Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE BRIEFING DOCUMENT

LANTIDRA™ (donislecel)

for the

TREATMENT OF BRITTLE TYPE 1 DIABETES MELLITUS

Meeting Date: 15 April 2021

AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ALT	Alanine transaminase
AMA	American Medical Association
anti-IL-2	Non-depleting monoclonal anti-interleukin-2
AST	Aspartate transaminase
BLA	Biologics License Application
BSC	Biological Safety Cabinet
cGMP	Current Good Manufacturing Practice
CIT	Clinical Islet Transplantation Consortium
CMRL	Connaught Medical Research Laboratories
CMV	Cytomegalovirus
CNC	Controlled Not Classified
CPT	Current Procedural Terminology
DCCT	Diabetes Control and Complications Trial
DRAI	Donor Risk Assessment Interview
EDIC	Epidemiology of Diabetes Interventions and Complications
eGFR	Estimated glomerular filtration rate
ELISA	Enzyme-linked immunosorbent assay
EU	Endotoxin units
FDA	Food and Drug Administration
GLP-1	Glucagon-like peptide-1
GSI	Glucose Stimulation Index
HbA1c	Glycated hemoglobin A1c
HEPES	2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid
HLA	Human leukocyte antigen
HYPO	Hypoglycemia
IE	Islet equivalents
IND	Investigational New Drug Application
ISO	International Organization for Standardization
ITA	Islet transplant alone
IVGTT	Intravenous glucose tolerance test
JDRF	Juvenile Diabetes Research Foundation International
LDL	Low-density lipoprotein
LI	Lability index
MAGE	Mean Amplitude of Glycemic Excursions score
MMT/MMTT	Mixed Meal Test/Mixed Meal Tolerance Test
mTOR	Mammalian target of rapamycin
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health
OGTT	Oral glucose tolerance test
PCS	Potentially clinically significant
PP	Pancreatic polypeptide
PRA	Panel-reactive antibodies
SAE	Serious adverse event
SHE	Severe hypoglycemic event

SOC	System Organ Class
TEAE	Treatment-emergent adverse event
T1D	Type 1 diabetes mellitus
TNFα	Tumor necrosis factor alpha
UIC	University of Illinois at Chicago
UI Health	University of Illinois Hospital and Health Sciences Center
UNOS	United Network for Organ Sharing
WDRS	Wisconsin Diabetes Registry Study

1. EXECUTIVE SUMMARY

CellTrans, Inc. ("CellTrans") is seeking approval of Lantidra™ (donislecel), which is an allogeneic pancreatic islet cellular therapy indicated for the treatment of brittle type 1 diabetes mellitus (labile diabetes; brittle T1D) in adults whose symptoms are not well controlled despite intensive insulin therapy.

The islets that comprise the active portion of donislecel are isolated from donated pancreata from deceased organ donors and obtained by CellTrans from the United Network for Organ Sharing (UNOS). UNOS is the private, non-profit organization that manages the nation's organ transplant system under contract with the federal government and serves as the model for transplant systems around the world. CellTrans gratefully acknowledges the generosity of the organ donors and their families, without whom allogeneic islet transplantation would not be possible.

It has been 20 years since the initial reports of success with clinical islet transplantation for the treatment of brittle T1D, and since that time, more than 1000 patients have received islet transplants in the U.S. and around the world. In addition, several national and provincial governments, including Australia, several provinces in Canada, France, Italy, Switzerland, and the United Kingdom, have approved islet transplantation as a reimbursable procedure for the treatment of brittle T1D. Donislecel would be the first approved islet cell therapy in the U.S.

1.1. Targeted Indication – Brittle Type 1 Diabetes

The targeted indication for donislecel is the treatment of brittle T1D in adults whose symptoms are not well controlled despite intensive insulin therapy.

T1D (brittle and non-brittle) is characterized by the autoimmune-mediated loss of insulin-producing β-cells within the islets of Langerhans in the pancreas and results in the complete deficiency of insulin, causing several potentially life-threatening conditions such as hyper- and hypoglycemia, ketoacidosis, and dehydration.

While around 1.4 million Americans suffer from T1D [1], "brittle" T1D is a rare T1D subtype, with current estimates suggesting fewer than 80,000 affected individuals in the U.S. UI Health received the first Orphan Drug Designation for allogeneic islets of Langerhans (donislecel) for the treatment of brittle T1D in 2017, which was subsequently transferred to CellTrans, and Orphan Drug Designation has since been granted to 5 additional sponsors. Brittle T1D is a particularly difficult form of T1D to treat and is characterized by severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia often requiring hospitalization. Hypoglycemia unawareness is one of the hallmarks of brittle T1D. Hypoglycemia unawareness is especially dangerous because the hypoglycemic individual will not know to take corrective action to prevent further deterioration. If left untreated, hypoglycemia may become severe, resulting in confusion, disorientation, loss of consciousness, or, in extreme cases of prolonged hypoglycemia, permanent brain damage or death [2].

Secondary complications, including neuropathy, cardiovascular disease, and retinopathy can be especially common in brittle T1D and there is a significant excess mortality in these patients despite intensive insulin therapy [3].

1.2. Currently Available Treatments and Unmet Medical Need

Keeping blood glucose levels tightly controlled represents the most effective way to prevent or reduce both the symptoms and chronic complications of T1D [4]. For most T1D patients, insulin therapy is sufficient to manage blood glucose levels in a way that preserves an adequate quality of life. However, for the limited cohort of patients with brittle T1D, insulin therapy, even in its most state-of-the-art and intensive form, often remains insufficient. Despite intensive insulin therapy and frequent blood sugar monitoring, these patients still suffer from debilitating symptoms and are left susceptible to numerous secondary complications of T1D. Furthermore, the risk of severe hypoglycemia increases with more intensive insulin regimens [5] and is further elevated in patients with hypoglycemia unawareness, with a reported 6-fold increase in the frequency of severe hypoglycemia in these patients [6].

Over the past few years, advanced medical devices that combine blood sugar monitoring and insulin delivery have been developed. Closed-loop systems (also referred to as an “artificial pancreas”) automate subcutaneous insulin delivery via a pump and have shown promise for reestablishing glycemic control in patients with TID [7-9]. However, these products cannot adequately control blood sugar in all patients with brittle T1D, and severe hypoglycemia remains an ongoing and debilitating problem in these patients [7]. Furthermore, sudden death associated with severe hypoglycemia has been reported even with the use of these advanced sensor-pump devices [10].

Beyond intensive insulin therapy, whether by pump or manual administration, treatment for patients with brittle T1D is limited to whole pancreas transplant, which carries with it both surgical and post-procedural risk and is not appropriate for all brittle T1D patients [11].

Because many brittle T1D patients are unable to achieve adequate glycemic control despite the most advanced therapies currently available, there remains an unmet medical need for additional modalities for the safe and effective treatment of brittle T1D. CellTrans seeks to fulfill this unmet need with donislecel to help patients who are suffering from this debilitating and potentially life-threatening rare disease.

1.3. Donislecel

1.3.1. Regulatory and Development History

The CellTrans IND was opened in 2004 by the University of Illinois at Chicago (UIC) and later managed through University of Illinois Hospital and Health Sciences Center (UI Health), the medical center associated with UIC. This was an investigator-initiated commercial IND prepared by Jose Oberholzer, MD, MHCM, FACS, and his team to support an initial Phase 1/2 proof-of-concept study (UIH-001) to investigate the use of transplanted islets (donislecel) for the treatment of brittle T1D. The clinical program (Table 1) subsequently included an additional study, a Phase 3 pivotal trial known as UIH-002. All clinical investigations and manufacturing related to this IND were performed at facilities at the UI Health campus in Chicago, Illinois. In 2016, the IND was transferred from UI Health to CellTrans, which was founded by Dr. Oberholzer and is currently led by him.

CellTrans is a company with12 employees and with clean room facilities at UIC. The primary focus of CellTrans is to improve patient care via the development and approval of donislecel for the treatment of brittle T1D.

In 2017, CellTrans received Orphan Drug Designation (transferred from UI Health) for donislecel for the treatment of brittle T1D, and the FDA has approved the CellTrans expanded access protocol, enabling patients to continue to receive donislecel outside of the primary clinical studies (i.e., UIH-001 and UIH-002). The justification for granting expanded access was the sufficiency of evidence for the safe and effective use of donislecel and that the potential patient benefit of donislecel justifies its potential risks in this context.

In addition to the 2 core studies under its own IND, UIC/UI Health also participated in 3 studies under IND BB-9336 as part of the National Institutes of Health (NIH) Clinical Islet Transplantation (CIT) Consortium (Studies CIT-02, CIT-06, and CIT-07) and 1 study in collaboration with the University of Chicago under IND BB-11228 (Study 12176A). While CellTrans has submitted data collected from these supplemental studies in the donislecel BLA to support the full scope of clinical experience with donislecel, CellTrans intends to rely solely on data from its own 2 core studies to support the eventual product label for donislecel. Therefore, results from these supplemental studies will not be presented in this briefing document except for a high-level summary in the appendix (Table 45).

Table 1. Clinical Trials Utilizing Donislecel

Study Number	Study Phase	Study Title	Patients	Transplants
Core Studies (Under UIC/UI Health/CellTrans IND BB-11807)				
UIH-001	1/2	Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid Free Immunosuppression	10 [a]	21
UIH-002	3	Islet Transplantation in Type 1 Diabetic Patients Using the UIC Protocol, Phase 3	21 [a]	35
Supplemental Studies (Collaborations under INDs of Other Sponsors)				
CIT-02	2	Strategies to Improve Long Term Islet Graft Survival	2	3
CIT-06	3	Islet Transplantation in Type I Diabetic Kidney Allograft Recipients: Efficacy of Islet After Kidney Transplantation	4	6
CIT-07	3	Allogeneic Purified Human Pancreatic Islet Transplantation for Treatment of Type 1 Diabetes	4	7
12176A	1/2	Allogeneic Islet Cell Transplantation	3	3
		TOTAL	**43** [a]	**75**

Notes: CIT-02, CIT-06, and CIT-07 were conducted under the NIH IND BB-9336. Study 12176A was conducted under University of Chicago IND BB-11228. For the CIT studies, only patients enrolled at UI Health are included in this table. For 12176A, only patients receiving UI Health manufactured islets are included in this table; all patients in this study were transplanted and followed by University of Chicago under their protocol, not UI Health.

[a] 1 patient from UIH-001 was also subsequently enrolled into UIH-002 and is counted in this table under both studies. The total number at the bottom of the table counts this patient only once.

1.3.2. Product Description

Donislecel consists of a suspension of allogeneic pancreatic islets in Connaught Medical Research Laboratories (CMRL) 1066 transplant medium buffered with HEPES (2-[4-(2-

hydroxyethyl)piperazin-1-yl]ethanesulfonic acid; 10 mM final concentration) and supplemented with human serum albumin (0.5% final concentration).

Donislecel is contained in one 1000 mL infusion bag filled with a supplied volume of 400 mL, containing not more than 10 cc of estimated packed islet tissue. The 1000 mL infusion bag is aseptically connected to a smaller 750 mL bag containing 200 mL of supplied volume for use in rinsing the 1000 mL bag and line following transplant to assure complete transfer of islets to the patient.

1.3.3. Mechanism of Action

Pancreatic islets regulate blood glucose levels through highly regulated, pulsatile secretion of multiple hormones in response to fluctuations in blood glucose. Endocrine cells within pancreatic islets release insulin, glucagon, somatostatin, pancreatic peptide, and ghrelin. Insulin enables glucose uptake by peripheral tissues, glucagon mobilizes glucose from the liver into circulation, somatostatin inhibits both α- and β-cell secretions, pancreatic peptide inhibits pancreatic exocrine secretion, and ghrelin inhibits insulin secretion. Together, these hormones help maintain blood glucose levels within the normal range [12].

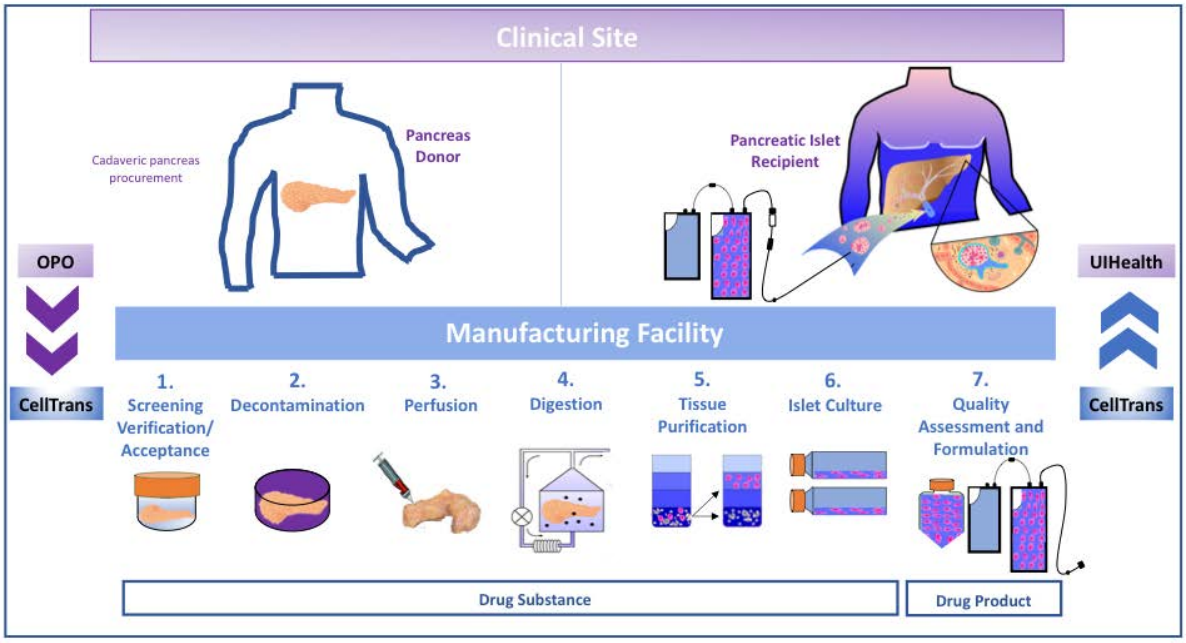
1.3.4. Manufacturing

The CellTrans current Good Manufacturing Practice (cGMP) islet manufacturing facility is located at UI Health in Chicago, IL. Manufacturing and support operations (approx. 2,250 square feet) consist of classified areas (International Organization for Standardization [ISO] 7 and ISO 8) with ISO 5 Biological Safety Cabinets (BSCs) and Controlled Not Classified (CNC) areas. The facility is intended for the manufacture of isolated pancreatic islets and has been used for the manufacture of all lots of isolated pancreatic islets transplanted under the CellTrans IND.

Islets are sourced from the pancreas of a deceased donor. Donor pancreas allocation to the intended recipient occurs through UNOS, and organ procurement is handled by an organ procurement organization (OPO) and the transplant center's transplant surgeons. The manufacture of purified pancreatic islets from the eligible donor pancreas is a complex process with multiple manufacturing steps. Once the pancreas is procured, delivered, and accepted for processing at the facility, all manufacturing steps involving the pancreas and pancreatic tissue are performed in certified ISO 5 BSCs in the ISO 7 classified area using aseptic processing techniques. The manufacturing process is continuous from the time the donor organ is received at CellTrans through release of the final drug product (donislecel). The process is broken down into drug substance manufacturing steps (pre-islet culture) and drug product manufacturing steps (post-islet culture). A flow diagram of the principal steps in the overall manufacturing process are provided in Figure 1.

Each donislecel lot consists of islets isolated from a single donor pancreas intended for a single designated islet recipient. The donor pancreas is considered incoming raw material and is screened and qualified prior to acceptance. Due to the nature of donislecel and its intended use, there is always a batch size of one unit. Quality Control testing of donislecel is performed prior to release.

Figure 1. Donislecel Manufacturing Process Overview



1.3.5. Dosage and Administration

The targeted minimum total donislecel dose is 10,000 islet equivalents (IE)/kg for successful engraftment and achieving insulin independence; however, multiple transplants may be required to reach this minimum number, and some patients may need more than 10,000 IE to achieve insulin independence. The recommended minimum dose of donislecel is 5,000 IE/kg for initial transplant and 4,000 IE/kg for subsequent transplants in the same recipient. No maximum dose has been defined, but there is a 10-cc limit on packed cell volume for each transplant.

Donislecel is infused into the hepatic portal vein via percutaneous or transvenous transhepatic access, or if these are not feasible, then via laparoscopic or open surgical (mini-laparotomy) access. Following transplant, the patient is monitored for graft function, immunosuppression levels, and safety.

Subsequent islet transplants may be performed at the discretion of the transplant physician or other qualified medical professional. During donislecel clinical trials, patients were eligible for subsequent islet infusions if after a period of at least 30 days post-transplant they had not reached insulin independence, defined as absence of exogenous insulin use while achieving glycated hemoglobin A1c (HbA1c) ≤6.5% at the time of evaluation, or if after at least 30 days of insulin independence they presented with declining islet function requiring the reintroduction of exogenous insulin.

While patients enrolled in donislecel clinical trials received up to 3 transplants, no maximum number of transplants has been defined; rather, the maximum number will depend upon a given patient's response to treatment, whether the minimum number of islets to be

transplanted has been achieved, the presence/absence of ongoing islet graft function, and the medical judgment of the physician(s).

Patients receiving donislecel also require certain pre-medications and concomitant medications to promote patient safety and graft survival. Pre-medications provided on the day of the transplant procedure include:

- Non-depleting monoclonal anti-interleukin-2 (anti-IL-2) receptor antibody (e.g., basiliximab)
- Calcineurin inhibitor (e.g., tacrolimus)
- Mammalian target of rapamycin (mTOR) inhibitor (e.g., sirolimus)
- Tumor necrosis factor alpha (TNFα) inhibitor (e.g., etanercept)
- Glucagon-like peptide-1 (GLP-1) inhibitor (e.g., exenatide)
- Periprocedural antibiotic prophylaxis is recommended

Anti-infective medications (e.g., sulfamethoxazole/trimethoprim and valganciclovir) are also provided on the day of transplant and continuing for an appropriate duration post-transplant. Ongoing administration of the non-depleting monoclonal anti-IL-2 receptor antibody, TNFα receptor agonist, and GLP-1 inhibitor are provided for appropriate durations post-transplant.

Maintenance immunosuppression must be continued permanently to prevent islet graft rejection and adjusted as needed based upon patient blood levels of these drugs. The steroid-free maintenance immunosuppression regimen typically includes a combination of a calcineurin inhibitor and an mTOR inhibitor or appropriate alternatives.

1.3.6. Efficacy

Efficacy has been examined in two core studies under the CellTrans IND (UIH-001 and UIH-002; Pooled Population; N=30).

A composite efficacy endpoint consisting of HbA1c ≤6.5% and absence of severe hypoglycemic events (SHEs) through 1 year after a patient's last transplant is a clinically meaningful endpoint that is supported by the United States Food and Drug Administration (FDA)'s 2008 Guidance for Industry on allogeneic islet products [13], a publication from FDA by Tiwari et al. [14], and the collective experience of the islet transplantation field. In addition to the composite endpoint, insulin independence (i.e., freedom from exogenous insulin use) and other assessments of glycemic control have been included to provide a more complete understanding of the clinically meaningful benefits of islet transplantation.

In the Pooled Population, 19/30 patients (63%) met the composite efficacy endpoint and 20/30 (67%) were insulin independent at 1 year after last transplant. Other measures of efficacy, including hypoglycemia (HYPO) score, basal and stimulated blood glucose, and basal and stimulated C-peptide, also showed marked improvement at 1 year after last transplant in the Pooled Population. Importantly, improvements in glycemic control have persisted over time. In Pooled Population patients, 8/12 (67%) evaluable patients still met requirements for success on the composite efficacy endpoint as well as insulin independence at 6-years post-last transplant. Patient demographics (age, sex) did not meaningfully impact long-term efficacy.

A dose-efficacy relationship exists for the composite efficacy endpoint and insulin independence where success increases with increasing islet dose, at least up to a minimum cumulative dose where maximum benefit is achieved. Based upon donislecel results and published data [15-19], the minimum recommended cumulative dose is 10,000 IE/kg (across 1 or more transplants) to ensure ≥500,000 total IE are transplanted.

The evidence from the donislecel development program, especially in the context of nearly 2 decades of published results from other transplant centers using similar study designs and islet products, supports the efficacy of donislecel for the treatment of brittle T1D. Based upon these data and comparisons to historical data, islet transplantation provides a compelling alternative to intensive insulin therapy (the current standard of care) for treating brittle T1D.

1.3.7. Safety

Safety has been examined in 2 core studies under the CellTrans IND (UIH-001 and UIH-002; Pooled Population; N=30).

The primary safety follow-up period used to support the CellTrans BLA is from initial transplant through one year after last transplant. Long-term safety has also been assessed.

For the Pooled Population from initial transplant through 1 year after last transplant:

- Treatment-emergent adverse events (TEAEs) occurred in all patients, regardless of the number of transplants.
- There were no TEAEs leading to early discontinuation
- There were no TEAEs leading to death.
- Approximately 53% of patients experienced a serious adverse event (SAE, ~3% of all TEAEs)
- Approximately 83% of patients experienced a TEAE of Grade 3 or higher (~13% of all TEAEs).
- Approximately one quarter of all TEAEs reported during primary follow-up occurred within the first week post-transplant, and approximately one half occurred within the first month.

Donislecel demonstrated a safety profile consistent with known risks of the transplant procedure and concomitant medication use, especially long-term use of immunosuppressants. During primary follow-up, the most reported (≥60% of patients) TEAEs in the Pooled Population were acne (87%), anemia (83%), nausea (83%), fatigue (80%), abnormal loss of weight (73%), diarrhea (73%), headache (63%), increased transaminases (63%), and vomiting (60%); only anemia accounted for >5% of all TEAEs reported. The most common ≥Grade 3TEAEs (≥20% of patients) were diarrhea (23%), anemia (20%), and nausea (20%).

Procedure-associated TEAEs were uncommon across all studies, with 6 total events (of which 3 events were SAEs). All 6 events were bleeding related (intra-abdominal hemorrhage [x3], hepatic hematoma [x2], and hemoperitoneum). Infusion was terminated in 1 patient due to elevated portal pressure during the procedure.

During primary follow-up (i.e., from initial transplant through 1 year after last transplant), most SAEs in the Pooled Population occurred only once and affected a single patient. Only anemia, pneumonia, hyponatremia, and nausea SAEs occurred more than once, and only

anemia, pneumonia, and nausea SAEs affected more than 1 patient. During long-term follow-up (i.e., beyond 1 year after last transplant), only SAEs of fracture (various), hyponatremia, basal cell carcinoma, squamous cell carcinoma, myocardial ischemia, syncope, and peripheral artery stenosis occurred more than once; with the exception of peripheral artery stenosis, which occurred in 1 patient, all SAEs reported during long-term follow-up occurred in 2 patients each.

Laboratory measurements were generally stable through 1 year after the last transplant, although transient abnormalities that were classified as adverse events were reported, including anemia, leukopenia, abnormal electrolytes, increased low density lipoprotein, and elevated liver enzymes (alanine transaminase [ALT]/aspartate transaminase [AST]).

Vital signs were generally stable during through 1 year after the last transplant. Abnormal electrocardiograms were observed but were not common, and there were few cardiovascular TEAEs during follow-up, with myocardial ischemia being the only cardiovascular TEAE reported in more than 1 patient. No observable trends were noted.

There was no discernible relationship between safety outcomes and islet dose, number of transplants, or patient sex.

A relationship between safety outcomes and patient age may exist. During primary follow-up, Pooled Population patients >47 years of age had more TEAEs per patient, SAEs per patient, and ≥Grade 3 TEAEs per patient, a greater decline in renal function, and a higher percentage of patients with worsened electrocardiograms post-transplant than patients ≤47 years of age. Older patients experienced a higher rate of blood and lymphatic disorders, certain infections, increased liver enzyme levels, and hyponatremia than younger patients, although TEAE incidence was similar for most other AE categories. Because there were only 2 patients ≥65 and no patients <21 years of age at initial transplant, conclusions for geriatric and pediatric populations are not possible.

Donislecel safety outcomes were comparable to those of similar islet products from other islet transplant centers [20], and together these results support the safety of islet transplantation as a less invasive alternative to whole pancreas transplantation. Most risks identified during the donislecel program and in studies at other islet transplant centers, except for procedural risks, appear to mirror those observed for patients on immunosuppression. While islet transplantation involves additional treatment-related risk relative to standard-of-care insulin therapy, this must be balanced against the risks associated with brittle T1D patients remaining on insulin therapy, which has proven inadequate in these patients and therefore presents a significant burden on patient safety and quality of life.

In summary, the evidence from the donislecel clinical program, especially in the context of nearly 2 decades of published results from other transplant centers using similar study designs and islet products, supports the safety of donislecel for the treatment of brittle T1D.

1.3.8. Benefit-Risk Assessment

For those suffering from brittle T1D, islet transplantation fulfills a significant medical need, is effective at restoring good glycemic control in most patients, can slow or possibly reverse common secondary complications of T1D [21, 22], improves patient quality of life, and poses an acceptable safety risk. The islet transplantation procedure is minimally invasive and

generally safe and includes less procedural risk than whole pancreas transplantation. The primary risk from islet transplantation is related to concomitant medications, especially immunosuppressants, and the long-term safety outcomes of donislecel clinical trials (and the clinical trials of other allogeneic islet products) are consistent with what has been observed with chronic immunosuppressant use.

While donislecel is generally safe, maintenance of the islet graft still requires immunosuppression, which carries potentially significant risks to patient safety. Therefore, donislecel is only indicated for the treatment of brittle T1D and not T1D more broadly. Brittle T1D is characterized by severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia that severely disrupt quality of life, often requiring assistance from a third party and frequent hospitalizations. Patients with brittle T1D are unable to adequately control their blood sugar with intensive insulin therapy (the current standard of care). While, more recently, closed-loop insulin pumps (artificial pancreas) have been shown in short-term follow-up trials to be effective for the most patients, there is a subgroup of patients with brittle T1D whose symptoms cannot be optimally controlled by contemporary artificial pancreas systems. In such cases, donislecel, once approved, could be offered as a therapeutic alternative to patients for whom closed-loop control fails to reduce their risk for hypoglycemia, restore hypoglycemia awareness, or prevent severe hypoglycemic episodes.

Patients with brittle T1D suffer from serious disease-related complications. The negative consequences of simply maintaining standard-of-care treatment in these patients can be significant. As such, the amount of acceptable risk from an effective new therapy will be greater than it would be for a non-brittle T1D patient.

1.4. Conclusions

The benefits of donislecel outweigh the risks in patients with brittle T1D who have failed state-of-the-art insulin therapy based upon the totality of evidence from the donislecel clinical program and published literature, including the following factors:

- Islet transplantation is effective at restoring good glycemic control in most patients, and this beneficial effect persists for at least several years.
- Islet transplantation improves patient quality of life, allowing patients to perform activities that they could not do prior to receiving an islet transplant.
- Islet transplantation can slow or reverse many debilitating secondary complications and comorbidities of T1D (e.g., atherosclerosis, retinopathy, cognitive decline).
- Even with partial graft function, islet transplantation can lead to improved glycemic control, reduced reliance on exogenous insulin, and improved quality of life.
- Donislecel and the transplantation procedure are generally safe. The islet transplantation procedure is minimally invasive, with lower procedural risk than whole pancreas transplantation.
- Most risks associated with islet transplant are associated with immunosuppressant drugs, which are already approved for use in transplant recipients based upon their own favorable benefit-risk profiles.
- Brittle T1D is a debilitating disease that is not well-managed with standard-of-care insulin therapy, and the risk of these patients remaining on an ineffective treatment is

significant. While whole pancreas transplantation is an option in some of these patients, for others, the risks associated with an open surgical technique are too high.
- More than 2 decades of experience across multiple islet transplantation centers in the United States and around the world demonstrate the safety and effectiveness of islet transplantation for patients with brittle T1D.

2. INTRODUCTION

2.1. Brittle Type 1 Diabetes

Type 1 diabetes, which affects around 1.4 million Americans [1], is a disease characterized by the autoimmune-mediated loss of insulin-producing β-cells within the islets of Langerhans in the pancreas. The disease results in the complete or near-complete deficiency of insulin, causing certain acute, life-threatening conditions such as hyper- and hypoglycemia, ketoacidosis, and dehydration. Secondary complications associated with T1D include renal failure, neuropathy, cardiovascular disease, and retinopathy. T1D leads to significant excess mortality despite intensive management with insulin therapy [3].

Brittle T1D is a rare, difficult to treat T1D subtype that affects fewer than an estimated 80,000 individuals in the U.S. (UI Health received Orphan Drug Designation for donislecel for the treatment of brittle T1D in 2017, which was subsequently transferred to CellTrans).

The concept of “brittle diabetes” as a clinical condition was introduced in the 1930s, and its definition has been refined in the intervening decades [23, 24]. Brittle T1D is differentiated from standard (non-brittle) T1D by the presence of severely unstable blood glucose levels with frequent and unpredictable episodes of hypoglycemia (i.e., plasma glucose <70 mg/dL [3.9 mmol/L]) that often require assistance from a third party and frequent hospitalizations, significantly reducing a patient’s quality of life. These unpredictable episodes are due to an absolute insulin dependency in these patients and are more commonly seen with intensive insulin therapy than with conventional insulin therapy [25]. Despite advances in diabetes technologies, severe hypoglycemia remains a life-long challenge for patients with brittle T1D.

Symptoms of hypoglycemia may include anxiety, heart palpitations, tremor, sweating, hunger, and paresthesia, among others [2]. While most non-brittle T1D patients can sense these symptoms and address them proactively as they arise, one of the hallmarks of brittle T1D is hypoglycemia unawareness. The etiology of hypoglycemia unawareness is multifactorial and may result from chronic exposure to low glucose, antecedent hypoglycemia, recurrent severe hypoglycemia, and the failure of counter-regulatory hormones due to attenuated sympathetic neural and adrenomedullary responses [2, 26, 27]. Hypoglycemia unawareness is especially dangerous because the hypoglycemic individual will not know to take corrective action to prevent further deterioration. Indeed, hypoglycemia unawareness has been associated with an increased incidence of severe hypoglycemia [28]. If left untreated, hypoglycemia may become severe, resulting in confusion, disorientation, loss of consciousness, and, in extreme cases of prolonged hypoglycemia, permanent brain damage or death [2].

Although the life expectancy of patients with T1D has much improved since the introduction of insulin therapy, chronic complications, including blindness and renal failure, hamper

quality of life and represent a multi-billion dollar annual burden on the healthcare systems of industrialized countries [29, 30].

2.2. Currently Available Treatments and Unmet Medical Need

Keeping blood glucose levels under tight control represents the most effective way to either prevent the onset or reduce the progression of the chronic complications of T1D [4]. Insulin replacement has been the standard of care for T1D since its discovery in 1922; however, it requires continuous monitoring to ensure tight glycemic control and to avoid potentially life-threatening hypoglycemia or the development of secondary diabetic complications.

For the vast majority of T1D patients, insulin therapy is sufficient to manage blood glucose levels in a way that preserves an adequate quality of life. For more difficult cases, intensive insulin therapy, which requires multiple insulin injections and more frequent blood glucose monitoring, may be required. However, administration of subcutaneous insulin can never approximate the pulsatile insulin secretory patterns of the normal β-cell, and rarely attains normal blood glucose levels without the risk of major hypoglycemic episodes. Indeed, hypoglycemia is a common side-effect of insulin treatment. Risk of severe hypoglycemia increases with more intensive insulin therapy regimens and is further elevated in patients with impaired hypoglycemia awareness, with a reported 6-fold increase in the frequency of severe hypoglycemia in these patients [6]. Intensive insulin therapy is therefore only suitable for certain patients.

The challenge with the brittle T1D subtype is that it is not well managed with insulin therapy. This means that these patients still suffer from debilitating symptoms and are left susceptible to numerous secondary complications of T1D. As such, there is an inherent risk associated with these patients remaining on insulin therapy that may be abbreviated when more effective treatments are used (e.g., islet or whole pancreas transplant).

In recent years, the development of advanced sensors and insulin pumps (e.g., closed-loop systems or “artificial pancreas” [AP]) has allowed some patients to manage their T1D effectively [7-9]. However, there is evidence to suggest that brittle T1D cannot be optimally controlled by the closed-loop systems, and these patients can still suffer from the debilitating effects of severe hypoglycemia [7, 31]. Furthermore, sudden death associated with severe hypoglycemia has been reported even with the use of these advanced sensor-pump devices [10].

A 2016 report from International Pancreas and Islet Transplant Association and the Transplantation Society (IPITA-TTS) discussed the advantages and key challenges to AP systems compared to islet transplantation [31]. Among the advantages noted in the report were improved average glycemia, increased time in range, and reduced time in hypoglycemia, all without immunosuppression. However, the report also noted that because insulin is infused subcutaneously with these systems, which is suboptimal, the result is inferior insulin action and a hindrance of the ability of AP systems to cope with meals, exercise, and illness.

Subsequent studies confirmed this. Table 2 presents brief results from a clinical trial by Anderson et al. in patients with T1D with hypoglycemia unawareness and a history of severe hypoglycemia [32]. Over 1 month, the AP reduced the time that blood glucose was below 70 mg/dL by over 3-fold but did not completely normalize glycemic control and did not

restore hypoglycemia awareness or epinephrine response to hypoglycemia induced in a hospital setting.

Table 2. Glycemic Control in High-Risk Patients with Type 1 Diabetes Who Used an Artificial Pancreas System for One Month

	Hybrid Closed-Loop System (AP)		Sensor-Augmented Pump		Relative Improvement	
	Pre	Post	Pre	Post	F	p value
% time between 70-180 mg/dL	67.8 ± 13.5	78.2 ± 10	65.6 ± 12.9	59.6 ± 16.5	14.8	<0.001
% time below 70 mg/dL	7.2 ± 5.3	2.0 ± 1.4	5.8 ± 4.7	4.8 ± 4.5	11.8	0.001
% time above 180 mg/dL	25.1 ± 15.3	19.8 ± 10.1	28.6 ± 14.6	35.6 ± 17.6	7.5	0.009

Note: Values are reported as mean ± standard deviation. A repeated-measures general linear model was used to compare HCLC versus SAP data collected during the baseline week (pre) versus the last week of study(post).

AP, artificial pancreas; F, F statistic

Source: [32]

At the 2020 American Diabetes Association Conference, Brown et al. [33] reported observations from an 18-month follow-up with a closed loop system in the iDCL Trial Protocol 3, the largest AP study done to date [34]. While patients generally preserved glycemic control better than they did prior to the study, there were still 4 severe hypoglycemic events and 4 diabetic ketoacidosis events.

Further analysis of a subgroup (55 of 168 total patients) in the iDCL Trial Protocol 3 [34] who were at high risk for hypoglycemia at baseline (defined as >4% continuous glucose monitoring time below 70 mg/dL) showed improved overall glycemic control and time-in-range (70-180 mg/dL), but patients still had residual hypoglycemia and their hypoglycemia awareness did not improve [35].

Therefore, while AP systems are effective in many patients, these systems still fail to reduce hypoglycemia risk, fail to restore hypoglycemia awareness, and may not prevent severe hypoglycemic episodes in some patients with brittle T1D.

When insulin therapy fails, whole pancreas transplant has traditionally been the method of choice for T1D patients with intractable hypoglycemia unawareness (first recommended by the American Diabetes Association in 2000; [36]). Although mortality and morbidity following pancreas transplantation have improved over the years [37], whole pancreas transplantation is still a major surgical procedure that involves significant risk. Technical complications such as thrombosis, bleeding, and duodenal leaks can lead to re-laparotomy and are a risk factor for graft loss and morbidity [11]. Furthermore, in patients with certain comorbidities (e.g., cardiovascular disease), pancreas transplant surgery may present an unacceptable risk.

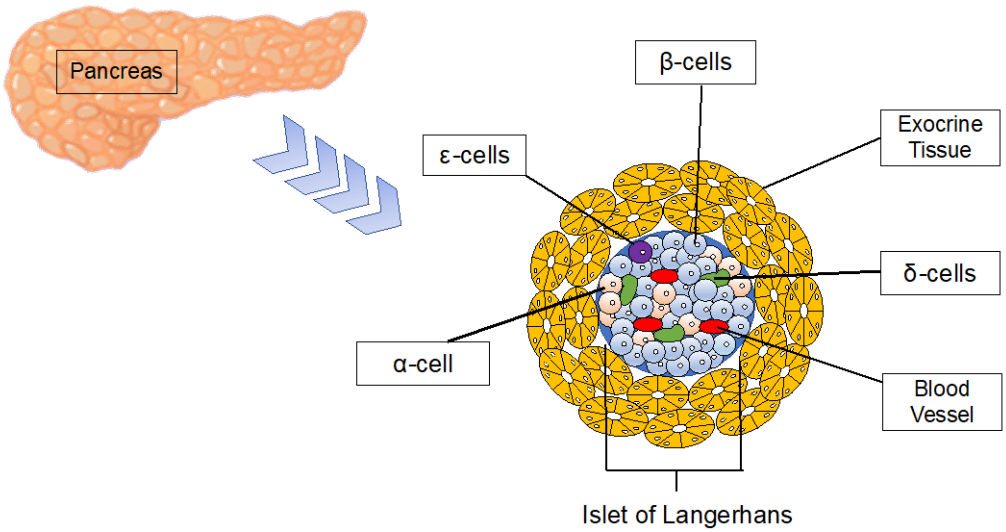
Because many brittle T1D patients are unable to achieve adequate glycemic control despite the most advanced therapies currently available, there remains an unmet medical need for additional modalities for the safe and effective treatment of brittle T1D. CellTrans seeks to fulfill this unmet need with donislecel.

2.3. Allogeneic Pancreatic Islet Transplantation

2.3.1. Islets of Langerhans – Description and Function

Donislecel consists of a suspension of donated pancreatic islets of Langerhans ("islets") in transplant medium. In their native location within the body, islets comprise the endocrine component of a normal pancreas (Figure 2). Islets are structurally well-defined, spheroid-like cell aggregates of about 1500-2000 cells with diameters ranging in size from <50 µm up to 500 µm [38]. Because of this size variation, it is standard practice in the islet field to express the total volume of isolated islets as islet equivalents (IEs, also seen abbreviated as IEQ or alternatively as EIN [equivalent islet number]) [39]. One IE is equal to an islet of 150 µm diameter, according to the criterion set at the Second Congress of the International Pancreas and Islet Transplantation Association that established the IE as the standard unit of islet volume [40]. Assuming a spherical shape, a standard islet would have a volume of approximately 1,800,000 μm^3.

Figure 2. Pancreatic Islets of Langerhans



Some key characteristics of islets are summarized in Table 3. Given the variability inherent in cellular preparations and islets in particular, precise values are difficult to determine; therefore, estimates have been provided based upon standard characteristics of an islet.

Table 3. Characteristics of Islets of Langerhans

Property	Standard Characteristic
Islet Shape	Spherical
Islet Diameter, mean [a]	150 µm
Islet Volume, mean	~1,800,000 μm^3
Islet Composition, adult (typical estimates)	β-cells (~55%) α-cells (~35%) PP-cells, δ-cells (~10% combined) ε-cells (<1%)
Islet Function [b]	Insulin secretion (β-cell) Glucagon secretion (α-cell) Somatostatin secretion (δ-cell) Pancreatic peptide secretion (PP-cell) Ghrelin secretion (ε-cell)

Note: "Standard" characteristics are considered to be representative of a typical islet.
[a] Islet diameters typically range from <50 µm to 500 µm.
[b] Secretion levels vary in response to glucose stimulation and are subject to regulation via local signaling (e.g., by autocrine feedback or in response to secretions by surrounding cells); therefore, secretion values/ranges are not enumerated here.
Source: [40, 41]

Functionally, islets regulate blood glucose levels through highly regulated, pulsatile secretion of multiple hormones in response to fluctuations in blood glucose. There are five principal endocrine cells that make up an islet: β-cells (secrete insulin), α-cells (secrete glucagon), PP-cells (secrete pancreatic polypeptide [PP]), δ-cells (secrete somatostatin), and ε-cells (secrete ghrelin). β-cells constitute approximately 55% of the islet cell mass, α-cells constitute approximately 35%, and the other cell types comprise the remaining 10% (Reviewed in [41]), although very few (<1%) ε-cells are observed in adult islets [42]. The secretion of islet hormones maintains glucose homeostasis through actions on peripheral tissues such as liver, muscle, and adipose tissue. Insulin enables glucose uptake by peripheral tissues, glucagon mobilizes glucose from the liver into circulation, somatostatin inhibits both α- and β-cell secretions, PP may exert an inhibitory effect on pancreatic exocrine secretion, and ghrelin inhibits insulin secretion. All islet endocrine cells therefore play a central role in maintaining appropriate levels of blood glucose (Reviewed in [41]).

Insulin is released from islets into the blood in a biphasic manner in response to a square-wave increase in arterial glucose concentration (i.e., a rapid rise in glucose concentration that is kept constant for the desired duration; the clinical counterpart is the hyperglycemic clamp with primed-continuous infusion of glucose) [43, 44]. The first phase consists of a brief spike at 2-4 minutes followed by a decrease to a nadir at 10-15 minutes before gradually increasing to a pseudo-steady state at 2-3 hours. While this biphasic release is a real phenomenon of β-cell function, square-wave stimulation is not physiological – when food or even concentrated glucose solutions are ingested, blood glucose and plasma insulin rise gradually with no clear phasicity in the insulin response [43].

Regardless of the precise mechanism, the primary pharmacodynamic effect of islets is maintenance of euglycemia. Acute effects (e.g., after a meal or following oral or intravenous administration of carbohydrates) are readily reflected by directly quantifying blood glucose. Long-term effects are better understood using HbA1c, which indicates the average amount of

glucose attached to hemoglobin over the past ~3 months (approximate lifetime of a red blood cell) [45].

2.3.2. History of Islet Transplantation

The history of islet transplantation research stretches back several decades. The genesis occurred in 1967 when Lacy and Kostianovsky developed a method for isolating islets from rat pancreata using collagenase [46]. By 1972, Ballinger and Lacy were able to cure chemically induced diabetes in the rat using islet transplantation [47]. Seventeen years later, in 1989, Lacy's team completed the first successful human islet transplant [48]. Following the transplant, the patient was insulin independent for approximately 1 month before the transplant was rejected, with the rejection likely due to inadequate immunosuppression. Several clinical studies followed, but the success rate was in general limited to a smaller proportion of patients and was of variable duration [49]. Even with the observed challenges, however, all of these earlier studies showed that islet transplantation could control glycemia similarly to a whole pancreas transplant [50].

A major advance in the field of clinical islet transplantation ocurred in 2000 with the initial report of success using the "Edmonton Protocol," in which islets from a deceased human donor were transplanted into the hepatic portal vein of a recipient with T1D using a steroid-free protocol of immunosuppression [15]. Insulin independence, no further episodes of hypoglycemic coma, normalization of HbA1c, and reduction in the mean amplitude of glycemic excursion were reported in 7 consecutive recipients with T1D, with a median follow-up time of 12 months. The immunosuppression regimen employed in this study combined a novel T lymphocyte-directed induction therapy utilizing the anti-IL-2 receptor monoclonal antibody daclizumab, and maintenance therapy with the calcineurin-inhibitor tacrolimus and the mTOR pathway inhibitor sirolimus, both of which reduce endogenous levels of IL-2. This more targeted and potent immunosuppression allowed the omission of steroids, which likely had previously hampered the success rate of islet cell transplantation. These groundbreaking studies laid the foundation for the next 2 decades of research and clinical development of islet transplantation for the treatment of brittle T1D.

Despite these significant advances, when the donislecel IND was opened in 2004 (then sponsored by UIC), significant knowledge gaps existed regarding organ selection, manufacturing processes and controls, patient selection, clinical administration, and even the best metrics to determine clinical benefit. Over the next 2 decades, processes and procedures have been tested and updated through the collective efforts of many islet transplant centers, including UIC/UI Health. This growth and consistent drive toward a more optimal process and improved patient outcomes is evident in the donislecel development program.

2.4. Donislecel Regulatory and Development History

Since the initial reports of success with clinical islet transplantation, several national and provincial governments have made islet transplantation for the treatment of brittle T1D a an approved and reimbursable procedure, including Australia, several provinces in Canada, France, Italy, Switzerland, and the United Kingdom [51]. Donislecel would be the first approved islet cell therapy in the U.S.

As of March 2021, the U.S. National Library of Medicine website clinicaltrials.gov listed a total of 158 islet transplantation clinical trials, including 72 completed trials. Of the 72 completed trials, 39 were Phase 2 trials and 7 were Phase 3 trials.

According to the Collaborative Islet Transplant Registry (CITR; see Section 9.3.3 for more details on this registry) 10th Annual report, as of 2015, there were 1,086 patients included in the registry who had received at least 1 islet transplant, including 877 who had received islet transplant alone (the others had received islet transplant in conjunction with kidney transplant) [20].

Key regulatory and development milestones for donislecel are provided in Table 4. The CellTrans IND was opened in 2004 by the University of Illinois at Chicago (UIC) and later managed through University of Illinois Hospital and Health Sciences Center (UI Health)—the medical center associated with UIC. This was an investigator-initiated commercial IND prepared by Jose Oberholzer, MD, MHCM, FACS, and his team to support an initial Phase 1/2 proof-of-concept study (UIH-001) to investigate the use of transplanted islets (donislecel) for the treatment of brittle T1D. The IND subsequently included one additional clinical study, a Phase 3 pivotal trial known as UIH-002. All clinical investigations and manufacturing related to this IND were performed at facilities at the UI Health campus in Chicago, Illinois. In 2016, the IND was transferred from UI Health to CellTrans, Inc., which was founded by Dr. Oberholzer and is currently led by him. CellTrans remains a small company (12 employees) whose primary focus is on improving patient care via the development and approval of donislecel for the treatment of brittle T1D.

In addition to the 2 core studies under its own IND, UIC/UI Health also participated in 3 studies under IND BB-9336 as part of the National Institutes of Health (NIH) Clinical Islet Transplantation (CIT) Consortium (Studies CIT-02, CIT-06, and CIT-07) and 1 study in collaboration with the University of Chicago under IND BB-11228 (Study 12176A). While CellTrans has submitted data collected from these supplemental studies in the donislecel BLA to support the full scope of clinical experience with donislecel, CellTrans intends to rely solely on data from its own 2 core studies to support the eventual product label for donislecel. Therefore, results from these supplemental studies will not be presented in this briefing document except for a high-level summary in Table 45.

Following 2 Type C meetings (2015 and 2016) and a Pre-BLA meeting with FDA (2016), CellTrans submitted a BLA in May 2017. However, after consultation with FDA, the BLA was withdrawn in July 2017 prior to the filing decision date to allow CellTrans to address several FDA recommendations related to their clinical and manufacturing programs. Over the next 3 years, CellTrans consulted several experts in the field, collected and analyzed additional clinical data to improve their safety and efficacy databases, and implemented several key improvements to their manufacturing procedures and quality systems.

Having addressed FDA's recommendations from the initial submission, CellTrans resubmitted the BLA in May 2020, and the BLA was filed in July 2020.

Table 4. Donislecel Regulatory and Development Milestones

Regulatory Milestone	Date
Initial IND (BB-11807) opened by University of Illinois at Chicago (UIC)	May 2004
Study UIH-001 initiated	November 2004
Study UIH-002 initiated	June 2007
Study CIT-02 initiated at UIC site	January 2009
Study CIT-06 initiated at UIC site	February 2009
Study CIT-07 initiated at UIC site	September 2008
Study UIH-001 completed	July 2020 [a]
Study UIH-002 completed	exp. December 2023 [b]
Study CIT-02 completed at UIC site	September 2012
Study CIT-06 completed at UIC site	May 2017
Study CIT-07 completed at UIC site	January 2014
FDA Type C Meeting (clinical, nonclinical, CMC)	April 2015
FDA Type C Meeting (CMC)	January 2016
FDA Pre-BLA Meeting	August 2016
Transfer of IND from UIC/UI Health to CellTrans	December 2016
Orphan Drug Designation granted to UIC/UI Health	February 2017
Transfer of ODD from UIC/UI Health to CellTrans	February 2017
Initial BLA submitted by CellTrans	May 2017
Initial BLA withdrawn by CellTrans	July 2017
BLA resubmitted by CellTrans	May 2020
BLA filed	July 2020
Advisory Committee Meeting	April 2021
PDUFA decision date	August 2021

BLA, Biologics License Application; CIT, Clinical Islet Transplantation (consortium); CMC, chemistry, manufacturing, and controls; IND, Investigational New Drug application; ODD, orphan drug designation; PDUFA, Prescription Drug User Fee Act; UIC, University of Illinois at Chicago; UIH, University of Illinois Hospital and Health Sciences Center

[a] Final 10-year follow-up visit (also known as UI Health; previously UIC)

[b] Expected month and year of final 10-year follow-up visit.

While donislecel is being submitted for marketing approval by CellTrans based upon data collected under their IND, UI Health also engaged in 3 multi-center collaborations as part of the CIT Consortium and 1 limited collaboration with University of Chicago. In each case, the partners with which CellTrans engaged were independent transplant centers that were codeveloping their own islet products. This speaks to an important distinction between islet transplantation and what can be considered “traditional” drug development programs. While nearly all new drugs are developed by a single sponsor or at most a few competitors working on different variations on a theme, islet transplantation is unique as many institutions across the country and around the world are actively and simultaneously investigating similar islet products developed using similar manufacturing techniques and similar clinical administration protocols and collectively have been doing so for over 20 years. Many of these centers, like CellTrans, have opened INDs to study their products.

An overview of studies involving donislecel administration is provided in Table 1, with key study design information and efficacy results summarized in Table 45. In total, 43 patients received 1-3 transplants (75 transplants total) across all studies using donislecel.

2.5. Donislecel Product Description

2.5.1. Target Indication

The target indication for donislecel is treatment of brittle T1D in adults whose symptoms are not well controlled despite intensive insulin therapy.

2.5.2. Mechanism of Action

Like the islets that reside in situ in a normally functioning pancreas (description and function summarized in Section 2.3.1), transplanted islets, like those in donislecel, exert their pharmacological effects via secretion of hormones (most notably insulin) in response to fluctuations in blood glucose levels.

2.5.3. Manufacturing

2.5.3.1. Manufacturing Process

This section provides information pertaining to the manufacturing and control of donislecel for Studies UIH-001 and UIH-002. A total of 56 donislecel lots are presented. The focus is placed on the manufacturing process and critical quality attributes of these lots, in particular purity and potency. Proprietary information is not disclosed.

The isolation of purified pancreatic islets is a complex process with multiple manufacturing steps. A major consideration for manufacturing donislecel is to have a well-controlled and established manufacturing process that can consistently produce islets that are safe, pure, and potent. In order to control the manufacturing process for consistency, it is necessary to thoroughly understand the manufacturing process and critical product quality attributes.

The manufacturing process is continuous from the time the donor organ arrives at CellTrans manufacturing site, through processing, to release of the final drug product (donislecel). The manufacturing process is broken down into drug substance manufacturing steps (pre-islet culture) and drug product manufacturing steps (post-islet culture).

The donor pancreas is considered the starting raw material for the manufacturing process. The donor organ allocation to the intended recipient occurs through UNOS. Medical centers identify potential organ donors and report this to the local OPOs that then screen, test, and manage the organ donor and determine donor eligibility. This includes verification of the donor medical records to include donor information, donor examiner information/report of the physical assessment, donor ABO verification, organ donor consent, donor communicable disease screening results, and donor medical history interview. The OPOs then inform UNOS about what organs are potentially eligible for transplantation, UNOS allocates the organ based on a national waitlist of transplant recipients, and the transplant centers accept or decline the organ as deemed medically appropriate for their waitlisted patients.

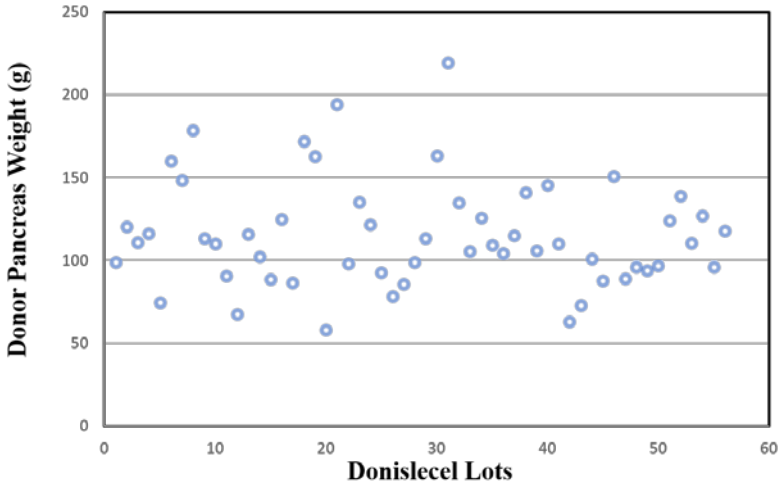
The following donor-related criteria are predictive of poor islet yield or quality; thus, donor organs with any of these characteristics are rejected (Table 5).

Table 5. Criteria for Pancreas Rejection

Criteria for Pancreas Rejection
HbA1c is greater than 6.0.
Donor age is less than 18 or greater than 70 years.
Donor body mass index is less than 19 Kg/m^2.
Estimated cold ischemia time is greater than 16 hours.
Warm ischemia time greater than 30 minutes (for donation after cardiac death).

Upon arrival at CellTrans, final screening verification and acceptance of the organ for processing is performed. Each donor pancreas is from an individual donor, with its own unique tissue composition (e.g., percentage fat, percentage fibrotic tissue) and size (Figure 3).

Figure 3. Donor Pancreas Weights for Donislecel Lots Used in Studies UIH-001 and UIH-002

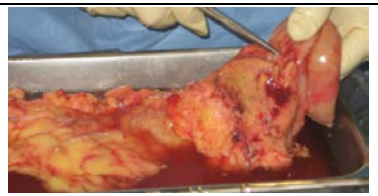


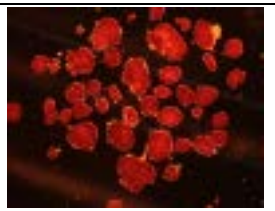
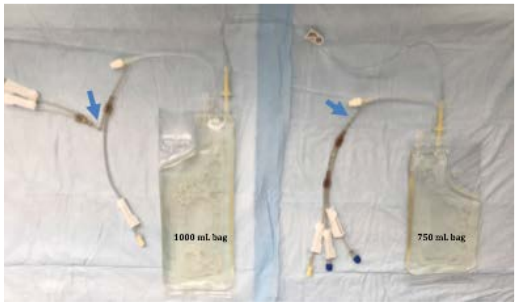
Note: Results are for 56/56 lots presented.

Additionally, all raw materials used in the manufacture of donislecel are sourced and supplied sterile and are controlled through GMP quality systems and management. Suppliers and materials are qualified to ensure suitability for use in the manufacture of donislecel.

Pancreas and islet manufacturing steps are performed using aseptic technique in five dedicated BSCs (ISO 5), within the CellTrans islet manufacturing facility. Aseptic process simulation is performed every six months to demonstrate that the islet manufacturing procedure is performed without the introduction of microbial/fungal contamination. Furthermore, environmental monitoring of the islet manufacturing facility is performed during each islet manufacture. Both the manufacturing environment and personnel are monitored to ensure islet manufacture occurs in a controlled environment that minimizes the risk of introducing potential contamination into the process. The principal steps in the manufacturing process are summarized in Table 6.

Table 6. Principal Steps in the Islet Manufacturing Process

Manufacturing Step	Description	Figure Representation
Drug Substance		
1. Screening Verification and Acceptance for Processing	Final screening verification of donor medical records and acceptance of organ for processing	
2. Pancreas Decontamination	Incoming pancreas is trimmed of excess fat tissue, spleen, and duodenum. Pancreas is decontaminated by a triple anti-microbial/fungal agent treatment.	
3. Pancreas Perfusion	The pancreas is cannulated and perfused with a collagenase/neutral protease solution. Following perfusion, the pancreas is cut into pieces for digestion.	
4. Pancreas Digestion	Pancreas pieces are placed into the Ricordi/digestion chamber. Enzymatic and mechanical digestion of the pancreatic tissue occurs and, upon release of islets, the digested pancreatic tissue is collected.	

Manufacturing Step	Description	Figure Representation
5. Tissue Purification	The digested pancreatic tissue is placed into a COBE 2991 cell processor. The processor purifies islets from the rest of the pancreatic tissue (exocrine) into different islet purity fractions Top (100-70%), Middle (69%-40%) and Bottom (39-10%).	
6. Islet Culture	Islet fractions are cultured at 37°C for up to 48 hours. Quality Control sampling for potency (Glucose Stimulation Index) from the Top (100-70%) islet purity fraction is taken prior to culture.	
Drug Product		
7. Quality Assessment and Formulation	Post culture, islet fractions are harvested, washed and formulated into excipient (refer to Table 7). Quality control sampling for safety, identity, potency (islet yield and viability) and purity. The drug product is packaged in the final container closure (bag), labelled, and released. The drug product (donislecel) is transplanted within 6 hours.	 

2.5.3.2. Final Formulation

The final donislecel formulation (drug product) is comprised of allogeneic islets of Langerhans suspended in serum-free transplant media (indicator-free CMRL 1066 without sodium bicarbonate and supplemented with HEPES and human albumin). The quantity of islet tissue in each donislecel batch for transplant is defined by both limits on islet equivalents per kg of recipient body weight (IE/kg), as well as limits on total packed tissue volume. A summary of the components of the final formulation, their function and quantity, and islet limits by transplant (i.e., initial vs. a subsequent transplant) is provided in Table 7.

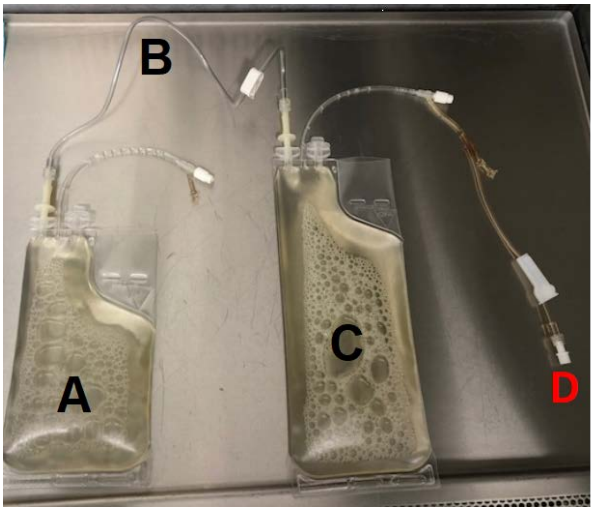
Table 7. Composition of the Final Donislecel Drug Product

Component	Function	Quantity
Purified Allogeneic Human Islets of Langerhans	Transplant Tissue	≤10 cc estimated packed cell tissue volume ≥5000 IE/kg (1st dose) ≥4000 IE/kg (2nd, 3rd dose)
CMRL 1066 Transplant Medium	Excipient	400 mL in drug product bag and 200 mL in separate rinse bag
HEPES	Excipient	10 mM
Human Serum Albumin	Excipient	0.5%

2.5.3.3. Packaging

The final donislecel product is contained in a 1000 mL infusion bag filled with a supplied volume of 400 mL (transplant medium supplemented with HEPES and human albumin), containing not more than 10 cc of estimated packed islet tissue and not more than 1 x 106 IE. The 1000 mL infusion bag is aseptically connected to a smaller 750 mL bag containing a supplied volume of 200 mL (transplant medium supplemented with HEPES and human albumin) for use in rinsing the 1000 mL bag and line following transplant. The 1000 mL bag containing donislecel and the connected 750 mL bag containing the transplant media for rinsing are placed in a flexible sterile outer package and transferred for transplant to UI Health in an insulated cooler. CellTrans performed a pancreatic islet stability study to access the quality and functionality of the final drug product (donislecel) at a maximum allowable holding time of 6 hours. The drug product (donislecel) is prepared and transplanted within a 6-hour period in order to control viability and potency of the final product. An image of the final container closure is provided in Figure 4.

Figure 4. Final Packaging Components for Donislecel



(**A**) CryoMACS 750 mL bag (rinse bag) (**B**) Spike adapter tubing (**C**) CryoMACS 1000 mL bag (containing donislecel) (D) Leur lock attachment for intravenous extension set and catheter.

2.5.3.4. Critical Quality Attributes

The critical quality attributes (CQAs) are defined as the donislecel quality attributes that have the greatest potential impact on product safety, identity, potency, and purity. The CQAs have been attributed to donislecel based on knowledge gained during the development of the islet isolation program. Quality Control release testing is performed on the drug product (donislecel) to control for safety, identity, potency, and purity. The Quality Control Specifications for the drug product (donislecel) are summarized in Table 8. Additional details on each of the quality parameters are provided below the table.

Table 8. Quality Control Specification for Donislecel

Quality Parameter		Test Method	Acceptance Criteria
Donor Eligibility		Screening, Testing, and Determination of Donor Eligibility	Eligible
Container Closure Integrity		Visual Inspection	No evidence of tampering or damage to drug product container
Appearance		Visual Inspection	No visible foreign objects or turbidity
Safety	**Sterility**	Rapid Culture Method (aerobic and anaerobic)	No growth in 14 days
	Fungal	Mycology Culture	No growth in 28 days
	Gram stain	Gram Stain and Microscopic Evaluation	Negative for presence of contamination
	Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe	Each transplant will contain ≤ 5 EU/kg of patient weight per hour
Identity	**Estimated Tissue volume**	Visual Quantification of Pelleted Islets (packed tissue volume)	≤ 10 cc

Quality Parameter		Test Method	Acceptance Criteria
	Islet morphology	DTZ Stain and Microscopic Evaluation	Islets Present: Stain red/orange with Dithizone, Rounded Shape 50 µm or greater in Size
Potency	**Glucose Stimulation Index (GSI)**	ELISA Quantification of Glucose Stimulated Islets	Ratio of insulin secretion under high glucose stimulation to that under low glucose stimulation ≥1
	Islet yield	DTZ stain and Microscopic Quantification (Islet Yield)	≥ 5,000 IE per kg for initial transplant (1st dose). ≥ 4,000 IE per kg for subsequent transplants (same recipient) (2nd and 3rd dose)
	Viability	SYTO® 13 Green/Ethidium Bromide Staining and Microscopic Evaluation	≥ 70% viable islets
Purity	**Endotoxin**	Endotoxin (Limulus Amebocyte Lysate), EndoSafe	Each transplant will contain ≤ 5 EU/kg of patient weight
	Islet purity	DTZ stain and Microscopic Quantification	≥ 30%

Note:. SYTO is a registered trademark of Thermo Fisher Scientific (Waltham, MA) and its subsidiaries.
DTZ = Dithizone; ELISA = Enzyme-Linked Immunosorbent Assay; EU = endotoxin units; IE = Islet Equivalent

Donor Eligibility: Determination of donor eligibility based on screening and testing. Prior to acceptance of the pancreas for processing, the donor undergoes donor eligibility screening and infectious disease testing in accordance with FDA 21 CFR Part 1271 *Human Cells, Tissues, and Cellular and Tissue Based Products (HCT/Ps)* requirements.

Container/Closure Integrity: The drug product (donislecel) is packaged in one intact, sterile, single-use infusion bag as described in Section 2.5.3.3. Evidence of tampering or damage to drug product container and the product is rejected.

Appearance: Cloudiness and turbidity are indicators of potential contamination. Presence of cloudiness, turbidity or visible foreign objects raises safety concerns, and the product is rejected.

Safety:

- **Sterility:** No microbial growth present after 14 days culture. Due to the 6-hour shelf life of the drug product (donislecel), the drug product is released for transplantation prior to the 14 day sterility result. In the event of a positive sterility result during or at 14 days culture, the medical team is immediately notified and all regulatory notification requirements are met. The microorganism is identified and reported and an investigation is initiated.
- **Fungal:** No fungal growth present after 14 days culture. Due to the 6-hour shelf life of the drug product (donislecel), the drug product is released for transplantation prior to the result. In the event of a positive sterility result during or at 14 days culture, the medical team of the recipient is immediately notified and all regulatory notification requirements are met. The microorganism is identified and reported and an investigation is initiated.

- **Gram Stain:** A negative gram stain is required prior to transplantation.
- **Endotoxin:** The endotoxin limit for the drug product is ≤ 5 EU/kg of patient weight and was established based on compendial limits for endotoxin exposure for infusions/injections of one hour or less in duration.

Identity:

- **Estimated Packed Tissue Volume:** Estimated packed tissue volume is limited to not more than 10 cc. This limit was instituted during clinical development as a precaution against pressure increase in the portal vein and the associated risk of thrombosis.
- **Morphology:** The presence of islets by dithizone stain (dithizone stains islets red/orange) and microscopic evaluation confirms the identity of islet product. Dithizone (diphenylthiocarbazone) is a sulfur-containing organic dye that forms colored complexes with metals such as lead and mercury and is a well-known zinc chelating agent. It is used to selectively stain beta cells within the islets because of their elevated zinc content (insulin is stored in zinc complexes in human beta-cells). Identity is confirmed by visualizing the dithizone-stained islet sample under a light microscope.

Potency:

Potency criteria for drug product lot release ensure that each released drug product (donislecel) contains the minimum number of viable, insulin producing islets required for clinical administration.

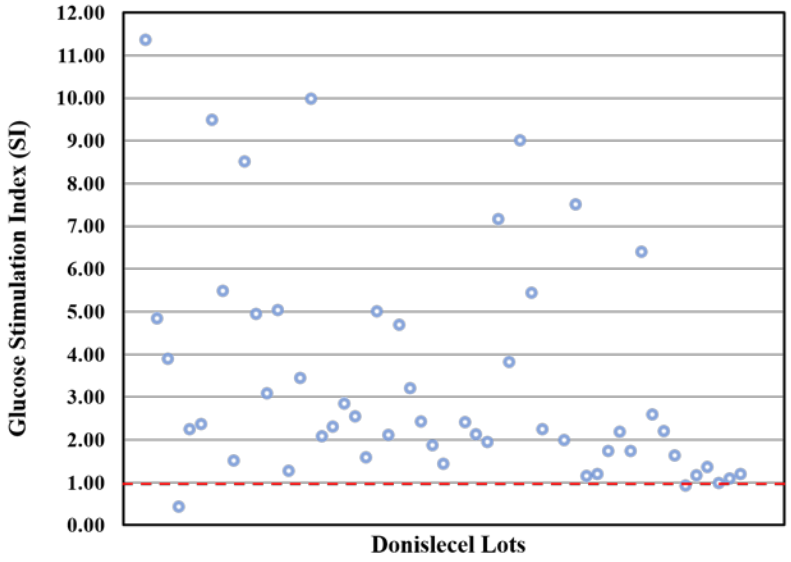
- **Glucose Stimulation Index (GSI):** Measures the amount of insulin released from islets upon glucose stimulation, mimicking islet function in vivo. An insulin enzyme-linked immunosorbent assay (ELISA) is used to quantify the amount of insulin released and results are reported as a stimulation index, which is calculated as the ratio of the insulin released following high glucose stimulation (28 mM) to the insulin released following low glucose stimulation (2.8 mM). The Quality Control sampling for GSI is performed prior to culture (drug substance) from the purest islet fraction (Top fraction, 100 – 70% purity). The top fraction makes up the vast majority of the total islets present. This sampling point has been used for the entirety of the islet program. The stimulation index result is available prior to product release. The release criterion for the final product is a Stimulation Index result of 1 or greater. Stimulation Index results are presented in Figure 5. Because of the limited shelf life of the drug product, and the length of the assay that would exceed the shelf life, the GSI cannot be performed on the drug product.
- **Islet Yield:** The islet equivalent (IE) yield for the drug product (donislecel) is determined by the total number of islets present for a given batch. The IE yield is determined by dithizone staining of the islet sample (dithizone stains islets red/orange) and counting by microscopic evaluation. The minimum dose of donislecel is 5,000 IE/kg for initial transplant (1st dose) and 4,000 IE/kg for subsequent transplants in the same recipient (2nd and 3rd dose)., is based upon standards established by the Edmonton Protocol [40]. Total IE yield results for donislecel are presented in Figure 6. The correlation between islet dose and achievement of the composite primary endpoint of HbA1c ≤6.5% are described in Section 4.1.10.

- **Viability:** Islet viability testing using SYTO 13 Green and Ethidium bromide. SYTO 13 Green is a cell permeable dye that fluoresces brightly green when bound to nucleic acids and is used to visualize viable cells. A counterstain with ethidium bromide, which is impermeable to cell membranes and acts as an exclusion dye, allows live cells to be distinguished from dead or dying cells. A minimum viability of 70% was established. Viability results for donislecel are presented in Figure 7.

Purity:

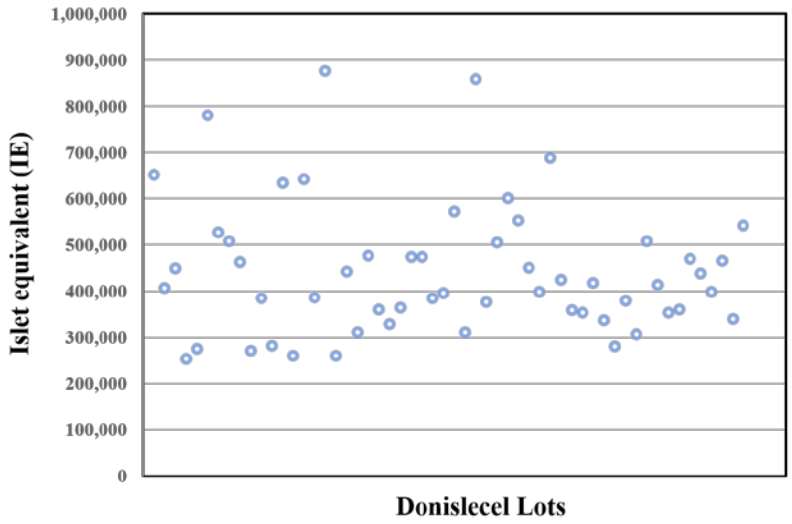
- **Islet purity:** The ≥ 30% acceptable islet purity is determined based on the data derived from product development throughout IND studies and industry standard. Islet purity results for donislecel are presented in Figure 8.
- **Endotoxin:** The endotoxin limit for the drug product is ≤5 endotoxin units (EU)/kg of patient weight.

Figure 5. Glucose Stimulation Index for Drug Substance Lots for Studies UIH-001 and UIH-002



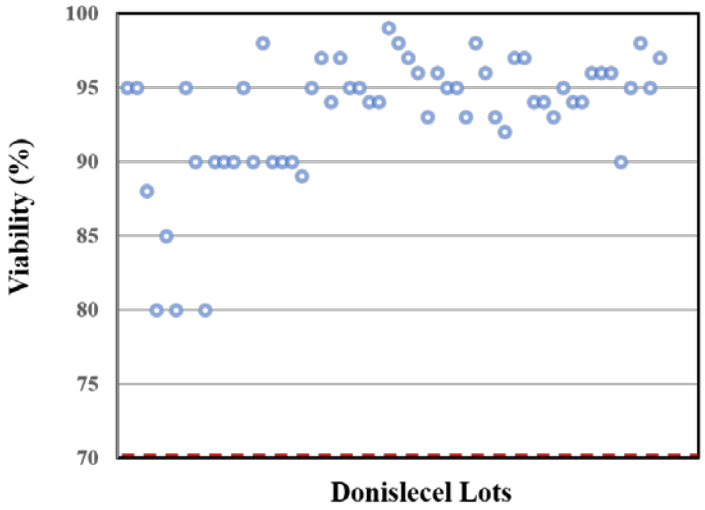
Note: The dotted red line indicates the minimum acceptance value (≥1). Results are for 53/56 lots presented.

Figure 6. Total Yield (Islet Equivalents) for Donislecel Lots for Studies UIH-001 and UIH-002



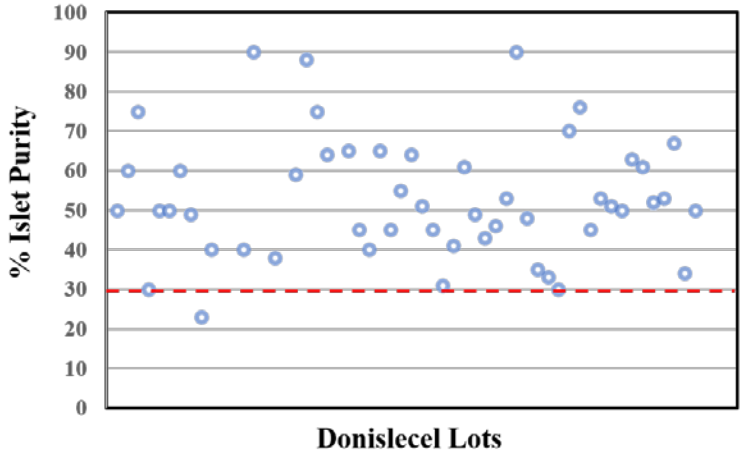
Note: Results are for 56/56 lots presented.

Figure 7. Viability Results for Donislecel Lots for Studies UIH-001 and UIH-002



Note: The dotted red line indicates the minimum acceptance value (≥70%). Results are for 56/56 lots presented.

Figure 8. Islet Purity Results for Donislecel Lots for Studies UIH-001 and UIH-002



Note: The dotted red line indicates the minimum acceptance value (≥30%). Results are for 51/56 lots presented.

In conclusion, donislecel has a well-established manufacturing process, beginning in 2005, which results in a product that consistently meets product quality attributes. The mechanism of action of donislecel is well defined and has been supported through in vitro data and clinical data. The donislecel manufacturing process has been developed to produce a safe, pure, and potent product. From control of the donor organ and incoming raw materials, to the manufacturing environment, to product testing and release of final product, all provide assurance that donislecel is manufactured consistently and safely. In the donislecel clinical trials, no adverse events were observed that could have been related to the quality of the islet preparation.

2.5.4. Dosage and Administration

2.5.4.1. Donislecel

Donislecel dose is defined as the number of islets, normalized to the size of an average islet (150 µm diameter) and expressed as IE, per kilogram of the recipient's body weight.

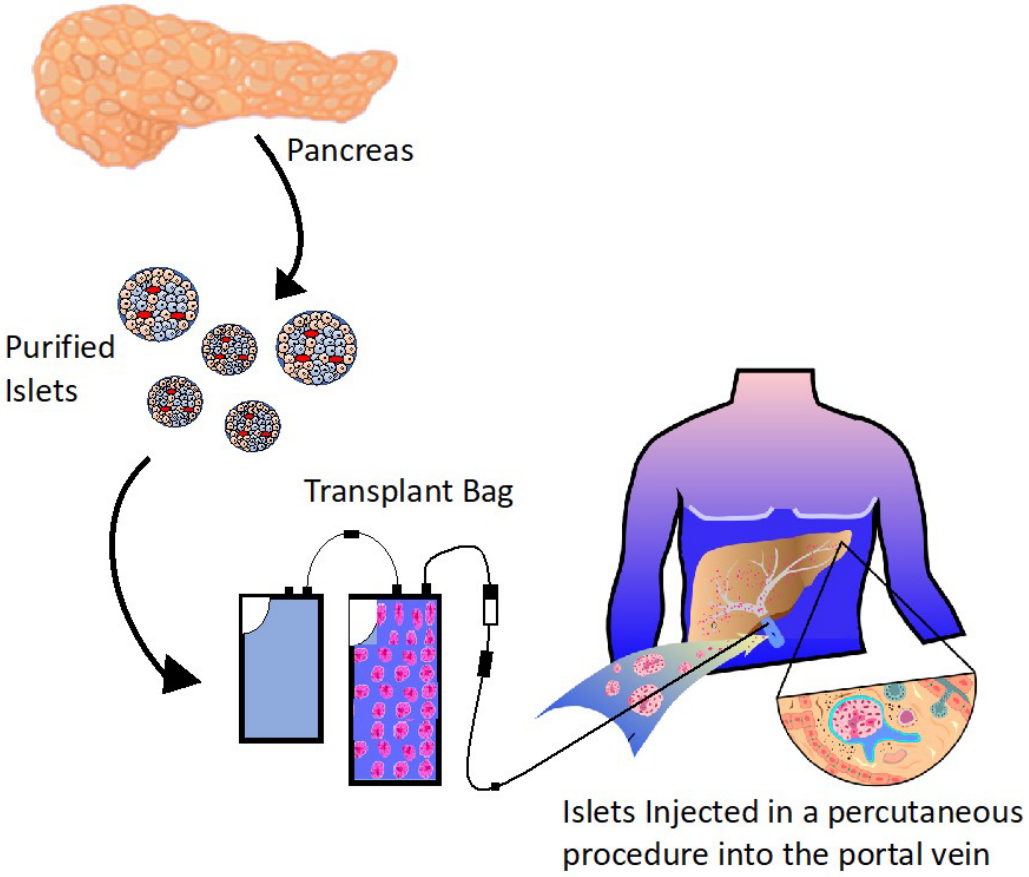
The recommended minimum dose is 5,000 IE/kg for initial transplant and 4,000 IE/kg for subsequent transplants in the same recipient, with a targeted minimum total dose of 10,000 IE/kg across all transplants. This dose level is recognized as the minimum amount required for successful engraftment and confirmed C-peptide expression and is supported by results from donislecel clinical studies (Section 4.1.10; [52]) and results from other transplant centers [15-19]. No maximum dose has been defined, but a practical limit is achieved by a 10-cc restriction on packed cell volume, which was chosen to reduce the risk of portal venous hypertension and thrombosis.

Patients in the donislecel Phase 1/2 and Phase 3 studies (UIH-001 and UIH-002, respectively) received a median islet dose of 6,570 IE/kg (range 4,186 IE/kg to 13,633 IE/kg), for a median total islet number of 399,178 IE (range 253,924 IE to 858,856 IE) per transplant. Cumulatively, patients received a median total islet dose of 724,184 IE (range 260,902 to 1,831,236) across all transplants.

While a single islet transplant almost always leads to improvements in clinically meaningful outcomes like HbA1c level, incidence of SHEs, and need for exogenous insulin, more than 1 islet transplant may be required to achieve the target dose and an adequate clinical response. Based upon an analysis by CITR as part of their 10th Annual Report [20], the total number of islets transplanted, whether in a single infusion or over 2-3 infusions, consistently yielded improved outcomes across a variety of important efficacy parameters including insulin independence, C-peptide, HbA1c, fasting blood glucose, and absence of SHEs. In particular, infusing ≥325,000 IE (across 1 or more infusions) was a common favorable factor across all efficacy outcomes; infusing ≥500,000 IE was especially favorable for both insulin independence post-last infusion (p=0.0009) and prevalence of C-peptide ≥0.3 ng/mL post-last infusion (p=0.0109). Results from donislecel clinical trials support these conclusions about the association of islet dose and efficacy outcomes (Section 4.1.10), while no association was found between islet dose and safety outcomes (Section 5.2.6).

Donislecel is infused into the hepatic portal vein (Figure 9), which may be accomplished through percutaneous or transvenous transhepatic access, or if these are not feasible, then via laparoscopic access. Sheath introducers and/or catheters in sheath introducers are used to infuse the pancreatic islets into the portal vein. The specific use of sheath introducers and/or catheters in sheath introducers as the delivery vehicle of choice for islet transplantation is also defined in the American Medical Association (AMA) Current Procedural Terminology (CPT) codes, also known as service codes (a universal system that identifies medical procedures). The CPT code for the Description of Procedure (0X63T) for pancreatic islet cell transplantation states "*pass guidewire into main portal vein, upsize percutaneous access to accept a 6 French introducer. Advance a 6 French arrow sheath into main portal vein and perform portal venogram. Infuse islet preparation following the manufacturer's instruction under intermittent portal vein pressure monitoring*".

Figure 9. Islet Transplantation Schematic



Following transplant, the patient is monitored for graft function and safety. Subsequent islet transplants are performed at the discretion of the transplant physician or other qualified medical professional. During donislecel clinical trials, patients were eligible for subsequent islet infusions if after a period of at least 30 days they had not reached insulin independence, defined as absence of exogenous insulin use while achieving HbA1c ≤6.5% at the time of evaluation, or if after at least 30 days of insulin independence they presented with declining islet function requiring the reintroduction of exogenous insulin.

While patients enrolled in donislecel clinical trials received no more than 3 transplants, no maximum number of transplants has been defined; rather, the maximum number will depend upon a given patient's response to treatment, whether the minimum number of islets to be transplanted has been achieved, the presence/absence of ongoing islet graft function, and the professional judgment of the physician(s).

There is also no defined dosing interval for donislecel. Instead, follow-up infusions are scheduled as needed based upon patient monitoring and physician discretion.

2.5.4.2. Premedication and Concomitant Medications

Premedication (induction immunosuppression) should be provided 30-360 minutes prior to donislecel infusion and should include the following, at the discretion of the physician:

- Non-depleting monoclonal anti-IL-2 receptor antibody (e.g., basiliximab 20 mg

intravenously within 120 minutes prior to islet transplant)
    - Note: In sensitized patients, a polyclonal T-cell-depleting antibody should be used instead (e.g., anti-human thymocyte immunoglobulin). If a T-cell-depleting antibody is used, administration of acetaminophen, antihistamines, and steroids should be considered.
- Calcineurin inhibitor (e.g., tacrolimus 1 mg by mouth immediately pre-transplant)
- mTOR inhibitor (e.g., sirolimus 0.2 mg/kg immediately pre-transplant)
- TNFα inhibitor (e.g., etanercept 50 mg intravenously before islet transplantation).
- GLP-1 inhibitor (e.g., exenatide 5 mcg subcutaneously within 60 minutes before transplantation)
- Periprocedural antibiotic prophylaxis is recommended.

Anti-infective medications should be provided immediately following infusion of donislecel and continued for an appropriate duration based upon the approved labeling of these products. For example, sulfamethoxazole (400 mg) and trimethoprim (80 mg), 2 tablets by mouth per week for a minimum period of 6 months for prevention of pneumocystis carinii pneumonia and valganciclovir (450 mg my mouth daily) for 3 months post-transplant for prevention of cytomegalovirus (CMV) infection. CMV monitoring is recommended.

A non-depleting monoclonal anti-IL-2 receptor antibody should be provided at the same dose as for premedication (e.g., basiliximab 20 mg intravenously) at week 2 after transplant for a total of 2 doses, except in sensitized patients, who should instead be administered a polyclonal, T-cell-depleting antibody.

A TNFα receptor agonist should be administered on post-transplant days 3, 7, and 10 (e.g., etanercept 25 mg subcutaneously).

A GLP-1 inhibitor should be continued for 6 months (or longer, at the physician's discretion), starting at lower doses as recommended by the approved product labeling and increased over time to the patient's maximum tolerated dose. For example, exenatide may be given at 5 mcg subcutaneously twice daily for 1 week after transplant, increasing to higher doses at the physician's discretion.

The maintenance immunosuppression regimen should be steroid-free and typically should include a combination of a calcineurin inhibitor and an mTOR inhibitor or appropriate alternatives, at the discretion of the physician. Maintenance immunosuppression must be continued permanently to prevent islet graft rejection. Trough levels of maintenance immunosuppressant drugs should be monitored at the discretion of the physician and adjustments in dose should be made to maintain appropriate levels in the blood.

2.6. Key Aspects of the Donislecel Clinical Program

2.6.1. Efficacy Parameters

Efficacy parameters collected during the donislecel clinical program are defined in Table 9.

Table 9. Key Efficacy Parameters and Definitions

Blood glucose levels	Blood glucose levels provide the most direct measurement of islet function and of the pharmacodynamic effects of transplanted islets. Blood glucose levels can vary throughout the day and especially in response to food intake. When blood glucose levels rise, islets release insulin in response, which reduces blood glucose levels. Fasting (basal) blood glucose levels <100 mg/dL are normal, 100 – 125 mg/dL are pre-diabetic, and ≥126 mg/dL are indicative of diabetes. Following food intake, blood glucose levels rise. In patients without diabetes, stimulated blood glucose levels should return to <140 mg/dL within 2 hours (due to the action of insulin). Levels that remain between 140 – 199 mg/dL after 2 hours indicate pre-diabetes and ≥200 mg/dL indicate diabetes.
C-peptide levels	C-peptide comprises part of the proinsulin molecule along with the A- and B-chain of insulin. When proinsulin is cleaved, C-peptide is released, along with a mature insulin molecule (A-chain and B-chain joined by disulfide bonds). C-peptide exists in a 1 to 1 ratio with insulin. Thus, measuring C-peptide levels in the blood can be used to accurately assess insulin secretion. C-peptide levels will increase following food intake, as islets within the pancreas (or islet graft) secrete insulin in response to increased blood glucose levels. Basal C-peptide levels <0.3 ng/mL indicate a lack of islet function.
Graft failure	Graft failure is defined as having C-peptide levels <0.3 ng/mL during at least 2 consecutive follow-up visits.
Graft failure, Primary	Primary graft failure occurs when a patient never achieves measurable (i.e., ≥0.1 ng/mL) basal C-peptide levels at any time point post-transplant.
HbA1c	HbA1c levels in the blood correlate with average blood glucose levels over the prior 3 months. This allows for a snapshot of glycemic control over time that is less variable than acute blood glucose measurements. HbA1c <5.7% is normal, from 5.7 – 6.4% indicates pre-diabetes, and ≥6.5% indicates diabetes.
HYPO score	The HYPO score is a composite hypoglycemia score based on the frequency, severity, and degree of hypoglycemia unawareness. A HYPO score ≥90th percentile (1047) of values derived from an unselected group of T1D patients is evidence for serious problems with hypoglycemia.
Insulin Independence	Two definitions of insulin independence were assessed in this program. The combined efficacy assessment utilized the *conventional* definition of insulin independence which is a patient not requiring exogenous insulin at the time of assessment. The *strict* definition is a patient not requiring exogenous insulin for a cumulative period of longer than 2 weeks during the period beginning 2 weeks after the patient's last transplant and ending at the time of assessment. The strict definition was utilized in the Phase 1/2 Study (Study UIH-001); however, it is no longer favored in the field, with deference given to the conventional definition.
MMT or MMTT	The Mixed Meal Test (MMT; also known as the Mixed Meal Tolerance Test; MMTT) involves taking fasting blood samples, providing a "mixed meal" (typically Boost or Ensure; 6 mL/kg up to 360 mL maximum, consumed within 5 minutes) that contains protein, carbohydrates, and fat, and then taking additional blood samples at 90 minutes (stimulated). Blood samples are assayed for glucose and C-peptide levels. The goal of the test is to determine how much insulin the islets are producing in response to food.
SHE	A Severe Hypoglycemic Event (or episode; SHE) is an event with symptoms compatible with hypoglycemia in which the subject requires the assistance of another person and which is associated with either a blood glucose level <50 mg/dL (2.8 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

2.6.1.1. Study Design

According to the 2009 FDA guidance "Considerations for Allogeneic Pancreatic Islet Cell Products", a single-arm, open-label trial is sufficient to provide substantial evidence of efficacy and safety of allogeneic islet transplantation. This conclusion is based on extensive published data demonstrating that allogeneic islet transplantation in metabolically unstable T1D patients can result in complete insulin independence (or alternatively good metabolic control with some exogenous insulin use) and without occurrences of severe hypoglycemia—outcomes that do not appear in the natural course of the disease.

2.6.1.2. Composite Efficacy Endpoint

The 2009 FDA islet guidance [13] suggests a clinically meaningful primary efficacy endpoint for islet transplantation studies: HbA1c ≤6.5% (i.e., normalization of glycated hemoglobin) and absence of SHEs at 1 year following the first and/or last transplant. Patients achieving this endpoint may require some exogenous insulin or may be completely independent of insulin, but the FDA and the medical community have recognized that this outcome (HbA1c ≤6.5% and absence of severe hypoglycemia) is clinically beneficial.

Consistent with FDA's guidance, the composite efficacy endpoint used in the donislecel BLA is HbA1c ≤6.5% and absence of SHEs at 1 year after a patient's last transplant.

2.6.1.3. Additional Efficacy Assessments

In addition to the composite endpoint, insulin independence (i.e., freedom from exogenous insulin use) and other assessments of glycemic control have been included to provide a more complete understanding of the clinically meaningful benefits of islet transplantation.

Insulin independence is a key benefit of islet transplantation. It enhances quality of life because a patient no longer requires regular insulin injections, and it eliminates the risk of SHEs resulting from or exacerbated by intensive insulin therapy. However, as more experience has been gained in the islet transplantation field, researchers and clinicians have realized that many of the primary benefits of islet transplantation (e.g., improved glycemic control and resolution of severe hypoglycemic events) can still be achieved without complete insulin independence [16]. This means that even patients who cannot completely ween off insulin following islet transplantation can still experience substantial and clinically meaningful improvements in glycemic control.

In addition to insulin independence, other key secondary efficacy parameters collected as part of the donislecel clinical program include blood glucose levels, C-peptide levels, HYPO score, and mixed meal test (MMT) results. These parameters are defined alongside other efficacy parameters in Table 9.

2.6.2. Study Population Size

According to a 2012 publication from FDA by Tiwari et al. [14], given fixed values of power (80%) and alpha level (5%), the adequacy of the population size for determining efficacy in an islet transplantation trial is driven by the success rates of the composite endpoint (free of SHEs and maintaining HbA1c levels ≤6.5%) in the hypothetical control and treatment arms

(Table 10). "Hypothetical control" refers to historical data derived from patients undergoing standard diabetes care; thus, the hypothetical control rate would be the proportion of brittle T1D patients on insulin therapy who would spontaneously transition from a state of chronic, severe hypoglycemia with unawareness to one of easily managed glycemic control, as defined by HbA1c ≤6.5% and absence of SHEs.

The observed treatment effect of islet transplantation is large and thus the required sample size for a single-arm, Phase 3 study will be relatively small. In addition, the stipulation of a 20% of even 10% success rate in hypothetical controls is likely to be overly conservative given the natural history of T1D in patients who have longstanding disease and are chronically metabolically unstable. Based upon a review of historical published and registry data, the control rate would likely be <1%. These lower success rates in the control arm will result in smaller required sample size for determining efficacy.

Given the observed success rate in the pivotal Phase 3 UIH-002 study (52%) and that from the combined population from Studies UIH-001 and UIH-002 (i.e., Pooled Population; 63%), even assuming a hypothetical control rate of 20% would require as few as 16 patients to adequately support efficacy. Based upon this, Study UIH-002 (n=21) has an adequate number of patients by itself to demonstrate the efficacy of donislecel for treating brittle T1D; the addition of Study UIH-001 patients to form the combined Pooled Population (n=30) population provides further robustness.

Table 10. Sample Size Requirements for Islet Transplantation Clinical Trials

Hypothetical Control Rate (π_0)	Expected Rate in Islet Transplant Arm (π_1)			
	0.50	**0.60**	**0.70**	**0.80**
0.05	4	4	3	3
0.10	7	6	4	3
0.15	10	8	4	4
0.20	16	10	6	6
0.25	27	15	8	6

Source: [14]

2.6.3. Dose Rationale

Because donislecel is a cellular product derived from a donor organ, the number of islets transplanted during a single infusion (i.e., the per-transplant dose) will vary from patient to patient. Despite this variability, targets for minimum islet number have been established to promote adequate graft function and limits on the total volume of cells that can be infused per transplant have been established to ensure patient safety.

With respect to minimum islet dose, based upon the original report about the Edmonton protocol, at least 9,000 IE/kg recipient body weight were needed to achieve insulin independence [15]. Therefore, a patient with a body weight of 70 kg would require at least 630,000 islet equivalents to achieve insulin independence, or approximately half of the islet content of a normal adult pancreas.

Other published findings since the original Edmonton study also demonstrate that achievement of clinically relevant endpoints following islet transplantation is dependent on the total islet dose [16-19, 52]. Across these studies, a total islet mass of ≥8,000 to 9,000 IE/kg (over 1 to 3 transfusions) was considered necessary for sustained improvement in clinically important endpoints.

As part of the CITR 10th Annual Report [20], an analysis was performed on variables that could affect efficacy outcomes. Of the islet characteristics assessed, only the total number of islets transplanted, whether in a single infusion or over 2-3 infusions, consistently yielded improved outcomes across a variety of important parameters including C-peptide, HbA1c, and fasting blood glucose. In particular, infusing ≥325,000 IE (across one or more infusions) was a common favorable factor across all efficacy outcomes; infusing ≥500,000 IE was especially favorable for prevalence of C-peptide ≥0.3 ng/mL post-last infusion (p=0.0109).

With respect to maximum islet dose, there are safety considerations that limit the number of islets per transplant – specifically, larger packed tissue volumes (e.g., >10 mL) may increase the risk of transient increases in portal venous pressure during the transplant procedure and/or may lead to portal vein thrombosis [53] and are therefore not recommended. A limit of 10 mL packed tissue volume per transplant was put in place for donislecel clinical studies to help promote patient safety.

2.6.4. Historical Controls

According to the 2009 FDA guidance "Considerations for Allogeneic Pancreatic Islet Cell Products," historical controls are appropriate to use with a single-arm, open-label trial evaluating allogeneic islet cell products [13].

There are several reasons why the use of historical data is more appropriate for islet transplantation trials versus a traditional randomized control trial design, including:

1. Difficulty in recruitment stemming from an unwillingness of patients to receive standard diabetes care with multiple protocol-mandated visits and tests for one or more years when such standard care has failed to manage their T1D prior to the trial.
2. An inability to blind patients and investigators to treatment assignment due to the nature of the treatment (i.e., transplantation procedure, immunosuppressants, and other concomitant medications), thus limiting the value of comparative information.
3. The likelihood of a high dropout rate among the control group
4. The inability to power a study to detect treatment-related effects (e.g., microvascular complications) given the limited availability of islets for transplantation and high per patient study cost.

For the donislecel BLA, the FDA indicated via correspondence with CellTrans that "a comparative efficacy analysis of your product with standard-of-care treatment [is necessary]. For a single-arm trial, the outcomes should be compared to those of a historical control."

To determine appropriate historical comparators, CellTrans reviewed available data from public databases and other publicly available sources. Based upon this review, the following key comparators were identified (in addition to relevant published literature reports of other studies and sources):

- Standard-of-Care Insulin Therapy

  - Wisconsin Diabetes Registry Study (WDRS; Section 9.3.1)
  - Diabetes Control and Complications Trial [controlled; 1982-1993] / Epidemiology of Diabetes Interventions and Complications [observational; 1994-present] (DCCT/EDIC) (Section 9.3.2)
- Islet Transplantation
  - CITR [10th Annual Report covers the years 1999-2015] (Section 9.3.3)
- Approved product labeling for common concomitant medications used in islet transplantation protocols

3. DESCRIPTION OF DONISLECEL CLINICAL STUDIES COMPRISING THE POOLED POPULATION

3.1. Study UIH-001 (Phase 1/2)

3.1.1. Study Design Overview

Study UIH-001 (IND BB-11807) was a Phase 1/2, nonrandomized, single-center study, in which 1 to 3 allogeneic pancreatic islet transplants were administered to patients with brittle T1D. The primary study objective was to demonstrate the safety of allogeneic islet transplantation in brittle T1D patients.

The study was performed by UI Health with the purpose of reproducing the Edmonton protocol to demonstrate that pancreatic islets manufactured at UI Health are safe and of sufficient quality to provide reproducible graft function, as well as to determine outcomes for patients treated with an alternative concomitant medication regimen (i.e., the UIC protocol). This study was intended to provide a basis for future clinical trials using donislecel.

A total of 10 patients were planned for the study.

Primary follow-up was through one year after last transplant. Long-term follow-up for both safety and efficacy was up to 10 years after last transplant.

The primary efficacy endpoint was independence from insulin injections with adequate control of blood glucose levels. Secondary efficacy assessments included HbA1c levels, oral glucose tolerance test (OGTT), MMT, glucagon stimulation test, and intravenous glucose tolerance test (IVGTT).

3.1.2. Study Treatment

Patients were enrolled into 1 of 2 cohorts to receive transplanted islets (1 to 3 total islet infusions per patient) plus a concomitant medication regimen reflecting 1) the regimen provided in the Edmonton Protocol [15], which involved immunosuppression with daclizumab, sirolimus, and tacrolimus, or 2) the UIC Protocol, which includes the Edmonton regimen supplemented with etanercept (a soluble TNFα inhibitor) and exenatide (a GLP-1 receptor agonist; incretin memetic).

Corticosteroids were omitted from the post-transplant immunosuppressive regimen for all patients. Other medications were administered as needed, including prophylactic anti-infective drugs, local anesthetics, contrast media, and heparin.

Patients who were sensitized to human leukocytes, as determined by the presence of preformed antibodies against human leukocyte antigens, could have received a more intense induction protocol with a polyclonal anti-T-cell antibody preparation (anti-thymocyte globulin; Thymoglobulin®) instead of basiliximab/daclizumab for the initial transplant. Also, mycophenolate mofetil (CellCept®) could have been used for subjects who did not tolerate the adverse effects of sirolimus or tacrolimus.

3.1.3. Inclusion Criteria

Enrolled patients must have had type 1 diabetes mellitus for more than 5 years, complicated by at least one of the following situations that persisted despite intensive insulin management efforts:

1. Reduced awareness of hypoglycemia, as defined by the absence of adequate autonomic symptoms at plasma glucose levels of < 54 mg/dL (3 mmol/L); as reported by the patient
2. Metabolic lability/instability, characterized by two or more episodes of documented severe hypoglycemia, or two or more hospital visits for diabetic ketoacidosis over the last year
3. Despite efforts at optimal glucose control, progressive secondary complications of diabetes as defined by:
    a. Retinopathy – a minimum of a three step progression using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system [54], or an equivalent progression as certified by an ophthalmologist familiar with diabetic retinopathy, or
    b. Nephropathy – a confirmed rise of 50 µg/min (72 mg/24 h) of microalbuminuria or greater over at least three months (beginning anytime within the past two years) despite the use of an ACE inhibitor, or
    c. Neuropathy – persistent or progressing autonomic neuropathy (gastroparesis, postural hypotension, neuropathic bowel or bladder) or persistent or progressing severe peripheral painful neuropathy not responding to usual management (e.g., tricyclics, gabapentin, or carbamazepine)

3.2. Study UIH-002 (Phase 3)

3.2.1. Study Design Overview

Study UIH-002 (IND BB-11807) was a Phase 3, nonrandomized, open-label, single-center study in which 1 to 3 allogeneic pancreatic islet transplants were administered to patients with brittle T1D. The primary study objective was to demonstrate the safety and efficacy of allogeneic islet transplantation in patients with T1D using the UIC Protocol.

A total of 50 patients were planned for the study based on initial discussions with the FDA, but this number was subsequently reduced based upon new guidance from the FDA.

Primary follow-up was through one year after last transplant. Long-term follow-up for both safety and efficacy was up to 10 years after last transplant.

The primary efficacy endpoint was the proportion of patients who, at 1 year after the last islet cell infusion, had HbA1c ≤6.5% and had been free of SHEs from Day 28 to Day 365 post-transplant. This endpoint is the same as that recommended by the FDA in the 2008 guidance [13] on allogeneic pancreatic islet transplantation and subsequently presented by FDA-affiliated authors in a publication on efficacy outcomes and trial design for islet trials in Tiwari et al. (2012) [14]. Secondary endpoints included insulin independence, absence of exogenous insulin, fasting capillary and plasma glucose levels, postprandial capillary glucose levels, and C-peptide levels.

3.2.2. Study Treatment

Donislecel and concomitant study medications, including immunosuppressants, were administered according to the UIC protocol (as described in Section 3.1.2).

3.2.3. Inclusion Criteria

To qualify for this study, patients must have had T1D for more than 5 years, complicated by the following situations that persisted despite intensive insulin management efforts:

1. At least 1 episode of severe hypoglycemia in the past 3 years, defined as an event with symptoms compatible with hypoglycemia in which the patient required the assistance of another person, and that was associated with either a blood glucose level <50 mg/dL (2.8 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.
2. Reduced awareness of hypoglycemia, as defined by the absence of adequate autonomic symptoms at capillary glucose levels of <54 mg/dL (3 mmol/L), as reported by the patient.

4. EFFICACY OF DONISLECEL IN BRITTLE TYPE 1 DIABETES

4.1. Pooled Population – Studies UIH-001 and UIH-002

4.1.1. Disposition

Donislecel administration was well tolerated in Studies UIH-001 and UIH-002, with approximately 93% of patients who received at least 1 islet transplant in the Pooled Population completing the primary endpoint assessment at 1 year after the last transplant (Table 11). There were no discontinuations due to a TEAE.

Table 11. Patient Disposition and Reason for Early Discontinuation for Studies UIH-001, UIH-002, and the Pooled Population

Outcome	UIH-001 N=10 N (%)	UIH-002 N=21 N (%)	Pooled Population [a] N=30 N (%)
Completed	10 (100)	19 (90.5)	28 (93.3)
Early Discontinuation	0	2 (9.5)	2 (6.7)
Death	0	0	0
TEAE	0	0	0
Consent Withdrawn	0	2 (9.5)	2 (6.7)

Note: 1 patient in Study UIH-002 was discontinued prior to receiving an islet transplant during the study and is not included in this table.

TEAE, treatment-emergent adverse event

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

4.1.2. Demographics

Patient demographics are summarized in Table 12. Most patients in Studies UIH-001 and UIH-002 were female (80%), White (100%), and non-Hispanic (97%). The median age was 46.5 years. Most patients had a body mass index (BMI) in the normal range.

Table 12. Demographics for Patients in Studies UIH-001, UIH-002, and the Pooled Population

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population [a] N=30
Age (years)			
Mean (SD)	46.4 (10.2)	47.8 (12.6)	46.8 (11.6)
Median (Min, Max)	45.0 (35, 63)	47.0 (21, 67)	46.5 (21, 67)
Sex n (%)			
Female	9 (90)	15 (71.4)	24 (80)
Male	1 (10)	6 (28.6)	6 (20)
Race n (%)			
Caucasian	10 (100)	21 (100) [b]	30 (100) [b]
Native American	0	1 (4.8) [b]	1 (3.3) [b]
Black	0	0	0
Oriental	0	0	0
Other	0	0	0
Ethnicity n (%)			
Hispanic	0	1 (4.8)	1 (3.3)
Non-Hispanic	10 (100)	20 (95.2)	29 (97)
Weight (kg)			
Mean (SD)	62.4 (4.5)	64.5 (8.8)	63.8 (7.8)
Median (Min, Max)	61.8 (55.6, 71.4)	63.8 (52.5, 83.4)	62.4 (52.5, 83.4)
Height (cm)			
Mean (SD)	166.6 (5.6)	166.5 (7.6) [c]	166.6 (6.9) [d]
Median (Min, Max)	166.0 (155.2, 175.4)	165.0 (150.9, 181.9) [c]	166.0 (150.9, 181.9) [d]

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population [a] N=30
BMI (kg/m^2)			
Mean (SD)	22.5 (0.95)	23.4 (2.03) [c]	23.1 (1.8) [d]
Median (Min, Max)	22.5 (20.9, 24.1)	23.5 (20.2, 27.3) [c]	23.0 (20.2, 27.3) [d]

BMI, body mass index; SD, standard deviation

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b 1 patient in UIH-002 identified as both Caucasian and Native American.

c N=19

d N=29

4.1.3. Baseline Diabetes Care and Control

Baseline diabetes control characteristics are provided in Table 13 (additional information on these parameters and assessments is provided in Table 9). All patients reported hypoglycemia unawareness at baseline, and all patients were receiving intensive insulin therapy prior to enrollment and transplant, either via self-injection or insulin pump.

Table 13. Baseline Diabetes Control Characteristics for Patients in Studies UIH-001, UIH-002, and the Pooled Population

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population [a] N=30
Insulin Requirement (units/kg/day), n (%)	10 (100)	21 (100)	29 (96.7)
Mean (SD)	0.52 (0.135)	0.47 (0.134)	0.51 (0.142)
Median (Min, Max)	0.55 (0.3, 0.7)	0.50 (0.1, 0.8)	0.53 (0.3, 0.8)
Missing, n (%) [b]	0	0	1 (3.3)
HbA1c (%), n (%)	9 (90.0)	21 (100)	29 (96.7)
Mean (SD)	7.21 (1.205)	7.37 (0.867)	7.35 (0.918)
Median (Min, Max)	6.90 (5.9, 9.5)	7.30 (5.7, 9.0)	7.30 (5.7, 9.5)
Missing, n (%) [b]	1 (10.0)	0 (0.0)	1 (3.3)
Frequency of SHE (episodes/month), n (%) [c]	5 (50.0)	11 (52.4)	16 (55.2)
Mean (SD)	0.16 (0.054)	1.138 (1.477)	0.832 (1.294)
Median (Min, Max)	0.13 (0.1, 0.2)	0.36 (0.05, 4.24)	0.22 (0.05, 4.24)
Missing, n (%) [b]	5 (50.0)	10 (47.6)	14 (46.7)
HYPO Score, n (%) [c]	7 (70.0)	12 (57.1)	18 (60.0)
Mean (SD)	88.18 (67.987)	428.49 (491.671)	319.06 (429.43)
Median (Min, Max)	88.05 (11.1, 211.9)	265.87 (2.4, 1638.0)	109.14 (2.4, 1638.0)
Missing, n (%) [b]	3 (30.0)	9 (42.9)	12 (40.0)
Fasting Plasma Glucose (mg/dL), n (%)	9 (90.0)	20 (95.2)	28 (93.3)
Mean (SD)	143.3 (87.87)	171.8 (61.18)	165.1 (70.50)
Median (Min, Max)	105.0 (69, 348)	172.5 (78, 291)	168.0 (69, 348)
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)
90-min Glucose, post glucose challenge (mg/dL), n (%)	9 (90.0)	20 (95.2)	28 (93.3)
Mean (SD)	312.1(94.18)	368.4 (69.90)	352.6 (81.94)
Median (Min, Max)	305.0 (122, 438)	365.5 (279, 559)	365.0 (122, 559)
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population [a] N=30
Reduced awareness of hypoglycemia, n (%) [d]	10 (100)	21 (100)	30 (100)
Missing, n (%) [b]	0	0	0
MMT: Fasting C-peptide <0.1 ng/mL, n (%) [e]	9 (90.0)	19 (90.5) [f]	27 (90.0) [f]
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)
MMT: 90-min C-peptide, post glucose challenge, <0.1 ng/mL, n (%) [e]	8 (80.0) [f]	19 (90.5) [f]	26 (86.7) [f]
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)

Note: Group n is the number of patients who had data for a given parameter at baseline.

HYPO, hypoglycemia; MMT, mixed meal test; SD, standard deviation; SHE, severe hypoglycemic event.

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b "Missing" indicates data not obtained or patient did not provide adequate information for quantification.

c Baseline values were calculated based on hypoglycemic events self-reported by the patient during the screening/waiting period between enrollment and initial transplant, which varied in length for each patient.

d Reported qualitatively only at enrollment.

e 0.1 ng/mL = lower limit of detection for C-peptide

f 1 patient from UIH-002 had low, but detectable C-peptide (0.1 ng/mL) when fasting, and 1 patient each from UIH-001 and UIH-002 had low, but detectable C-peptide (0.1, 0.27 ng/mL) at 90-minute time point.

4.1.4. Glycated Hemoglobin A1c, Severe Hypoglycemic Events, and Composite Efficacy Endpoints

Most patients (63.3%) in the Pooled Population achieved success on the composite efficacy endpoint of HbA1c ≤6.5% and free of SHEs at 1 year after last transplant (Table 14). Employing a less strict but commonly used standard for glycemic control of HbA1c <7.0% and free of SHEs, the percentage of successful patients increases to 70% (21/30 patients).

Among all patients for whom adequate data are available (and regardless of success or failure on the composite endpoint), 26/28 (93%) showed improvements in HbA1c levels at 1 year after last transplant compared to baseline (Figure 10), and more than half experienced a reduction from baseline of at least 1% (e.g., HbA1c 7.0% to HbA1c 6.0%; Figure 11).

Importantly, even in patients who failed to meet the composite efficacy endpoint, glycemic control was improved: HbA1c levels were reduced from baseline by approximately 16% and the number of SHEs per month was reduced from baseline by approximately 87% at 1 year following last transplant (Table 15).

Long-term efficacy is discussed in Section 4.1.8. With respect to the composite efficacy endpoint, among Pooled Population patients who had reached yearly milestone assessments after their last transplant, most remained successful on the composite endpoint at each assessment, including 8/12 (67%) at 6 years after the last transplant.

Table 14. Composite Efficacy Endpoint at 1 Year after Last Transplant – Studies UIH-001, UIH-002, and Pooled Population

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population N=30 [a]
Success (HbA1c ≤6.5% + Free of SHE); n (%) [b]	9 (90.0)	11 (52.4)	19 (63.3)
95% C.I. [c]	56, 100	30, 74	44, 80
Failure, n (%)	1 (10.0)	10 (47.6) [d]	11 (36.7) [d]
HbA1c >6.5%; n (%)	0	5 (23.8)	5 (16.7)
Any SHE; n (%) [b]	1 (10.0)	6 (28.6)	7 (23.3)

C.I., confidence interval; HbA1c, glycated hemoglobin; SHE, severe hypoglycemic event

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b Any SHE occurring between Day 28 and Day 365 (Day 0 = day of transplant)

c Calculated by the Clopper-Pearson exact method

d Includes patients who discontinued early and patients who were missing HbA1c and/or SHE data at 1 year after last transplant. These patients were imputed as failures on the primary endpoint.

Figure 10. HbA1c% Change from Baseline, by Patient (Studies UIH-001 and UIH-002)

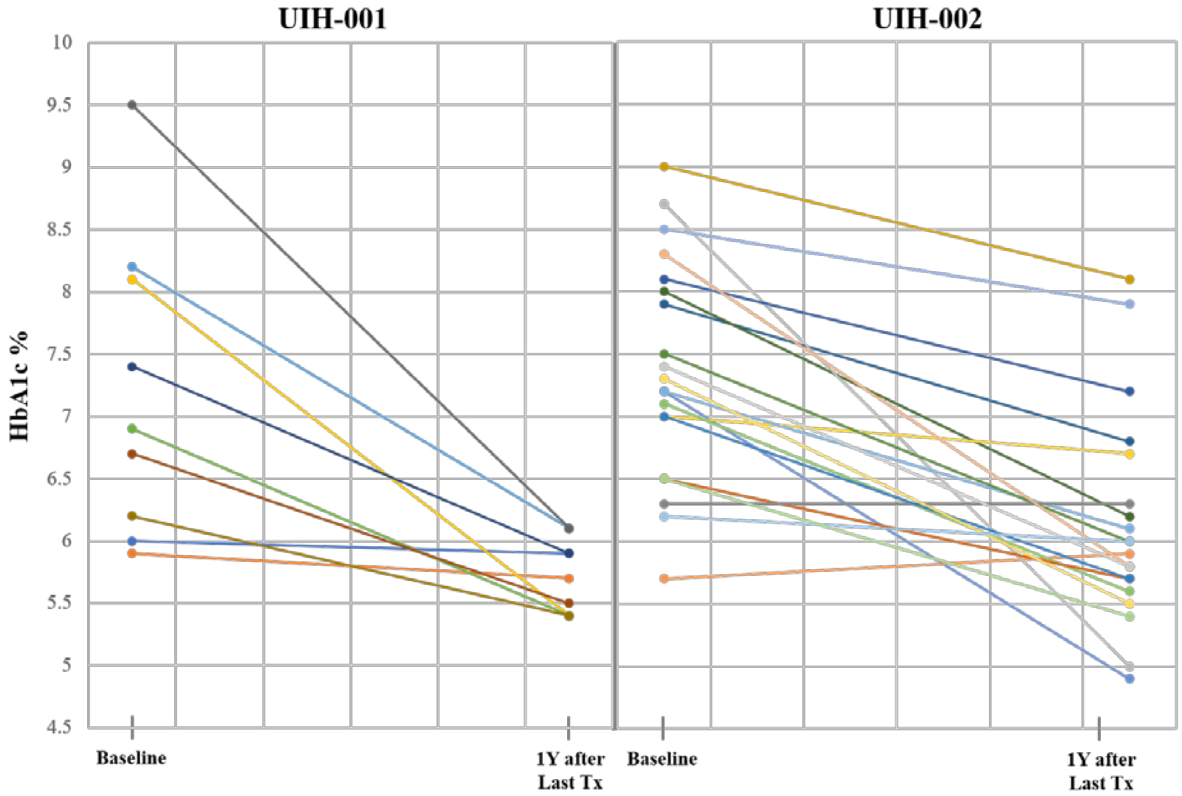
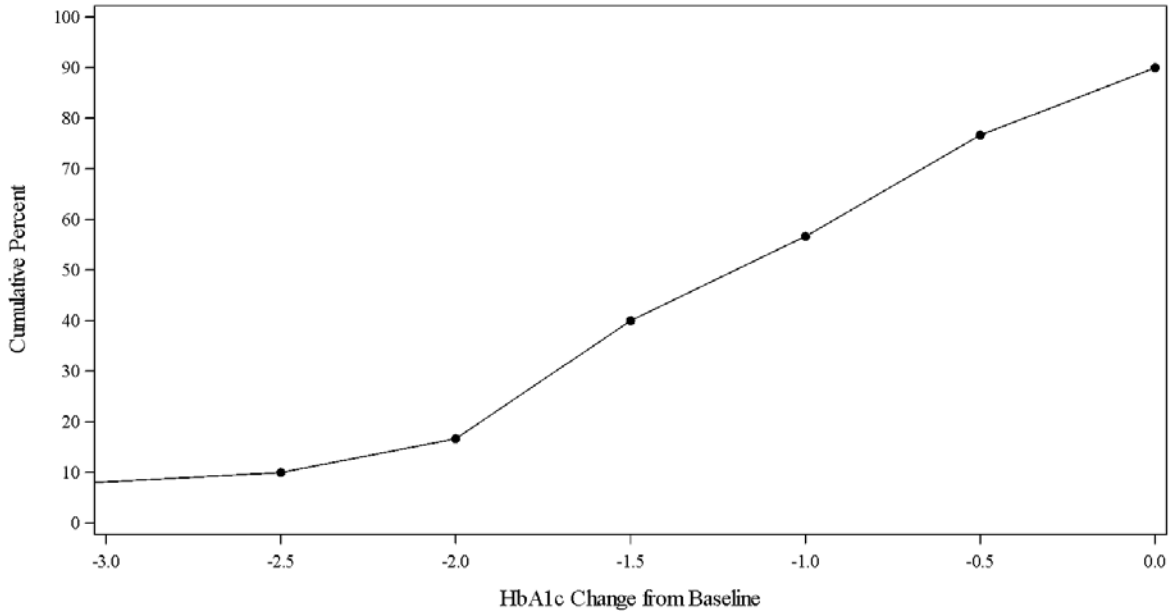


Figure 11. Patients (%) Attaining HbA1c Reductions from Baseline of a Particular Level or Greater at 1 Year after Last Transplant (Pooled Population)



Note: N=28

Table 15. HbA1c Percentage and SHE Frequency at Baseline and 1 Year after Last Transplant (Pooled Population)

		Baseline		1 Year after Last Transplant	
Parameter		**n**	**Mean (SD)**	**n**	**Mean (SD)**
HbA1c (%)		29	7.38 (0.936)	29	6.01 (0.738)
	PE = Success	18	7.14 (0.730)	19	5.74 (0.336)
	PE = Failure	11	7.77 (1.128)	10	6.51 (1.019)
SHE Frequency (#/month) [a]		16	0.99 (1.454)	28	0.11 (0.313)
	PE = Success	12	0.51 (0.838)	19	0.01 (0.039)
	PE = Failure	4	2.43 (2.071)	9	0.31 (0.506)

Note: Missing data were counted as failures. Baseline occurs prior to first transplant.

HbA1c, glycated hemoglobin; PE, primary endpoint (HbA1c ≤6.5% and free of SHEs at 1 year after last transplant); SHE, severe hypoglycemic event

a Baseline values were calculated based on hypoglycemic events self-reported by the patient during the screening/waiting period between enrollment and initial transplant, which varied in length for each patient. Baseline SHE frequency data were not collected and/or retained in all cases.

4.1.5. Insulin Independence

Insulin independence, which is defined as not requiring exogenous insulin, is a key benefit of islet transplantation. It enhances quality of life because a patient no longer requires regular insulin injections, and it eliminates the risk of SHEs resulting from or exacerbated by intensive insulin therapy. However, as more experience has been gained in the islet transplantation field, researchers and clinicians have realized that many of the primary benefits of islet transplantation (e.g., improved glycemic control and resolution of severe

hypoglycemic events) can still be achieved without complete insulin independence [16]. This means that even patients who cannot completely ween off insulin following islet transplantation can still experience substantial and clinically meaningful improvements in glycemic control.

Insulin independence was achieved by approximately 67% of patients in the Pooled Population at 1 year after last donislecel transplant, including 84% of patients who were successful for the composite efficacy endpoint (i.e., HbA1c ≤6.5% and free of SHEs) and 36% of patients who failed the composite efficacy endpoint (Table 16). Importantly, among patients who failed the composite efficacy endpoint, the mean daily insulin requirement was still reduced by approximately 29% (Table 18).

Figure 12 illustrates the duration of insulin use and insulin independence for each subject following initial donislecel transplant and throughout follow up to data cutoff or withdrawal from the study. Most patients experienced extended periods of insulin independence lasting up to several years following donislecel administration.

Long-term efficacy is discussed in Section 4.1.8. With respect to insulin independence, among Pooled Population patients who had reached yearly milestone assessments after their last transplant, most retained insulin independence at each assessment, including 8/12 (67%) at 6 years after the last transplant.

Table 16. Insulin Independence at 1 Year after Last Transplant (Pooled Population)

Outcome	Pooled Population N=30 [a]
Insulin Independence, n/N (%) [b]	20/30 (66.7)
Missing, n (%)	2 (6.7)
Primary Endpoint = Success; n/N (%)	16/19 (84.2)
Missing, n (%)	0
Primary Endpoint = Failure; n/N (%)	4/11 (36.4) [c]
Missing, n (%)	2 (18.2)

Note: Missing data were counted as failures.

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b Insulin independence is defined as a patient's not requiring exogenous insulin at the time of assessment (i.e., at 1 year after last transplant).

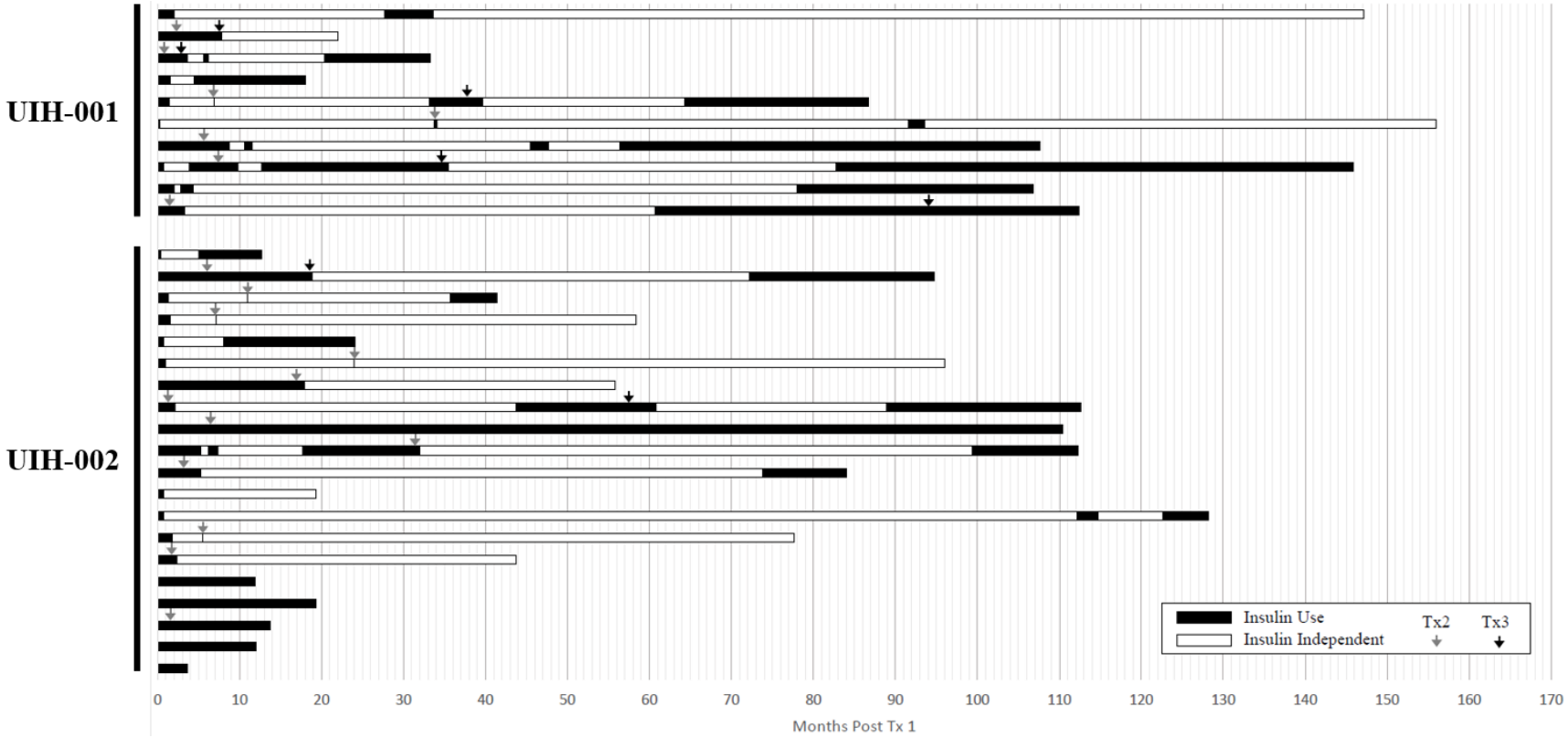
c Patients were weaned off insulin if they were no longer experiencing hyperglycemia. Despite insulin independence at the time of the primary endpoint assessment, some patients failed the primary endpoint (e.g., SHE assessed over a window from Day 28-365 post-transplant; therefore, a patient could experience a SHE early but still be off insulin by the 1-year post-last transplant assessment).

Table 17. Insulin Dose at Baseline and 1 Year after Last Transplant (Pooled Population)

		Baseline		1 Year after Last Transplant	
Parameter		**n**	**Mean (SD)**	**n**	**Mean (SD)**
Insulin Dose (units/kg/day)		30	0.355 (0.1725)	28	0.117 (0.2135)
	PE = Success	19	0.326 (0.1544)	19	0.035 (0.0909)
	PE = Failure	11	0.406 (0.1970)	9	0.290 (0.2928)

Note: Missing data were counted as failures. Baseline occurs prior to first transplant.

Figure 12. Periods of Insulin Use and Insulin Independence following Initial Donislecel Administration, by Patient (Pooled Population)



Note: Each horizontal bar represents a single patient's experience with insulin use following initial donislecel transplant. Black segments represent periods of insulin use. White segments represent periods of insulin independence. Subsequent donislecel transplants are indicated by downward arrows (gray arrows for the second transplant and black arrows for the third). No patient received more than 3 donislecel transplants.

4.1.6. Other Measures of Glycemic Control: HYPO Score, Mixed Meal Test, and Fasting Blood Glucose Levels

Marked improvements in glycemic control parameters were observed in the Pooled Population, not only in patients who achieved the composite efficacy endpoint (i.e., HbA1c ≤6.5% and absence of SHEs at 1 year after last transplant) but also in those who did not meet that endpoint. This includes improvements in HYPO score, which considers the frequency, severity, and degree of hypoglycemia awareness, and the MMT, which is designed to measure islet function by quantifying insulin production (as determined by C-peptide levels) and blood glucose levels following a meal (see Table 9 for more information on these assessments).

Relative to baseline, at 1 year after last transplant, mean HYPO score was approximately 4 times lower, fasting and stimulated glucose were sharply reduced, and fasting and stimulated C-peptide were substantially improved from nearly undetectable levels to normal (non-diabetic) levels (Table 18).Even in patients who failed to meet the primary efficacy endpoint, there were substantial improvements in HYPO score and MMT results at 1 year after the last donislecel transplant compared to baseline measurements. These results add support to the clinical benefit of donislecel even in cases where primary efficacy goals were not met.

Table 18. Secondary Efficacy Endpoints: Insulin Dose, HbA1c Level, Hypoglycemic Episodes, and Mixed Meal Test Results at 1 Year after Last Transplant (Pooled Population)

Parameter		Baseline n	Baseline Mean (SD)	1 Year after Last Transplant n	1 Year after Last Transplant Mean (SD)
HYPO Score		18	319.06 (429.432)	28	77.66 (232.472)
	PE = Success	13	203.60 (238.004)	19	22.44 (50.190)
	PE = Failure	5	619.25 (676.640)	9	194.23 (392.683)
MMT (All)	Glucose, Basal; mg/dL	28	165.11 (70.497)	25	107.90 (21.953)
	Glucose, 90-minute; mg/dL	28	352.57 (81.936)	25	157.12 (57.550)
	C-peptide, Basal; ng/mL [a]	28	0.01 (0.024)	25	1.31 (0.610)
	C-peptide, 90-minute; ng/mL [a]	28	0.02 (0.055)	25	3.74 (1.739)
MMT (PE Success)	Glucose, Basal; mg/dL	18	169.50 (80.480)	19	108.00 (24.745)
	Glucose, 90-minute; mg/dL	18	350.89 (92.917)	19	145.63 (56.258)
	C-peptide, Basal; ng/mL [b]	18	0.01 (0.027)	19	1.38 (0.562)
	C-peptide, 90-minute; ng/mL [b]	18	0.2 (0.064)	19	3.47 (1.501)
MMT (PE Failure)	Glucose, Basal; mg/dL	10	157.20 (50.666)	6	107.17 (10.400)
	Glucose, 90-minute; mg/dL	10	355.60 (61.778)	6	193.50 (49.136)
	C-peptide, Basal; ng/mL [b]	10	0.01 (0.016)	6	1.07 (0.747)
	C-peptide, 90-minute; ng/mL [b]	10	0.02 (0.034)	6	4.60 (2.290)

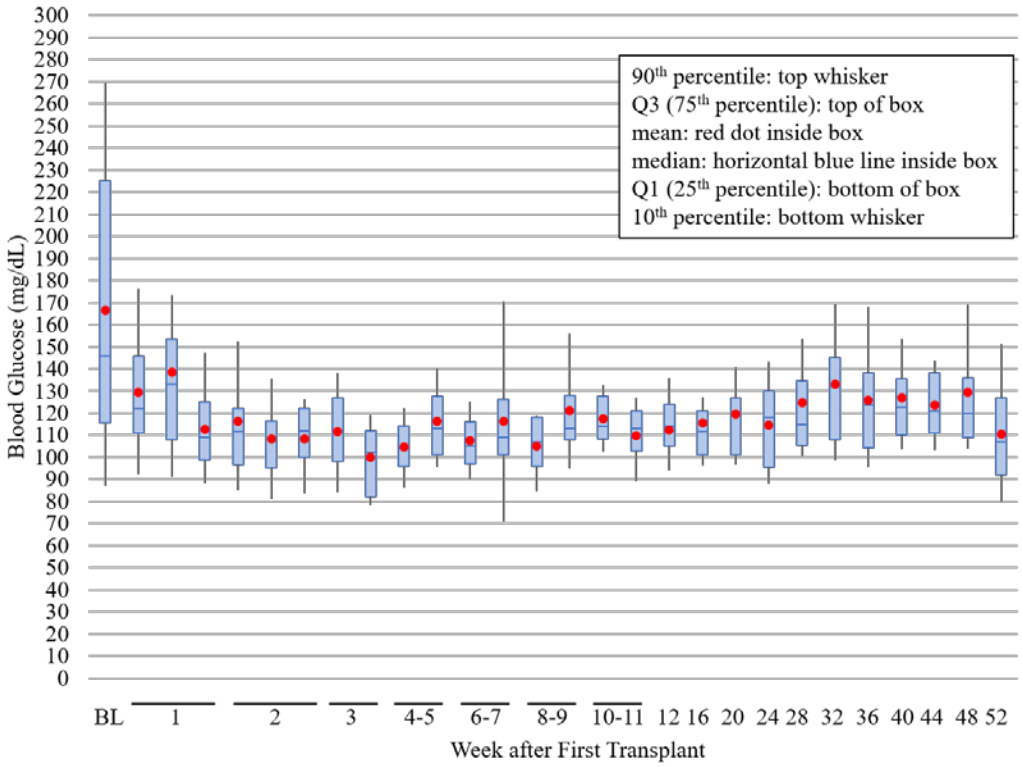
Note: Missing data were counted as failures. Baseline occurs prior to first transplant.

HYPO, hypoglycemia; MMT, mixed meal test; PE, primary endpoint (HbA1c ≤6.5% and free of SHEs at 1 year after last transplant)

In addition to MMT results, fasting blood glucose was measured at regular intervals during follow-up as part of a patient's regular study visits (in addition to multiple daily

self-measurements between visits). Importantly, the effect of islet transplantation on fasting blood glucose levels occurs rapidly following infusion. Within the first week after transplant, there was a sizeable drop in fasting blood glucose levels. Improvements were maintained over subsequent weeks, and at 52 weeks after the first transplant, fasting blood glucose levels remained well below baseline levels. A plot of mean fasting blood glucose levels (measured during planned study visits) over time between initial transplant and 1 year after initial transplant is provided in Figure 13.

Figure 13. Fasting Blood Glucose Levels from Baseline through 1 Year after First Transplant (Pooled Population)



4.1.7. Graft Failure

Basal C-peptide levels <0.3 ng/mL indicate a lack of islet function; therefore, this cutoff is used to define graft failure following donislecel administration. Specifically, graft failure is defined as basal C-peptide <0.3 ng/mL for 2 consecutive follow-up visits after last transplant and is a useful quantitative measure for identifying previously functional islet grafts that have lost their ability to effectively produce insulin. Graft failure was observed in approximately 17% of Pooled Population patients (Table 19).

Primary graft failure is defined as never achieving measurable (i.e., ≥0.1 ng/mL) basal C-peptide at any time post-transplant. Primary graft failure was not observed in Pooled Population patients.

Table 19. Graft Failure at 1 Year after Last Transplant (Pooled Population)

Outcome	Pooled Population N=30 [a]
Graft Failure, N (%) [b]	5 (16.7)
Missing, n (%)	0
Primary Endpoint = Success; n/N (%)	1/19 (5.3) [c]
Missing, n (%)	0
Primary Endpoint = Failure; n/N (%)	4/11 (36.4)
Missing, n (%)	0

Note: Missing data were counted as failures.

HbA1c, glycated hemoglobin; SHE, severe hypoglycemic event

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b Graft failure is defined as C-peptide levels <0.3 ng/mL for 2 consecutive follow-up visits after last transplant. This is not the same as primary graft failure, which indicates an islet graft that never resulted in production of C-peptide. Primary graft failure was not observed in any patient in the Pooled Population.

c This patient experienced low C-peptide, indicative of graft failure, and went back onto insulin but was able to maintain good glycemic control.

4.1.8. Long-Term Efficacy

Glycemic control, as determined by the composite efficacy endpoint of HbA1c ≤6.5% and no SHEs as well as the separate metric of insulin independence, persisted over time in most Pooled Population patients (Table 20). By 6 years post-last transplant, two-thirds of patients assessed (8/12) exhibited good glycemic control, with these results comparing favorably to results at 1 year following the last transplant. These results indicate that islet transplantation effectiveness is maintained for several years (at least) in brittle T1D patients who, prior to islet transplantation, exhibited poor glycemic control.

The persistence of efficacy following islet transplantation is supported by composite results provided in the CITR 10th Annual Report [20]. Based upon CITR data, HbA1c <7.0% was maintained in 60% of patients receiving islet alone transplants over 5 years of follow-up time, while the absence of SHEs was maintained in around 90% of patients over the same period. Achievement of both HbA1c <7.0% and absence of SHEs was maintained in around 50% of patients at 5 years of follow-up time. Furthermore, >50% of islet transplant recipients retained C-peptide ≥0.3 ng/mL at 5 years post-last infusion, and >70% of patients maintained fasting blood glucose in the range of 60-140 mg/dL at the 5-year time point. Insulin requirements also fell dramatically following islet transplantation and remained low through the 5-year time point, albeit with some rebound over time.

Table 20. Long-term Assessment of Efficacy Outcomes for the Pooled Population, by Year after Last Transplant

	Time After Last Transplant (Year)					
Outcome	**1**	**2**	**3**	**4**	**5**	**6**
Total Evaluable; n [a]	30	26	20	17	15	12
HbA1c ≤6.5% + Free of SHE; n (%) [b]	19 (63.3)	14 (53.8)	15 (75.0)	11 (64.7)	11 (73.3)	8 (66.7)
Insulin Independence; n (%) [b]	20 (66.7)	17 (65.4)	14 (70.0)	12 (70.6)	8 (53.3)	8 (66.7)

Note: Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

HbA1c, glycated hemoglobin; SHE, severe hypoglycemic event

a The total number of evaluable patients decreases with each subsequent year after last transplant in part because some of the patients have not yet reached certain yearly milestones (as of data cutoff).

b Insulin independence is defined as absence of exogenous insulin use at the time of assessment. Percentage is relative to the total number of patients followed beyond the previous anniversary.

4.1.9. Effect of Intrinsic Factors on Efficacy

Subgroup analyses were performed with respect to baseline diabetes control, primary and secondary efficacy, and long-term efficacy by patient age and patient sex. Given the relative ethnic and racial homogeneity of the population (predominantly White and non-Hispanic), subgroup analysis by race or ethnicity is of no utility. Notably, the patient population within the CITR is also predominantly White (98.1%) and non-Hispanic (98.7%) [20].

Mean and median age for the Pooled Population at the time of first infusion were both approximately 47 years (range 21-67 years; standard deviation approximately 12 years), which is nearly the same as that observed for the CITR data set (mean 46.2 years) [20]. Given this, the Pooled Population was divided into two age groups for subgroup analysis:

1. ≤47 years of age (n=18; min=21)
2. >47 years of age (n=12; max=67)

There is limited experience with the donislecel in patients who at the time of initial transplant were ≥65 years of age (N=2) and no experience with patients under age 21. This appears to be reflective of the islet transplantation field more broadly, as evidenced by the small number of pediatric or geriatric patients in the CITR dataset, especially relative to the overall patient population [20].

For the age-based analysis, mean baseline values for insulin requirement, HbA1c levels, SHE frequency, HYPO score, and fasting plasma glucose tended to be higher in the younger group (≤47 years) compared with the older group (>47 years), although there was substantial variability (Table 21). All patients exhibited reduced awareness of hypoglycemia at baseline.

There was no substantial effect of age on efficacy following donislecel administration (Table 22 and Table 23), although younger patients did experience a slightly greater incidence of graft failure than older patients. In addition, the efficacy response was durable regardless of patient age at the time of initial transplant (Table 24).

For the sex-based analysis, the donislecel Pooled Population included 24 females (80%) and 6 males (20%). At baseline, insulin requirements and HbA1c levels were similar between sexes (Table 21). Males tended to have more SHEs per month and higher HYPO scores, and

females tended to have higher fasting plasma glucose levels, although variabilities were high for these parameters. All participants reported a reduced awareness of hypoglycemia.

There was no substantial effect of sex on efficacy following donislecel administration (Table 22 and Table 23). In addition, the efficacy response was durable regardless of patient sex (Table 24).

Based upon the analyses performed, no adjustments to donislecel administration are necessary based upon patient age or sex.

Table 21. Baseline Diabetes Control (Pooled Population), by Patient Age and Sex

	Age		Sex	
Outcome	**≤47 Years N=18 [a]**	**>47 Years N=12 [a]**	**Female N=24 [a]**	**Male N=6 [a]**
Insulin Requirement (units/kg/day), n	18	11	23	6
Mean (SD)	0.55 (0.121)	0.45 (0.157)	0.51 (0.141)	0.52 (0.156)
Median (Min, Max)	0.55 (0.3, 0.8)	0.42 (0.3, 0.8)	0.53 (0.3, 0.8)	0.52 (0.3, 0.8)
Missing [b]; n (%)	0	1 (8.3)	1 (4.2)	0
HbA1c (%), n	17	12	23	6
Mean (SD)	7.51 (0.890)	7.12 (0.945)	7.40 (0.982)	7.15 (0.644)
Median (Min, Max)	7.50 (5.7, 9.0)	6.90 (5.9, 9.5)	7.40 (5.7, 9.5)	7.10 (6.2, 8.1)
Missing [b]; n (%)	1 (5.6)	0	1 (4.2)	0
Frequency of SHE (episodes/month), n [c]	12	4	14	2
Mean (SD)	0.954 (1.4595)	0.466 (0.5722)	0.640 (0.9801)	2.177 (2.9156)
Median (Min, Max)	0.216 (0.05, 4.24)	0.236 (0.09, 1.30)	0.216 (0.05, 3.39)	2.177 (0.12, 4.24)
Missing [b]; n (%)	6 (33.3)	8 (66.7)	10 (41.7)	4 (66.7)
HYPO Score, n [c]	12	6	15	3
Mean (SD)	353.05 (487.997)	251.06 (307.845)	305.40 (439.402)	387.35 (455.612)
Median (Min, Max)	109.14 (17.7, 1638.0)	125.80 (2.4, 738.7)	92.54 (2.4, 1638.0)	230.81 (30.6, 900.6)
Missing [b]; n (%)	6 (33.3)	6 (50.0)	2 (8.3)	3 (50.0)
Fasting Plasma Glucose (mg/dL), n	16	12	22	6
Mean (SD)	170.1 (81.17)	158.5 (55.96)	172.5 (75.51)	138.2 (42.18)
Median (Min, Max)	171.5 (69, 348)	152.5 (84, 279)	168.0 (69, 348)	141.0 (88, 182)
Missing [b]; n (%)	2 (11.1)	0	2 (8.3)	0
90-min Glucose post glucose challenge (mg/dL), n	16	12	22	6
Mean (SD)	347.9 (82.16)	358.8 (84.86)	362.3 (85.72)	316.8 (58.68)
Median (Min, Max)	373.0 (122, 456)	349.5 (255, 559)	373.5 (122, 559)	295.0 (279, 432)
Missing [b]; n (%)	2 (11.1)	0	2 (8.3)	0
Reduced awareness of hypoglycemia, n (%) [d]	18 (100.0)	12 (100)	24 (100)	6 (100)
Missing, n (%)	0	0	0	0
Mixed Meal Test: Fasting C-peptide <0.1 ng/mL, n (%) [e]	15 (83.3)	12 (100)	21 (87.5)	6 (100)
Missing, n (%)	2 (11.1)	0	2 (8.3)	0

Outcome	Age ≤47 Years N=18 [a]	Age >47 Years N=12 [a]	Sex Female N=24 [a]	Sex Male N=6 [a]
Mixed Meal Test: 90-min C-peptide post-glucose challenge <0.1 ng/mL, n (%) [e]	15 (83.3)	11 (91.7)	20 (83.3)	6 (100)
Missing, n (%)	2 (11.1)	0	2 (8.3)	0

HbA1c, glycated hemoglobin; HYPO, hypoglycemia; SD, standard deviation; SHE, severe hypoglycemic event.

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b Value of missing is reported when data were not obtained or the patient did not provide adequate information for quantification.

c Baseline values were calculated based on hypoglycemic events self-reported by the patient during the screening/waiting period between enrollment and initial transplant, which varied in length for each patient. However, baseline SHE frequency data were not collected and/or retained in all cases.

d Reported qualitatively only at enrollment.

e 0.1 ng/mL is the undetectable lower limit for C-peptide.

Table 22. Composite Efficacy Endpoint through 1 Year After Last Transplant (Pooled Population), by Patient Age and Sex

Outcome	Age ≤47 Years N=18 [a]	Age >47 Years N=12 [a]	Female N=24 [a]	Male N=6 [a]
Success (HbA1c ≤6.5% + Free of SHE); n (%), 95% C.I.	12 (66.7), (40.99, 86.66)	7 (58.3), (27.67, 84.83)	15 (62.5), (40.59, 81.20)	4 (66.7), (22.28, 95.67)
Failure (Total); n (%)	6 (33.3)	5 (41.7)	9 (37.5)	2 (33.3)
HbA1c >6.5%; n (%)	4 (22.2)	1 (8.3)	4 (16.7)	1 (16.7)
Any SHE; n (%)	3 (16.7)	4 (33.3)	6 (25.0)	1 (16.7)
Missing; n (%) [b]	1 (5.6)	0	0	1 (16.7)

Abbreviations: C.I., confidence interval; HbA1c, glycated hemoglobin; NC, not calculated; SHE, severe hypoglycemic event

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b Missing values correspond to patients who discontinued early or did not have available data and are imputed as failures.

Table 23. Alternative Composite Endpoint, Insulin Independence, and Graft Failure through 1 Year after Last Transplant, by Patient Age and Sex

Outcome	Age ≤47 Years N=18 [a]	Age >47 Years N=12 [a]	Female N=24 [a]	Male N=6 [a]
Success (HbA1c <7.0% and free of SHEs); n/N (%) [b]	13/18 (72.2)	8/12 (66.7)	17/24 (70.8)	4/6 (66.7)
Missing, n (%)	1 (5.6)	0 (0.0)	0	1 (16.7)
Insulin Independence (Total); n (%) [c]	11/18 (61.1)	9/12 (75.0)	17/24 (70.8)	3/6 (50.0)
Primary Endpoint = Success; n/N (%)	11/12 (91.7)	5/7 (71.4)	13/15 (86.7)	3/4 (75.0)
Missing, n (%	0 (0.0)	0 (0.0)	0	0
Primary Endpoint = Failure; n/N (%)	0/6 (0.0)	4/5 (80.0) [e]	4/9 (44.4) [e]	0
Missing, n (%)	2 (33.3)	0 (0.0)	0	2 (100)
Graft Failure (Total); n (%) [d]	4 (22.2)	1 (8.3)	3/24 (12.5)	2/6 (33.3)
Primary Endpoint = Success; n/N (%)	0	1/7 (14.3) [f]	0/15 (0.0)	1/4 (25.5) [f]
Missing, n (%	0	0	0	0
Primary Endpoint = Failure; n/N (%)	4/7 (66.7)	0	3/9 (33.3)	1/2 (50.0)
Missing, n (%)	0	0	0	0

Note: Missing data were counted as failures. Percentages are based upon respective group N.

Abbreviations: HbA1c, glycated hemoglobin; SHE, severe hypoglycemic event

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population.

b Alternative goal of glycemic control

c Insulin independence is defined as a patient's not requiring exogenous insulin at the time of assessment (i.e., at 1 year after last transplant).

d Graft failure is defined as C-peptide levels <0.3 ng/mL for 2 consecutive follow-up visits after last transplant.

e Patients were weaned off insulin if they were no longer experiencing hyperglycemia. Despite insulin independence at the time of the primary endpoint assessment, some patients failed the primary endpoint (e.g., SHE assessed over a window from Day 28-365 post-transplant; therefore, a patient could experience a SHE early but still be off insulin by the 1 year post-last transplant assessment).

f This patient experienced low C-peptide, indicative of graft failure, and went back onto insulin but was able to maintain good glycemic control.

Table 24. Long-Term Efficacy (Pooled Population), by Patient Age and Sex

		Time After Last Transplant (Year)					
Outcome	**Age**	**1**	**2**	**3**	**4**	**5**	**6**
Total Evaluable; n [a]	≤47	18	14	11	10	9	7
	>47	12	12	9	7	6	5
HbA1c ≤6.5% + Free of SHE; n (%) [b]	≤47	12 (66.7)	7 (50.0)	9 (81.8)	7 (70.0)	7 (77.8)	5 (71.4)
	>47	7 (58.3)	7 (58.3)	6 (66.7)	4 (57.1)	4 (66.7)	3 (60.0)
Absence Exogenous Insulin; n (%) [b]	≤47	11 (61.1)	10 (71.4)	9 (81.8)	8 (80.0)	5 (55.6)	5 (71.4)
	>47	9 (75.0)	7 (58.3)	5 (55.6)	4 (57.1)	3 (50.0)	3 (60.0)
Outcome	**Sex**	**1**	**2**	**3**	**4**	**5**	**6**
Total Evaluable; n [a]	F	24	22	17	14	13	11
	M	6	4	3	3	2	1
HbA1c ≤6.5% + Free of SHE; n (%) [b]	F	15 (62.5)	11 (50.0)	12 (70.6)	10 (71.4)	10 (76.9)	7 (63.6)
	M	4 (66.7)	3 (75.0)	3 (100)	1 (33.3)	1 (50.0)	1 (100)
Absence Exogenous Insulin; n (%) [b]	F	17 (70.8)	14 (63.6)	12 (70.6)	11 (78.6)	7 (53.8)	7 (63.6)
	M	3 (50.0)	3 (75.0)	2 (66.7)	1 (33.3)	1 (50.0)	1 (100)

Note: Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population. Age is reported in years.

Abbreviations: HbA1c, glycated hemoglobin; SHE, severe hypoglycemic event

a The total number of evaluable patients decreases with each subsequent year after last transplant because some of the patients have not yet reached certain yearly milestones (as of data cutoff).

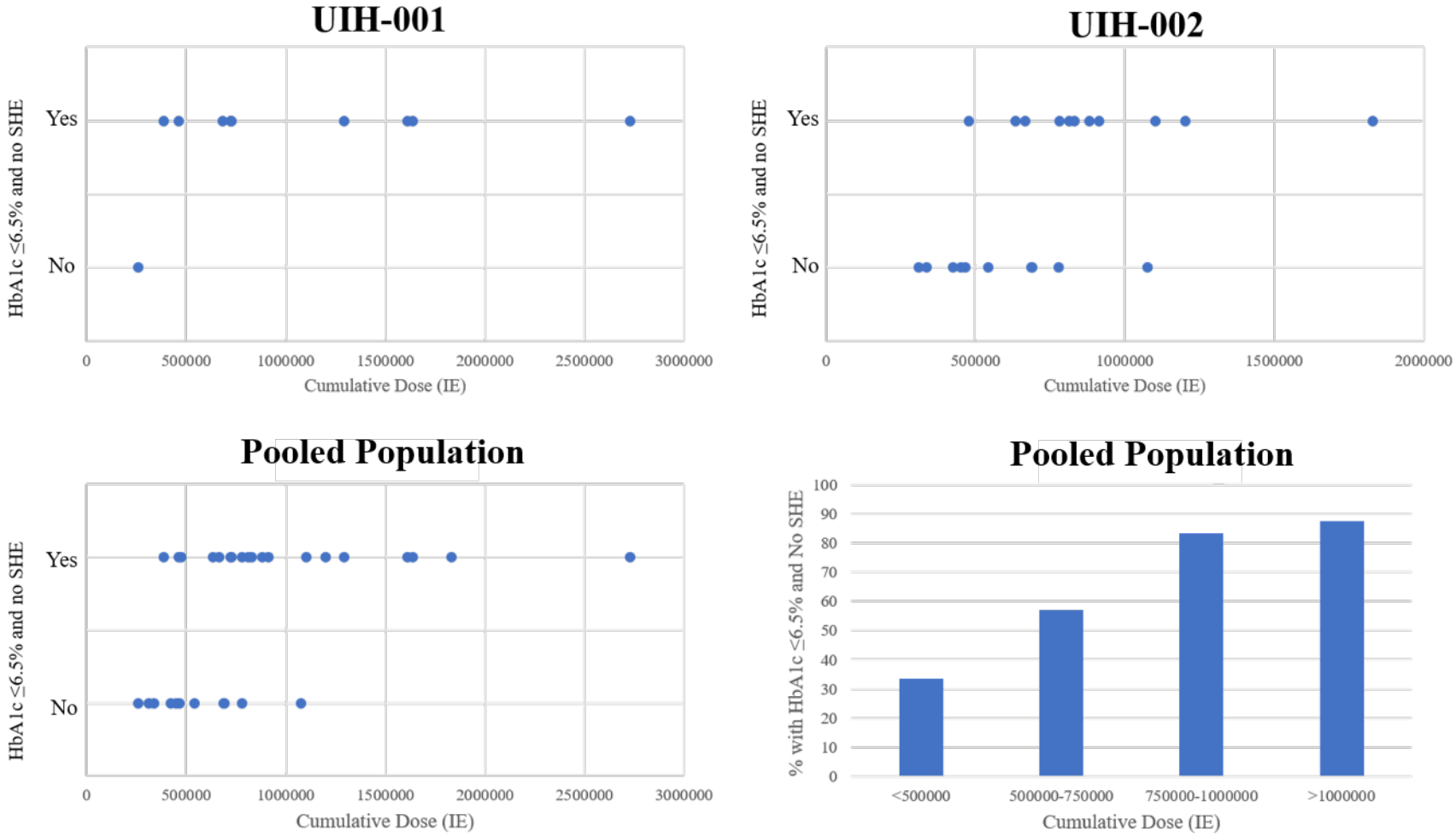
b Percentage is relative to total number of patients followed at each time point

4.1.10. Exposure-Efficacy Relationships

Plots of the relationship between cumulative donislecel dose and achievement of the composite efficacy endpoint of HbA1c ≤6.5% and no SHEs at 1 year after last transplant are provided for Studies UIH-001, UIH-002, and the Pooled Population in Figure 14, along with a graph showing success at various dose ranges for the Pooled Population. As dose increases, achievement of the composite endpoint likewise increases. While 33% (3/9) of patients receiving fewer than 500,000 IE were successful, this increased to 57% (4/7) for those receiving 500,000-750,000 IE, 83% (5/6) for those receiving 750,000-1,000,000 IE, and 88% (7/8) for those receiving greater than 1,000,000 IE (all islet totals are cumulative across all transplants).

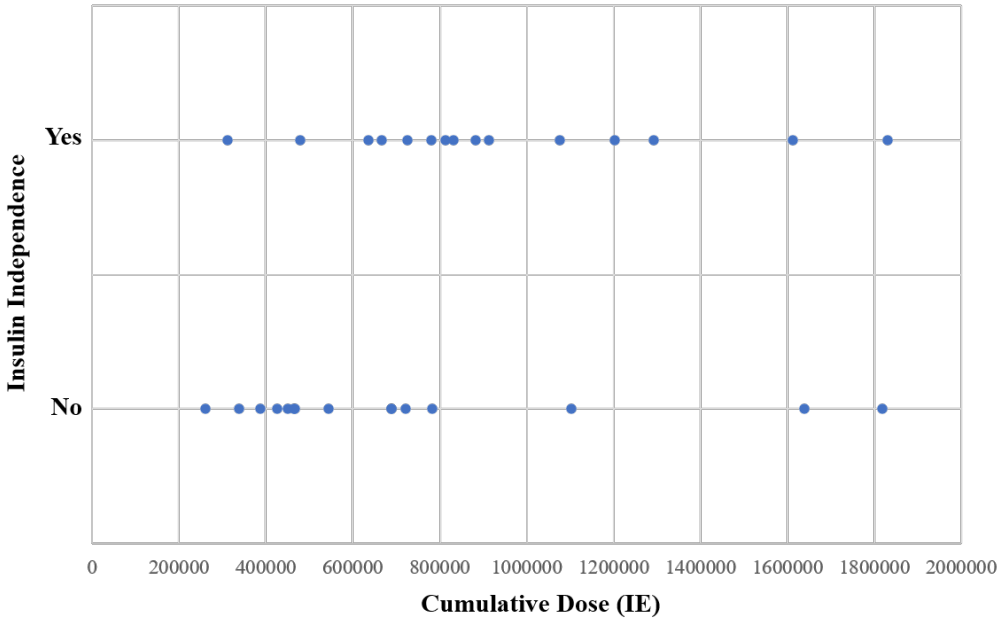
Importantly, nearly all patients showed some level of improvement in both HbA1c and C-peptide levels from baseline to 1 year following last transplant—among patients with both baseline and 1 year post-last transplant data available, 26/28 (93%) showed improvement in HbA1c levels and 24/25 (96%) showed improved C-peptide levels. Additionally, out of all patients with 1 year post-last transplant data, 25/30 (83%) achieved HbA1c ≤6.5% and 25/26 (96%) achieved fasting C-peptide ≥0.3 ng/mL. Among the 5 patients who failed to meet the HbA1c threshold, 3 received <500,000 IE (cumulative) and the other 2 received <700,000 IE. The lone patient to fail to meet the C-peptide threshold received <500,000 IE.

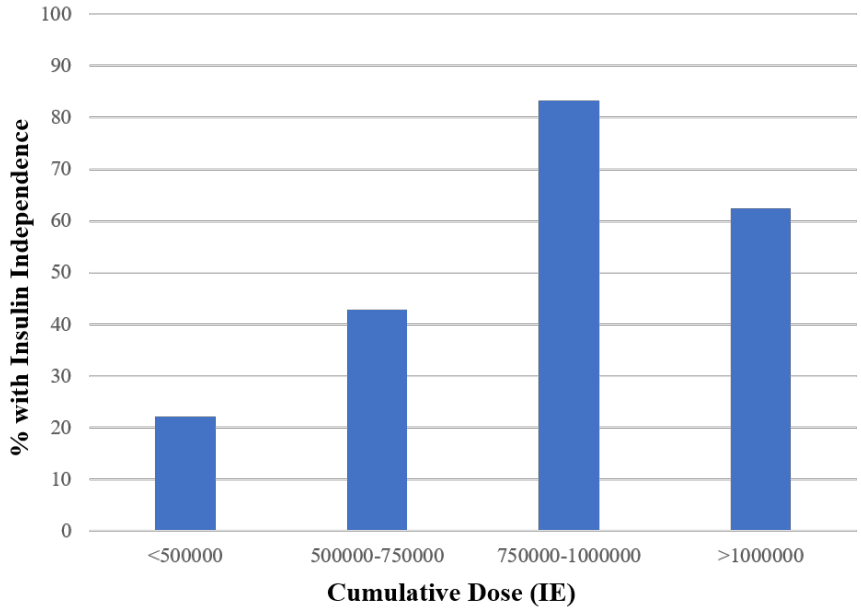
Figure 14. Achievement of the Composite Efficacy Endpoint of HbA1c ≤6.5% and free of SHEs at 1 Year after Last Transplant, by Cumulative Dose, Studies UIH-001, UIH-002, and Pooled Population



Insulin independence at 1 year after last transplant was observed with greater frequency with increased donislecel dose (cumulative) up to a total dose of between 750,000 and 1,000,000 IE (Figure 15). While 22% (2/9) of patients receiving fewer than 500,000 IE achieved insulin independence, this increased to 43% (3/7) for those receiving 500,000-750,000 IE, and to 83% (5/6) for those receiving 750,000-1,000,000 IE. Beyond 1,000,000 IE, insulin independence decreased slightly to 62.5% (5/8) but was still more frequent than in patients receiving <750,000 IE. Together, these results support the conclusion that doses ≥750,000 IE are favorable for promoting insulin independence.

Figure 15. Insulin Independence at 1 Year after Last Transplant, by Cumulative Dose (Pooled Population)





Based upon an analysis by CITR as part of their 10th Annual Report [20], the total number of islets transplanted, whether in a single infusion or over 2-3 infusions, consistently yielded improved outcomes across a variety of important efficacy parameters including insulin independence, C-peptide, HbA1c, fasting blood glucose, and absence of SHEs. In particular, infusing ≥325,000 IE (across one or more infusions) was a common favorable factor across all efficacy outcomes; infusing ≥500,000 IE was especially favorable for both insulin independence post-last infusion (p=0.0009) and prevalence of C-peptide ≥0.3 ng/mL post-last infusion (p=0.0109).

4.2. Efficacy Comparison to Historical Controls

4.2.1. Wisconsin Diabetes Registry Study

The WDRS [55-57] is a population-based cohort of incident cases with T1D and includes both longitudinal clinical assessments and questionnaires. The study originally identified and enrolled 590 participants with newly diagnosed T1D between May 1987 and April 1992. The participants were <30 years of age at the time of enrollment and living in 28 contiguous counties in southern and central Wisconsin. Patients were followed for up to 20 years. Additional details regarding study design are described in Section 9.3.1.

Demographics for the WDRS [56] are provided in Table 25. Only a minority of T1D patients in the WDRS were able to adequately manage their T1D over time (22% had HbA1c <7.0%; n=112), despite nearly all of these patients (96%) being on intensive insulin therapy by the time that the long-term assessment was made (Table 26). Importantly, only 8% of patients met success criteria for at least 1 of the 2 glycemic control parameters in the CellTrans clinical studies (i.e., HbA1c and SHEs) and <1% (a single patient) achieved success on both. These findings support the conclusion that spontaneously transitioning from a state of poor glycemic control to one of good glycemic control with insulin therapy alone is an extremely rare event.

Table 25. Wisconsin Diabetes Registry Study Participants – Demographics and Baseline Characteristics

Total evaluated, n		415
Age; %	<5 years	2.9
	5-14 years	57.8
	15-24years	30.4
	25-34 years	8.9
	>34 years	0
Sex; % Female		48.7
Race; % White		96.6
HbA1c %; mean±standard deviation		11.5±2.4

HbA1c, glycated hemoglobin

Source: [58]

Table 26. Wisconsin Diabetes Registry Study – Spontaneous Transitions for HbA1c and Occurrence of SHEs from a Condition of Poor Glycemic Control to One of Good Glycemic Control in Patients on Insulin Therapy

		Transitioned from HbA1c >6.5% to ≤6.5%?	
		No	**Yes**
Transitioned from Severe Hypoglycemic Episodes to No Episodes?	**No**	312 (92%)	7 (2%)
	Yes	19 (6%)	1 (<1%)

Note: Study examinations were scheduled at 4 months (for southern Wisconsin only) and at 4, 7, 9, 14, and 20 years.

Source: [58]

4.2.2. Other Historical Comparators

A comparison of efficacy outcomes (HbA1c level, SHEs, and insulin independence) for donislecel, islet transplantation at other transplant centers, and insulin therapy is provided in Table 27. Given their comparatively large population sizes, CITR [20] (Section 9.3.3) and DCCT [25, 59] (Section 9.3.2) data are included as historical controls for islet transplantation and standard-of-care insulin therapy, respectively. Two additional studies, TRIMECO [60] and UBC [61], are included because they contained within-study comparisons of patients receiving islet transplantation versus patients receiving insulin therapy.

As observed for donislecel, islet transplantation consistently improved HbA1c levels, dramatically reduced the number of patients experiencing SHEs, and allowed a significant proportion of patients to become insulin independent compared to baseline [60, 61].

Patients remaining on conventional insulin therapy (DCCT) did not experience any improvement in glycemic control parameters from baseline over time. While patients switching from conventional to intensive insulin therapy did experience an improvement in HbA1c levels, a significant proportion of them still experienced SHEs and, importantly, the switch to intensive insulin therapy had the unintended consequence of significantly increasing the prevalence of severe hypoglycemia (comparing DCCT conventional insulin versus intensive insulin groups). The TRIMECO and UBC studies indicate no spontaneous improvement in glycemic control from baseline in patients who were on intensive insulin therapy at baseline.

Together, these results support the effectiveness of islet cell therapies for promoting good glycemic control and suggest a favorable efficacy profile compared to standard-of-care insulin therapy.

Table 27. Comparison of Efficacy Outcomes for Donislecel (Pooled Population), Islet Transplantation at Other Transplant Centers, and Insulin Therapy

Study		HbA1c (%)	Patients with SHEs (%)	Insulin Ind. (%) [a]
Donislecel (CellTrans)				
Pooled Population	Baseline	7.4±0.9	100	0
	1 year post-last transplant [b]	6.0±0.7	23	67
Islet Transplantation				
CITR	Baseline	7.9±0.0	80	0
	1 year post-last transplant	~6.5±NR	6	52
TRIMECO	Baseline	8.1 (7.4, 8.9)	72 [c]	0
	6 months post-first transplant	5.6	8	44
	1 year post-first transplant	5.8	15	59
UBC	Baseline	8.1±1.2	NR	0
	Assessment time not stated	6.7±0.2	NR	38
Insulin Therapy				
DCCT	Baseline (all patients)	9.1±1.6 [d]	NR	0
	Conventional insulin [e]	9.1±1.3	35	0
	Intensive insulin [e]	7.2±0.9	65	0
TRIMECO	Baseline	8.1 (7.7, 8.6)	82 [c]	0
	6 months	8.2	64	0
UBC	Baseline	8.1±1.2	NR	0
	Assessment time not stated	7.8±0.3	NR	0

Note: HbA1c % is reported as mean ± standard deviation for CellTrans, CITR, UBC, DCCT. HbA1c % is reported as median for TRIMECO (excluding baseline assessments). HbA1c % is reported as median (interquartile range) for TRIMECO baseline assessments. Baseline for UBC is for the total population (i.e., those who received islet transplants and those who remained on insulin). Baseline for DCCT includes the total population (i.e., those who received intensive insulin therapy and those who continued on conventional insulin therapy). For the donislecel population, SHE is defined as an event with symptoms compatible with hypoglycemia in which the subject requires the assistance of another person and which is associated with either a blood glucose level <50 mg/dL (2.8 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration.

DCCT, Diabetes Control and Complications Trial; IQR, interquartile range; NR, not reported; SD, standard deviation; TRIMECO, Trial Comparing Metabolic Efficiency of Islet Graft to Intensive Insulin Therapy for Type 1 Diabetes's Treatment; UBC, University of British Columbia

a Defined as lack of exogenous insulin use

b Primary follow-up

c ≥2 SHEs in year prior to randomization

d Baseline HbA1c was 9.1±1.6% for both the conventional and intensive therapy groups independently. All patients at baseline were on conventional insulin therapy.

e Average 6.5 years of follow-up

Source: Studies UIH-001 and UIH-002; DCCT [25, 59], CITR [20], TRIMECO [60], UBC [61]

5. SAFETY OF DONISLECEL IN BRITTLE TYPE 1 DIABETES

5.1. Patient Exposure

5.1.1. Donislecel

For patients in Studies UIH-001 and UIH-002, the median islet number per transplant was 399,178 IE (range 253,924 to 858,856 IE), or 6,570 IE/kg (range 4,186 to 13,633 IE/kg). Cumulatively, patients received a median total islet dose of 724,184 IE (range 260,902 to 1,831,236) across all transplants.

5.1.2. Concomitant Medications

In addition to donislecel, patients were also exposed to several concomitant medications as part of the islet transplantation and immunosuppression protocol. These concomitant medications can be a significant contributor to adverse safety outcomes following islet transplant, and many of these medications, especially immunosuppressants, are known to have serious side effects, especially with chronic use. Table 28 presents the numbers and percentages of subjects in Studies UIH-001 and UIH-002 who received immunosuppressants and other key study medications.

Table 28. Comparison of Key Administered Medications for Patients in Studies UIH-001 and UIH-002 up to 1 Year after Last Transplant

Medication	UIH-001 N=10; Patients (%)	UIH-002 N=21; Patients (%)	Pooled Population N=30 [a]; Patients (%)
Basiliximab	0	16 (76)	16 (53)
Mycophenolate mofetil or sodium	3 (30)	6 (29)	9 (30)
Daclizumab	10 (100)	5 (24)	15 (50)
Etanercept	6 (60)	21 (100)	27 (90)
Exenatide	6 (60)	21 (100)	27 (90)
Sirolimus	10 (100)	20 (95)	30 (100) [b]
Tacrolimus	10 (100)	21 (100)	30 (100)
Anti-thymocyte globulin	1 (10)	5 (24)	6 (20)

a Pooled Population = total patient population from UIH-001 and UIH-002; 1 patient previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single patient for the Pooled Population. This patient received daclizumab, sirolimus, and tacrolimus in UIH-001 and mycophenolate mofetil, etanercept, exenatide, tacrolimus, and thymoglobulin in UIH-002. Duplicate entries for this patient were eliminated from the Pooled Population total.

b All patients received sirolimus. The 1 patient not receiving it during UIH-002 was the reenrolled patient, who was administered sirolimus during UIH-001.

5.2. Pooled Population – Studies UIH-001 and UIH-002

5.2.1. Treatment-Emergent Adverse Events

5.2.1.1. Overview

For the Pooled Population during primary follow-up (i.e., from initial transplant through 1 year after last transplant; Table 29):

- TEAEs occurred in all patients, regardless of the number of transplants.
- There were no TEAEs leading to early discontinuation
- There were no TEAEs leading to death.
- Treatment-related TEAEs (including those related to immunosuppression or other study treatments/procedures) were reported in all patients.
- Approximately 53% of patients experienced an SAE (~3% of all TEAEs).
- Approximately 83% of patients experienced a ≥Grade 3 TEAE (~13% of all TEAEs).
- Approximately one quarter of all TEAEs reported from initial transplant through 1 year after initial transplant occurred within the first week post-transplant, and approximately one half occurred within the first month.
- There was no discernible relationship between islet dose or transplant number and TEAE incidence.

TEAEs were analyzed by patient demographics, including age and sex. Race and ethnicity were not assessed because nearly all patients who were administered donislecel were White and Non-Hispanic. The results of these analyses are provided in Section 5.2.5.

Within the Pooled Population (Table 30), during the period from initial transplant through 1 year after the last transplant, System Organ Classes (SOCs) accounting for >10% of all reported TEAEs included gastrointestinal disorders and metabolism and nutrition disorders (both were observed in all patients); during long-term follow-up, only infections and infestations comprised >10%.

Within the Pooled Population (Table 31), SOCs accounting for ≥5% of SAEs at any time during follow-up included:

- Neoplasms Benign, Malignant, and Unspecified
- Infections and Infestations
- Metabolism and Nutrition Disorders
- Gastrointestinal Disorders
- Injury, Poisoning, and Procedural Complications
- Cardiac Disorders
- Blood and Lymphatic Disorders
- Nervous System Disorders

Together, these SAEs account for more than 75% of all SAEs observed during follow-up. Of note, certain SAEs were more prevalent during primary follow-up (i.e., between initial transplant and 1 year after the final transplant), while others were more prevalent during long-term follow-up (i.e., the period beyond the primary follow-up). In particular, infections and infestations, gastrointestinal disorders, and blood and lymphatic disorder SAEs occurred much more frequently (i.e., ≥70% of the total number of SAEs for that SOC at any time during follow-up) during primary follow-up, while neoplasms and cardiac disorder SAEs occurred less frequently early in follow-up but more frequently during long-term follow-up. The remainder tended to be evenly balanced between follow-up periods.

Table 29. Summary of Treatment-Emergent Adverse Events for the Pooled Population, including by Time after First Transplant and Transplant Number

		Cumulative from Transplant to Specified Time after First Transplant Events, n Patients, n (%)					By Total Transplants Received Events, n Patients, n (%)		
Category	**Total [a] N = 30**	**1 week N = 30**	**30 days N = 30**	**90 days N = 30**	**180 days N = 30**	**1 year N = 30**	**1 Tx N = 11**	**2 Tx N = 12**	**3 Tx N = 7**
TEAEs	1417 30 (100)	293 30 (100)	549 30 (100)	796 30 (100)	929 30 (100)	1194 30 (100)	376 11 (100)	687 12 (100)	355 7 (100)
SAEs	38 16 (53.3)	7 6 (20.0)	11 7 (23.3)	14 8 (26.7)	20 11 (36.7)	32 13 (43.3)	18 6 (54.5)	12 6 (50.0)	8 4 (57.1)
TEAEs leading to discontinuation	0	0	0	0	0	0	0	0	0
TEAEs with an outcome of death	0	0	0	0	0	0	0	0	0
TEAEs related to study treatments/ procedures [b]	1116 30 (100)	231 29 (96.7)	433 30 (100)	635 30 (100)	743 30 (100)	953 30 (100)	249 11 (100)	628 12 (100)	239 7 (100)
TEAEs rated Grade 3 or higher [c,]	185 25 (83.3)	34 17 (56.7)	65 20 (66.7)	92 21 (70.0)	108 22 (73.3)	146 24 (80.0)	45 8 (72.7)	85 11 (91.7)	55 6 (85.7)

NR, not reported; SAE, serious TEAE, TEAE; treatment emergent adverse event; Tx, transplant.

a Total includes AEs that occurred from first transplant to 1 year after last transplant.

b AEs were reported as “possibly related” or “not possibly related” to immunosuppressive agents or other study drugs/procedures.

c TEAEs that were missing severity grades are included in this count.

Table 30. System Organ Classes for Treatment-Emergent Adverse Events by Follow-up Period (Pooled Population)

	Any Time Post-Initial Transplant		Through 1 Year Post-Last Transplant		Long-term Follow-up	
System Organ Class	**Events n (%)**	**Patients n (%) N=30**	**Events n (%)**	**Patients n (%) N=30**	**Events n (%)**	**Patients n (%) N=26**
Any adverse event	2292 (100.0)	30 (100.0)	1406 (100.0)	30 (100.0)	886 (100.0)	25 (96.2)
Gastrointestinal disorders	284 (12.4)	30 (100.0)	204 (14.5)	30 (100.0)	80 (9.0)	21 (80.8)
Metabolism and nutrition disorders	243 (10.6)	30 (100.0)	187 (13.3)	30 (100.0)	56 (6.3)	17 (65.4)
Infections and infestations	211 (9.2)	26 (86.7)	82 (5.8)	24 (80.0)	129 (14.6)	22 (84.6)
Nervous system disorders	200 (8.7)	27 (90.0)	119 (8.5)	27 (90.0)	81 (9.1)	21 (80.8)
Skin and subcutaneous tissue disorders	184 (8.0)	30 (100.0)	114 (8.1)	30 (100.0)	70 (7.9)	17 (65.4)
Investigations	173 (7.5)	26 (86.7)	94 (6.7)	26 (86.7)	79 (8.9)	16 (61.5)
General disorders and administration site conditions	168 (7.3)	29 (96.7)	113 (8.0)	29 (96.7)	55 (6.2)	21 (80.8)
Respiratory, thoracic and mediastinal disorders	132 (5.8)	28 (93.3)	84 (6.0)	26 (86.7)	48 (5.4)	17 (65.4)
Blood and lymphatic system disorders	131 (5.7)	27 (90.0)	117 (8.3)	27 (90.0)	14 (1.6)	6 (23.1)
Musculoskeletal and connective tissue disorders	123 (5.4)	24 (80.0)	57 (4.1)	20 (66.7)	66 (7.4)	18 (69.2)
Psychiatric disorders	94 (4.1)	23 (76.7)	59 (4.2)	21 (70.0)	35 (4.0)	14 (53.8)
Renal and urinary disorders	84 (3.7)	28 (93.3)	40 (2.8)	21 (70.0)	44 (5.0)	15 (57.7)
Injury, poisoning and procedural complications	51 (2.2)	19 (63.3)	24 (1.7)	17 (56.7)	27 (3.0)	11 (42.3)
Eye disorders	45 (2.0)	18 (60.0)	21 (1.5)	15 (50.0)	24 (2.7)	10 (38.5)
Ear and labyrinth disorders	32 (1.4)	18 (60.0)	18 (1.3)	12 (40.0)	14 (1.6)	9 (34.6)
Reproductive system and breast disorders	28 (1.2)	18 (60.0)	19 (1.4)	14 (46.7)	9 (1.0)	8 (30.8)
Neoplasms benign, malignant and unspecified	28 (1.2)	15 (50.0)	7 (0.5)	6 (20.0)	21 (2.4)	14 (53.8)
Hepatobiliary disorders	27 (1.2)	16 (53.3)	18 (1.3)	12 (40.0)	9 (1.0)	7 (26.9)
Vascular disorders	20 (0.9)	13 (43.3)	13 (0.9)	9 (30.0)	7 (0.8)	5 (19.2)
Cardiac disorders	20 (0.9)	12 (40.0)	9 (0.6)	7 (23.3)	11 (1.2)	8 (30.8)
Endocrine disorders	6 (0.3)	6 (20.0)	2 (0.1)	2 (6.7)	4 (0.5)	4 (15.4)
Immune system disorders	4 (0.2)	4 (13.3)	3 (0.2)	3 (10.0)	1 (0.1)	1 (3.8)
Surgical and medical procedures	3 (0.1)	3 (10.0)	2 (0.1)	2 (6.7)	1 (0.1)	1 (3.8)
Social Circumstances	1 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (3.8)

Note: Long-term follow-up means after primary follow-up (i.e., from 1 year after a patient's last transplant until the patient leaves study or data cutoff, whichever comes first).

Table 31. System Organ Classes for Serious Adverse Events by Follow-up Period (Pooled Population)

	Any Time Post-Initial Transplant		Through 1 Year Post-Last Transplant		Long-term Follow-up	
System Organ Class	SAEs n (%)	Patients n (%) N=30	SAEs n (%)	Patients n (%) N=30	SAEs n (%)	Patients n (%) N=26
Any serious adverse event	79 (100.0)	25 (83.3)	37 (100.0)	16 (53.3)	42 (100.0)	17 (65.4)
Neoplasms benign, malignant and unspecified [b]	12 (15.2)	10 (33.3)	3 (8.1)	3 (10.0)	9 (21.4)	8 (30.8)
Infections and infestations	10 (12.7)	9 (30.0)	7 (18.9)	7 (23.3)	3 (7.1)	3 (11.5)
Metabolism and nutrition disorders	9 (11.4)	3 (10.0)	3 (8.1)	1 (3.3)	6 (14.3)	3 (11.5)
Gastrointestinal disorders	8 (10.1)	5 (16.7)	6 (16.2)	5 (16.7)	2 (4.8)	2 (7.7)
Injury, poisoning and procedural complications	8 (10.1)	5 (16.7)	3 (8.1)	2 (6.7)	5 (11.9)	4 (15.4)
Cardiac disorders	6 (7.6)	6 (20.0)	1 (2.7)	1 (3.3)	5 (11.9)	5 (19.2)
Blood and lymphatic system disorders	4 (5.1)	4 (13.3)	4 (10.8)	4 (13.3)	0	0
Nervous system disorders	4 (5.1)	4 (13.3)	1 (2.7)	1 (3.3)	3 (7.1)	3 (11.5)
General disorders and administration site conditions	3 (3.8)	3 (10.0)	2 (5.4)	2 (6.7)	1 (2.4)	1 (3.8)
Musculoskeletal and connective tissue disorders	3 (3.8)	3 (10.0)	2 (5.4)	2 (6.7)	1 (2.4)	1 (3.8)
Investigations	2 (2.5)	2 (6.7)	1 (2.7)	1 (3.3)	1 (2.4)	1 (3.8)
Reproductive system and breast disorders	2 (2.5)	2 (6.7)	1 (2.7)	1 (3.3)	1 (2.4)	1 (3.8)
Surgical and medical procedures	2 (2.5)	2 (6.7)	1 (2.7)	1 (3.3)	1 (2.4)	1 (3.8)
Vascular disorders	2 (2.5)	1 (3.3)	0	0	2 (4.8)	1 (3.8)
Endocrine disorders	1 (1.3)	1 (3.3)	1 (2.7)	1 (3.3)	0	0
Hepatobiliary disorders	1 (1.3)	1 (3.3)	1 (2.7)	1 (3.3)	0	0
Psychiatric disorders	1 (1.3)	1 (3.3)	0	0	1 (2.4)	1 (3.8)
Respiratory, thoracic and mediastinal disorders	1 (1.3)	1 (3.3)	0	0	1 (2.4)	1 (3.8)

Note: Long-term follow-up means after the primary follow-up period (i.e., from 1 year after a patient's last transplant until the patient leaves the study or data cutoff, whichever comes first).

5.2.1.2. Specific Adverse Events

Regarding specific TEAEs, among all TEAEs reported between initial transplant through 1 year after a patient's last transplant, only anemia accounted for >5% of all TEAEs reported. The remainder were ≤3%. Among TEAEs accounting for ≥1% of all TEAEs, all of them affected >20% of patients in Studies UIH-001 and UIH-002.

During primary follow-up, the most common Grade 3 or higher TEAEs were diarrhea (23%), anemia (20%), and nausea (20%).

TEAEs experienced by ≥ 20% of patients in the Pooled Population up to 1 year after the last transplant, along with the percentage of patients experiencing events of these types graded as severity grade 3 or higher, are summarized in Table 32. Most of these TEAEs are commonly observed with chronic immunosuppression and are not likely due to the islets themselves or the transplantation procedure. Some may also result from underlying conditions/diseases (including secondary to T1D) or other medications the patients were taking during follow-up.

Table 32. Treatment-Emergent Adverse Events Occurring in ≥20% of Patients from Initial Transplant through 1 Year After Final Transplant (Pooled Population)

Adverse Reaction	Any Grade (%) N=30	Grade 3 or Higher (%) N=30
Blood and Lymphatic Disorders		
Anemia	83	20
Leukopenia	27	0
Cardiac Disorders		
Palpitations	20	0
Ear and Labyrinth Disorders		
Ear pain	20	0
Tinnitus	20	3
Eye Disorders		
Vision blurred	27	0
Gastrointestinal Disorders		
Nausea	83	20
Diarrhea	73	23
Vomiting	60	13
Abdominal pain	57	17
Stomatitis	43	0
Mouth ulceration	40	3
Dry mouth	37	7
General Disorders and Administration Site conditions		
Fatigue	80	10
Asthenia	57	7
Edema peripheral	37	0
Chills	30	7
Thirst	20	0
Hepatobiliary Disorders		
Hyperbilirubinemia	33	0

Adverse Reaction	Any Grade (%) N=30	Grade 3 or Higher (%) N=30
Infections and Infestations		
Upper respiratory tract infection	40	7
Urinary tract infection	23	3
Sinusitis	20	10
Injury, Poisoning and Procedural Complications		
Contusion	37	0
Investigations		
Transaminases increased	63	7
Blood bicarbonate decreased	40	0
Low density lipoprotein increased	30	17
Metabolism and Nutrition Disorders		
Abnormal loss of weight	73	7
Hyponatremia	53	10
Hypoalbuminemia	43	3
Hypocalcemia	37	3
Decreased appetite	27	0
Hypomagnesemia	27	3
Hypercholesterolemia	23	0
Anorexia and bulimia syndrome	20	3
Appetite disorder	20	0
Musculoskeletal and Connective Tissue Disorders		
Myalgia	30	3
Muscle spasms	23	3
Musculoskeletal stiffness	23	0
Arthralgia	20	0
Nervous System Disorders		
Headache	63	10
Dizziness	50	7
Tremor	47	3
Disturbance in attention	37	3
Hypoesthesia	23	7
Psychiatric Disorders		
Insomnia	43	0
Depressed mood	27	3
Anxiety	23	10
Renal and Urinary Disorders		
Nocturia	27	10
Pollakiuria	27	3
Hypertonic bladder	20	3
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	53	7
Cough	40	0
Nasal congestion	30	0
Sinus disorder	30	0
Dysphonia	23	0
Dyspnea	23	3

Adverse Reaction	Any Grade (%) N=30	Grade 3 or Higher (%) N=30
Skin and Subcutaneous Tissue Disorders		
Acne	87	7
Onychoclasis	20	0
Pruritus	53	0
Rash	43	7
Dry skin	40	3
Vascular Disorders		
Hypertension	20	7

Less common adverse reactions (occurring in ≥10% but <20% of patients) observed between initial transplant and 1 year following final transplant include:

Blood and Lymphatic Disorders: increased bruising, lymphadenopathy, neutropenia

Eye disorders: eye pain

Gastrointestinal disorders: toothache

General disorders and administration site conditions: chest pain, feeling cold, feeling of body temperature change, influenza-like illness, mucosal inflammation, pyrexia

Infections and infestations: cytomegalovirus infection (including cytomegalovirus viremia), gastroenteritis (including viral), herpes zoster, nail infection, oral herpes, pneumonia, rhinitis, vaginal infection

Investigations: increased alanine transaminase, increased aspartate transaminase, increased blood alkaline phosphatase, decreased hemoglobin, weight increased

Metabolism and nutrition disorders: hyperchloremia, hyperkalemia, hypertriglyceridemia, hypokalemia, hypophosphatemia

Musculoskeletal and connective tissue disorders: musculoskeletal pain

Nervous system disorders: cognitive disorder, poor quality sleep

Psychiatric disorders: anhedonia, depression, decreased libido, nervousness

Renal and urinary disorders: urinary incontinence

Reproductive system and breast disorders: menorrhagia, irregular menstruation

Respiratory, thoracic, and mediastinal disorders: epistaxis, rhinorrhea, wheezing

Skin and subcutaneous disorders: alopecia, skin lesion

5.2.1.3. Deaths and Other Serious or Clinically Significant Adverse Events

There were no deaths from initial transplant to 1 year after last transplant in any patient administered donislecel. One patient from Study UIH-002 died approximately 20 months after receiving donislecel. An investigation of the death concluded that the patient died due to multi-organ failure secondary to an infection and that the event was probably related to immunosuppression. A second patient from Study UIH-002 died approximately 9 years after receiving donislecel. The death occurred following an SAE of confusional state (the patient

had previously been diagnosed with progressive dementia) that had occurred approximately 1 month prior to the death.

Individual SAEs identified during primary (from initial transplant through 1 year after last transplant) and long-term (any time after primary) follow-up are summarized in Table 33. A summary by system organ class (SOC) is provided in Table 31.

From initial transplant through 1 year after last transplant, most SAEs occurred only once and affected a single patient. Only anemia, pneumonia, hyponatremia, and nausea SAEs occurred more than once from initial transplant through 1 year after last transplant, and only anemia, pneumonia, and nausea SAEs affected more than 1 patient.

During long-term follow-up, most SAEs occurred only once and affected a single patient. Only fracture (various types combined for this analysis), hyponatremia, basal cell carcinoma, squamous cell carcinoma, myocardial ischemia, syncope, and peripheral artery stenosis occurred more than once; with the exception of peripheral artery stenosis, which occurred in 1 patient, all SAEs reported during long-term follow-up occurred in 2 patients each.

Most SAEs are typical of those observed with use of concomitant study medications, especially immunosuppressants, or of comorbid conditions (e.g., heart disease). Relatively few have plausible causation by the islets themselves or the transplant procedure.

One notable concern with long-term immunosuppression is the increased likelihood of developing cancer. While one instance each of papillary thyroid cancer, squamous cell carcinoma, and uterine leiomyoma appeared during primary follow-up, there were additional neoplasms and related disorders that emerged during long-term follow-up, including 2 additional cases of squamous cell carcinoma, 2 cases of basal cell carcinoma, and 1 case each of breast cancer, malignant melanoma, and post-transplant lymphoproliferative disorder. While cancers occur in the general population, it is likely that at least some of the cancers observed during the donislecel clinical program are a result of persistent immunosuppression.

Table 33. Serious Adverse Events Identified during Primary and Long-term Follow-up (Pooled Population)

Through 1 Year Post-Last Transplant			Long-term Follow-up		
Serious Adverse Event	**Events n (%)**	**Patients n (%) N=30**	**Serious Adverse Event**	**Events n (%)**	**Patients n (%) N=26**
Any SAE	37 (100)	16 (53.0)	Any SAE	42 (100)	17 (65.4)
Anemia	3 (8.1)	3 (10.0)	Hyponatraemia	4 (9.5)	2 (7.7)
Pneumonia	3 (8.1)	3 (10.0)	Basal Cell Carcinoma	2 (4.8)	2 (7.7)
Hyponatremia	2 (5.4)	1 (3.3)	Myocardial Ischaemia	2 (4.8)	2 (7.7)
Nausea	2 (5.4)	2 (6.7)	Squamous Cell Carcinoma of Skin	2 (4.8)	2 (7.7)
Abdominal Pain	1 (2.7)	1 (3.3)	Syncope	2 (4.8)	2 (7.7)
Asthenia	1 (2.7)	1 (3.3)	Peripheral Artery Stenosis	2 (4.8)	1 (3.8)
Blood Creatinine Increased	1 (2.7)	1 (3.3)	Abdominal Hernia	1 (2.4)	1 (3.8)
Chills	1 (2.7)	1 (3.3)	Acute Respiratory Failure	1 (2.4)	1 (3.8)
Cholecystitis	1 (2.7)	1 (3.3)	Breast Cancer	1 (2.4)	1 (3.8)
Colitis	1 (2.7)	1 (3.3)	Cervix Neoplasm	1 (2.4)	1 (3.8)
Cytomegalovirus	1 (2.7)	1 (3.3)	Confusional State	1 (2.4)	1 (3.8)
Dehydration	1 (2.7)	1 (3.3)	Coronary Artery Bypass	1 (2.4)	1 (3.8)
Exposure to Communicable Disease	1 (2.7)	1 (3.3)	Coronary Artery Disease	1 (2.4)	1 (3.8)
Hepatic Hematoma	1 (2.7)	1 (3.3)	Cytomegalovirus Infection	1 (2.4)	1 (3.8)
Hypoglycemia	1 (2.7)	1 (3.3)	Foot Fracture	1 (2.4)	1 (3.8)
Hysterectomy	1 (2.7)	1 (3.3)	Fracture	1 (2.4)	1 (3.8)
Intra-Abdominal Hemorrhage	1 (2.7)	1 (3.3)	Hip Fracture	1 (2.4)	1 (3.8)
Muscle Necrosis	1 (2.7)	1 (3.3)	Hypoglycaemia	1 (2.4)	1 (3.8)
Myalgia	1 (2.7)	1 (3.3)	Hypoglycaemia Unawareness	1 (2.4)	1 (3.8)
Myocardial ischemia	1 (2.7)	1 (3.3)	Intervertebral Disc Protrusion	1 (2.4)	1 (3.8)
Optic Neuritis	1 (2.7)	1 (3.3)	Left Ventricular Dysfunction	1 (2.4)	1 (3.8)
Oral Herpes	1 (2.7)	1 (3.3)	Lower Limb Fracture	1 (2.4)	1 (3.8)
Osteomyelitis	1 (2.7)	1 (3.3)	Malignant Melanoma	1 (2.4)	1 (3.8)
Ovarian Cyst Ruptured	1 (2.7)	1 (3.3)	Multi-organ Failure	1 (2.4)	1 (3.8)
Pancytopenia	1 (2.7)	1 (3.3)	Neutrophil Count Decreased	1 (2.4)	1 (3.8)
Papillary Thyroid Cancer	1 (2.7)	1 (3.3)	Pericardial Effusion	1 (2.4)	1 (3.8)
Procedural Complication	1 (2.7)	1 (3.3)	Pneumonia	1 (2.4)	1 (3.8)

Through 1 Year Post-Last Transplant			Long-term Follow-up		
Serious Adverse Event	**Events n (%)**	**Patients n (%) N=30**	**Serious Adverse Event**	**Events n (%)**	**Patients n (%) N=26**
Squamous Cell Carcinoma	1 (2.7)	1 (3.3)	Post-transplant Lymphoproliferative Disorder (PTLD)	1 (2.4)	1 (3.8)
Uterine leiomyoma	1 (2.7)	1 (3.3)	Rectocele	1 (2.4)	1 (3.8)
Viral pericarditis	1 (2.7)	1 (3.3)	Serotonin Syndrome	1 (2.4)	1 (3.8)
Vomiting	1 (2.7)	1 (3.3)	Squamous Cell Carcinoma	1 (2.4)	1 (3.8)
			Subdural Hemorrhage	1 (2.4)	1 (3.8)
			Urosepsis	1 (2.4)	1 (3.8)
			Vomiting	1 (2.4)	1 (3.8)

Note: Long-term follow-up means after the primary follow-up period from initial transplant through 1 year after the last transplant.

5.2.2. Clinical Laboratory Evaluations

Potentially clinically significant (PCS) laboratory values from initial transplant through 1 year after a patient's last transplant were generally consistent between Studies UIH-001 and UIH-002 (Table 34).

These excursions from the normal range were expected given the known effects of the concomitant medications used in these studies (especially long-term immunosuppression).

For Study UIH-001, the most common clinical laboratory-related PCS events (≥20% of patients) during primary follow-up were related to microalbumin/creatinine ratio, red blood cells, hemoglobin, albumin in 24-hour urine, AST, creatinine, and sodium.

For Study UIH-002, the most common clinical laboratory-related PCS events (≥20% of patients) during primary follow-up were related to microalbumin/creatinine ratio, AST, red blood cells, and PRA class I.

Table 34. Number of PCS Events and Patients with PCS Laboratory Values, by Parameter through Primary Follow-up (1 Year after Last Transplant)

	Primary Follow-up			
	UIH-001 (N=10)		UIH-002 (N=21)	
Laboratory Parameter	Events	Patients, n (%)	Events	Patients, n (%)
Any PCS Laboratory Value	100	9 (90)	130	19 (91)
Alanine Transaminase	1	1 (10)	10	3 (14)
Albumin in 24-hour urine	4	3 (30)	–	–
Amylase	1	1 (10)	3	1 (5)
Aspartate Transaminase	4	2 (20)	12	6 (29)
Calcium	1	1 (10)	–	–
Creatinine	14	2 (20)	5	2 (10)
Hemoglobin	8	3 (30)	7	3 (14)
Potassium	1	1 (10)	5	4 (19)
Microalbumin/Creatinine Ratio	38	6 (60)	31	7 (33)
Sodium	13	2 (20)	12	3 (14)
Panel Reactive Antibodies Class I	3	1 (10)	10	5 (24)
Panel Reactive Antibodies Class II	–	–	20	4 (19)
Platelets	2	2 (20)	4	3 (14)
Red Blood Cells	10	4 (40)	8	6 (29)
Total Bilirubin	–	–	1	1 (5)
White Blood Cells, Total Count	–	–	2	1 (5)

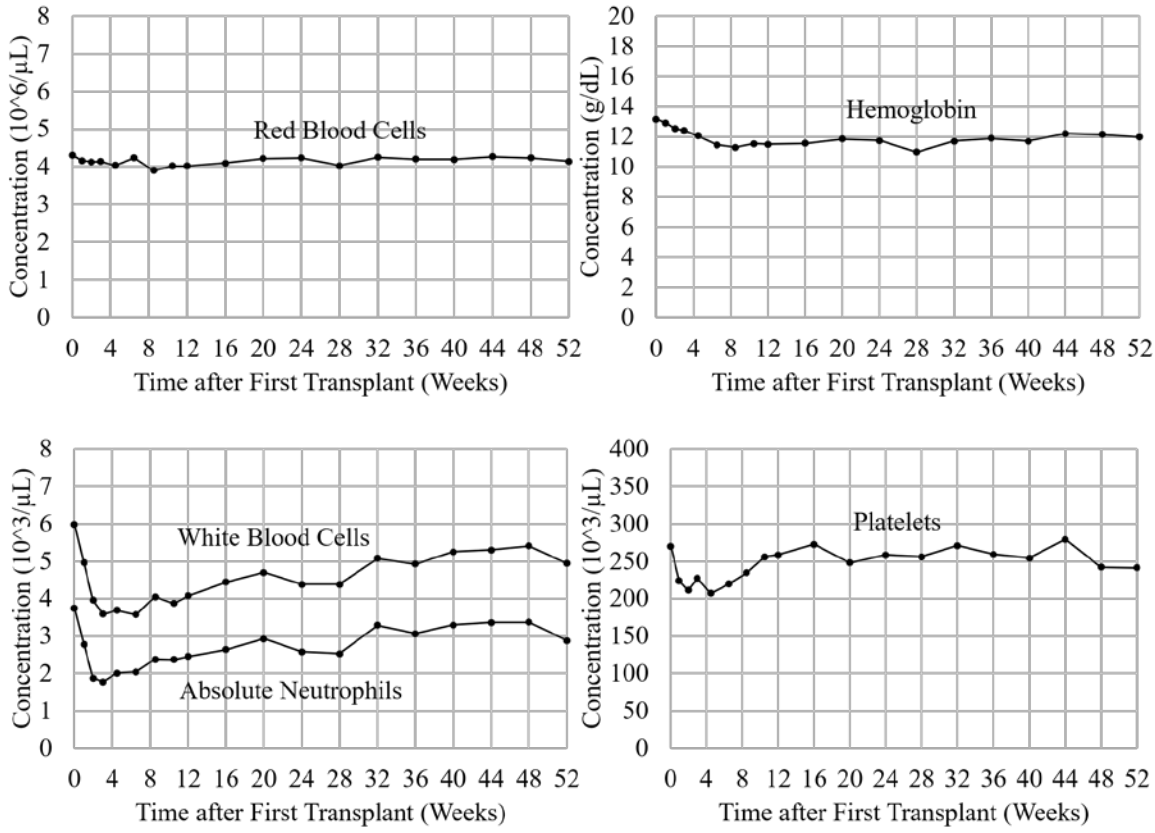
5.2.2.1. Hematology

Among Pooled Population patients, red blood cells, hemoglobin, and platelets were generally stable from initial transplant through 1 year following last transplant, while leukocyte counts tended to drop from baseline levels following transplant and gradually increase toward baseline over time (Figure 2). These results are important because of the prevalence of anemia, leukopenia, and neutropenia in donislecel-treated patients (>10%), patients from other islet transplant centers [20, 62, 63], and individuals receiving immunosuppression (based upon the

product labels for these medications). While thrombocytopenia was rare in donislecel-treated patients (n=2 events), it is a common adverse reaction in individuals administered immunosuppressants and anti-infectives [64-69].

Notably, most leukopenia (80%; 12/15 events) and neutropenia (58%; 7/12 events) adverse events during total follow-up in Pooled Population patients occurred within 1 month following a transplant. By comparison, while anemia was common in the month following a transplant, these cases accounted for a minority (33%; 30/90 events) of the total anemia adverse events reported during follow-up.

Figure 16. Mean Red Blood Cell, Hemoglobin, White Blood Cell, Absolute Neutrophil, and Platelet Levels from Baseline through 1 Year after First Transplant (Pooled Population)



Normal ranges: absolute neutrophils = 1.8-7.7×10^3/µL, hemoglobin = 11.7-16.0 g/dL (female) and 13.2-18 g/dL (male), platelets = 150-450×10^3/µL, red blood cells = 3.8-5.4×10^6/µL, white blood cells = 3.9-12×10^3/µL.

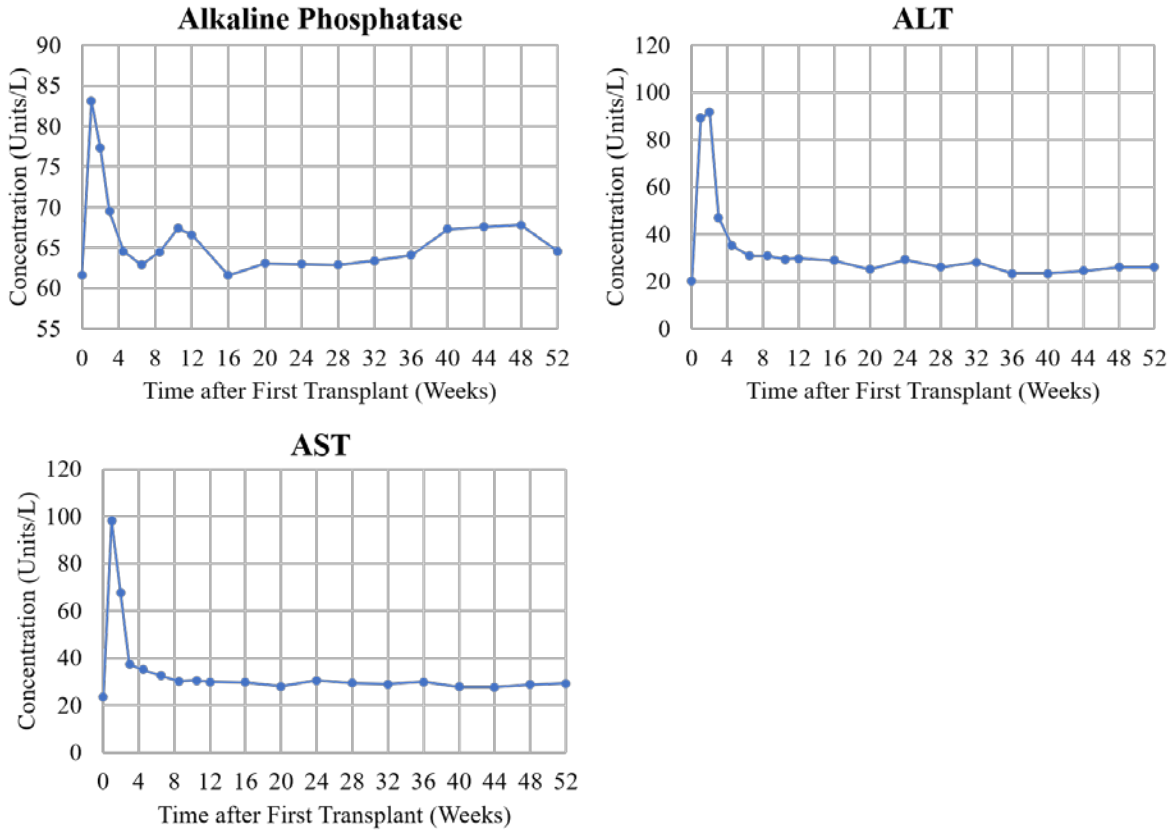
5.2.2.2. Liver Function

Liver function parameters, including plasma concentrations of ALT, AST, total bilirubin, alkaline phosphatase, and albumin, were generally stable at most timepoints from initial transplant through 1 year following last transplant. However, alkaline phosphatase, ALT, and AST levels all experienced transient spikes shortly after transplant before returning to near-baseline levels over time (Figure 17). These spikes generally resolved within 4-6 weeks without sequelae. Such increases are common following islet transplantation and have been reported in

the literature for more than 2 decades [70, 71]. According to the CITR 10th Annual Report, hepatic enzyme abnormalities were among the most commonly reported adverse events in islet recipients within the registry [20].

Across the Pooled Population, TEAEs related to abnormal hepatic enzymes that occurred at any time post-transplant included 32 events of increased transaminases (19 [63%] patients), 11 events of increased AST (8 [27%] patients), 6 events of increased ALT (5 [17%] patients), and 5 events of increased alkaline phosphatase (5 [17%] patients). None of these TEAEs were serious.

Figure 17. Mean Liver Enzyme Levels in the Blood from Baseline through 1 Year after First Transplant (Pooled Population)



ALT, alanine transaminase; AST, aspartate transaminase

5.2.2.3. Renal Function

Declining renal function is a natural progression of aging, a common comorbidity in T1D [72], and is commonly observed in islet transplant recipients [20] and in others receiving immunosuppression. Abnormal renal function and nephrotoxicity are common adverse reactions in patients treated with tacrolimus, and the combination of tacrolimus with sirolimus is associated with additional risk [64].

Renal function is graded by the National Kidney Foundation according to estimated glomerular filtration rate (eGFR), as follows:

- Normal to High: ≥90 mL/min/1.73 m^2
- Mildly decreased: 60-89 mL/min/1.73 m^2
- Mildly to Moderately decreased: 45-59 mL/min/1.73 m^2
- Moderately to Severely decreased: 30-44mL/min/1.73 m^2
- Severely decreased: 15-29 mL/min/1.73 m^2
- Kidney failure: <15 mL/min/1.73 m^2

In a 2011 report by Thompson et al. (prospective, crossover; [61]), the authors found that the rate of decline in GFR is more rapid for T1D patients while on insulin therapy than after the patients had received islet transplantation. Sixteen subjects had sufficient GFR measurements in both the insulin phase and post-islet transplant phases to allow an intraindividual comparison using a paired t test. The median (interquartile range) decline for patients while on insulin was -6.7 mL/min/1.73 m^2/year (-2.5 to -12.2 mL/ min/1.73 m^2/year) and for patients receiving islet transplantation was -1.3 mL/min/1.73 m^2/year (-4.1 to 0.1 mL/min/1.73 m^2/year) (P=0.01).

While no comparisons were made to an insulin-alone control group as part of the donislecel clinical trials, eGFR values were calculated at baseline and at prescribed timepoints following administration for patients receiving donislecel. At baseline (n=30), 69% of patients in the donislecel Pooled Population had mild or moderate renal impairment. At 1 year after last transplant, 52% of patients were in the same functional category as they were at baseline, 31% of patients had worsened to a lower functional category, 17% of patients had improved to a higher category (mean follow-up was 2.3±1.8 years). There were no cases of severe renal impairment or renal failure.

A summary of eGFR data from baseline and 1 year after last transplant, including change from baseline and change from baseline per year, is provided in Table 36. Median eGFR reduction from baseline was -3.7 mL/min/1.73 m^2/year.

Table 35. Renal Function Category at Baseline and 1 Year after Last Transplant (Pooled Population)

	Patients in Category N (%)		Category at 1 Year after Last Transplant Relative to Baseline		
Renal Function	**Baseline**	**1 Year after Last Transplant**	**Improved**	**No Change**	**Worsened**
Normal or High	9	10	–	7	2
Mildly Decreased	14	8	3	5	6
Mildly to Moderately Decreased	4	9	1	2	1
Moderately to Severely Decreased	2	2	1	1	0
Severely Decreased	0	0	0	0	0
Kidney Failure	0	0	0	0	0

Table 36. Estimated Glomerular Filtration Rate at Baseline and 1 Year after Last Transplant and Change from Baseline (Pooled Population)

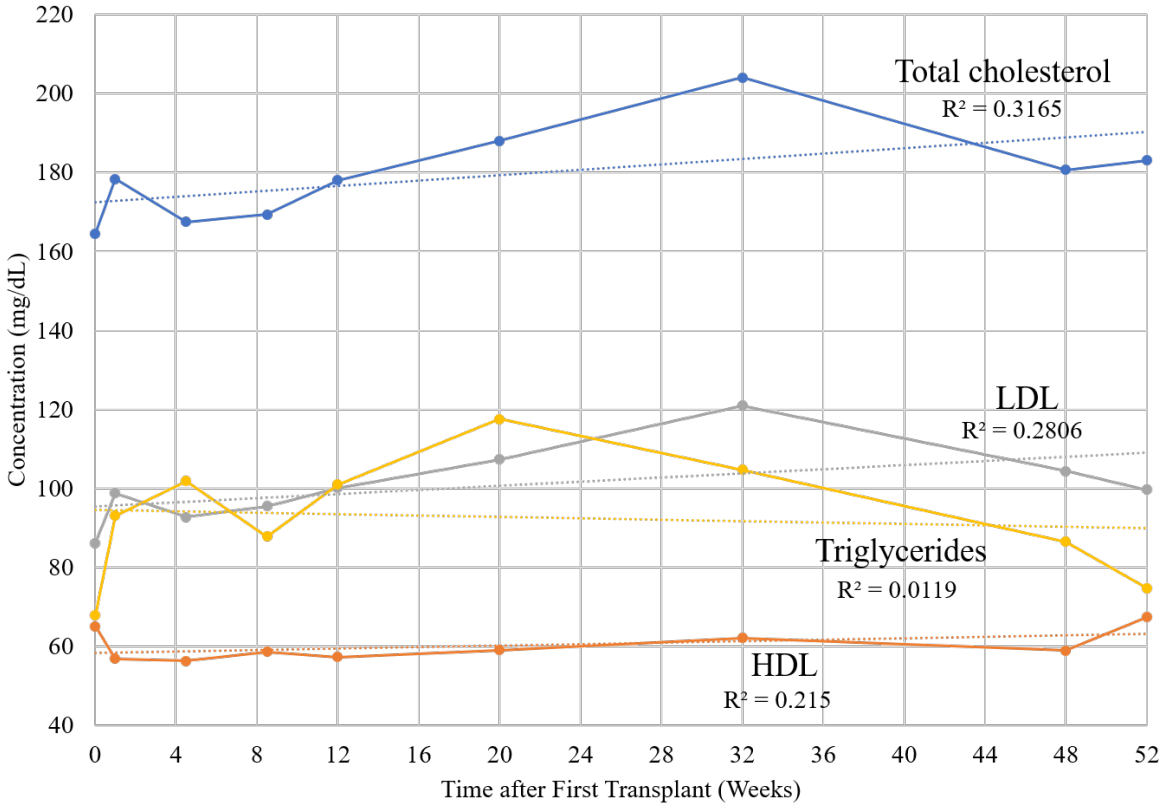
Statistic	Baseline	1 Year after Last Transplant	Change from Baseline	Change from Baseline per Year
eGFR (mL/min/1.73m^2)				
N	29	29	29	29
Mean±SD	84.7±25.75	78.9±30.20	-5.8±25.21	-3.9±19.14
Median (Min, Max)	81.6 (43.3, 144.0)	77.1 (35.1, 152.9)	-7.8 (-61.0, 42.1)	-3.7 (-61.0, 27.3)

eGRF, estimated glomerular filtration rate

5.2.2.4. Lipid Profile

Among Pooled Population patients, there was an increase in total cholesterol and low-density lipoprotein (LDL) over time, HDL levels were stable albeit marginally lower than at baseline at most time points post-transplant, and triglyceride levels were generally elevated but gradually returning to normal levels by 1 year after initial transplant (Figure 18).

Figure 18. Mean Blood Lipid Levels from Baseline through 1 Year after First Transplant (Pooled Population)



Note: Plots only include data from timepoints at which at least 6 patients (~20%) were assessed.
HDL, high-density lipoprotein; LDL, low-density lipoprotein

5.2.3. Vital Signs and Physical Findings

5.2.3.1. Periprocedural Portal Pressure

Transient increased portal venous pressure is a risk factor during islet transplantation, and larger packed tissue volumes [53] and elevated infusion rates can increase this risk. For this reason, recommended limits on infusion rate and packed tissue volume, as well as recommendations for periprocedural monitoring, should be followed.

As part of the islet transplantation protocol, periprocedural portal pressure measurements were monitored to ensure that portal pressures did not rise above 22 mmHg. If they did, infusions were to be paused and not resumed until portal pressure fell below 18 mmHg. If portal pressure remained above 22 mmHg for more than 10 minutes, the infusion procedure was to be terminated. The increase in median periprocedural portal blood pressure from baseline was 3 mmHg (range -3 to 18 mmHg; Table 37). Infusion was terminated in 1 patient due to elevated portal pressure.

Table 37. Periprocedural Portal Pressure (Pooled Population; N=30, 56 Transplants)

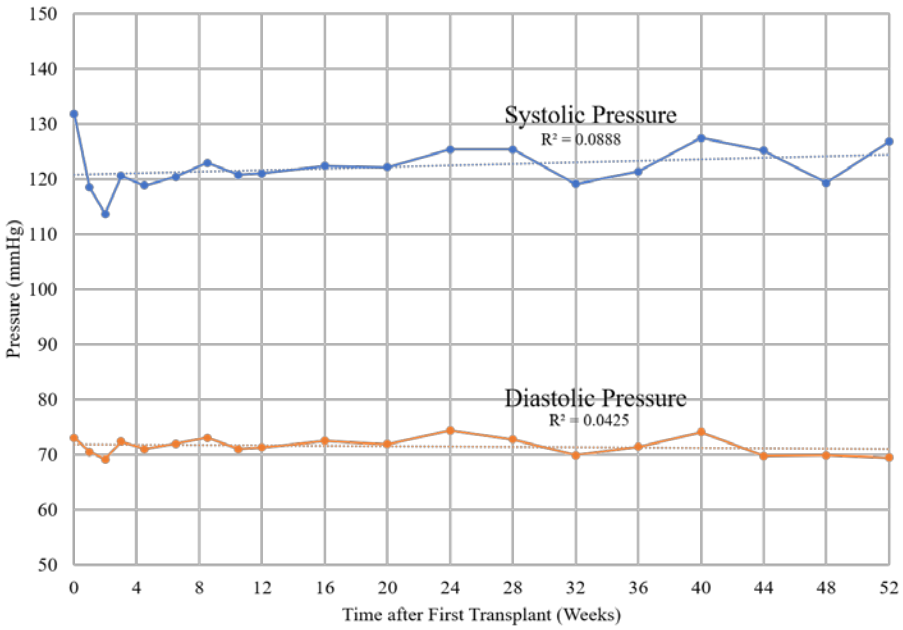
	Periportal Pressure (mmHg)		
Parameter	**Median**	**Min**	**Max**
Baseline	8	4	19
Peak	11.5	4	29
End of Procedure	11	2	29
Change from Baseline at Peak Pressure	3	–3	18
Change from Baseline at End of Procedure	3	–4.5	18

5.2.3.2. Blood Pressure, Heart Rate, and Body Temperature

Systolic blood pressure, diastolic blood pressure, heart rate, and temperature were generally stable during the period from initial transplant through 1 year following last transplant in the Pooled Population.

Because hypertension is a concern for patients with T1D and is a significant adverse reaction in patients on immunosuppression, a longitudinal assessment of blood pressure is provided in Figure 19. For the Pooled Population at baseline (n=30), mean systolic blood pressure was 131.9 mmHg (median 132.0 mmHg, range 106-162 mmHg) and mean diastolic blood pressure was 73.1 mmHg (median 71.5 mmHg (range 48-109 mmHg). At 52 weeks post-first transplant (n=13), mean systolic blood pressure was 126.8 mmHg (median 123.0 mmHg, range 112-159 mmHg) and mean diastolic blood pressure was 69.5 mmHg (median 71.0 mmHg, range 57-90 mmHg).

Figure 19. Mean Blood Pressure from Baseline through 1 Year after First Transplant (Pooled Population)



5.2.3.3. Electrocardiogram

Most patients did not experience clinically significant electrocardiogram deterioration from baseline (Table 38), and there were few cardiovascular adverse events reported during follow-up. Cardiovascular effects may be related to immunosuppressant medications, which are known to cause abnormal electrocardiogram readings (e.g., the PROGRAF [tacrolimus] product label indicates a >3% but <15% incidence each of: abnormal electrocardiogram, electrocardiogram QRS complex abnormal, and electrocardiogram ST segment abnormal, as well as a number of other cardiovascular-related adverse events; [64]). Abnormal cardiovascular observations could also be due to other underlying medical conditions.

Table 38. Electrocardiogram – Worsening from Baseline to 1 Year Post Last Transplant, by Transplant Number (Pooled Population)

	Total Worsened; n/N (%) [a]	
	Week 20 [b]	**Week 52 [b]**
Transplant 1	1/17 (5.9)	1/9 (11.1)
Transplant 2	2/15 (13.3)	3/7 (42.9)
Transplant 3	0/5 (0)	0/2 (0)
	Total Worsened	3/23 (13.0)

[a] Worsening is defined as a change from a rating of "normal" or "abnormal not clinically significant" on both of the pre-transplant assessments to "abnormal clinically significant" at the time of assessment.

[b] Relative to last transplant

5.2.4. Immunogenicity

Alloimmunization is an immune response to foreign antigens after exposure to genetically different cells or tissues. Human leukocyte antigen (HLA) sensitization following islet transplantation can pose a barrier to future transplantation (either islet or whole organ).

Based upon CITR data and independent reports published by other transplant centers, evidence of alloimmunization is common following islet transplantation. In most studies, despite low levels of preformed antibodies, approximately 30-70% of islet transplant recipients developed post-transplant alloantibodies [73-76].

The presence of anti-HLA antibodies pre-transplant has been associated with worse islet graft functional outcomes in some studies, while showing no negative effect in others. The development of de novo anti-HLA antibodies post-transplant has also been associated with islet graft failure, although some islet transplant recipients who develop panel-reactive antibodies (PRA) may continue to have well-functioning islet grafts. Regardless of the mechanism of islet graft deterioration, patients who discontinue immunosuppressive drugs following complete or partial islet graft loss seem to be at high risk for HLA sensitization.

HLA sensitization in islet transplant patients is generally reported as percent PRA against class I HLA. PRA provides the percent of cells that were either killed by a patient's serum or the percent of cells that showed binding of immunoglobulins to HLA proteins.

In a 2012 publication based on CITR data (n=303), a transition from PRA <20% at baseline to ≥20% post-transplant was observed in approximately 17% (42/254) of patients for whom adequate data were available [77]. Multiple islet infusions did not increase the risk of developing class I PRA ≥20% when compared to single infusion.

Historical data are congruent with data from the donislecel development program. Among Pooled Population patients, 6/28 (21%) patients transitioned from PRA (either Class I, Class II, or both) <20% at baseline to ≥20% following transplant (Table 39). Receiving multiple islet infusions did not increase the likelihood of developing Class I PRA ≥20% when compared to single infusion (in agreement with CITR; [77]). Two out of the 3 (67%) patients who transitioned from Class II PRA <20% at baseline to ≥20% post-transplant did so only after receiving more than one transplant (second infusion in both cases) (Class II PRA was not examined within CITR, so comparison for this class is not possible.).

Importantly, the development of post-transplant PRA ≥20% did not seem to affect islet graft function, as 5/6 (83%) patients who transitioned from PRA <20% at baseline to ≥20% post-transplant were successful for the composite efficacy endpoint of HbA1c ≤6.5% and free of SHEs at 1 year post-last transplant. These results are congruent with results from CITR [77].

Table 39. Transition from Baseline PRA <20% to ≥20% for Studies UIH-001 and UIH-002 by the Total Number of Transplants Received

Total Transplants Received	PRA Class	Transition to PRA ≥20%, N/N (%)
Overall	Any	6/28 (21)
	Class I	4/28 (14)
	Class II	3/28 (11)
1	Any	1/9 (11)
	Class I	1/9 (11)
	Class II	1/9 (11)
2	Any	3/12 (25) [a]
	Class I	1/12 (8) [a]
	Class II	2/12 (17) [a]
3	Any	2/7 (29) [b]
	Class I	2/7 (29) [b]
	Class II	0

Note: Total population is 28 patients instead of 30 because 1 patient withdrew from Study UIH-002 prior to assessment and another had Class I PRA ≥20% at baseline.

a Patients receiving 2 (total) transplants who transitioned from PRA <20% to ≥20% did so after first transplant.

b Patients receiving 3 (total) transplants who transitioned from PRA <20% to ≥20% did so after third transplant.

In addition to testing alloimmunity via PRA, autoimmunity was also assessed by measuring antibodies against islet antigens or insulin. These antibodies are associated with development of T1D and were used to determine the baseline immunity profile and to dissect the role of immune-mediated reactions in islet allograft loss if graft loss occurred. Immunological assessments were made for antibodies against the following:

- Islet cell
- GAD65
- IA2
- Insulin

Results from these assessments are summarized in Table 40. At a population level, islet transplantation did not increase the level of autoantibodies from baseline to 48 weeks after last transplant.

Table 40. Islet Cell, GAD65, IA2, and Insulin Antibodies at Baseline and Week 48 after Last Transplant – Pooled Population

	Islet Cell	GAD65	IA2	Insulin
Baseline				
n	23	26	25	21
Mean (SD); %	NC	48 (78.5)	1.0 (0.49)	16.5 (19.2)
Median (Min, Max); units	<1:4 (<1:4, 1:256) [titer]	5 (1, 250)	0.8 (0.8, 2.8)	5.6 (0.4, 50.0)
BLQ, n	19 (<0.4)	6 (<1), 7 (<5)	19 (<0.8)	2 (<0.4), 1 (<1)
ALQ, n	0	2 (>250)	0	4 (>50)
Week 48				
n	28	28	29	25
Mean (SD); %	NC	43 (72.7)	0.9 (0.32)	6.1 (11.0)
Median (Min, Max); units	<1:4 (<1:4, 1:32) [titer]	5 (1, 250)	0.8 (0.8, 2.1)	1.0 (0.4, 50.0)
BLQ, n	25 (<1:4)	2 (<1), 9 (<5)	20 (<0.8)	10 (<0.4), 2 (<1)
ALQ, n	0	2 (>250)	0	1 (>50)

Note: For all antibody categories, values below and above the limit of quantification for the assay were set to those limits to allow calculation of summary statistics. Limits are indicated in the table.

ALQ = Above the limit of quantification; BLQ = Below the limit of quantification; SD = standard deviation

5.2.5. Effect of Intrinsic Factors on Safety

Subgroup analysis for safety outcomes was performed by patient age and patient sex. Given the relative ethnic and racial homogeneity of the population (predominantly white and non-Hispanic), subgroup analysis by race or ethnicity is of no utility.

A summary of TEAEs during the primary follow-up period (i.e., from initial transplant through 1 year after last transplant) is provided by patient age and sex in Table 41.

Table 41. Summary of Treatment-Emergent Adverse Events from Initial Transplant to One Year after Last Transplant by Age and Sex (Pooled Population)

	Patient Age at First Transplant Events, n Patients, n (%)		Sex Events, n Patients, n (%)	
Category	**≤47 Years (N=18)**	**>47 Years (N=12)**	**Female (N=24)**	**Male (N=6)**
TEAEs	695	722	1086	331
	18 (100)	12 (100)	24 (100)	6 (100)
Serious TEAEs	17	21	30	8
	9 (50)	7 (58.3)	12 (50)	4 (66.7)
TEAEs leading to discontinuation	0	0	0	0
TEAEs with an outcome of death	0	0	0	0
TEAEs related to treatment	515	601	832	284
	18 (100)	12 (100)	24 (100)	6 (100)
TEAEs rated Grade 3 or greater	95	90	151	34
	15 (83.3)	10 (83.3)	20 (83.3)	5 (83.3)

AE = adverse event; TEAE = treatment-emergent adverse event

5.2.5.1. Patient Age

TEAEs were more frequent in older patients (>47 years), and SAEs occurred in a slightly greater percentage of older patients, while there was no age difference in the frequency of Grade 3 or greater TEAEs. In both age groups, most TEAEs and Grade ≥3 TEAEs reported during the first year after initial transplant occurred within the first 3 months post-transplant, while more SAEs occurred after the initial 3-month period post-transplant and likely reflect effects of long-term immunosuppression. In general, older patients experienced a higher rate of certain blood and lymphatic disorders, blood chemistry disorders, and infections than did younger patients. Most other TEAE categories were observed at similar rates regardless of age group.

Renal function, as measured by eGFR, was lower in older patients (>47 years) than in younger patients (≤47 years) both at baseline and at later time points, as expected given the natural decline in renal function with advancing age. Renal function declined between baseline and later time points in both groups, but more so in the older group. There were no clinically meaningful age-related differences in other laboratory parameters.

Older patients (>47 years) tended to have higher mean systolic blood pressure than younger patients (≤47 years), both at baseline and at later timepoints, although diastolic pressure was slightly higher in younger patients at most timepoints. Other vital signs were generally similar between groups and did not show clinically meaningful age-related differences that would be relevant to the safety analysis.

5.2.5.2. Patient Sex

There were considerably more females (24/30; 80%) than males in the donislecel Pooled Population. The low number of males makes determining significant sex-related differences challenging. TEAEs were more frequent in males, but there was no difference between males and females in the frequency of SAEs or Grade ≥3TEAEs. In both groups, most TEAEs and Grade ≥3TEAEs reported during the first year after initial transplant occurred within the first 3

months post-transplant, while more SAEs occurred after the initial 3-month period post-transplant. A higher percentage of women experienced infections than men (88% vs. 50%), while most other TEAE categories were observed at similar rates regardless of patient sex.

Baseline renal function tended to be higher in males (106 mL/min/1.73m^2) than females (79 mL/min/1.73m^2), although some of this difference could be due to the limited number of males in these studies. Renal function declined over time in both groups. There were no discernible, clinically meaningful sex-related differences in other laboratory parameters.

No substantial sex-related differences were apparent for any vital sign parameters, although blood pressure tended to be slightly higher in males.

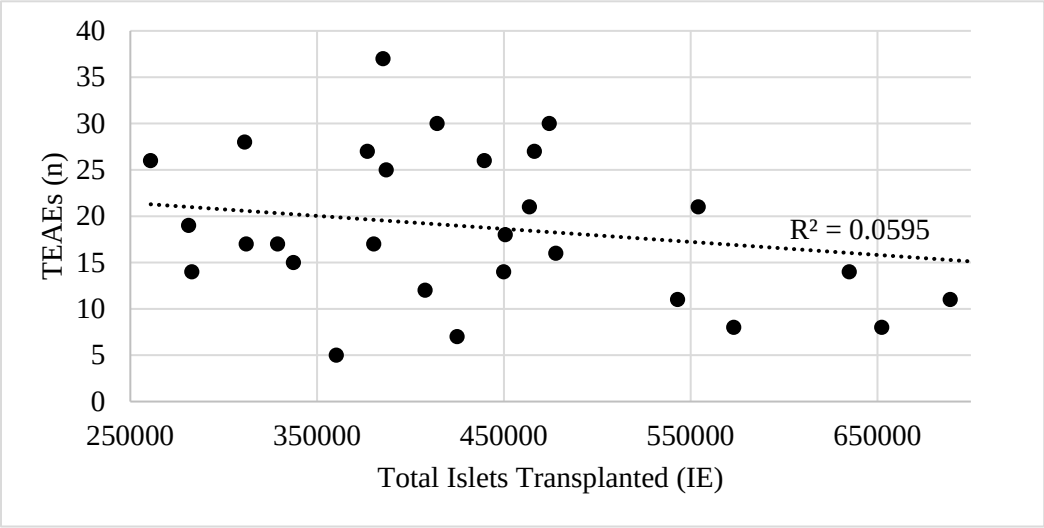
5.2.6. Exposure-Safety Relationships

Patient exposure (i.e., islet dose) to donislecel is summarized in Section 5.1 for the Pooled Population. Figure 20 plots the number of TEAEs occurring within the first month after transplant (first transplant only) by the total number of islets received (i.e., the islet dose). This 30-day window was chosen because most TEAEs related to the islet transplant procedure or the islets themselves should occur within that time. TEAEs after that are more likely to be due to concomitant medication use or underlying conditions. Additionally, only the first transplant was used to prevent confounding due to the effects of multiple transplants and/or long-term immunosuppression. Based upon these results, there was no distinguishable relationship between islet number and the number of TEAEs.

The incidence of TEAEs was similar for Pooled Population patients who had 1, 2, or 3 total islet transplants. For procedure-associated injuries and complications, there was no obvious relationship to the total number of islet transplants received. However, because there were so few procedure-associated TEAEs overall (n=6), firm conclusions are difficult.

Because so few patients experienced SAEs during the first 30 days post-first transplant, no relationship between islet number and the number of SAEs was observable.

Figure 20. Relationship of Islet Dose to the Number of Treatment-Emergent Adverse Events from First Transplant to 30 Days after the First Transplant (Pooled Population)



Note: 1 patient who received their second transplant <1 month after their first transplant is not included in this display.

5.3. Safety Comparison to Historical Controls

For nearly every AE category, islet transplantation carries a higher risk potential than insulin therapy, which is not unexpected. However, the risk due to the islets or to the transplant procedure appears to be minimal and includes the potential for alloimmunization and procedure-related bleeding events. Most AEs following islet transplantation are a consequence of concomitant medications, especially immunosuppressants. Importantly, each of these drugs is approved for use in transplant procedures, and each has an acceptable benefit-risk relationship for this purpose. In addition to the influence of concomitant medications on the safety profile of the CellTrans product, it is also likely that underlying disease, whether complications from long-standing brittle T1D or a comorbid disease or condition, is responsible for some observed AEs.

Safety outcomes and risks from the donislecel development program are mostly similar to those observed for other islet transplant centers, including the composite data from CITR [20]. Where these outcomes and risks diverge may be a result of differences in follow-up duration, treatment regimens, infusion techniques, sample size, or other variables.

Because the donislecel safety profile reflects, in large measure, the safety profile of the medications used to maintain the islet graft over time (i.e., immunosuppressants), a summary of known adverse reactions to common immunosuppressants is provided as an appendix to this briefing document in Section 9.4.

6. MEASURES TO REDUCE OR MANAGE ADVERSE EVENTS POST-APPROVAL

Measures to reduce or manage adverse events post-approval are summarized in Table 42.

Table 42. Summary of Risk Management Processes following Approval

Element	Action
Site and prescriber onboarding	Safety training and site certification (in person and/or web-based training conducted by CellTrans) • Donislecel prescribing information • Safety management and risk minimization strategies • Process and patient management
Ongoing site support and education	Training and educational materials provided to site Additional training related to the product, product administration, and aftercare, if requested Ongoing communication with sites for product-related updates Medical information hotline
Pharmacovigilance	Pharmacovigilance Plan submitted Patient Safety Database (CellTrans) – continuously updated; includes both active and passive surveillance Patient Registry – safety data submitted to CITR at least annually

CITR = Collaborative Islet Transplant Registry

Donislecel is only to be administered in an institutional setting (e.g., hospital, transplant center). All sites must be certified by CellTrans to administer donislecel. CellTrans will manage onboarding and training of sites to ensure safe use.

At product launch, donislecel will be available at a single transplant center, University of Illinois Hospital (part of UI Health). This center was the same one used for all islet transplants conducted under the donislecel clinical development program under Studies UIH-001, UIH-002, CIT-02, CIT-06, and CIT-07.

Once certification and training have been completed, the clinical site will be responsible for the following:

- Confirm a diagnosis of brittle type 1 diabetes in the patient.
- Confirm that the patient is medically fit to undergo the transplantation procedure and that the patient does not have any pre-existing conditions that would make long-term immunosuppression inappropriate.
- Ensure that appropriate premedication is provided prior to the transplant procedure.
- Ensure that donislecel is administered only by a qualified medical professional with adequate training and experience with islet transplantation.
- Ensure that appropriate post-infusion medications are administered and/or prescribed and that patients are adequately informed about the identity, purpose, and risks associated with these medications.
- Ensure that patients are instructed on self-monitoring (e.g., blood glucose, adverse reactions) and on the importance of immediately reporting adverse reactions.
- Ensure that up-to-date product labels for concomitant medications, including immunosuppression drugs, are available to the attending healthcare professional.
- Ensure that appropriate patient materials are available to the patient and that the patient is given an opportunity to discuss these materials with a qualified healthcare professional.

7. BENEFIT-RISK ASSESSMENT

7.1. Structured Benefit-Risk Assessment

Data from Studies UIH-001 and UIH-002, with supporting evidence from other clinical studies in which UIC/UI Health participated and a wealth of published literature and registry data, strongly support the clinical benefit of donislecel for the treatment of brittle T1D in adult patients (Table 43).

Table 43. Structured Benefit-Risk Assessment

Factor and Supporting Evidence	Conclusion and Reasons
Analysis of Condition • Brittle T1D is a rare indication. • Brittle T1D results from the autoimmune-mediated loss of insulin-producing β-cells within the pancreas and results in absolute insulin dependency in these patients. • Patients with brittle T1D experience unpredictable and debilitating hypoglycemia, often requiring hospitalization • Hypoglycemia unawareness is a hallmark of brittle T1D and can exacerbate the incidence of severe hypoglycemia. • Secondary complications can be especially common in brittle T1D and there is a significant excess mortality in these patients.	Brittle T1D is associated with severe and potentially life-threatening episodes of hypoglycemia, significant comorbidity, excess mortality, and a diminished quality of life.

Factor and Supporting Evidence	Conclusion and Reasons
Unmet Medical Need	
• Brittle T1D is currently treated by intensive insulin therapy, closed-loop insulin pump, or whole pancreas transplant. • Brittle T1D is often poorly managed with insulin therapy. • Whole pancreas transplant is considered curative but requires major surgery and involves significant procedural and post-procedural risk. • Whole pancreas transplant is not appropriate for all patients.	There are limited treatment options for patients with brittle T1D. A subgroup of patients with brittle T1D are not able to adequately manage their disease with insulin therapy, and pancreas transplant involves significant risk.
Clinical Benefit	
• Most patients administered donislecel exhibited improved HbA1c levels, reduced/eliminated occurrence of SHEs, insulin independence (or at least a lower insulin requirement), and improvements across a wide range of other glycemic assessments and parameters, including HYPO score, MMT (C-peptide levels and blood glucose levels), and fasting blood glucose levels. • Efficacy is durable in most patients following donislecel administration, with clinically meaningful improvements in glycemic control lasting several years at least. • Islet transplantation can slow the progression of secondary complications of diabetes. • Islet transplant recipients often experience an improved patient quality of life.	Donislecel demonstrates substantial clinical benefit via durable improvements in glycemic control in most patients, often coupled with insulin independence (or at least reduced insulin dependence). Islet transplantation also contributes to a reduction in secondary complications of diabetes and an improved patient quality of life.
Risks	
• Safety across the donislecel clinical program was consistent between studies. • Most TEAEs and SAEs were consistent with those observed for the concomitant medications used as part of the transplant or maintenance regimen, especially immunosuppressants. • The primary identified risk associated with donislecel itself is the potential for sensitization of the recipient to donor antigens, resulting in graft loss or difficulty obtaining future transplants. • Observed risks associated with the transplant procedure include bleeding, portal vein hypertension, and transient elevation of liver enzyme levels. • Important concomitant medication risks include but are not limited to blood cell disorders, blood chemistry disorders, cardiovascular disorders, gastrointestinal disorders, infections, neoplasms, and renal disorders.	The safety profile of donislecel and related allogeneic islet products is well characterized based on the donislecel clinical program and over 20 years of patient experience at other islet transplant centers around the U.S. and worldwide. Procedural risks are limited and manageable by appropriately trained healthcare providers. Long-term risks are consistent with extended use of immunosuppressants.
Risk Management	
• Careful donor selection by UNOS/OPO was done to reduce the risk of disease and malignancy transmission from donor to recipient. • Careful processing of islets and rigorous sterility testing during donislecel manufacturing was done to reduce the risk of microbial contamination. • Patient selection was done to ensure an appropriate benefit-risk profile. • Bleeding risk was managed by using hemostatic agents to seal the liver parenchymal tract following catheter removal and post-transplant monitoring using abdominal ultrasound and Doppler examination of the liver. • Adverse events were managed by monitoring islet recipients during and after transplant and providing appropriate supportive care as needed.	Risks will be minimized by: 1. Restricting administration to patients with brittle T1D whose diabetes is not well controlled with insulin and who do not have a concomitant disease or condition that contraindicates the use of immunosuppression 2. Adequate training of sites and physicians, including about risks associated with the transplant

Factor and Supporting Evidence	Conclusion and Reasons
• Certain infections and malignancies required reduction or discontinuation of immunosuppression, reintroduction (or increase) of exogenous insulin, and standard-of-care therapy for the infection or cancer.	procedure and immunosuppression and patient education (e.g., about risks and self-monitoring) 3. Product label will provide instructions for infusion, including pre-medication and post-infusion medication regimens

7.2. Benefits

7.2.1. Overview

Insulin therapy can be inadequate to control symptoms in a subgroup of patients with severe brittle T1D, leaving them vulnerable to unpredictable and debilitating hypoglycemia and progressive secondary complications. Successful islet transplantation alleviates T1D patients of life-threatening hypoglycemia and psychosocially crippling glycemic lability. While the long-term durability of these responses is uncertain for a given patient, they persist for as long as some graft function is maintained. Even 15 years ago, partial function, as indicated by continued C-peptide production, was present in as many as 80% of recipients after 5 years [78]. Furthermore, as long as graft function is maintained, fear of hypoglycemia and anxiety are significantly lower after islet transplantation [79]. This change in affect is justified, as T1D participants in the DCCT who had persistent C-peptide production had a significantly reduced risk of severe hypoglycemia despite intensive insulin therapy [80].

Success for islet transplantation may be measured by outcomes other than insulin independence, although this is the most common indicator of graft success in published clinical trials [81]. While some transplant recipients may experience only a temporary reprieve from exogenous insulin therapy, others have maintained insulin-independent graft function for several years. Improved strategies for promoting the engraftment or survival of transplanted islets have led to improved long-term graft function and furthered the duration of insulin independence after transplantation, including reductions in the secondary complications of T1D.

The benefits of clinical islet transplantation for the treatment of T1D are well documented in published literature [81] and include improved glycemic control and quality of life, as well as the potential to slow or reverse secondary diabetes complications.

7.2.2. Glycemic Control

The efficacy outcomes of patients receiving donislecel as part of the donislecel development program provide strong support for the benefits of islet therapy. These findings are supported by results from multiple islet transplant centers and aggregated data analyzed by CITR [20]. Based upon these results, islet transplantation is often superior to insulin therapy for improving glycemic control. This is especially important in patients with brittle T1D, precisely because state-of-the-art insulin therapy has consistently failed to control the symptoms and secondary complications of their T1D.

While full graft function leading to good glycemic control without the need for exogenous insulin is the optimal outcome for islet transplantation, even partial graft function can lead to

insulin dose reductions for brittle T1D patients, relief from the hypoglycemic events and unawareness symptoms that they previously experienced, and stabilization and even reversal of some of the secondary complications of diabetes (Section 7.2.3) [16]. This represents improved glycemic control, even if patients are still insulin dependent.

For many patients who have received islet transplants as part of the donislecel clinical program (and similar products at other transplant centers), improvements in glycemic control, especially the reduction or elimination of SHEs and large swings in blood sugar, have afforded a much improved quality of life and the opportunity to participate in activities that had previously been impossible or severely limited for them (Section 7.2.4) [62, 81].

7.2.3. Progression of Secondary Complications and Comorbid Conditions

The benefits of islet transplantation should be considered not only regarding short- or long-term glycemic control, but also regarding the natural history of the complications of chronic diabetes. A recent (2019) review of published literature by Maffi et al. supports the conclusion that islet transplantation is effective at mitigating certain secondary complications of diabetes [11]. According to this review, islet-after-kidney long-term follow-up studies have shown improved clinical outcomes after the normalization of glycemic control following transplantation. These patients demonstrated longer survival, fewer cardiovascular events, better transplanted kidney function, and improvements in peripheral and central neuropathy when compared with patients with T1D who underwent kidney transplant alone.

Maffi et al. also highlighted that solitary islet transplantation has demonstrated several advantages in slowing the progression of complications from chronic diabetes. For retinopathy, a comparison between patients undergoing islet transplantation and those on a waiting list revealed that central retinal velocity blood flow improved significantly 1 year after islet transplantation. In addition, in a one-way crossover cohort study by Thompson et al. [61] comparing intensive insulin therapy to islet transplantation, participants who received islet transplantation showed no progression of retinopathy, while insulin-treated patients had significant progression regardless of baseline grading (mild/moderate/severe non-proliferative retinopathy, proliferative retinopathy).

In a study of brain impairment, chronic cerebrovascular disease, and cognitive decline, which are all characteristics of T1D, patients who received islet transplantation showed an improvement at 15 months post-transplant in cerebral morphology, metabolism, and hemostatic profile using magnetic resonance imaging, nuclear magnetic resonance spectroscopy, and enzyme-linked immunosorbent assay (ELISA)/electron microscopy, along with neuropsychological evaluation. In the same study, platelet activation and prothrombic factors reached near-normal values, leading to a reduced risk of hyper-coagulation when compared with patients on a waiting list for transplantation.

According to the Maffi et al. review [11], the role of islet transplantation in nephropathy remains controversial. In an earlier study from 2007 [82], Maffi et al. observed a decline in kidney function under tacrolimus and sirolimus only in patients suffering from mild nephropathy prior to islet transplantation. In a similar setting, an abnormal GFR and albuminuria at baseline have been reported as predictors of poorer kidney function. In the 2011 crossover study by Thompson et al., a more rapid decline of GFR was observed in insulin-treated patients than in islet recipients already affected by micro- or overt albuminuria [61].

In a study by UI Health (at the time UI Health was the sponsor of the donislecel IND), islet transplantation demonstrated a beneficial effect on reducing carotid intima-media thickness (CIMT), which is a hallmark of atherosclerosis [21]. There was a statistically significant decrease in common carotid artery IMT at 12 months (-0.058 mm; p = 0.006). Between 12 and 50 months after transplantation, a progression of common artery IMT was observed, on average 0.011 mm/year. However, at 50 months post-transplant, the combined CIMT score continued to be significantly reduced compared to pre-transplant levels, suggesting that islet transplantation may slow the progression of T1D-associated atherosclerosis.

7.2.4. Improved Patient Quality of Life

Quality of life was not formally assessed as part of the donislecel clinical program. Based on several reports in published literature, there is consensus that islet transplantation can improve health-related quality of life for patients with type 1 diabetes. In a literature review of over 1,300 sources, Health Quality Ontario summarized existing observational comparative studies and observational case series studies, including glycemic outcomes [81]. These studies examined both generic and diabetes-specific health-related quality of life measures, although different measurement tools were used. Importantly, the patient outcomes measured by these health-related quality of life tools may not be able to capture the full extent of the impact of islet transplantation.

Häggström et al. [83] surveyed 11 patients who had received islet transplants at Uppsala University Hospital about their fear of hypoglycemia, and used the 36-Item Short Form Health Survey and Swedish Hypoglycemic Fear Survey to investigate health-related quality of life. Authors also examined patients' social life situation in relation to their fear of hypoglycemia. While the results for health-related quality of life were lower than in the normal population, changes in fear of hypoglycemia suggested an improvement for the patients who had undergone islet transplantation. Patients felt they experienced improved control over their social situations. It was noted that, pre-transplantation, patients "struggled for control of social life situations," while post-transplantation, patients "regained power and control" of these situations.

Radosevich et al. [84] examined 41 patients with type 1 diabetes who were screened for islet transplant alone (ITA) with 27 patients who had undergone that procedure at the University of Minnesota. ITA was found to be related to reductions in behaviors adopted to avoid hypoglycemia ($P < 0.001$) and attenuation in concerns about hypoglycemic episodes ($P < 0.001$). Health status among the patients who had undergone ITA was also found to have improved, according to scores on the Euro Quality of Life scale ($P = 0.002$) and the Beck Depression Inventory scale ($P = 0.003$). Non-significant changes were found between groups for the 36-Item Short Form Health Survey and the Diabetes Distress Scale. The authors concluded that there are socio-emotional benefits related to ITA that may be independent of islet graft function.

D'Addio et al. [85] reported on results of the Profile of Mood States test in patients who had received islet transplantation versus those remaining on intensive insulin therapy. Significant improvements were found for the depression/dejection and confusion/bewilderment domains for islet recipients compared to patients receiving insulin therapy; non-significant results were found for the other domains such as tension/anxiety, anger/hostility, vigor/activity, and fatigue/inertia.

According to a 2005 report from Hafiz et al. at the University of Miami [62], following islet transplantation, most patients had been able to commence activities like vacationing, had become

less reliant on family assistance, and had started vigorous physical activities (e.g., hiking, sprinting, weightlifting, jogging) due to their improved metabolic control. Many of their patients claimed that the debilitating nature of their disease had prevented them from performing these activities pre-transplant. Psychological assessments and quality of life questionnaires on 20 of those patients showed that islet transplantation had a positive impact on quality of life.

7.3. Risks

7.3.1. Overview

Risks associated with allogeneic islet transplantation include those related to the islets themselves, to the transplant procedure, and to concomitant medication use, including long-term immunosuppression. An overview of risks is provided in Table 44.

Table 44. Summary of Important Identified Risks, Potential Risks, and Missing Information for Donislecel, the Transplant Procedure, and Key Concomitant Medications Needed to Maintain a Functional Islet Graft

Important Identified Risks	**Donislecel** Sensitization to donor antigens **Transplant Procedure** Bleeding Portal vein hypertension Transient elevation of liver enzyme levels **Concomitant Medications** Blood cell disorders Blood chemistry disorders Cardiovascular disorders Gastrointestinal disorders Infections Neoplasms and malignancies Renal and urinary disorders
Important Potential Risks	**Donislecel** Donor-derived disease transmission Microbial contamination of the islet product Portal vein thrombosis **Concomitant Medications** Developmental and reproductive toxicity
Important Missing Information	Safety in pediatric patients (donislecel is indicated for use in adults only) Safety in elderly patients Safety in patients with hepatic impairment or severe renal impairment Safety in patients with BMI above or below the normal range

Note: In addition to the missing information listed above, there is currently limited or missing information related to risks in pregnant or breast-feeding women and in patients with non-brittle T1D; however, these populations are not appropriate to receive donislecel due to the risks associated with immunosuppression. There is also limited experience with islet transplantation in non-White and Hispanic populations; however, given the mechanism of action of donislecel, it is not likely that these patients would experience increased risk relative to White and non-Hispanic patients from donislecel itself or the transplant procedure; however, concomitant medications will involve additional risks and should be considered before administering donislecel.

In patients administered donislecel, most adverse events were neither serious nor severe and did not result in sequelae. The same is true of many observed laboratory abnormalities. One example is elevations in liver enzymes (i.e., alkaline phosphatase, ALT, AST)—while common, elevations were transient and had no long-term impacts on patient safety. Therefore, the risks associated with these adverse events and abnormalities are low in most cases.

Based upon an extensive literature review by Health Quality Ontario [81] and additional assessments of both literature and registry data by CellTrans, the totality of evidence from the islet transplantation field supports a similar risk profile to that for donislecel. Like donislecel, most adverse events reported by other centers are not generally serious and do not lead to sequelae. Procedure-associated adverse events have been observed, but the use of hemostatic agents has minimized the occurrence of bleeding events, and the risks of other procedural complications (e.g., portal vein thrombosis) are low. Bleeding events were uncommon in the donislecel Pooled Population. Death related to the islet transplantation procedure is also very rare. There were 2 deaths reported in the donislecel Pooled Population, but neither was related to the procedure and both occurred long after donislecel administration (multi-organ failure due to an infection of unknown etiology and attributed to immunosuppression, and confusional state considered probably related to study drug).

Beyond procedural risk, nearly all other risks associated with islet transplantation are side effects of immunosuppressants and other concomitant medications. In many cases, the rates of specific adverse events are similar between islet transplant recipients and rates presented in the concomitant medication product labels. When observed rates are higher in islet recipients, this may reflect differences in the patient populations (i.e., each population will have its own underlying risk profile from underlying disease, comorbidities, additional medications used to treat these, and so forth), or may be due to other variables like medication dose or dose regimen. Differences in patients' drug tolerability can also lead to immunosuppression regimen changes between patients. This is important because withdrawal of immunosuppression regimens or alterations in immunosuppressive agents is a transition point where immunosuppression-related adverse events may occur.

Additional details about risks associated with transplanted allogeneic islets, the transplantation procedure, and immunosuppressant and anti-inflammatory concomitant medications, are provided in the following sections.

7.3.2. Donislecel

7.3.2.1. Transmission of Disease from Donor to Recipient

Any time that allogeneic tissues are transplanted, there is a risk of disease transmission from donor to recipient. To minimize this risk, selection of potential donors for islet isolation is performed according to stringent screening and testing guidelines. This includes a 2-step screening verification process, including an initial screen by the Organ Recovery Coordinator (a nurse) and a final screening by CellTrans using a Donor Risk Assessment Interview (DRAI) form or, if the organ is not obtained through an OPO, and alternative DRAI form with a checklist to identify any risk factors. The aim of this process is to avoid using any donor that might harbor transmissible viral disease or malignancy. A potential donor must have a favorable medical, sexual, and social history, and clear all standard laboratory tests for low risk of transmission of

donor disease. Donor families are questioned about high-risk lifestyle, and detailed medical history and donor blood samples are screened.

The routine administration of valganciclovir post-transplant may minimize the risk from certain viral pathogens, like CMV. CMV can either be transmitted with the transplant or a latent CMV infection already existing in the recipient can be reactivated under immunosuppression (most patients and indeed much of the world's population are CMV positive). Patients who are CMV naïve and receive islets from a CMV-positive donor are at highest risk for CMV infection. However, the risk of transmission of CMV disease from donor to recipient has been low in recipients of islet allografts, particularly in the most recent era with routine use of purified islet preparations. The fact that islet preparations are purified and are contaminated with only a low number of passenger lymphocytes may explain why the risk of CMV transmission from donor to recipient is much less in islet transplantation than in solid organ transplant grafts.

Epstein-Barr virus (EBV) transmission and post-transplant lymphoproliferative disorder (PTLD) are rarely reported in the recent era of clinical islet transplantation, suggesting that the risk of these complications is low.

There were no reports of EBV transmission in patients administered donislecel (there were 2 patients who had infectious mononucleosis, but both were >2 years after last transplant) and a single report of ocular PTLD (occurred approximately 10 years after last transplant, with full remission after treatment).

7.3.2.2. Microbial Contamination of Islet Preparations

To reduce the possibility of a contaminated final islet product, triple anti-microbial/fungal agent treatment of the incoming organ is performed as a standard operating procedure by CellTrans to decontaminate the pancreas prior to islet isolation. Additionally, the processed islets must fulfill stringent product release criteria, including Gram stain and endotoxin testing, before being released for transplantation. A sample of the drug product is also collected for microbial and fungal sterility testing. Due to the 6-hour shelf life of donislecel, the drug product is released for transplantation prior to the 14-day sterility result. In the event of a positive result (i.e., microbial contaminant detected), the medical team is immediately notified, and all regulatory notification requirements are completed. The microorganism is identified and reported, and an investigation is initiated. This process is standard practice in the islet field.

Sterility testing of the 56 donislecel batches from Studies UIH-001 and UIH-002 indicates that 54 out of 56 drug product batches produced were negative for microbial and fungal contaminants. No patient had an infection transmitted by the islet graft, and no donislecel recipient exhibited any signs of infection post-transplant. Furthermore, endotoxin levels in all these batches were all within defined parameters (≤5 EU/kg).

All manufacturing steps of the pancreatic tissue and isolated islets occur using aseptic technique in ISO 5 BSCs. Additionally, CellTrans has an extensive cleaning and Environmental Monitoring Program to help eliminate any potential contaminants.

7.3.2.3. Sensitization of the Recipient to Donor Antigens

As with any allogeneic transplant, the recipient may become sensitized against donor antigens. The available information suggests that there is a strong correlation between islet allograft failure

and a rise in anti-donor HLA sensitization as detected by PRA testing. Data on the development of cytotoxic antibodies against donor HLA antigens in islet allotransplant recipients with failing grafts have been communicated from several islet transplant centers [86-88]. Data from five participating centers in the current CIT consortium indicate that approximately 25% of the ITA recipients developed a PRA >20% while on maintenance immunosuppression. These results are comparable to those reported for recipients of kidney transplant with stable serum creatinine and on maintenance immunosuppression [89-91].

Among donislecel Pooled Population patients, 6/29 (21%) patients developed PRA ≥20% post-transplant. However, the development of post-transplant PRA ≥20% did not affect islet graft function substantially, as 5/6 (83%) patients who developed PRA ≥20% post-transplant were successful for the composite efficacy endpoint.

7.3.3. Transplantation Procedure

Islets are infused into the hepatic portal vein using a percutaneous transhepatic approach. Transhepatic portal vein catheterization has complications and morbidity similar to those associated with transhepatic cholangiography and percutaneous core needle biopsies of the liver. The most common morbidity of transhepatic portal vein catheterization (percutaneous approach) is abdominal or right shoulder tip referred pain. In addition, liver hemorrhage and intra-abdominal bleeding have been known to occur, as well as pneumothorax, hemothorax, gall bladder damage, and pleural effusion. If a percutaneous approach is used, ablative techniques are employed to reduce the risk of acute bleeding after catheter withdrawal. This procedure is usually carried out in interventional radiology using a combination of ultrasound and fluoroscopic guidance with administration of radio-opaque contrast media to assure proper localization of the infusion. Though the use of contrast media is minimized, some patients can develop local or systemic reactions to such products.

Based upon CITR data and independent published reports from other transplant centers, procedural complications associated with islet transplantation are uncommon, especially with the adoption of products to mitigate bleeding events (e.g., D-STAT®, Gelfoam® or similar products) used to seal the catheter tract [11, 20, 62, 92-94].

According to a 2019 review by Maffi and Secchi [11], no significant adverse events related to intraportal islet infusion have been observed in clinical studies. Ultrasonography combined with fluoroscopic guidance for portal puncture was associated with a low risk of hemorrhage (5%), which resolved spontaneously. Furthermore, partial portal thrombosis, another complication related to the post-infusion period, was observed in 3.7% of cases, with spontaneous recovery after medical treatment.

Bleeding events, portal hypertension, and portal vein thrombosis are among the most significant potential risks associated with the islet transplantation procedure. However, these events were uncommon or not observed in patients administered donislecel (bleeding occurred 6 times, portal hypertension resulting in termination of islet infusion occurred 1 time, and portal vein thrombosis did not occur).

7.3.3.1. Bleeding

Bleeding risk can be reduced by avoiding pre-transplant aspirin and the use of effective measures to seal the catheter tract in the liver [95]. When effective methods are used to seal the transhepatic portal catheter tract, bleeding can be avoided completely. At the University of Minnesota, no bleed-related complications occurred in 20 consecutive subjects when the catheter tract was sealed with combined coils and Gelfoam® (Pfizer, New York, NY) [96].

Bleeding events occurring in patients administered donislecel included 3 intra-abdominal hemorrhages (1 SAE), 2 hepatic hematomas (1 SAE), and 1 hemoperitoneum (1 SAE). During these studies, microfibrillar collagen paste was found to be effective and safe for liver track embolization to prevent bleeding after islet transplant and appeared superior to the use of a gelatin sponge [97].

7.3.3.2. Portal Hypertension

Elevation in portal pressure following intraportal islet transplantation is temporary in most instances. As part of the donislecel infusion protocol, periprocedural portal pressure measurements were monitored to ensure that portal pressures did not rise above 22 mmHg. If they did, infusions were to be paused and not resumed until portal pressure fell below 18 mmHg. If portal pressure remained above 22 mmHg for more than 10 minutes, the infusion procedure was to be terminated.

To reduce the risk of periprocedural portal hypertension in patients receiving donislecel, infusion flow rate is limited to 25 mL/kg/h and packed tissue volume is limited to 10 cc. In patients receiving donislecel, median portal pressure was 8 mmHg (range 4-19 mmHg) at baseline and 11.5 mmHg (range 4-29 mmHg) at peak. The increase in median periprocedural portal blood pressure from baseline was 3 mmHg (range -3 to 18 mmHg). Infusion was terminated in 1 patient due to elevated portal pressure. Persistent portal hypertension was not observed in any patient.

7.3.3.3. Portal Vein Thrombosis

There were no cases of portal vein thrombosis in patients receiving donislecel. However, portal vein thrombosis is still a potential risk. This is because transplanted islets release tissue factor and exhibit prothrombotic properties when infused to an intravascular site such as the portal vein [98]. The management of partial vein thrombosis includes anticoagulation therapy, which may lead to intra-abdominal hemorrhage requiring transfusion and surgical intervention [99]. A right upper quadrant ultrasound including Doppler examination of the portal vein is performed on islet transplant recipients on Days 1 and 7 post-transplant. Early diagnosis and prompt management of branch vein portal occlusion with systemic heparinization may prevent clot propagation. Repeated intraportal islet infusions are generally contraindicated in patients who have experienced prior portal thrombus.

According to a 2019 review by Maffi and Secchi [11], partial portal thrombosis was observed in 3.7% of cases from published literature, with spontaneous recovery after medical treatment. Providing therapeutic anticoagulation and limiting the packed tissue volume that a patient receives have been effective at reducing the risk of portal vein thrombosis [100].

In order to reduce the risk of portal vein thrombosis as much as possible, donislecel packed tissue volume is limited to no more than 10 cc.

7.3.3.4. Transient Elevation of Liver Enzymes Post-Transplant

Transient abnormalities in liver enzyme tests have been observed immediately following intraportal islet transplantation [70, 71]. Elevations of liver enzymes requiring prolongation of post-transplant hospitalization or admission are very rare [101]. Persistence of laboratory abnormalities indicative of liver dysfunction following islet transplantation is also a rare event, with abnormalities in liver function tests usually resolving within about 4 weeks [70].

These results are congruent with findings from patients receiving donislecel. While alkaline phosphatase, ALT, and AST levels spiked immediately following transplant, these abnormalities resolved quickly, with levels returning to near baseline within about 4-6 weeks.

Because liver enzyme elevation following islet transplantation is transient and there is no evidence of clinically significant, persistent liver dysfunction, sequelae, or detrimental effects on graft function, the clinical impact appears to be limited.

7.3.4. Concomitant Medications

Because an individual patient may tolerate some medications better than others, medication regimens may need to be tailored to patient needs. Concomitant medication risks will vary depending upon the medication regimen prescribed. Of special relevance to islet transplantation are the risks associated with long-term immunosuppression. While most immunosuppressants involve many of the same risks, there are differences that could impact patient safety. For a complete overview of important safety risks associated with concomitant medications, reference should be made to the full prescribing information of each respective product label.

Administration of all immunosuppressive and immunomodulatory therapies used to prevent rejection of transplanted tissues carry general risks of opportunistic infection and malignancy, including lymphoma and skin cancers. These agents are not recommended for nursing mothers, and it is recommended that women of childbearing potential use effective contraception before, during, and for an appropriate time following administration of these agents.

Important and commonly observed risks associated with immunosuppressant medications include but are not limited to:

- Blood cell disorders (Section 9.4.1)
- Blood chemistry disorders (Section 9.4.2)
- Cardiovascular disorders (Section 9.4.3)
- Gastrointestinal disorders (Section 9.4.4)
- Infections (Section 9.4.5)
- Neoplasms and malignancies (Section 9.4.6)
- Renal and urinary disorders (Section 9.4.7)

Nearly all the adverse events associated with the donislecel clinical program and with islet transplantation in general are also commonly observed with immunosuppressant medications outside of the context of islet transplantation. As such, these adverse events can reasonably be attributed to the use of these medications rather than to donislecel itself.

7.4. Benefit-Risk Conclusions

Insulin therapy is a safe and effective treatment for most patients with non-brittle T1D. In these patients, insulin therapy provides adequate glycemic control with low safety risk. While islet transplantation may be effective in this context, it would impose considerably more safety risk than insulin therapy and, in most cases, this risk would outweigh the potential benefits. One exception where the benefits may outweigh the risks in non-brittle T1D is in patients who have previously received a solid organ transplant (e.g., kidney). Since these patients will already be on immunosuppression and because the major safety risks of islet transplantation are due to the use of immunosuppressant medications, islet transplantation could be an option in these patients. Similarly, patients who will be receiving another solid organ transplant could simultaneously receive an islet transplant with little increase to overall safety risk.

In contrast to the benefit-risk profile of non-brittle T1D patients who are not already on immunosuppression, the profile for brittle T1D is very different. Brittle T1D is characterized by severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia that severely disrupt quality of life, often requiring assistance from a third party and frequent hospitalizations. Because patients with brittle T1D are unable to adequately control their blood sugar with intensive insulin therapy (the current standard of care) or with modern closed-loop insulin pumps and consequently suffer from serious disease-related complications, the negative consequences of simply maintaining standard-of-care treatment in these patients can be significant. As such, the amount of acceptable risk from an effective new therapy will be greater than it would be for a non-brittle T1D patient.

For those suffering from brittle T1D, islet transplantation fills a significant medical need, is effective at restoring good glycemic control in most patients, can slow or possibly reverse common secondary complications of T1D, improves patient quality of life, and poses an acceptable safety risk. The islet transplantation procedure is minimally invasive and generally safe and includes less procedural risk than whole pancreas transplantation. The primary risk from islet transplantation is related to concomitant medications, especially immunosuppressants.

The side effects associated with a steroid-free immunosuppression regimen are expected, although with education of transplant recipients and close follow-up, most AEs can be treated and made self-limiting [62]. Most patients find these AEs less debilitating when compared to severe hypoglycemic reactions, chronic complications, and unstable metabolic control. Patients also report improved quality of life following islet transplantation, including the ability to participate in life activities that were not possible pre-transplant [62, 81, 83-85]. These results are reflective of outcomes and observations across the islet transplantation field (Section 7.2.4).

In conclusion, the benefits of islet transplantation outweigh the risks in patients with brittle T1D based upon the totality of evidence from the donislecel clinical program and published literature, including the following factors:

- Islet transplantation is effective at restoring good glycemic control in most patients, and this beneficial effect persists for at least several years.
- Even with partial graft function, islet transplantation can lead to improved glycemic control, reduced reliance on exogenous insulin, and improved quality of life.
- Islet transplantation can slow or reverse many debilitating secondary complications and comorbidities of T1D (e.g., retinopathy, cognitive decline, atherosclerosis).

- Islet transplantation improves patient quality of life, allowing patients to perform activities that they could not do prior to receiving an islet transplant.
- The islet product and the islet transplantation procedure are generally safe. The islet transplantation procedure is minimally invasive, with lower procedural risk than whole pancreas transplantation.
- Most risks associated with islet transplant are associated with immunosuppressant drugs, which are already approved for use in transplant recipients based upon their own favorable benefit-risk profiles.
- Brittle T1D is a debilitating disease that is not well-managed with standard-of-care insulin therapy, and the risk of these patients remaining on an ineffective treatment is significant. While whole pancreas transplantation is an option in some of these patients, for others, the risks associated with an open surgical technique are too great.
- Information has been provided in the draft product label to optimize benefits and minimize risks, including instructions to medical personnel related to pre-infusion, peri-infusion, and post-infusion actions and recommendations for the prevention, monitoring, and mitigation of adverse outcomes and maximization of graft survival.
- A risk management plan has been prepared that describes key risk management strategies to maximize patient safety.
- More than 2 decades of experience across multiple islet transplantation centers in the United States and around the world demonstrate the safety and effectiveness of islet transplantation for patients with brittle T1D.

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9. APPENDICES

9.1. Islet Transplantation Procedure

IMPORTANT NOTES

- Donislecel is only to be administered by a qualified health professional.
- Donislecel is to be used as supplied and without further dilution.
- Perform all steps aseptically.
- Donislecel is recommended to be delivered through a 5 or 6 French sheath or catheter. The catheter length should be 65 cm or less. The sheath length should be 24 cm or greater. The internal diameter of the 5 or 6 French sheath or catheter should be 0.038 inches or greater.
- Infuse the contents of all infusion bags over approximately 30 minutes.
- The infusion rate should not exceed 25 mL/kg/h. The infusion rate should be reduced if the fluid load is not tolerated. The infusion should be discontinued in the event of an allergic reaction or if the patient develops a moderate to severe infusion reaction.
- Do not administer donislecel in the same tubing concurrently with products other than physiological saline.
- Periodically clear the infusion lines and measure portal pressure during the infusion. Infusion should be paused if portal pressure rises above 22 mmHg and not resumed until it falls below 18 mmHg. Infusion should be terminated if portal pressure remains above 22 mmHg for longer than 10 minutes.
- Blood glucose levels should be monitored every 15 minutes during the infusion and then every 30 minutes for the first 4 to 8 hours after infusion. Provide appropriate treatment if blood glucose levels fall below 55 mg/dL. Monitor blood glucose levels as needed once blood glucose levels have stabilized. After the acute period (first 4 to 8 hours following transplant), use of a continuous glucose monitoring system is recommended.
- Monitor the patient for portal vein branch thrombosis. Early diagnosis and prompt management with systemic heparinization may prevent clot propagation. Anticoagulation therapy may lead to intra-abdominal hemorrhage requiring transfusion and surgical intervention.
- To prevent graft loss, ensure that the recipient is on an adequate non-steroidal immunosuppression regimen at the time of transplant and maintained on an appropriate maintenance regimen thereafter. Monitor for decreasing C-peptide levels and signs of declining glycemic control.

PROCEDURE

<u>Pre-Infusion</u>

1. Confirm the identity of the patient for the specified unit of donislecel.
2. Confirm the patient has received appropriate premedication.
3. Confirm that appropriate medications are available to manage any potential emergencies, such as allergic reactions, pain, hypoglycemia, or bleeding.

4. Confirm the patient is hydrated adequately prior to infusion. It is recommended to use saline/glucose infusion and an intravenous insulin pump during the periprocedural period.
5. Inspect the donislecel batch for any abnormalities, such as unusual particulates, and for breaches of container integrity prior to administration. If product irregularities are present, discuss these with the issuing laboratory prior to infusion.

Infusion

6. Gently agitate the donislecel infusion bag to ensure that the islets are suspended and to prevent clumping. Do not shake the bag, as this may damage the islets. This step should be repeated periodically throughout the infusion process.
7. Remove the first drape bag and transfer the product to a qualified infusion operator to remove the second drape bag.
8. Ensure that the intravenous tubing is closed, connect the islet infusion bag, fill the drip chamber, and open the roller clamp to fill the tubing and remove air.
9. Once the intraportal catheter is in place, connect the islet infusion bag using a Luer lock to the catheter (or extension).
10. Allow the islet infusion to proceed by gravity flow.
11. Once the islet infusion is complete, open the roller clamp on the rinse bag tubing to allow refilling and rinsing of the islet infusion bag. Gently agitate the islet infusion bag with small amounts of rinse solution to ensure that all islets have been administered. Repeat until the rinse bag is empty.
12. Withdraw the catheter tip from the main portal vein into the liver parenchyma until it lies within a few cm of the liver capsule. If a percutaneous, transhepatic approach was used to gain access to the transplant site, the catheter track may be sealed with a hemostatic agent.

Post-infusion

13. Perform an abdominal ultrasound and Doppler examination of the liver after catheter removal to detect portal vein thrombosis and intra-abdominal bleeding. At a minimum, these examinations should be repeated at 1 and 7 days after the procedure.
14. Continue to monitor the patient for adverse reactions and for blood glucose levels following infusion.

9.2. Tabular Summary of Clinical Efficacy Studies

Table 45. Description of Clinical Efficacy Studies

Study Number and Status	Study Title, Description, and Objectives	Number of UI Health Patients	Number of Islet Transplants	Main Inclusion Criteria	Primary Efficacy Endpoint(s) and Results
Core Donislecel Studies (Pooled Population)					
UIH-001 Completed (Final 10-year follow up in July 2020) Last transplant: 2009	Title: Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid Free Immunosuppression Description: Phase 1/2, nonrandomized, open-label, single-center study. Patients were enrolled in 1 of 2 cohorts to receive allogeneic pancreatic islets according to the Edmonton protocol or a modified Edmonton protocol. Primary Objective: To demonstrate the safety of allogeneic islet transplantation performed at UI Health for the treatment of patients with T1D.	Total: N = 10 (9F, 1M) Cohort 1: N = 4 (Edmonton Protocol – immuno-suppression with daclizumab, sirolimus, and tacrolimus) Cohort 2: N = 6 (UI Health protocol = immune-suppression per Edmonton Protocol plus etanercept and exenatide)	21	• Reduced awareness of hypoglycemia, defined by the absence of adequate autonomic symptoms at plasma glucose levels <54 mg/dL (3 mmol/L), as reported by the patient. • Metabolic lability/instability, characterized by 2 or more episodes of documented severe hypoglycemia OR 2 or more hospital visits for diabetic ketoacidosis over the last year. • Progressive secondary complications of diabetes, such as retinopathy, nephropathy, or neuropathy.	Primary Efficacy Endpoint: original – full success = insulin independence and HbA1c ≤6.5% partial success = ≥50% reduced insulin, ≥0.3% absolute decrease from baseline HbA1c, and 50% reduction from baseline HYPO score. post hoc composite – success = HbA1c ≤6.5% and no SHEs through 1 year after last transplant. Results: original – 3 full success (30%), 6 partial success (60%) at 1 year after last transplant; thus 9/10 (90%) achieved at least partial success.

Study Number and Status	Study Title, Description, and Objectives	Number of UI Health Patients	Number of Islet Transplants	Main Inclusion Criteria	Primary Efficacy Endpoint(s) and Results
					post hoc composite – 9 out of 10 (90%) patients achieved HbA1c ≤6.5% and no SHEs through 1 year after last transplant.
UIH-002 Long-term follow-up ongoing (last 10-year follow up expected Dec 2023) Last transplant: 2016	Title: Islet Transplantation in Type 1 Diabetic Patients Using the UIC protocol, Phase 3 Description: Phase 3, open-label, nonrandomized, single-center, ongoing study. Primary Objective: To demonstrate the safety and efficacy of allogeneic islet transplantation in patients with T1D performed at UI Health. The islet transplantation method included etanercept and exenatide treatments in addition to the immunosuppressants in the Edmonton protocol, which was used in Study UIH-001.	Total: N = 21 (15F, 6M)	35	• At least one episode of severe hypoglycemia in prior 3 years, defined as an event with symptoms compatible with hypoglycemia in which the patient required the assistance of another person, and which was associated with either a blood glucose level <50 mg/dL (2.8 mmol/L) or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. • Reduced awareness of hypoglycemia, defined as the absence of adequate autonomic symptoms at capillary glucose levels of <54 mg/dL (3 mmol/L), as reported by the patient.	Primary Efficacy Endpoint: Success – HbA1c ≤6.5% and free of SHEs through 1 year after last transplant. Results: 11 out of 21 (52%) patients achieved HbA1c ≤6.5% and no SHEs through 1 year after last transplant and were deemed successes.

Study Number and Status	Study Title, Description, and Objectives	Number of UI Health Patients	Number of Islet Transplants	Main Inclusion Criteria	Primary Efficacy Endpoint(s) and Results
Supplementary Studies (performed under the INDs of other sponsors)					
CIT-02 Completed (2014; final data collection for primary outcome measure was in 2011)	Title: Strategies to Improve Long Term Islet Graft Survival Description: Phase 2, open-label, randomized prospective, single-arm, multi-centered trial. Study duration was 5 years. Immunosuppression per UIH protocol (i.e., same as UIH-001 and UIH-002) Primary Objective: The primary objective was to determine the proportion of subjects who were insulin independent after a single islet transplant at 75 ± 5 days post-transplant in patients treated with Lisofylline added to a standard islet transplant regimen.	2	3	• C-peptide (<0.3 ng/mL) in response to a mixed meal tolerance test at 60 and 90 minutes after the start of meal consumption. • Involvement in intensive diabetes management, defined as self-monitoring of glucose values ≥ 3 times/day (mean) and administration of ≥3 insulin injections/day or insulin pump therapy under direction of an endocrinologist, diabetologist, or diabetes specialist. • During the 6 months prior to randomization and during the screening period, subject met 1 of the following 3 options: (1) reduced awareness of hypoglycemia, defined by Clarke score ≥ 4, or a HYPO score ≥90th percentile (1047); or (2) marked glycemic lability characterized by wide swings in blood glucose despite optimal diabetes therapy, defined as glycemic lability index score ≥90th percentile (433 mmol/L2/h·wk-1); or (3) composite of Clarke score of ≥ 4 and HYPO score ≥75th percentile (423) and a lability index ≥75th percentile (329).	Of the 2 UIH patients, 1 achieved HbA1c <7.0% and free of SHEs through 1 year after last transplant; and none were insulin independent at 1 year after last transplant.

Study Number and Status	Study Title, Description, and Objectives	Number of UI Health Patients	Number of Islet Transplants	Main Inclusion Criteria	Primary Efficacy Endpoint(s) and Results
CIT-06 Completed (2017; final data collection for primary outcome measure was in 2015)	Title: Islet Transplantation in Type I Diabetic Kidney Allograft Recipients: Efficacy of Islet After Kidney Transplantation. Description: Phase 3, prospective, single-arm, multi-center trial assessing the benefit of islet transplantation in T1D kidney transplant recipients. Primary Objective: To test the hypothesis that islet transplantation in T1D patients with established kidney transplants leads to a reduced risk of diabetes-related complications as assessed by improved metabolic control measured by serial HbA1c levels and/or reduced occurrence of hypoglycemic events compared with intensive insulin therapy.	4	6	• C-peptide (<0.3 ng/mL) in response to a mixed meal tolerance test at 60 and 90 minutes after the start of meal consumption. • At ≥ 3months postrenal transplant and taking appropriate calcineurin inhibitor-based maintenance immunosuppression. • Stable renal function, defined as creatinine no more than one third greater than the average creatinine determination performed in the 3 previous months prior to islet transplantation, until rejection, obstruction or infection is ruled out. • Subject met one of the following options: (1) reduced awareness of hypoglycemia, defined as Clarke score ≥4 and ≥1 episode of severe hypoglycemia during 12 months prior to study enrollment (this criterion required intensive diabetes management under direction of an endocrinologist, diabetologist, or diabetes specialist with ≥3 clinical evaluations); or (2) after enrollment followed by 4 months of intensive insulin therapy, reduced awareness of hypoglycemia, defined by Clarke score ≥4 and ≥1 episode of severe hypoglycemia; or (3) subject who did not meet hypoglycemia option must have received intensive insulin therapy for ≥12 months under care of a diabetes specialist; at end of this period, HbA1c ≥7.5% and HbA1c value within 95% confidence interval of HbA1c during the previous month of intensive insulin therapy; or (4) subjects who did not meet 1 of the 3 options above may have continued intensive insulin therapy beyond 12 months and was eligible if the second or third option was met after a 12-month interval of intensive insulin therapy.	Of the 4 UIH patients, 1 achieved the HbA1c ≤6.5% and free of SHEs through 1 year after last transplant; and 1 was insulin independent at 1 year after last transplant.

Study Number and Status	Study Title, Description, and Objectives	Number of UI Health Patients	Number of Islet Transplants	Main Inclusion Criteria	Primary Efficacy Endpoint(s) and Results
CIT-07 Completed in 2014 (final data collection for primary outcome measure was in 2012)	Title: Islet Transplantation in Type 1 Diabetes (Protocol CIT-07) Description: This was a phase 3, prospective, open-label, single-arm, multi-center study to evaluate the safety and efficacy of transplantation of purified human pancreatic islets. Study duration was 7 years (03 Nov 2006 to 19 May 2014). Immunosuppression per UIH protocol (i.e., same as UIH-001 and UIH-002) Primary Objective: To demonstrate the safety and efficacy of the purified human pancreatic islets product for the treatment of T1D in subjects with hypoglycemia unawareness and a history of severe hypoglycemic episodes, as demonstrated by glycemic control and elimination of severe hypoglycemic episodes.	4	7	Eligibility criteria were the same as described above for Study CIT-02 and at least 1 episode of severe hypoglycemia in the 12 months prior to study enrollment, which must have been documented by an endocrinologist, diabetologist, or diabetes specialist.	Of the 4 UIH patients, 3 achieved HbA1c ≤6.5% and free of SHEs through 1 year after last transplant; and 3 were insulin independent at 1 year after last transplant.

Study Number and Status	Study Title, Description, and Objectives	Number of UI Health Patients	Number of Islet Transplants	Main Inclusion Criteria	Primary Efficacy Endpoint(s) and Results

12176A
 	
Ongoing
	Title:
	Allogenic Islet Cells (Human, U. of Chicago) Administered via Intraportal Infusion; and Immunosuppressive Therapy.
	
	Description:
	Prospective, single-arm trial assessing the safety and effectiveness of islet transplantation for the treatment of brittle type 1 diabetes.
	
	Primary Objective:
	To assess the safety of islet transplantation and protocol-regulated treatment products (i.e., concomitant therapy) as determined by the incidence, timing, and severity of adverse events as well as their relationship to the islet procedure and other protocol-regulated products.
		3*
		
		* Patients were treated with islets prepared at UIH, but these patients were transplanted and followed at the University of Chicago.
			3	• On an intensive regimen of glucose monitoring and exogenous insulin injection.
				• Despite intensive therapy have at least one of the following:
				  • brittle diabetes (defined by elevated mean amplitude of glycemic excursion)
				  • hypoglycemia unawareness (≥1 episode of severe hypoglycemia in past 2 years)
				  • progressive diabetic complications (nephropathy, retinopathy, neuropathy)
					Of the 4 UIH patients, 2 achieved the HbA1c ≤6.5% and free of SHEs through 1 year after last transplant; and 2 were insulin independent at 1 year after last transplant.

HbA1c, glycated hemoglobin; HYPO, hypoglycemia; SHE, severe hypoglycemia event; UIH = University of Illinois Hospital and Health Sciences Center

9.3. Historical Comparator Descriptions

9.3.1. Wisconsin Diabetes Registry Study

The WDRS [55-57] is a population-based cohort of incident cases with T1D and includes both longitudinal clinical assessments and questionnaires. The study originally identified and enrolled 590 participants with newly diagnosed T1D between May 1987 and April 1992. The participants were <30 years of age at the time of enrollment and living in 28 contiguous counties in southern and central Wisconsin.

All participants were interviewed by telephone to record socioeconomic data, clinic type, and physician information. Glycated hemoglobin (Ghb and HbA1c) levels were monitored every 4 months up to the year 2000, followed by yearly assessments in 2001 and 2002. Questionnaires regarding status of diabetes management, including the need for emergency care and routine care, as well as follow-up socioeconomic and clinic informational questions, were sent to participants biannually/annually. Participants were examined at 4 months (southern Wisconsin only), and at 4, 7, 9, 14, and 20 years [56].

There were 442 subjects remaining in the study after 20 years. At that time, about half of cohort members were male. Mean age at diagnosis was 11.4 years, and 46% of the cohort was age <10 years, 42% age 10–19 years and 12% ≥ 20 years old at diagnosis [56].

9.3.2. Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications Follow-up Study

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) funded the DCCT to determine if people with T1D who kept their blood glucose levels as close to normal as safely possible with intensive diabetes treatment (3 or more shots of insulin per day or an insulin pump with self-monitoring of blood glucose at least 4 times per day) could slow the development of eye, kidney, and nerve disease, compared to people who used the conventional treatment at the time of the study (1 or 2 shots of insulin per day with daily self-monitoring of urine or blood glucose) [102]. The DCCT (1982-1993) was a controlled clinical trial in 1,441 subjects with T1D. Data were collected across 29 medical centers and included subjects from 13-39 years of age. Participants who used conventional therapy during DCCT were transitioned to intensive insulin therapy at the end of the study. A follow-up to the DCCT, the ongoing EDIC study, has continued to follow DCCT participants for more than 20 years [59].

The DCCT followed ~99% (1422/1441 patients completed study) of the cohort for a mean of 6.5 years. After another 20 years of follow-up in EDIC, 88% of the original cohort (95% of survivors) were still being actively followed.

9.3.3. Collaborative Islet Transplant Registry (CITR)

The CITR is an organization dedicated to publishing data from 1999 onward on all islet/beta cell transplants being conducted in North America and funded European and Australian sites for the purpose of promoting development and safety of islet/beta cell transplants. The Registry is supported by NIDDK funding as well as a grant provided by Juvenile Diabetes Research Foundation International (JDRF). [20]. Results are primarily disseminated in the form of the CITR Annual Report.

The CITR 10th Annual Report (the most recent as of the donislecel BLA submission date), which includes data collected from 1999-2015, focuses on 1,086 islet allograft recipients (877 islet-transplant-alone (ITA), 183 islet-after-kidney (IAK), 24 simultaneous-islet-kidney (SIK), and 2 kidney after islet) receiving a total of 2,150 allograft infusions [20].

Information published in the Registry is obtained from CITR member investigators in the form of transplant recipients' medical records and prepared scientific reports, as dictated by regulatory requirements of the region.

Primary outcomes in the Registry include insulin use, severe hypoglycemic episodes, HbA1c, fasting blood glucose, and C-peptide. Follow-up data for these endpoints is collected at 1, 2.5, 6, and 12 months post-infusion and annually. Follow-up schedules are revised following each new islet infusion. Secondary outcomes include laboratory testing, metabolic panel testing, records of concomitant medications, and quality of life assessments. Additionally, safety data including vital signs, adverse events, non-islet-related transplants, and islet graft loss are collected. Patients who are lost to follow-up or transferred to a different transplant center are documented.

9.4. Safety Summary for Immunosuppressant and Anti-infective Medications

Information from the product labels of the induction immunosuppressant THYMOGLOBULIN (anti-thymocyte globulin) [69], maintenance immunosuppressants PROGRAF (tacrolimus) [64], RAPAMUNE (sirolimus) [65], and CELLCEPT (mycophenolate mofetil) [66], and anti-infective drugs BACTRIM (sulfamethoxazole/trimethoprim) [68] and VALCYTE (valganciclovir) [67], is summarized to provide important context to the safety results from islet transplantation. This information is important because many of the safety signals that arise following islet transplantation are a result of concomitant medications, especially immunosuppressants, rather than of the islets themselves or the transplant procedure.

High-level conclusions and comparisons based upon information in the approved labeling of common concomitant medications used as part of the CellTrans studies are provided in this section.

9.4.1. Blood and Lymphatic System Disorders

- Immunosuppressants and anti-infectives can lead to a significantly increased risk of blood and lymphatic disorders. Anemia, leukopenia, and thrombocytopenia, are commonly reported in the product labels of medications commonly used for induction immunosuppression [69] and maintenance immunosuppression following transplant [64-66]. The product labels for anti-infectives GANCICLOVIR (active drug) and VALCYTE (prodrug) both contain boxed warnings for hematologic disorders [67, 103]. Neutropenia, anemia, leukopenia, and thrombocytopenia were reported in ≥20% of patients administered VALCYTE. Numerous blood disorders are also common with BACTRIM, with life-threatening and fatal cases of severe thrombocytopenia reported [68].

9.4.2. Blood Chemistry Disorders

- Immunosuppressants and anti-infectives increase the risk for blood chemistry disorders, including electrolyte imbalances, lipid imbalances, increased levels of hepatic enzymes

(ALT/AST) and creatinine, all of which are commonly reported following administration of these products [64-67, 69, 103].

9.4.3. Cardiovascular Disorders

- Immunosuppressants and anti-infectives increase the risk of cardiovascular disorders [64-67, 103]. PROGRAF may prolong the QT/QTc interval and may cause Torsade de Pointes. Arrythmias, hypertension, hypotension, and pericardial effusion (among others) have been reported in ≥15% of patients with at least some of these medications. Abnormal ECG and myocardial ischemia have also been reported.

9.4.4. Gastrointestinal Disorders

- Gastrointestinal disorders are among the most common side effects of immunosuppressants and anti-infective drugs [64-68, 103]. Constipation, diarrhea, abdominal pain, nausea, and vomiting were the most commonly reported gastrointestinal adverse reactions. Anorexia was also common with BACTRIM.

9.4.5. Infections

- Patients receiving immunosuppressants are at increased risk of developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections and activation of latent viral infections [64-66]. These infections may lead to serious, including fatal, outcomes. Serious infections reported include:
    - Polyomavirus-associated nephropathy (PVAN), mostly due to BK virus infection, which can lead to deteriorating renal function
    - JC virus-associated progressive multifocal leukoencephalopathy (PML), which can be fatal. PML commonly presents with hemiparesis, apathy, confusion, cognitive deficiencies, and ataxia.
    - Cytomegalovirus infections: CMV seronegative transplant patients who receive an organ from a CMV seropositive donor disease are at higher risk of developing CMV viremia and CMV disease.
    - Pneumocystis carinii pneumonia has been reported in transplant patients not receiving antimicrobial prophylaxis.

9.4.6. Neoplasms

- All immunosuppressant labels contain a black box warning related to an increased risk of malignancies [64-66]. More specifically, patients receiving immunosuppressants are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent.
- Post-transplant lymphoproliferative disorder (PTLD) has been reported in immunosuppressed organ transplant recipients. The majority of PTLD events appear related to Epstein-Barr Virus (EBV) infection. The risk of PTLD appears greatest in those individuals who are EBV seronegative, a population which includes many young children.

- All immunosuppressant labels include carcinogenesis data from nonclinical species that indicate an increase in malignancies following administration.

9.4.7. Renal and Urinary Disorders

- Abnormal renal function was among the most commonly observed adverse events (≥30%) in clinical studies of PROGRAF (tacrolimus) [64]. Nephrotoxicity was reported in approximately 40% and 36% of liver transplantation patients receiving PROGRAF in US and European randomized trials, 59% of heart transplant patients in the European trial supporting the label, and 52% of kidney transplant recipients. The combination of sirolimus and tacrolimus, which is a commonly used immunosuppressant combination in islet transplantation, is associated with additional risk of renal impairment [64].