eye disorder	.	3	1	.	.	.
	Ocular surface disease	.	1	.	.	.	.
	Retinal detachment	1	1	3	.	.	.
	Retinal haemorrhage	.	.	.	1	.	.
	Vitreous haemorrhage	1	1	3	.	.	.
Gastrointestinal disorders	Abdominal pain	.	.	2	2	1	.
	Abdominal pain upper	.	1	.	.	.	.
	Appendix disorder	.	.	3	.	.	.
	Ascites	2	2	.	.	.	.
	Colitis	1	5	1	.	.	.
	Constipation	.	.	1	.	.	.
	Diarrhoea	9	17	18	4	3	.
	Food poisoning	.	.	.	1	.	.
	Gastritis	.	.	1	.	.	.
	Gastrointestinal disorder	2	15	1	2	2	.
	Gastrointestinal haemorrhage	2	3	.	.	.	.
	Gastrointestinal obstruction	1	6	1	.	.	.
	Gastrointestinal perforation	.	.	1	.	.	.
	Haemoperitoneum	.	.	1	5	1	.
	Haemorrhoids	.	1	.	.	.	.
	Ileus	.	1	.	.	.	.
	Intestinal obstruction	.	.	.	1	.	.
	Intra-abdominal haemorrhage	.	1	1	1	.	1
	Mouth ulceration	.	.	.	.	2	1
	Nausea	1	1	1	4	1	.
	Pancreatic haemorrhage	.	1	.	.	.	.
	Pancreatitis	1	.	.	.	.	.
	Peritoneal haemorrhage	13	15	9	6	1	.
	Small intestinal obstruction	.	.	.	9	.	.
	Umbilical hernia	.	.	.	1	.	.
	Vomiting	6	7	10	14	13	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
General disorders and administration site conditions	Adverse event	1	1	2	.	.	1
	Asthenia	.	.	1	.	.	.
	Chest pain	.	.	2	1	.	.
	Chills	.	1	.	.	.	.
	Death	10	4	2	3	.	.
	Fatigue	1	.	3	.	.	.
	Generalised oedema	.	.	.	1	.	.
	Impaired healing	.	.	.	1	.	.
	Influenza like illness	.	.	1	.	.	.
	Mucosal inflammation	2	5	1	.	.	.
	Multiple organ dysfunction syndrome	.	.	1	.	.	.
	Oedema peripheral	.	3	2	1	.	.
	Pain	11	13	4	1	.	.
	Pyrexia	3	.	1	4	.	.
	Systemic inflammatory response syndrome	.	1	3	.	.	.
	Ulcer	.	1	.	.	.	.
	Unevaluable event	.	2	1	.	1	.
Hepatobiliary disorders	Biliary tract disorder	.	1	.	.	.	.
	Cholecystitis	5	3	2	.	.	.
	Cholecystitis acute	.	.	.	1	.	.
	Hepatic artery stenosis	.	.	.	1	.	.
	Hepatic haematoma	.	3	.	2	.	.
	Hepatic haemorrhage	.	1	.	2	.	.
	Hepatitis cholestatic	.	.	1	.	.	.
	Hepatobiliary disease	.	1	.	1	.	.
	Portal vein thrombosis	4	5	2	.	1	1
	Subcapsular hepatic haematoma	.	.	5	2	1	.
Immune system disorders	Autoimmune disorder	.	.	1	.	.	.
	Cytokine release syndrome	.	.	1	.	.	.
	Graft versus host disease	.	.	.	2	.	.
	Hypersensitivity	3	10	5	3	.	.
	Pancreas transplant rejection	.	.	1	1	.	.
	Sensitisation	.	1	.	1	.	.
	Serum sickness	.	.	2	.	1	.
	Transplant rejection	.	.	.	2	1	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Infections and infestations	Appendicitis	.	.	.	4	.	.
	Appendicitis perforated	.	.	.	2	.	.
	Arthritis bacterial	.	1	.	.	.	.
	BK virus infection	.	.	.	.	1	.
	Bacterial sepsis	.	1	.	.	.	.
	COVID-19	.	.	.	.	1	.
	COVID-19 pneumonia	.	1	.	.	.	.
	Clostridium difficile colitis	.	1	1	.	.	.
	Clostridium difficile infection	.	1	.	1	.	.
	Coccidioidomycosis	.	.	.	1	.	.
	Coronavirus infection	.	.	.	.	1	.
	Cytomegalovirus hepatitis	.	.	.	1	.	.
	Cytomegalovirus infection	.	.	.	1	1	.
	Cytomegalovirus viraemia	.	.	.	.	1	.
	Dermo-hypodermitis	.	.	.	.	.	1
	Encephalitis cytomegalovirus	.	.	.	1	.	.
	Epididymitis	.	2	.	.	.	.
	Erysipelas	.	.	1	.	.	.
	Escherichia pyelonephritis	.	.	.	.	1	.
	Escherichia sepsis	.	2	.	.	.	.
	Gangrene	.	.	1	.	.	.
	Herpes simplex	.	.	1	.	.	.
	Infection	38	43	16	2	1	.
	Joint abscess	.	1	.	.	.	.
	Kidney infection	.	.	.	2	.	.
	Klebsiella sepsis	.	.	.	1	.	.
	Large intestine infection	.	.	1	.	1	.
	Localised infection	.	1	.	.	.	.
	Metapneumovirus infection	.	.	.	1	.	.
	Norovirus infection	.	.	.	4	.	.
	Oesophageal candidiasis	.	.	.	1	.	.
	Opportunistic infection	.	.	2	.	.	.
	Oral herpes	.	1	.	.	.	.
	Osteomyelitis	.	1	.	.	.	.
	Pneumocystis jirovecii pneumonia	.	.	1	.	1	.
	Pneumonia	1	2	14	5	5	.
	Pneumonia cytomegaloviral	.	1	.	.	1	.
	Pneumonia legionella	.	1	.	.	.	.
	Pneumonia pseudomonal	.	.	.	.	2	.
	Polyomavirus viraemia	.	.	.	.	1	.
	Polyomavirus-associated nephropathy	.	.	.	2	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Infections and infestations	Pyelonephritis	.	1	.	5	1	.
	Renal graft infection	.	.	.	1	.	.
	Sepsis	.	1	.	1	.	.
	Skin infection	.	.	4	.	.	.
	Staphylococcal bacteraemia	.	.	.	.	.	1
	Staphylococcal infection	.	1	.	.	.	.
	Trench fever	1	.	.	.	.	.
	Urinary tract infection	.	.	4	15	.	.
	Urosepsis	.	1	.	1	.	.
	Vestibular neuronitis	.	.	1	.	.	.
	Viral infection	.	.	.	1	.	.
Injury, poisoning and procedural complications	Combined tibia-fibula fracture	.	1	.	.	.	.
	Foot fracture	.	1	.	.	.	.
	Fracture	3	2	4	.	.	.
	Hip fracture	.	1	6	2	.	.
	Incision site pain	.	.	.	1	.	.
	Injury	1	1	1	.	.	.
	Limb injury	.	1	.	.	.	.
	Lower limb fracture	.	1	.	.	.	.
	Overdose	.	.	.	.	1	.
	Post procedural haemorrhage	.	.	1	.	.	.
	Procedural pain	.	.	2	.	.	.
	Subdural haemorrhage	.	.	1	.	.	.
	Toxicity to various agents	.	.	1	1	.	.
	Upper limb fracture	.	.	.	1	.	.
	Vascular injury	.	.	1	.	.	.
	Wound	.	.	1	.	.	.
	Wound complication	3	3	6	.	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Investigations	**BK polyomavirus test positive**	.	.	.	1	.	.
	Blood alkaline phosphatase	4	10	.	.	.	.
	Blood creatine phosphokinase	.	1	.	.	.	.
	Blood creatinine	2	8	2	1	.	.
	Blood creatinine increased	.	1	2	4	.	.
	Blood glucose abnormal	.	.	.	1	.	.
	Blood glucose increased	.	.	.	.	1	.
	Blood potassium increased	.	.	.	1	1	.
	Clostridium test	.	.	.	.	1	.
	Coagulation factor	.	.	1	.	.	.
	Donor specific antibody present	.	.	.	3	.	.
	Glomerular filtration rate	.	1	.	.	.	.
	Glomerular filtration rate decreased	.	.	1	.	.	.
	Granulocytes abnormal	21	25	10	.	.	.
	Haemoglobin	4	9	4	.	.	.
	Haemoglobin decreased	.	2	.	2	.	.
	Hepatic enzyme increased	.	.	.	1	.	.
	Laboratory test	.	1	.	.	.	.
	Liver function test abnormal	19	17	.	.	.	.
	Neutrophil count	.	.	3	.	.	.
	Neutrophil count decreased	.	1	3	.	.	.
	Renin increased	.	.	.	1	.	.
	Troponin I	.	1	.	.	.	.
	Troponin T	.	.	1	.	.	.
	Weight decreased	.	1	.	.	.	.
Metabolism and nutrition disorders	**Dehydration**	1	3	2	2	.	.
	Diabetes mellitus	.	.	.	1	.	.
	Diabetic ketoacidosis	.	1	.	7	.	.
	Hyperglycaemia	1	.	.	5	.	.
	Hyperkalaemia	.	.	.	4	.	.
	Hypoglycaemia	5	24	13	34	4	.
	Hypoglycaemia unawareness	.	.	1	.	.	.
	Hypokalaemia	.	1	.	.	.	.
	Hypomagnesaemia	.	1	.	.	.	.
	Hyponatraemia	.	7	.	.	.	.
	Hypophosphataemia	.	1	.	.	.	.
	Hypovolaemia	.	.	.	2	.	.
	Ketoacidosis	3	8	5	1	.	.
	Malnutrition	.	1	.	.	.	.
	Metabolic disorder	1	.	.	.	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Musculoskeletal and connective tissue disorders	**Arthralgia**	.	.	.	1	.	1
	Arthritis	.	1	1	.	.	.
	Arthritis reactive	.	.	.	.	.	1
	Arthropathy	.	.	1	.	.	.
	Hip fracture	.	.	1	.	.	.
	Intervertebral disc protrusion	.	.	1	.	.	.
	Muscle necrosis	.	1	.	.	.	.
	Musculoskeletal disorder	3	2	.	.	.	.
	Myalgia	.	.	1	.	.	.
	Neuropathic arthropathy	.	.	3	.	.	.
	Osteoarthritis	1	.	.	.	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adenocarcinoma	.	.	.	2	.	.
	B-cell lymphoma	.	.	.	1	.	.
	Basal cell carcinoma	.	3	9	3	.	.
	Basosquamous carcinoma	.	1	1	.	.	.
	Breast cancer	.	3	.	2	.	.
	Cervix carcinoma	.	.	.	.	1	.
	Cholangiocarcinoma	.	.	.	1	.	.
	Colorectal cancer stage IV	.	.	.	1	.	.
	Diffuse large B-cell lymphoma	.	.	1	.	.	.
	Gastrointestinal carcinoma	.	1	.	.	.	.
	Intraductal papillary-mucinous carcinoma of pancreas	1	.	.	.	.	.
	Intraductal proliferative breast lesion	.	.	1	.	.	.
	Invasive ductal breast carcinoma	1	.	.	.	.	.
	Lung carcinoma cell type unspecified stage III	.	.	.	1	.	.
	Lung neoplasm malignant	.	.	2	.	.	.
	Lymphoma	.	1	.	.	.	.
	Malignant melanoma	.	1	1	.	.	.
	Malignant pleural effusion	1	.	.	.	.	.
	Neoplasm	1	.	1	.	.	.
	Neoplasm malignant	8	7	2	.	.	.
	Ovarian adenoma	.	1	.	.	.	.
	Papillary thyroid cancer	.	2	.	.	.	.
	Plasma cell myeloma	.	.	.	.	1	.
	Polycythaemia vera	.	.	.	1	.	.
	Post transplant lymphoproliferative disorder	.	1	1	4	.	.
	Prostate cancer	.	.	.	4	.	.
	Small intestine carcinoma	.	.	1	.	.	.
	Squamous cell carcinoma	1	18	6	3	.	.
	Squamous cell carcinoma of head and neck	.	.	1	.	.	.
	Squamous cell carcinoma of lung	.	1	.	.	.	.
	Squamous cell carcinoma of skin	.	.	6	.	.	.
	Transitional cell carcinoma	.	1	.	1	.	.
	Uterine leiomyoma	.	.	.	.	1	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Nervous system disorders	Amnesia	.	.	1	.	.	.
	Cerebellar ischaemia	.	.	1	.	.	.
	Cerebellar stroke	.	.	3	.	.	.
	Cerebral ischaemia	3	1	2	4	.	.
	Cognitive disorder	.	.	1	.	.	.
	Dizziness	.	2	1	.	.	.
	Frontotemporal dementia	.	.	1	.	.	.
	Generalised tonic-clonic seizure	.	.	.	1	.	.
	Headache	.	.	2	2	.	.
	Hydrocephalus	.	.	6	.	.	.
	Hypoglycaemic coma	.	.	.	2	.	.
	Hypoglycaemic seizure	.	.	.	1	.	.
	Loss of consciousness	.	1	.	.	.	.
	Nervous system disorder	2	2	2	.	.	.
	Neuroleptic malignant syndrome	.	.	.	1	.	.
	Neurological symptom	.	.	.	1	.	.
	Neuropathy peripheral	.	.	.	1	.	.
	Optic neuritis	.	1	.	.	.	.
	Psychogenic seizure	.	.	.	2	.	.
	Seizure	1	.	.	4	.	.
	Serotonin syndrome	.	1	.	.	.	.
	Spinal cord compression	.	.	.	2	.	.
	Subarachnoid haemorrhage	.	.	.	1	.	.
	Syncope	1	2	3	1	1	.
	Transient ischaemic attack	.	.	1	1	.	.
	Tremor	1	.	.	.	.	.
Psychiatric disorders	Acute psychosis	.	.	.	1	.	.
	Anxiety	.	.	.	2	.	.
	Confusional state	1	.	2	.	.	.
	Delusion	.	.	.	9	.	.
	Insomnia	1	.	.	.	.	.
	Mood altered	2	1	.	.	.	.
	Psychotic disorder	1	.	.	.	.	.
	Suicidal ideation	.	.	.	1	.	.
	Suicide attempt	.	.	.	3	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Renal and urinary disorders	Acute kidney injury	.	2	1	3	.	.
	End stage renal disease	1	.	.	.	.	.
	Ketonuria	.	1	.	.	.	.
	Nephropathy	1	.	.	.	.	.
	Proteinuria	.	2	.	1	.	.
	Renal artery stenosis	.	.	.	1	.	.
	Renal disorder	3	3	2	.	.	.
	Renal failure	10	6	5	5	2	.
	Renal infarct	.	.	.	1	.	.
	Tubulointerstitial nephritis	.	.	1	.	.	.
	Urinary bladder haemorrhage	1	1	1	.	.	.
	Urinary retention	.	.	.	1	.	.
Reproductive system and breast disorders	Cervical dysplasia	.	.	.	1	.	.
	Lactation disorder	.	1	.	.	.	.
	Ovarian cyst	.	1	.	.	.	.
	Ovarian cyst ruptured	.	1	.	.	.	.
	Rectocele	.	.	.	.	1	.
	Sexual dysfunction	2	4	1	.	.	.
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	1	1	.	.	.	.
	Acute respiratory failure	.	.	.	.	1	.
	Aspiration	1	.	1	.	.	.
	Asthma	.	1	.	.	.	.
	Cough	1	1	.	.	.	.
	Dyspnoea	2	1	1	1	.	.
	Hypoxia	.	1	3	.	.	.
	Lung disorder	1	4	2	1	.	.
	Lung infiltration	.	.	4	.	.	.
	Pleural effusion	.	.	1	.	.	.
	Pneumonitis	3	1	1	.	.	.
	Pulmonary embolism	.	.	.	1	.	.
	Pulmonary hypertension	.	.	3	.	.	.
Skin and subcutaneous tissue disorders	Decubitus ulcer	.	2	.	.	.	.
	Exfoliative rash	.	.	1	.	.	.
	Rash	.	.	1	.	.	.
	Skin disorder	1	.	.	.	.	.
	Skin lesion	.	1	.	.	.	.

Exhibit 7 –10 (continued)
All SAEs Classified by Era

		Era					
		1999-2002	2003-2006	2007-2010	2011-2014	2015-2018	2019-2022
		N	N	N	N	N	N
Surgical and medical procedures	**Amputation**	.	.	1	.	.	.
	Brain operation	.	.	.	1	.	.
	Breast reconstruction	.	.	.	1	.	.
	Cholecystectomy	.	.	.	2	.	.
	Coronary arterial stent insertion	.	1	.	.	.	.
	Coronary artery bypass	.	1	1	1	.	.
	Hernia repair	.	.	.	1	.	.
	Ileostomy	.	1	.	.	.	.
	Skin neoplasm excision	.	.	2	.	.	.
	Surgery	2	1	3	.	.	.
	Thymectomy	.	1	.	.	.	.
	Toe amputation	.	1	.	.	.	.
Vascular disorders	**Arterial stenosis**	.	.	1	.	.	.
	Arterial thrombosis	.	1	.	.	.	.
	Blood pressure inadequately controlled	.	.	1	.	.	.
	Haematoma	3	4	1	2	.	.
	Haemorrhage	2	6	3	1	1	.
	Hypertension	1	1	2	1	.	.
	Intermittent claudication	.	1	.	.	.	.
	Lymphoedema	.	1	.	.	.	.
	Orthostatic hypotension	.	.	.	1	.	.
	Peripheral arterial occlusive disease	1	.	.	.	.	.
	Peripheral ischaemia	2	2	.	.	.	.
	Shock haemorrhagic	.	.	.	.	1	.
	Thrombosis	2	.	.	.	.	.
	Vascular occlusion	.	.	.	1	.	.

Chapter 8
Registry Data Quality Review

Introduction

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

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 - 2002	216	210	210	206	203	200	86	80	80	78	76	76	130	130	130	128	127	124
2003 - 2006	271	270	269	268	264	257	105	105	105	104	104	99	166	165	164	164	160	158
2007 - 2010	256	255	252	250	246	238	110	109	109	108	108	106	146	146	143	142	138	132
2011 - 2014	392	390	389	385	379	369	202	200	199	199	196	195	190	190	190	186	183	174
2015 - 2018	235	233	229	203	152	104	140	139	135	123	97	67	95	94	94	80	55	37
2019 - 2022	56	50	31	1	0	0	40	35	22	1	0	0	16	15	9	0	0	0

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

Exhibit 8 – 1

Missing Data for Insulin Independence by Era and Continent

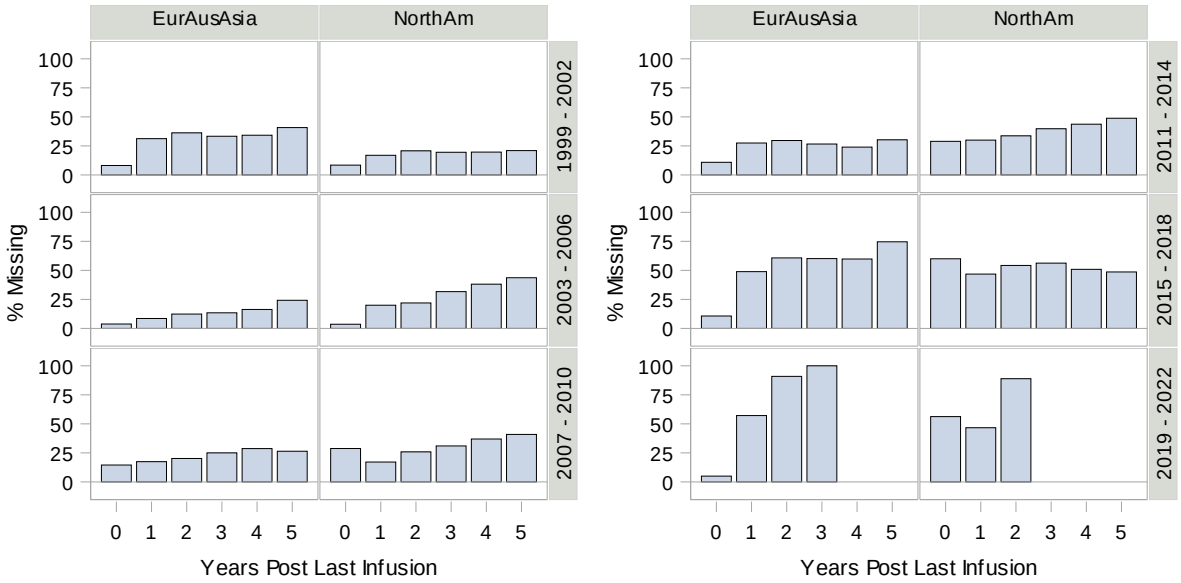

Exhibit 8 – 2

Missing Data for Fasting C-Peptide by Era and Continent

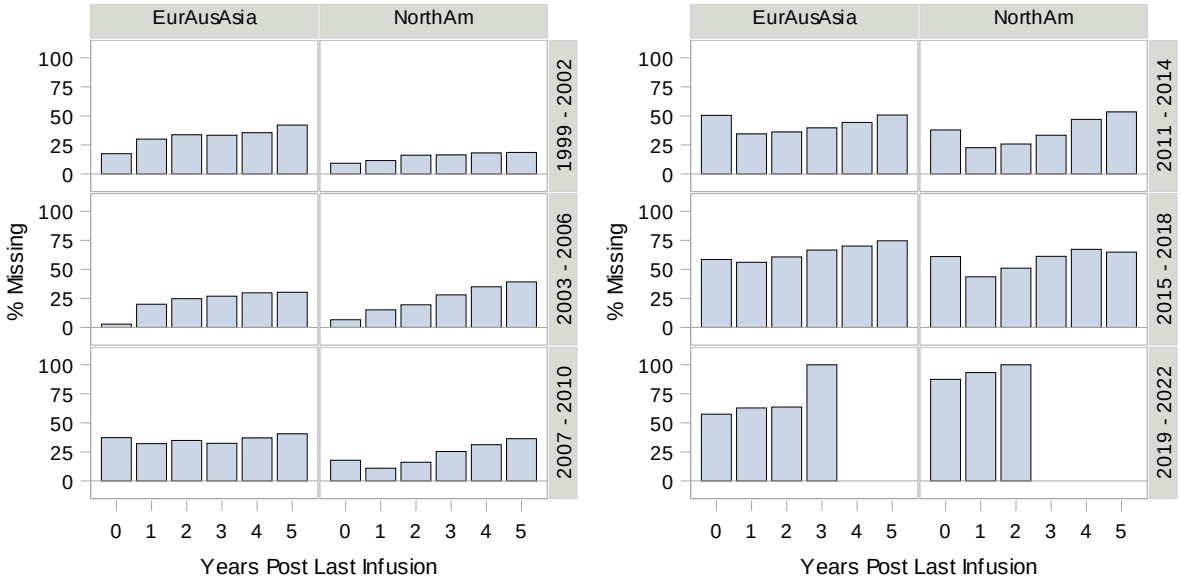

Exhibit 8 – 3

Missing Data for Hemoglobin A1c by Era and Continent

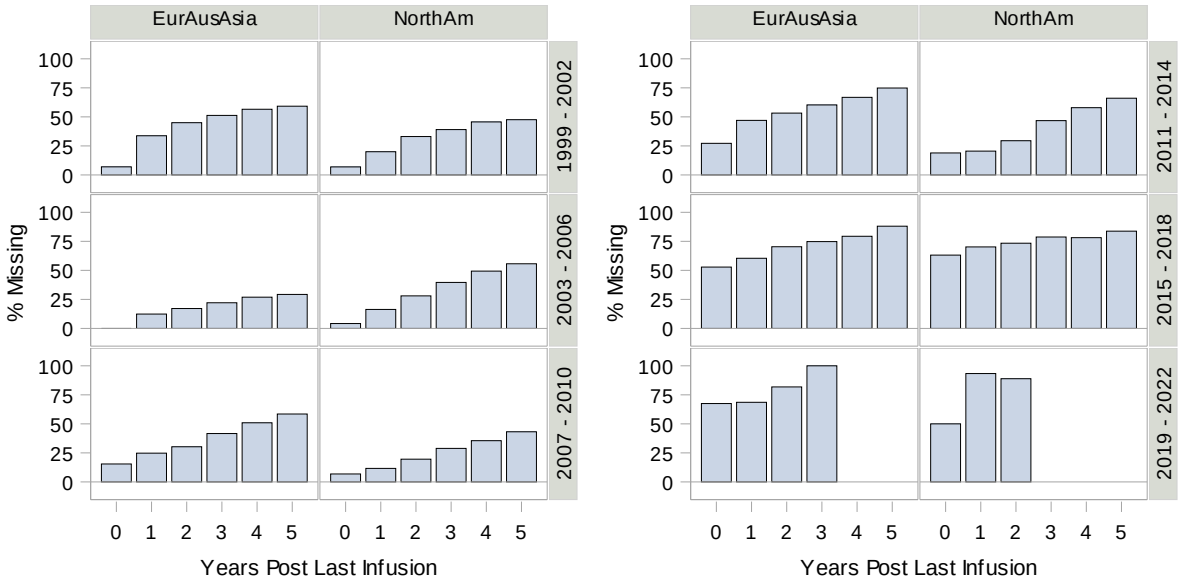

Exhibit 8 – 4

Missing Data for Fasting Blood Glucose by Era and Continent

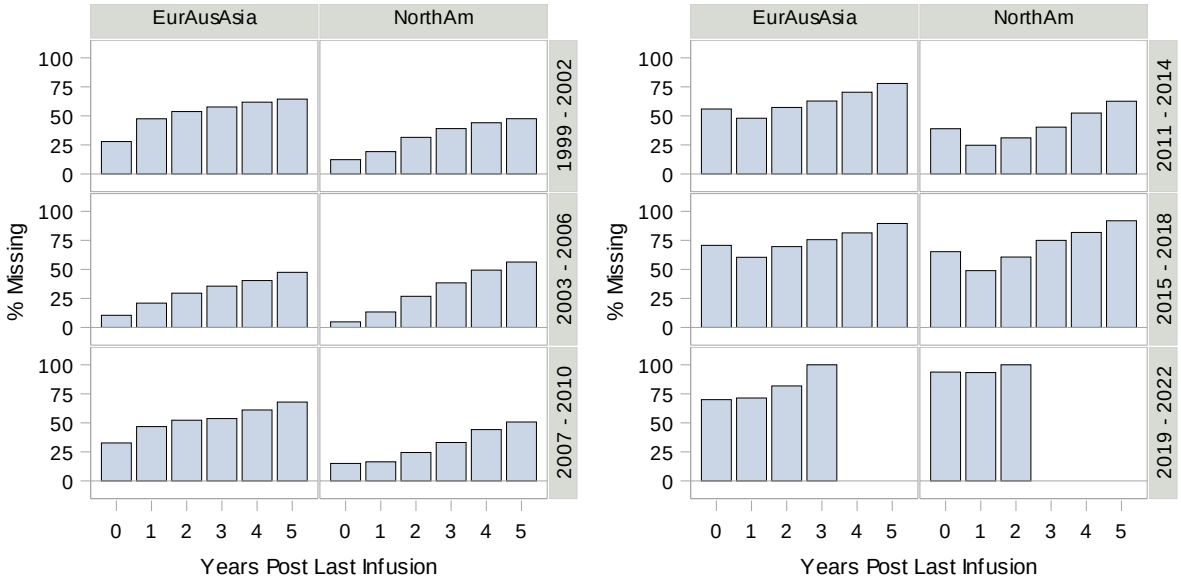

Exhibit 8 – 5

Missing Data for Severe Hypoglycemia by Era and Continent

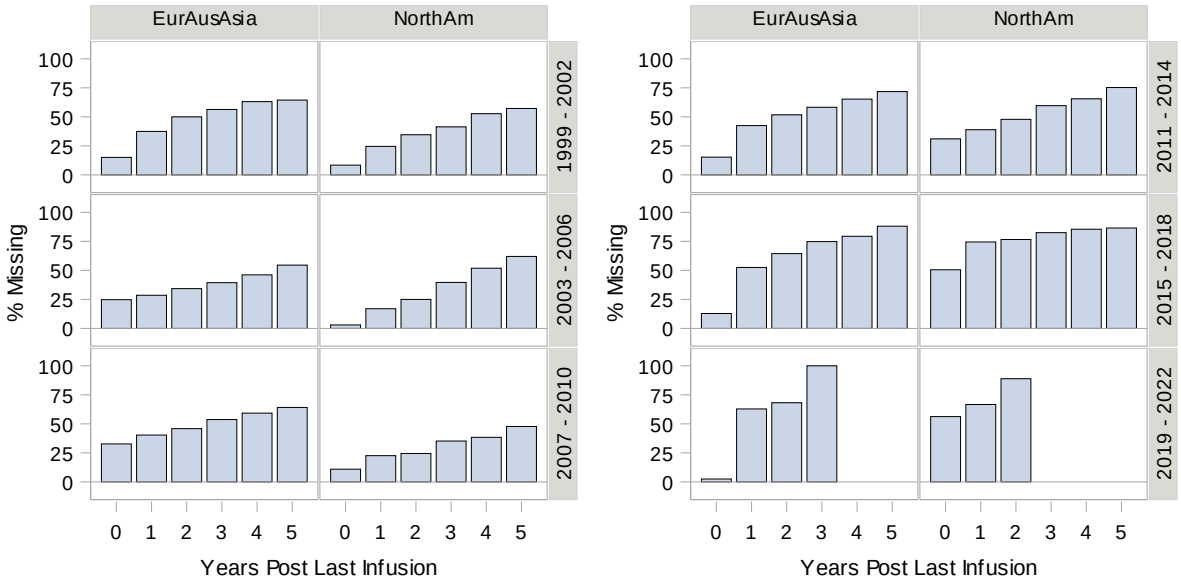

Exhibit 8 – 6

Missing Data for BMI by Era and Continent

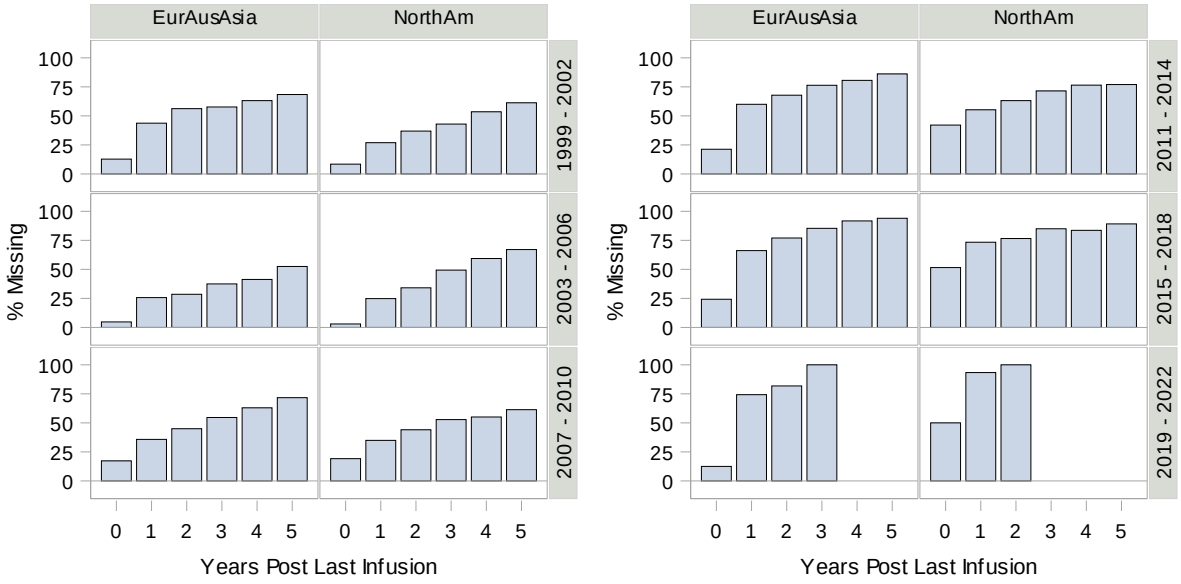

Exhibit 8 – 7

Missing Data for Clarke Score by Era and Continent

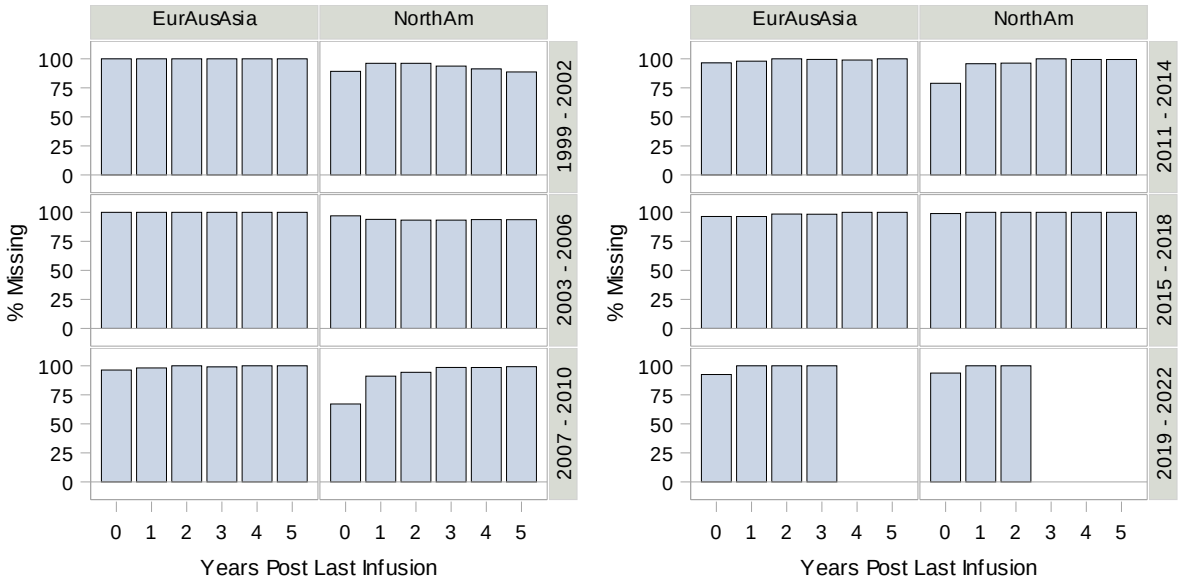

Exhibit 8 – 8

Missing Data for Ryan Hypo by Era and Continent

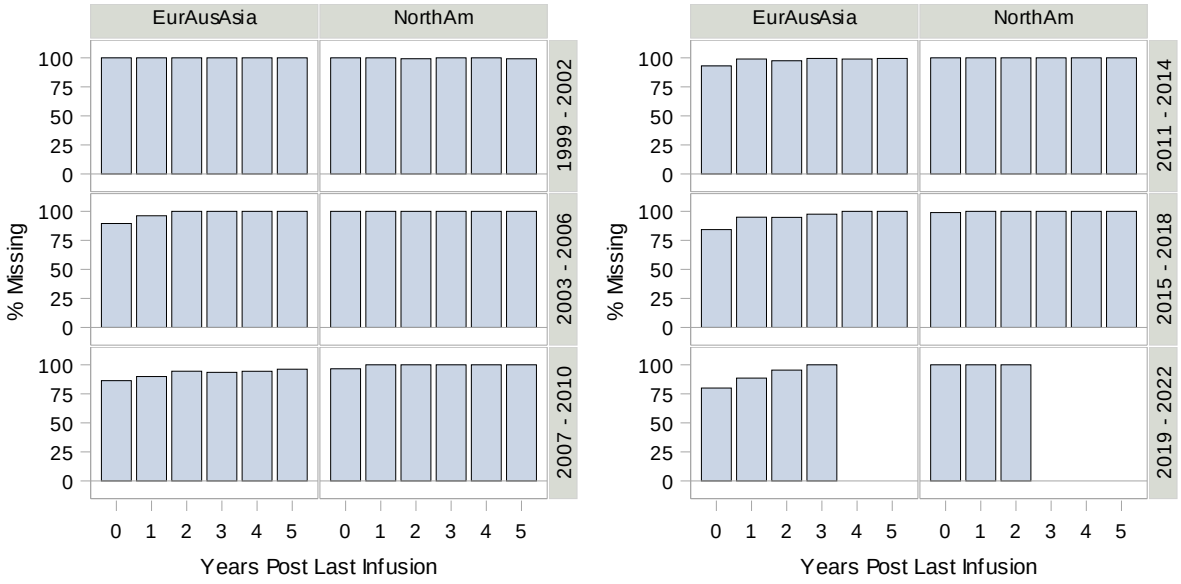

Exhibit 8 – 9

Missing Data for C-Peptide AUC by Era and Continent

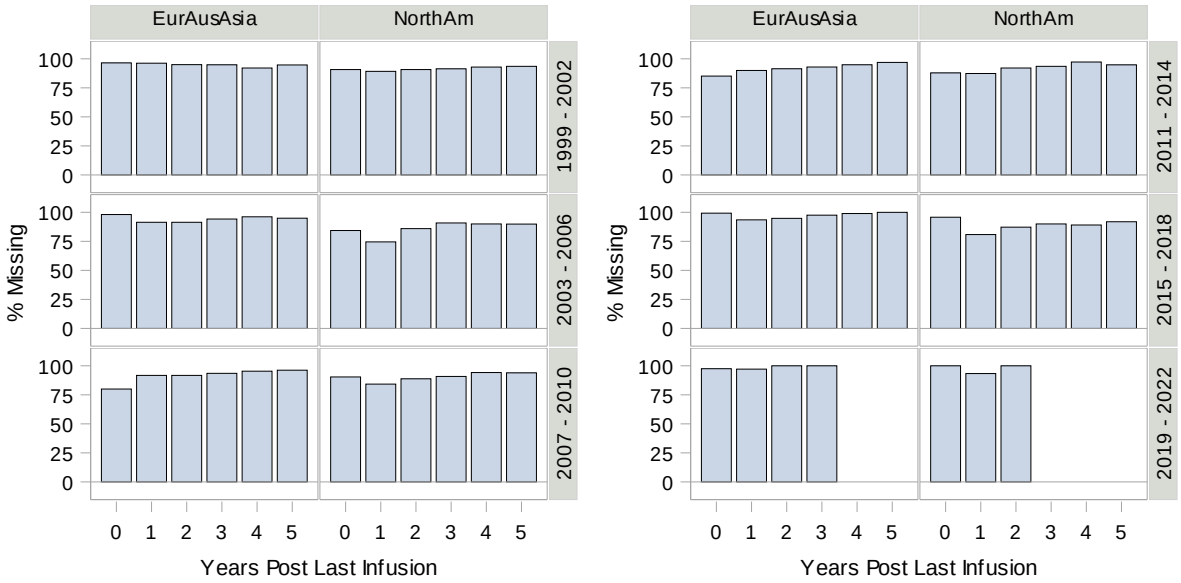

Exhibit 8 – 10

Missing Data for Cockcroft-Gaullt by Era and Continent

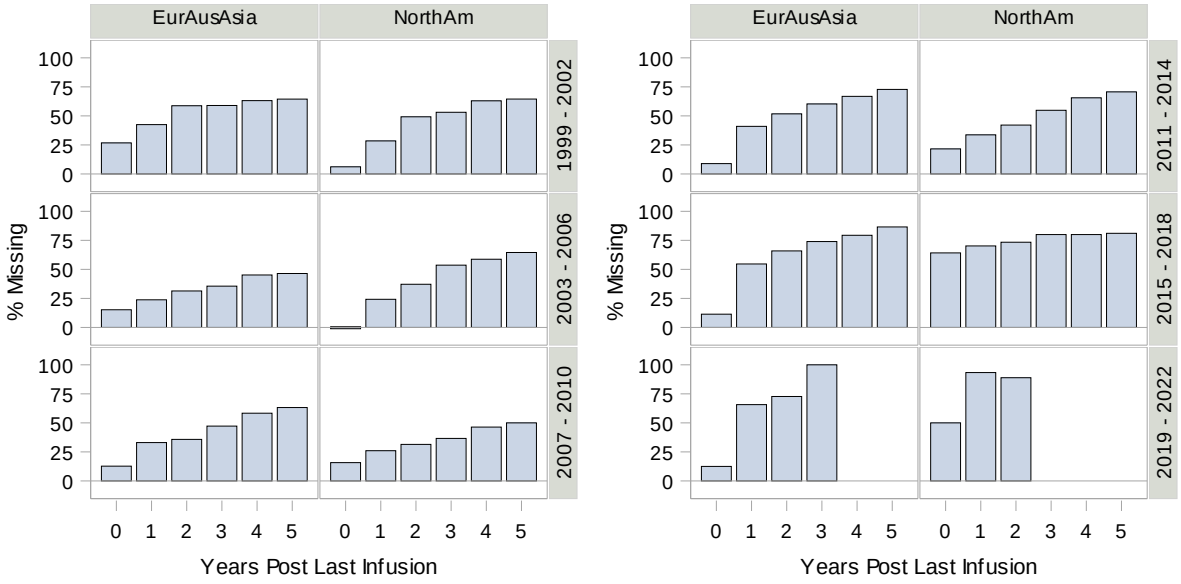

Exhibit 8 – 11

Missing Data for Creatinine by Era and Continent

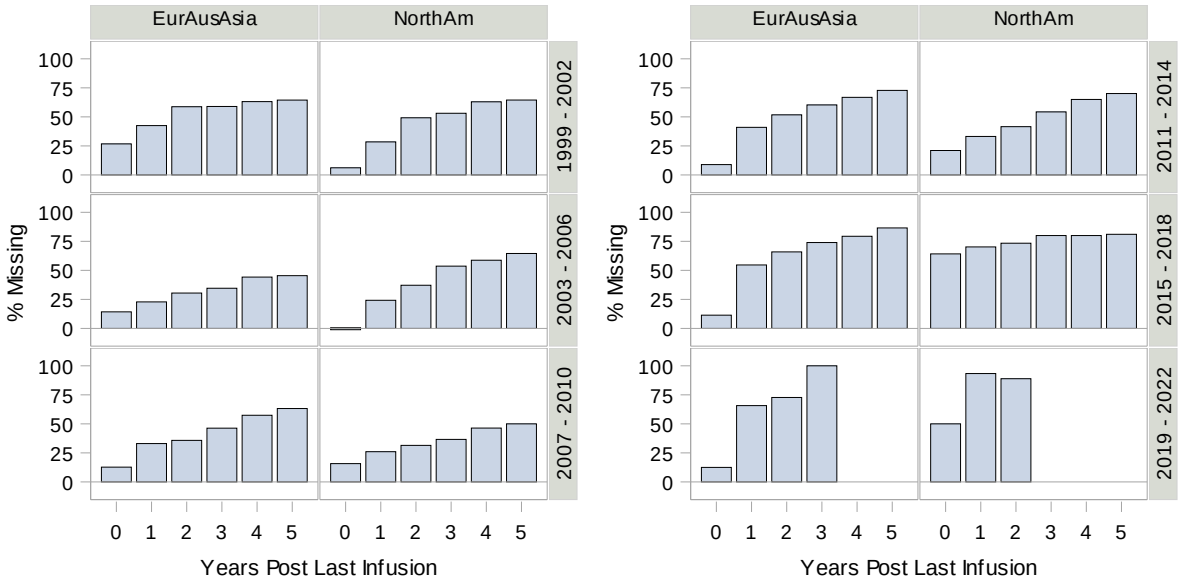

Exhibit 8 – 12

Missing Data for Cholesterol by Era and Continent

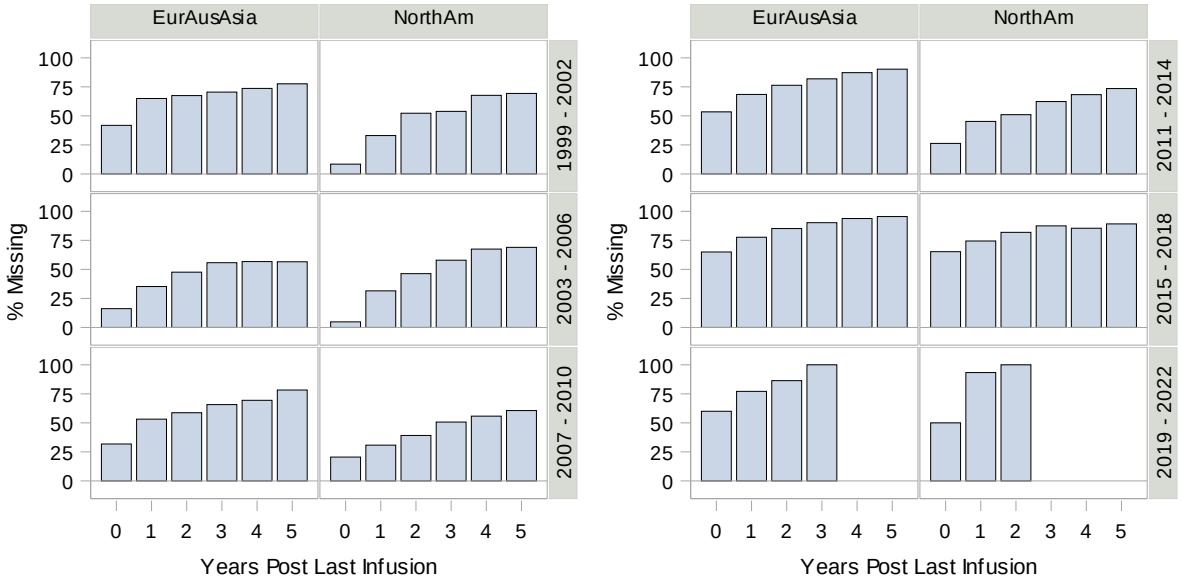

Exhibit 8 – 13
Missing Data for HDL by Era and Continent

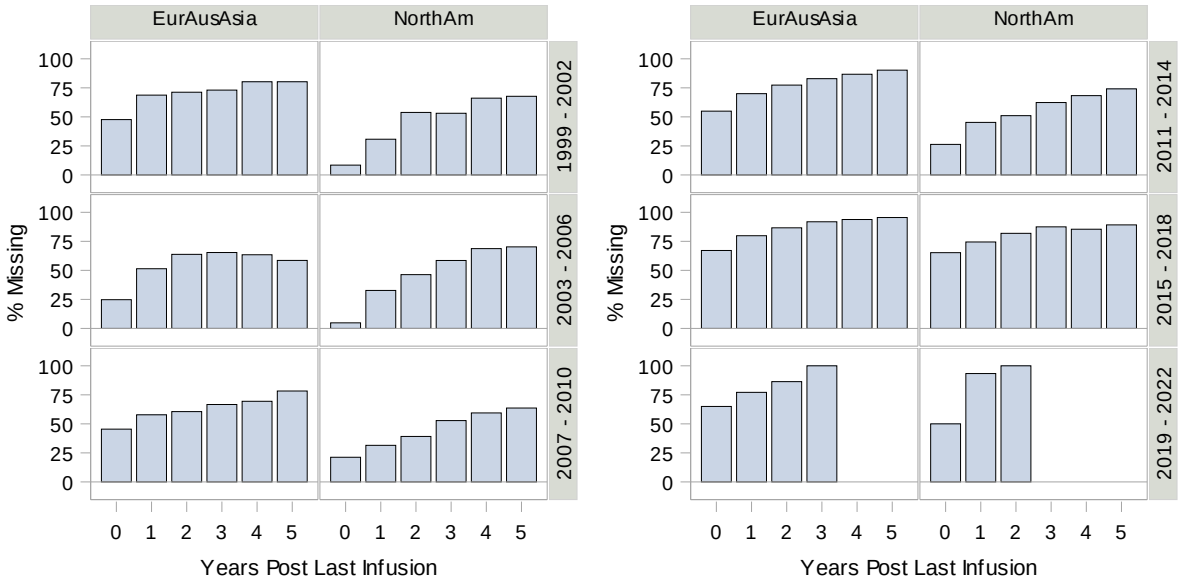

Exhibit 8 – 14
Missing Data for LDL by Era and Continent

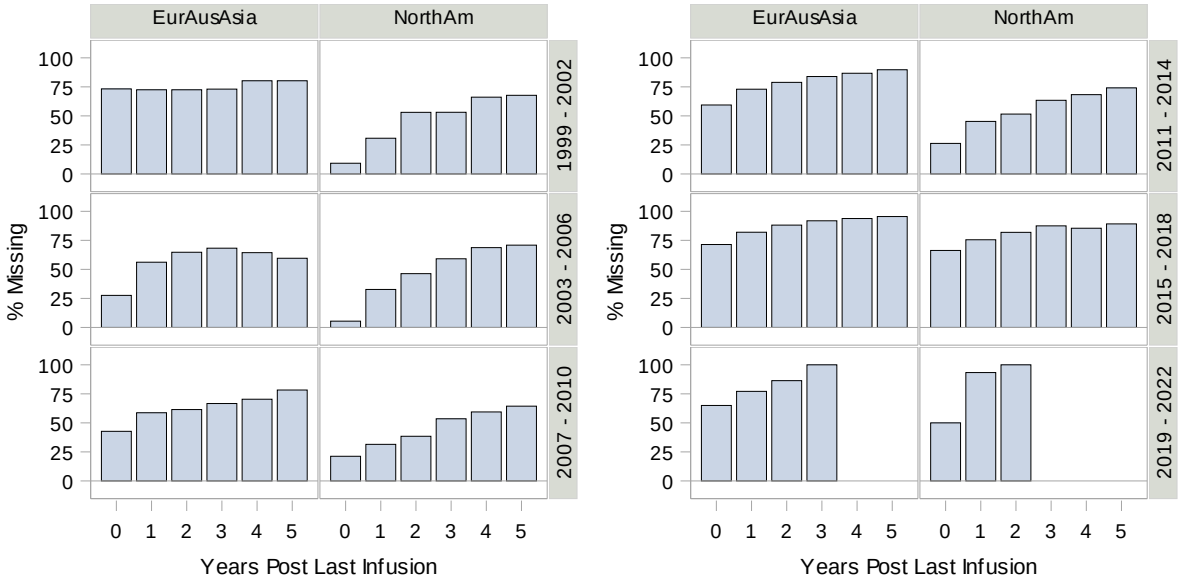

Exhibit 8 – 15
Missing Data for Triglycerides by Era and Continent

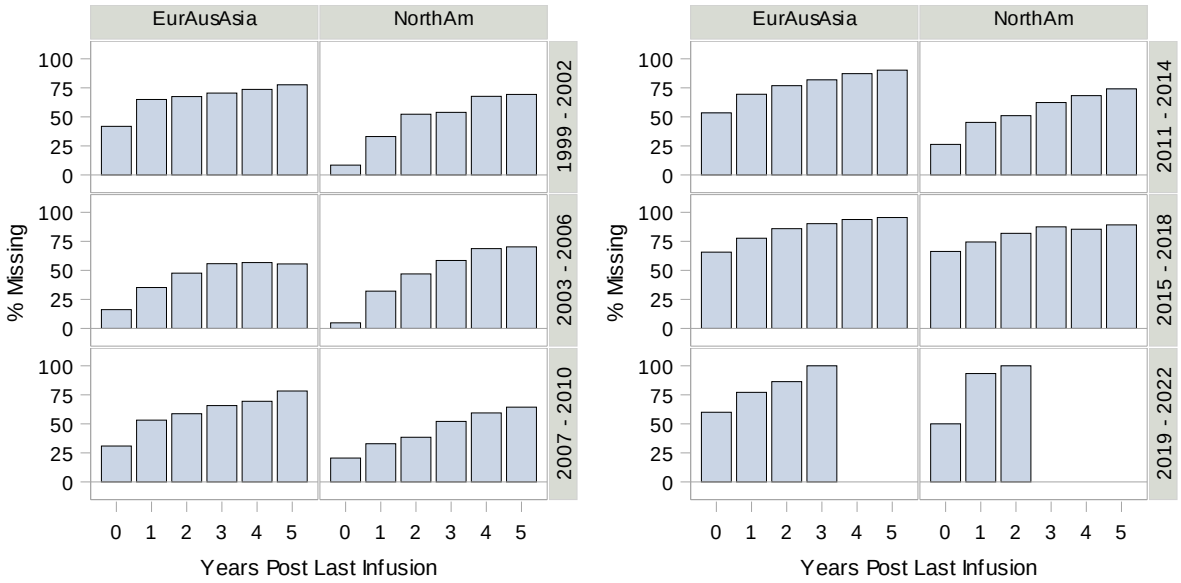

Exhibit 8 – 16
Missing Data for Bilirubin by Era and Continent

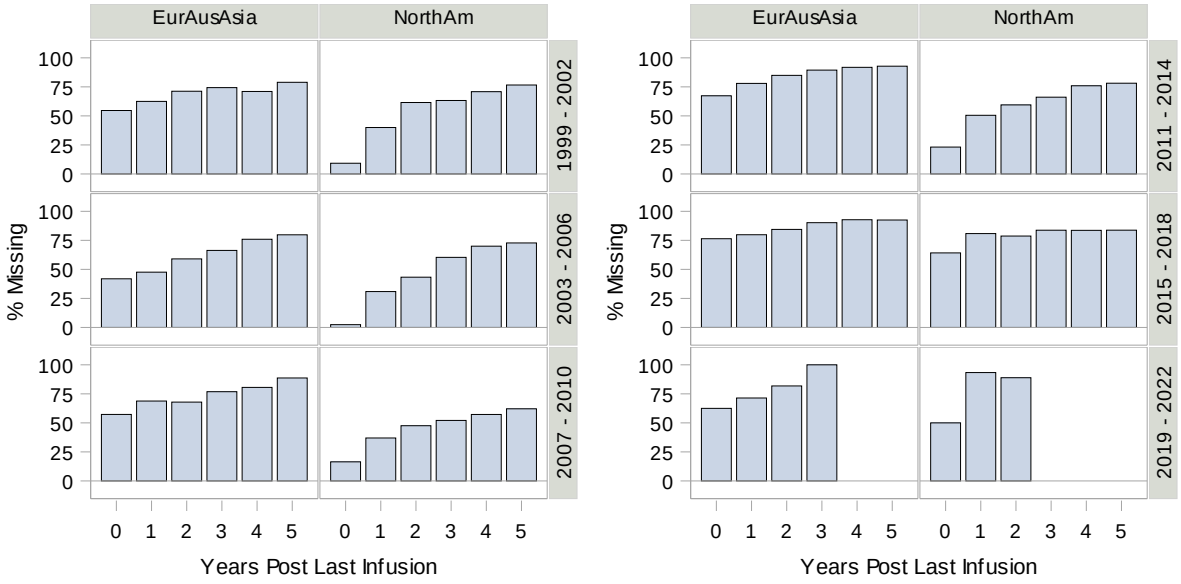

Exhibit 8 – 17

Missing Data for ALT by Era and Continent

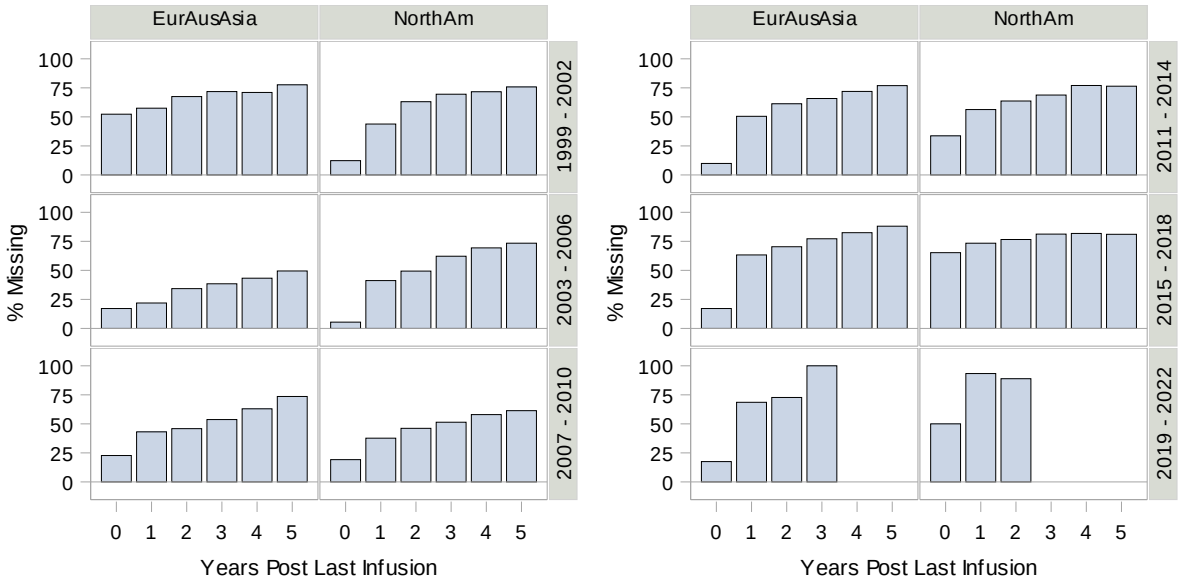

Exhibit 8 – 18

Missing Data for AST by Era and Continent

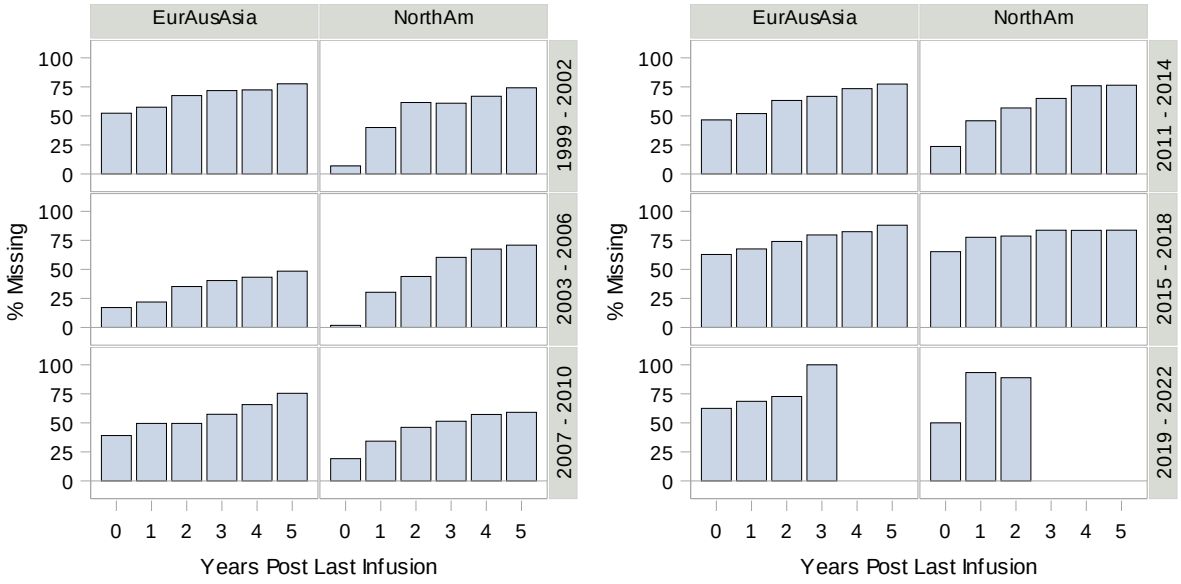

Exhibit 8 – 19

Missing Data for Alkaline Phosphate by Era and Continent