BLA Clinical Review Memorandum

Application Type	BLA
STN	125734
Initial BLA CBER Received Date	May 19, 2020
Original BLA Decision & Datee	Complete Response Issued May 21, 2021
Resubmission Date (Response to CR)	December 30, 2022
PDUFA Date for BLA Resubmission	June 28, 2023
Division / Office	DCEGM/OCE/OTP
Priority Review (Yes/No)	No
Reviewer Name(s)	Patricia Beaston, MD, PhD
Review Completion Date / Stamped Date	Patricia R. Beaston -S Digitally signed by Patricia R. Beaston -S Date: 2023.07.28 16:36:15 -04'00'
Original BLA Review Supervisory Concurrence	Elizabeth Hart, MD, Branch Chief, GMB1 Ilan Irony, MD, Deputy Director, DCEPT
Supervisory Concurrence for CR Response	Elizabeth Hart, MD, Branch Chief, GMB1, Acting Division Director, (DCEGM) Elizabeth Hart -S Digitally signed by Elizabeth Hart -S Date: 2023.07.28 16:39:22 -04'00'
Applicant	Cell Trans, Inc
Established Name	DONISLECEL (PURIFIED ALLOGENEIC ISLETS OF LANGERHANS FOR TRANSPLANT)
(Proposed) Trade Name	LANTIDRA
Pharmacologic Class	human allogeneic cellular suspension
Formulation(s), including Adjuvants, etc.	allogeneic pancreatic islets of Langerhans in Connaught Medical Research Laboratories (CMRL) 1066 transplant medium buffered with HEPES (2-[4-(2-hydroxyethyl) piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and supplemented with human serum albumin (0.5% final concentration)
Dosage Form(s) and Route(s) of Administration	intravascular administration within the portal vein of the liver
Dosing Regimen	Single isolate transplant, minimum 5,000 equivalent islet number (EIN) per kg patient body weight for 1st transplant, 4,500 EIN per kg for subsequent transplant. Up to 3 transplants.
Indication(s) and Intended Population(s)	Treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education
Orphan Designated (Yes/No)	Yes

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GLOSSARY

AE	Adverse Event
AEPT	Adverse Event Preferred Term
ATG	Rabbit anti-human thymocyte immunoglobulin
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
CMC	Chemistry, Manufacturing and Controls
CMV	Cytomegalovirus
CFR	Code of Federal Regulations
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
HbA1c	Glycosylated hemoglobin
HYPO Score	Hypoglycemia Score
IND	Investigational New Drug Application
IV	Intravenous
kg	Kilograms
LI	Lability Index
max	Maximum
mg	Milligram
min	Minimum
MMTT	Mixed Meal Tolerance Test
N	Number
OBE	Office of Biostatistics and Epidemiology
OPTN	Organ Procurement and Transplantation Network
PI	Package insert
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
SOC	System Organ Class
T1DM	Type 1 Diabetes Mellitus
Tx	Transplant
UCSF	University of California, San Francisco

UIH	University of Illinois Hospital and Health Sciences System; UI Health
UNOS	United Network for Organ Sharing

1. Executive Summary

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

The treatment goals with insulin are to avoid the short-term complication of diabetic ketoacidosis and the long-term complications associated with prolonged hyperglycemia by achieving near normal glycemic control with insulin administration without precipitating severe hypoglycemic events. Some patients with long-standing diabetes develop the inability to perceive mild to moderate hypoglycemia and lose the warning symptoms that could allow them to react to avoid more severe, potentially life-threatening, hypoglycemia. Despite the development of insulins with improved pharmacokinetic and pharmacodynamic profiles and improved devices for delivering insulin and for the patient's self-monitoring of blood glucose, some patients are unable to achieve target glycemic control because of the ongoing risk of severe hypoglycemic events.

To date, insulin remains the primary treatment for patients with T1DM. For some patients, allogenic transplant of cadaveric donor pancreata has been used to restore the production of endogenous insulin. The use of pancreatic islet cells isolated from donor pancreata and implanted in the patient's liver by infusion into the portal vein provides a less invasive approach. Furthermore, it allows for the use of donor pancreata that are not suitable for whole organ transplantation.

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

The Applicant's primary evidence of effectiveness and safety was generated from two open-label studies, UIH-001 (Phase 1/2) and UIH-002 (Phase 3). They provided a primary efficacy analysis that combines the results of these two studies. The primary efficacy analysis used a composite endpoint consisting of an HbA1c $\leq$ 6.5% and absence of severe hypoglycemic events (SHE) through one year after the subject's last transplant, in accordance with FDA Guidance[2]. 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

[1] The predominant cause of T1DM, less frequently it is associated with recurrent pancreatitis or is iatrogenic.
[2] 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.

had previously documented hypoglycemic unawareness[3] 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 HbA1c ≤ 7% as the most recent HbA1c 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[4]. While FDA considers insulin independence[5] 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), 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.

Based on the data submitted in the initial BLA application, the clinical review team believes that there is adequate clinical data to support a favorable benefit-risk profile for donislecel for a limited population of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. For this limited population, the benefit of insulin independence may outweigh the risks associated with the procedure and long-term immunosuppressants that are necessitated by the islet cells. However, the original BLA was issued a Complete Response due to Chemistry and Manufacturing Controls (CMC) deficiencies on August 18, 2021. The Applicant has adequately addressed the CMC deficiencies raised in the Complete Response in this submission. As part of this cycle of the BLA review, the sponsor provided additional clinical data from 2 patients treated under expanded access (including one subject originally treated in UIH-002) and updates on the subjects enrolled under studies UIH-001 and UIH-002. The clinical data continues to support a favorable benefit-risk analysis of donislecel for the previously discussed limited population of patients with T1DM.

Consistent with 21 USC 355, substantial evidence of effectiveness for donislecel for this rare population with an unmet is based adequate and well controlled investigation with confirmatory data. Specifically, we consider the integrated data from UIH-001 and UIH-002 compared to the well-established natural-history of T1DM to compose a single adequate and well controlled

[3] Defined in 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".
[4] In all 25 (83.3%) of 30 subjects were able to achieve insulin independence for any duration 4 days to 12.9 years.
[5] The term "insulin independence" is used in this document to represent the lack of a requirement for exogenous insulin administration.

investigation[6]. Based on the objective endpoint, insulin independence, and large treatment effect, an external control is adequate to provide substantial evidence of effectiveness, consistent with the regulatory requirements of section 351 of the Public Health Act. The results of the 4 subjects contributed by the applicant to the CIT-07 trial is consistent with those observed for the 30 subjects in UIH studies. Thus, this clinical data and biologic plausibility of beta cell replacement serves as confirmatory evidence.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The 30 subjects enrolled in main two studies (UIH-001 and UIH-002) were 21 to 63 years of age at the time of treatment and had type 1 diabetes from 9 to 53 years. All subjects identified as Caucasian, with 1 also identifying as Native American and 1 identifying as Hispanic. The predominance of Caucasian subjects is consistent with the demographics of adult subjects who would have been diagnosed with type 1 diabetes before 2000 (National Diabetes Data Group (US), 1995)[7].

1.2 Patient Experience Data

The Applicant did not provide a patient experience report for the subjects enrolled in UIH-001 or UIH-002. The Applicant did, however, include testimonials from subjects who participated in the studies during the April 15, 2021 Advisory Committee Meeting.

The FDA Science of Patient Input, Office of Biostatistics and Epidemiology (OBE) group collaborated with UCSF on a project for patient preference in islet cell therapy. The group presented a poster "Preferences of those with Type1 Diabetes for risks and benefits of islet cell transplantation: A discrete choice experiment to inform regulatory approval" at the FDA Science Forum (2021). The authors conclusion was that their study "suggests that hard-to-control T1DM patients may be willing to accept a certain level of risk (e.g., 5% risk of serious complications) to achieve a certain extent of benefit (the possibility of having 5-years of insulin independence)."

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	

[6] UIH-001 was a phase 1/2 study and UIH-002 a phase 3 study using the modified Edmonton protocol for islet cell transplantation and immunosuppression. These two studies were sufficiently similar to allow for a combined analysis of efficacy and safety.
[7] It should be considered that the reported racial and ethnic distribution of patients with type 1 diabetes is influenced by the geographic region within the U.S. in which the data were collected.

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☒	Other: (please specify)	2.5 Clinical Overview - Section 6.2.4 provides information reported by other transplant programs
☐	If no patient experience data were submitted by Applicant, indicate here.	
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☒	Other: (please specify)	Patient/subjects from Studies UIH-001 and UIH-002 provided statements as part of the Applicants submission of the April 15, 2021 Advisory Committee meeting

2. Clinical and Regulatory Background

2.1 Disease or Health-Related Condition(s) Studied

Type 1 Diabetes Mellitus (T1DM) results from autoimmune destruction of pancreatic islet cells that contain the β-cells responsible for the production of insulin. [8] 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) (DCCT Research Group 1986) 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 (The Diabetes Control and Complications Trial Research Group 1993) 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 pre-prandial (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 HbA1c ≤ 6.05%. These goals are commonly 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”.

[8] The predominant cause of T1DM, less frequently it is associated with recurrent pancreatitis or is iatrogenic. Rarer is monogenic diabetes.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

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 integrated 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 (Atkinson MA 2014) 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 immediate risk of DKA and long-term risks of 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 (Maffi 2019). 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 [9], 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 (Gruessner and Gruessner 2016).

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

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 transplant10. There are no approved islet cell products for transplantation.

2.3 Safety and Efficacy of Pharmacologically Related Products

Donislecel is the first allogenic islet cell product submitted for marketing approval. There are no other drugs or biologics that can restore endogenous insulin production in patients with type 1 diabetes. As described above, allogenic pancreatic transplant is, to date, the only available treatment to restore endogenous insulin production.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

As reviewed by Rickels (2019), investigation of islet cell transplantation began in the 1980s with islet autotransplantation for the treatment of chronic pancreatitis. This led to investigations of allogenic islet cell transplantation for patients with type 1 diabetes and development of an automated method for isolation of human pancreatic islet cells. In 2000 the Edmonton group developed a steroid sparing regimen using an immunosuppression regimen that resulted in improvement in the ability to achieve insulin independence (Lakey 2006). In the United States, the National Institutes of Health (NIH) has sponsored the Clinical Islet Transplantation Consortium (CIT) (Hering 2016) under which a number of centers are participating in several trials, including the Applicant (see Table 7). In the United States, islets cells are a regulated as a manufactured biologic product and need to be administered under an Investigational New Drug Application (IND). In contrast, allogenic islet cell administration in the European Union is regulated similar to whole organ transplantation and does not require clinical trial authorization or marketing review by a regulatory authority.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

IND 11807 submitted and received 7/8/2004

- Study may proceed, 8/5/2004
- Meeting/teleconference held 2/28/2007 to discuss FDA comments from 11/18/05
- Type C meeting held 4/16/2015

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

- Type C meeting held by Division of Manufacturing and Product Quality (DMPQ), 1/12/2016
- Pre-BLA meeting held 8/3/2016
- Approved Expanded Access (amd 86) on 6/20/2018

Previous BLA: STN# (b) (4)

- Sponsor meeting held 7/6/17, Clinical and Chemistry and Manufacturing Controls (CMC) Filing issues identified
- Withdrawn on 7/28/2017

BL STN# 125734/0:

Major Amendment letter issued 1/5/2020, revised Action Due Date changed to 8/18/2021

Complete Response letter issued 8/18/2021

All clinical issues were resolved during the initial review. However, a Complete Response Letter was issued August 18, 2021 due to unresolved Chemistry and Manufacturing Controls (CMC) deficiencies. A six-month extension was granted for resubmission of the application until 2/18/2023 The Applicant submitted a response on December 30, 2022.

Requests for additional clinical information were sent April 17, 2023 regarding the status of two patients treated under expanded access (IND 11807) and April 24, 2023 for updates on the subjects enrolled under studies UIH-001 and UIH-002. Responses to these information requests were received April 19, 2023 (AMD 50) and April 27, 2023 (AMD 51), respectively.

2.6 Other Relevant Background Information

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The Applicant's submission contained the elements required to support filing of the BLA. However, the quality of the submission was poor. First, the initial submission did not contain a full table of contents allowing ready navigation of the submission. A full table of contents was requested and submitted (Seq 4). Even with this information it was challenging to find the information required to fully understand the experience of subjects within the UIH program. As discussed in Section 5.3, while the Applicant provides summary information for the subjects they contributed to other studies neither the information nor data sets allowed for integration with that provided for the UIH program. As discussed in Section 5.1, studies UIH-001 and UIH-002 were the primary data that supported the efficacy and safety of donislecel.

In order to identify factors that affected product efficacy and subject safety, multiple documents and source data files needed to be reviewed. The review was complicated by missing and inconsistent data. Examples include, but are not limited to:

- As presented in Section 7.1.4, the Applicant proposed to use the occurrence of severe hypoglycemic events (SHE) as a co-primary efficacy endpoint. The primary endpoint required demonstration of an absence in SHE in the year after the subject's last transplant. However, the Applicant did not provide baseline SHE values for 15 of 30 subjects (50%). FDA submitted an information request (IR) on the baseline SHE events. The Applicant's initial response showed that many of the recorded baseline events did not meet the accepted definition of SHE. Therefore, another IR was sent asking the Applicant to submit identify only those SHE events occurring in the 1-year period prior to the subject's first transplant. This response revealed that 5 of the 30 subjects (17%) had SHE prior to transplant. Therefore, the Applicant did not provide data that could demonstrate an improvement in SHE from baseline.
- As presented in Section 7.1.5, the Applicant proposed to use a hypoglycemic (HYPO) score as a secondary efficacy endpoint to demonstrate an improvement in glycemic variability. The Applicant did not provide baseline HYPO scores for 12 (40%) of subjects. FDA submitted an IR on the baseline HYPO scores. The Applicant's initial response (Seq 14) provided a line listing of the elements used to calculate the subject's HYPO score. An evaluation of this new data by the clinical reviewer raised concern that the subjects enrolled in the study may not have had HYPO scores suggestive of high glycemic variability. Therefore, another IR was sent requesting the protocol used to calculate the subject's HYPO score. The Applicant's response (Seq 28 and Seq 30) showed that they did not use the method for calculating the HYPO score described by the authors who developed this score (Ryan 2004b). Therefore, the HYPO score presented by the Applicant was uninterpretable.
- The Applicant proposed approach was to examine efficacy at the 1-year after the subject's last transplant and safety through 1-year after the subject's last transplant. As stated throughout the review, immunosuppression is required to maintain islet cell survival. Therefore, FDA believes that it important to examine the entirety of the time the subject was treated. Therefore, FDA sent an IR requesting information regarding the length of time each subject was followed for each transplant period and in total. The IR also requested a report for the duration the subject was able to achieve insulin independence during each transplant period and in total. The Applicant provided a response containing this information (Seq 22). However, on FDA review it was noted that subject (b) (6) was reported to have received only 2 transplants. However, all other documentation reported that this subject received 3 transplants. Therefore, FDA requested the Applicant provide clarifying information for this subject. In response, the Applicant resubmitted the data for all subjects (Seq 24). The data provided in this update did not match the data provided in the Applicant's first response. On

spot check from other data sources, the clinical reviewer found the second response more accurate, so this data was used in the analyses for benefit.

- As presented in Section 8.2.3, there were several significant adverse events that did not have attributions of severity or relatedness. This resulted in an underestimation of adverse events until the totality of the documentation included subject narratives, adverse events reports, case report forms (CRF) and procedure notes were reviewed, and the adverse event database updated by the clinical reviewer. There were additional adverse events found within the subject narratives but not captured within the adverse event data base. These events did not have sufficient data to allow them to be included in the data base to generate tables or figures but were included in the discussion of adverse events of interest when appropriate.
- Subject (b) (6) was noted to have stopped Imuran, azathioprine, secondary to an adverse event (ae.xpt, column AEACTOTH). But this medication is not listed as part of the subject's concomitant medications in either the data file (cm.xpt) or the "patient display" (Amended Clinical Study Report.pdf, Section 11.3.6.18, Table 33).
- Study UIH-001 was amended to use exenatide for 6-months after transplant to enhance β-cell function. The initial submission did not adequate identify the subjects' adherence to the protocol specified concomitant medication. Therefore, FDA submitted an IR for adherence to exenatide use. The Applicant's responses (Seq 22 and Seq 24) revealed not only discontinuation of exenatide during this this 6-month period because of adverse events attributable to exenatide but also significant use of exenatide beyond the 6-month period. Further evaluation of exenatide use within the concomitant medication data base (cm.xpt) revealed that subjects were using other diabetes medications during the study that were not identified within the protocol.
- The protocols for UIH-001 and UIH-002 required donislecel to be administered by transhepatic catheterization into the portal vein (See Section 6.1.5). The Applicant did not provide sufficient information within the submission on the devices used in the transplantation procedures for UIH-001 and UIH-002. FDA submitted an IRs on the devices used for the transplantation procedures. These IRs revealed that only 6 of 56 (10.7%) transplantation procedures used a catheter (Seq 2, Seq 26). Furthermore, the responses revealed that in some cases (for example the 2nd transplant for Subject (b) (6) the device identified in the procedure report did not match the device identified in the accompanying radiographic report.

The totality of these examples shows that there were numerous protocol deviations across the studies that could impair the interpretation of both efficacy and safety data. Based on the quality of the submission with missing and incongruent data, there was insufficient data monitoring during the study or in preparing the documents submitted to the FDA. Given that this was a single center study, enrolling only 30 subjects, the poor quality of the program and submission was unexpected. None the less, through Information Requests and working with the Applicant, and review of submitted source data, we believe that there was adequate data for a substantive, complete review of this BLA.

3.2 Compliance with Good Clinical Practices and Submission Integrity

Please see Section 3.1

3.3 Financial Disclosures

Covered clinical study (UIH-001 and UIH-002):
Was a list of clinical investigators provided? ☑ Yes ☐ No (Request list from applicant)
Total number of investigators identified: 31
Number of investigators who are sponsor employees (including both full-time and part-time employees): 1 Jose Oberholzer, MD was the principal investigator for all studies using donislecel at the University of Illinois Hospital and Health Sciences System (UI Health)
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 1 Jose Oberholzer, MD
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 1 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 1 Significant equity interest held by investigator in sponsor of covered study: 1 Is an attachment provided with details of the disclosable financial interests/arrangements? ☐ Yes ☒ No (Request details from applicant) Is a description of the steps taken to minimize potential bias provided? ☐ Yes ☒ No (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0 Is an attachment provided with the reason? ☐ Yes ☒ No (Request explanation from applicant)

Clinical Reviewer Comment: Jose Oberholzer, MD is the principal investigator and is listed as founder and president of CellTrans. This creates a financial conflict of interest as defined by 42 CFR part 50 and 45 CFR part 94, as the principal investigator has a significant financial interest in CellTrans.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry, Manufacturing, and Controls

Please see the CMC review.

4.2 Assay Validation

The Applicant used HbA1c, c-peptide, and glucose as assessments of efficacy.

HbA1c was a component of coprimary endpoints for the assessment of efficacy. HbA1c is an accepted measure for estimating the average glycemic control over the previous 90 days. For people without diabetes, the normal range is 4-5.6%. Target glycemic control for most patients with type 1 diabetes is < 6.5% to decrease the risk of long-term complications. There are numerous HbA1c assays on the market with different performance characteristics and different intended use (CFR 862.7470 and 21 862.1373). Furthermore, the accuracy requirements for the HbA1c have tightened over time. For patient management, the standard of care requires frequent (approximately every 3 months) assessment to determine if the patient is meeting treatment goals. Therefore, variations in the accuracy are small enough in this context that they should not adversely affect patient management. In contrast, to increase the interpretability of outcomes in clinical trials is it generally recommended that the study employs a central laboratory to use the same assay for all samples and control for changes across the duration of the study. The primary studies submitted to support the application for donislecel, UIH-001 and UIH-002, occurred over a period of > 15 years. There is no evidence that the applicant used a central laboratory to process the samples for HbA1c. Please refer to Section 7.1.4 for discussion of the use of HbA1c in the UIH program.

Blood glucose is a standard assay with an accuracy of ± 6 mg/dL when measured in clinical labs.

C-peptide is (CFR 862.1150 Class I exempt from review) The intended use for the measurement of C-peptides of proinsulin is for the diagnosis and treatment of patients with abnormal insulin secretion, including diabetes mellitus. The clinical use of c-peptide is as an aide in diagnosis of type 1 diabetes versus type 2 diabetes. A cut-off of < 0.6041 ng/mL (0.2 nmol/L) is used in the diagnosis of type 1 diabetes (Leighton 2017). C-peptide measurement is also used to diagnose other conditions such as insulinoma or factitious hypoglycemia. The Applicant used fasting and stimulated c-peptide as part of their inclusion criteria and as a determinant of transplanted β-cell function. This use is not inconsistent with the use for diagnosis of type 1 diabetes and the production of insulin. While c-peptide is a surrogate for endogenous insulin release, it has not been validated to demonstrate clinical benefit (e.g. there is no specific value associated with decrease in exogenous insulin needs for type 1 diabetes). Please refer to Section 4.4.2 for discussion of the use of c-peptide in the UIH program.

4.3 Nonclinical Pharmacology/Toxicology

Please see the Pharmacology/Toxicology review.

4.4 Clinical Pharmacology

Please see the Clinical Pharmacology review.

4.4.1 Mechanism of Action

Pancreatic islets regulate blood glucose levels through secretion of multiple hormones in response to increases and decreases in blood glucose. Endocrine cells within pancreatic islets release insulin, glucagon, somatostatin, pancreatic peptide, and ghrelin. With regard to regulation of glucose metabolism, insulin stimulates glucose uptake by peripheral tissues, glucagon mobilizes glucose from the liver into circulation, somatostatin inhibits both α- and β-cell secretions, pancreatic peptide inhibits pancreatic exocrine secretion, and ghrelin inhibits insulin secretion. The primary mechanism of action of donislecel is believed to be secretion of insulin by the β- cell component of the product.

4.4.2 Human Pharmacodynamics (PD)

The pharmacodynamic effects of donislecel are a result of hormones, especially insulin, that are secreted by the transplanted islets in response to fluctuations in blood glucose levels.

Basal and stimulated blood glucose were determined at baseline and at 1 year following a patient's last transplant during Studies UIH-001 and UIH-002 using a mixed meal tolerance (MMT) test.

Insulin secretion can be assessed by measuring C-peptide levels in the blood (C-peptide comprises part of the proinsulin molecule and when proinsulin is cleaved, C-peptide is released. C-peptide exists in a 1 to 1 ratio with insulin). C-peptide levels <0.3 ng/mL are considered indicative of a lack of adequate islet function.

The Applicant proposed the following summary Table 1 for the package insert:

Table 1. Effect of Lantidra on Levels of HbA1c, Blood Glucose, and C-peptide at Baseline and 1 Year After Final Transplant (Studies UIH-001 and UIH-002) – (Original)

		Baseline		1 Year after Last Transplant	
Parameter		**n**	**Mean (SD)**	**n**	**Mean (SD)**
HbA1c (%)		29	7.38 (0.936)	29	6.01 (0.738)
Mixed Meal Tolerance Test	Glucose, Basal; mg/dL	28	165 (70.5)	25	108 (22.0)
	Glucose, 90-minute; mg/dL	28	353 (81.9)	25	157 (57.6)
	C-peptide, Basal; ng/mL	28	0.01 (0.024)	25	1.31 (0.610)
	C-peptide, 90-minute; ng/mL	28	0.02 (0.055)	25	3.74 (1.739)

[Source: Original BLA 125734/002; draft-label-text-for-review-word.docx, p. 9.]

Clinical Reviewer Comment: FDA noted that 6 subjects (16.7%) did not provide baseline and or 1-year (after the last transplant) data and requested additional data on the MMT testing performed in UIH-001 and UIH-002, which is presented below in Table 2.

The following is a summary of the updated MMT results:

Table 2. Effect of donislecel on Levels of Blood Glucose (mg/dl), and C-peptide (ng/ml) at Baseline and 1 Year After Final Transplant (Studies UIH-001 and UIH-002) – (Updated)

	Insulin Independence at time of 1-year MMT					**Not Insulin Independence at time of 1-year MMT**				
	N	Mean	Std Dev	Min	Max	N	Mean	Std Dev	Min	Max
Baseline Glucose Basal	19	178	76	78	348	5	126	52	69	208
Baseline Glucose 90-min	19	357	91	122	559	5	341	67	285	456
Baseline C-peptide Basal	19	0.1	0.0	0.1	0.1	5	0.1	0.0	0.1	0.1
Baseline C-peptide 90-min	19	0.1	0.0	0.1	0.3	5	0.1	0.0	0.1	0.1
1-year Glucose Basal	19	106	17	81	144	5	113	36	62	162
1-year Glucose 90-min	19	142	40	65	202	5	216	77	120	302
1-year C-peptide Basal	19	1.5	0.5	0.6	2.3	5	0.5	0.5	0.1	1.2
1-year C-peptide 90-min	19	4.2	1.6	1.5	7.1	5	1.9	1.4	0.0	3.3

[Source: Adapted from BLA 125734/039, ise-secondary-endpoints.csv]

For those subjects providing baseline data, unstimulated and stimulated baseline c-peptide of was reported as < 0.1 or < 0.05 ng/ml for all but one subject. This subject's baseline unstimulated value was 0.1 and stimulated value was 0.27 ng/ml.
Data provided (6/15/2021) by Applicant in response to an IR (6/9/2021)
Table generated by the clinical reviewer.

Clinical Reviewer Comment: On review of the totality of the data, FDA did not agree that this table provides an accurate representation of the pharmacodynamics of donislecel for the following reasons:

1) While c-peptide represents of the release of insulin by the β-cells, the pharmacodynamic effect of insulin is demonstrated by blood glucose levels.

2) Despite the updated information provided by the Applicant, there continues to be significant missing data. Six (6) subjects (20%) did not provide baseline and/or 1-year follow-up MMT data. Specifically, 1 subject who was insulin independent did not provide baseline data and 5 subjects who were not insulin independent did not provide follow-up data.

3) Some subjects were taking exenatide (which stimulates the beta cells to produce insulin) at the time of the MMT. According to the protocol they should have only been taking exenatide for 6-months after the transplant and as such should have not been taking it at the time of the pharmacodynamic assessment. Exenatide was added to these studies with the premise that it may enhance β-cell function early after transplantation. The continued and inconsistent use of exenatide at the time of MMT would preclude a clear understanding of transplanted β-cell function.

4) Some subjects were taking biotin during the study. At least 6 subjects were taking biotin in sufficient levels to interfere with the assay. As recording of concomitant medications, especially dietary supplements is often challenging, and there may be additional subjects who were on biotin and whose data for this C-peptide assay wouldn't be interpretable.

The subjects enrolled into studies UIH-001 and UIH-002 had long-term type 1 diabetes and had a c-peptide response to glucagon stimulation (1 mg IV) of < 0.3 ng/ml. This is consistent with the baseline values reported. Of the 30 subjects, 20 (66.7%) were insulin independent at the time of the MMT performed 1-year after the last transplant, and 10 (33.3%) were not. The Applicant did not provide baseline and or 1-year MMT data for 6 subjects: 1 subject who was reported to be insulin independent at 1-year and 5 subjects who were not. These subjects are not represented in Table 2.

There are limitations in the utility of the data from the MMT because of missing data and off-protocol use of exenatide. However, it is not possible to repeat these studies. FDA believes the pharmacodynamic profile of the allogenic islet cells, with possible additional pharmacological action from exenatide, is most clearly demonstrated in subjects who are free from the requirement of exogenous insulin. Therefore, Table 3 was produced for the package insert.

Table 3 Effect of donislecel on Levels of Blood Glucose (mg/dl) at Baseline and 1 Year After Final Transplant (Studies UIH-001 and UIH-002) for Subjects Insulin Independent at the time of Mixed Meal Tolerance Test.

Subjects Insulin Independence at time of 1-year MMT	N	Mean	Std Dev	Min	Max
Baseline Glucose Basal	19	178	76	78	348
Baseline Glucose 90-min	19	357	91	122	559
1-year Glucose Basal	19	106	17	81	144
1-year Glucose 90-min	19	142	40	65	202

[Source: Adapted from BLA 125734/039, ise-secondary-endpoints.csv]

4.4.3 Human Pharmacokinetics (PK)

Human insulin has a half-life of 7 minutes in the blood. C-peptide is released in a 1:1 ratio with insulin as part of the prohormone and is used as a biomarker for endogenous insulin release, and has a half-life of 30-35 minutes.

Clinical Reviewer Comment: For reasons stated above in 4.4.2, FDA believes that the use of C-peptide for the determination of PK and PD is not supportable.

4.5 Statistical

Please see the Statistical review.

Please note that the Applicant primary efficacy analysis was not used in the FDA's assessment of efficacy. Please see Section 7.1.4 and Section 7.1.5.

4.6 Pharmacovigilance

In this BLA, CellTrans proposes to limit manufacturing to a single site and to limit administration to a single site, University of Illinois Hospital (UIH) based on "shipping" standard operating procedures (SOP) developed by CellTrans and agreed on by the FDA chemistry and manufacturing controls (CMC) review team. Given the site personnel have extensive training and experience with the product during the clinical trials, the identified risks during the clinical trials, potential risks based on the product, and the limited target population we do not believe that Risk Evaluation and Mitigation Strategies (REMS) are necessary or recommended. We believe that the risks can be adequately conveyed through labeling, including a detailed patient information section.

Enhanced pharmacovigilance is being recommended. This entails routine pharmacovigilance with additional reporting in the post-market setting. The enhanced pharmacovigilance is being recommended based on the observed safety signals and uncertainty about potential new safety signals due to the limited pre-market study population and manufacturing and administration changes since the clinical studies were conducted.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

As identified in Table 7 in Section 5.3 the Applicant participated in the Clinical Islet Transplantation consortium (CIT) as well as performed their own clinical studies, UIH-001 and UIH-002. The clinical review focused on studies UIH-001 and UIH-002, which provided the majority of the data for the donislecel. The summary for the 4 subjects who received donislecel in the CIT-07 study were reviewed and presented in section 6.3 of this review. However, the data sets provided for these subjects were not in a format that allowed integration into the analysis of efficacy and safety. The Applicant also provided summary information for 9 subjects who received donislecel; CIT-06 – 4 subjects who also received kidney transplant and therefore not comparable to the patient population studied in the UIH program, CIT-02 and 12176A – 5 additional subjects enrolled to examine changes in the treatment protocol to enhance islet cell survival. The Applicant did not provide data sets that could be integrated into the evaluation of safety. Because of the difference in studies in studies CIT-06, CIT-02, and 1217A, the small number of subjects receiving donislecel, and the lack of analyzable data, these studies are not presented in this review.

5.2 BLA/IND Documents that Serve as the Basis for the Clinical Review

Seq	Date	Reason	Contents
001	05/19/2020	Original Submission	
002	06/17/2020	Response to 6/12/2020 IR	catheter New label
003	06/24/2020	IR response REMs	New REMs
004	07/10/2020	IR response	Comprehensive Table of OC Contents ClinPharm IR response (assays)
007	08/07/2020	Proprietary name	

Seq	Date	Reason	Contents
008	08/18/2020	Admin	Orphan Drug Waiver
009	09/10/2020	CMC IR response	Includes updated (b) (4)
010	09/16/2020	120-day safety update	
011	09/25/2020	Amended Clinical Study Reports and New Full CRF for Patient (b) (6) BL 125734	
014	10/20/2020	Response to Clinical IR 10/05/2020	1st clinical IR SHE, exenatide, transplant reason
016	10/26/2020	Response to CMC records request 10/02/2020	Comprehensive (b) (4)
017	12/01/2020	Response to 11/20/2020 IR	Labeling
019	12/23/2020	Response to Statistics 12/21/2020 IR	Efficacy (SHE and HbA1c) Data for Tables 12 and 13 UIH-002
020	12/30/2020	Response to CMC 12/03/2020 IR	Comprehensive (b) (4) Equipment
021	01/06/2020	Response to CMC 12/22/2020 IR	GSI Potency Issue
022	01/08/2021	Response to Clinical 12/18/2020 IR	SHE, Immunosuppression, insulin independence, criteria for new transplant, exenatide
024	01/19/2021	Amend Response to Clinical 12/18/2020 IR	Revised tabular information
025	02/02/2021	1/27/2021 IR	Product name
026	02/10/2021	Response to CMC 2/9/2021 IR	Use of sheaths and catheters
027	02/10/2021	Response to Clinical 2/8/2021 IR	Inclusion Criteria UIH-001
028	02/16/2021	2nd Response to Clinical 2/8/2021 IR	HYPO Scores
030	03/10/2021	3rd Response to Clinical 2/8/2021 IR	HYPO Score method
031	03/16/2021	Response to CMC 3/12/2021 IR	Delivery devices, potency - GSI
032	03/22/2021	Response to CMC 3/18/2021 IR	Delivery devices 510(k), site certification - clarification
034	04/30/2021	Response to CMC 4/29/2021 IR	Delivery devices
037	05/27/2021	Response to discussion – late cycle meeting 4/1/2021	Revised RMP and Label
038	06/2/2021	Response to 6/1/2021 IR	Redlined label (PI)
039	06/15/2021	Response to 6/9/2021 IR for labeling review	Data 120-day updated safety report PD information
041	07/09/2021	Response to CMC 7/01/2021 IR	Product – commercial versus investigational, method of delivery
043	7/21/2021	Response to 7/19/2021 IR	Post-marketing plan for 15-day alert reports and periodic safety reports
044	7/27/2021	Response 7/20/2021	Updated labelling
045	06/01/2022	Response to 8/18/2021 Complete Response (CR) letter	Request for 6-month extension to resubmit application
46	12/30/2022	Response to 8/18/2021 Complete Response (CR) letter	Response to the deficiencies outlined in a Complete Response Letter
47	01/20/2023	Response to 01/18/2023 IR	Package Insert – "clean" and tracked version Request for Propriety Name Review Request for Proposed Suffix Review
48	01/30/2023	Response to 01/26/2023 IR	Package insert Tracked Changes – Word version
50	04/19/2023	Response to 04/17/023 IR	Information on additional administration of donislecel under expanded

Seq	Date	Reason	Contents
51	04/28/2023	Response to 04/24/2023 IR	Update for deaths, cancer, loss of insulin independence after withdrawal of immunosuppression due to adverse event, and subjects who continue to have insulin independence
52	05/02/2023	Response to 05/01/2023 IR	Information on drug delivery device
59	06/15/2023	Response to request from Office of Orphan Products Development	Update letter for waiver of orphan exclusivity
061	06/23/2023	Response to 06/19/2023 IR	Revisions and comments to FDA proposed labeling
063	06/27/2023	Response to 06/27/2023 IR	Post-marketing CMC commitment
066	06/28/2023	Response to 06/28/2023 IR	Revisions and comments to FDA proposed labeling

5.3 Table of Studies/Clinical Trials

Table 4. Clinical Trials Utilizing UI Health-derived Islets

Study Number	ClinicalTrials.gov Identifier	Study Title	Patients	Transplants
UIH-001	NCT00566813	Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid Free Immunosuppression	10[a]	21
UIH-002	NCT00679042	Islet Transplantation in Type 1 Diabetic Patients Using the UIC Protocol, Phase 3	21[a]	5
CIT-02	NCT00464555	Strategies to Improve Long Term Islet Graft Survival	2	3
CIT-06	NCT00468117	Islet Transplantation in Type I Diabetic Kidney Allograft Recipients: Efficacy of Islet After Kidney Transplantation	4	6
CIT-07	NCT00434811	Allogeneic Purified Human Pancreatic Islet Transplantation for Treatment of Type 1 Diabetes	4	7
12176A	NCT00160732	Allogeneic Islet Cell Transplantation	3	3
TOTAL			43[a]	75

Notes: The CellTrans IND was formerly owned by the University of Illinois Hospital and Health Sciences System (UI Health) and the University of Illinois at Chicago (UIC). UIH-001 and UIH-002 were conducted under CellTrans IND BB-11807. CIT-02, -06, and -07 were conducted under the NIH IND BB- 9336. Study 12176A was conducted under University of Chicago IND BB-11228. For the CIT studies, only patients enrolled at UI Health are included in this table. For 12176A, all patients were transplanted and followed by University of Chicago under their protocol and not at UI Health; only patients receiving UI Health manufactured islets are included in this table.

[a] One patient from UIH-001 was also subsequently enrolled into UIH-002 and is counted in this table under both studies. The total number at the bottom of the table counts this patient only once.
[Source: Original BLA125734; 2.5 Clinical Overview.pdf, p. 8]

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

An Advisory Committee Meeting was held April 15, 2021.[11] There were 2 clinical discussion questions and 1 clinical voting question. Below are the clinical discussion topics and voting question and summary of Committee discussion as described in the summary meeting minutes:[12]

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.

Summary of Discussion:

The 2 endocrinologists on the panel, Drs. David Harlan and Ellen Leschek agreed that 4-5 years of insulin independence would represent a clinically meaningful treatment benefit.

The panel agreed given the risks of the immunosuppression, donislecel should be limited to a very small subset of patients with type 1 diabetes for whom available therapy and technology are insufficient at preventing life-threatening complications from insulin induced hypoglycemia.

[11] Due to the SARS-COV-2 pandemic, this Advisory Committee Meeting was virtual with public access.
[12] https://www.fda.gov/media/148461/download

Some committee members voiced that donislecel would be appropriate for patients who are not surgical candidates but would otherwise be candidates for whole pancreas transplant.

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.

The results of the vote were as follows: Yes = 12; No = 4; Abstain = 1.

Thus, the Committee voted in favor of the determination, that based on the totality of the scientific evidence available, the benefits of donislecel (purified allogeneic deceased donor pancreas derived Islets of Langerhans) outweighs its risks, based on the evidence from clinical studies reported in the biologics license application (BLA) 125734.

5.4.2 External Consults/Collaborations

5.5 Literature Reviewed (if applicable)

Atkinson MA, E.G., Michels AW,, *Type 1 Diabetes.* Lancet, 2014. 383(9911): p. 69-82.

Bhat M, M.K., Dierkhising R, Watt KDS,, *Immunosuppression, Race, and Donor-Related Risk Factors Affect De novo Cancer Incidence Across Solid Organ Transplant Recipients.* Mayo Clinic Proceedings, 2018. 93(9): p. 1236-1246.

Boggi, U., et al., *Results of pancreas transplantation alone with special attention to native kidney function and proteinuria in type 1 diabetes patients.* Rev Diabet Stud, 2011. 8(2): p. 259-67.

DCCT Research Group, *The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase.* Diabetes, 1986. 35: p. 530-45.

The Diabetes Control and Complications Trial Research Group, *The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus.* N Engl J Med, 1993. 329(14): p. 977-86.

Gruessner, A.C. and R.W. Gruessner, *Long-term outcome after pancreas transplantation: a registry analysis.* Curr Opin Organ Transplant, 2016. 21(4): p. 377-85.

Hering, B.J., et al., *Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia.* Diabetes Care, 2016. 39(7): p. 1230-1240.

Issa N, K.A., Ibrahim HN,, *Calcineurin Inhibitor Nephrotoxicity: A Review and Perspective of the Evidence.* Am J Nephrol, 2013. 37: p. 602-612.

Lakey, J.R.T., M. Mirbolooki, and A.M.J. Shapiro, *Current Status of Clinical Islet Cell Transplantation*, in *Transplantation Immunology: Methods and Protocols*, P. Hornick and M. Rose, Editors. 2006, Humana Press: Totowa, NJ.: p. 47-103.

Larsen, J., *Pancreas Transplantation: Indications and Consequences.* Endocrine Reviews, 2004. 25(6): p. 919-946.

Leighton, E., Sainsbury, C.A.R., and Jones, G.C. *A Practical Review of C-Peptide Testing in Diabetes*, Diabetes Ther, 2017: p. 475-487.

Maffi P, S.A., *Islet Transplantation Alone Versus Solitary Pancreas Transplantation: an Outcome-Driven Choice?* Curr Diab Rep., 2019. 25(5): p. 26.

Ryan EA, P.B., Senior PA and Shapiro, AMJ *Risks and side effects of islet transplantation.* Curr Diab Rep, 2004a. 4: p. 304–309.

Ryan E, et al., *Assessment of the Severity of Hypoglycemia and Glycemic Lability in Type 1 Diabetic Subjects Undergoing Islet Transplantation.* Diabetes, 2004b. 53(4): p. 955-962.

Rickels MR and Robertson RP, Pancreatic Islet Transplantation in Humans: Recent Progress and Future Directions. Endocr Rev. 40: p. 631-668.

Seaquist ER, A.J., Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R, *Hypoglycemia and Diabetes: A report of a Workgroup of the American Diabetes Association and the Endocrine Society.* J Clin Endocrinol Metab, 2013. 98: p. 1845-1859.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1 UIH-001

Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid Free Immunosuppression, Phae1/2

6.1.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study was to demonstrate the safety of allogeneic islet transplantation in Type 1 diabetic patients performed at the University of Illinois at Chicago (UIC).

"The purpose is to reproduce the Edmonton protocol at the University of Illinois to demonstrate that pancreatic islets isolated at UIC and within the CIC are safe and of sufficient quality to provide reproducible graft function. The series of transplants performed with the herein described protocol will provide a base for future trials investigating strategies to further improve

the outcome of allogeneic islet transplantation in diabetic patients and to reduce the need for multiple donors may be addressed."

6.1.2 Design Overview

Single-center, open-label, uncontrolled trial, in which 1-4 allogeneic pancreatic islet transplants per subject will be applied to a total of 10 study participants.

6.1.3 Population

Inclusion Criteria

Enrolling subjects must have Type 1 diabetes mellitus for more than 5 years, complicated by at least one of the following situations that persist despite intensive insulin management efforts.

1. Reduced awareness of hypoglycemia, as defined by the absence of adequate autonomic symptoms at plasma glucose levels of < 54 mg/dL (3 mmol/l); as reported by the subject;
2. Metabolic lability/instability, characterized by two or more episodes of documented severe hypoglycemia,

   OR

   two or more hospital visits for diabetic ketoacidosis over the last year

3. Despite efforts at optimal glucose control, progressive secondary complications of diabetes as defined by:
   a. Retinopathy—a minimum of a three-step progression using the Early Treatment Diabetic Retinopathy Study (ETDRS) grading system, or an equivalent progression as certified by an ophthalmologist familiar with diabetic retinopathy, OR
   b. Nephropathy—a confirmed rise of 50 μg/min (72 mg/24h) of microalbuminuria or greater over at least three months (beginning anytime within the past two years) despite the use of an ACE inhibitor, or
   c. Neuropathy—persistent or progressing autonomic neuropathy (gastroparesis, postural hypotension, neuropathic bowel or bladder) or persistent or progressing severe peripheral painful neuropathy not responding to usual management (e.g., tricyclics, gabapentin, or carbamazepine).

Exclusion Criteria

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 > New York Heart Association (NYHA) Class 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. Tuberculosis (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).
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

6.1.4 Study Treatments or Agents Mandated by the Protocol

Donislecel

Donislecel is a cellular suspension of allogeneic pancreatic islets (islets of Langerhans). Each single-donor islet batch consists of two infusion bags connected to each other via a sterile connector. One bag contains LANTIDRA up to a maximum of $1x10^6$ EIN in 400 ml of transplant media and the second bag contains transplant media used to rinse bag 1 and the infusion line. The dosage strength is represented by the total EIN in a single preparation and varies between product batches

Immunosuppressive regimen

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.

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. Table 5 provides a summary of concomitant study medications.

Table 5: Summary of Administered Concomitant Study Medications for UIH-001

Medication	All Patients **(N=10)**
Anakinra; n (%)	1 (10%)
Daclizumab; n (%)	10 (100%)
Basiliximab; n (%)	5 (10%)
Mycophenolate mofetil; n (%)	6 (60%)
Etanercept; n (%)	6 (60%)
Everolimus; n (%)	1 (10%)
Sirolimus; n (%)	10 (100%)
Tacrolimus; n (%)	10 (100%)
Cyclosporine	1 (10%)
Anti-thymocyte immunoglobulin; n (%)	1 (10%)
Exenatide; n (%)	6 (60%)

[Source: Adapted from BLA 125734 "cm.xpt" for UIH-001]

Additional treatments

During the transplant procedures, additional medications, local anesthetics, and contrast media are also used. During and for 1 week following the transplant, heparin and s.c. longer acting low molecular weight heparin (enoxaparin Lovenox® are used to reduce coagulation risks that may lead to liver thrombosis. Study subjects will be monitored for hemorrhage and bruising while receiving these anticoagulants. Subjects will be expected to self-administer sub-cutaneous doses of Lovenox® 30 mg bid for the week after each transplant or obtain the assistance of another person in doing so.

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

Neupogen® (filgrastim) was to be given to post transplant patients presenting with neutropenia secondary to sirolimus, Valcyte®, and/or Bactrim®.

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. Exenatide was to be administered at a dose of 5 mcg subcutaneously 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, the dose was

to be increased to 10 mcg b.i.d. Exenatide was to be given for a total of 6 months after the last islet transplant.

6.1.5 Directions for Use

Allogenic Pancreatic Islet Cell Infusion

Potential organ donors were screened against safety and organ quality criteria. Details of organ donor testing and islet cell isolation procedures are described in the study protocol (Appendix 16.1.1). Pancreatic islet cells were isolated in clean room facilities at the Cell Isolation Laboratory at UI Health.

Eligible patients received islets injected into the portal vein by transvenous or percutaneous transhepatic access under fluoroscopic and ultrasound guidance.

Please refer to the CMC review for a discussion of donislecel product preparation.

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.

[Source: Original BLA 125734; uih-001-amended-report-body, p. 13]

Devices Use

The Applicant's proposed labeling provides the protocol for islet cell transplantation using a catheter and gravity bag transfusion.

Clinical Reviewer Comment: In response to requests for information (6/12/2020, 7/1/201) the Applicant provided information (AMD 002, and AMD 41) on the devices and methods used to deliver donislecel. In the 56 transplantation procedures, only 6 (10.7%) used a catheter. The remainder of the procedures used introducer systems which are not cleared or approved for the delivery of drugs or therapeutic agents. Furthermore, only 21 (37.5%) of the procedures used gravity bag infusion, with the remaining 35 (62.5%) being done by syringe. A flush was used after gravity infusion, but none was used after syringe infusion.

The majority of delivery devices used in studies UIH-001 and UIH-002 were used off-label. And when used, the bags used to convey the donislecel product are not the same bags that will be used in the marketed product. The devices which could be identified within the package insert instructions for use was a complex review topic addressed in greater detail in the CMC review.

6.1.6 Sites and Centers

University of Illinois Hospital & Health Science System

This was a single center study. A full list of investigators and support team can be found in "16.1.4 Description of Investigators and Sites.pdf".

6.1.7 Surveillance/Monitoring

Year 1 Safety Monitoring Plan

- All study participants who received an islet cell transplantation were to be followed for safety for 1 year following the last transplantation. The safety of the islet transplantation and associated immunosuppressive therapies was evaluated by analysis of adverse experiences, clinical laboratory tests, and physical examination. Safety events were analyzed by their incidence, severity, and relationship to islet cell transplantation. In particular, the following parameters were assessed [laboratory measures and signs and symptoms were followed at specified intervals (see Appendix A)
- Frequency of AEs including laboratory abnormalities
- HbA1c (less than 6.1% is considered normal)
- 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 event (SHE)
- Renal function, measured both by serum creatinine and calculated glomerular filtration rate (GFR) using the Cockroft & Gault
- Lipid profiles for cholesterol, TGs, LDL and high density lipoprotein (HDL)
- PRA
- Doppler ultrasound to exclude or document portal vein thrombosis
- Immunosuppressive drug trough levels
- Renal clearance (GFR)
- Liver function tests
- Diagnosis of opportunistic infections, e.g., cytomegalovirus (CMV)

Long-Term Safety Monitoring

Subjects who completed the original 52-week post-transplant evaluation period were asked to continue follow-up evaluations every three months for 5 to 10 years for safety and efficacy monitoring. All subjects could voluntarily withdraw from follow-up at any time.

6.1.8 Endpoints and Criteria for Study Success

Primary Efficacy Endpoint

The initial efficacy endpoints for UIH-001 are provided for completeness of this review. However, in the Applicant's Integrated Summary of Efficacy the same efficacy assessments were used for UIH-001 and UIH-002. Please refer to Section 7 of this review.

Success – Insulin Independence

Transplant was considered a success when, beginning two weeks after their last transplant, patients were not using insulin and achieved an HbA1c ≤ 6.5%. During the year after last transplant, a patient was still considered a success if an intercurrent illness or other event caused a patient to require insulin use for a period not exceeding a total of 14 days. Thus, a durable period of insulin independence from 2 weeks up to each point of evaluation during the 1-year follow-up after last transplant was considered a success at that time point.

Partial Success - Reduction in Insulin Requirements, HbA1c and Hypoglycemic Episodes

At each point of evaluation, patients who did not achieve insulin independence were considered to have had partial success of islet transplantation at the time point if they 1) had a reduction in insulin requirement that was no less than 50% relative to baseline, 2) were present with a reduction in HbA1c that was at least a 0.3% absolute decrease from baseline, or alternatively a HbA1c ≤ 6.5%, and 3) had a reduction in hypoglycemic (HYPO) score that was no less than 50% relative to baseline or a HYPO score being 0 for the duration of evaluation.

Failure – Absence of Adequate Insulin Secretion or Graft Function

Failure to achieve full success or partial success – not meeting any of the pre-determined levels for reduction of insulin requirement, HbA1c levels or HYPO score – at any point of evaluation was to be considered a failure of islet transplantation at that time point. Within the failure group, any patient with basal C-peptide levels less than 0.3 ng/ml for two consecutive follow-up visits after last transplant was to be determined complete graft loss (CGL), and the proportion of patients having CGL out of the total ITT population was to be determined at each time of evaluation.

The definition of "failure" for the primary endpoint has been extended to include a group previously undefined in the protocol: patients who do not achieve "success" or "partial success", but still presented with detectable C-peptide production. This modification aims to account for the whole ITT population more accurately.

Secondary Efficacy Parameters

The secondary efficacy parameters are surrogate markers of islet mass and islet function, specifically:

- HbA1c levels
  - HbA1c levels reaching normal values of less than 6.1% by Day 90 ± 14 days, Day 180 ± 21 days and Day 365 ± 35 days following the first transplant (denoting the day of first transplant as Day 0) and continuing for 365 days following their final transplant (by Day 365 ± 35 days, denoting the day of last transplant as Day 0, if patient has more than one transplant) were to be considered a success.
- Oral glucose tolerance
  - Oral glucose tolerance was to be judged normal if blood glucose levels were lower than 7.8 mmol/L (140 mg/dL) after a 2-hour oral glucose tolerance test, as impaired if blood glucose levels were between 7.89 and 11.1 mmol/L (140 and 199 milligrams mg/dL) and as diabetic if blood glucose levels were higher than 11.1 mmol/L (199 mg/dL).
- Mixed meal test (glucose and C-peptide levels)
  - Acute C-peptide response and blood glucose level to a standard mixed meal test was to be used to compare values at enrollment to values at 12 months following final transplant.
- The acute C-peptide response to the glucagon stimulation test
  - The fold-increase in C-peptide levels 6 minutes after glucagon injection was to be evaluated
- Intravenous glucose tolerance
  - Glucose disappearance rate constant (kG) was to be evaluated
  - The acute insulin response to an intravenous glucose challenge (AIR-IVGGT) was to be calculated as indicator of islet mass

6.1.9 Statistical Considerations & Statistical Analysis Plan

The planned primary analysis was to estimate the true rate of insulin independence (full success, composite of not using exogenous insulin and achieving an HbA1c ≤ 6.5%) at each point of evaluation up to one year after last transplantation in patients in the intent-to-treat (ITT) population. The proportion of success at the last point of evaluation was used as the point estimate. An exact (Clopper-Pearson) two-sided 95% confidence interval was constructed assuming an underlying binomial distribution for the ITT population via SAS.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

All subjects were diagnosed with T1DM and had a history of hypoglycemia unawareness. All subjects receiving donislecel were included in the efficacy and safety analyses.

6.1.10.1.1 Demographics

Table 6 through Table 9 contain the baseline demographics for the 10 subjects in UIH-001[13].

Table 6. Age of Subjects in Study UIH-001

Age (years)	**(N=10)**
Mean (SD)	46.4 (10.16)
Median (Min, Max)	45.0 (35, 63)

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 162]

Table 7. Sex Subjects in Study UIH-001

Sex n (%)	**(N=10)**
Female	9 (90.0)
Male	1 (10.0)

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 163]

Table 8. Race of Subjects in Study UIH-001

Race n (%)	**(N=10)**
Caucasian	10 (100)
Black	0
Asian	0
Native American	0

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

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 163]

Table 9. Ethnicity of Subjects in Study UIH-001

Ethnicity n (%)	**(N=10)**
Hispanic	0
Non-Hispanic	10 (100)

Source: Tables for demographics generated by clinical reviewer

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 163]

[13] 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.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 10 and Table 11 contain anthropometric measurements for the 10 subjects in UIH-001.

Table 10. Weight of Subjects in Study UIH-001

Weight (kg)	**(N=10)**
Mean (SD)	62 (4.5)
Median (Min, Max)	62 (56, 71)

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 162]

Table 11. BMI of Subjects in Study UIH-001

BMI (kg/m2)	**(N=10)**
Mean (SD)	22 (0.95)
Median (Min, Max)	23 (21, 24)

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

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 163]

Table 12 contains the baseline diabetes characteristics for the 10 subjects in UIH-001.

Table 12. 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 use (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

[Source: Adapted from BLA 125734/014, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]
[Source: Adapted from BLA 125734/022, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]
[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Clinical Reviewer Comment: Please refer to the Clinical Reviewer Comment in Section 7.1.4, with regard to the baseline diabetes characteristics of the study populations in UIH001 and UIH-002 in the integrated analysis of the primary efficacy endpoint.

6.1.10.1.3 Subject Disposition

Please refer to Section 7.1.3

6.1.11 Efficacy Analyses

Please refer to the integrated review of efficacy, Section 7.

6.1.12 Safety Analyses

6.1.12.1 Methods

Please refer to integrated review of safety, Section 8.

6.2 Trial #2 - UIH-002

Islet Transplantation in Type 1 Diabetic Patients Using the UIC Protocol, Phase 3

6.2.1 Objectives (Primary, Secondary, etc.)

The primary objective of this study was to demonstrate the safety and efficacy of allogeneic islet transplantation in type 1 diabetic patients performed at UIC.

The purpose was to demonstrate that islet transplantation achieves better glycemic control than state-of-the-art insulin treatment in the management of type 1 diabetic patients with brittle control and a history of severe hypoglycemic episodes with hypoglycemia unawareness.

6.2.2 Design Overview

Single-center, Open-label, Nonrandomized, Uncontrolled Phase 3 Study

6.2.3 Population

Inclusion Criteria

The main inclusion criteria were for individuals to be between 18-75 years of age, diagnosed with T1DM for more than 5 years, and with their T1DM complicated by the following situations that persisted despite intensive insulin management efforts:

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

Exclusion Criteria

Patients were excluded from the study if any of the following conditions was present:

1. Diagnosis of co-existing cardiac disease, characterized by any one of these conditions:

   a. Recent myocardial infarction (within past 6 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 patients with a history of ischemic disease), or
   d. Heart failure above New York Heart Association Functional Class II.
2. Active alcohol or substance abuse, including cigarette smoking within the past 6 months. Active alcohol abuse was determined using the current National Institute on Alcohol Abuse and Alcoholism definitions.
3. Psychiatric disorder making the patient an unsuitable candidate for transplantation, e.g., schizophrenia, bipolar disorder, or major depression that was unstable or uncontrolled on current medication (a psychological or psychiatric consultation was 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, or human immunodeficiency virus (HIV).
6. Tuberculosis (TB; by medical history or current infection as evidenced by a positive QuantiFERON® -TB Gold test or if under treatment for suspected TB).
7. Any history of malignancies except squamous or basal cell skin cancer. Any patient found to have squamous or basal cell cancer was required to have it removed prior to transplant.
8. Known family history of multiple endocrine neoplasia type 2 (MEN2) or medullary carcinoma of the thyroid (MCT).
9. History of stroke within the past 6 months.
10. Body Mass Index (BMI) > 27 kg/m^2.
11. C-peptide response to glucagon stimulation (1 mg IV), evidenced by any C-peptide ≥ 0.3 ng/mL.
12. Inability to provide informed consent.
13. Age < 18 or > 75 years.
14. Creatinine clearance < 80 mL/min/1.73 m^2 by 24-hour urine collection. If corrected creatinine clearance was < 80 and serum creatinine was < 1.2 mg/dl, then a nuclear renal scan was required to determine glomerular filtration rate (GFR).
15. Serum creatinine consistently > 1.5 mg/dL.
16. Macroalbuminuria (urinary albumin excretion rate > 300 mg/24 h).
17. Baseline Hb < 12 g/dL in women or < 13 g/dL in men.
18. Baseline liver function tests (LFT) outside of normal range (initial LFT panel with any values > 1.5 times the upper limit of normal (ULN) resulted in patient exclusion without a re-test. A re-test was performed for any values between normal and 1.5 ULN, with patient exclusion if the values remained elevated above normal limits).
19. Untreated proliferative retinopathy.

20. Positive pregnancy test, intent for future pregnancy, male patients' intent to procreate, unwillingness to follow effective contraceptive measures, or presently breast-feeding.
21. Previous transplant (except islet transplant), or evidence of hypersensitization on Panel Reactive Antibody (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 patients required a negative crossmatch with the donor before transplant.
22. Insulin requirement > 0.7 IU/kg/day.
23. HbA1c > 12%.
24. Hyperlipidemia (fasting low density lipoprotein [LDL] cholesterol > 130 mg/dL, treated or untreated, and/or fasting triglycerides > 200 mg/dL).
25. Undergoing treatment for a medical condition requiring chronic use of steroids.
26. Use of Coumadin or other antiplatelet or anticoagulant therapy, or patient with prothrombin time-international normalized ratio (PT-INR) > 1.5. Low-dose aspirin was allowed after transplantation.
27. History of Factor V deficiency.
28. Currently smoking tobacco.
29. Addison's disease.
30. Symptomatic cholecystolithiasis.
31. Acute or chronic pancreatitis.
32. Symptomatic peptic ulcer disease.
33. Severe unremitting diarrhea, vomiting, or other gastrointestinal disorder 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. Receipt of live attenuated vaccine(s) within 2 months of enrollment.
37. Any medical condition that, in the opinion of the Investigator, might interfere with safe participation.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Donislecel is a cellular suspension of allogeneic pancreatic islets (islets of Langerhans) in buffered transplant media containing sodium chloride, dextrose, minerals, amino acids, vitamins, and other compounds supplemented with HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration)). Each single-donor islet batch consists of two infusion bags connected to each other via a sterile connector. One bag contains LANTIDRA up to a maximum of $1x10^6$ EIN in 400 ml of transplant media and the second bag contains transplant media used to rinse bag 1 and the infusion line.

The dosage strength is represented by the total EIN in a single preparation and varies between product batches. Dosage strength information for an individual batch is provided on the container label and in accompanying documentation. Islet injections were administered via portal vein delivery to reach the target total of 10,000 IE/kg of the recipient's body weight. Up to 3 injections could have been administered if insulin independence, or other glycemic goals (that were not further defined), was not achieved by the fourth week after each infusion.

Clinical Reviewer Comment: The Applicant stated that a greater islet mass usually led to a more stable and functional islet graft, there are also safety concerns about transplanting too much cellular volume. As a result, the maximum packed cell volume was set at ≤ 10 mL.

Dosing and administration of concomitant medications are described under Study UIH-001, Section 6.1.4. The number of subjects using each medication in UIH-002 is provided in Table 13.

Table 13. Summary of Administered Concomitant Study Medications for UIH-002

Concomitant Medications	All Patients **(N=20)**
Daclizumab; n (%)	5 (24%)
Basiliximab; n (%)	19 (95%)
Mycophenolate mofetil; n (%)	5 (24%)
Etanercept; n (%)	20 (100%)
Everolimus; n (%)	2 (10%)
Sirolimus; n (%)	20 (100%)
Tacrolimus; n (%)	20 (100%)
Cyclosporine	3 (15%)
Anti-thymocyte immunoglobulin; n (%)	4 (20%)
Exenatide; n (%)	20 (100%)

[Source: Adapted from BLA 125734 "cm.xpt" for UIH-002]

6.2.5 Directions for Use

Described in detail under UIH-001 Section 6.1.5

6.2.6 Sites and Centers

University of Illinois Hospital & Health Science System

This was a single center study. A full list of investigators and support team can be found in "16.1.4 Description of Investigators and Sites.pdf".

6.2.7 Surveillance/Monitoring

Patients were followed through 1 year after their last islet transplant and as part of a regular follow-up schedule thereafter.

Evaluations were planned for study participants at the Clinical Research Center 3 times a week for the first 2 weeks after transplantation, then twice per week for another 2 weeks, then weekly until Week 12, and then were tapered gradually to monthly visits through the first year. Additional visits were allowed as needed. The last study visit was 52 weeks after transplantation, with a patient option to continue in the study through 5 years and then again through 10 years. Additional evaluations were allowed if medical conditions presented during the study period; in these cases, each patient was evaluated according to best medical practice.

If a second or third transplant was performed on a single patient, the follow-up visit schedule was restarted to permit careful follow-up during the immediate post-operative period. In the event that a second transplant was not needed due to successful engraftment, insulin independence, and stable blood glucose levels, the follow-up schedule was maintained at monthly intervals following Week 12 through the one-year study period according to the Schedule of Evaluation in Table 3.

6.2.8 Endpoints and Criteria for Study Success

Primary endpoint

- The proportion of patients with an HbA1c ≤ 6.5% and free of SHE for at least 1 year after the first and 1 year after the last islet cell infusion.

The primary composite endpoint was to be the proportion of patients with HbA1c ≤ 6.5% at Day 365 and free of SHE from Day 28 to Day 365, inclusive, following the first and last islet transplant, with the day of transplant designated as Day 0 [40/2545]

Secondary efficacy endpoints included:

- measurements of insulin independence
- hypoglycemic episodes (quantified using a composite hypoglycemic (HYPO) score based on the frequency, severity, and degree of unawareness of hypoglycemia)
- glucose variability and hypoglycemia duration (measured by continuous glucose monitoring system [CGMS]).

6.2.9 Statistical Considerations & Statistical Analysis Plan

The primary analysis was to estimate the true rate of the composite endpoint (HbA1c ≤ 6.5% and absence of SHE) at 1 year after first and last transplant in patients in the intent-to-treat (ITT) population. The proportion of favorable outcomes was used as the point estimate. An exact (Clopper-Pearson) two-sided 95% confidence interval was constructed assuming an underlying

binomial distribution for the ITT population via SAS. Failure to achieve the favorable outcome was summarized in 2 subgroups: the rate of patients having an HbA1c > 6.5% at Day 365, and the rate of patients who experienced any SHE from Day 28 to Day 365. The primary endpoint was assessed for all treated patients from first transplant (including patients with > 1 transplant within 1 year of first exposure) and from last transplant.

Clinical Reviewer Comment: This is one efficacy endpoint recommended in the FDA guidance. Although the guidance was not explicit, the concept is that a high proportion of responders (for example, a lower bound of the 95% confidence interval greater than 50%) would be very unlikely to be observed in the natural course of T1D. If such treatment effect is observed, a single arm trial would be acceptable to provide substantial evidence of effectiveness, against a performance goal threshold based on natural history (the implied control).

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

All subjects were diagnosed with T1DM and had a history of hypoglycemia unawareness. All subjects receiving donislecel were included in the efficacy and safety analyses.

6.2.10.1.1 Demographics

Table 14 through Table 18 contain the baseline demographics for the 20 subjects in UIH-00214.

Table 14. Age of Subjects in Study UIH-002

Age (years)	**(N=20)**
Mean (SD)	47.0 (12.5)
Median (Min, Max)	47.0 (21, 67)

[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 46]

Table 15. Sex of Subjects in Study UIH-002

Sex n (%)	**(N=20)**
Female	15 (75%)
Male	5 (25%)

[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 46]

Table 16. Race Subjects in Study UIH-002

Race n (%)	**(N=20)**
Caucasian	20 (100%) [a]

[14] 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.

Race n (%)	(N=20)
Black	0
Asian	0
Native American	1 (5%) [a]

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

[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 46]

Table 17. Ethnicity of Subjects in Study UIH-002

Ethnicity n (%)	(N=20)
Hispanic	1 (5%)
Non-Hispanic	19 (95%)

[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 46]

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 18 through Table 20 contain anthropometric measurements for the 30 subjects in UIH-001 and UIH-002 combined.

Table 18. Weight of Subjects in Study UIH-002

Weight (kg)	(N=20)
Mean (SD)	65 (8.5)
Median (Min, Max)	64 (53, 83)

[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 46]

Table 19. BMI of Subjects in UIH-002

BMI (kg/m^2)	(N=20)
Mean (SD)	24 (1.9)
Median (Min, Max)	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

[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 46]

Table 20. 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: Adapted from BLA 125734/014, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]
[Source: Adapted from BLA 125734/022, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]
[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Clinical Reviewer Comment: Please refer to the Clinical Reviewer Comment in Section 7.1.4, with regard to the baseline diabetes characteristics of the study populations in UIH001 and UIH-002 in the integrated analysis of the primary efficacy endpoint.

6.2.10.1.3 Subject Disposition

Please refer to Section 7.1.3

6.2.11 Efficacy Analyses

Please refer to the integrated review of efficacy, Section 7.

6.2.12.1 Methods

Please refer to the integrated review of safety, Section 8.

6.3 Trial #3 CIT-07

Islet Transplantation in Type 1 Diabetes

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.

6.3.1 Objectives (Primary, Secondary, etc.)

The primary objective of this trial was to demonstrate the safety and efficacy of allogeneic islet transplantation for the treatment of T1DM in subjects with hypoglycemia unawareness and a history of severe hypoglycemic episodes, as demonstrated by glycemic control and elimination of severe hypoglycemic episodes.

6.3.2 Design Overview

Prospective, open-label, single-arm, multi-center Phase 3 trial assessing the benefit of islet transplantation in type 1 diabetes (T1D) patients

6.3.3 Population

Patients who met all of the following criteria were eligible for participation in the study:

1. Male and female subjects age 18 to 65 years of age.
2. Ability to provide written informed consent.
3. Mentally stable and able to comply with the procedures of the study protocol.
4. Clinical history compatible with T1DM with onset of disease at < 40 years of age, insulin dependence for ≥ 5 years at the time of enrollment, and a sum of subject age and insulin dependent diabetes duration of ≥ 28.
5. Absent stimulated C-peptide (<0.3 ng/mL) in response to a mixed meal tolerance test (Boost® 6 mL/kg body weight to a maximum of 360 mL; another product with equivalent caloric and nutrient content may be substituted for Boost) measured at 60 and 90 min after the start of consumption.
6. 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.
7. 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.
8. 8a. 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.

   OR

   8b. Marked glycemic lability characterized by wide swings in blood glucose despite optimal diabetes therapy and defined by a 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

   8c. 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.

Clinical Reviewer Comment: In general, the CIT-07 exclusion criteria were similar to those for UIH-001 and UIH-002, see Table 21 for additional details.

Table 21. 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

6.3.4 Study Treatments or Agents Mandated by the Protocol

The final islet product was a ≥70% viable, ≥30% pure, sterile, allogeneic islets suspension containing ≥20,000 total islet equivalents (IE) per milliliter of settled tissue. The final product was a suspension of purified human pancreatic islets containing ≥4,000 IE/kg recipient body weight in 200 mL of CIT Transplant Media [CMRL 1066 with HEPES (b) (4)] and Human Serum Albumin, (b) (4)) supplied in a 600 mL infusion bag. All subjects received an initial PHPI product dose of ≥5,000 IE/kg recipient body weight by intraportal infusion.

All patients received 1 or 2 islet transplants. Patients received induction immunosuppression with rabbit antithymocyte globulin, anti-coagulation concomitant with administration of the islet product, anti-inflammatory treatment with etanercept and pentoxifylline, maintenance immunosuppression with tacrolimus and sirolimus, and anti-infective prophylaxis.

6.3.5 Directions for Use

The donislecel was infused into a branch of the right portal vein that was accessed by percutaneous trans-hepatic cannulation using ultrasound and/or fluoroscopic guidance, or under direct visualization of the portal vein via a mini-laparotomy.

6.3.6 Sites and Centers

University of Illinois Hospital & Health Science System

This was a multicenter study. A full list of investigators and support team can be found in "16.1.4 Description of Investigators and Sites.pdf".

6.3.7 Surveillance/Monitoring

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

6.3.8 Endpoints and Criteria for Study Success

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

Key Secondary Endpoints:

1. The proportion of subjects with an HbA1c ≤6.5% at Day 365 AND free of SHE from Day 28 to Day 365, inclusive, following initial islet transplant

2. The proportion of subjects free of SHE from Day 28 to Day 365, inclusive, following islet transplant.
3. The proportion of subjects with HbA1c <7.0% at Day 365 following initial islet transplant.
4. The proportion of subjects with HbA1c ≤6.5% at Day 365 following initial islet transplant.
5. The proportion of insulin-independent subjects at Day 365 following islet product transplant.

Insulin independence required that the following criteria were met during a seven-day period without exogenous insulin:

- One HbA1c level, one fasting serum glucose level, and a Mixed Meal Tolerance Test were documented within the visit window (e.g. 70 - 80 days at Day 75) and 7 consecutive days of blood sugar and insulin readings were documented within +/- 7 days of the visit window (e.g. 63 – 87 days at Day 75)
- HbA1c < 7.0% or a ≥ 2.5% decrease from Baseline
- Fasting capillary glucose level did not exceed 140 mg/dL (7.8 mmol/L) more than three times in the 7 consecutive days (fasting was defined as 1st blood sugar reading of the day not noted as postprandial or bedtime)
- Post-prandial serum glucose ≤ 180 mg/dL (10.0 mmol/L) at 90 minutes during the MMT testing
- Fasting serum glucose level ≤ 126 mg/dL (7.0 mmol/L): if the fasting serum glucose level was > 126 mg/dL (7.0 mmol/L), it had to be confirmed in an additional one out of two measurements
- At least one MMT testing fasting or stimulated C-peptide ≥ 0.5 ng/mL

6.3.9 Statistical Considerations & Statistical Analysis Plan

Clinical Reviewer Comment: The Applicant only provided 4 subjects to CIT-07. Therefore, statistical analysis was not performed.

6.3.10 Study Population and Disposition

6.3.10.1 Populations Enrolled/Analyzed

The outcomes for all 4 subjects are reported individually.

6.3.10.1.1 Demographics

Subjects were 56.9 (10.4) years old; 3 female and 1 male, all Caucasian – non-Hispanic.

Anthropomorphic measurements: 69.9 (4.9) kg, 169 (7.9) cm, 23.1 (1.18) (kg/m^2).

6.3.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

Table 22. 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]**
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: Original BLA 125734, 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. All 4 subjects (100%) had reduced awareness of hypoglycemia and 3 of 4 subjects (75%) had a least 1 SHE.

6.3.10.1.3 Subject Disposition

Of the 4 subjects enrolled, 3 (75%) competed the study, 1 (25%) was discontinued early for non-compliance.

Three (3) subjects received a second transplant, including the subject who discontinued early.

6.3.11 Efficacy Analyses

Only 4 subjects contributed data to this study. The summary data for these subjects is presented.

6.3.11.1 Analyses of Primary Endpoint(s)

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. The occurrence of SHE was not reported.

6.3.11.2 Analyses of Secondary Endpoints

The 3 subjects who completed the Day730 follow up were insulin independent at the time.

6.3.12.2 Overview of Adverse Events

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.

6.3.12.3 Deaths

No deaths were reported in the study period.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

LANTIDRA is an allogeneic pancreatic islet cellular therapy indicated for the treatment of brittle Type 1 diabetes (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.

The proposed indication stated in the paragraph above does not identify a specific patient population. As presented and discussed at the Advisory Committee Meeting (AC), brittle Type 1 diabetes (labile diabetes) is a concept and not well defined. Similarly, "symptoms are not well controlled" is not defined. In general, these patients would be unable to achieve glycemic goals because of severe metabolic events, severe hypoglycemic events (SHE) and / or diabetic ketoacidosis (DKA), despite treatment/supervision by clinicians with expertise in the treatment of type 1 diabetes and access to the appropriate insulins and devices based on the patient's requirements. It is important to recognize that the insulin products, available devices, and standard of care have changed significantly since the onset of the islet cell investigational programs.

The recommended indication for use is:

LANTIDRA is an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

While it may be tempting to specify a specific target of HbA1c in the indication, this approach would not be reasonable as the target can be different based on the patient's age, duration of diabetes, and presence of complications (neuropathy, nephropathy, retinopathy).

The use of "current repeated episodes" identifies a patient population who is at risk for SHE at the time islet cell transplantation would be delivered, rather than those patients who may have had 1 or more SHE episodes more than 1 year prior to initial transplantation. For a favorable benefit risk determination, patients should have an ongoing risk of SHE to balance against the significant risks of the procedure and required immunosuppression.

7.1.1 Methods of Integration

UIH-001 was a phase 1/2 study and UIH-002 a phase 3 study using the modified Edmonton protocol for islet cell transplantation and immunosuppression. These two studies were sufficiently similar to allow for a combined analysis of efficacy and safety.

7.1.2 Demographics and Baseline Characteristics

Table 23 through Table 26 contain the baseline demographics for the 30 subjects in UIH-001 and UIH-002 combined[15].

Table 23. Age of Subjects in Study UIH-001 and UIH-002

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)

[Source: Adapted from BLA125734; 2.5 Clinical Overview.pdf, p. 11]

Table 24. Sex of Subjects in Study UIH-001 and UIH-002

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

[Source: Adapted from BLA125734; 2.5 Clinical Overview.pdf, p. 11]

Table 25. Race of Subjects in Study UIH-001 and UIH-002

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.
[Source: Adapted from BLA125734; 2.5 Clinical Overview.pdf, p. 11]

Table 26. Ethnicity of Subjects in Study UIH-001 and UIH-002

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

[Source: Adapted from BLA125734; 2.5 Clinical Overview.pdf, p. 11]

Clinical Reviewer Comment: Subjects were predominantly non-Hispanic Caucasian, which is consistent with the demographics of adult patients with type 1 diabetes mellitus in the U.S. population at the time the UIH studies were initiated. Additionally, the UIH studies were

[15] 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.

performed at a single center and enrolled only 30 subjects. Therefore, the lack of representation from other racial or ethnic groups study population is not unexpected.

No subgroup analyses were performed.

7.1.3 Subject Disposition

Of the 30 subjects enrolled into UIH-001 and UIH-002, 11 received only 1 transplant, 12 received only 2 transplants, and 7 received 3 transplants. The total dose (EI/kg) received by number of transplants is shown in Table 27.

Table 27. Donislecel Dose for UIH-001 and UIH-002

		Number of Transplants		
Study		**1**	**2**	**3**
UIH-001	N	3	2	5
Cumulative Dose (EI/kg)	Mean	5769.7	12632.0	25213.2
	Std Dev	1353.5	544.5	4963.8
	Min	4208	12247	17336
	Max	6605	13017	29404
UIH-002	N	8	10	2
Cumulative Dose (IE/kg)	Mean	7048.9	13158.7	23701.0
	Std Dev	1776.2	2217.2	6645.4
	Min	5097	10250	19002
	Max	9578	16850	28400

[Source: Adapted from Original BLA 125734, uih-001-amended-report-body.pdf, p. 59]
[Source: Adapted from Original BLA 125734, uih-002-amended-report-body.pdf, p. 57]

Ten (10) of 10 subjects (100%) in UIH-001 completed the 1-year follow-up after the last transplant per protocol. The total duration subjects were followed after the first transplant was: 3 subjects for 1-5 years, 5 subjects for 5-10 years, and 3 subjects for > 10 years.

Eighteen (18) of 20 subjects (90.0%) in UIH-002 completed the 1-year follow-up after the last transplant per protocol. Two (2) subjects (10.0%) withdrew consent within the first year: 1 subject because of adverse effects of immunosuppression, and 1 subject became non-adherent to the immunosuppression regimen (this subject did provide 1-year data). Neither subject achieved insulin independence for any duration. The total duration subjects were followed after the first transplant was: 3 subjects for 1-year, 9 subjects for 1-5 years, 7 subjects for 5-10 years, and 1 subject for > 10 years.[16]

Table 28 shows the disposition of subjects in UIH-001 and UIH-002 and the reason for discontinuation.

[16] One subject (b) (6) withdrew consent prior to first transplant and was excluded from the total population count and analyses.

Table 28. Disposition of Subjects for UIH-001 and UIH-002

UIH-001	UIH-002
Two (2) subjects (20.0%) had insulin independence at their last follow-up visit and remain on immunosuppression. These subjects continue to be followed. The total duration of follow-up was 11.6 and 12.8 years. Neither subject had SHE at baseline.	Four (4) subjects (20.0%) had insulin independence at their last follow-up visit and remain on immunosuppression. These subjects continue to be followed. However, because of the varied time since first transplant, the duration of follow-up ranged from 3.7 to 8.0 years. Of these 4 subjects, 2 had SHE at baseline (4 and 3 events in the previous year).
Two (2) subjects (20.0%) stopped immunosuppression related to adverse events related to immunosuppression. The two subjects had severe infections; both had insulin independence for some period. Neither subject had baseline SHE.	Five (5) subjects (25.0%) stopped immunosuppression related to adverse events related to immunosuppression**.** Two (2) subjects had severe intolerance to immunosuppression, 1 of these 2 was never insulin independent. Two (2) subjects had severe infections; both had insulin independence for some period. And 1 subject had post-transplant lymphoproliferative disease. This last subject had baseline SHE (1 event); the other 5 subjects did not.
One (1) subject (10 %) remained on immunosuppression without being insulin independent at the time. This subject did not have baseline SHE.	Three (3) subjects (15.0%) remained on immunosuppression without being insulin independent at the time. One (1) subject was never insulin independent. None had baseline SHE.
	Three (3) subjects (15.0%) 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.
One (1) subject (10 %) had a serious medical condition. This subject was insulin independent after the 3rd transplant, but a diagnosis of breast cancer required discontinuation of immunosuppression. This subject did not have baseline SHE.	One (1) subject (5.0%) had a serious medical condition. This subject became insulin independent after the 3rd transplant but required coronary artery bypass surgery. The subject had loss of islet cell function and eventual withdrawal of immunosuppression. The subject did not have baseline SHE.
Two (2) subjects (20.0%) lost islet cell function and immunosuppression was discontinued. Both subjects had insulin independence, 4.7 and 6.2 years. One subject had baseline SHE (1 event).	One (1) subject (5.0%) lost islet cell function and immunosuppression was discontinued. This subject had insulin independence 5.7 years. The subject did not have baseline SHE.
	One subject (3.3%) lost function and had donor-specific antigens. Never insulin independent. No baseline SHE.
One (1) subject (10 %) 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 (1) subject (10 %) had been insulin independent but became non-adherent to immunosuppression, lost graft function and immunosuppression stopped. No baseline SHE.	

Note to reader: Blank cell means there were no comparable subjects in the other study.
[Source: Adapted from Original BLA 125734 and multiple IR responses]

The Applicant's April 27, 2023 (AMD 51) to an April 24, 2023 request for an update on the subjects who required withdrawal of immunosuppression due to intolerance that results in loss of insulin dependence reported that two additional subjects required withdrawal of immunosuppression due to intolerance that result in loss of insulin independence; 1 subject (UIH-001) after 5,901 days of insulin independence and 1 subject (UIH-002) after 2,185 days of insulin independence after their islet transplant. Both subjects had received 2 transplants.

7.1.4 Analysis of Primary Endpoint(s)

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 29 provides the results of this combined analysis.

Table 29. 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). The applicant's classification of SHE was 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

[Source: Adapted from Original BLA 125734, 2.5 Clinical Overview.pdf, p. 12]

Clinical Reviewer Comment: As discussed in the following sections, there were significant issues with missing baseline data and inclusion of 25/30 (83.3%) subjects without recent 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 (10/5/2020) from the FDA, the Applicant performed a chart/ record review and provided a listing (AMD 014, 10/19/2020) 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)*" (Seaquist 2013). 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 30. 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%

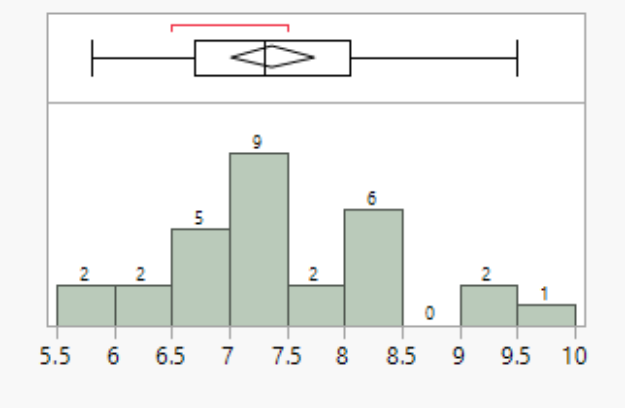
[Source: Adapted from BLA 125734/022, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Table 30 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 ≤ 7% prior to transplant, and 6 (20%) had ≤ 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 31 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: Adapted from BLA 125734/014, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Table 31. 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

[Source: Adapted from BLA 125734/014, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Therefore, FDA believes that the Applicant's proposed composite efficacy primary endpoint of HbA1c ≤ 6.5% and absence of SHE is not supported by the data provided.

7.1.5 Analysis of Secondary Endpoint(s)

Clinical Reviewer Comment: 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.

Insulin Independence

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 32 and Table 32 provide summary statistics for the duration of insulin independence for all thirty subjects in UIH-001 and UIH-002, respectively, by the total number of transplants in the individual transplant interval.

Table 32. Duration (years) 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

[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Table 33. Duration (years) of Insulin Independence by Number of Transplants Received for UIH-002

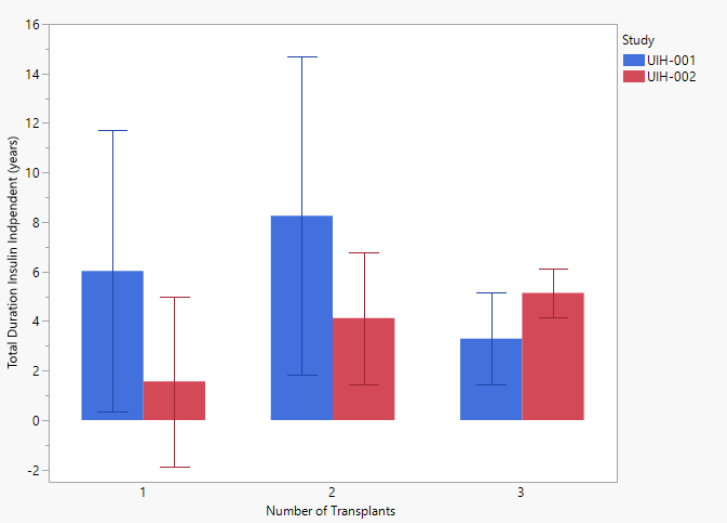
Total Number of Transplants	Transplant	N	Mean	SD	Min	Max
1	Tx#1	**8**	1.6	3.4	0	9.9
2	Tx#1	**10**	0.4	0.6	0	1.9
-	Tx#2	-	3.7	2.3	0	6.0
3	Tx#1	**2**	0	0	0	0
-	Tx#2	-	1.7	2.5	0	3.5
-	Tx#3	-	3.4	1.5	2.4	4.5

[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Figure 2 is provided to compare the outcomes for all subjects in UIH-001 and UIH-002 showing the total duration in years (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

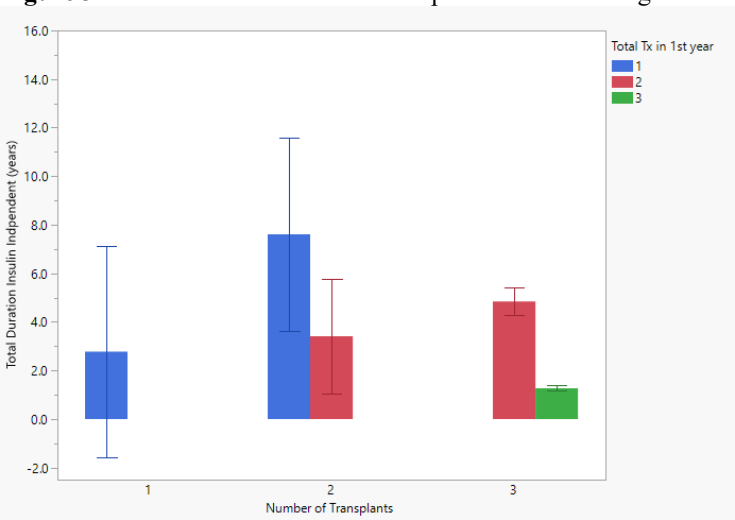


Mean ± SD

[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

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: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

Table 34 provides summary statistics describing the total duration of insulin independence from the first transplant for each study[17].

Table 34. Total Duration (in years) of Insulin Independence for UIH-001 and UIH-002

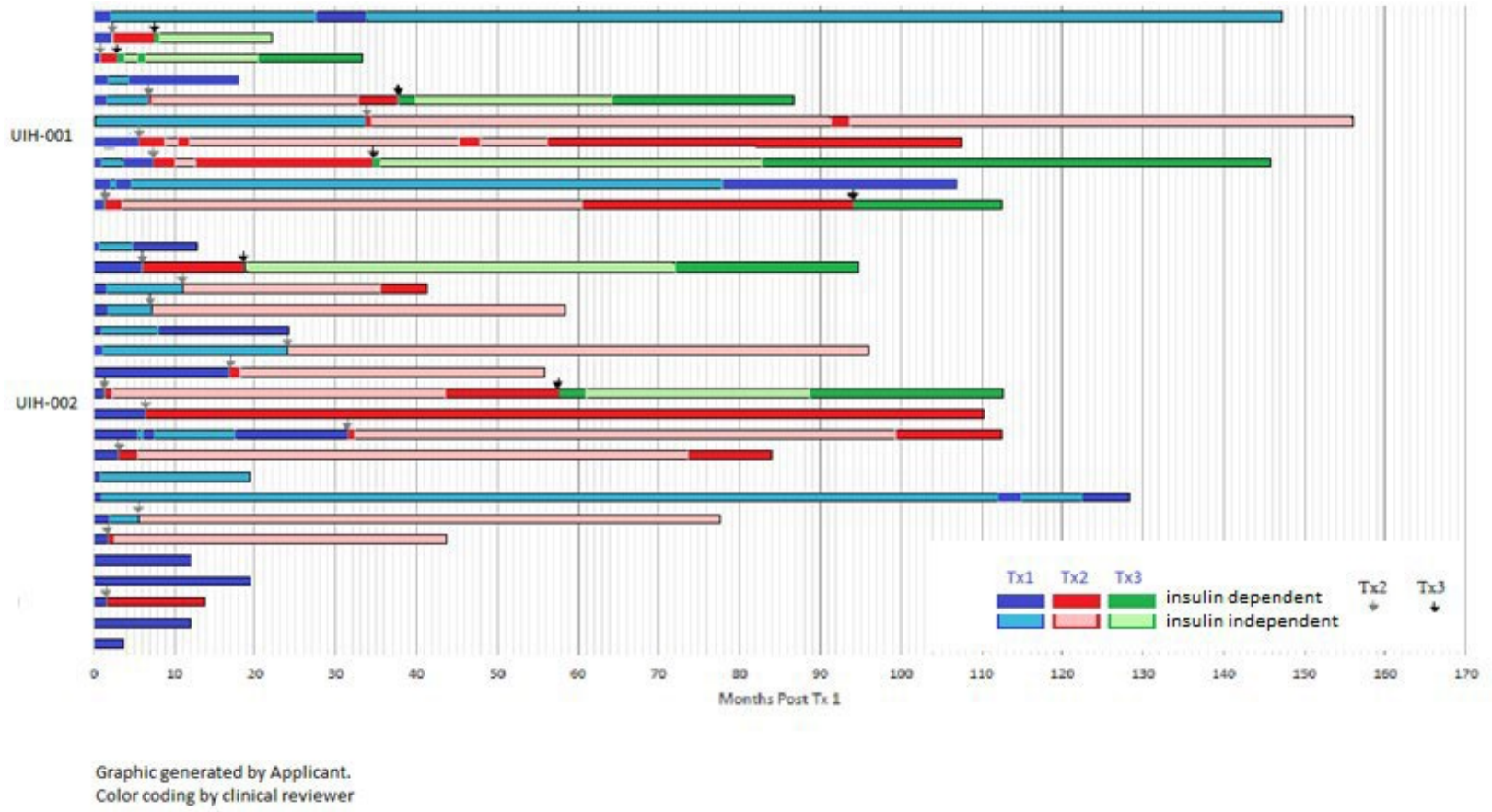
Total Duration Insulin Independent (years)	N	Mean	SD	Min	Max
UIH-001	10	5.1	4.2	0.24	12.8
UIH-002	20	3.2	3.1	0	9.9

[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

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.

[17] 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 (in months) of Insulin Dependence or Independence by Transplant for Each Subject.



(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.
[Source: BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf. p. 10]

Figure 4 shows the total duration for each subject. The transplant period color coded by transplant number

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 35 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 35. 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: Adapted from BLA 125734/022, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]
[Source: Adapted from BLA 125734/024, clinical-ir-response-incl-criteria-demog-disp-transplant.pdf]

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 HbA1c >8%, 4 (57 %) who achieved insulin independence. (One subject did not have a baseline HbA1c). The number of transplants and duration of insulin independence were consistent with what was seen in the total study population.

The Applicant provided an update on the subjects who maintained insulin independence after the September 20, 2018 data cut-off on April 27, 2023 (AMD 51) shows that 4 of the 30 subjects who received all transplants during the initial studies (UIH-001 and UIH-002) have maintained insulin independence through April 24, 2023. Duration of insulin independence for these subjects range from 11.0 to 17.6 years from their first transplant.

The Applicant provided an update for patients treated with donislecel outside of UIH studies following the original BLA data-cut on April 19, 2023 (AMD 50). Under

expanded access (IND 11807) two subjects were treated. Subject (b) (6), who received the first transplant under UIH-002, lost insulin independence and received a second transplant under expanded access. A total of 460 days of insulin independence (total follow-up 2954 days) were reported for this subject/patient. Patient (b) (6) has had 34 weeks of follow-up. Insulin independence occurred for 7 weeks, between follow-up appointments, Weeks 12 and 24.

Hypoglycemic (HYPO) Score

The HYPO Score (Ryan 2004b) 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 (90^{th} percentile) indicates serious problems with hypoglycemia, scores 423 - 1,046 indicate moderate problems, and scores < 423 indicate less serious problems. Based on the criteria for the HYPO Score, only 1 subject met the criterion for serious problems with hypoglycemia.

Eighteen (18) of 30 subjects (60%) had a reported baseline HYPO Score (see 6.1.10.1.2 and 6.2.10.1.2). 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.

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 HYPO Scores, as reported, are difficult to interpret and were not used in the efficacy analysis.

7.1.6 Other Endpoints

Clinical Reviewer Comment: In addition to insulin independence, FDA considered that patients may have benefit from islet cell transplantation if they could achieve target glycemic control by only using either basal or bolus insulin which could significantly decrease the risk of hypoglycemia and subsequent SHE. The FDA requested (12/18/2020) additional data for such subjects in UIH-001 and UIH-002. The Applicant's response (AMD 22, 1/8/2021) showed that of the 5 subjects who were unable to achieve insulin independence no subjects were able to maintain glycemic target glycemic control with only basal or bolus insulin. The Applicant did not provide data for those subjects who achieved but did not maintain insulin independence. Furthermore, as described above, because 25 of 30 subjects enrolled in these studies did not have documented SHE in the year prior to treatment, an improvement in this parameter cannot be examined.

7.1.7 Subpopulations

There was little variability in the 30 subjects enrolled in UIH-001 and UIH-002. Therefore, an analysis of subpopulations was not warranted.

7.1.8 Persistence of Efficacy

Section 7.1.5 and Figure 4 show provides information on the total duration of insulin independence achieved by each subject. It should be noted that persistence of efficacy is dependent on, but not guaranteed by, continued immunosuppression.

7.1.9 Product-Product Interactions

Immunosuppression is required to maintain islet cell survival; no direct interactions have been reported.

Exenatide is a glucagon-like peptide-1 (GLP-1) agonist added to the protocol to enhance insulin secretion by the transplanted islet cells. (Please see Section 6.1.5)

As described in Section 7.1.9, donislecel was to be delivered via catheter into the portal vein. The initial deliveries allow use of a syringe delivery or an infusion bag and gravity infusion. The transfer of the product to the container closure (syringe or infusion bag) and infusion through a catheter can all result in damage to the islets which could adversely affect the efficacy of the product. The results and limitations of the bench testing performed to demonstrate the compatibility of the product with these devices can be found within the CMC review.

7.1.10 Additional Efficacy Issues/Analyses

Unlike most drug products the dosing of biologics, especially cell products, does not allow for discrete and accurate dosing. Furthermore, the use of delivery devices has the potential to affect the amount and quality of the cell product being delivered. Full details of the characteristics cell product and potential effect of delivery devices on the cell product can be found in the CMC review.

An attempt was made, in conjunction with the CMC reviewer, to determine if factors such as the number of transplants, cell product characteristics (number of cells, viability, purity, and potency), and delivery device could be associated with occurrence or duration of insulin independence. As discussed throughout this review and the CMC review, there are too many variables, to be able to identify clear patterns.

7.1.11 Efficacy Conclusions

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.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

There are three main risks associated with treatment with LANTIDRA. These are the risks of the cell product, the transplantation procedure, and the concomitant medications.

Allogeneic cell transplantation poses a risk of communicable disease transmission from donor to recipient. The development of panel reactive antibodies (PRA) can adversely impact potential donor matching for patients who may require renal transplantation (Ryan 2004a). As with any invasive procedure there are the risks of anesthesia, infection, and bleeding. Liver laceration, hemorrhage and intra-abdominal bleeding have occurred with portal administration islet cells. Infusion of pancreatic islets and other cells into the portal venous system results in microembolization. There is a potential for these micro emboli to cause portal hypertension. Portal vein branch thrombosis may also occur following islet transplantation procedures. Concomitant medications included immunosuppression, which is required for β-cell survival, and exenatide, which was proposed to improve β-cell function after transplantation. Patients receiving immunosuppressants are at increased risk of developing lymphomas and other malignancies, particularly of the skin; developing bacterial, viral, fungal, and protozoal infections, including opportunistic infections; and anemia, sometimes requiring transfusion (Ryan 2004a and Larsen 2004). Exenatide, a glucagon-like peptide-1 (GLP-1) agonist, is known to cause nausea, vomiting, and diarrhea. Therefore, review of the adverse events in UIH-001 and UIH-002 was done considering the multiple factors that may contributed to their occurrence.

The safety analysis was based on 30 subjects (56 total transplants) who were enrolled in the Phase 1/2 study (UIH-001) and Phase 3 study (UIH-002). Subjects were followed for a mean of 6.5 years (range 0.3 – 13.0 years).

In these clinical studies, subjects may have only received 1 transplant, or received subsequent transplants at different time points; therefore, parallel comparison of rates of AEs was not 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. While this approach also has limitations in that it results in significant variability in the period in which adverse events are collected for each subject, it does provide insight to

the ongoing risk of immunosuppression required for β-cell survival to weigh against the potential for prolonged insulin independence.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The safety evaluation was performed using all adverse events reported for studies UIH-001 and UIH-002. The data reported in the Applicant's 120-safety analysis were used in the final analyses.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The demographics are presented in Section 6.1.3 (UIH-001) and Section 6.2.3 (UIH-002).

8.2.3 Categorization of Adverse Events

Adverse event assessment was not limited to the adverse event data bases (ae.xpt) provided within the submission but included all available information (please see below for sources). Because of the variable duration of follow up, assessments were not limited to the 1-year period after the subject's last transplant but instead represents all adverse reactions that occurred from the time of first transplant through the last follow-up. For the purposes of this document all adverse events during the studies are considered to be adverse reactions. This approach was taken because on inspection of the 2305 adverse events in the 120-day safety update, 1174 were reported as "probably related", 432 "not related", and 99 "missing". Further investigation showed that of those adverse events that were designated as "not related" or "missing", there were 25 events of anemia which could likely be attributable to periprocedural complications or a result of immune suppression, and 49 events of infections which could reasonably be attributable to the use of immunosuppression. There were 5 events: hepatic hematoma, hemoperitoneum, pleural effusion, and 2 cases of ascites that were temporally associated with transplant procedures and could reasonably be determined to be "probably related". Additionally, many of the 60 gastrointestinal adverse events, such as nausea, vomiting, diarrhea, and abdominal pain could be attributed to the concomitant use of exenatide. Exenatide was associated with other adverse events contained within the data base and the gastrointestinal symptoms were identified as reasons for early discontinuation of this medication in the database, subject narratives, and response to an information request (IR) (December 18, 2020) requesting information on adherence to exenatide use during the studies. In contrast, adverse event of "arthropod bite" was identified as "probably related". A full adjudication of the relatedness of adverse events was not practicable. When easily identifiable as not attributable to the product, procedure, or concomitant medications required under the protocol (immunosuppression and exenatide), adverse events were removed from the list of adverse reactions. For example, arthropod bite. The

review team recognizes the limitations in this approach to the safety assessments, particularly for common adverse events, as there is no concurrent control group for comparison, and some or most of these events are common the target population.

The Adverse Event data base containing the 120-day safety up-date information (dated September 16, 2020). The data base (DB) was reviewed for the severity attribution as follows

- AEs lacking an attribution of severity ("missing") were identified
- Columns "AEACTOTH", "AEOACTOT", "AEDRG", and "AEOACT3" were queried for additional information regarding the reported AE.
- Narratives for each subject were reviewed in
    - UIH-**001**-amended-report-body.pdf
    - UIH-**002**-amended-report-body.pdf
    - **120-d**ay-safety-update-report.pdf
    - **CRF** for the individual subject
    - **Procedure** report for each infusion

The following severity attribution was changed in the 120-day safety update AE file for the following subjects. The reason for the change is provided and the source of information used to support the change is provided in Table 36.

Table 36. Updated Adverse Event Severity

Subject ID	AE date	AEPT	Original severity	Change/reason	Source (p = page)
(b) (6)	(b) (6)	Hepatic hematoma	Moderate	**Severe** – extended hospitalization (narrative)	001 p 149
	(b) (6)	Vomiting	Moderate	**Severe** – sent to ER for IV fluids	120-d AE DB AEOACTOT
	(b) (6)	Exposure to communicable disease	Mild	Exposure mild but INH tx resulted in severe complication – optic neuritis (severe)	n/c
(b) (6)	(b) (6)	Gingival abscess	Moderate	**Severe** – Required surgical drainage (invasive)	120-d AE DB AEOACTOT
(b) (6)	(b) (6)	Pneumonia	Mild	**Moderate** – treated with oral antibiotics	CRF p510/825
	(b) (6)	Pneumonia	Missing	**Severe** – Required oral and **IV antibiotics**	CRF p784/825
	(b) (6)	Pneumonia	Missing	**Moderate** – treated with oral antibiotics	CRF p798/825
(b) (6)	(b) (6)	Nausea	Moderate	**Severe** – Required hospitalization	120-d AE DB AEOACTOT
	(b) (6)	Nausea	Mild	**Severe** – Required hospitalization	120-d AE DB

Subject ID	AE date	AEPT	Original severity	Change/reason	Source (p = page)
					AEOACTOT
	(b) (6)	Muscle necrosis	Missing	**Severe** – Required hospitalization	120-d AE DB AEOACT3
	(b) (6)	Anemia	Moderate	**Severe** – required transfusion	120-d AE DB AEOACTOT
	(b) (6)	Herpes Zoster	Missing		
(b) (6)	(b) (6)	Viral Pericarditis	Moderate	**Severe** – Required hospitalization	001 – p 135 120-d AE DB AEOACT3
(b) (6)	(b) (6)	Pericardial Effusion		**Severe** – Required pericardial window for recurrent pericarditis, interruption and change of IS	001 P 121
(b) (6)	(b) (6)	Tooth abscess	Mild	**Severe** – Required tooth extraction	120-d AE DB AEOACTOT
(b) (6)	(b) (6)	Tooth infection	Moderate	**Severe** – Required tooth extraction	120-d AE DB AEOACTOT
(b) (6)	(b) (6)	Anemia	Mild	**Severe** – required hospitalization and transfusion (re AE DB) or Procrit (re 001 narrative)	120-d AE DB AEOACTOT – or 001 P 137
	(b) (6)	Procedural Complication Hepatic Hematoma		**Severe** **-**transfer to transplant unit for observation	52/203 of procedure reports
	(b) (6)	Dehydration	Moderate	**Severe** – Required hospitalization	120-d AE DB AEOACTOT – or 001 P 142
(b) (6)	(b) (6)	Inguinal Hernia	Mild	**Severe** – Required hospitalization	120-d AE DB AEOACT3
(b) (6)	(b) (6)	Catheter Displacement		Severe – Required transfer to ICU, no embolization.	P 52/203 of procedure reports
(b) (6)				Reproductive disorder -vaginal discharge- monistat – not reported as an infection	
(b) (6)	(b) (6)	Stomatitis	Mild	**Moderate**- required viscous lidocaine	120-d AE DB AEOACTOT
(b) (6)	(b) (6)	Neutrophil count decreased	Life-threatening	Not listed under “Blood” under investigations	
(b) (6)	(b) (6)	Anemia	Moderate	**Severe** – Bleeding	120-d AE DB AEOACTOT
		Intraabdominal hemorrhage	Severe	Under Gastrointestinal disorder -2-units PRBC	120-d AE DB AEOACTOT

Subject ID	AE date	AEPT	Original severity	Change/reason	Source (p = page)
				Should be procedural injury	
	(b) (6)	Abdominal hernia	Moderate	**Severe**- Gastrointestinal disorder – required surgery/hospitalization	120-d AE DB AEOACTOT
(b) (6)	(b) (6)	Procedural complication	severe	**Life-threatening** – liver laceration/hemorrhage, required emergency surgery, 4 units of blood and was placed on a ventilator	120-d AE DB AEOACTOT – or 002 P 185
(b) (6)	(b) (6)	Herpes		Oral (improving)	CRF p377/1154
	(b) (6)	Squamous cell carcinoma of head and neck	Missing	**Severe** -required surgery	120-d AE DB AEOACTOT – or 002 P 182
(b) (6)	(b) (6)	Cervical neoplasm	severe	cervical intraepithelial neoplasia (Grade 3/4) – required LEEP Added to count of cancers	120-d AE DB AEOACTOT – or 002 P 190
(b) (6)	(b) (6)	Myocardial Ischemia	severe	Not in AE DB States no longer on IS – stopped 22MAR2016 – this doesn't make any sense. Angioplasty in DB 29MAR2016	002 P 201
(b) (6)	(b) (6)	Stomatitis	Mild	**Moderate** – required lidocaine	120-d AE DB AEOACTOT
	(b) (6)	Subdural hemorrhage	Moderate	**Severe** – required hospitalization (run down by horse)	120-d AE DB AEOACTOT 002 P 172

[Source: BLA 125734, multiple sources, stated in table]

The updated safety data were used for the analysis presented in the Prescribing Information, Section 6 using the parameters ≥20% and severity ≥ 3 (severe), those ≥5% and < 20%.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

None

8.4 Safety Results

8.4.1 Deaths

There were 2 (6.7%) deaths reported, both in Study UIH-002.

Subject (b) (6) (who received 1 transplant) died as a result of multi-organ failure with sepsis 1.6 years after the first (and only) transplant. This subject was insulin independent after transplant and on immunosuppression up to the time of the event. Immunosuppression was stopped secondary to the sepsis and the subject did not recover.

Immunosuppression is associated with increased risk of infection. Therefore, the occurrence of sepsis and subsequent death of this subject can reasonably be attributed to the investigational treatment.

Subject (b) (6) (who received 2 transplants) died with reported progressive confusion, global atrophy and micro-ischemic disease 9.7 years after the first transplant. This subject experienced 27 severe or life-threatening adverse reactions including neutropenia, pneumonia, anemia, and squamous cell carcinoma. Despite these adverse events and not achieving insulin independence, this subject on immunosuppression up to the fatal event. Of note, this subject also experienced a life-threatening complication during the second transplant procedure requiring emergent surgery and prolonged hospitalization.

The Applicant's April 27, 2023 (AMD 51) to an April 24, 2023 request for an update on any additional deaths after the September 20, 2018 data cut-off reported that Subject (b) (6) (who received 3 transplants, UIH-002) died more than 10 years after her first islet cell infusion due to heart failure. This subject was reported to have left ventricular dysfunction 5 years after receiving her first islet cell infusion. The subject was noted to be 68 years old at the time of this adverse event. Patients with T1DM have an increase relative risk of cardiovascular disease than the general population. Therefore, the clinical review team does consider this death as unexpected.

8.4.2 Nonfatal Serious Adverse Events

A total of 1,180 adverse events occurred during the first year after the first transplant: 9 life-threatening, 77 severe, 211 moderate, 813 mild, and 70 "missing"18.

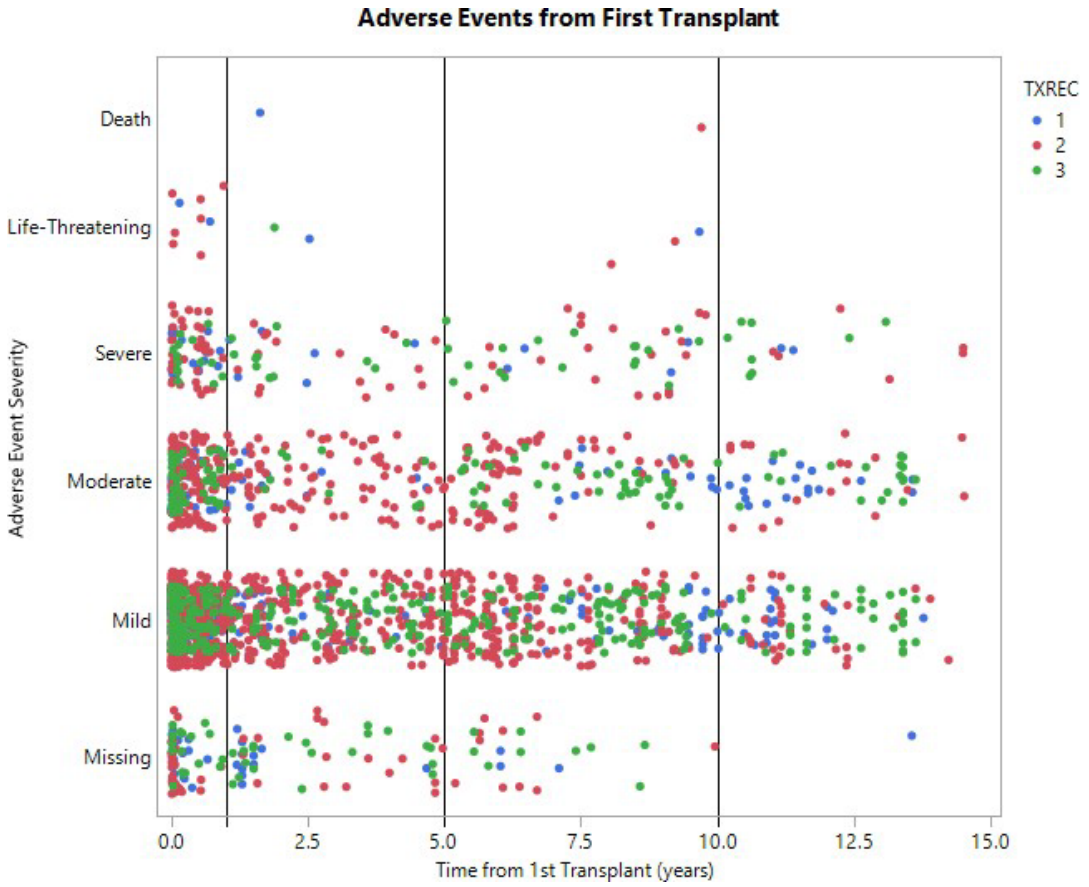
In Years 2 through 5 after the first transplant, there were a total of 501 adverse events: 1 death, 2 life-threatening, 35 severe, 108 moderate, 308 mild, and 47 "missing". Twenty-two (22) subjects contributed data to the safety data base after the first year.

Five (5) or more years after the first transplant, there was a total of 624 adverse events: 1 death, 3 life-threatening, 60 severe, 169 moderate, 368 mild, and 23 "missing". Eighteen (18) subjects contributed to the safety data base after 5 years, and 6 subjects after 10years.

This is more easily appreciated in Figure 5.

[18] The Applicant's adverse event data base did not include a severity score for these events. The level of severity was added or modified in the data base as described in Section 8.2.3

Figure 5. Adverse Events from First Transplant.



[Source: Adapted from BLA 125734/039, updated ae.xpt for UIH-001 and UIH-002, and Table 36]

Deaths are reported in Section 8.4.2. Those 186 adverse events with the designation of "severe" or "life-threatening" are presented in Table 37.

Table 37. Non-fatal Serious Adverse Events

System Organ Class (SOC)	Preferred Term (AEPT)	Life-Threatening	Severe
Blood and lymphatic system disorders			
	Anemia	1	10
	Lymphopenia	0	1
	Neutropenia	3	8
	Pancytopenia	1	0
	Thrombocytopenia	0	1
Cardiac disorders			
	Coronary artery disease	0	1
	Left ventricular dysfunction	0	2
	Myocardial ischemia	0	3
Ear and labyrinth disorders			
	Tinnitus	0	1

System Organ Class (SOC)	Preferred Term (AEPT)	Life-Threatening	Severe
Endocrine disorders			
	Hypoglycemia	0	1
Gastrointestinal disorders			
	Abdominal hernia	0	1
	Abdominal pain	0	2
	Colitis	0	3
	Diarrhea	0	4
	Inguinal hernia	0	1
	Intra-abdominal hemorrhage	0	1
	Nausea	0	2
	Vomiting	0	2
General disorders and administration site conditions			
	Asthenia	0	3
	Chills	0	1
	Fatigue	0	1
	Gait disturbance	0	1
Hepatobiliary disorders			
	Cholecystitis	0	1
Infections and infestations			
	Cytomegalovirus infection	0	2
	Fungal skin infection	0	1
	Gingival abscess	0	1
	Oral herpes	0	1
	Osteomyelitis	0	2
	Pneumonia	0	4
	Pneumonia legionella	0	1
	Pyelonephritis	0	1
	Sinusitis	0	2
	Tooth abscess	0	1
	Tooth infection	0	1
	Upper respiratory tract infection	0	1
	Urinary tract infection	0	3
	Urosepsis	1	0
	Viral pericarditis	0	1
Injury, poisoning and procedural complications			
	Fall	0	1
	femur radius Fracture	0	1
	fibula/tibia fracture	0	1
	Foot fracture	0	1
	Hepatic hematoma	0	1
	Hip fracture	0	1
	Incisional hernia	0	1
	Procedural complication	1	0
	Subdural hemorrhage	0	1
	ulna Fracture	0	1
	Wrist fracture	0	1
Investigations			
	Blood creatinine increased	0	5

System Organ Class (SOC)	Preferred Term (AEPT)	Life-Threatening	Severe
	Blood parathyroid hormone increased	0	1
	Glomerular filtration rate decreased	0	1
	hemoglobin decreased	0	1
	Low density lipoprotein increased	0	15
	Neutrophil count decreased	2	0
	Transaminases increased	0	4
	Urine protein/creatinine ratio increased	0	1
Metabolism and nutrition disorders			
	Decreased appetite	0	1
	Dehydration	0	1
	Hypercholesterolemia	0	1
	Hyperlipasemia	1	0
	Hyperlipidemia	0	1
	Hypoalbuminemia	0	1
	Hypoglycemia	0	1
	Hypoglycemia unawareness	0	1
	Hyponatremia	0	8
	Hypophosphatemia	0	1
Musculoskeletal and connective tissue disorders			
	Arthritis	0	1
	Intervertebral disc protrusion	0	1
	Muscle necrosis	0	1
	Musculoskeletal pain	0	1
	Myalgia	0	1
	Trigger finger	0	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
	Basal cell carcinoma	0	3
	Breast cancer	1	0
	Cervix neoplasm CIN (Grade 3/4)	0	1
	Malignant melanoma	0	1
	Papillary thyroid cancer	1	0
	Post transplant lymphoproliferative disorder	1	0
	Squamous cell carcinoma	0	8
	Uterine leiomyoma	0	1
Nervous system disorders			
	Carpal tunnel syndrome	0	2
	Headache	0	1
	Optic neuritis	0	1
	Serotonin syndrome	0	1
	Syncope	0	6
Psychiatric disorders			
	Agitation	0	1
	Confusional state	0	1
	Depression	0	1
Renal and urinary disorders			

System Organ Class (SOC)	Preferred Term (AEPT)	Life-Threatening	Severe
	Proteinuria	0	1
Reproductive system and breast disorders			
	Menstruation irregular	0	1
	Ovarian cyst ruptured	0	1
	Rectocele	0	1
	Vaginal hemorrhage	0	1
Respiratory, thoracic and mediastinal disorders			
	Acute respiratory failure	1	0
Surgical and medical procedures			
	Coronary artery bypass	0	1
	Hysterectomy	0	1
Vascular disorders			
	Hypertension	0	2
	Peripheral artery stenosis	0	2

[Source: Adapted from BLA 125734/039, updated ae.xpt for UIH-001 and UIH-002, and Table 36]

Adverse reactions of special interest (infection, malignancy, anemia, procedural complications, and panel reactive antibodies) are discussed in Section 8.4.8.

There was a total of 284 gastrointestinal adverse reactions with all 30 subjects reporting at least 1 gastrointestinal adverse reaction. Those adverse reactions reported ≥ 10% of subjects were abdominal pain, constipation, diarrhea, dry mouth, dyspepsia, gastroesophageal reflux, nausea, oral pain, stomatitis, toothache, and vomiting. These adverse reactions are consistent with the implantation procedure, use of exenatide, and immunosuppression. It should be noted that oral pain (17% of subjects) and stomatitis (50% of subjects) may have been attributable to herpes or candida infections. Toothache (17% of subjects) may have been attributable to gum infections; 2 subjects required tooth extraction secondary to infection.

There were 8 fractures reported by 5 subjects (17%). Immunosuppression is associated with increase in bone loss and osteoporosis. However, there is insufficient data from the subject's demographic data and medical history to determine if immunosuppression is causative or contributory to fracture.

8.4.3 Study Dropouts/Discontinuations

Please refer to Section 6.1.10 (UIH-001) and Section 6.2.10 (UIH-002) for the disposition of the subjects in these two studies.

8.4.4 Common Adverse Events

Table 38. Adverse Reactions Occurring in ≥20% of Subjects from Initial Transplant through 1 Year After Final Transplant (Studies UIH-001 and UIH-002; 30 Subjects)

Adverse Event System Organ Class (AESOC)	Adverse Event Preferred Term (AEPT)	% Subjects Any Severity	% Subjects Severity ≥ Grade 3
Blood and lymphatic system disorders			
	Anemia	80	27
	Leukopenia	27	
Cardiac disorders			
	Palpitations	23	
Ear and labyrinth disorders			
	Ear pain	30	
	Tinnitus	30	3
Eye disorders			
	Eye pain	27	
	Vision blurred	37	
Gastrointestinal disorders			
	Abdominal pain	67	7
	Diarrhea	80	13
	Dry mouth	47	
	Mouth ulceration	57	
	Nausea	83	7
	Stomatitis	50	
	Vomiting	60	7
General disorders and administration site conditions			
	Asthenia	67	7
	Chills	40	3
	Edema peripheral	47	
	Fatigue	83	3
	Feeling cold	20	
	Thirst	23	
Hepatobiliary disorders			
	Hepatic steatosis	23	
	Hyperbilirubinemia	33	
Infections and infestations			
	Herpes zoster	20	
	Pneumonia	20	17
	Sinusitis	40	7
	Upper respiratory tract infection	63	3
	Urinary tract infection	53	10
Injury, poisoning and procedural complications			
	Contusion	43	
Investigations			
	Aspartate aminotransferase increased	27	
	Blood bicarbonate decreased	60	
	Blood cholesterol increased	37	
	hemoglobin decreased	37	3

Adverse Event System Organ Class (AESOC)	Adverse Event Preferred Term (AEPT)	% Subjects Any Severity	% Subjects Severity ≥ Grade 3
	Low density lipoprotein increased	43	37
	Transaminases increased	63	7
Metabolism and nutrition disorders			
	Abnormal loss of weight	73	
	Anorexia and bulimia syndrome	20	
	Appetite disorder	20	
	Decreased appetite	27	3
	Hypercholesterolemia	20	3
	Hyperkalemia	30	
	Hypoalbuminemia	47	3
	Hypocalcemia	40	
	Hypomagnesemia	30	
	Hyponatremia	63	13
Musculoskeletal and connective tissue disorders			
	Arthralgia	47	
	Muscle spasms	33	
	Musculoskeletal stiffness	30	
	Myalgia	43	3
	Pain in extremity	20	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
	Thyroid neoplasm	20	
Nervous system disorders			
	Disturbance in attention	50	
	Dizziness	57	
	Headache	67	3
	Hypoesthesia	33	
	Tremor	57	
Psychiatric disorders			
	Anhedonia	27	
	Anxiety	30	
	Depressed mood	47	
	Depression	20	3
	Insomnia	53	
	Nervousness	27	
Renal and urinary disorders			
	Hematuria	20	
	Hypertonic bladder	20	
	Nocturia	53	
	Pollakiuria	40	
	Urinary incontinence	33	
Reproductive system and breast disorders			
	Menstruation irregular	20	3
Respiratory, thoracic and mediastinal disorders			
	Cough	60	

Adverse Event System Organ Class (AESOC)	Adverse Event Preferred Term (AEPT)	% Subjects Any Severity	% Subjects Severity ≥ Grade 3
	Dysphonia	43	
	Dyspnea	30	
	Nasal congestion	40	
	Oropharyngeal pain	60	
	Sinus disorder	37	
Skin and subcutaneous tissue disorders			
	Acne	90	
	Dry skin	60	
	Onychoclasis	27	
	Pruritus	57	
	Rash	53	
Vascular disorders			
	Hypertension	23	7

Less common adverse reactions (occurring in ≥5% but <20% of subjects) observed between initial transplant and 1 year following final transplant include:

Blood and lymphatic system disorders: increased tendency to bruise, lymphadenopathy, neutropenia, thrombocytopenia

Cardiac disorders: myocardial ischemia

Ear and labyrinth disorders: deafness, vertigo

Endocrine disorders: hypoglycemia, thyroid cyst

Eye disorders: cataract, conjunctival hemorrhage, eye edema, eye pruritus

Gastrointestinal disorders: Barrett's esophagus, bowel movement irregularity, colitis, constipation, dyspepsia, gastroesophageal reflux disease, oral pain, toothache

General disorders and administration site conditions: catheter site pain, chest pain, feeling of body temperature change, gait disturbance, influenza like illness, injection site extravasation, mucosal inflammation, pain, pyrexia

Hepatobiliary disorders: cholelithiasis

Immune system disorders: sensitization

Infections and infestations: bacterial vaginosis, cellulitis, cytomegalovirus infection, ear infection, Epstein-Barr infection, eye infection, fungal infection, gastroenteritis, gastroenteritis viral, localized infection, nail infection, nasopharyngitis, onychomycosis, oral candidiasis, oral herpes, osteomyelitis, rhinitis, tooth infection, vaginal infection, viral upper respiratory tract infection, vulvovaginal mycotic infection

Injury, poisoning and procedural complications: hepatic hematoma, limb injury, meniscus injury

Investigations: alanine aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, glomerular filtration rate decreased, neutrophil count decreased, urine albumin/creatinine ratio, urine protein/creatinine ratio increased, weight decreased, weight increased

Metabolism and nutrition disorders: dehydration, hyperchloremia, hyperlipidemia, hypertriglyceridemia, hypokalemia, hypophosphatemia

Musculoskeletal and connective tissue disorders: arthritis, back pain, intervertebral disc protrusion, joint stiffness, joint swelling, muscular weakness, musculoskeletal pain, neck pain, osteoarthritis, osteopenia, osteoporosis

Neoplasms benign, malignant and unspecified (incl cysts and polyps): basal cell carcinoma, squamous cell carcinoma

Nervous system disorders: carpal tunnel syndrome, cognitive disorder, dysgeusia, dyskinesia, head titubation, migraine, neuropathy peripheral, paresthesia, poor quality sleep, sinus headache, syncope

Psychiatric disorders: agitation, decreased interest, libido decreased

Renal and urinary disorders: hemoglobinuria, hydronephrosis, proteinuria, urine flow decreased

Reproductive system and breast disorders: erectile dysfunction, menorrhagia, vaginal hemorrhage

Respiratory, thoracic and mediastinal disorders: dyspnea exertional, epistaxis, pleural effusion, rhinorrhea, wheezing

Skin and subcutaneous tissue disorders: alopecia, dermatitis, erythema, hidradenitis, nail disorder, night sweats, rash pruritic, rosacea, skin exfoliation, skin lesion

Vascular disorders: peripheral artery stenosis

8.4.5 Clinical Test Results

8.4.6 Systemic Adverse Events

The systemic adverse events are those related to the immunosuppression required to maintain islet cell survival. Please see Section 8.4.8.

8.4.7 Local Reactogenicity

8.4.8 Adverse Events of Special Interest

Immunosuppression Related Adverse events

Infection risk is known to increase with immunosuppression, both for common community-acquired infections and those rarely seen in the absence of immunosuppression, either from underlying disease or iatrogenic. In total, 211 AEs of infection were reported for 26 subjects; 1event was life-threatening, 22 events severe, and 115 events moderate in severity. Additionally, one subject died of multi-organ failure from sepsis in the second year after transplant. 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 herpes and 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 (27%) subjects.

Malignancy risk is known to increase with immunosuppression. In total, 16 AEs of malignancy were reported for 11 subjects; 3 events were life-threatening and 13 severe. The events included 12 skin cancers and 1post-transplant lymphoproliferative disease.

The Applicant's April 27, 2023 (AMD 51) to an April 24, 2023 request for an update on any additional diagnoses of malignancy after the September 20, 2018 data cut-off reported one additional subject (b) (6) was reported to have squamous cell carcinoma of the left hand 16 years after the first transplant.

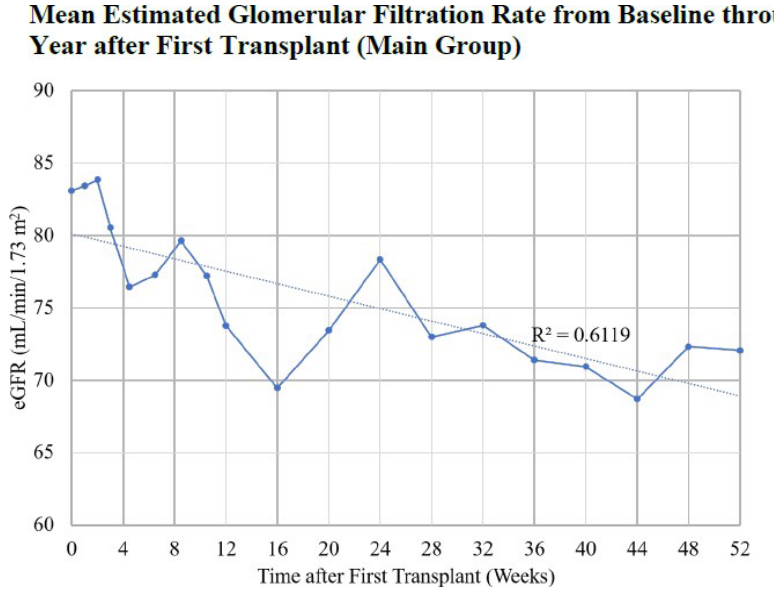
Clinical Reviewer Comment: The occurrence of skin cancers is consistent with those reported in whole pancreas transplants (Bhat 2018).

Anemia was reported for 24 (80%) of subjects. Of the 90 AEs reported, 1 event was life-threatening, 9 events severe, and 27 events moderate in severity. Causes of anemia were attributed to bleeding because of procedural complications and or immunosuppression. Transfusion was required for severe and life-threatening events. Alterations in red blood cell turnover and transfusion can alter the accuracy of HbA1c measurements may affect its use in the monitoring of glycemic control.

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 (Issa 2013). The Applicant performed analysis of changes in eGFR from baseline to 1 year after the first transplant (Figure 6 and Table 39).

Figure 6. Mean eGFR in the First Year After Transplant



[Source: Original BLA 125734, Summary of Clinical Safety.pdf, p. 49]

At baseline (n=30), 10 (33%) subjects had normal renal function (eGFR >90 mL/min/1.73 m2), 14 (47%) had mild impairment (eGFR 60-89 mL/min/1.73 m2), and 6 (20%) had moderate impairment (eGFR 30-59 mL/min/1.73 m2). 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 m2). 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 39. 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: Adapted from BLA 125734, 2.7.4 Summary of Clinical Safety.pdf, p. 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[19] 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 (Boggi 2011).

Procedural Complications

Serious Adverse Events (SAEs) related to the 56 transplant procedures included 1 life-threatening liver laceration, 1 severe intraabdominal hemorrhage, and 2 severe perihepatic hematomata resulting in prolonged hospitalization. The median peak portal blood pressure increase from baseline was 3 mmHg (range -3 to 18 mmHg). Elevated portal pressures ≥ 22 mmHg were reported in procedures for 2 subjects. One requiring cessation of the procedure and incomplete delivery of donislecel; this subject never achieved insulin independence.

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

Portal vein branch thrombosis was not observed.

The Applicant's April 19, 2023 (AMD 50) to an April 17, 2023 request for additional information for patients who received donislecel under expanded access (IND 11807) reported that two subjects were treated under expanded access reported that two additional islet cell transplants were performed under expanded access. No procedural related adverse events were reported.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

Due to the nature of the product, there are two ways to consider dose. The first is according to the number of islet equivalents/kg (EI/kg) delivered per transplant, or the total islet EI/kg received. The second is according to the number of transplants received. (See Section 7.1.3, Table 27). First, the therapy consists of cell aggregates (islets) delivered into the portal vein so they will implant into the liver in the form of micro emboli. Although, an increase in portal pressures were observed during 2 of 58 transplantation procedures, no persistent portal hypertension was reported. Additionally, while increased bilirubin was reported post-transplant, these increases were not persistent. No association between the EI/kg, either per transplant or in total, was identified. Second, there is a risk of injury for each transplant procedure, therefore it would be expected that patients receiving more than one transplant would have a greater risk.

8.5.2 Time Dependency for Adverse Events

As discussed through-out the review, immunosuppression is required to maintain islet cell viability. Therefore, the risks associated with immunosuppression exist over the duration of use. The occurrence of adverse events related to immunosuppression are discussed in Section 8 and the occurrence of all adverse events can best be seen in Section 8.4.2 Figure 5.

8.5.3 Product-Demographic Interactions

There is insufficient variability in the subject population to evaluate for product-demographic interactions.

8.5.4 Product-Disease Interactions

The product is intended to provide viable β-cells which will restore endogenous insulin production. Patients with type 1 diabetes have a lack of endogenous insulin production. Therefore, there is a direct product-disease interaction.

8.5.5 Product-Product Interactions

Immunosuppression is required to maintain viability of the islet cells. No direct toxicity to the islets cells from immunosuppressive drugs were identified.

Exenatide is a glucagon-like peptide-1 (GLP-1) agonist added to the protocol to enhance insulin secretion by the transplanted islet cells. (Please see Section 6.1.5) There is no evidence that the safety of exenatide on transplanted β-cells was different compared to pancreatic β-cells in patients with type 2 diabetes (the indicated population).

Device (see 7.1.9)

8.5.6 Human Carcinogenicity

Neoplasms from allogenic transplants of β-cells has not been described.

An increase in cancers, especially skin cancer, is a known complication of treatment with immunosuppressive drugs.

8.5.7 Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The is no evidence to suggest that allogenic transplants of β-cells can result in unregulated production of insulin.

Failure to adhere to immunosuppression or withdrawal of immunosuppression because of intercurrent illness or complication related immunosuppression can result in loss of islet cell viability and any insulin independence achieved by the patient. (See Section 7.1.3 for examples occurring within the UIH program)

8.5.8 Immunogenicity (Safety)

Of the 30 subjects who received donislecel, 28 subjects provided panel reactive antibody (PRA) data. Overall, 6/28 (21%) had a transition from baseline Class I PRA < 20% to ≥ 20% after transplant. Of these, 1/9 (11%) who received 1 transplant, 3/12 (25%) who received 2 transplants, and 2/7 (29%) who received 3 transplants. Elevated PRA can adversely impact potential donor matching for patients who may require renal transplantation.

8.5.9 Person-to-Person Transmission, Shedding

8.6 Safety Conclusions

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.

9. Additional Clinical Issues

9.1 Special Populations

N/A

9.1.1 Human Reproduction and Pregnancy Data

No pregnancies were reported for studies UIH-001 or UIH-002.

9.1.2 Use During Lactation

N/A

9.1.3 Pediatric Use and PREA Considerations

The studies were limited to adult subjects.

9.1.4 Immunocompromised Patients

Immunocompromised patients were not enrolled into studies UIH-001 or UIH-002. However, because of the requirements for immunosuppression as concomitant therapy to maintain islet cell survival, all subjects were immunocompromised when on these drugs.

9.1.5 Geriatric Use

Clinical studies of donislecel did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger adult patients.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

10. Conclusions

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.

11. Risk-Benefit Considerations and Recommendations

11.1 Risk-Benefit Considerations

Table 40. Benefit Risk Considerations

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Type 1 diabetes mellitus (T1DM) is an autoimmune disease that results in the destruction of the pancreatic islet beta cells and results in absolute insulin dependence to maintain life. T1DM is a serious condition. • A percentage of patients develop hypoglycemic unawareness; defined as the lack of symptoms of when capillary blood glucose is < 54 mg/dl. This removes the ability to react and treat the hypoglycemia to prevent progression to more severe hypoglycemia that if untreated can result in death. • The study population all had documented hypoglycemic awareness. However, the majority (83.3%) of subjects did not have documented SHE in the year prior to their first transplant.	• Severe hypoglycemia - increases the risk of death - can prevent some patients from attaining glycemic goals in order to prevent SHE • adversely affects that quality of life for those patients with recurrent SHE.
Unmet Medical Need	• Current type 1 diabetes treatment includes basal and analog insulins, insulin pumps and pens for improved delivery, insulin dose calculators to decrease dosing errors, and glucose measurement devices. • State of the art systems consist of insulin pumps, continuous glucose monitors (CGM), and complex algorithms that can pause insulin delivery when the interstitial glucose reaches or is predicted to reach a set threshold to reduce the risk of SHE. • Current therapies are unable to mimic or restore the physiologic response to increasing and decreasing glucose. • Donislecel contains allogenic islets of Langerhans that contain β-cells that produce insulin. This results in a restoration of endogenous insulin production in some patients. • Donislecel is the first drug product, save for whole pancreas transplant, that would restore endogenous insulin production.	• Despite the advances in insulin pharmacokinetic and pharmacodynamic profiles, and advances that can control insulin delivery, some patients continue to experience recurrent SHE. • By restoring endogenous insulin production, donislecel restores the normal physiologic response to increasing and decreasing glucose.

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Clinical Benefit	• For those patients who achieve full insulin independence, restoration of the normal physiological response to increasing and decreasing glucose prevents the occurrence of hypoglycemia. Therefore, these patients are no longer at risk for SHE • There are insufficient data from these studies to suggest that patients who do not achieve full insulin independence achieve a clinical benefit.	• Duration of insulin independence
Risk	• There are three main categories of risk – risk of the donislecel product, risk of the transplant procedure and risk of the immunosuppression required to protect the transplanted islet cells from rejection.	• There were 2 deaths in the study, • All subjects in the study had an adverse event of moderate or higher • Twenty-seven (27) subjects had an adverse event of severe or higher. • The adverse events that occurred are consistent with those associated with invasive procedures and immunosuppression.
Risk Management	• For a favorable benefit risk determine, only patients who are unable to approach glycemic control due to recurrent SHE should receive donislecel due to the procedural and immunosuppression risks. • Failure to appropriate select patients can result in harm to patients who are unable or unwilling to adhere to the requirements for immunosuppression and follow-up. • Failure to administer the product properly can result in harm to the patient during the procedure. Failure to administer the product using the appropriate device for administration could damage the product and impair efficacy.	• Appropriate patient population is clearly described in the Indication statement within Section 1 of the package insert • Extensive patient counseling information are provided in Section 17 and Patient Information handout of the package insert, • Appropriate administration and device selection criteria are within Section 2.3 of the package insert • Enhanced pharmacovigilance with early annual reporting requirements

11.2 Risk-Benefit Summary and 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, there were 2 (6.7%) deaths; 1 death from multi-organ failure with sepsis occurred at 1.6 years after the first transplant, and 1 death from progressive confusion, global atrophy and micro-ischemic disease, occurred 9.7 years after the first transplant. Both subjects were using immunosuppression up to the time of the event. Procedural

complications included 1 life-threatening liver laceration, 1 severe intraabdominal hemorrhage, and 2 severe perihepatic hematomata resulting in prolonged hospitalization. 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.

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.

The Advisory Panel from the April 15, 2021 Advisory Committee Meeting agreed given the risks of immunosuppression, donislecel should be limited to a very small subset of patients with type 1 diabetes for whom available therapy and technology are insufficient at preventing life-threatening complications from insulin induced hypoglycemia. The two endocrinologists on the panel agreed that 4-5 years of insulin independence would represent a clinical meaningful treatment benefit. As would be expected, the patient preference study showed that patients would prefer the greatest benefit for the lowest risk; a 5% risk of serious complications with the possibility of 5-years of insulin independence.

11.3 Discussion of Regulatory Options

As discussed throughout this review, there were many protocol deviations for both the infusion procedure and significant missing data for the Applicant's primary efficacy endpoint. However, there is substantial evidence from the results from UIH studies that transplantation of pancreatic β-cells (within the donislecel product) into the portal vein can restore insulin independence to patients with type 1 diabetes. 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, the occurrence of insulin independence can provide an objective measure of the efficacy of donislecel transplant.

11.4 Recommendations on Regulatory Actions

As was discussed during the Advisory Committee Meeting, while there can be significant benefits from treatment with donislecel, there are also significant risks from the procedure to deliver the product and concomitant medications to maintain islet cell survival, and potential risks from the product itself. Therefore, in agreement with the AC Panel, treatment with donislecel should be limited to a small subset of patients with type 1 diabetes. Our recommendation is for Approval with the following indication:

LANTIDRA is an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

11.5 Labeling Review and Recommendations

Extensive revisions of the package insert and patient information sheet were done in preparation for approval of LANTIDRA in consultation with Advertising & Promotional Labeling Branch (APLB). The revisions were done to bring the final labeling in compliance with 21CFR201.57.

The final version of the labeling is attached to this review.

APPENDIX A – FINAL PACKAGE INSERT

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use LANTIDRA safely and effectively. See full prescribing information for LANTIDRA.

LANTIDRA (donislecel-jujn) Allogeneic Pancreatic Islet Cellular Suspension for hepatic portal vein infusion
Initial US Approval: 2023

----------INDICATIONS AND USAGE----------
LANTIDRA is an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. Use in conjunction with concomitant immunosuppression. (1)

----------DOSAGE AND ADMINISTRATION----------
For infusion into the hepatic portal vein only.

- Do not irradiate.
- Do not use leukodepleting filters.
- Do not use if product time exceeds 6-hours post product release or if temperature is not maintained between 15 and 25 C
- The recommended minimum dose is 5,000 equivalent islet number (EIN) per kg patient body weight for initial infusion (transplant) and 4,500 EIN/kg for subsequent infusions (same recipient). (2.1)
- Administer cells through the hepatic portal vein (2.3). The estimated tissue volume should not exceed 10 cc per transplant infusion. (2 1)

----------DOSAGE FORMS AND STRENGTHS----------
The dosage form is a cellular suspension. Dosage strength depends on the total number of islets packaged for infusion, which is reported on the container label and associated documents. (3)

----------CONTRAINDICATIONS----------
LANTIDRA is contraindicated in patients for whom immunosuppression is contraindicated. (4)

----------WARNINGS AND PRECAUTIONS----------
- Risks from Concomitant Immunosuppression: Increased risk of severe infections including opportunistic infections, malignancy, and severe anemia. Monitor closely. Administer PCP and CMV prophylaxis. (5.1)
- Procedural Complications: Liver laceration and hemorrhage have occurred. Monitor for bleeding, portal hypertension, and portal vein thrombosis during and immediately following infusion. (5 2)
- Increased Risk of Graft Rejection: Patients with a positive T- and B-cell crossmatch between recipient serum and donor lymphocytes may be at increased risk for graft rejection. (5.3)
- Transmission of Donor-Derived Infections: Monitor for signs of infection following infusion and treat accordingly. (5.4)
- Panel Reactive Antibodies (PRA): Product administration may elevate PRA and negatively impact candidacy for renal transplant. (5.5)

----------ADVERSE REACTIONS----------
Ninety percent (90%) of subjects had at least one serious adverse reaction. (6.1)
The major causes are attributed to:
- Infusion procedure
  - liver laceration/hematoma, hemorrhage, and intra-abdominal bleeding (13%)
  - elevation of portal pressure (7%)
- Immunosuppression
  - Infection (87%)
  - Malignancy (37%)

To report SUSPECTED ADVERSE REACTIONS, contact CellTrans at 1-800-500-1617 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2023

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

LANTIDRA is an allogeneic pancreatic islet cellular therapy indicated for the treatment

of adults with Type 1 diabetes who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. Use LANTIDRA in conjunction with concomitant immunosuppression.

Limitations of Use
When considering the risks associated with the infusion procedure and long-term immunosuppression, there is no evidence to show a benefit of administration of LANTIDRA in patients whose diabetes is well-controlled with insulin therapy or patients with hypoglycemic unawareness who are able to prevent current repeated severe hypoglycemic events (neuroglycopenia requiring active intervention from a third party) using intensive diabetes management (including insulin, devices, and education).

Repeated intraportal islet infusions are not recommended in patients who have experienced prior portal thrombosis, unless the thrombosis was limited to second- or third-order portal vein branches.

There is no evidence to support the safe and effective use of LANTIDRA in patients with liver disease, renal failure, or who have received a renal transplant.

DOSAGE AND ADMINISTRATION

For infusion into the hepatic portal vein only.

2.1 Dose

The recommended minimum dose is 5,000 EIN/kg for initial infusion and 4,500 EIN/kg for subsequent infusion in the same recipient. The maximum dose per infusion is dictated by the estimated tissue volume, which should not exceed 10 cc per infusion, and the total EIN present in the infusion bag (up to a maximum of 1×10^6 EIN per bag).

A second infusion may be performed if the patient does not achieve independence from exogenous insulin within one year of infusion or within one year after losing independence from exogenous insulin after a previous infusion. A third infusion may be performed using the same criteria as for the second infusion. There are no data regarding the effectiveness or safety for patients receiving more than three infusions.

Pre-procedural medications

Provide pre-procedural induction immunosuppression 30 – 360 minutes prior to LANTIDRA infusion. Include the following, at the discretion of the treating physician who is experienced with management of immunosuppression regimens for islet cell transplantation:

- Non-depleting monoclonal anti-interleukin-2 (anti-IL-2) receptor antibody 120 minutes prior to islet infusion

    - Note: In patients who are sensitized (hypersensitivity with a past history of anaphylactic reaction) to non-depleting monoclonal anti-interleukin-2 (anti-IL-2) receptor antibody therapies, a polyclonal, T-cell-depleting antibody should be used instead.
- Calcineurin inhibitor
- Mammalian target of rapamycin (mTOR) inhibitor
- Tumor necrosis factor (TNF) blocker.
- Periprocedural antibiotic prophylaxis is recommended.

2.2 Preparation

- Keep LANTIDRA in the insulated container at 15°C to 25°C no longer than 6 hours from time of product release (See carton label and certificate of analysis). Dispose of any product not used within 6 hours.
- Do not irradiate.
- Select and prepare units under the direction of a medical professional who is experienced in islet infusion (transplantation).
- Use LANTIDRA as supplied and without further dilution.

2.3 Administration

Failure to follow these directions may result in damage and decreased viability of the islets.

Do not administer with leukodepleting filters.

- To optimize viability, administer LANTIDRA as soon as possible after product release.
- Interventional radiologists and surgeons with expertise in islet cell infusion may administer LANTIDRA in an interventional radiology suite or operating suite under controlled aseptic conditions.
- Perform all steps aseptically.
- Use a 5 or 6 French angiographic catheter indicated for the delivery of drugs or other therapeutic fluids for infusion of LANTIDRA.
    - Catheter length: 65 cm or less.
    - Internal diameter: 0.97mm (0.038 inches) or greater.
- Use only sheaths and introducers in combination with a catheter with the specified dimensions listed above to deliver LANTIDRA.

Pre-Infusion Patient Preparation

1. Confirm the identity of the patient for the specified unit of LANTIDRA.
2. Confirm that the patient has received appropriate premedication *[See Pre-procedural medication (2.1)]*.
3. Confirm that appropriate medications and blood products are available to manage any potential emergencies, such as hemorrhage, portal vein thrombosis, allergic reactions, glycemic lability, bleeding, and pain.

4. Confirm that the patient is hydrated adequately prior to infusion.
5. If indicated, administer a saline/glucose infusion and administer insulin using an intravenous insulin pump during the periprocedural period.

Pre-Infusion LANTIDRA Preparation

6. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.
    a. LANTIDRA is a cellular suspension (light yellow liquid with the presence of visible cellular aggregates).
    b. The Rinse Bag contains transplant media (light yellow liquid only with no cellular aggregates present).
7. Inspect the LANTIDRA infusion bag and the Rinse Bag for leaks and breaches of container integrity.

8. Ensure the connector between the LANTIDRA infusion bag and the Rinse Bag is secure and closed.

Note: If there are any product irregularities present or if the container appears damaged or otherwise compromised, do not infuse product and immediately notify the transplant physician/team and CellTrans at 1-800-500-1617

9. Gently agitate the LANTIDRA infusion bag to ensure that the islets are suspended and to prevent clumping. Do not shake the bag, as this may damage the islets. Repeat gentle agitation periodically throughout the infusion process.
10. Remove the first drape bag and transfer the product to an infusion operator to remove the second drape bag.
11. Ensure that the intravenous tubing is closed, then connect the LANTIDRA infusion bag, fill the drip chamber, and open the roller clamp to fill the tubing and remove air.

LANTIDRA Infusion Procedure

12. Insert the catheter into the portal vein.
13. Once the catheter placement in the portal vein is confirmed, connect the intravenous tubing from the LANTIDRA infusion bag to the catheter using a Luer lock connector.
14. Infuse all infusion bags by gravity flow over approximately 30 minutes at rates ≤ 25 mL/kg/h.
15. Flush the infusion lines periodically to clear them.
16. Do not administer LANTIDRA (islet cell product and rinse bag) through intravenous lines that contain any other medications or infusates other than physiological saline.
17. Reduce infusion rate if the fluid load is not tolerated.
18. Discontinue the infusion in the event of an allergic reaction or if the patient develops a moderate to severe infusion reaction.

19. Once the islet infusion is complete, open the roller clamp on the Rinse Bag tubing to allow refilling and rinsing of the LANTIDRA infusion bag. Gently agitate the LANTIDRA infusion bag with small amounts of rinse solution to ensure that all cells have been administered. Repeat until the Rinse Bag is empty.
20. Withdraw the catheter tip from the main portal vein into the liver parenchyma until it lies within a few centimeters (cm) of the liver capsule. Before withdrawing the catheter completely, manage hemostasis in the catheter track using standard practices to reduce the risk of bleeding.

Monitoring during LANTIDRA Infusion

- Measure portal pressure during the infusion.
    - Pause infusion if portal pressure rises above 22 mmHg and do not resume until it falls below 18 mmHg.
    - Terminate infusion if portal pressure remains above 22 mmHg for longer than 10 minutes.
- Monitor blood glucose levels every 15 minutes during the infusion and then every 30 minutes for the first 4 to 8 hours after infusion. Provide appropriate treatment if blood glucose levels fall below 70 mg/dL. Monitor blood glucose levels as needed once blood glucose levels have stabilized. After the acute period (first 4 to 8 hours following infusion), continue to monitor blood glucose (laboratory, capillary blood glucose, or continuous glucose monitor). Only use blood glucose meters and continuous glucose monitoring systems labelled for use in the hospital.
- Monitor the patient for portal vein branch thrombosis. Early diagnosis and prompt management with systemic heparinization may prevent clot propagation. However, anticoagulation therapy may lead to intra-abdominal hemorrhage requiring blood transfusion and surgical intervention.

Post-Infusion

- Monitor the patient in hospital for a minimum of 24 hours.
- Perform an abdominal ultrasound and Doppler examination of the liver after catheter removal to detect portal vein thrombosis and intra-abdominal bleeding. Repeat these examinations at least on days 1 and 7 post infusion procedure.
- Continue to monitor the patient for adverse reactions.
- Continue to monitor blood glucose levels following infusion and manage according to inpatient standard of care.

Post-Infusion Medications

- Anti-infective medications: Administer *Pneumocystis jirovecii* pneumonia (PCP) and cytomegalovirus (CMV) prophylaxis immediately following infusion of LANTIDRA and continue treatment as described in the prescribing information for the specific anti-infective medications.
- A non-depleting monoclonal anti-IL-2 receptor antibody: Administer at Week 2 after infusion for a total of two (2) doses, except in sensitized patients, who

should instead be administered a polyclonal, T-cell-depleting antibody.
- Tumor necrosis factor (TNF) blocker: Administer on post-infusion Days 3, 7, and 10.

Long-term Medications

Immunosuppression: Continue immunosuppression permanently to prevent islet graft rejection. *[See Warnings and Precautions (5.1)]*. (See Section 5.1 for reasons to discontinue immunosuppression.)

Avoid systemic steroids. Use a combination of a calcineurin inhibitor and an mTOR inhibitor or appropriate alternatives, at the discretion of the physician. Monitor trough levels of maintenance immunosuppressant drugs, and adjust the dose to maintain appropriate blood levels.

DOSAGE FORMS AND STRENGTHS

LANTIDRA is a cellular suspension of allogeneic pancreatic islets (islets of Langerhans) in buffered transplant media containing sodium chloride, dextrose, minerals, amino acids, vitamins, and other compounds supplemented with HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration).

Each infusion uses one lot of LANTIDRA which consists of islets manufactured from the pancreas of a single deceased donor. Each dose of LANTIDRA is provided as two (2) infusion bags connected to each other via sterile connector. One bag contains LANTIDRA up to a maximum of 1 x 10^6 EIN in 400 ml of transplant media and the second bag (Rinse Bag) contains transplant media used to rinse the LANTIDRA bag and the infusion line.

The dosage strength is represented by the total EIN in a single preparation and varies between product batches. Dosage strength information for an individual batch is provided on the container label and in accompanying documentation (Final Islet Product Certificate of Analysis).

CONTRAINDICATIONS

Do not administer LANTIDRA to patients who have concomitant diseases or conditions, including pregnancy, that contraindicate the procedure for LANTIDRA infusion or immunosuppression.

WARNINGS AND PRECAUTIONS

5.1 Risks from Concomitant Immunosuppression

Concomitant use of immunosuppression is required to maintain islet cell viability. The

use of immunosuppression in patients receiving LANTIDRA increases the risk of serious and potentially fatal adverse reactions. *[Adverse Reactions (6.1)]*

Patients receiving immunosuppressants are at increased risk of:
Bacterial, viral, fungal, and parasitic infections, including opportunistic infections.
Lymphomas and other malignancies, particularly of the skin.
Severe anemia, sometimes requiring transfusion.

Before Treatment

- Vaccination: To mitigate the risk of infection, patients should receive recommended immunizations prior to treatment.

After Treatment

- Administer PCP and CMV prophylaxis following administration of LANTIDRA.
- Avoid live vaccination while receiving immunosuppression.
- Monitor for fever and other signs of infection; initiate appropriate treatment early.
- Clinically monitor for malignancy, including skin cancer.
- Monitor hemoglobin/hematocrit and give blood products as indicated.

Considerations for discontinuation of immunosuppression

- If a patient develops a life-threatening infection or cancer and treatment requires discontinuation of immunosuppression.
- If a patient has been dependent on exogenous insulin for two years after their last infusion, then immunosuppression should be discontinued. However, the treatment team may consider continuation of immunosuppression if they determine that the patient has achieved target HbA1c without recurrent severe hypoglycemia in the presence of clinically relevant C-peptide, that provides a potential ongoing benefit that outweighs the risks of severe and potentially life-threatening effects of immunosuppression.
- If a patient becomes pregnant.

5.2 Procedural Complications

Liver laceration, hemorrhage and intra-abdominal bleeding have occurred with portal administration of LANTIDRA. Manage hemostasis in the catheter track using standard practices following infusion of LANTIDRA to reduce the risk of bleeding. Monitor for bleeding clinically and with laboratory assessments. Blood transfusions have been required.

Elevation in portal blood pressure has occurred during and following intraportal islet infusion *[Adverse Reactions (6.1)]*. Monitor portal pressure; pause infusion if portal pressure rises above 22 mmHg and do not resume until it falls below 18 mmHg.

Terminate infusion if portal pressure remains above 22 mmHg for longer than 10 minutes. *[Dosage and Administration (2.3)]*

Portal vein branch thrombosis may occur following infusion of LANTIDRA. Repeated intraportal islet infusions are not recommended in patients who have experienced prior portal thrombosis unless the thrombosis was limited to second- or third-order portal vein branches. *[Limitations of Use (2.1)]*

5.3 Increased Risk of Islet Graft Rejection

Patients with a positive T- and B-cell crossmatch between recipient serum and donor lymphocytes may immediately reject the islet cells. The T- and B-cell crossmatch assay is binary. T- and B-cell both need to be negative.

5.4 Transmission of Donor-Derived Infections

There is a risk of communicable disease transmission from donor to recipient that exists for LANTIDRA. Monitor patients for signs of active infection following LANTIDRA infusion and treat appropriately if infection is suspected.

5.5 Panel Reactive Antibodies (PRA)

Product administration may elevate PRA and negatively impact candidacy for renal transplant. Consider benefit-risk of administering LANTIDRA to a patient who may require a renal transplant in the future.

ADVERSE REACTIONS

Ninety percent (90%) of subjects had at least one serious adverse reaction. The major causes were attributed to:

- Infusion procedure
  - liver laceration/hematoma, hemorrhage, and intra-abdominal bleeding (13%)
  - elevation of portal pressure (7%)

- Immunosuppression
  - Infection (87%)
  - Malignancy (37%)

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety of LANTIDRA in subjects with type 1 diabetes and hypoglycemic

unawareness was demonstrated in two clinical trials (Study 1, Study 2) involving a total of 30 subjects who received between one and three doses of LANTIDRA. Duration between first and second transplant was one month to 2.8 years and between second and third dose from 3 months to 7.8 years (See Figure 1). Because of the variable duration of follow-up, number of infusions, and interval between infusions, adverse reactions were reported for the total duration for which each subject was followed. *[Clinical Studies (14)]* Subjects were followed for 0.3 to 14.5 years (mean 3 ± 3.7 years) after the first infusion.

Serious reactions were reported in 27 (90%) of subjects. There were two (7%) deaths; one death from multi-organ failure with sepsis (1.6 years after the first infusion), and one from progressive confusion, global atrophy and micro-ischemic disease (9.7 years after the first infusion). Both subjects were using immunosuppression at the time of the event. Additionally, 8 (27%) subjects experienced at least one life-threatening adverse reaction and 26 (87%) subjects experienced at least one severe reaction before their last follow-up.

Immunosuppression-Related Adverse Reactions

Risks of common community-acquired infections and opportunistic infections increases with immunosuppression. In total, 211 infections were reported for 26 subjects; one was life-threatening, 22 reactions severe, and 115 events moderate in severity. Additionally, one subject died of multi-organ failure from sepsis in the second year after infusion.

Discontinuation of immunosuppression resulted in loss of islet cell function and if achieved insulin independence. This was described for 8 (27%) subjects.

Malignancy risk is known to increase with immunosuppression. In total, 16 adverse reactions of malignancy were reported in 11 subjects; three malignancies were life-threatening. The malignancies included 12 skin cancers, and one post-transplant lymphoproliferative disease, one breast cancer, and one thyroid cancer.
Anemia was reported in 24 (80%) of subjects. Of the 90 adverse reactions reported, one reaction was life-threatening (Hgb <6.5gm/dL), 9 reactions were severe (<8-6.5 gm/dL), and 27 reactions were moderate in severity (<10-8 gm/dL).

Anemia was attributed to bleeding because of procedural complications as well as immunosuppression. Transfusion was required for severe and life-threatening reactions. Overall, five transfusions were administered to five subjects. Three transfusions were for procedural related complications and two were non-procedure related. Alterations in red blood cell turnover and transfusion can alter the accuracy of HbA1c measurements. Therefore, in addition to monitoring for the development of anemia as a result of immunosuppression or a result of a procedural complications, healthcare providers should consider the occurrence of anemia in the interpretation and use of HbA1c in the management of patients with type 1 diabetes who have received LANTIDRA.

Procedural Complications

Serious reactions related to the 56 infusion procedures included one life-threatening liver laceration, one intraabdominal hemorrhage, and two perihepatic hematomata resulting in prolonged hospitalization. Manage hemostasis in the catheter track using standard practices following infusion of LANTIDRA to reduce the risk of bleeding.

Elevation in portal blood pressure may occur following intraportal islet infusion but is usually temporary. During clinical trials with LANTIDRA, the median peak portal blood pressure increase from baseline was 3 mmHg (range -3 to 18 mmHg). Elevated portal pressures ≥ 22 mmHg were reported during procedures for two subjects requiring cessation of the procedure, and incomplete delivery of LANTIDRA for one subject. Monitor portal pressure and halt islet infusion if portal pressure rises above 22 mmHg.

Panel Reactive Antibodies

Of the 30 subjects who received LANTIDRA, 28 subjects had panel reactive antibody (PRA) data. Overall, 6 of 28 (21%) had a transition from baseline Class I PRA < 20% to ≥ 20% after infusion. These included 1 of 9 (11%) who received one infusion, 3 of 12 (25%) who received two infusions, and 2 of 7 (29%) who received three infusions.

Table 1: Adverse Reactions Occurring in ≥20% of Subjects, with some Subjects Experiencing Grade 3 Adverse Events (reactions) from Initial Infusion (Transplant) through 1 Year After Final Infusion (Transplant) (Study 1 and Study 2; 30 Subjects)

Adverse Reaction	% Subjects Any Severity	% Treated Subjects Severity ≥ Grade 3*
Nausea	83	7
Fatigue	83	3
Anemia	80	27
Diarrhea	80	13
Abdominal pain	67	7
Asthenia (loss of overall energy)	67	7
Headache	67	3
Hyponatremia (low levels of sodium)	63	13
Transaminases increased	63	7
Upper respiratory tract infection	63	3
Vomiting	60	7
Urinary tract infection	53	10
Hypoalbuminemia (low levels of albumin)	47	3
Low density lipoprotein	43	37

Adverse Reaction	% Subjects Any Severity	% Treated Subjects Severity ≥ Grade 3*
increased		
Myalgia (muscle pain)	43	3
Sinusitis	40	7
Chills	40	3
Hemoglobin decreased	37	3
Tinnitus	30	3
Decreased appetite	27	3
Hypertension	23	7
Pneumonia	20	17
Hypercholesterolemia (increased cholesterol)	20	3
Depression	20	3
Menstruation irregular	20	3

Common Terminology Criteria for Adverse Events (CTCAE) Version 5
Grade 3: (Severe) Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living.
Grade 4: (Life-threatening) consequences; urgent intervention indicated.
Grade 5: Death related to the adverse event.

Common adverse reactions (occurring in ≥20% but ≤ 90% of subjects) independent of severity observed between initial infusion and 1 year following final infusion include:

Blood and lymphatic system disorders: anemia, leukopenia

Cardiac disorders: palpitations

Ear and labyrinth disorders: ear pain, tinnitus

Eye disorders: eye pain, vision blurred

Gastrointestinal disorders: abdominal pain, diarrhea, dry mouth, mouth ulceration, nausea, stomatitis, vomiting

General disorders and administration site conditions: asthenia, chills, edema peripheral, fatigue, feeling cold, thirst

Hepatobiliary disorders: hepatic steatosis, hyperbilirubinemia

Infections and infestations: herpes zoster, pneumonia, sinusitis, upper respiratory tract infection, urinary tract infection

Injury, poisoning and procedural complications: contusion

Investigations: aspartate aminotransferase increased, blood bicarbonate decreased, blood cholesterol increased, hemoglobin decreased, low density lipoprotein increased, transaminases increased

Metabolism and nutrition disorders: abnormal loss of weight, anorexia and bulimia syndrome, appetite disorder, decreased appetite, hypercholesterolemia, hyperkalemia, hypoalbuminemia, hypocalcemia, hypomagnesemia, hyponatremia

Musculoskeletal and connective tissue disorders: arthralgia, muscle spasms, musculoskeletal stiffness, myalgia, pain in extremity

Neoplasms benign, malignant and unspecified (including cysts and polyps): thyroid neoplasm

Nervous system disorders: disturbance in attention, dizziness, headache, hypoesthesia, tremor

Psychiatric disorders: anhedonia, anxiety, depressed mood, depression, insomnia, nervousness

Renal and urinary disorders: hematuria, hypertonic bladder, nocturia, pollakiuria, urinary incontinence

Reproductive system and breast disorders: menstruation irregular

Respiratory, thoracic and mediastinal disorders: cough, dysphonia, dyspnea, nasal congestion, oropharyngeal pain, sinus disorder

Skin and subcutaneous tissue disorders: acne, dry skin, onychoclasis, pruritus, rash

Vascular disorders: hypertension

Less common adverse reactions (occurring in ≥5% but <20% of subjects) observed between initial infusion and 1 year following final infusion include:

Blood and lymphatic system disorders: increased tendency to bruise, lymphadenopathy, neutropenia, thrombocytopenia

Cardiac disorders: myocardial ischemia

Ear and labyrinth disorders: deafness, vertigo

Endocrine disorders: hypoglycemia, thyroid cyst

Eye disorders: cataract, conjunctival hemorrhage, eye edema, eye pruritus

Gastrointestinal disorders: Barrett's esophagus, bowel movement irregularity, colitis, constipation, dyspepsia, gastroesophageal reflux disease, oral pain, toothache

General disorders and administration site conditions: catheter site pain, chest pain, feeling of body temperature change, gait disturbance, influenza like illness, injection site extravasation, mucosal inflammation, pain, pyrexia

Hepatobiliary disorders: cholelithiasis

Immune system disorders: sensitization

Infections and infestations: bacterial vaginosis, cellulitis, cytomegalovirus infection, ear infection, Epstein-Barr infection, eye infection, fungal infection, gastroenteritis, gastroenteritis viral, localized infection, nail infection, nasopharyngitis, onychomycosis, oral candidiasis, oral herpes, osteomyelitis, rhinitis, tooth infection, vaginal infection, viral upper respiratory tract infection, vulvovaginal mycotic infection

Injury, poisoning and procedural complications: hepatic hematoma, limb injury, meniscus injury

Investigations: alanine aminotransferase increased, blood alkaline phosphatase increased, blood creatinine increased, glomerular filtration rate decreased, neutrophil count decreased, urine albumin/creatinine ratio, urine protein/creatinine ratio increased, weight decreased, weight increased

Metabolism and nutrition disorders: dehydration, hyperchloremia, hyperlipidemia, hypertriglyceridemia, hypokalemia, hypophosphatemia

Musculoskeletal and connective tissue disorders: arthritis, back pain, intervertebral disc protrusion, joint stiffness, joint swelling, muscular weakness, musculoskeletal pain, neck pain, osteoarthritis, osteopenia, osteoporosis

Neoplasms benign, malignant and unspecified (including cysts and polyps): basal cell carcinoma, squamous cell carcinoma

Nervous system disorders: carpal tunnel syndrome, cognitive disorder, dysgeusia, dyskinesia, head titubation, migraine, neuropathy peripheral, paresthesia, poor quality sleep, sinus headache, syncope

Psychiatric disorders: agitation, decreased interest, libido decreased

Renal and urinary disorders: hemoglobinuria, hydronephrosis, proteinuria, urine flow decreased

Reproductive system and breast disorders: erectile dysfunction, menorrhagia, vaginal

hemorrhage

Respiratory, thoracic and mediastinal disorders: dyspnea exertional, epistaxis, pleural effusion, rhinorrhea, wheezing

Skin and subcutaneous tissue disorders: alopecia, dermatitis, erythema, hidradenitis, nail disorder, night sweats, rash pruritic, rosacea, skin exfoliation, skin lesion

Vascular disorders: peripheral artery stenosis

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Pregnancy risk has not been assessed for LANTIDRA. No animal reproductive and development toxicity studies have been conducted with LANTIDRA. However, there is a risk of fetal malformations associated with certain immunosuppression medications that may be used following LANTIDRA administration. Additionally, the risks to the patient and fetus from the procedure for LANTIDRA infusion in pregnant women has not been assessed.

In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

8.2 Lactation

Risk Summary

The risk of exposing a child to LANTIDRA components during breastfeeding has not been assessed. However, some required concomitant medications, including immunosuppressants, may be excreted in milk at least in trace amounts. Because of this, a decision should be made about whether to discontinue breastfeeding in patients who will receive a LANTIDRA infusion.

8.3 Females and Males of Reproductive Potential

Pregnancy Testing

Due to the risk of fetal malformations associated with required concomitant medications, including immunosuppressants, females of reproductive potential should have a confirmed negative pregnancy test prior to LANTIDRA infusion.

Female patients of reproductive potential should be counselled to contact their transplant

team immediately if they become pregnant.

Contraception

Because long-term immunosuppression is required following LANTIDRA administration, women of childbearing potential should be informed of the potential risks that these medications pose during pregnancy and should be told to use effective contraception prior to initiation of immunosuppression and thereafter for as long as they retain reproductive potential.

Infertility

Male and female fertility may be compromised by certain medications used for maintenance immunosuppression following LANTIDRA administration.

For male patients, review the concomitant medications and determine if there is a potential for production of abnormal sperm.

8.4 Pediatric Use

The safety and effectiveness of LANTIDRA have not been established in pediatric patients with type 1 diabetes.

8.5 Geriatric Use

The safety and effectiveness of LANTIDRA have not been established in geriatric patients with type 1 diabetes and hypoglycemic unawareness. Clinical studies of LANTIDRA did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

11 DESCRIPTION

LANTIDRA consists of a suspension of allogeneic pancreatic islets in buffered transplant medium containing sodium chloride, dextrose, minerals, amino acids, vitamins, and other compounds supplemented with HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration).

The active ingredient in LANTIDRA is allogeneic islets of Langerhans derived from a donor pancreas. Islets contain several types of endocrine (hormone-secreting) cells, including β-, α-, pancreatic peptide- (PP-), δ-, and ε-cells.

Each single-donor islet batch consists of two infusion bags connected to each other via a sterile connector. One LANTIDRA bag containing up to a maximum of 1 x 10^6 EIN in 400 ml of transplant media, and the second Rinse Bag containing 200 ml transplant media used to rinse the LANTIDRA bag and the infusion line.

Ingredients present in transplant media are:
$CaCl_2$, anhydrous, biotin, $MgSO_4$, anhydrous, folic acid, Na acetate, anhydrous, riboflavin, $NaH_2PO_4H_2O$, cocarboxylase, dextrose, Li3 coenzyme A 2 H_2O, KCl, cozymase, NaCl, Na_2 flavin adenine dinucleotide, Na gluconate H_2O, Na triphosphopyridine nucleotide, L-alanine, Na3 uridine 5'-triphosphoric acid H_2O, L-arginine HCl, ascorbic acid, L-aspartic acid, D-Ca-pantothenate, L-cysteine HCl H_2O, choline chloride, L-cystine 2 HCl, i-inositol, L-glutamic acid, nicotinic acid, glycine, nicotinamide, L-histidine HCl H_2O, para-aminobenzoic acid, hydroxy-L-proline, pyridoxine HCl, L-isoleucine, thiamine HCl, L-leucine, glutathione (reduced), L-lysine HCl, thymidine, L-methionine, 2D-adenosine, L-phenylalanine, 2D-cytidine HCl, L-proline, 2D-guanosine, L-serine, 5-methyl-2'- deoxycytidine, L-threonine, cholesterol, L-tryptophan, Tween 80, L-valine, L-alanyl-L-glutamine, L-tyrosine 2 Na 2 H_2O

CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Pancreatic islets regulate blood glucose levels through secretion of multiple hormones in response to increases and decreases in blood glucose. Endocrine cells within pancreatic islets release insulin, glucagon, somatostatin, pancreatic peptide, and ghrelin. Insulin stimulates glucose uptake by peripheral tissues; glucagon mobilizes glucose from the liver into circulation; somatostatin inhibits both α- and β-cell secretions; pancreatic peptide inhibits pancreatic exocrine secretion; and ghrelin inhibits insulin secretion. The primary mechanism of action of LANTIDRA is believed to be secretion of insulin by infused (transplanted) β- cells.

12.2 Pharmacodynamics

The pharmacodynamic effects of LANTIDRA are a result of hormones, especially insulin, that are secreted by the infused (transplanted) islets in response to fluctuations in blood glucose levels.
Basal and stimulated blood glucose were determined at baseline and at 1 year following a subject's last transplant during Study 1 and Study 2 using a mixed meal tolerance test (MMTT). Combined results from these studies are summarized in Table 2. *[Clinical Studies (14)]*
The pharmacodynamic profile of the allogeneic islet cells is most clearly demonstrated in subjects who are free from the requirement of exogenous insulin.

TABLE 2: Effect of donislecel on Levels of Blood Glucose (mg/dl) at Baseline and 1 Year After Final Infusion (Study 1 and Study 2) for Subjects Insulin-Independent at the time of Mixed Meal Tolerance Test (MMT).

Subjects Insulin Independent at time of 1-year MMT	N	Mean **(mg/dl)**	Std Dev **(mg/dl)**	Min **(mg/dl)**	Max **(mg/dl)**
Baseline Glucose Basal	19	178	76	78	348
Baseline Glucose 90-min	19	357	91	122	559
1-year Glucose Basal	19	106	17	81	144
1-year Glucose 90-min	19	142	40	65	202

14 CLINICAL STUDIES

The effectiveness of LANTIDRA in subjects with type 1 diabetes and hypoglycemic unawareness was demonstrated in 2 clinical trials (Study 1, Study 2) involving a combined 30 subjects, all of whom received at least one islet infusion and a maximum of 3 infusions. Both trials were prospective, open-label, single-arm studies.

Subject demographics: median age 46.5 (range: 21 – 67) years, 80% female, 100% white, 97% non-Hispanic.

Subjects received a median islet number of 399,178 EIN (range 253,924 EIN to 858,856 EIN) per infusion. Subjects received a median islet dose of 6,570 EIN/kg (range 4,186 EIN/kg to 13,633 EIN/kg) per infusion.
Thirty subjects participated in the combined Study 1 and Study 2, with 11 subjects receiving one infusion, 12 subjects receiving two infusions, and 7 subjects receiving three infusions. Of the 19 subjects who received a second infusion, 6 were insulin-independent at the time of their second infusion. Of the 11 subjects who did not receive a second infusion, 4 were insulin-independent, 3 did not have a donor, and 4 were intolerant to immunosuppression or withdrew from the study within 6 months. All 7 subjects who received a third infusion were insulin-dependent. One subject was not able to get a third infusion because of infection. No subject was unable to receive a third infusion because of lack of a donor or intolerance to immunosuppression.

Concomitant study medications were provided as described in Table 3:

Table 3: Summary of Administered Concomitant Study Medications

Medication	Study 1 (N=10)	Study 2 (N=20)
Anakinra; n (%)	1 (10%)	0 (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; n (%)	1 (10%)	3 (15%)
Anti-thymocyte immunoglobulin; n (%)	1 (10%)	4 (20%)

A glucagon-like peptide-1 (GLP-1) agonist (e.g., exenatide 5 mcg subcutaneously within 60 minutes before infusion), was administered and was supposed to be continued (5 mcg BID), for up to 6 months after transplant. Exenatide was not given to the first 4 subjects in Study 1, and 11 of the remaining 26 subjects used exenatide less than the per protocol 6-months post-transplant because of adverse reactions. Because of the variability of exenatide use in the clinical studies, there are insufficient data to support exenatide use in patients receiving LANTIDRA.

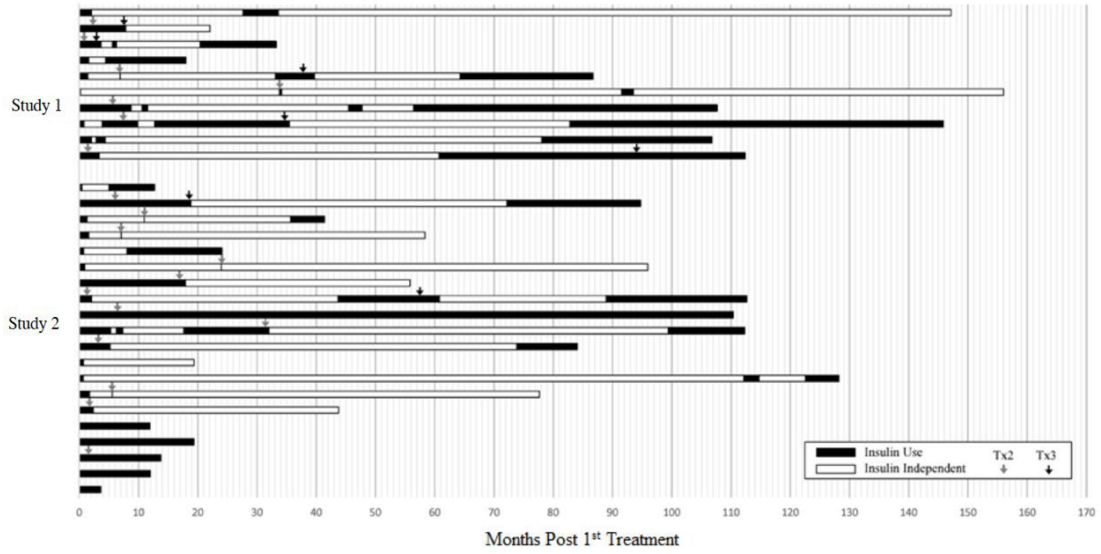
Insulin independence, defined as not requiring exogenous insulin to achieve adequate glycemic control, was also determined. Results are summarized in Table 4.

Table 4: Achievement and Maintenance of Glycemic Control following LANTIDRA Infusion (Studies Study 1 and Study 2)

Total Duration Insulin Independent (years)	N	Mean	Std Dev	Min	Max
Study 1	10	5.1	4.2	0.2	12.8
Study 2	20	3.2	3.1	0	9.9

Five subjects had no days of insulin independence. For the 25 subjects who achieved insulin independence, 4 subjects (13.3%) were insulin independent for less than one year, 12 subjects (36.7%) for 1 to 5 years, and 9 subjects (33.3%) for greater than 5 years. Figure 1 shows the entire experience of the individual subjects.

Figure 1: Periods of Insulin Use and Insulin Independence following Initial Infusion, by Patient (Pooled Population)



This figure shows the total duration of follow-up for each subject. The period of insulin dependence (use) is denoted in black and the period of insulin independence in white. Time zero (0) is the time of the first infusion. The arrows denote the time of second and third infusions.

16 HOW SUPPLIED/STORAGE AND HANDLING

LANTIDRA (NDC 73539-001-01) is supplied as purified allogeneic islets of Langerhans suspended in buffered transplant medium containing sodium chloride, dextrose, minerals, amino acids, vitamins, and other compounds supplemented with HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration)). *[Description (11)]*.

LANTIDRA is contained in one 1000 mL infusion bag filled with a supplied volume of 400 mL, containing not more than 10 cc of estimated packed islet tissue and not more than 1 x 10^6 EIN. The 1000 mL infusion bag is aseptically connected to a smaller 750 mL Rinse Bag (NDC 73539-002-01) containing 200 mL of supplied volume of transplant media for use in rinsing the 1000 mL bag containing LANTIDRA and infusion line following infusion to assure complete transfer of islets to the patient. Additional product information, including islet number, is included on the Final Islet Product Certificate of Analysis and the container label.

- Store in the insulated container at 15°C to 25°C for up to 6 hours from time of product release.
- Dispose used bags and infusion lines as biohazard material.

PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Patient Information).

Prior to prescribing LANTIDRA discuss the following:

Procedural risks

- Portal vein delivery
  - liver laceration and hematoma with severe, potentially life-threatening bleeding, which may require prolonged hospitalization and blood transfusions
  - liver injury from portal vein thrombosis and possible portal hypertension
- Acute infusion reaction
  - symptoms may include fever, chills, fatigue, breathing problems, dizziness, nausea, vomiting, headache, or muscle aches
  - a minimum 24-hour stay in the hospital after the procedure will be required for monitoring

Immunosuppression requirements and risks

- Treatment with immunosuppression
  - Is required long-term
  - If stopped would lead to loss of islet cell function and insulin production
  - Can interfere with response to immunizations and that they should avoid live vaccines
- Increased risk of infection
  - Infections can be severe and life-threatening
  - Infections may require withdraw of immunosuppression
- Development of lymphoma and other malignancies
  - Skin malignancies are most common
  - Lymphoma and some malignancies may require discontinuation of immunosuppression
- Can interfere with usual response to immunizations
  - Patients should receive all appropriate immunizations prior to treatment.

Requirements for ongoing diabetes management and risks

- Not all patients who receive LANTIDRA are able to achieve independence from exogenous insulin (stop insulin injections).
- Not all patients who achieve independence from exogenous insulin can maintain this independence.
- Continued blood glucose monitoring is required after the procedure. Advise patient to follow all instructions regarding glucose monitoring from their endocrinologist and transplant physician.
  - Failure to perform continued monitoring can increase the risk of hypoglycemia and hyperglycemia.
- Continued insulin treatment is required after the procedure. Advise patient to follow all instructions regarding insulin dosing from their endocrinologist and transplant physician.

- Failure to continue or restart insulin when required puts patients at risk for severe and potentially life-threatening hyperglycemia, including diabetic ketoacidosis (DKA).
- Patients should seek emergency medical care for severe hypoglycemic episodes and DKA.

Considerations for pregnancy, lactation, and infertility

Pregnancy

- Inform female patients who are of childbearing potential that immunosuppressive drugs required to maintain islet cell survival can cause serious harm, including malformations in the fetus.
  - Advise female patients that if they are able to become pregnant, then they should use effective birth control.
  - Advise female patients to notify their endocrinologist and transplant physician if they become pregnant.
- Inform male patients receiving LANTIDRA who have female partners who are able to become pregnant that they should use effective birth control before and during treatment.
  - If applicable, advise male patients whose partner becomes pregnant, to inform her that she should seek medical advice from her healthcare provider.

Lactation

If the immunosuppressive drugs have the potential to affect the ability of the patient to breast feed, inform the patient that breast feeding would be discontinued prior to starting the pre-procedural medications needed for administration of LANTIDRA.

Fertility

Inform patients that treatment with immunosuppression drugs may impair fertility and the ability to achieve pregnancy in the future.

Considerations for future transplants

Inform patients that administration of LANTIDRA has been associated with the development of panel reactive antibodies (PRA). PRA can adversely affect the ability to achieve a donor match for those patients who require kidney transplant.

After infusion of LANTIDRA, discuss the following:

In preparation for discharge after the procedure and at appropriate follow up appointments, repeat the information for immunosuppression, diabetes management, reproductive considerations (pregnancy, lactation, and fertility).

Manufactured by:
CellTrans Inc.
2201 W. Campbell Park Drive
Chicago, IL 60612
24-Hour Contact Phone Number: 800-500-1617

Patient Information

LANTIDRA (donislecel-jujn)
Allogeneic Pancreatic Islet Cellular Suspension for Hepatic Portal Vein Infusion

Read this patient information before you start treatment with LANTIDRA. There may be new information.

This information does not take the place of talking with your healthcare provider about your medical condition, your treatment options or the potential benefits and risks of treatment with LANTIDRA.

What is the most important information I should know about LANTIDRA?

LANTIDRA is only for adult patients with Type 1 diabetes who have repeated episodes of severe low blood glucose, those that they need help from someone to treat, and cannot get their HbA1c at the goal set by their endocrinologist and diabetes team, despite intensive diabetes management and education.

LANTIDRA is a cell therapy that is infused (transplanted) into your liver. Talk to your transplant doctor or endocrinologist about your risks from the infusion procedure and the long-term immune suppression medicine that you will need to use after you get the infusion.

Risks from the infusion can include

- damage to the liver with severe bleeding that may require blood transfusions or prolonged hospitalization.
- risk of viruses from the organ donor.
- the infusion may be stopped if the procedure increases pressure in the blood vessels of your liver. If this happens, all of the cells may not be infused.

You will need to take medicines that suppress your immune system regularly for your transplant to survive.

Risks of long-term immune suppression are increased risk of infection, including serious infection, organ failure, and death, and increased risk of certain cancers, including skin and lymph node cancer (lymphoma). Regular follow up appointments are needed.

Call your doctor right away if you have any symptoms of an infection, including:

- fever
- sweats or chills

- cough or flu-like symptoms
- muscle ache
- stiff neck
- warm, red, or painful areas on your skin
- confusion

Follow instructions for regular skin exams and notify your endocrinologist and transplant team if you are told you have skin cancer.

You will need to continue to take insulin and check your blood glucose (sugar) as instructed by your endocrinologist and transplant team.

Insulin independence is not immediate and can take several weeks to occur. Following treatment with LANTIDRA, not every patient becomes insulin independent and some patients who become insulin independent may need to restart insulin.

Monitor your blood glucose levels after getting LANTIDRA. Not all patients are able to stop taking insulin after getting the infusion. Do not stop taking insulin without talking to your doctor. It is very important to follow your doctor's instructions for blood glucose monitoring and keep your follow-up appointments to decrease the chance of serious and life-threatening high glucose or diabetic ketoacidosis.

What is LANTIDRA?

LANTIDRA is an islet cell therapy that is for people with Type 1 Diabetes. Islet cells come from the pancreas of a deceased organ donor.

Pancreatic islet cells include cells, called *beta cells*, that make insulin. In some people with Type 1 Diabetes, the infused beta cells can make enough insulin to allow the diabetic to control blood glucose without taking insulin.

Who should not take LANTIDRA?

LANTIDRA requires continuing use of medicines that suppress your immune system. Do not get the infusion if you cannot have these medicines because the islet cells will not survive.

Do not get LANTIDRA if you are pregnant or want to become pregnant. Immune suppression medicines can cause serious harm, including death, to you and your developing baby.

If you are male and have a female partner who can become or desires pregnancy, you should ask your transplant team if your immunosuppression drugs can cause abnormal sperm. If your immunosuppression drugs can cause abnormal sperm, advise your female partner to discuss the potential increased risks to her and the developing baby/infant with

her healthcare provider.

How will I get LANTIDRA?

LANTIDRA islet cells are infused into your liver through a catheter that is placed into a large blood vessel going into your liver (called the hepatic portal vein). This is done under anesthesia. You will need to stay in the hospital for at least 24 hours.

Before getting LANTIDRA, you will need to start the immune suppression medicine. You will need to continue this medicine after the infusion to keep the islet cells alive.

What should I avoid when I get LANTIDRA?

Because immune suppression can increase your risk of infection, it is important that you:

- follow instructions from your transplant team about avoiding people who have infections, such as colds and flu.
- do not get immunization with live vaccines. Talk to your transplant team before getting any shots to prevent infections.

You can ask your transplant team if there are additional things you should avoid because of your specific immune suppression drugs.

What are the possible or reasonably likely side effects of LANTIDRA?

Injury can occur during the delivery of LANTIDRA into the large blood vessel going to your liver (the hepatic portal vein).

You have a higher risk of infections and cancer because of the immune suppression needed to keep the islet cells alive. In some cases, the immune suppression will be stopped because of these side effects and the islet cells will die and stop making insulin.

You can make antibodies from your islet cell infusion that can make it harder to get a match for transplants, such as a kidney transplant.

You can ask your doctor for information about LANTIDRA that is written for health professionals. Call your doctor about any side effects that concern you.

What should I tell my endocrinologist and transplant physician before receiving LANTIDRA?

For your LANTIDRA (islet cells) to survive, you must strictly follow the instructions for your immune suppression medicines. If you have any questions or problems about taking these medicines, ask your endocrinologist or transplant doctor for help.

If you can become pregnant, you should use effective birth control after getting

LANTIDRA. Talk with your doctor about the birth control regimens that may be right for you.

Some immunosuppressive drugs may cause formation of abnormal sperm. Ask your doctor if your immunosuppression drugs can cause abnormal sperm. If so, and you have a female partner who can become pregnant, you should discuss this with your partner and use effective birth control before starting treatment with immunosuppression drugs.

What are the ingredients of LANTIDRA?

In addition to the cells in LANTIDRA the delivery fluid contains:
$CaC1_2$, anhydrous, biotin, $MgSO_4$, anhydrous, folic acid, sodium acetate, anhydrous, riboflavin, NaH_2PO4H_2O, Cocarboxylase, dextrose, Li_3 Coenzyme A 2 H_2O, KCl, Cozymase, NaCl, Na_2 Flavin adenine dinucleotide, Na Gluconate H_2O, Na Triphosphopyridine Nucleotide, L-alanine, Na3 Uridine 5'-Triphosphoric Acid H_2O, L-arginine HCl, ascorbic acid, L-aspartic acid, D-Ca-Pantothenate, L-cysteine HCl H_2O, choline chloride, L-cystine 2 HCl, i-inositol, L-glutamic acid, nicotinic acid, glycine, nicotinamide, L-histidine HCl H_2O, para-aminobenzoic acid, Hydroxy-L-proline, pyridoxine HCl, L-isoleucine, thiamine HCl, L-leucine, glutathione (reduced), L-lysine HCl, thymidine, L-methionine, 2D-adenosine, L-phenylalanine, 2D-cytidine HCl, L-proline, 2D-guanosine, L-serine, 5-methyl-2'- deoxycytidine, L-threonine, cholesterol, L-tryptophan, Tween 80, L-valine, L-alanyl-L-glutamine, L-tyrosine 2 Na 2 H_2O

Name and Place of manufacturer:
CellTrans Inc.
1740 W. Taylor St., STE C200
Chicago, IL, 60612
24-Hour Contact Phone Number: 800-500-1617