FDA Briefing Document

Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

April 15, 2021

BLA 125734
DONISLECEL
Applicant: CellTrans, Inc.

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Food and Drug Administration (FDA) for the members of the advisory committee. The FDA background package often contains assessments and/or conclusions and recommendations written by individual FDA reviewers. Such conclusions and recommendations do not necessarily represent the final position of the individual reviewers, nor do they necessarily represent the final position of the Review Division or Office. We bring the Biologics License Application (BLA) for donislecel, a first-in-class product, with the Applicant's proposed indication, to this Advisory Committee to gain the Committee's insights and opinions. The background package may not include all issues relevant to the final regulatory recommendation and instead is intended to focus on issues identified by the FDA for discussion by the advisory committee. The FDA will not issue a final determination on the issues at hand until input from the advisory committee process has been considered and all reviews have been finalized. The final determination may be affected by issues not discussed at the advisory committee meeting.

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ABBREVIATIONS

AE	Adverse Event
AEPT	Adverse Event Preferred Term
BLA	Biologics License Application
BW	Body weight
CGM(S)	Continuous Glucose Monitor (System)
CTGTAC	Cellular, Tissue, and Gene Therapies Advisory Committee
CIT	Clinical Islet Transplantation Consortium
CMV	Cytomegalovirus
CRF	Case Report Form
DCCT	Diabetes Control and Complications Trial
DKA	Diabetic Ketoacidosis
EIN	Equivalent Islet Number
FDA	Food and Drug Administration
eGFR	Estimated glomerular filtration rate
HbA_{1c}	Glycosylated hemoglobin
IND	Investigational New Drug Application
IV	Intravenous
kg	Kilograms
LI	Lability Index
max	Maximum
mg	Milligram
min	Minimum
N	Number
OPTN	Organ Procurement and Transplantation Network
PD	Pharmacodynamics
PK	Pharmacokinetics
PO	“Per os” meaning oral administration
PRA	Panel reactive antibodies
QD	Once daily
SAE	Serious adverse event
SD	Standard Deviation
SEM	Standard Error of the Mean
SHE	Severe Hypoglycemic Event
T1DM	Type 1 Diabetes Mellitus
TEAE	Treatment-Emergent Adverse Event
Tx	Transplant
UIH	University of Illinois Hospital and Health Sciences System; UI Health
UNOS	United Network for Organ Sharing

1 CLINICAL INDICATION

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

2 EXECUTIVE OVERVIEW

Topic

This Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) Meeting is convened to discuss the BLA submitted by Cell Trans, Inc. (the Applicant) for donislecel for the treatment of patients with "brittle type 1 diabetes mellitus".

Issues

The primary evidence of effectiveness and safety is generated from two open-label studies, UIH-001 (Phase 1/2) and UIH-002 (Phase 3). The Applicant provided a primary efficacy analysis that combines the results of these two studies. The primary efficacy analysis used a composite of an $HbA_{1c} \leq 6.5\%$ and absence of severe hypoglycemic events (SHE) through one year after the subject's last transplant, in accordance with FDA Guidance[1]. However, the FDA believes that the combination of substantial missing data and inclusion of a significant proportion of subjects who, at baseline, had already met or nearly met the primary endpoint makes this efficacy analysis difficult to interpret. Specifically, although all subjects had previously documented hypoglycemic unawareness[2] only 5 of 30 (16.7%) subjects had at least 1 documented SHE event in the year prior to their first transplant, based on a commonly accepted definition of hypoglycemia that requires third party assistance for treatment, a definition that was included in the study protocols. Additionally, 11 of 30 (37%) subjects had a $HbA_{1c} \leq 7\%$ as the most recent HbA_{1c} prior to their first transplant. Therefore, the FDA believes that the Applicant has not demonstrated that allogenic islet cell transplant with donislecel reduces the incidence of SHE or restores hypoglycemia awareness in the subject population.

Nonetheless, the Applicant has provided data demonstrating 21 of 30 (70%) subjects were able to achieve more than 1 year of independence from exogenous insulin while maintaining or improving glycemic control[3]. While FDA considers insulin independence a significant benefit to patients, the transplantation procedure and concomitant immunosuppression treatment pose significant risks. Therefore, it is important to understand the characteristics of the subjects who participated in the trials, transplantation experience (number of procedures/islet cell dose),

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[1] Guidance for Industry: Considerations for Allogenic Pancreatic Islet Cell Production. (September 2009) U.S. Department of Health and Human Services, Food and Drug Administration, Center for Biologics Evaluation and Research.

[2] Defined in the protocols for UIH-001 and UIH-002 as "the absence of adequate autonomic symptoms at capillary glucose levels of < 54 mg/dL (3 mmol/L as reported by the subject".

[3] In all 25 (83.3%) of 30 subjects were able to achieve insulin independence for any duration 4 days to 12.9 years.

duration of insulin independence, and nature and severity of adverse events in order to determine for whom the use of donislecel may provide a benefit that outweighs its risk.

The FDA seeks the opinion of the Committee regarding the following issues:

(This section is provided early in draft for the Committee)

Topic for Discussion #1

The primary composite efficacy endpoint in Study UIH-002 is the proportion of subjects achieving absence of severe hypoglycemic events (SHEs) and HbA1c of <6.5% in the year after the first transplant and year after the last transplant. The primary endpoint in Study UIH-001, was insulin independence at one year after the first transplant and 1 year after the last transplant. In their BLA the Applicant applied the same primary composite endpoint from Study UIH-002 to both studies. However, 83% of subjects in Studies UIH-001 and UIH-002 did not have SHE in the year prior to their first transplant and 37% of subjects had HbA1c at target at baseline. Therefore, the study's pre-specified primary endpoint is difficult to interpret. However, FDA believes that the proportion of subjects with freedom from exogenous insulin administration could support the efficacy of cadaveric allogenic pancreatic islet cells (donislecel).

Please discuss the minimum duration of insulin independence that you would consider to be clinically meaningful (i.e., would represent a benefit for the individual patient).

Topic for Discussion #2

The applicant has proposed "Treatment of Brittle Type 1 Diabetes" as the indication for cadaveric allogenic pancreatic islet cells (donislecel). Given that there is no specific definition for "brittle type 1 diabetes" and the eligibility and baseline characteristics of the population actually enrolled in Studies UIH-001 and UIH-002, please discuss the benefit-risk profile for the product in general and define the subset of type 1 diabetics as the appropriate target population.

Discussion and Draft Voting Question

Does donislecel delivered by intraportal administration have an overall favorable benefit-risk profile for some patients with Type 1 diabetes? In considering this question, please incorporate the risks of the transplantation procedure(s) and long-term immunosuppression as risks of the product.

3 BACKGROUND

3.1 Regulatory Background

To support programs developing islet cell transplants, the FDA released guidance (September 2009) titled "*Guidance for Industry: Considerations for Allogenic Pancreatic Islet Cell Products*" on establishing the safety, purity, and potency of this biological product[4]. This guidance describes considerations for the target T1DM sub-population and efficacy endpoints. However, Study UIH-001 was initiated in 2004 and Study UIH-002 was initiated in 2007, prior to publication of the guidance.

3.2 Type 1 Diabetes

Type 1 Diabetes Mellitus (T1DM) results from autoimmune destruction[5] of pancreatic islet cells that contain the β-cells responsible for the production of insulin. T1DM is a fatal condition in the absence of exogenous insulin treatment.

Short-term complications from an inadequate amount of insulin include hyperglycemia and diabetic ketoacidosis (DKA) which is a serious condition that can result in diabetic coma and/or death. Long-term, persistent hyperglycemia is associated with microvascular disease and the development of retinopathy, neuropathy, and nephropathy. These conditions can lead to serious clinical manifestations, such as vision loss and blindness; neuropathic pain and autonomic dysfunction, poor wound healing and amputation; and kidney failure and dialysis, respectively. A landmark study initiated in 1983, the Diabetes Control and Complication Trial (DCCT) [1] demonstrated that intensive glycemic management delayed the onset and slowed the progression of these complications in patients with T1DM. However, these advantages of improved glycemic control were [2] accompanied by a significant increase in the occurrence of severe hypoglycemic events (SHE).

Hypoglycemia can cause neurologic and autonomic symptoms. Autonomic symptoms associated with hypoglycemia include anxiety, heart palpitations, tremor, sweating, hunger, and paresthesia. If left untreated, hypoglycemia may become severe and cause neurocognitive changes (neuroglycopenic), such as confusion, disorientation, loss of consciousness, seizures and potentially permanent brain injury in extreme cases and, in the most severe cases, death.

The treatment goals for the intensive treatment arm in the DCCT were a preprandial (fasting) capillary blood glucose (finger-stick) of 70 to 120 mg/dL, a postprandial (90-120 minutes after meal) glucose of less than 180 mg/dL, and an $HbA_{1c} \leq 6.05\%$. These goals are commonly

[4] The guidance was not intended to identify all of the product, preclinical, and clinical data that might be needed to successfully support a biologics license application (BLA).
[5] The predominant cause of T1DM, less frequently it is associated with recurrent pancreatitis or is iatrogenic.

referred to as “tight glycemic control”. For a small sub-population of patients with T1DM, target glycemic control cannot be achieved because they have significant metabolic instability and episodes of DKA and SHE. These subjects are generally referred to as having “brittle diabetes”. This is further complicated by the inability of some patients to develop the autonomic symptoms associated with hypoglycemia and therefore lose this protective response to alert them that immediate intervention is required to prevent worsening hypoglycemia that can lead to neuroglycopenic symptoms, and rapidly to loss of consciousness and death. This is commonly referred to as “hypoglycemia unawareness”.

3.3 Treatment

To date, the mainstay of treatment for T1DM remains insulin treatment. Since the DCCT, there have been changes in the formulations of insulin, resulting in improvements in pharmacokinetic (PK) and pharmacodynamic (PD) profiles. The use of basal and analog insulins allows patients to better manage their diabetes according to their daily activities, whereas previously patients would need to schedule their activities and meals based on the PK/PD of their insulins. Advances in insulin pumps have similarly improved the patient’s self-management through insulin variable basal rates and boluses throughout the day. Blood glucose meters (BGM) have become more user friendly and with the use of insulin dose calculator applications facilitates tailored insulin dosing. Continuous glucose monitoring (CGM) devices measure interstitial glucose and provide nearly continuous glucose measurements and alerts for preset out-of-range measurements. Device systems composed of an insulin pump and CGM and software programs can temporarily suspend insulin delivery when the sensor glucose value is below the low threshold. More complex systems are designed to increase or decrease insulin delivery in response to the sensor glucose towards a set goal. While these advancements have improved the ability of patients to manage their diabetes and achieve treatment goals, some patients still experience significant metabolic instability [3] and continue to be at increased risk for SHE. To decrease the risk of these potentially life-threatening events, some patients avoid “tight” glycemic control, and the subsequent hyperglycemia increases their risk of DKA and microvascular and macrovascular complications from T1DM.

Whole pancreas transplantation

Whole pancreas transplantation, with or without concurrent kidney transplant, has been the only option to address the unmet need for the patients with frequent, acute, and severe metabolic complications. While this approach frequently restores endogenous insulin production, it requires major surgery with its inherent risk and immunosuppression to maintain function of the transplant [4]. The allocation of pancreata is controlled under the policies of the Organ Procurement and Transplantation Network (OPTN) and implemented through the United

Network for Organ Sharing (UNOS). According to the OPTN data base [6], patients identified with a diagnosis of type 1 diabetes received 175 pancreas transplants alone and 1,255 pancreas plus kidney transplants during 2019 and 2020. The 5-year and 10-year reported outcomes for transplant function for pancreas and pancreas plus kidney have significantly improved over the 1984 to 2009 period examined. By 2008/2009 the pancreas graft function, defined by the authors as complete insulin independence, was 53% pancreas alone and 81% for simultaneous pancreas plus kidney at 5 years, and 40% and 56% at 10 years[5].

Islet cell transplantation

As with whole pancreas transplantation the goal of allogenic islet cell transplantation is restoration of endogenous insulin production that would allow the patient to become independent of exogenous insulin. Islet cell transplantation also requires immunosuppression to maintain function, but the procedure is less invasive than whole pancreas transplant, decreasing the risk of the procedure. Furthermore, the use of islet cells expands the pool of donor pancreata, allowing the use of those pancreata not suitable for whole organ transplant[7]. There are no approved islet cell products for transplantation.

The subject of this application is the first allogenic islet cell transplant product submitted for review under a marketing application.

The Applicant is a member of the Clinical Islet Transplantation (CIT) consortium[6] that has conducted numerous studies using pancreatic islet cells to treat patients with type 1 diabetes. Each study center in the consortium manufactures their own islet cell product for transplantation at their site. While the process for manufacture of the islet cell product is similar at each site, FDA considers each to be a separate product and those transplants not using donislecel are not the subject of this BLA.

3.3 Product

Donislecel consists of isolated allogeneic pancreatic islets of Langerhans. Islets contain several types of endocrine (hormone-secreting) cells, including β-, α-, pancreatic peptide- (PP-), δ-, and ε-cells. (Please refer to the CMC section for full details).

It should be noted that cadaveric donor pancreata are used as a basis for the product. Therefore, there is a limited supply of islets for transplantation.

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[6] https://optn.transplant.hrsa.gov/data/, accessed 3/2/2021

[7] OPTN Pancreas Transplantation Committee Continuous Distribution Workgroup Meeting Summary November 20, 2020

3.3.1 Physiologic Role of Pancreatic Islet Cells

The goal of islet cell transplantation is to deliver β-cells and restore endogenous insulin production. In addition, the transplanted islets contain α-cells which produce glucagon, an important counterregulatory hormone in response to hypoglycemia. There is evidence that for some patients the delivery of the islets with their various cell types can fully or partially provide the counterregulatory response to hypoglycemia [7].

3.4 Transplantation of Allogenic Pancreatic Islet Cells

3.4.1 Procedure

The islets of Langerhans from a deceased human donor were transplanted into the hepatic portal vein. The full procedure is described in Appendix 1.

3.4.2 Immunosuppression

Immunosuppression is a critical component of an allogenic islet cell transplant to prevent rejection. The Edmonton Protocol employs a steroid-sparing approach that was modified during the product development program (please refer to Section 4.3, Study Medications).

3.5 Known Risks associated with allogenic transplantation

Procedure

Risks from the intraportal transplantation procedure include damage to the liver, gall bladder or intraabdominal blood vessels, possibly requiring surgery, and bleeding from puncture of the liver which may require blood transfusion and infection.

Product

Risks from the islet cell product include transmission of infection; thrombus formation in the portal vein could result in liver damage, and if complete, could be catastrophic requiring liver transplantation, and patient death. Sensitization may occur to the foreign antigen tissue and decrease the ability to receive future additional transplants, such as liver or kidney[8].

Immunosuppression

Each component of the immunosuppressive regimen has its own adverse event profile. In general, prolonged immunosuppression can increase the risk of infection, cancers, neurological symptoms, kidney damage, anemia, gastrointestinal symptoms, electrolyte imbalances, and decreased bone density. These adverse events can range from mild to life-threatening [8, 9].

Some immunosuppressive drugs are associated with severe adverse events in pregnancy, including but not limited to an increased risk of prematurity, fetal malformations, and fetal demise [10].

Transmission of disease from donor

There is a risk of transmission of communicable diseases from the donor. However, this risk is mitigated by the screening and testing programs of the organ procurement agencies.

4 CLINICAL STUDIES

To obtain marketing approval, the Federal Food, Drug, and Cosmetics Act (FD&C Act) requires that sponsors provide substantial evidence of effectiveness of their products based on the conduct of adequate and well-controlled studies. While clinical evidence of safety and effectiveness for licensure is often derived from prospective, randomized, controlled clinical trials, substantial evidence of effectiveness may come from a single-arm study compared to a performance goal based on well-characterized natural history of the disease, in this case metabolically unstable Type 1 diabetes.

The Applicant provided primary safety and efficacy information from 2 prospective clinical trials and supporting information from a subset of subjects enrolled in the Clinical Islet Transplant Consortium (CIT) for treatment of “brittle” type 1 diabetes mellitus (T1DM) at the applicant’s clinical site, conducted over more than 15 years. Donislecel is not approved in the US for any indication.

The Phase 1/2 trial (UIH-001) was initiated in 2004, and the Phase 3 trial (UIH-002) was initiated in 2007. The data cut-off for the BLA was September 30, 2018 with a 120-day safety update May 19, 2020. In the two studies, a total of 30 subjects received 56 transplants. Of the other studies in which the Applicant contributed subjects to the database, CIT-07 was the most similar to studies UIH-001 and UIH-002. However, Clinical Islet Transplantation Consortium (CIT) data provided for CIT-07 were not in the same format and did not allow for integration into the body of FDA’s review. A summary of CIT-07, a multi-center study in which the Applicant contributed 4 of 48 subjects, is provided in Appendix 4 for comparison.

4.1 Phase 1/2 Study - Study UIH-001

4.1.1 Study Design

Study UIH-001 was an open-label study in which 10 subjects received intraportal administration of donislecel, which will subsequently be referred to as transplants. Subjects received between 1 and 3 transplants at varied intervals. Protocol UIH-001 included optional 5-year and 10-year follow-up periods after the initial 1-year minimum follow-up after last transplant.

4.1.2 Study Objectives

The primary objective of this study was to demonstrate the safety of allogeneic islet transplantation in Type I diabetic subjects performed at the University of Illinois at Chicago (UIC).

4.1.3 Key Enrollment Criteria

Inclusion Criteria

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 subject;
2. Metabolic lability/instability, characterized by two or more episodes of documented severe hypoglycemia,

   OR

1. Two or more hospital visits for diabetic ketoacidosis over the last year;
2. Despite efforts at optimal glucose control, progressive secondary complications of diabetes as defined by: retinopathy[8], or nephropathy[9], or neuropathy[10].

Exclusion Criteria[11]

1. Younger than 18 or older than 65 years
2. C-peptide response to glucagon stimulation (1 mg IV) (any C-peptide ≥ 0.3 ng/mL)
3. Insulin requirement > 0.7 IU/kg/day
4. HbA1C > 12%
5. BMI > 26 kg/m^2 or body weight > 70 kg at screening visit
6. Treatment with antidiabetic medication other than insulin within 4 weeks of enrollment
7. Serum creatinine > 1.5 mg/dL or Creatinine clearance < 80 mL/min/1.73 m^2 by 24-hour urine collection. If corrected creatinine clearance is < 80 and serum creatinine is < 1.2 mg/dL, then a nuclear renal scan is required to determine glomerular filtration rate.
8. Macroalbuminuria (urinary albumin excretion rate > 300 mg/24hours)
9. Untreated proliferative retinopathy
10. Positive pregnancy test, intent for future pregnancy, or male subjects' intent to procreate, unwilling to follow effective contraceptive measures, or presently breastfeeding
11. Previous transplant, or evidence of sensitization on PRA (determined by demonstration of positive results for anti-HLA antibodies using solid phase immunoassay with soluble HLA Class I molecules as a target, or a general PRA panel with reactivity > 20%). If PRA panel reactivity is > 20%, the subject requires a negative crossmatch with the donor before transplant (UNOS requirement).

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[8] A minimum of a three-step progression using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system, or an equivalent progression as certified by an ophthalmologist familiar with diabetic retinopathy

[9] A confirmed rise of 50 µg/min (72 mg/24hours) of microalbuminuria or greater over at least three months (beginning anytime within the previous two years) despite the use of an ACE inhibitor

[10] 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)

[11] The full list of exclusion criteria is found in Appendix 2

4.1.4 Treatment Plan

Dose Regimen

Initial dose delivery

Islets were delivered to the portal vein via transhepatic access under fluoroscopic and ultrasound guidance. A minimum islet dose of approximately 10,000 IE/kg recipient body weight was targeted. No maximum number of delivered islets was specified as long as packed cell volume did not exceed 10 mL per transplant. (Details on the procedure are found in Appendix 1.)

Criteria for repeat islet cell transplantation.

If pre- or post-prandial blood glucose levels exceed 180 mg/dL on repeated occasions after the first transplant and following withdrawal of insulin therapy, and the EIN (equivalent islet number) with first transplant is < 10,000, then an additional islet transplant was required. No maximum number of delivered islets was specified, except that the number must exceed 10,000 IE/kg following 2 islet transplants, and packed cell volume may not exceed 10 mL per transplant. A third transplant could be considered if insulin independence cannot be achieved with two islet transplants exceeding a total of 10,000 IE/kg.

Concomitant Medications used in the Transplant Protocol

Please refer to Section 4.3

4.1.5 Study Assessments

Primary Efficacy Endpoint

Success – Insulin Independence

Insulin independence was defined as not using insulin and having a $HbA_{1c} \leq 6.5\%$ beginning 2 weeks after transplant. Final duration of insulin independence was 1 year following the last transplant. Subjects were still considered insulin independent if they required insulin for <14 days during an intercurrent illness.

This definition of success was modified in January 2016[12], to be subjects who for 48/50 weeks after their last transplant were not using insulin and had fasting glucose levels 140 mg/dL ≥3 times in a week, two-hour post-prandial values 180 mg/dL at least four times in a week.

The Applicant planned to assess insulin independence at 2 weeks, and 1, 3, 6, and 12 months following their final transplant. FDA did not agree to these definitions for a Phase 3 study. As

[12] The primary efficacy endpoint was changed after all transplants had been performed and before the September 2018 data cutoff

described in the 2009 Guidance on development of islet cells, the Agency has concern with interpretability of short-term insulin independence, and believes that a minimum of 12-months duration from final transplant is necessary to assess durability of insulin independence.[13]

Partial Success - Reduction in Insulin Requirements, HbA_{1c} and Hypoglycemic Episodes
Partial success was defined as reduction of insulin ≥50% of baseline use and a decrease in HbA1c of ≥0.3% compared to baseline, or HbA1c ≤ 6.5% and a HYPO score[14] [11] of 0 or ≤ 50% decrease compared to baseline.

Failure – Absence of Adequate Insulin Secretion or Graft Function
Failure was defined as not meeting the requirements for success or partial success.

Complete Graft Loss (CGL) – Failure of Graft based on c-peptide
Within the failure group, any patient with basal C-peptide levels less than 0.3 ng/mL at 2 consecutive follow-up visits was considered to have CGL.

Other endpoints:

- HbA1C (less than 6.1% is considered euglycemia)
- Glucose control and absence of hypoglycemic coma/unawareness, as evidenced by no further requirement for third-party assistance or hospital attendance resulting from a severe hypoglycemic episode

Safety Assessments:

All study participants who receive an islet cell transplant were followed for safety for at least 1 year following the last transplantation.

The safety of the islet transplantation and associated immunosuppressive therapies were evaluated by analysis of adverse experiences, clinical laboratory tests, and physical examination.

- Frequency of adverse events, including laboratory abnormalities
- Renal function, measured both by serum creatinine and calculated GFR using the Cockroft & Gault method
- Lipid profiles for cholesterol, triglycerides, low density lipoprotein (LDL) and high density lipoprotein (HDL)
- Panel Reactive Antibodies (PRA)
- Immunosuppressive drug trough levels
- Renal clearance (GFR)
- Serum liver enzymes and function tests
- Diagnosis of opportunistic infections, e.g., CMV

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[13] FDA Guidance, "*Guidance for Industry: Considerations for Allogenic Pancreatic Islet Cell Products*" (September 2009).
[14] A change in the occurrence of Severe Hypoglycemic Events (SHE) was not specified in the protocol.

Short-term post-procedural assessments

- Doppler ultrasound to exclude or document portal vein thrombosis. An elevated absolute intraportal pressure (> 20 mmHg, or > 27 cm H_2O) confirmed at the beginning of the procedure was considered to be a contraindication for continuing with the transplant infusion. If the intraportal pressure rose above 22 mmHg the infusion was to be held until the pressure fell below 18 mmHg. If the portal pressure remained elevated for more than 10 minutes the procedure was to be stopped.

- The following parameters were assessed to determine the safety of each islet preparation for transplant:
  - Microbial contamination (preliminary Gram stain and subsequent culture results)
  - Endotoxin content
  - Final packed cell volume (mL)

4.2 Phase 3 Study – Study UIH-002

4.2.1 Study Design

Study UIH-002 was a single-arm, open-label study in which twenty (20) subjects received intraportal administration of donislecel (referred to transplants). Subjects received between 1 and 3 transplants, the intervals for additional transplant varied as did the actual criteria used for additional transplant. Protocol UIH-002 included optional 5-year and 10-year follow-up periods after the initial 1-year minimum post-transplant follow-up period.

4.2.2 Study Objective

For UIH-002, the primary efficacy endpoint was "*the proportion of subjects with an HbA1c ≤ 6.5% and free of severe hypoglycemic events*[15] *at 1 year after the first islet cell infusion*".

4.2.3 Key Enrollment Criteria

Inclusion Criteria

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 subject 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.

[15] Applicant's Definition: "An event with symptoms compatible with hypoglycemia in which the subject 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". Source Applicant's uih-002-protocol.pdf, page 14

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 subject.

Exclusion Criteria[16]

The exclusion criteria for UIH-002 were essentially the same as for UIH-001. One notable change was the following exclusion due to the addition of exenatide as a concomitant medication: known family history of Multiple Endocrine Neoplasia Type 2 or Medullary Cancer of the Thyroid.

4.2.4 Treatment Plan

Dose Regimen

Criteria for repeat islet cell transplantation.
Subjects were to be eligible for subsequent islet infusions if after a period of insulin independence of at least 30 days, they present with declining islet function requiring reintroduction of exogenous insulin. Subjects could receive this additional islet infusion anytime during the first year after the last islet infusion, or anytime during the 5-year follow-up, as long as no exclusion criteria are present and avoiding any HLAs (human leukocyte antigens) against which the recipient may have developed donor-specific antibodies.

No maximum number of delivered islets is specified, except that the number must exceed 10,000 IE/kg following 2 islet transplants, and packed cell volume may not exceed 10 mL per transplant.

Concomitant Medications used in the Transplant Protocol

Please refer to Section 4.3

4.2.5 Study Assessments

The key efficacy assessments included[17]:

Primary Efficacy Endpoint: The proportion of subjects with an HbA1c ≤ 6.5% and free of severe hypoglycemic events at 1 year after the first islet cell infusion.

The Applicant defined a severe hypoglycemic event as "An event with symptoms compatible with hypoglycemia in which the subject required the assistance of another person and which

[16] The full list of exclusion criteria is found in Appendix 2
[17] (Protocol V A1, March 2007)

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".[18]

Secondary Efficacy Endpoints

Insulin independence: The proportion of subjects presenting with insulin independence while fulfilling the primary endpoint.

Definition of insulin independence:

- Absence of exogenous insulin injection
- HbA1c ≤ 6.5%
- Fasting capillary glucose level should not exceed 140 mg/dL more than three times in the past week (based on measuring capillary glucose levels a minimum of 7 times in a seven-day period).
- Fasting plasma glucose level ≤ 126 mg/dL; if the fasting plasma glucose level is > 126 mg/dL.
- 2-hour postprandial capillary glucose should not exceed 180 mg/dL more than three times in the past week based on measuring capillary glucose levels a minimum of 21 times in a seven-day period.
- Evidence of endogenous insulin production defined as fasting or stimulated C-peptide levels 0.5 ng/mL or greater.

Hypoglycemic episodes were measured by the number and severity of hypoglycemic episodes quantified by the HYPO Score, and the percent reduction were reported.

Glucose variability and hypoglycemia duration were to be measured by continuous glucose monitoring system (CGMS) for a 3-day period at three different time points: 1) at screening, 2) one year after first islet transplant, and 3) one year after last islet transplant. The following measurements and analysis were to be reported:

1. Mean glucose concentration
2. Percent of time in the following ranges:
   < 60 mg/dL
   60-140 mg/dL
   141-200 mg/dL
   > 200 mg/dL

Safety assessments

The following were evaluated one year after first transplant and one year after the last islet transplant:

1. Procedure-Related Events
   The incidence and severity of adverse events related to the islet infusion procedure, including:
   - Bleeding (> 2 g/dL decrease in hemoglobin concentration)

[18] FDA Comment: This is the primary endpoint recommended in the 2009 FDA Guidance.

- Portal vein thrombosis, branch or main
- Biliary puncture
- Wound complication (infection or subsequent hernia)
- Increased aminotransferase levels (> 5 times upper level of normal)

2. Immunosuppression-Related Events

   The incidence and severity of adverse events related to immunosuppression, including allergy:

   - Reduction in GFR (> 25% reduction in estimated GFR from baseline by Cockroft and Gault formula)
   - Increase in urinary albumin excretion
   - New-onset microalbuminuria (albumin > 30 mg/day confirmed by 24-hour urine collection) in subjects who were previously within normal limits
   - For those patients with baseline microalbuminuria (30-300 mg/day), new-onset overt albuminuria (greater than 300 mg/day confirmed by 24-hour urine collection)
   - Addition or intensification of antihypertensive therapy
   - Oral ulcers
   - Lower extremity edema
   - Gastrointestinal toxicity (diarrhea)
   - Neutropenia (neutrophils < 1.3 thous/µL)
   - Anemia (hemoglobin men < 12.1, women < 11.7 g/dL)
   - Thrombocytopenia (platelets < 150 thous/µL)
   - Infections (viral, bacterial, or fungal)
   - Neoplasms, benign or malignant

   Severity was graded according to Collaborative Islet Transplant Consortium Terminology Criteria for Adverse Events (TCAE) In Trials of Adult Pancreatic Islet Transplantation, Version5.0

3. Islet Preparations for Transplant

   The following parameters will be assessed to determine the safety of each islet preparation for transplant:

   - Microbial contamination (preliminary Gram stain and subsequent culture results)
   - Endotoxin content
   - Final packed cell volume (mL)

4.3 Study Medications

Subjects received a combination that may have included daclizumab, basiliximab, sirolimus, tacrolimus, and etanercept. Daclizumab, sirolimus, and tacrolimus were to be given according to the Edmonton protocol [12], and the TNF alpha receptor antagonist, etanercept, was given to improve islet graft function and engraftment [13]. This protocol did not employ corticosteroids in the post-transplant immunosuppressive regimen. Table 1 provides a summary of the medications used and the percent of subjects exposed to the individual medications.

Table 1. Summary of Administered Concomitant Study Medications for UIH-001 and UIH-002

Medication	UIH-001 All Patients (N=10)	UIH-002 All Patients (N=20)
Anakinra; n (%)	1 (10%)	0
Daclizumab; n (%)	10 (100%)	5 (24%)
Basiliximab; n (%)	5 (10%)	19 (95%)
Mycophenolate mofetil; n (%)	6 (60%)	5 (24%)
Etanercept; n (%)	6 (60%)	20 (100%)
Everolimus; n (%)	1 (10%)	2 (10%)
Sirolimus; n (%)	10 (100%)	20 (100%)
Tacrolimus; n (%)	10 (100%)	20 (100%)
Cyclosporine	1 (10%)	3 (15%)
Anti-thymocyte immunoglobulin; n (%)	1 (10%)	4 (20%)
Exenatide; n (%)	6 (60%)	20 (100%)

Source: Generated by the clinical reviewer from the Applicant's data base

Anakinra – 100 mg QD

Daclizumab –1 mg/kg peripheral intravenously (IV) given immediately pretransplant and 75 mg IV at 2, 4, 6, and 8 weeks after transplant for a total of 5 doses (over 8 weeks). If a subsequent islet infusion is required beyond this induction period, then a further 5-dose course of daclizumab 75 mg IV is given according to the same schedule. During the course of Study UIH-001, daclizumab was removed from the market and was replaced with basilixumab (protocol A7, August 2012).

Basiliximab – 20 mg IV given within two hours before transplant, and 20 mg IV at week 2 after transplant, for a total of 2 doses. If a second or third transplant occurred and no basiliximab was given in the preceding seven days, then the dose regimen begins at the time of transplant. Basiliximab was not administered for the initial transplant in patients who are sensitized to human leukocytes and receive thymoglobulin.

Mycophenolate mofetil – for subjects who do not tolerate the adverse effects of sirolimus or tacrolimus, administered at a dose of 500 mg to 1500 mg PO bid for the duration of islet graft functioning.

Etanercept – 50 mg IV before islet transplantation and continued at a dose of 25 mg subcutaneously on the 3rd, 7th, and 10th post-transplantation days.

Everolimus – initial dose 0.5 mg PO daily, then increased to 0.5 mg PO bid

Sirolimus – loading dose of 0.2 mg/kg per day PO immediately pre-transplant and continued at a dose of 0.1 mg/kg/day each morning, and the dose was adjusted to the target range of 12-15 ng/mL for the three months following the most recent islet infusion. When a subsequent transplant occurs, the loading dose is not used, and the subject continues on the current dosing regimen. After three months following last transplant, the target serum level is lowered to 7-10 ng/mL.

Tacrolimus – 1-mg PO given immediately before transplantation and to be continued at a dose of 1 mg PO given twice per day. Dose adjusted to maintain target trough levels of 3-6 ng/mL throughout the study. When a subsequent transplant occurs, the subject continues on the current dosing regimen.

Cyclosporine – 50 to 200 mg PO daily

Rabbit anti-human thymocyte immunoglobulin (ATG) – administered to subjects sensitized to human leukocyte antigens for the initial transplant only. The first dose 1 to 1.5 mg/kg IV given over 6 hours immediately pre-transplant. The second dose 1 to 1.5 mg/kg IV over 6 hours on Day 1 after transplant. Three subsequent doses of 1 to 1.5 mg/kg IV over 6 hours 2, 3, and 4 days post-transplant.

Other medications

Due to the prolonged immunosuppression, patients also received prophylactic anti-infective drugs including trimethoprim/sulfamethoxazole and valganciclovir.

During the transplant procedures, additional medications, local anesthetics, and contrast media were used. During and for 1 week following the transplant, heparin and SC longer-acting low molecular weight heparin (enoxaparin) were given to reduce coagulation risks that may lead to liver thrombosis.

Exenatide regimen – The protocol for UIH-001 was modified in June 2005 to include exenatide, a glucagon-like peptide-1 (GLP-1) agonist, to enhance insulin secretion by the transplanted islet cells. The regimen included 5 mcg SC given twice daily for 1 week at any time within a 60-minute period before the morning and evening meals. After 1 week of therapy, if tolerated well, dose was increased to 10 mcg twice daily. Exenatide was to be given for a total of 6 months after each islet transplant. The duration of use was increased from 4 months to 6 months post-transplant in December 2006.

5 Study Population

Studies UIH-001 and UIH-002 were similar in design and patient population. As described in Section 4, the two protocols initially had different primary efficacy endpoints. For the final

efficacy assessment, the Applicant applied the same efficacy criteria to both studies as described below.

5.1 Baseline

5.1.1 Demographics

Table 2 through Table 5 contain the baseline demographics and Table 6 and Table 7 contain anthropometric measurements for the 30 subjects in UIH-001 and UIH-002 combined[19].

Table 2. Demographics of Subjects in Study UIH-001 and UIH-002 – Age

Age (years)	UIH-001 (N=10)	UIH-002 (N=20)
Mean (SD)	46.4 (10.16)	47.0 (12.5)
Median (Min, Max)	45.0 (35, 63)	47.0 (21, 67)

Table 3. Demographics of Subjects in Study UIH-001 and UIH-002 – Sex

Sex n (%)	UIH-001 (N=10)	UIH-002 (N=20)
Female	9 (90.0)	15 (75%)
Male	1 (10.0)	5 (25%)

Table 4. Demographics of Subjects in Study UIH-001 and UIH-002 – Race

Race n (%)	UIH-001 (N=10)	UIH-002 (N=20)
Caucasian	10 (100)	20 (100%) [a]
Black	0	0
Asian	0	0
Native American	0	1 (5%) [a]

[a] One subject double identified as both Caucasian and Native American.

Table 5. Demographics of Subjects in Study UIH-001 and UIH-002 – Ethincity

Ethnicity n (%)	UIH-001 (N=10)	UIH-002 (N=20)
Hispanic	0	1 (5%)
Non-Hispanic	10 (100)	19 (95%)

Source: Tables for demographics generated by clinical reviewer

[19] One (1) subject was initially enrolled in UIH-001 and received two islet cell transplants; this subject was subsequently enrolled into UIH-002 and received one transplant. The Applicant has presented data for this subject under both UIH-001 and UIH-002 resulting in the number of subjects for each study being reported as 10 and 21 respectively. Because This subject received 3 transplants in total, FDA has counted this subject only once in the analyses, under UIH-001, and as having received 3 transplants.

Table 6. Anthropometric Measurements of Subjects in Study UIH-001 and UIH-002 – Weight

Weight (kg)	UIH-001 (N=10)	UIH-002 (N=20)
Mean (SD)	62 (4.5)	65 (8.5)
Median (Min, Max)	62 (56, 71)	64 (53, 83)

Table 7. Anthropometric Measurements of Subjects in Study UIH-001 and UIH-002

BMI (kg/m^2)	UIH-001 (N=10)	UIH-002 (N=20)
Mean (SD)	22 (0.95)	24 (1.9)
Median (Min, Max)	23 (21, 24)	23 (21, 27)

Abbreviations: BMI, body mass index; SD, standard deviation
One subject did not provide height
Source: Tables for anthropomorphics generated by clinical reviewer

Table 8 and **Table 9** contain the baseline diabetes characteristics for the 30 subjects in UIH-001 and UIH-002 combined.

Table 8. Baseline Diabetes Characteristics for UIH-001

	N	Mean	SD	Min	Max
Age at diagnosis (years)	10	18.4	13.5	6	53
Time since diagnosis (years)	10	28	9.8	10	41
Age at treatment (years)	10	46.4	10.2	35	63
Baseline insulin (units/kg/day)	10	0.52	0.14	0.25	0.68
HbA_{1c} baseline	9[a]	7.3	1.1	5.9	9.5
Frequency of SHE at baseline (events in 1 year)*	10	0.1	0.3	0	1
HYPO Score** at baseline	7	88.2	68.0	11.1	211.9

N = number of subjects
*Using updated information provided by Applicant in response to a request for additional information.
**As calculated by the Applicant
Source: Table generated by clinical reviewer

Table 9. Baseline Diabetes Characteristics for UIH-002

	N	Mean	SD	Min	Max
Age at diagnosis (years)	20	17.4	13	1	39
Time since diagnosis (years)	20	29.4	13.4	9	53
Age at treatment (years)	20	46.9	12.5	21	67
Baseline insulin (units/kg/day)	20	0.47	0.14	0.14	0.78
HbA_{1c} baseline	20	7.4	0.9	5.8	9.3
Frequency of SHE at baseline (events in 1 year)*	20	0.5	1.1	0	4
HYPO Score** at baseline	12	428.5	491.7	2.4	1638

N = number of subjects
*Using updated information provided by Applicant in response to a request for additional information.
**As calculated by the Applicant
Source: Table generated by clinical reviewer

The enrolled population was limited to adults with long-standing T1DM; all subjects had T1DM for at least 9 years. Subjects' HbA_{1c} was not markedly elevated; no subject had a HbA_{1c} >10%, and only 2 subjects had HbA_{1c} > 8.5% at baseline. Only 3 (10%) subjects had recurrent SHE at

baseline. Only 1 (3.3%) subject had a HYPO score at baseline that was consistent with a serious problem with hypoglycemia.

The HYPO Score is used as an objective system to quantify the degree and severity of hypoglycemia to standardize assessment of patients undergoing solitary pancreas or islet cell transplantation. A HYPO Score ≥ 1,047 (90th percentile) indicates serious problems with hypoglycemia, scores 423 - 1,046 indicate moderate problems, and scores < 423 indicate less serious problems.

Eighteen of 30 (60%) subjects had baseline HYPO Scores data in the study reports. Of these 18 subjects, only 1 (5.5%) subject had a HYPO Score ≥ 1,047; 3 (16.7%) subjects had a HYPO Scores 423 to 1,046; and 14 (77.8%) subjects had HYPO Scores < 423. Based on the criteria for the HYPO Score, only 1 subject met the criterion for serious problems with hypoglycemia. Additionally, in response to a request for additional information, the Applicant provided their method for calculating the HYPO Score. The Applicant's calculation was not performed according to the method described by the authors who developed the score. Therefore, these data, as presented, are difficult to interpret.

5.1.2 Diabetic Complications

Of the 10 subjects in UIH-001, 7 (70%) had complication of diabetes; 1 with retinopathy, neuropathy, and nephropathy, 2 with retinopathy and neuropathy, 3 with neuropathy, and 1 with retinopathy[20].The presence of diabetic complications was one of the elements included in inclusion criteria for UIH-001.

Of the 20 subjects in UIH-002, 6 (30%) had complications of diabetes; 1 with retinopathy and neuropathy, 3 with retinopathy, and 2 with neuropathy. [21]

The presence of these microvascular complications from type 1 diabetes in this study population is not unexpected given the duration of diabetes since diagnosis [14].

5.2 Subject Disposition

Twenty-nine (29) of 30 subjects (96.7%) completed the 1-year follow-up after the last transplant. Two (2) subjects (6.7%) withdrew consent within the first year: 1 because of adverse effects of immunosuppression, and 1 became non-adherent to the immunosuppression regimen (this subject did provide 1-year data). Neither subject achieved insulin independence for any duration.

[20] Data provided obtained from the Applicant's response to a request for additional information.
[21] From Applicant's data base.

Of the remaining 28 subjects (% of total subjects reported)

- Seven subjects (23.3%) had insulin independence at their last follow-up visit. These subjects continue to be followed. However, because of the varied time since first transplant, the duration of follow-up ranged from 2.5 to 12.25 years. Of these 7 subjects, 2 had SHE at baseline (4 and 3 events in the previous year).
- Seven subjects (23.3%) stopped immunosuppression related to adverse events related to immunosuppression. 2 subjects had severe intolerance to immunosuppression, 1 of these 2 was never insulin independent. 4 subjects had severe infections; all 4 had insulin independence. And 1 subject had post-transplant lymphoproliferative disease. This last subject had baseline SHE (1 event); the other 6 subjects did not.
- Four subjects (13%) remained on immunosuppression without being insulin independent. 1 subject was never insulin independent. None had baseline SHE.
- Three subjects (10%) lost islet cell function after the first transplant, but no donor organ was available; immunosuppression was discontinued. 2 of the 3 had transient insulin independence. The only subject with baseline SHE (2 events) never became insulin independent.
- Two subjects (6.7%) had serious medical conditions. One subject was insulin independent after the 3rd transplant, but a diagnosis of breast cancer required discontinuation of immunosuppression. One subject became insulin independent after the 3rd transplant but required coronary artery bypass surgery. This subject had loss of islet cell function and eventual withdrawal of immunosuppression. Neither subject had baseline SHE.
- Two subjects (6.7%) lost islet cell function and immunosuppression was discontinued. Both subjects had insulin independence, 4.7 and 5.7 years. One subject had baseline SHE (1 event).
- One subject (3.3%) had 3 transplants with insulin independence for 1.3 years after the third transplant but then had declining islet cell function. The subject withdrew from study and underwent whole pancreas transplantation. This subject had initial insulin independence but later lost pancreas function. The subject did not have SHE at baseline.
- One subject (3.3%) lost function and had donor-specific antigens. Never insulin independent. No baseline SHE.
- One subject (3.3%) had been insulin independent but became non-adherent to immunosuppression, lost graft function and immunosuppression stopped. No baseline SHE.

5.3 Transplants Received

5.3.1 Number of Transplants

The protocols for UIH-001 and UIH-002 allowed for repeated transplants based on the criteria described in Sections 4.1.4 and 4.2.4 respectively. There was no set interval between the transplants. This section describes the number of transplants received by each subject in total (Table 10) and within the first year (Table 11). The variability in total duration of each transplant interval by study is summarized in Table 13 and Table 14.

Table 10. Number of subjects receiving 1, 2 or 3 total transplants for UIH-001 and UIH-002

Number of Transplants Received	UIH-001 Subjects N=10	UIH-002 Subjects N=20	Total Transplants
1	3	8	**11**
2	2	10	**24**
3	5	2	**21**
Total	-	-	**56**

Source: Table generated by clinical reviewer

Table 10 shows 11 (37%) subjects received a single transplant, 12 (40%) subjects received 2 transplants, and 7 (23%) subjects received 3 transplants. Table 11 and Table 12 shows that 47 of the 56 (84%) total transplants performed in Studies UIH-001 and UIH-002 were performed within the first year. Twenty-one (21) subjects (70%) received all of their transplants within the first year, and 9 subjects (30%) had one additional transplant after the first year.

Table 11. Number of subjects receiving 1, 2 or 3 transplants in the first year for UIH-001

Total Transplants Received	1 Transplant Received in the First Year	2 Transplants Received in the First Year	3 Transplants Received in the First Year
1	3	0	0
2	1	1	0
3	0	3	2

Table 12. Number of subjects receiving 1, 2 or 3 transplants in the first year for UIH-002

Total Transplants Received	1 Transplant Received in the First Year	2 Transplants Received in the First Year
1	8	0
2	3	7
3	0	2

Source: Table generated by clinical reviewer

Nineteen (19) of 30 subjects (63.3%) received a second transplant. Of these, 6 (31.6%) were insulin independent at the time of transplant. Three (10%) did not receive a second transplant because a donor organ was not available. Four (4) subjects (36.4%) did not receive a second transplant due to intolerance to immunosuppression or withdrawing from the study within 6 months. Seven (7) of 30 subjects (23.3%) received a third transplant. All were insulin dependent at the time of the third transplant. No subject did not receive a third transplant due to unavailable organs. Three (3) subjects did not receive a third transplant due to intolerance or non-adherence with immunosuppression, and 1 subject due to infection.

5.3.2 Duration of follow up

Table 13 and Table 14 provide summary statistics describing the follow up duration of each transplant by the number of transplants received by subjects and for the total follow up duration of the study. This demonstrates the variability in the number and duration of follow up periods after transplants.

Table 13. Total follow up duration of all transplant intervals by total number of transplants for UIH-001

Total Number of Tx	Transplant	N	Mean (years)	SD	Min	Max
1	Tx#1	3	7.6	5.5	1.5	12.3
2	Tx#1	2	1.6	1.7	0.5	2.8
-	Tx#2	-	9.3	1.2	8.5	10.2
3	Tx#1	5	0.3	0.3	0.1	0.6
-	Tx#2	-	2.6	3.0	0.2	7.7
-	Tx#3	-	3.7	3.3	1.2	9.3

Source: Table generated by the clinical reviewer

Table 14. Total follow up duration of all transplant intervals by total number of transplants for UIH-002

Total Number of Tx	Transplant	N	Mean (years)	SD	Min	Max
1	Tx#1	8	2.4	3.4	0.3	10.7
2	Tx#1	10	0.9	0.8	0.1	2.6
-	Tx#2	-	4.9	2.3	1.0	8.7
3	Tx#1	2	0.3	0.3	0.1	0.5
-	Tx#2	-	2.9	2.6	1.0	4.7
-	Tx#3	-	5.5	1.2	4.6	6.4

Source: Table generated by the clinical reviewer

Table 15 provides summary statistics describing the total duration of follow up from the first transplant for each study[22].

Table 15 Total Duration of Follow up for UIH-001 and UIH-002

Total Duration Subject Followed (years)	N	Mean	SD	Min	Max
UIH-001	10	7.8	4.4	1.5	13
UIH-002	20	4.7	3.5	0.3	10.7

Source: Table generated by the clinical reviewer

The Applicant performed their efficacy and safety analyses using the period 1 year after the first transplant and one year after the last transplant. This approach results in unequal periods of follow-up, 1 year for those subjects receiving only 1 transplant, up to 2 years for those subjects receiving all transplants within the first year, and longer for the 9 subjects receiving additional

[22] The first transplant occurred in UIH-001 on 1/11/2005 and the last transplant occurred in UIH-002 on 7/15/2016. The data cut-off for the BLA submission was 9/30/2018. As a result the potential duration for follow up was greater for those subjects enrolled in UIH-001 compared to those enrolled in UIH-002.

transplants after the first year. For those subjects who achieve insulin independence, immunosuppression must be continued to maintain islet cell viability. Limiting the duration for analysis to 1 year does not fully describe the experiences of subjects who received donislecel by intraportal infusion and remain on immunosuppression after the 1-year period. The risks from continued immunosuppression are concurrent with the benefit of insulin independence.

FDA believes durability of clinical effect and number of transplants could inform the benefit-risk decision. Therefore, FDA included the entire follow-up period and number of transplants in their analyses of efficacy and safety.

6 Efficacy

6.1 Applicant's Primary Efficacy Analysis

The Applicant's primary efficacy analysis for their two main studies, UIH-001 and UIH-002, used a composite efficacy endpoint of absence of SHE and HbA1c ≤ 6.5%. Table 16 provides the results of this combined analysis.

Table 16. Primary Efficacy Endpoint at 1 Year after Last Transplant – Studies UIH-001 and UIH-002, Integrated Summary of Efficacy Main Group

Outcome	Main Group N=30 [a]
Success n (%) [b]	19 (63.3)
Success (HbA_{1c} ≤ 6.5% + Free of SHE) 95% C.I. [c]	44, 80
Failure HbA_{1c} > 6.5% **n (%)**	5 (16.7)
Failure Any SHE **n (%)**	7 (23.3)

C.I., confidence interval; SHE, severe hypoglycemic event

[a] Main Group = total subject population from UIH-001 and UIH-002; one subject previously enrolled in UIH-001 was reenrolled in UIH-002 and was counted as a single subject for the Main Group population.

[b] Any SHE occurring between Day 28 and Day 365 (Day 0 = day of transplant). This is applicant's classification of SHE based on a definition of "event with symptoms compatible with hypoglycemia in which the subject required the assistance of another person, and which was associated with either a blood glucose < 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration."

[c] Calculated by the Clopper-Pearson exact method

Source: Modified by from the Applicant's Table 5, Integrated Summary of Efficacy

As stated in the Executive Overview, there were significant issues with missing baseline data and inclusion of 25/30 (83.3%) subjects without baseline SHE and with 6/30 (20%) with a HbA1c at the target HbA1c; this limits the interpretability of the Applicant's primary analysis.

SHE

The Applicant's primary efficacy requires that there is an absence of SHE in the year after the first transplant or year after the last transplant. In protocol UIH-002, severe hypoglycemia was defined as an event with symptoms compatible with hypoglycemia in which the subject required the assistance of another person, and which was associated with either a blood glucose < 50 mg/dL or prompt recovery after oral carbohydrate, intravenous glucose, or glucagon administration. The Applicant did not provide baseline data on the number of SHE for 15 of 30

(50%) subjects. Failure to have recorded SHE prior to transplant makes it impossible to demonstrate an improvement in these events after transplant. In response to a request from the FDA, the Applicant performed a chart/ record review and provided a listing of all subjects with SHE in the year prior to their first transplant using the definition "*cognitive dysfunction (confusion) requiring the assistance of a third party (someone else)*" [15]. The Applicant used the inclusion criterion of one episode of SHE in the 3 years prior to the first transplant. FDA examined the number of SHEs prior to the first transplant to provide an equivalent period for comparison to the one year after the first transplant or one year after the last transplant.

Table 17. Number of SHE in the Year Prior to First Transplant for UIH-001 and UIH-002

# SHE	# Subjects N=30	% of Total
0	25	83.3%
1	2	6.7%
2	1	3.3%
3	1	3.3%
4	1	3.3%
Total	**30**	100%

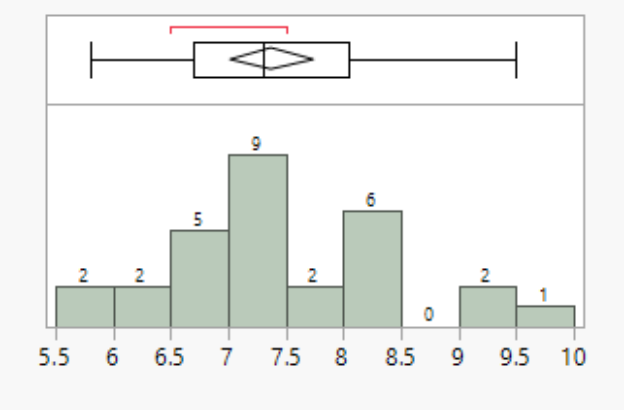
Source: Generated by the clinical reviewer

Table 17 demonstrates that of the 30 subjects, 25 (83.3%) did not have documented SHE in the year prior to their first transplant. Therefore, the absence of SHE in the year after transplant would not represent a change for these 25 subjects.

HbA_{1c}

There was large inter-subject variability in the time from screening to the first transplant. As the HbA1c value available at screening was sometimes reported years prior to first transplant, the FDA utilized the HbA1c values obtained within the shortest time period prior to the first transplant as the baseline value for FDA's analysis. (The mean interval of sampling before first transplant was 50 days, minimum 3 days and maximum 141 days.) Of the thirty subjects, 11 (37%) had an HbA_{1c} of $\leq 7\%$ prior to transplant, and 6 (20%) had $\leq 6.5\%$, with 6.5% and 7% being accepted targets for good glycemic control in diabetic patients. Figure 1 shows the distribution of HbA1c and Table 18 the summary statistics for subjects at baseline. A baseline HbA_{1c} was not reported for one subject. As summarized in the adverse event section (Section 7.3), 25 of 30 (83.3%) subjects in the studies had mild to severe anemia during the study. Conditions that increase the rate of red blood cell turnover, such as anemia, can falsely lower HbA_{1c} and affect the interpretation of this endpoint. Therefore, there are limitations in the ability to demonstrate a clinically meaningful improvement in HbA_{1c}.

Figure 1. HbA_{1c} prior to the First Transplant for UIH-001 and UIH-002



Source: Generated by the clinical reviewer

Table 18: Baseline HbA1c (%)

N [a] Subjects	Mean	SD	Min	Max	SEM	Median
29	7.4	0.94	5.8	9.5	0.17	7.3

[a] One subject did not have a baseline HbA_{1c} reported

Therefore, FDA believes that the Applicant's proposed composite efficacy primary endpoint of $HbA_{1c} \leq 6.5\%$ and absence of SHE is not supported by the data provided.

6.2 FDA's Efficacy Analysis

While the data describing the changes in the occurrence of SHE and HbA_{1c} were not supportive of the efficacy of donislecel transplant, the FDA review team noted that 21/30 (70%) subjects in the combined studies achieved insulin independence. This was the primary endpoint in UIH-001 and a pre-specified secondary endpoint in UIH-002. To our knowledge, reversal to insulin independence without therapeutic intervention in patients with established T1DM (i.e., after the so called "honeymoon period") has not been reported outside of errors in diagnosing monogenetic diabetes, or onset of insulinoma. Therefore, FDA performed extensive analyses of the ability of study subjects to achieve insulin independence and the durability of insulin independence.

FDA evaluations consider the variability in the number of transplants received by subjects and duration of follow-up.

It is very important to note that FDA does not endorse a change in primary efficacy endpoint for an integrated analysis of efficacy after trials are conducted and analyzed, with rare exceptions in the past. However, in this circumstance, the review team understood that durable insulin independence without evidence of hypoglycemia is a stronger demonstration of clinical benefit compared to adequate glycemic control without serious hypoglycemia, is a more conservative

endpoint and, in addition, has been proposed in the 2009 FDA Guidance as an alternative primary efficacy endpoint.

6.2.1 Occurrence of Insulin Independence in Study UIH-001 and UIH-002

Of the 30 subjects in UIH-001 and UIH-002, 25 (83.3%) subjects became insulin independent for any duration. Five (5) subjects (16.7%), all of whom were enrolled in UIH-002, never became insulin independent; 4 of these 5 received only 1 transplant; and the other subject who never achieved insulin independence received 2 transplants.

Table 19 and Table 20 provides summary statistics for the duration of insulin independence for all thirty subjects in UIH-001 and UIH-002 by the total number of transplants in the individual transplant interval.

Table 19. Duration of Insulin Independence by Number of Transplants Received for UIH-001

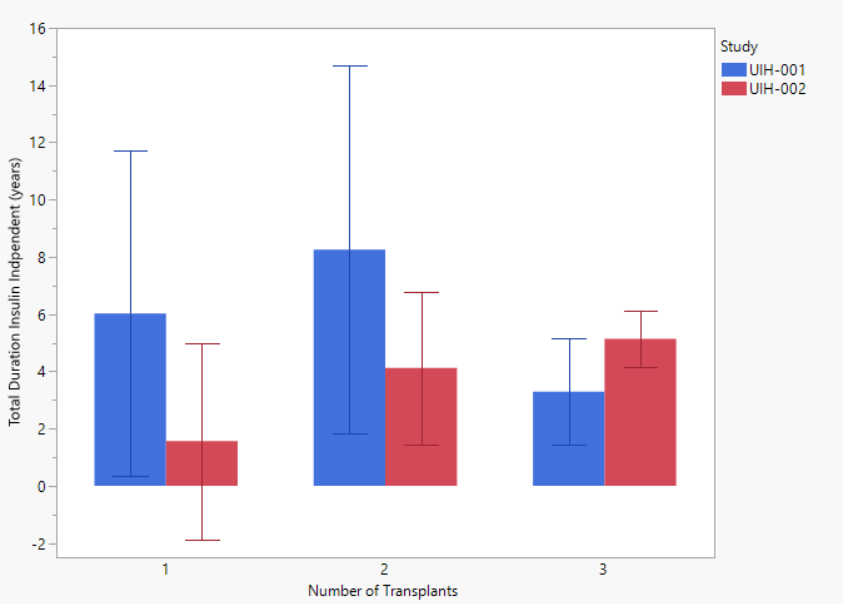
Total Number of Transplants	Transplant	N	Mean	SD	Min	Max
1	Tx#1	**3**	6.0	5.7	0.24	11.6
2	Tx#1	**2**	1.4	2.0	0	2.8
-	Tx#2	-	6.9	4.4	3.7	10.0
3	Tx#1	**5**	0.14	0.2	0	0.5
-	Tx#2	-	1.4	2.1	0	4.8
-	Tx#3	-	1.7	1.5	0	4.0

Table 20. Duration of Insulin Independence by Number of Transplants Received for UIH-002

Total Number of Transplants	Transplant	N	Mean	SD	Min	Max
1	Tx#1	**8**	1.6	3.4	0	9.9
2	Tx#1	**10**	0.4	0.6	0	1.9
-	Tx#2	-	3.7	2.3	0	6.0
3	Tx#1	**2**	0	0	0	0
-	Tx#2	-	1.7	2.5	0	3.5
-	Tx#3	-	3.4	1.5	2.4	4.5

Figure 2 is provided to compare the outcomes for all subjects in UIH-001 and UIH-002 showing the total duration (mean ± SD) of insulin independence by the number of transplants. This figure suggests that duration of insulin independence achieved after donislecel treatment cannot be predicted by the number of transplants received.

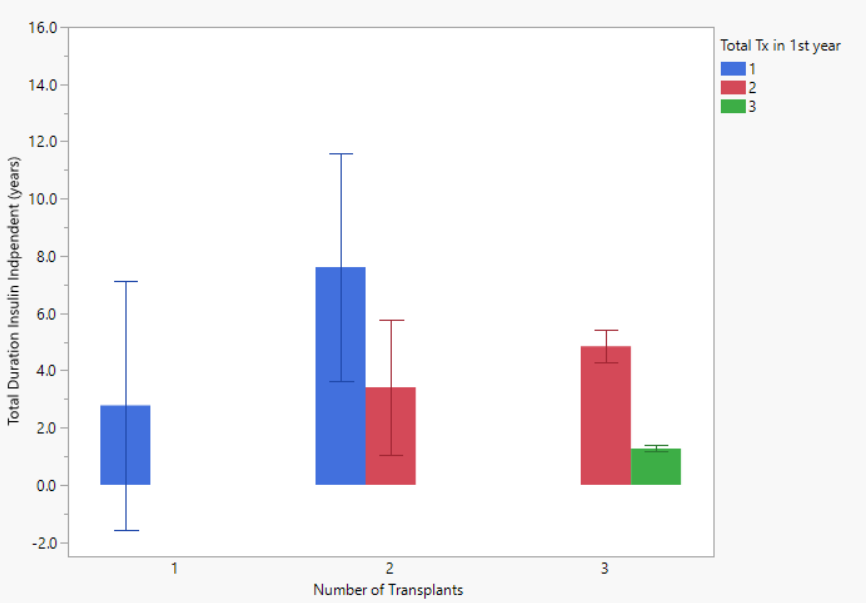
Figure 2. Duration of Insulin Independence According to Number of Transplants Received by UIH-001 and UIH-002



Mean ± SD
Source: Generated by clinical reviewer

Figure 3 is provided to compare the outcomes for all subjects in UIH-001 and UIH-002 showing the total duration of insulin independence by the number of transplants received in the first year.

Figure 3. Mean Duration of Insulin Independence According to Number of Transplants Received in the First Year



Source: Generated by clinical reviewer

Table 21 provides summary statistics describing the total duration of insulin independence from the first transplant for each study[23].

Table 21. Total Duration of Insulin Independence for UIH-001 and UIH-002

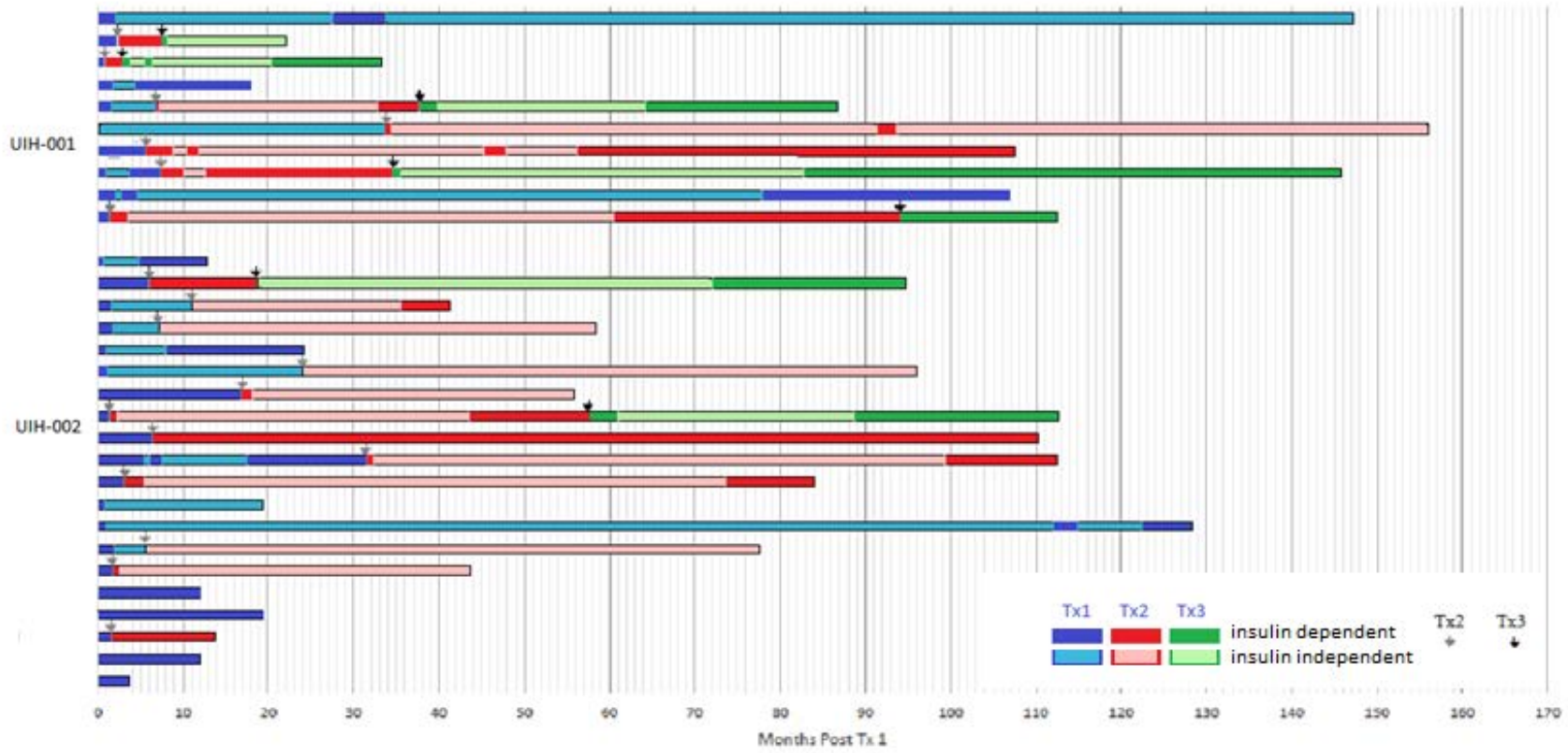
Total Duration Insulin Independent (years)	N	Mean	SD	Min	Max
UIH-001	10	5.1	4.2	0.24	12.8
UIH-002	20	3.2	3.1	0	9.9

Source: Table generated by the clinical reviewer

For those 25 subjects ever insulin independent, 4 subjects (13.3%) were insulin independent for less than 1 year, 11 subjects (36.7%) for 1 to 5 years, and 10 subjects (33.3%) for greater than 5 years. To account for the variable duration of follow-up, the following graphic (Figure 4) shows the entire experience of the individual subjects.

[23] The first transplant occurred in UIH-001 on 1/11/2005 and the last transplant occurred in UIH-002 on 7/15/2016. The data cut-off for the BLA submission was 9/30/2018. As a result, the potential duration for insulin independence was greater for those subjects enrolled in UIH-001 compared to those enrolled in UIH-002.

Figure 4. Duration of Insulin Dependence or Independence by Transplant for Each Subject.



Graphic generated by Applicant.
Color coding by clinical reviewer

Figure 4 shows the total duration for each subject. The transplant period color coded by transplant number (Transplant 1 blue, Transplant 2 red, Transplant 3 green), and insulin dependence (darker blue, red, and green) and independence (lighter blue, pink, and lighter green). Time zero (0) is the time of the first transplant. The arrows denote the time of second and third transplant.

FDA compared the total duration of insulin independence by the total duration followed for all subjects in UIH-001 and UIH-002 according to the number of transplants received. This did not suggest that the duration of insulin independence could be predicted by the total number of transplants received.

FDA examined whether any baseline factors impacted duration of insulin independence. Specifically, the FDA looked at baseline SHE, baseline HbA1c, duration of diabetes, age and sex and did not identify any major differences. The results in these small sub-populations were generally consistent with the overall data.

FDA examined the duration of insulin independence based on baseline number of SHEs. Table 22 provides the duration of insulin independence achieved by subjects with SHE in the year prior to their first transplant. Baseline SHE was not predictive of insulin independence.

Table 22. Insulin Independence Based on Baseline SHE

Baseline # SHE	Insulin independence	Duration in Years Median (Range)
1	2/2 (100%)	7.3 (4.7, 9.9)
2	0/1	0
3	1/1 (100%)	3.4
4	1/1 (100%)	4.7

Source: Generated by Clinical reviewer based on data provided by Applicant

The restoration of insulin independence removes the risk of hypoglycemia from exogenous insulin; therefore, for subjects who were able to achieve insulin independence, there is a reasonable expectation that severe hypoglycemia would not occur.

There were 7 subjects with baseline HbA_{1c} >8%, 4 (57 %) who achieved insulin independence. (One subject did not have a baseline HbA_{1c}). The number of transplants and duration of insulin independence were consistent with what was seen in the total study population.

6.3 Efficacy Conclusion

Intraportal transplantation of donislecel, allogenic pancreatic islet cells, using the modified Edmonton Protocol can provide prolonged insulin independence for a subset of patients with type 1 diabetes.

7 SAFETY

7.1 Study Population

The safety analysis was based on 30 subjects (56 total transplants) who were enrolled in the Phase 1/2 study and Phase 3 study. Subjects were followed for a mean of 6.5 years (range 0.3 – 13.0 years).

7.2 Study Discontinuation

Study discontinuations are described in Section 5.2. Subject Disposition.

7.3 Adverse Events (AEs)

In the clinical studies, different subjects received donislecel at different time points; therefore, parallel comparison of rates of AEs is not always possible, especially since there was no control group. The Applicant performed their safety evaluation for the duration of 1 year after the last transplant. Twenty-one (70%) of the 30 subjects received all transplants within the first year. This would limit the assessment of safety for the majority of subjects to 2 years. Given the potential risks associated with the donislecel and the immunosuppression required to maintain the viability of donislecel, FDA believes that this duration for assessment for adverse events is insufficient. Therefore, FDA performed an assessment of safety based on all adverse events that occurred after the first transplant through the last date followed.

7.3.1 Overall Summary of Treatment-Emergent Adverse Events (TEAEs)

All 30 subjects (10 in UIH-001 and 20 in UIH-002) in the clinical studies had TEAEs (Table 23). A list of all TEAEs Grade 2 and above is found in Appendix 3. Unless otherwise noted, FDA evaluated all adverse events that occurred during the entire time the subject had been followed in the study.

Table 23. Total Treatment-Emergent Adverse Events by UIH-001 and UIH-002

Adverse Event Severity	N	UIH-001	UIH-002
Death	1	0	1
Life-Threatening	11	4	7
Severe	124	46	78
Moderate	420	161	259
Mild	1344	513	831
Missing Severity Category	142	92	50

Source: Generated by Clinical reviewer

A total of 1,319 adverse events occurred during the first year after the first transplant: 8 life-threatening, 75 severe, 240 moderate, 906 mild, and 90 “missing”[24].

In Years 2 through 5 after the first transplant, there were a total of 452 adverse events: 1 death, 1 life-threatening, 28 severe, 106 moderate, 271 mild, and 45 “missing”. Twenty-two (22) subjects contributed data to the safety data base after the first year.

[24] The Applicant’s adverse event data base did not include a severity score for these events.

Five (5) or more years after the first transplant, there was a total of 271 adverse events; 2 life-threatening, 21 severe, 74 moderate, 167 mild, and 7 "missing". Twelve (12) subjects contributed to the safety data base after 5 years, and 3 subjects after 10years.

7.3.2 Deaths

One (1) subject (3.3%) died of multiorgan failure secondary to infection of unknown origin 592 days after the first transplant. The Applicant's determination of causality was "probably related to immunosuppression/study drug."[25] This subject was on immunosuppression up to the time of the described event. FDA agrees that this subject's death was probably related to the investigational treatment.

7.3.3 Life-Threatening Serious Adverse Events (SAEs)

Table 24. Life-Threatening Adverse Events

Adverse Event Preferred Term (AEPT)	N events
Neutropenia	4
Anemia	1
Breast cancer	1
Hyperlipasemia	1
Pancytopenia	1
Papillary thyroid cancer	1
Post-transplant lymphoproliferative disease PTLD)	1
Urosepsis	1

Source: Generated by Clinical reviewer

Six (6) subjects (20%) of subjects experienced 11 life-threatening adverse events (Table 24).

7.3.4 Adverse Events of Special Interest

Of the 142 adverse events without a designation of severity, 13 (9.2%) were adverse events that may be considered significant. Ten of these events were contained within the adverse event database. An additional three events were left ventricular hypertrophy, nausea and vomiting requiring hospitalization and lymphoproliferative disorder of the lacrimal gland.

[25] This subject only received 1 transplant. As such, under the Applicant's approach to evaluating adverse events, this death was not counted in the primary analysis of safety because it was after the first year after the transplant.

Anemia

Table 25. Number of Adverse Events of Anemia

N	Life-Threatening	Severe	Moderate	Mild	Missing
83	1	6	24	51	1

Source: Generated by Clinical reviewer based on data provided by Applicant

In total, 83 AEs of anemia were reported in 25 of 30 subjects (83.3%). Three (3) subjects (10%) required transfusion (Table 25).

Neoplasm

Table 26. Subjects with Neoplasms

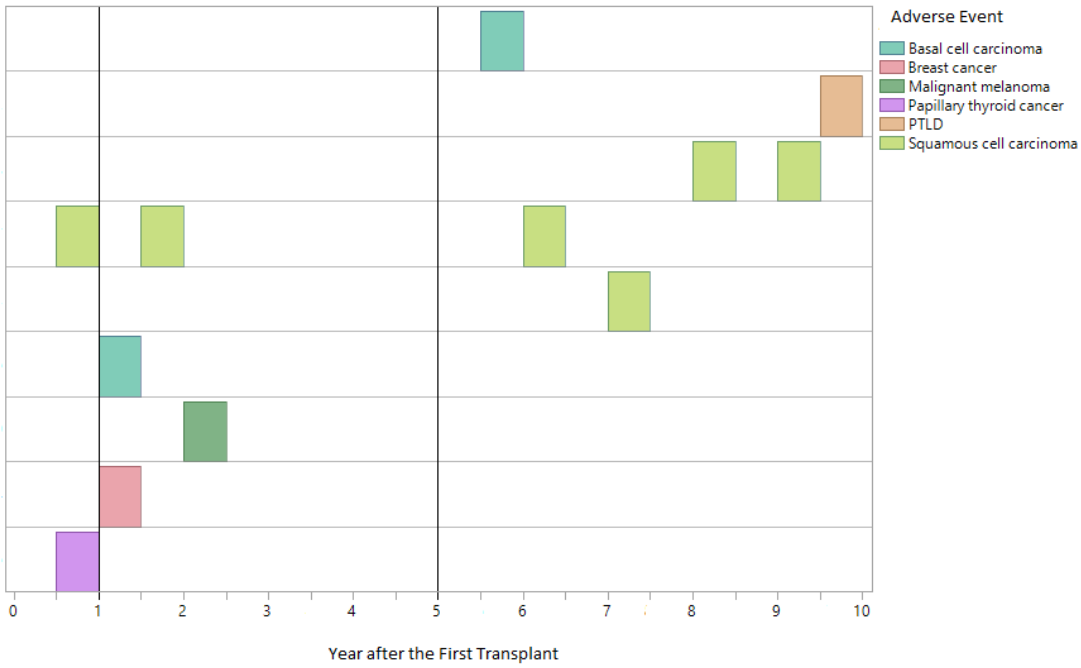
Adverse Event Preferred Term	N Events	N Subjects
Papillary thyroid cancer	1	1
Breast cancer	1	1
Squamous cell carcinoma	7	4
Basal cell carcinoma (face)	2	2
Malignant melanoma	1	1
Malignancy – PTLD	1	1

Source: Generated by Clinical reviewer based on data provided by Applicant

Fourteen (14) subjects (46.7%) had an adverse event of neoplasm. Table 26 lists the 13 cancers attributed to 9 subjects up to 10 years after the first transplant. Of these, 9 were skin cancers in 6 subjects; no subjects were reported to have had any skin cancer prior to their first transplant. This finding is consistent with that reported for the occurrence of skin cancers in whole pancreas transplants [16].

Figure 5 provides the timeline for the development of cancers up until data cut-off. Each line represents an individual subject. As can be seen, all cancers were diagnosed at least 6 months after the first transplant.

Figure 5 Time from Detection of Cancer from First Transplant



Source: Generated by Clinical reviewer

Injuries

Table 27 provides a summary of injuries of special interest, because of their association with the procedure for islet cell transplantation or may be related to immunosuppression.

Table 27. Procedural Complications and Selected Injuries

Adverse Event Preferred Term	Severe	Moderate	N events	N subjects
Hepatic hematoma	0	2	2	2
Fracture	3	0	3	3
Anemia postoperative	1	0	1	1
Procedural complication (Liver laceration)	1	0	1	1

Source: Generated by Clinical reviewer

Of the 30 subjects, 3 subjects (10%) experienced four serious procedure-related adverse events, one liver laceration and vascular injury at the time of the second transplant that required emergency surgery, and two hepatic hematomas. These adverse events are not unexpected in invasive procedures such as catheterization of the portal vein.

There were 2 (3.6%) of 56 transplants with reported elevated portal pressures during the infusion procedure.One (1) subject had a final portal pressure of 22 mgHg, the procedure was completed. One (1) subject had an elevated portal pressure during the procedure and did not receive the entire transplant. No long-term complications were reported related to these events.

Of the 30 subjects, 3 subjects (10%) experienced a fracture. There is insufficient information to fully describe the baseline fracture risk for these individual subjects. However, both T1DM [17] and immunosuppressive drugs after transplant [9] are known to be associated with decreased bone density, which increases the risk of fracture.

Infections

Immunosuppression is known to increase the risk of infection, both for those common community-acquired infections and those rarely seen in the absence of immunosuppression, either from underlying disease or iatrogenic.

In total, 178 AEs of infection were reported for 26 of 30 subjects (86.7%); 1 life-threatening (urosepsis), 12 severe, 94 moderate, 59 mild, and 12 without attribution (missing) that included 2 episodes of pneumonia, 2 of herpes, and 1 of cellulitis. (Table 28) Additionally, there was one subject who died of multi-organ failure from sepsis in the second year after transplant.

Table 28. Infections

Infections of Special Interest	N
Herpes virus infection	10
Pneumonia	6
Oral candidiasis	4
Cytomegalovirus infection	3
Osteomyelitis	2
Infectious mononucleosis	2
Cellulitis	2
Clostridium difficile colitis	1
Cryptosporidiosis infection	1
Epstein-Barr virus infection	1
Parotitis	1
Urosepsis	1
Viral pericarditis	1

Source: Generated by Clinical reviewer

Infections can be life-threatening and even result in death. Some infections, such as herpes primary infection or recurrence (zoster), can be mild or moderate as with cold sores, or become more serious causing significant pain or even have neurological sequelae and become life-threatening. Oral candidiasis, while not life-threatening, can cause severe pain and interfere with eating. This can be of concern in patients taking insulin because of the potential to have failure to complete a meal after injection of insulin, increasing the risk for hypoglycemia.

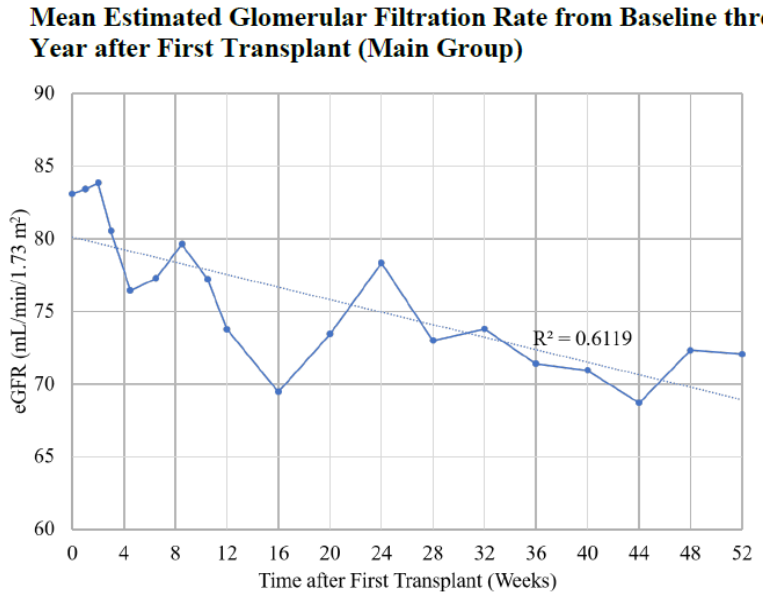
Infections such as pneumonia can be life-threatening and may require decrease or discontinuation of immunosuppression to treat the infection. The discontinuation of

immunosuppression is expected to result in loss of islet cell function and any insulin independence. This was described for 8 subjects in the section summarizing subject disposition.

Renal Impairment

While one of the goals of achieving glycemic control to near normal values is to reduce the risk of diabetic complications, including nephropathy, some immunosuppressants have been associated with deterioration of renal function[18]. The Applicant performed analysis of changes in eGFR from baseline to 1 year after the first transplant (Figure 6 and Table 29).

Figure 6. Mean eGFR in the First Year After Transplant



Source: Applicant's Figure 4, 2.7.4 Summary of Clinical Safety.pdf, page 49

At baseline (n=30), 10 (33%) subjects had normal renal function (eGFR >90 mL/min/1.73 m^2), 14 (47%) had mild impairment (eGFR 60-89 mL/min/1.73 m^2), and 6 (20%) had moderate impairment (eGFR 30-59 mL/min/1.73 m^2). There were no subjects with severe impairment (eGFR 15-30 mL/min/1.73 m2) and no subjects with end-stage renal disease (eGFR <15 mL/min/1.73 m^2). At 1 year after the first transplant, no subject changed by more than 1 category; 6 (20%) of 30 subjects had a persistent decline from mild to moderate impairment, 1 (3%) subject had a transient decline from moderate to severe impairment but no subjects had persistent decline to severe impairment or developed end-stage renal disease.

Table 29. eGFR and Serum Creatinine Levels at Baseline and 1 Year after the Indicated Transplant, by Transplant Number – Main Group

Parameter	Baseline N=31	Transplant #1 N=13 [a]	Transplant #2 N=17 [a]	Transplant #3 N=7 [a]
eGFR (mean±SD); mL/min/1.73 m^2	83.1±23.5	72.1±21.7	84.0±26.3	64.7±23.8
Serum creatinine (mean±SD); mg/dL	0.92±0.20	0.95±0.23	0.87±0.23	1.07±0.28

[a] N is the number of patients with evaluable data at 1 year after the indicated transplant.

Source: modified from Applicant's Table 10, 2.7.4 Summary of Clinical Safety.pdf, page 49

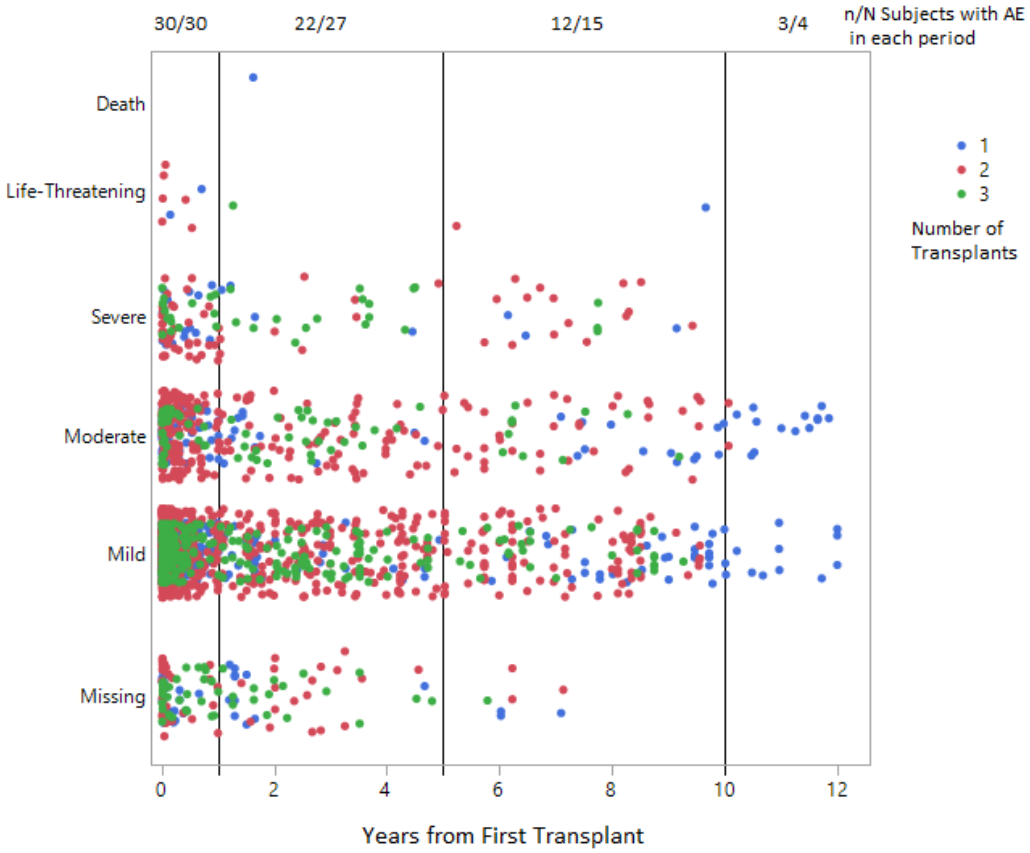
These data suggest that there may be a reduction in eGFR in subjects after receiving at least one transplant and concomitant medications. As stated previously, the Applicant's approach to limiting assessments to one year after the first transplant and one year after the last transplant results in a variable period of follow-up.

The development of microalbuminuria[26] is a measure of worsening of renal function in patients with type 1 diabetes. The expectation is that improvement in glycemic control can prevent or delay progression of microalbuminuria. At baseline, 5 subjects of 30 (16.7%) had microalbuminuria at baseline; none had macroalbuminuria. At 1 year after the first transplant, 6 additional subjects had microalbuminuria, and 3 had macroalbuminuria. Of those subjects with baseline microalbuminuria, 1 subject had improvement: 54 mg albumin/g creatinine to 12 mg/g, and one had worsening from 59 mg/g to 292 mg/g. Of those 10 subjects with significant progression in urine albumin, 5 were insulin independent. Therefore, even with the development of insulin independence, patients may still be at risk of nephropathy. The Applicant's database did not support further analysis of changes in eGFR or urine albumin. The results observed at 1 year are similar to those in a study examining kidney function in patients with type 1 diabetes and receiving a whole pancreas transplant [19].

Figure 7 shows the occurrence of adverse events over the entire course of follow-up by the number of transplants received. The lines represent 1-year, 5-years and 10-years after the first transplant. The number of subjects in each time segment is provided. As can be seen, serious adverse events continue to occur well past the first year after transplant.

[26] Microalbuminuria = 30-300 mg albumin/g creatinine, Macroalbuminuria > 300 mg/g.

Figure 7. Occurrence of Adverse Events by Day Since First Transplant



Each dot represents an individual event.
Source: Generated by clinical reviewer

7.4 Safety Summary

The adverse events observed in Studies UIH-001 and UIH-002 related to the procedure for donislecel transplantation and immunosuppression to maintain islet cell viability are not unexpected. There does not appear to be an excess of adverse events related to immunosuppression when compared to studies of whole pancreas transplantation in patients with type 1 diabetes. However, direct comparisons cannot be done due to the small number of patients and differences in study design.

8. Benefit-Risk Assessment

For patients with type 1 diabetes (T1DM), the use of exogenous insulin is an absolute requirement to maintain life. Insulin is the mainstay of therapy for T1DM. Over time, there have been improvements in the pharmacokinetics and pharmacodynamics of insulins to allow more tailored dosing. The evolution and development of devices to measure glucose, calculate insulin requirements, and deliver insulin have further improved the ability to tailor insulin dosing to

meet the individual needs of the patient. Nonetheless, there remains the risk of a mismatch of the insulin delivered to the needs of the patient, resulting in hypoglycemia.

Hypoglycemia can be severe with cognitive dysfunction, loss of consciousness, seizure, and death. Patients with hypoglycemic unawareness, due to loss of autonomic symptoms, are at increased risk of SHE. This risk may be particularly high in patients with high insulin sensitivity, as small increases in insulin doses can result in hypoglycemia. In addition to each episode of SHE being life-threatening, fear of SHE decreases health-related quality of life.

While all subjects enrolled into UIH-001 and UIH-002 were reported to have hypoglycemia unawareness, only 16.7% had documented SHE in the year prior to their first transplant. Therefore, an absence of SHE in either the year after the first transplant or year after the last transplant could not be attributed to treatment with donislecel. However, the ability of subjects to become independent from exogenous insulin can be attributed to treatment with donislecel. Seventy percent (70%), 21 of 30 subjects, achieved at least 1 year of insulin independence from exogenous insulin while maintaining or improving glycemic control, and 33% (10/30) subjects had insulin independence for at least 5 years. The maximum duration of reported insulin independence was 12.9 years. Restoration of complete endogenous insulin production would restore glucose homeostasis and avoid hypoglycemia in these subjects.

As presented in the safety section, there are significant risks associated with the treatment of donislecel, including but not limited to life-threatening procedural complications and complications from immunosuppression including serious infections, and cancers. Among the 30 subjects treated in UIH-001 and UIH-002, 1 subject (3.3%) died from multi-organ failure from an infection while on immunosuppression and attributed to the immunosuppression required for donislecel. Procedural complications included 1 (3.3%) subjects with a procedural liver laceration requiring emergency surgery, 2 (6.7%) subjects with hepatic hematomas, and 3 (10%) subjects requiring transfusions for severe anemia. While the procedural complications are mostly limited to the peri-procedural period, immunosuppression must continue to maintain islet cell viability. Therefore, the risk from immunosuppression exists for the entire period of insulin independence. Immunosuppression is associated with increased risk of infection, cancer, lymphoproliferative disease, anemia, fracture, and decreased renal function, all of which were observed in the UIH studies. There were 5 (16.7%) subjects with life-threatening neutropenia or pancytopenia, and 1 (3.3%) subject with a life-threatening infection, and 12 severe infections due to the immunosuppression. There were 14 subjects with neoplasms, and no subject had a prior history of malignancy; this includes 9 skin cancers in 6 (20%) subjects, 1 papillary thyroid cancer, 1 breast cancer, and 1 post-transplant lymphoproliferative disease. Consistent with the eligibility criteria, there were no pregnancies reported; however, chronic immunosuppression is associated with additional risks for pregnant women and their infants.

Transplantation with donislecel can restore insulin independence in some patients. Analyses of the sub-populations enrolled in UIH-001 and UIH-002 were unable to identify patient characteristics that would predict the likelihood of success. The procedure, product, and chronic immunosuppression can all contribute to severe and life-threatening adverse events. It is

important to consider these risks in the context of the potential benefit to subjects with T1DM with hypoglycemic unawareness and SHE.

Appendix 1. Allogenic Pancreatic Islet Cell Infusion

Product preparation is described in the CMC review

Route of administration intraportal administration

Access to the portal vein for islet transplantation is achieved by transvenous or percutaneous transhepatic access under fluoroscopic and ultrasound guidance. If a transvenous technique is used, access to the right jugular vein is obtained using a Microstik needle under ultrasound guidance. A guiding sheath is advanced through the right atrium and into the right hepatic vein. Position is confirmed with injection of contrast medium. Close monitoring of the cardiac rhythm by continuous ECG and pulse oximeter will be performed to allow rapid response to any cardiopulmonary events including cardiac dysrhythmias. Blood pressure will be monitored intermittently (every 2 minutes). A sheath needle is advanced anteromedially through the hepatic parenchyma under fluoroscopic guidance until access to a peripheral portal vein is obtained. The localization of portal vein puncture is confirmed similarly to the percutaneous technique described below, and the sheath advanced into the main portal vein. For the percutaneous approach, a local anesthetic agent (lidocaine) is injected subcutaneously, and a fine Chiba needle is used to puncture a peripheral branch of the right portal vein. Tiny amounts of angiographic contrast media are used to confirm satisfactory location of the puncture site in a peripheral portal vein. A thin, flexible guidewire is threaded into the main portal vein and the Chiba needle is exchanged for a 4 French catheter. This catheter is threaded over the guidewire to position the tip in the main portal vein. Contrast portogram is obtained using minimal contrast exposure, and the portal pressure is monitored by hooking up to an in-line pressure monitor via a 3-way tap after zeroing the monitor to room air pressure. Elevated absolute intraportal pressures (> 20 mmHg, or > 27 cm H_2O) confirmed at the beginning of the procedure will be considered a contraindication for continuing with the transplant infusion. If access to the portal vein cannot be gained by transvenous or transcutaneous approach, the subject will be brought to the operation theatre. A small laparotomy will be performed under local or general anesthesia, and portal access will be gained through cannulation of a mesenteric vein.

Portal pressure will be monitored before and after infusion of one syringe load (50 mL volume containing 1 mL of tissue). Any change in portal pressure will be documented, and if the intra-portal pressure rises above 22 mmHg, infusion of subsequent syringes must be held until the pressure falls below 18 mmHg. If the bag system is used, the portal pressure is taken intermittently, and if the intra-portal pressure rises above 22 mmHg, the infusion must be held until the pressure falls below 18 mmHg. The bag system must be repetitively and gently shaken to keep the islet preparation in suspension and avoid clumping. Following each infusion, if the

portal pressure remains elevated above 22 mmHg for longer than 10 minutes, then no further infusion will be administered through the hepatic vein and the procedure will be terminated.

After successful completion of the islet infusion, the catheter and syringe or bag system will be rinsed with an additional 20 mL of transplant media, which is infused through the cannula over approximately 2 minutes, and a final portal pressure documented. Under fluoroscopic guidance with very minimal further contrast exposure, the catheter tip is withdrawn from the main portal vein into the liver parenchyma until it lies within 2 cm of the liver capsule. Contrast media is used to confirm no flow into a portal or hepatic vein. While the subject continues to be monitored, a small Gelfoam® plug is placed in saline and is embolized into the peripheral catheter tract. This is done rapidly enough to make sure the Gelfoam® does not dissolve, and to ensure that the plug does not travel into an intrahepatic portal radicular branch or into a hepatic vein and into the lungs. The catheter is then removed completely and the subject returns to the ward with instructions to lie recumbent on the right side for 4 hours. Abdominal ultrasound and Doppler examination of the liver are performed the day after the procedure to exclude procedure related complications such as portal vein thrombosis or intraabdominal bleeding.
From Applicant's uih-001-amended-report-body, page 13]

Appendix 2. Full Exclusion Criteria

Subjects will be excluded from the study if one of the following conditions is present:

1. Diagnosis of co-existing cardiac disease, characterized by any one of these conditions:
   a. Recent myocardial infarction (within past six months), or
   b. Angiographic evidence of non-correctable coronary artery disease, or
   c. Evidence of ischemia on functional cardiac exam (with a stress echo test recommended for subjects with a history of ischemic disease).
   d. Heart failure > NYHA II
2. Active alcohol or substance abuse-includes cigarette smoking (must be abstinent for six months). Active alcohol abuse should be considered using the current NIAAA definitions.
3. Psychiatric disorder making the subject not a suitable candidate for transplantation, e.g., schizophrenia, bipolar disorder, or major depression that is unstable or uncontrolled on current medication. (A psychological or psychiatric consultation is required only if considered necessary by some current indication or history.)
4. History of non-adherence to prescribed regimens
5. Active infection including hepatitis C, hepatitis B, HIV
6. TB (by history or currently infected as evidenced by a positive QuantiFERON® -TB Gold test or under treatment for suspected TB)
7. Any history of malignancies except squamous or basal skin cancer. Any subject found to have squamous or basal cancers is recommended having it removed prior to transplant.
8. History of stroke within the past 6 months
9. BMI > 26 kg/m^2 or body weight > 70 kg at screening visit
10. C-peptide response to glucagon stimulation (1 mg I.V.) (any C-peptide ≥ 0.3 ng/mL)
11. Inability to provide informed consent
12. Age less than 18 or greater than 65 years
13. Creatinine clearance < 80 mL/min/1.73 m^2 by 24-hour urine collection. If corrected creatinine clearance is < 80 and serum creatinine is < 1.2 mg/dl, then a nuclear renal scan is required to determine glomerular filtration rate.
14. Serum creatinine > 1.5 mg/dL
15. Macroalbuminuria (urinary albumin excretion rate > 300 mg/24h)
16. Baseline Hb < 12 gm/dL in women, or < 13 gm/dL in men
17. Baseline liver function tests (LFT) outside of normal range (An initial LFT test panel with any values > 1.5 times normal upper limits will exclude a subject without a retest; a re-test for any values between normal and 1.5 times normal should be made, and if the values remain elevated above normal limits, the subject will be excluded.)
18. Untreated proliferative retinopathy
19. Positive pregnancy test, intent for future pregnancy, or male subjects' intent to procreate, unwilling to follow effective contraceptive measures, or presently breastfeeding
20. Previous transplant, or evidence of sensitization on PRA (determined by demonstration of positive results for anti-HLA antibodies using solid phase immunoassay with soluble HLA Class I molecules as a target, or a general PRA panel with reactivity > 20%). If PRA panel reactivity is > 20%, the subject requires a negative crossmatch with the donor before transplant (UNOS requirement).

(UIH-002)
Previous transplant (except islet transplant), or evidence of hyper sensitization on PRA (determined by demonstration of positive results for anti-HLA antibodies using solid phase immunoassay with soluble HLA Class I molecules as a target, or a general PRA panel with reactivity > 80%). All subjects require a negative crossmatch with the donor before transplant (UNOS requirement).

21. Insulin requirement > 0.7 IU/kg/day
22. HbA1C > 12%
23. Hyperlipidemia (fasting LDL cholesterol > 130 mg/dL, treated or untreated; and/or fasting triglycerides > 200 mg/dL)
24. Under treatment for a medical condition requiring chronic use of steroids
25. Use of coumadin or other anticoagulant therapy (except aspirin) or subject with PT-INR > 1.5. Low dose aspirin is allowed after transplantation
26. History of Factor V deficiency
27. Currently smoking tobacco
28. Addison's disease
29. Allergy to radiographic contrast material
30. Symptomatic cholecystolithiasis
31. Acute or chronic pancreatitis
32. Symptomatic peptic ulcer disease
33. Severe unremitting diarrhea, vomiting, or other gastrointestinal disorders that could interfere with the ability to absorb oral medications
34. Treatment with antidiabetic medication other than insulin within 4 weeks of enrollment
35. Use of any study medication within 4 weeks of enrollment
36. Received live attenuated vaccine(s) with 2 months of enrollment

(UIH-002)
37. Any medical condition that, in the opinion of the investigator, might interfere with safe participation.

Appendix 3. All Adverse Events in UIH-001 and UIH-002 Grade 2 and Higher by SOC and AEPT

The following is a summary of all adverse events characterized by the Applicant as Death, Life-Threatening, Severe, and Moderate. Those adverse events characterized as mild and those denoted as missing are not included in this table.

Adverse Events – Grade 2 and greater for UIH-001 and UIH-002

Adverse Event System Organ Class – Blood and lymphatic system disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Anemia	0	1	5	24
Increased tendency to bruise	0	0	0	1
Leukopenia	0	0	0	2
Lymphopenia	0	0	1	0
Neutropenia	0	3	8	0
Pancytopenia	0	1	0	0
Thrombocytopenia	0	0	1	0

Adverse Event System Organ Class – Cardiac disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Coronary artery disease	0	0	1	0
Left ventricular dysfunction	0	0	2	0
Myocardial ischemia	0	0	3	0
Palpitations	0	0	0	1
Pericardial effusion	0	0	0	1

Adverse Event System Organ Class – Ear and labyrinth disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Tinnitus	0	0	1	4
Vertigo	0	0	0	1

Adverse Event System Organ Class – Endocrine disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Hypoglycemia	0	0	2	0
Hypothyroidism	0	0	0	1

Adverse Event System Organ Class – Eye disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Cataract	0	0	0	2
Dacryoadenitis acquired	0	0	0	1
Eye edema	0	0	0	2
Vision blurred	0	0	0	1

Adverse Event System Organ Class – Gastrointestinal disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Abdominal hernia	0	0	0	1
Abdominal pain	0	0	2	4
Barrett's esophagus	0	0	0	1
Colitis	0	0	3	0
Diarrhea	0	0	4	17
Dry mouth	0	0	0	1
Hemorrhoids	0	0	0	2
Impaired gastric emptying	0	0	0	1
Intra-abdominal hemorrhage	0	0	1	0
Mouth ulceration	0	0	0	9
Nausea	0	0	1	14
Oral pain	0	0	0	1
Stomatitis	0	0	0	9
Toothache	0	0	0	1
Vomiting	0	0	1	9

Adverse Event System Organ Class – General disorders and administration site conditions

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Asthenia	0	0	3	0
Chills	0	0	1	0
Edema peripheral	0	0	0	4
Fatigue	0	0	1	4
Gait disturbance	0	0	1	0
Influenza like illness	0	0	0	4
Injection site extravasation	0	0	0	1
Mucosal inflammation	0	0	0	3
Multi-organ failure	1	0	0	0
Pain	0	0	0	1
Pyrexia	0	0	0	2
Stenosis	0	0	1	1

Adverse Event System Organ Class – Hepatobiliary disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Cholecystitis	0	0	1	0
Hepatic steatosis	0	0	0	5
Hyperbilirubinemia	0	0	0	2

Adverse Event System Organ Class – Immune system disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Sensitization	0	0	0	3

Adverse Event System Organ Class – Infections and infestations

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Acute sinusitis	0	0	0	2
Bacterial vaginosis	0	0	0	1
Cellulitis	0	0	0	1
Clostridium difficile colitis	0	0	0	1
Cryptosporidiosis infection	0	0	0	1
Cytomegalovirus infection	0	0	1	0
Cytomegalovirus viremia	0	0	1	0
Ear infection	0	0	0	3
Eye infection	0	0	0	2
Fungal skin infection	0	0	0	1
Gastroenteritis	0	0	0	1
Gastroenteritis viral	0	0	0	1
Gingival abscess	0	0	0	1
Herpes zoster	0	0	0	3
Hordeolum	0	0	0	1
Localized infection	0	0	0	1
Nail infection	0	0	0	1
Onychomycosis	0	0	0	2
Oral candidiasis	0	0	0	3
Oral herpes	0	0	1	2
Osteomyelitis	0	0	2	0
Parotitis	0	0	0	1
Pharyngitis streptococcal	0	0	0	1
Pneumonia	0	0	3	0
Rhinitis	0	0	0	1
Sinusitis	0	0	1	13
Skin bacterial infection	0	0	0	1
Tooth infection	0	0	0	4
Upper respiratory tract infection	0	0	0	24
Upper respiratory tract infection bacterial	0	0	0	1
Urinary tract infection	0	0	3	18
Urosepsis	0	1	0	0
Viral pericarditis	0	0	0	1
Vulvovaginal mycotic infection	0	0	0	1

Adverse Event System Organ Class – Injury, poisoning and procedural complications

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Anemia postoperative	0	0	1	0
Animal bite	0	0	0	1
Arthropod bite	0	0	0	1
Fall	0	0	1	0
Fracture	0	0	1	0
Hepatic hematoma	0	0	0	2
Hip fracture	0	0	1	0
Laceration	0	0	0	1
Lower limb fracture	0	0	1	0
Meniscus injury	0	0	0	1
Procedural complication	0	0	1	0
Stress fracture	0	0	0	1
Subdural hemorrhage	0	0	0	1
Wound	0	0	0	1

Adverse Event System Organ Class – Investigations

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Blood alkaline phosphatase increased	0	0	0	1
Blood cholesterol increased	0	0	0	1
Blood creatinine increased	0	0	3	0
Blood parathyroid hormone increased	0	0	1	0
Glomerular filtration rate decreased	0	0	1	2
Hemoglobin decreased	0	0	1	2
Low density lipoprotein increased	0	0	11	11
Neutrophil count decreased	0	1	0	0
Protein urine	0	0	0	1
Transaminases increased	0	0	4	3
Weight decreased	0	0	0	1
Weight increased	0	0	0	1

Adverse Event System Organ Class – Metabolism and nutrition disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Abnormal loss of weight	0	0	0	10
Anorexia and bulimia syndrome	0	0	0	1
Decreased appetite	0	0	0	3
Dehydration	0	0	0	2
Dyslipidemia	0	0	0	1
Food intolerance	0	0	0	1
Hypercholesterolemia	0	0	1	0
Hyperkalemia	0	0	0	2
Hyperlipasemia	0	1	0	0
Hyperlipidemia	0	0	1	0
Hypoalbuminemia	0	0	1	6
Hypocalcemia	0	0	0	3
Hypomagnesaemia	0	0	0	2
Hyponatremia	0	0	7	2
Hypophosphatemia	0	0	1	2

Adverse Event System Organ Class – Musculoskeletal and connective tissue disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Arthralgia	0	0	0	5
Arthritis	0	0	1	2
Back pain	0	0	0	3
Bursitis	0	0	0	1
Joint effusion	0	0	0	1
Joint stiffness	0	0	0	1
Joint swelling	0	0	0	1
Musculoskeletal chest pain	0	0	0	1
Musculoskeletal pain	0	0	1	0
Myalgia	0	0	1	3
Osteopenia	0	0	0	1
Pain in extremity	0	0	0	1
Trigger finger	0	0	0	1

Adverse Event System Organ Class – Neoplasms benign, malignant and unspecified (incl cysts and polyps)

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Basal cell carcinoma	0	0	2	0
Breast cancer	0	1	0	0
Malignant melanoma	0	0	1	0
Papillary thyroid cancer	0	1	0	0
PTLD	0	1	0	0
Squamous cell carcinoma	0	0	2	0
Squamous cell carcinoma of skin	0	0	3	0
Thyroid neoplasm	0	0	0	1
Uterine leiomyoma	0	0	1	0

Adverse Event System Organ Class – Nervous system disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Carpal tunnel syndrome	0	0	0	1
Cognitive disorder	0	0	0	1
Disturbance in attention	0	0	0	1
Dizziness	0	0	0	2
Head titubation	0	0	0	1
Headache	0	0	1	4
Migraine	0	0	0	2
Neuropathy peripheral	0	0	0	3
Optic neuritis	0	0	1	0
Serotonin syndrome	0	0	1	0
Syncope	0	0	5	0
Tremor	0	0	0	3

Adverse Event System Organ Class – Psychiatric disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Anhedonia	0	0	0	2
Anxiety	0	0	0	3
Confusional state	0	0	0	1
Decreased interest	0	0	0	1
Depressed mood	0	0	0	4
Depression	0	0	1	2
Insomnia	0	0	0	2
Nervousness	0	0	0	3
Panic attack	0	0	0	1

Adverse Event System Organ Class – Renal and urinary disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Albuminuria	0	0	0	1
Oliguria	0	0	0	1
Pollakiuria	0	0	0	1
Proteinuria	0	0	1	0

Adverse Event System Organ Class – Reproductive system and breast disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Erectile dysfunction	0	0	0	2
Menorrhagia	0	0	0	3
Menstruation irregular	0	0	1	1
Ovarian cyst ruptured	0	0	1	0
Vaginal hemorrhage	0	0	1	0

Adverse Event System Organ Class – Respiratory, thoracic and mediastinal disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Atelectasis	0	0	0	1
Cough	0	0	0	5
Dysphonia	0	0	0	3
Nasal congestion	0	0	0	2
Oropharyngeal pain	0	0	0	4
Productive cough	0	0	0	1
Sinus disorder	0	0	0	2
Wheezing	0	0	0	1

Adverse Event System Organ Class – Skin and subcutaneous tissue disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Acne	0	0	0	9
Dermatitis	0	0	0	1
Dry skin	0	0	0	1
Hidradenitis	0	0	0	1
Photosensitivity reaction	0	0	0	1
Pruritus	0	0	0	2
Rash	0	0	0	5
Rosacea	0	0	0	1
Skin ulcer	0	0	0	1

Adverse Event System Organ Class – Surgical and medical procedures

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Coronary artery bypass	0	0	1	0
Hysterectomy	0	0	1	0

Adverse Event System Organ Class – Vascular disorders

Adverse Event Preferred Term	Death	Life-Threatening	Severe	Moderate
Hypertension	0	0	2	6

Appendix 4. UIH Subjects Who Contributed to CIT-07

The Clinical Islet Transplantation (CIT) consortium conducted a Phase 3 trial (Protocol CIT-07).

Of the 8 centers that participated in CIT-07, the Applicant contributed 4 (8.3%) of 48 subjects. Because each site is considered to be producing a unique product, only the 4 subjects transplanted with donislecel are presented in this summary.
Per Protocol CIT-07, each subject received one, two or three doses of islet cell product by intraportal infusion (transplant) as described below. The initial transplant required a dose of ≥ 5,000 IEQ/kg recipient BW, and the second and third required a dose of ≥ 4,000 IEQ/kg recipient BW.

The follow-up period was 2 years after the final transplant.

Subjects

Inclusion Criteria

1. At least one episode of severe hypoglycemia in the 12 months prior to study enrollment, which must have been documented by endocrinologist, diabetologist, or diabetes specialist.
2. Reduced awareness of hypoglycemia as defined by a Clarke Score of 4 or more OR a HYPO Score greater than or equal to the 90th percentile (1047) during the Screening period and within the last six months prior to randomization[27].

OR

Marked glycemic lability characterized by wide swings in blood glucose despite optimal diabetes therapy and defined by a Lability (LI) Score greater than or equal to the 90th percentile (433 mmol/l2/h·wk-1) during the Screening period and within the last six months prior to randomization.

OR

A composite of a Clarke Score of 4 or more and a HYPO Score greater than or equal to the 75th percentile (423) and a LI greater than or equal to the 75th percentile (329) during the Screening period and within the last six months prior to randomization.

3. Male and female subjects age 18 to 65 years of age.
4. Ability to provide written informed consent.
5. Mentally stable and able to comply with the procedures of the study protocol.
6. Clinical history compatible with T1D with onset of disease at < 40 years of age, insulin dependence for ≥ 5 years at the time of enrollment.

[27] This was a single-arm study. The “randomization” was done when assigning subjects to a site specific Phase 2 study or a Phase 3 study within the CIT program (cit07-study-report-all-center.pdf, page 2)

7. Absent stimulated C-peptide (<0.3 ng/mL) in response to a mixed meal tolerance test measured at 60 and 90 min after the start of consumption.
8. Involvement in intensive diabetes management defined as self-monitoring of glucose values no less than a mean of three times each day averaged over each week and by the administration of three or more insulin injections each day or insulin pump therapy. Such management had to be under the direction of an endocrinologist, diabetologist, or diabetes specialist with at least three clinical evaluations during the previous 12 months prior to study enrollment.

The inclusion criteria used for CIT-07 are based on the subjects' baseline hypoglycemia characteristics are similar, but not the same as, those for UIH-001 or UIH-002. Notably, the requirement for baseline SHE was 1 event in the previous year for CIT-07, 1 in the previous 3 years in UIH-002, and not required in UIH-001.

Exclusion Criteria:

In general, the CIT-07 exclusion criteria were similar to those for UIH-001 and UIH-002, see Table 30 for additional details.

Table 30. Notable Differences in Exclusion Criteria in CIT-07 and UIH-001/UIH-002

CIT-07	UIH-001 and UIH-002
HbA_{1c} > 10%	> 12%
Negative screen for Epstein Barr Virus (EBV)	not mentioned
Unspecified lower limit for Hgb "below the lower limits of normal at the local laboratory"	Baseline Hb < 12 gm/dL in women, or < 13 gm/dL in men

Concomitant Medication used in the Transplant Protocol

The concomitant medications used in the transplant protocol include:

- rabbit antithymocyte globulin (ATG)
- etanercept
- pentoxifylline
- tacrolimus
- sirolimus
- heparin - concomitant with administration of the islet product
- enoxaparin
- anti-infective prophylaxis

Efficacy Endpoints

Primary Efficacy Endpoint: Proportion of subjects with HbA1c <7.0% at Day 365 AND free of SHE from Day 28 through Day 365, inclusive, following the initial islet transplant, with the day of transplant designated Day 0.

Secondary Endpoints:
Islet transplant recipients will be considered insulin-independent with full islet graft function at 75 ± 5 days following their first islet cell infusion if they are able to titrate off insulin therapy for at least 1 week and all of the following criteria are met:

- HbA1c ≤ 6.5% or a ≥ 2.5% decrease from baseline;
- Fasting capillary glucose level should not exceed 140 mg/dL (7.8 mmol/L) more than three times in the past week (based on measuring capillary glucose levels a minimum of 7 times in a seven-day period);
- 2-hour post-prandial capillary glucose should not exceed 180 mg/dl (10.0 mmol/L) more than three times in the past week (based on measuring capillary glucose levels a minimum of 21 times in a seven-day period);
- Fasting plasma glucose level ≤ 126 mg/dL (7.0 mmol/L); if the fasting plasma glucose level is > 126 mg/dL (7.0 mmol/L), it must be confirmed in an additional one out of two measurements;
- Evidence of endogenous insulin production defined as fasting or stimulated C-peptide levels ≥ 0.5 ng/mL (0.16 nmol/L).

The primary efficacy endpoint for CIT-07 was different compared to the primary efficacy endpoint in UIH-002 and the integrated efficacy endpoint for UIH-001 and UIH-002, in that the target for HbA1c was <7.0% rather than ≤6.5%. While absence of SHE after transplant was part of the composite primary efficacy endpoint and reported for all 4 subjects, the Applicant did not provide the criteria used to classify each event in the submission.

The secondary efficacy endpoint of insulin independence was similar to that for UIH-001 and UIH-002, except that the subject could be considered to be insulin independent for as few as 7 days. The Applicant did not report the total number of days each subject was insulin independent.

In total, there were 48 subjects in the CIT-07 study. Four (4) subjects were enrolled at the UIH site. Because the allogenic islet cells for transplant are considered to be different products from each study site, only those 4 subjects from UIH received donislecel. Table 31, Table 32 and Table 33 contain summaries for the 4 subjects.

Table 31. Disposition of CIT-07 Subjects Treated with Donislecel

ID	Time to 2nd Transplant (days)	Total duration followed (days)	Disposition
07-1[28]	n/a–	729	Completed study per protocol
07-2	122	161	Discontinued – non-compliance
07-3	86	809	Completed study per protocol
07-4	123	851	Completed study per protocol

Source: Adapted from Applicant's Table 3 cit07-study-report-uih-center.pdf, page 20

[28] Subject study numbers were reassigned for the purposes of this document.

Table 32. Demographics and Anthropomorphics of CIT-07 Subjects Treated with Donislecel

ID	Gender	Age at First Transplant (years)	Race	Ethnicity	Weight (kg)	BMI (kg/m^2)	Duration of Diabetes (years)	Age at T1DM Dx (years)
07-1	F	63.9	White	Non-Hispanic	66.0	23.0	30	34
07-2	F	42.9	White	Non-Hispanic	66.6	21.5	28	15
07-3	M	55.3	White	Non-Hispanic	71.9	24.0	49	6
07-4	F	65.5	White	Non-Hispanic	59.9	24.0	53	12

Source: Excerpted from Applicant's Table 4 and Table 5, cit07-study-report-uih-center.pdf page 21-22.

Table 33. Baseline Diabetes Characteristics of T1DM for CIT-07 Subjects Treated with Donislecel

Subject	Insulin Requirement (U/kg/day)	HbA1c (%)	SHE Frequency (N/year)	Hypo Score [a]
07-1	17.4	8.1	5	512
07-2	32.4	6.9	3	1710
07-3	29.9	6.2	3	3071
07-4	18.5	7.3	1	58
Mean (SD)	0.35 (0.075)	7.1 (0.79)	3 (2)	1338 (1349)
Median (max, min)	0.36 (0.26, 0.42)	7.1 (6.2, 8.1)	3 (1, 5)	1111 (58, 3071)

Abbreviations: HYPO, hypoglycemia; SD, standard deviation; SHE, severe hypoglycemic event

[a] Baseline values calculated based on hypoglycemic events self-reported by patient during screening/waiting period between enrollment and initial transplant; duration varied by patient.

Source: Excerpted from Applicant's Table 8, cit07-study-report-uih-center.pdf page 24.

At baseline 2 of the 4 subjects (50%) had mild non-proliferative retinopathy at baseline and none were reported to have neuropathy or nephropathy at baseline. Table 34 shows that all 4 subject (100%) had reduced awareness of hypoglycemia[29] and 3 of 4 subjects (75%) had a least 1 SHE.

[29] Reported at enrollment. Defined as a Clarke score of 4 or more or a HYPO score greater than or equal to the 90th percentile (1047) during the screening period and within the last 6 months.

Table 34. Pre-Transplant Medical History for CIT-07 Subjects treated with Donislecel

	07-01	07-02	07-03	07-04
Severe Hypoglycemia (SHE)				
In the past six months how often have you had hypoglycemia episodes where you felt confused, disoriented, or lethargic and were unable to treat yourself?	Once or twice	More than once a month	Once or twice	Never
In the past twelve months, how often have you had hypoglycemia episodes where you were unconscious or had a seizure and needed glucagon or intravenous glucose?	1 time	never	2 times	Never
How often in the last month have you had readings less than 70 mg/dl (3.9 mmol/L) without symptoms?	never	4-5 times/week	Almost daily	2-3 times/week

Source: Table generated by clinical reviewer from individual subject CRFs

Table 35,Table 36, Table 37, and Table 38 provide baseline values prior to the first transplant and follow up values for HbA_{1c}, SHE, and if the subjects was insulin independent or dependent. At baseline HbA_{1c} values were less than the target value of < 7% for 2 subjects (6.2% and 6.9%) and near the target value for 1 subject (7.3%). Therefore, the study did not provide the opportunity to demonstrate a clinically meaningful improvement in glycemic control for these three subjects. Additionally, according to this table, all subjects had an HbA_{1c} of < 6.0% at the Day 75 assessment, occurrence of SHE was not reported.

Table 35. Subject 07-1 – Transplant 1: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Failure**	**Failure**	**Dependent**	**8.1**	**5**
Day 75	-	-	Success	Success	Independent	5.7	-
Day 365	Success	Success	Success	Success	Independent	5.5	0
Day 730	Success	Success	Success	Success	Independent	5.6	0

Table 36. Subject 07-2 – Transplant 1: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Success**	**Failure**	**Dependent**	**6.9**	**3**
Day 75	-	-	Success	Success	Dependent	5.5	-
Day 365	Failure [a]	Failure [a]	Failure [a]	Failure [a]	Dependent [b]	-	-
Day 730	Failure [a]	Failure [a]	Failure [a]	Failure [a]	Dependent [b]	-	-

Table 37. Subject 07-3 – Transplant 1: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Success**	**Success**	**Dependent**	**6.2**	**3**
Day 75	-	-	Success	Success	Dependent	5.8	-
Day 365	Success	Success	Success	Success	Independent	5.4	0
Day 730	Success	Success	Success	Success	Independent	5.4	0

Table 38. Subject 07-4 – Transplant 1: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Failure**	**Failure**	**Dependent**	**7.3**	**1**
Day 75	-	-	Success	Success	Dependent	5.8	-
Day 365	Success	Success	Success	Success	Independent	5.7	0
Day 730	Success	Success	Success	Success	Independent	6.1	0

The actual criteria that led to subjects receiving a second transplant are unclear. Three subjects received a second transplant, Subject 07-2 at 112 days after the first transplant, Subject 07-3 at 85 days, and Subject 07-4 at 123 days. Therefore, for these subjects who received a second transplant, assessments performed for Day 365 and Day 730 occurred after the second transplant. The outcomes for these subjects are presented in Table 39, Table 40 and Table 41.

Table 39. Subject 07-2 – Transplant 2: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Success**	**Failure**	**Dependent**	**6.9**	**3**
Day 75	-	-	Failure [a]	Failure [a]	Dependent [b]	-	-
Day 365	Failure [a]	Failure [a]	Failure [a]	Failure [a]	Dependent [b]	-	-
Day 730	Failure [a]	Failure [a]	Failure [a]	Failure [a]	Dependent [b]	-	-

Table 40. Subject 07-3 – Transplant 2: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Success**	**Success**	**Dependent**	**6.2**	**3**
Day 75	-	-	Success	Success	Independent	5.5	-
Day 365	Success	Success	Success	Success	Independent	5.5	0
Day 730	Success	Success	Success	Success	Independent	5.3	0

Table 41. Subject 07-4 – Transplant 2: HbA1c, SHE and Insulin Independence CIT-07 Subject Treated with Donislecel

Time Point	HbA1c < 7.0 % and Free of SHE	HbA1c ≤ 6.5 % and Free of SHE	HbA1c < 7.0 %	HbA1c ≤ 6.5 %	Insulin independence	HbA1c (%)	# of SHE
Baseline	**Failure**	**Failure**	**Failure**	**Failure**	**Dependent**	**7.3**	**1**
Day 75	-	-	Failure [c]	Failure [c]	Dependent	-	-
Day 365	Success	Success	Success	Success	Independent	6	0
Day 730	Success	Success	Success	Success	Independent	5.9	0

Note: Dash (–) indicates data not available.
Abbreviations: HbA1c, hemoglobin A1c; SHE, severe hypoglycemic episodes.

[a] Subject 07-2 terminated participation prior to her Day 75 (post-transplant 2) follow-up visit and has been imputed as a failure for all subsequent timepoints.

[b] Insulin dependence was not directly reported but was hypothesized as a result of likely graft failure.

[c] Failure has been imputed based upon missing HbA1c data.

Source: Applicant's Table 10, cit07-study-report-uih-center .pdf, page 27/28.

For clarity, the information for Subject 07-1 was removed from the table for "Post Second Transplant" because this subject only received 1 transplant. It should be noted that in this table, Days 75, 365, and 730 refer to the days after the second transplant.

Insulin use data shows that the 3 subjects who completed the study had prolonged periods of insulin independence.

07-1 – insulin independent for 21 months
07-3 – insulin independent for 23 months
07-4 – insulin independent for 21 months

Significant Protocol Deviations

Subject 07-2 received islet product that did not meet sterility release criteria. The subject received a second transplant 112 days later.

Adverse Events (source: excerpted from Applicant's Adverse Event listing 16.2.7, and individual subject narratives 12.3.2)

Deaths

No deaths were reported in the study period.

Serious Adverse Events of Interest

Subject 07-1 experienced vomiting 3 days after transplant which required an ER visit and subsequent admission to the Transplant Unit (Grade 3 AE); febrile neutropenia 26 days after transplant which required admission to the Transplant Unit (Grade 3); and hip fracture 517 days after transplant which required surgery and rehabilitation (Grade 3).

Subject 07-2 experienced post-procedural hemorrhage 1 day after their first transplant requiring laparoscopy, hospitalization and transfusion of 2 units of PRBCs, and portal vein thrombosis 11 days later. (Grade 4)

Subject 07-3 experienced severe fatigue, nausea and dehydration 115 days after their second transplant, requiring hospitalization. (Grade 3)

Subject 07-4 experienced hemorrhage at the time of the first transplant procedure and required exploratory laparoscopy and coagulation of the puncture site in the liver, 1 unit of fresh frozen plasma and 3 units packed red blood cells (Grade 4); gastroenteritis 98 days after the second transplant, which required hospitalization. (Grade 3)

No neoplasms were reported during the 2-year follow-up period.

Appendix 16.2.7 (cit07-study-report-all-center.pdf) was reviewed. The Applicant's submission did not contain a data file for all subjects enrolled in CIT-07, limiting the level of analysis. The adverse events reported were similar to those in the 4 subjects UIH CIT-07 and 10 subjects in UIH-001 and 20 subjects in UIH-002. Notable serious adverse events (SAEs) included, but were not limited to, procedural complications (hemorrhage), portal vein thrombosis, pancytopenia, febrile neutropenia, and cytokine release syndrome. No neoplasms were reported in the 2 year follow-up for the 48 subjects in the CIT-07 study.

Conclusion:

The 4 subjects who received donislecel in CIT-07 had similar efficacy and safety as that observed in UIH-001 and UIH-002.

Appendix 5: Alternative Text

Alternative Text 1: Total Duration Insulin Independent (years)

Total Number of Transplants	Study	N subjects	Mean (years)	Std Dev	Min	Max
1	UIH-001	3.0	6.0	5.7	0.2	11.6
1	UIH-002	8.0	1.6	3.4	0.0	9.9
2	UIH-001	2.0	8.3	6.4	3.7	12.8
2	UIH-002	10.0	4.1	2.7	0.0	7.9
3	UIH-001	5.0	3.3	1.9	1.2	4.8
3	UIH-002	2.0	5.1	1.0	4.4	5.8

Alternative Text 2:Total Duration Insulin Independent (years)

Total Number of transplants	Number of Transplants in the first year	N subjects	Mean (years)	Std Dev	Min	Max
1	1	11.0	2.8	4.4	0.0	11.6
2	1	4.0	7.6	4.0	3.2	12.8
2	2	8.0	3.4	2.4	0.0	6.3
3	2	5.0	4.8	0.6	4.4	5.8
3	3	2.0	1.3	0.1	1.2	1.3

Alternative Text 3: Duration followed and duration insulin independence subjects who received 1 Transplant

Study	Subject	Total Years followed	Total Duration Transplant #1 (Years)	Duration Insulin Independent Tx#1 (Years)
UIH-001	1	12.3	12.3	11.6
UIH-001	4	1.5	1.5	0.2
UIH-001	9	8.9	8.9	6.2
UIH-002	1	1.1	1.1	0.4
UIH-002	5	2	2	0.6
UIH-002	12	1.6	1.6	1.6
UIH-002	13	10.7	10.7	9.9
UIH-002	16	1	1	0
UIH-002	17	1.6	1.6	0
UIH-002	19	1	1	0
UIH-002	20	0.3	0.3	0

Alternative Text 4: Duration followed and duration insulin independence 2 Transplants

Study	Subject	Total Years followed	Total Duration Transplant #1 (Years)	Duration Insulin Independent Tx#1 (Years)	Total Duration Transplant #2 (Years)	Duration Insulin Independent Tx#2 (Years)
UIH-001	6	13	2.8	2.8	10.2	10
UIH-001	7	9	0.5	0	8.5	3.7
UIH-002	3	3.5	0.9	0.8	2.5	2.5
UIH-002	4	4.9	0.6	0.5	4.3	4.3
UIH-002	6	8	2	1.9	6	6
UIH-002	7	4.7	1.4	0	3.2	3.2
UIH-002	9	9.2	0.5	0	8.7	0
UIH-002	10	9.4	2.6	0.9	6.7	5.6
UIH-002	11	7	0.3	0	6.7	5.7
UIH-002	14	6.5	0.5	0.3	6	6
UIH-002	15	3.6	0.1	0	3.5	3.4
UIH-002	18	1.2	0.1	0	1	0

Alternative Text 5: Duration followed and duration insulin independence 3 Transplants

Study	Subject	Total Years followed	Total Duration Transplant #1 (Years)	Duration Insulin Independent Tx#1 (Years)	Total Duration Transplant #2 (Years)	Duration Insulin Independent Tx#2 (Years)	Total Duration Transplant #3 (Years)	Duration Insulin Independent Tx#3 (Years)
UIH-001	2	1.8	0.2	0	0.4	0	1.2	1.2
UIH-001	3	2.8	0.1	0	0.2	0	2.5	1.3
UIH-001	5	7.2	0.6	0.5	2.6	2.2	4.1	2.1
UIH-001	8	12.2	0.6	0.3	2.3	0.2	9.3	4
UIH-001	10	9.4	0.1	0	7.7	4.8	1.5	0
UIH-002	2	7.9	0.5	0	1	0	6.4	4.4
UIH-002	8	9.4	0.1	0	4.7	3.5	4.6	2.3

Alternative Text 6: Number of adverse events for subjects who received 1 transplant by follow up time period and severity

AE FU Period	N	Death	Life-Threatening	Severe	Moderate	Mild	Missing
Year 1	375	0	2	18	57	273	25
Year 1-5	64	1	0	4	14	34	11
Year 5-10	52	0	1	3	13	32	3
Year 10+	26	0	0	0	13	13	0

Alternative Text 7: Number of adverse events for subjects who received 2 transplants by follow up time period and severity

AE FU Period	N	Death	Life-Threatening	Severe	Moderate	Mild	Missing
Year 1	697	0	6	41	148	466	36
Year 1-5	250	0	0	9	65	158	18
Year 5-10	147	0	1	15	36	92	3
Year 10+	2	0	0	0	2	0	0

Alternative Text 8: Number of adverse events for subjects who received 3 transplants by follow up time period and severity

AE FU Period	N	Death	Life-Threatening	Severe	Moderate	Mild	Missing
Year 1	247	0	0	16	35	167	29
Year 1-5	138	0	1	15	27	79	16
Year 5-10	44	0	0	3	10	30	1

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