Scientific Summary of the Collaborative Islet Transplant Registry (CITR) 2015 (Tenth) Annual Report

BACKGROUND AND PURPOSE

Pancreatic islets of Langerhans contain insulin producing beta cells that regulate the utilization of dietary sugars by all cells in the body. In persons with Type 1 diabetes mellitus (T1DM), most of the beta cells are destroyed by an autoimmune attack, resulting in the need for pharmaceutical insulin delivered by injection or pump to avoid diabetes-related illness and death. About 1.25 million people in the US have Type 1 diabetes mellitus, with this number expected to rise to 5 million by the year 2050. The only alternatives to daily insulin injections or pump currently available are solid organ pancreas transplant or transplantation of islets of Langerhans isolated from a donated pancreas.

Islet transplantation in the US is experimental and available only at sites that have received exemption from the US Food and Drug Administration (US-FDA) for clinical research of islet transplantation in T1DM. In the US, individual transplant centers may initiate their own independent research protocols. From 2005 through 2015 the Clinical Islet Transplant Consortium (www.CITIsletStudy.org) conducted studies designed to advance the field of islet transplantation. At the Canadian, European and Australian sites, both research and standard of care protocols have been available. Research investigators in clinical islet transplantation and islet science from all such programs have contributed data and collaborated on the data analysis to advance knowledge about the risks and benefits of islet transplantation. Each center may publish the results of their local protocols or aggregate experience, and disseminate information regarding their open and recruiting protocols through their own means and/or at the National Library of Medicine's developed website www.clinicaltrials.gov. In addition, CITR maintains interactive maps of North American and JDRF European and Australian islet transplant programs at www.citregistry.org.

In 2001, the National Institute of Diabetes & Digestive & Kidney Diseases established the Collaborative Islet Transplant Registry (CITR) to compile data from all islet transplant programs in North America from 1999 to the present. The Juvenile Diabetes Research Foundation (JDRF) granted additional funding to include the participation of JDRF-funded European and Australian centers from 2006 through 2015. The cumulated North American, European and Australian data are pooled for analyses included in the annual report. CITR Annual Reports are publicly available as open access and can be downloaded or requested in hard copy at www.citregistry.org. **This Scientific Summary highlights results from the CITR 2015 (10th) Annual Report, either by direct inclusion or by reference.**

PATIENTS AND METHODS

From 1999 through 2015 – the cut-off for the 10th Annual Report – CITR has collected data on the following groups of study subjects:

- Allogeneic islet transplantation (typically cadaveric donor), performed as either islet-transplant alone (ITA) or islet-after-kidney (IAK). A small number of cases have been performed as islet simultaneous with kidney (SIK) or kidney-after-islet (KAI). SIK and KAI

are included in the safety profile presented in Chapter 7 of this report, but were otherwise excluded from analyses to reduce heterogeneity in the transplant groups (SIK and KAI are more similar to ITA than IAK in terms of immunosuppression, but also similar to IAK in terms of kidney transplant).

- Autologous islet transplantation, performed after total pancreatectomy (N=819) are also reported to CITR. They are summarized in a separate report.

The 10th Annual Report and this Summary focus on the allogeneic islet transplant recipients. The autologous islet transplant recipients are the subject of a separate report.

The database for the 10th Annual Report was closed for analysis on January 6, 2017 for data on recipients that were first transplanted as of September 30, 2015.

At the time of their first Islet transplant,

- ITA recipients were 14-74 years of age (mean 46±10.5SD), had T1DM for 2-61 (29±11.5) years, and 77% had very poor diabetes control including hypoglycemia unawareness. Poor glycemic control can manifest as frequent episodes of critically low blood sugar levels (which often result as a reaction to injected insulin, requiring the assistance of another person to avert a possibly life-threatening loss of consciousness), wide swings in blood sugar levels (blood glucose lability), or consistently high HbA_{1C} levels (>8% of total hemoglobin).

- IAK recipients were 28-69 years of age (mean 47±8.6SD), had T1DM for 7-55 (34±8.5) years, and 49% had very poor diabetes control including hypoglycemia unawareness.

- SIK recipients were 6-62 years of age (mean 46±12SD), had T1DM for 2-57 (30±14) years, and 19% had very poor diabetes control including hypoglycemia unawareness.

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

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

All grade 3, 4 and 5 adverse events, according to the Clinical Islet Transplant Consortium (CIT) Terminology Criteria for Adverse Events (TCAE), and all serious adverse events (regardless of grade) are reported to CITR. A copy of the CITR data collection forms may be requested from the CITR Coordinating Center (citr@emmes.com), or viewed at the CITR website (www.citregistry.org).

CITR utilizes the Coordinating Center's (The Emmes Corporation, Rockville, MD; www.emmes.com) web-based data entry and management systems to capture data on recipients, donors and pancreata. Additional data are obtained through data sharing agreements with the United Network for Organ Sharing (UNOS)for US donor data, the Administrative and Bioinformatics Coordinating Center (ABCC, 2001-2009) of the Islet Cell Resource Centers for the islet data, and the Data Coordinating Center of the Clinical Islet Transplant Consortium (CIT, 2005-2015).

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

Statistical Analysis.

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

Descriptive analyses include tabular or graphical displays of sample means and their standard deviations (SD) or standard errors (SE), and whole-distribution statistics such as median, interquartile range and extremes.

First achievement of insulin independence, as well as complete graft failure, were analyzed by Kaplan-Meier time-to-event analysis with proportional hazards investigation of predictive factors, employing multivariate models to adjust for correlated or confounding factors.

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

- Insulin independence (≥14 consecutive days)
- C-peptide <0.3 ng/mL
- HbA1c <7.0%
- Fasting blood glucose of 60-140, and
- Absence of severe hypoglycemic events
- Combined HbA1c <7.0% and absence of severe hypoglycemic events

An “all-factors-on-all-outcomes” analytical approach was undertaken to uncover the most predictive recipient, donor, islet and medical management practices associated with the greatest success rates in the primary outcomes, within each of ITA and IAK. Analysis of IAK is the subject of a forthcoming publication. First, every covariate available on recipient, donor, islet, and immunosuppression was analyzed univariately to determine its effect on each outcome (insulin independence, HBa1c, etc.). Those variables significant at $p<0.05$ were then stepped into multivariate models to eliminate duplicative effects and narrow down the final effects. While some predictive variables (factors) consistently exerted a clear beneficial effect across all outcomes within ITA. To facilitate interpretation for translation into clinical practice for ITA, the set of favorable factors that were common to all the outcomes were identified, and the subgroup comprising all those with the favorable common factors was compared to the remainder (who may have none, one or more, but not all the favorable factors). Final results of the common favorable factors on the primary outcomes are exhibited together for ITA (Exhibit D). Targeting the common favorable factors somewhat dilutes the largest differences seen univariately for each outcome; however, this method identifies the factors that are clinically most relevant to the

recipients. These then comprise best practices in terms of patient selection and medical management for allogeneic islet transplantation.

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

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

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

Statistical analyses were conducted using SAS 9.4.

RESULTS

Islet Allograft Transplantation Activity 1999-2015. As of September 30, 2015, the CITR Registry included data on 1,086 allogeneic islet transplant recipients (877 islet transplant alone, ITA, and 183 islet after kidney, IAK, 24 simultaneous islet kidney, SIK, and 2 kidney after islet, KAI), who received 2,150 infusions from 2,619 donors (Exhibit A). The North American sites contributed 55%, while the European and Australian sites contributed 45% of the data. Combining the ITA and IAK recipients, 29% received a single islet infusion, 49% received two, 19% received three, and 3% received 4-6 infusions.

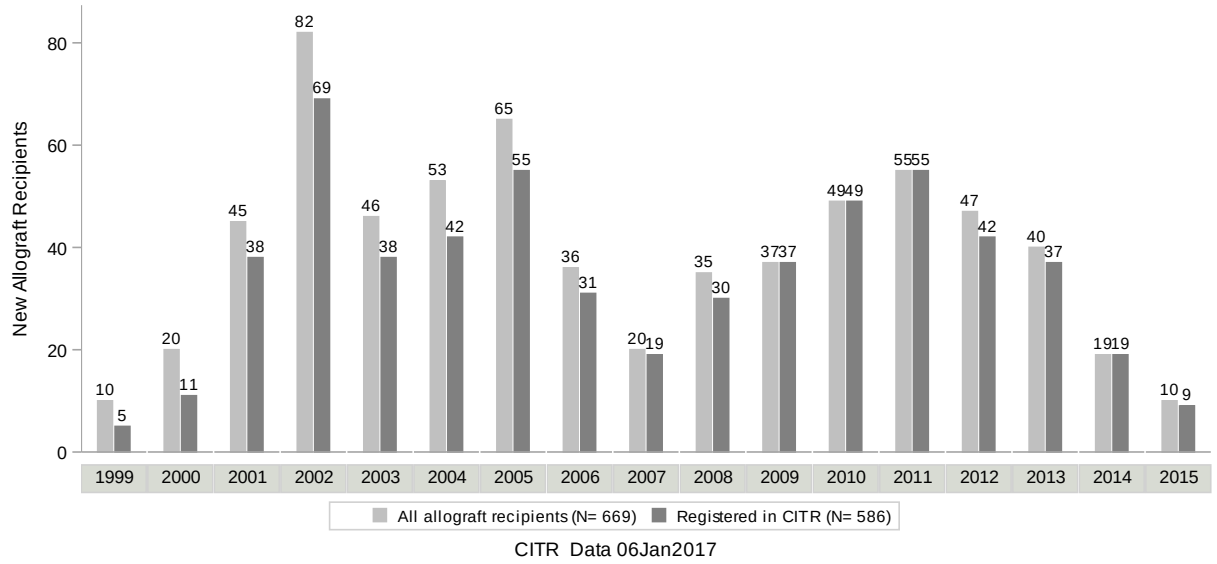
Exhibit A
CITR Recipients, Infusions and Donors by NIDDK/JDRF Sites and by ITA/IAK/SIK/KAI
Consented, Registered and First Infused in 1999-2015

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

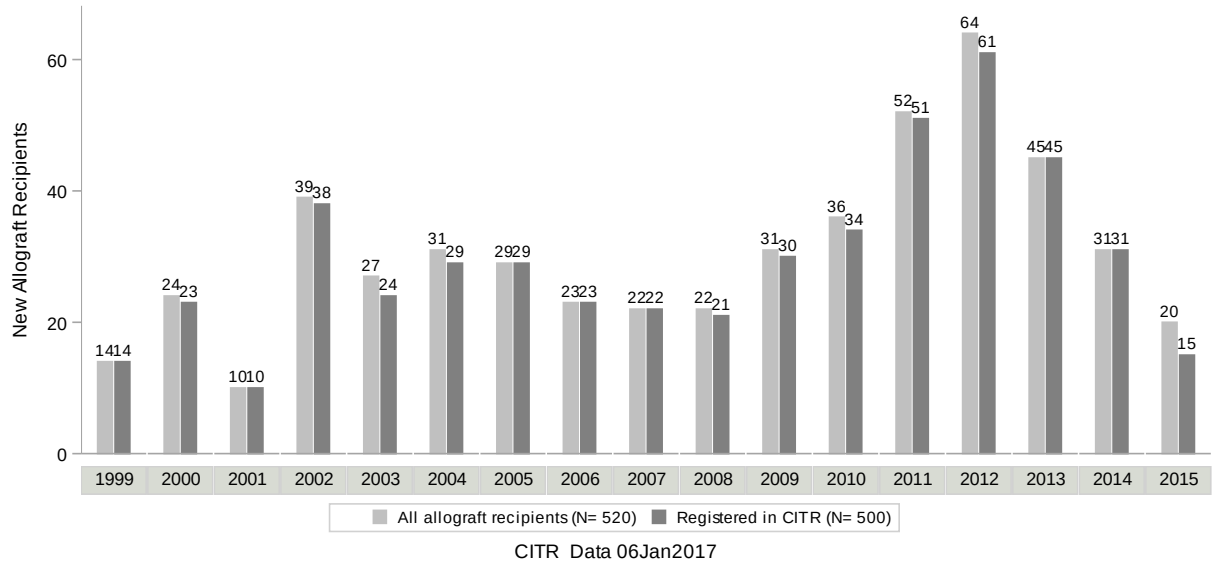
Exhibits B1 and B2 display the data collected from the islet transplant programs in North America and the JDRF European and Australian sites from 1999 through 2015. Of the 669 total North American recipients reported by general survey of the sites to have received an islet allograft in 1999-2015, 586 (88%) consented to and were registered in CITR. Of the 520 total reported JDRF European and Australian recipients, 96% (500) were consented and registered in CITR. Both North American and JDRF sites saw a decline in new recipients around 2007, followed by an increase in following years which peaked in 2011 for North American sites and in 2012 for JDRF sites. Both North American sites and JDRF sites again saw a decline in the number of new recipients over the 2013 to 2015 period.

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

1. Allograft recipients at CITR North American Centers 1999-2015



2. Allograft recipients at CITR European and Australian Centers 1999-2015



Islet Transplant Recipient Characteristics. Over the eras of the Registry, the following trends are observed for recipients of allogeneic islets:

- Recipients have been selected at older age (42±0.6* to 49±0.6) and longer wait time (240±22d to 340±32d) at initial transplant

- Recipients have been selected with higher HbA1c (7.9±0.1 to 8.2±0.1), increased use of insulin pump (31% to 56%), and higher prevalence of hypoglycemia unawareness (60% to 80%)
- Greater proportions had positive GAD65 autoantibody (32% to 58%) and lower proportions had positive insulin autoantibody (33% to 12%)
- Recipients had lower levels of total cholesterol (182±3 to 158±4) and LDL cholesterol (99±3 to 80±3) in recent eras

*Mean±SE

There were also notable differences in medical characteristics between ITA and IAK recipients, most notably, a much lower prevalence of hypoglycemia unawareness, and much lower initial eGFR in the IAK (64.1±2.1 vs. 88.5±1.0) recipients.

Donor Information. All allograft donors were deceased, at a mean age that rose from 43.8±0.7 SE to 44.3±0.6 years. "Infusions" (an "infusion" is defined as all islet products from one, two or three (maximum) donors given to a single recipient on a single day) were comprised of about 58% all male donors, 38% all female donors, and 4% mixed male and female donors. About 20% of infusions derived from Hispanic donors, while about 11% derived from non-white donors. About 60% of the donors had cerebrovascular accident/stroke as their cause of death while 27% experienced trauma.

About 30% of the donors received a transfusion during their terminal hospitalization, while only 6% received a transfusion intraoperatively. Sixty-seven percent (67%) of the donors received steroids and 94% received at least one vasopressor during the terminal hospitalization. Insulin administration during recovery increased from 34% in the earliest era to 52% in 2011-2014. A total of 11 donors tested positive for anti-HBC, two tested positive for RPR-VDRL and two for HCV. Mean serum creatinine of the donors remained steady around 1.1 mg/dL, while the mean maximum stimulated blood glucose decreased from 246±6 SE to 208±4 mg/dL over the eras of the registry.

The following trends are observed among donors of allogeneic islets over the eras:

- Substantial increase in donor weight and BMI (28.0±0.3 to 29.7±0.3)
- Lowered use of transfusion during hospitalization (34% to 16%)
- Increased use of insulin to donor during hospitalization (34% to 52%)
- Donor stimulated blood glucose (246±6 SE to 208±4 mg/dL) has declined

Pancreas Procurement and Processing.

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.

Islet product characteristics. Total cell volume infused has declined appreciably over the eras (4.0±0.1 in 1999-2002 to 3.1±0.1 in 2011-2014), while total IEQs and IEQ/Kg recipient have remained remarkably stable. Total Beta cells and β-cells/kg were higher for IAK (5.3±0.6 vs. 3.6±0.2) and have increased over the eras (3.0±0.3 to 4.5±0.4). Endotoxin (both total and /kg) has declined sharply over the eras (0.5±0.1 to 0.1±0.05). Stimulation index has declined over the eras (3.6±0.3 to 2.8±0.2).

Immunosuppression therapy. Induction with IL2R antagonists only, which comprised about 54% of all initial infusions in 1999-2002, was replaced or supplemented with regimens that included T-cell depletion with/without TNF antagonists in about 68% of the new infusions performed by 2011-2014. In 1999-2002, maintenance immunosuppression was predominantly (65%) calcineurin (CNI)+mTOR inhibitors. It was increasingly replaced or supplemented throughout the eras by a CNI and IMPDH-inhibitor combination; in the most recent era, CNI+mTOR inhibitors were used in 15% of new infusions while CNI+IMPDH inhibitors were used in about 56%.

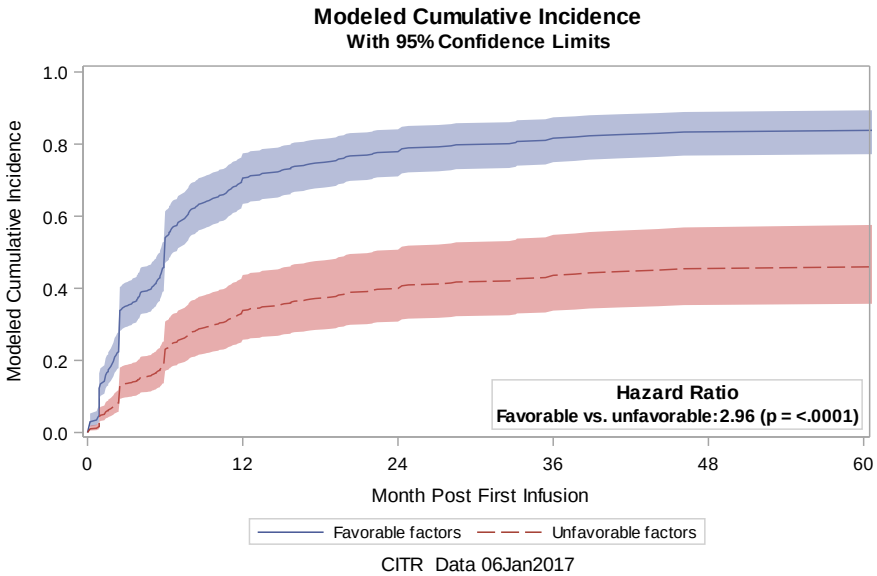
Graft Function. First achievement of insulin independence measured from initial islet infusion (Exhibit C), with or without subsequent infusion, is an indicator of the rate of engraftment under real-time conditions that include early graft loss, islet resource availability, patient/doctor decisions and myriad other factors, some of which are characterized in the CITR data and others not. It is notable that the cumulative rate of achievement of insulin independence follows the general shape of engraftment curves for solid organs, but with a slower initial slope, indicative of multiple infusions. While the overall rate of first achievement of insulin independence is, remarkably, nearly identical between ITA and IAK recipients, the most predictive factors of this endpoint in the two groups were different: for ITA, the most favorable factors were immunosuppression with IL2RA and recipient age ≥35. For IAK, the favorable factors were time from donor death to transplant < 36 hours and recipient BMI < 21 (Exhibit C).

Exhibit C
First Achievement of Insulin Independence Post First Infusion
ITA and IAK Recipients Separately

(Through all infusions, censored at final graft loss or end of follow-up)

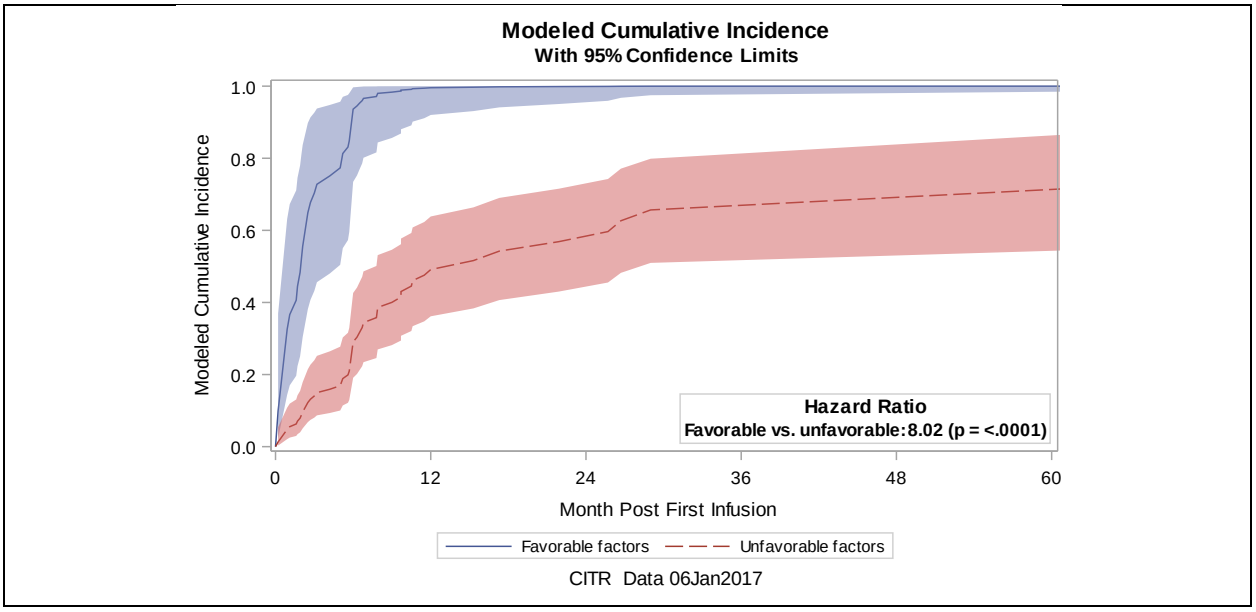
C1. ITA

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



C2. IAK

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



The primary endpoints are analyzed as prevalence at annual time points post last infusion to isolate the factors that optimized the outcomes. Remarkably, only a handful of common favorable factors emerge for ITA, and their combined effects appear to be additive, as exhibited by the final multivariate models of the various primary endpoints (Exhibit D). For each endpoint within ITA, the subgroup with all favorable common factors had significantly and clinically higher prevalence of all outcomes at $p<0.001$. The common favorable factors are:

For islet transplant alone (ITA, Exhibit D):

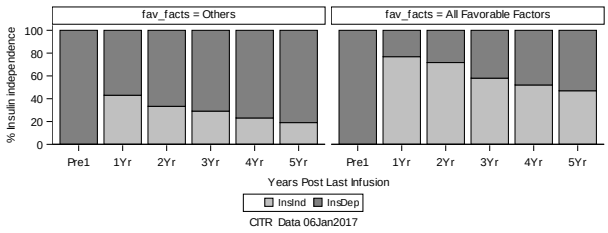
- Selection of patients aged 35 years or older. The remarkable consistency of this result runs across most of the primary outcomes including achievement and long-term retention of insulin independence or reduction in daily insulin requirement, higher levels of basal C-peptide, lowered HbA1c levels, and near elimination of severe hypoglycemia. As islet transplantation is not life-saving, this selection factor helps optimize use of scarce donor pancreas resources. Obviously, clinical judgment should drive the process: all other favorable factors being in place, someone younger than 35 may still be a good candidate for an islet transplant.
- Use of T-cell depletion and/or TNF-a inhibition and MTOR inhibition with calcineurin inhibitors continue to be associated with improved clinical outcomes with accruing data in CITR. A major limitation from the CITR data is that these strategies were not assigned at random and independently of each other; hampering the ability to isolate the effects of each factor separately. Nonetheless, from analyses of each factor alone (yes/no) and as combinations of induction and maintenance immunosuppression, the benefit of these agents continues to be well supported by the data.
- Islet product characteristics have remained consistently high over the eras of the Registry (Chapter 3). Because of the consistently high levels and narrow ranges of all islet product criteria used for clinical transplantation, it is difficult to statistically evaluate the effect of low-grade vs. high-grade products. The only factor that consistently yields improved outcomes is higher total IEQs infused, whether in a single infusion or over 2-3 infusions.

Exhibit D - ITA
Combined Effect of the Common Favorable Factors on Primary Outcomes Post Last Infusion (p-value of difference between the common favorable factors subgroup vs. the rest)

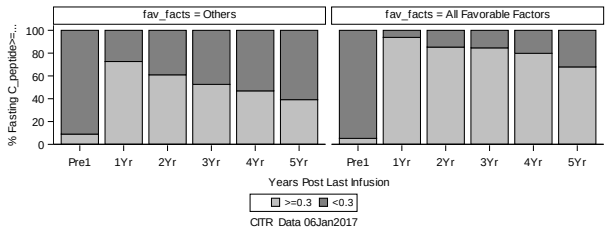
Common Favorable Factors for ITA:

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

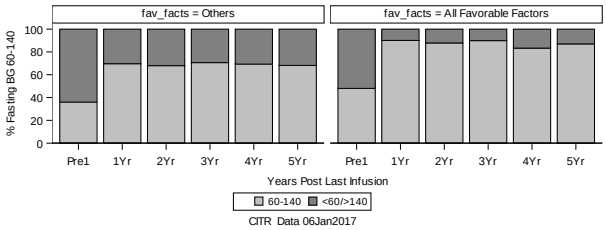
Insulin Independence (p<0.0001)



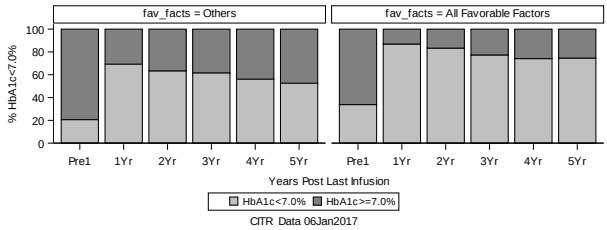
C-peptide ≥0.3 ng/mL (p<0.0001)



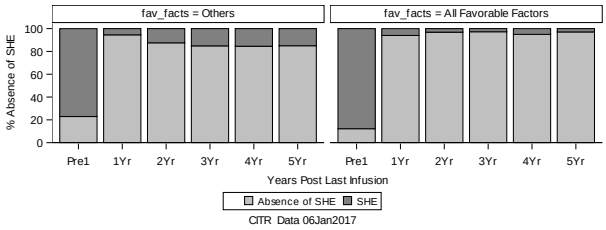
Fasting Blood Glucose 60-140 mg/mL (p<0.0001)



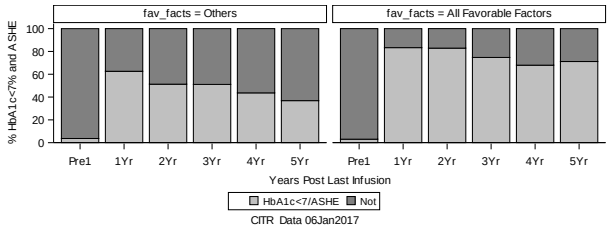
HbA1c<7.0% (p<0.0001)



Absence of Severe Hypoglycemic Events (p=0.0004)



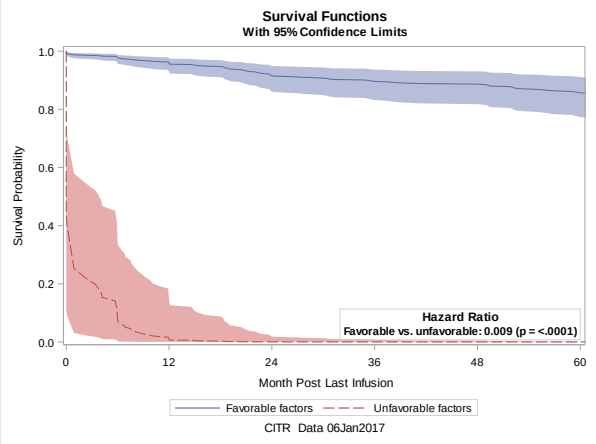
Combined HbA1c<7.0% & Absence of Severe Hypoglycemic Events (p<0.0001)

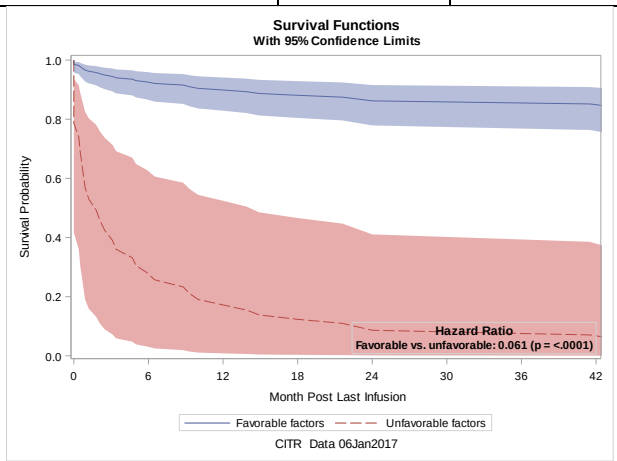


Basic graft function as measured by retention of fasting C-peptide≥0.3 ng/mL is sometimes lost over long-term follow-up, although it too varies substantially according to various factors. By Kaplan-Meier and Cox proportional hazards analysis, retention of C-peptide≥0.3 ng/mL post last infusion in ITA (Exhibit E1) is maximized by recipient age≥35 years (p<0.0001), number of infusions greater than one (p=0.01), use of T-cell depletion (p=0.04), use of calcineurin inhibitor (p<0.0001), and islet culture time ≥ 6 hours (p<0.0001). For IAK recipients (Exhibit E2), in addition to IEQs≥325K infused (p=0.003), era of 2003 or later (p=0.0002) is the other significant factor. With these factors combined, graft retention rates remain at 80% through 7-8 years in both transplant groups.

Exhibit E
Retention of C-peptide ≥0.3 ng/mL Post Last Infusion
Combined effects of most favorable factors

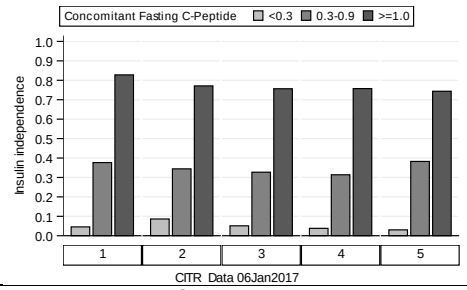
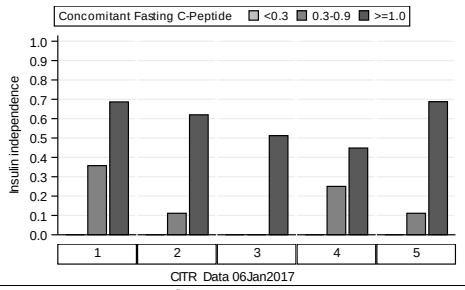
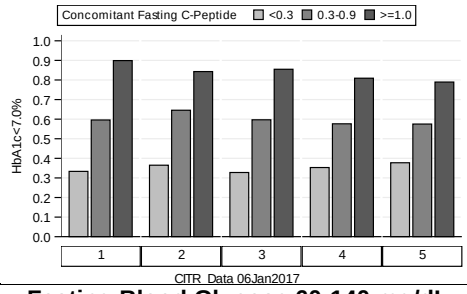
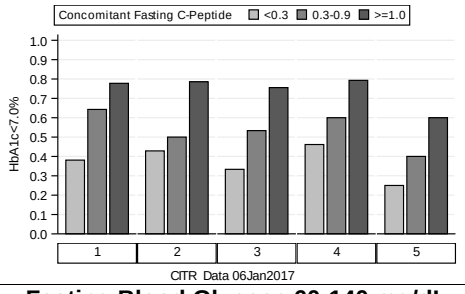
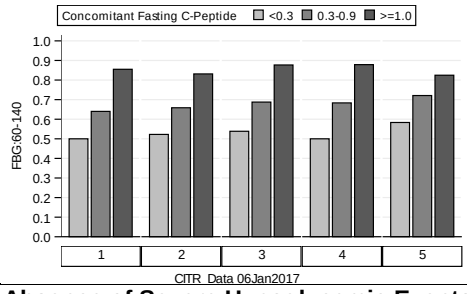
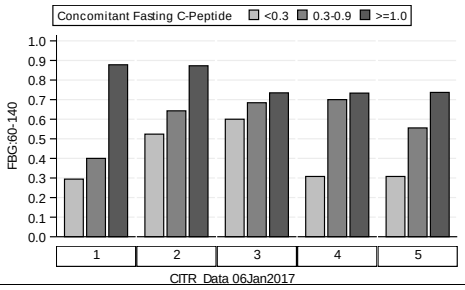
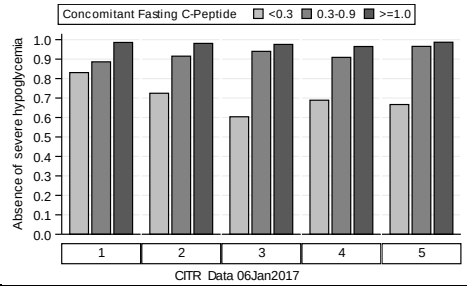
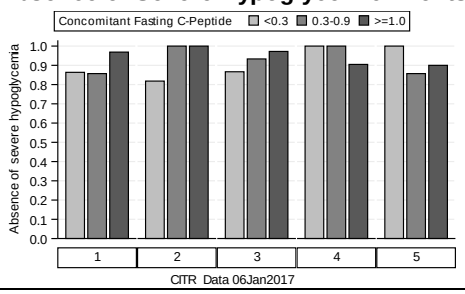
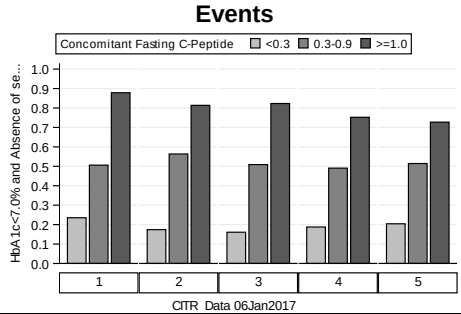
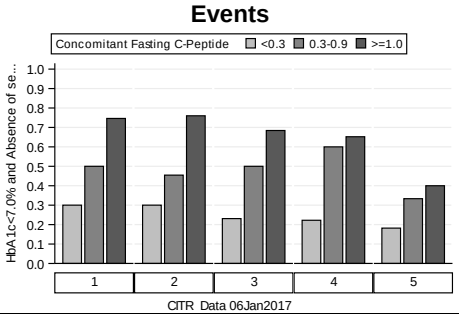
E1. ITA			E2. IAK		
Factors	**p-value**	**Hazard Ratio**	**Factors**	**p-value**	**Hazard Ratio**
Recipient Age (1= ≥35, 0= <35)	<0.0001	0.326	**IEQs Infused (1=IEQs ≥325K, 0=IEQs <325K)**	0.0032	0.231
Number of Infusions (1=two or more, 0=one)	0.0112	0.588			
T-cell Depletion (1=Yes, 0=No)	0.0395	0.576	**Era (1=2003 or later, 0=1999-2002)**	0.0002	0.263
Calcineurin Inhibitor (1=Yes, 0=No)	<0.0001	0.181			
Islets Cultured ≥ 6 hours (1=Yes, 0=No)	<0.0001	0.457			





In both transplant groups, the higher the fasting C-peptide level, the higher the likelihood of insulin independence, HbA1c<7.0%, FBG of 60-140, and the lower the likelihood of severe hypoglycemia (Exhibit F). 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.

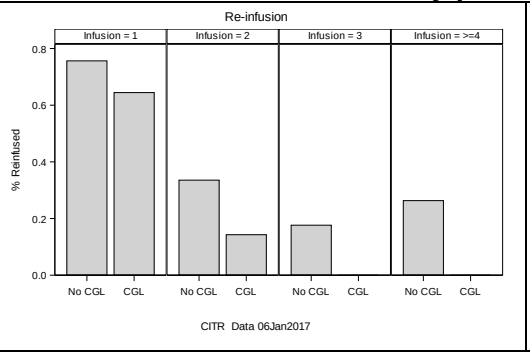
Exhibit F
Association of Fasting C-Peptide Level (ng/mL) with Other Primary Outcomes at Years1-5 Post Last Infusion

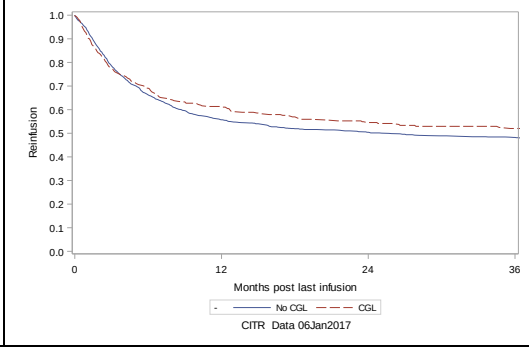
F1. ITA	F2. IAK
Insulin Independence	**Insulin Independence**
	
HbA1c <7.0%	**HbA1c <7.0%**
	
Fasting Blood Glucose 60-140 mg/dL	**Fasting Blood Glucose 60-140 mg/dL**
	
Absence of Severe Hypoglycemic Events	**Absence of Severe Hypoglycemic Events**
	
HbA1c <7.0% & Absence of Severe Hypoglycemic Events	**HbA1c <7.0% & Absence of Severe Hypoglycemic Events**
	

Over the years of the CITR data, reinfusion (Exhibit G) has been performed in about 73% of all allograft recipients. It may have been performed after complete graft failure, or while the recipient still had at least some graft function (C-peptide≥0.3 ng/mL), or even while the patient was fully insulin independent. The group most likely to be re-infused was those who were not insulin independent (Exhibit G2). This Kaplan-Meier also shows that time to re-infusion varied substantially from days to years, with a mean±SD of 26±32 months. Rates of second infusion by era show a substantially uniform rate over the eras (Exhibit G3) and did not differ significantly by transplant type (Exhibit G4).

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

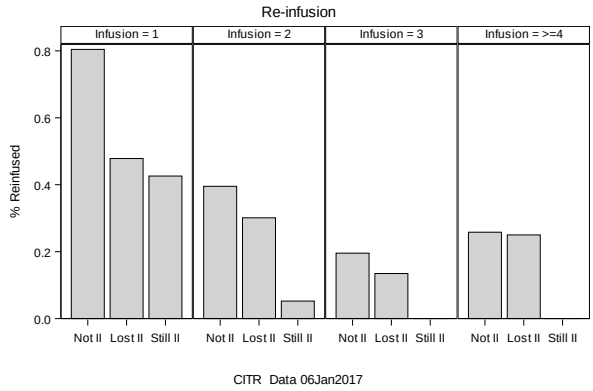
G1. By previous complete graft loss (CGL) (p=0.1)

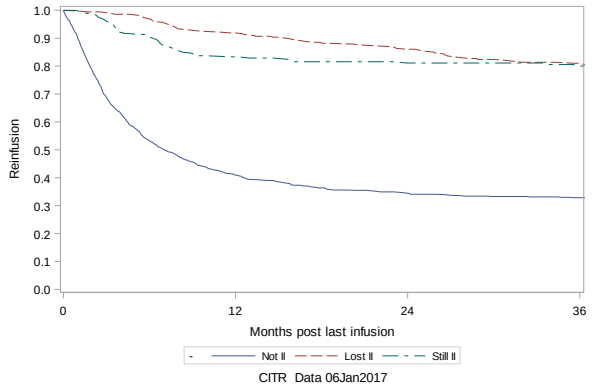




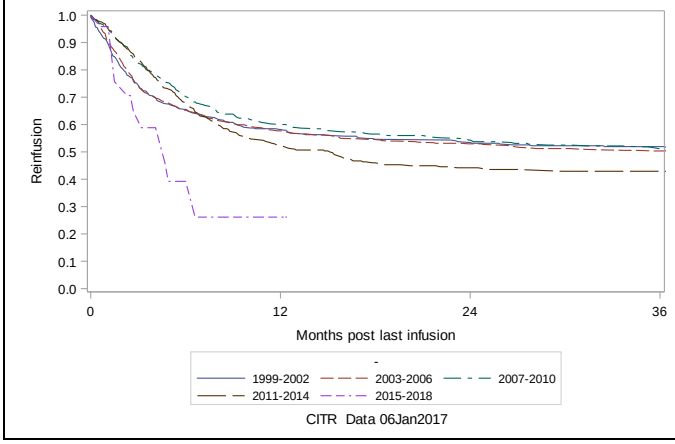
	Reinfusion		
	No	*Yes*	*Total*
	N	*N*	*N*
Infusion 1	275	730	1005
Infusion 2	504	226	730
Infusion 3	193	33	226
Infusion ≥ 4	33	10	43
All	1005	999	2004

G2. By concurrent insulin independence (p<0.0001)

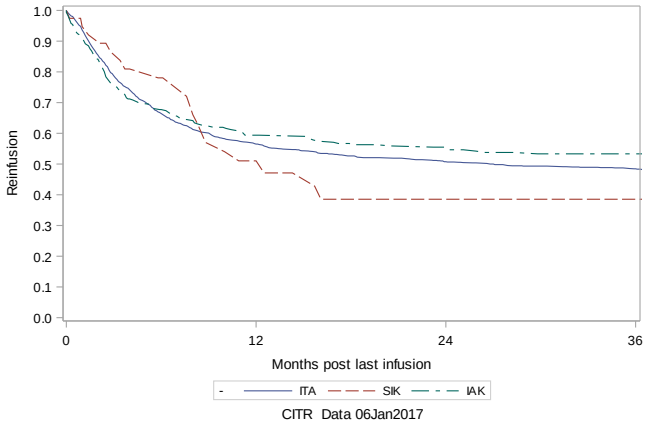




G3. By Era (p=0.04)



G4. By Transplant Type (p=0.3)



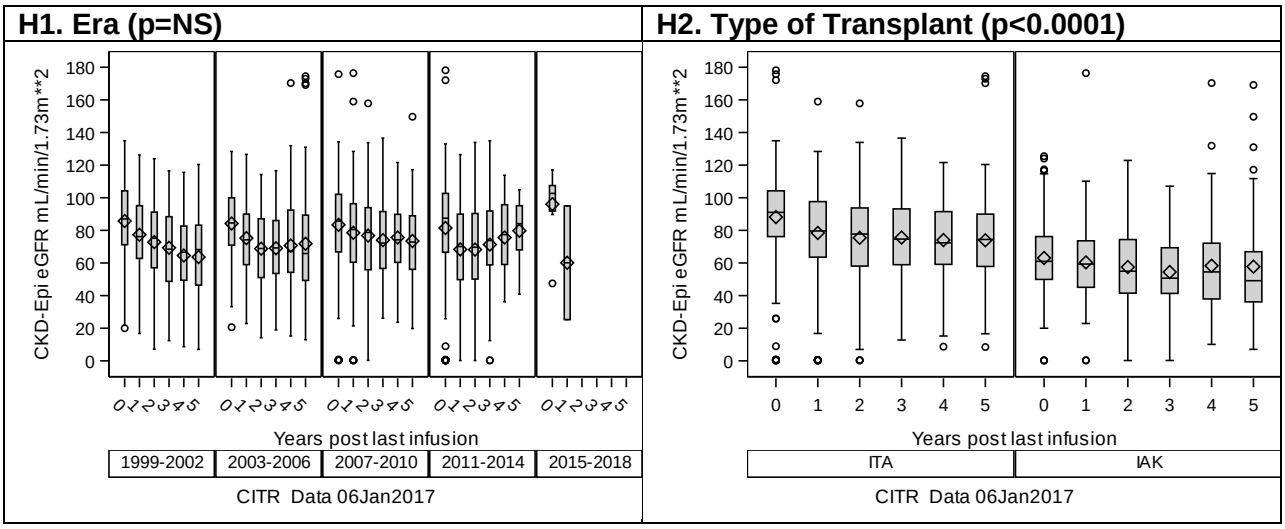
Adverse Effects (laboratory determinations and reported adverse events). Data collection on adverse events and other effects of islet transplantation continues for all islet transplant recipients. The data are confirmed via regularly scheduled site visits that include 100% data audit for adverse events. The reported data are coded for system/organ class and preferred term for tabulation and summary reporting, using the Medical Dictionary for Regulatory Activities, a part of the overall data quality and assurance process integral to The Emmes Corporation's Advantage EDC system. The coding is conducted by trained Emmes medical coders. Over the years of the Registry, both the MedDRA lexicon and coding processes, as well as the data structures for reporting adverse events have evolved. In the 10th Annual Report the entire history of adverse events has been re-coded to the current MedDRA lexicon (Version 19), using a uniform process and the most complete descriptions of all the reported adverse events.

From the laboratory determinations, ALT and AST levels typically rise after islet transplantation, then level off, with the rise being lower in the recent eras. Long-term recovery of AST appears to be better in recipients aged <35 years (p=0.002), but there was no significant age related effect observed for ALT.

Serum creatinine rose slightly but steadily over years of follow-up after initial islet transplant, in both ITA and IAK, but started higher in IAK. Those aged 35 and over also had higher initial levels. There were no significant differences by era, IEQ's infused, or immunosuppression.

The decline in eGFR (CKD-Epi) after islet transplantation is both statistically significant and clinically important. IAK had much lower pre-transplant levels than ITA, which then declined at a slower rate (Exhibit G2, p<0.001). Initial levels were also lower in recipients age 35 and older and declined at a slower rate compared to younger recipients. Levels were generally higher among recipients managed with both mTOR inhibitors and calcineurin inhibitors compared to other maintenance immunosuppression regimens (p<0.0001). Compared with an age-unadjusted cohort of 1,141 T1D followed by the Diabetes Control and Complications Trial and then by the Epidemiology of Diabetes Interventions and Complications (EDIC) (The DCCT/EDIC Research Group, 2011) who started with mean eGFR levels of 126 ml/min/1.73m^3, CITR allograft recipients had much lower mean eGFR (88.1±0.9SE for ITA and 63.1±1.8 for IAK) at their first transplant. CITR ITA recipients exhibited a decline in eGFR of 14.2 ml/min/1.73m3 and IAK experienced a mean decline of 5.3 ml/min/1.73m^3 in 5 years from last infusion, compared to a mean decline of about 9 ml/min/1.73m^3 over the first 5 years in the DCCT.

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



Neoplasms. A total of 51 instances of neoplasm have been diagnosed in 34 of the 1,086 islet recipients who collectively represent a total of 4,583 person-years of observed follow-up. This equates to about 0.01 neoplasms per person-year. There were 35 instances in 22 patients (1 in 18 recipients and multiple in 4 recipients) of basal or squamous cell carcinoma of the skin. Of the 18 patients with a single instance, 16 recovered (1 with sequelae) and 2 have an unknown recovery status. Of recipients with multiple instances, 3 have recovered from all instances (2 with sequelae) and 1 has not recovered.

There were 4 instances of breast cancer (2 instances in 1 recipient), 4 instances of thyroid cancer (2 instances in 1 recipient), 2 instances of PTLD and 1 instance of CNS lymphoma, 2 instances of lung cancer, and 1 instance of mucinous adenocarcinoma of the appendix. Of the recipients with non-skin cancers, 6 recovered, 1 was still recovering, 4 had not recovered, and 1 died (lung cancer). For 2 instances of cancer, the type of neoplasm was not specified, but the recipients were both reported to have recovered without sequelae.

Deaths. There have been 33 reports of death to the Registry for islet allograft recipients, for 3.0% crude mortality over a mean of 4.4 years elapsed follow-up per patient (including periods after complete graft failure and loss to observed follow-up). Causes of death were (# cases): cardiovascular (8), hemorrhage (3), pneumonia (2), renal failure (2), respiratory arrest (2), acute toxicity (1), cerebrovascular event (1), diabetic ketoacidosis (1), infection (1), lung cancer (1), multi-organ failure of unknown etiology (1), necrosis (1), pneumopathy (1), and viral meningitis (1). The remaining 7 deaths did not have a cause specified.

CONCLUSIONS

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

The safety-risk profile indicates that over 1999-2015, recipients of allogeneic islet transplantation were much more impacted by their disease than either of the DCCT-EPIC T1D cohorts, being substantially older, having diabetes for many more years, exhibiting much more impaired kidney function at initial transplant, and suffering from very poor glycemic control marked by frequent episodes of severe hypoglycemia. Despite the burden of immunosuppression, CITR allograft recipients exhibited substantial benefit with acceptable risk as evidenced by low levels of infusion-related complications, and relatively few events of immunosuppression-related cancer and death. Increased cancer risk is associated with both diabetes (Hemkens, et al., 2009; Suh, 2011; Noto, Osame, Sasazuki, and Noda 2010) and solid organ transplantation (Engels, et al., 2011), making it difficult to predict expected rates of neoplasm in T1D islet transplant recipients. Declining kidney function, while of concern, is not comparable to the full DCCT-EPIC cohorts: in CITR allograft recipients, eGFR started much lower relative to the DCCT-EPIC cohorts, declined at higher rates in the ITA group and declined at similar rates in the IAK group, which were very low to start with.

In terms of the clinical benefit of allogeneic islet transplantation, the cumulative CITR data now clearly points to the patient selection and medical practices that optimize long-term outcomes: insulin independence, clinically improved HbA1c levels, achievement and durability of blood

glucose levels in near-normal ranges, and the remarkable resolution of severe hypoglycemic episodes with a return of hypoglycemia awareness in the vast majority of the ITA recipients. The accumulated experience in islet transplantation indicates that the best practices for ITA are:

- For islet-alone: recipient age ≥35 years; >325K IEQs over all infusions; and use of T-cell depletion with TNF antagonism for induction, and CNI and/or mTOR inhibitors for maintenance immunosuppression;

The most remarkable clinical effect of islet transplantation are the very high levels of resolution of severe hypoglycemic events (Exhibit D, last panel), which are sustained long-term, even after complete loss of graft function (Exhibit F, last panel – while the event rates for absence of severe hypoglycemic events (ASHE) are lower when C-peptide is <0.3 ng/mL, they are still at least 60%). The fundamental determinant of clinical benefit is maintenance of C-peptide≥0.3 ng/mL: the higher, the better (Exhibit F, all panels). And the most important predictors of sustained high C-peptide levels are recipient age≥35, IEQs infused≥325K, and induction with TNF-a inhibitors for ITA; and ≥325 IEQs infused for IAKs (Exhibit E).

Acknowledgments and Disclaimers

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REFERENCES

The DCCT/EDIC Research Group (2011). Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med*, November 12, 2011: Epub ahead of print (10.1056/NEJMoa1111732).

Engels E, Pfeiffer R, Fraumeni J, Jr, Kasiske B, Israni A, Snyder J, Wolfe R … & Lin M (2011). Spectrum of cancer risk among US solid organ transplant recipients. *JAMA*, 306(17): 1891-1901.

Hemkens L, Grouven U, Bender R, Günster C, Gutschmidt S, Selke G & Sawicki P (2009). Risk of malignancies in patients with diabetes treated with human insulin or insulin analogues: A cohort study. *Diabetologia*, 52(9):1732-44. Epub: 2009 Jun 30.

Noto H, Osame K, Sasazuki T & Noda M (2010). Substantially increased risk of cancer in patients with diabetes mellitus: A systematic review and meta-analysis of epidemiologic evidence in Japan. *J Diabetes Complications, 24(5):* 345-353. Epub: 2010 Jul 24.

Suh S & Kim K (2011). Diabetes and cancer: Is diabetes causally related to cancer? *Diabetes Metab J, 35(3)*: 193-8. Epub; 2011Jun 30.

Prepared by:

CITR Coordinating Center
The Emmes Corporation, Rockville, MD
www.citregistry.org

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