

Summary Basis for Regulatory Action

Date:	June 28, 2023
From:	Sukhanya Jayachandra, Review Committee Chair, Office of Therapeutic Products (OTP), Office of Cellular Therapy and Human Tissue (OCTHT) CMC, Division of Cell Therapy 1 (DCT1), Cell Therapy Branch 1 (CTB1)
BLA STN:	125734/0
Applicant:	CellTrans Inc.
Submission Receipt Date:	Original submission date: May 19, 2020 Resubmission date: December 30, 2022
Action Due Date:	June 28, 2023
Proper Name:	donislecel-jujn
Proprietary Name:	LANTIDRA
Indication:	Treatment of adults with Type 1 diabetes (T1D) who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

Recommended Action: The Review Committee recommends regular approval of this product.

For Celia Witten, MD, PhD

Acting Director, Office of Clinical Evaluation, Office of Therapeutic Products

Director, Office of Compliance and Biologics Quality

Discipline Reviews	Reviewer / Consultant - Office/Division
CMC <ul style="list-style-type: none"> • CMC Product (OTP/OCTHT) • Facilities review (OCBQ/DMPQ) • Establishment Inspection Report (OCBQ/DMPQ and Product Office) • QC, Test Methods, Product Quality (OCBQ/DBSQC) 	<p>Sukhanya Jayachandra, PhD, CBER/OTP/OCTHT Irina Tiper, PhD, CBER/OTP/OCTHT Andrey Sarafanov, PhD, CBER/OTP/OPPT Prajakta Varadkar, PhD, formerly in CBER/OTP</p> <p>Timothy Martin, formerly in CBER/OCBQ/DMPQ Pankaj (Pete) Amin, CBER/OCBQ/DMPQ</p> <p>George Kastanis, CBER/OCBQ/DBSQC</p>
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Clinical <ul style="list-style-type: none"> • Clinical (OTP/OCE) • Postmarketing safety Pharmacovigilance review (OBPV/DE) • BIMO 	<p>Patricia Beaston, MD, PhD, CBER/OTP/OCE/DCEGM</p> <p>Jonathan Reich, CBER/OPV/DPV</p> <p>Kanaeko Ravenell, CBER/OCBQ/DIS Yakubu Wangabi, CBER/OCBQ/DIS</p>
Statistical <ul style="list-style-type: none"> • Clinical data (OBPV/DB) 	<p>Shuya (Joshua) Lu, CBER/OBPV/DB</p>
Nonclinical/Pharmacology/Toxicology	<p>Yongjie Zhou, CBER/OTP/OPT/DPT2</p>
Clinical Pharmacology	<p>Million Tegenge, CBER/OTP/OCE/DCEGM</p>
Labeling <ul style="list-style-type: none"> • Promotional (OCBQ/APLB) • Carton/Containers (OTP/OCTHT, OTP/ORMRR) 	<p>Michael Brony, CBER/OCBQ/DCM/APLB Sonny Saini, CBER/OCBQ/DCM/APLB</p> <p>Sukhanya Jayachandra, CBER/OTP/OCTHT Rommel Maglalang, CBER/OTP/OMRR</p>
Other Review(s) not captured above categories, for example: <ul style="list-style-type: none"> • Consults • Devices 	<p>N/A</p> <p>Zehra Tosun, Ph.D, CBER/OTP/OCTHT Andrea Gray, Ph.D, formerly CBER/OTP Carolyn Yong, Ph.D, CBER/OTP</p>

Discipline Reviews	Reviewer / Consultant - Office/Division
<ul style="list-style-type: none"> • Software • Human Factors • FONSI 	N/A
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1. Introduction

On May 19, 2020, CellTrans, Inc. submitted an original biologics license application (BLA) STN 125734 for licensure of donislecel-jujn with a proprietary name of LANTIDRA. LANTIDRA is a cellular therapy product composed of purified allogeneic deceased donor pancreas derived Islets of Langerhans. The Applicant proposed the indication, “for the treatment of “brittle T1D” (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.” Because the proposed indication is not well defined, the review focused on an indication for “adults with Type 1 diabetes (T1D) who are unable approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.” Currently, there are no FDA-approved cell-based treatments for patients with T1D who have recurrent hypoglycemia despite intensive diabetes management, which may include the use of currently available insulin analogs and device systems (insulin pumps and continuous glucose monitoring devices with control algorithms).

Each lot of LANTIDRA is manufactured from a deceased donor pancreas procured via the Organ Procurement and Transplantation Network (OPTN) and is for the treatment of one patient.

The manufacture of each LANTIDRA lot involves isolating and purifying islets of Langerhans cells from the pancreases. The purified islets are incubated up to 48 hours. Post incubation, the islets are harvested for final formulation in buffered transplant media supplemented with HEPES (2-[4-(2-hydroxyethyl)piperazin-1-yl] ethanesulfonic acid; 10 mM final concentration) and human serum albumin (0.5% final concentration). LANTIDRA cell suspension is supplied in a CryoMACS infusion bag packaged with a separate CryoMACS Rinse bag containing transplant medium to rinse the contents of the LANTIDRA bag.

The LANTIDRA and Rinse bags are placed in validated transport carriers and transported from the CellTrans Inc manufacturing facility. The manufacturing facility is located at University Illinois Health (UIH) campus, which is a 5-minute walk to the UIH Department of Radiology within the same building. The entire contents of both the LANTIDRA bag and the Rinse bag are infused into the patient’s hepatic portal vein by an interventional radiologist experienced in islet cell portal administration in one of the interventional radiology suites within UIH Department of Radiology.

Dosage strength of LANTIDRA depends on the total number of islets packaged for infusion. A patient may receive up to three doses of LANTIDRA over the course of treatment, where the recommended first dose is a minimum of 5000 Equivalent Islet Number per kilogram (EIN/kg) patient body weight and subsequent doses at a

recommended minimum of 4500 EIN/kg patient body weight. Each dose is manufactured from a different deceased donor pancreas.

Type 1 diabetes mellitus (T1D) results from autoimmune destruction of pancreatic islet cells that contain the β -cells responsible for the production of insulin. T1D 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 (SHE). SHE is defined as a hypoglycemia requiring the active assistance from another person to administer carbohydrates, glucagon or take other corrective action. 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 titrate their insulin to achieve target or near target glycemic control because of the ongoing risk of severe hypoglycemic events.

This document summarizes the basis of regulatory approval of LANTIDRA. The safety and effectiveness of LANTIDRA was evaluated in two non-randomized, single-arm clinical studies (UIH 001 and UIH 002) enrolling a total of 30 participants with T1D and hypoglycemic unawareness. The studies showed 21 subjects became insulin independent for at least one year after receiving between one and three infusions of LANTIDRA, and 10 subjects achieving insulin independence for more than five years. Five participants did not achieve any days of insulin independence. Restoration of endogenous insulin production and insulin independence does not occur spontaneously in T1D; the large treatment effect is attributed to LANTIDRA.

Adverse events related to the administration of LANTIDRA are due to the product itself, procedural complications related to delivery of LANTIDRA into the portal vein, and concomitant immunosuppression required to maintain islet cell viability and function. Two subjects died during the study period; one from sepsis and one from progressive micro-ischemic disease. Ninety percent of subjects had at least one serious adverse reaction. The most common are procedural complications and complications of immunosuppression.

An advisory committee (AC) meeting was held on April 15, 2021, to discuss the Critical Quality Attributes (CQAs) and composition of the product, as these aspects relate to consistent manufacturing, product quality, and product strength. The AC meeting also discussed the potential for insulin independence and subsequent clinical benefits from LANTIDRA and the risks from the immunosuppression regimen required to maintain islet cell viability. The AC also discussed the minimum duration of insulin independence that would be considered to be clinically meaningful and would support a favorable benefit risk assessment.

A Complete Response Letter (CRL) was issued on August 18, 2021 for the original BLA submission due to Chemistry, Manufacturing, and Controls (CMC) concerns. The CMC concerns included unresolved pre-license facility observations and inadequate information on commercial preparedness, reagent qualification, release testing, and training of quality control personnel. A Type A meeting was held with CellTrans on September 27, 2021, to discuss approaches to resolving the inspection observations and the CMC deficiencies. In response to FDA concerns, CellTrans satisfactorily addressed CRL deficiencies by implementing corrective actions to the facility design, quality program, additional process validation studies. CellTrans satisfactorily addressed all CRL items in the December 30, 2022 Resubmission.

The Applicant has provided substantial evidence of effectiveness and safety based on two non-randomized, single-arm clinical studies compared to the well-established natural history of T1D with supportive data. The review team recommends regular approval of this BLA with a CMC Post-marketing Commitment (PMC) regarding reassessment of extractables and leachables of the final container closure system captured in Sections 3.a, 3.e and 11.c of this document.

2. Background

Disease background

T1D results from autoimmune destruction of pancreatic islet cells that contain the β -cells responsible for production of insulin. T1D is a fatal condition in the absence of exogenous insulin treatment. To date, insulin (delivered by multiple daily injections or infusion by pump) remains the primary treatment for patients with T1D.

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.

For a very limited subset of patients, allogeneic transplant of cadaveric donor pancreata, with or without concurrent kidney transplant, has been used to restore the production of endogenous insulin. Whole pancreas transplantation requires major surgery, for which not all patients are candidates. There are limited available pancreata for whole organ transplant, and use of islet cells expands the pool of donor pancreata, allowing the use of those pancreata not suitable for whole organ transplant.

Product description

LANTIDRA is the first marketed cell-based therapy made from deceased allogeneic donor pancreatic islets of Langerhans (cluster of cells within the pancreas) for the treatment of T1D in adults who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education. LANTIDRA is composed of mixed populations of endocrine cells, including beta cells that produce insulin. At least 30% of the product is made of insulin-producing beta cells. Together, the cells composing LANTIDRA regulate blood glucose levels through secretion of hormones in response to glucose stimulation. LANTIDRA is a suspension of islet cells administered through the hepatic portal vein.

Regulatory History

The IND was initially submitted July 9, 2004. The BLA was initially submitted on May 19, 2020 and a Complete Response was issued on August 18, 2021. The product has Orphan Drug designation.

Table 1. Regulatory History

Regulatory Events / Milestones	Date
a) IND 11807 submission	July 09, 2004
b) Orphan Drug designation granted	February 1, 2017
c) Pre-BLA meeting	August 3, 2016
d) BLA 125734/0 submission	May 19, 2020
e) BLA 125734 filed	July 16, 2020
f) Mid-Cycle communication	November 10, 2020
g) Major Amendment	October 20, 2020
h) Late-Cycle meeting	April 1, 2021
i) Advisory Committee Meeting	April 15, 2021
j) Pre-licensure Inspection	June 07-June 11, 2021
k) Complete Response	August 18, 2021
l) Type A Meeting	September 27, 2021
m) Re-submission after Complete Response	December 30, 2022
n) Action Due Date	June 28, 2023

3. Chemistry Manufacturing and Controls (CMC)

a. Product Quality

Product Description

The cellular therapy LANTIDRA (proprietary name), donislecel-jujn (proper name) is composed of allogeneic islets of Langerhans manufactured from a deceased donor pancreas for the treatment of adults with T1D who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education.

Each lot of LANTIDRA is manufactured from a deceased donor pancreas procured via the Organ Procurement and Transplantation Network (OPTN). One lot is used for the treatment of one patient. A single patient can receive up to three lots of LANTIDRA

during the course of treatment, where each lot is manufactured from a different deceased donor pancreas.

Product Development

LANTIDRA development began in 2004 under IND11807 sponsored by Dr. Jose Oberholzer at the University of Illinois Hospital and Health Sciences System (UI Health). LANTIDRA was granted Orphan Designation in 2016. In 2017, the Applicant, CellTrans Inc (CEO, Dr. Jose Oberholzer), acquired the rights to the LANTIDRA developmental program (IND11807) from UI Health with the purpose of supporting a BLA.

LANTIDRA manufacturing remains at the UI Health manufacturing facility, now a CellTrans Inc facility, where commercial manufacturing is proposed to occur. UI Health will continue to be the only clinical site where LANTIDRA will be administered to patients under the supervision of an interventional radiologist and or a transplant surgeon with additional training in islet cell handling. LANTIDRA will not be shipped to other clinical sites.

Manufacturing Summary

The manufacture of each product lot of LANTIDRA is a continuous process from the time of procurement of the deceased donor pancreases, arrival of donor organ at the manufacturing facility through isolating of islets and placing the islets in tissue culture flasks (drug substance).

Each LANTIDRA lot manufacturing begins with acceptance of the donor pancreas at the manufacturing facility. The manufacture of each LANTIDRA lot involves enzymatic and mechanical digestion steps using the Ricordi chamber. The (b) (4) islet preparation is purified by a (b) (4) to isolate islet fractions which are segregated and pooled as top, middle, and bottom fractions based on islet purity. The islet fractions are incubated up to 48 hours. After incubation, the islets are harvested from the cell culture flasks for final formulation 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).

The final LANTIDRA product is supplied in a CryoMACS infusion bag that is connected to a Rinse bag via a sterile connector. LANTIDRA is infused into the liver via the hepatic portal vein. The minimum recommended dose for the first infusion is 5000 EIN/kg patient body weight. A second transplant may be performed if the patient does not achieve independence from exogenous insulin within one year of transplant or within one year after losing independence from exogenous insulin after a previous transplant. The minimum dose for the second and third infusions is 4500 EIN/kg patient body weight.

Manufacturing Controls

Each lot of LANTIDRA is manufactured from one donor pancreas organ. The organ is procured via the OPTN and is tracked via Chain of Identity and Chain of Custody (COI/COC) forms established at the time of organ procurement. The organ is considered the starting material.

The manufacturing control strategy begins with the starting material and reagent qualification program consisting of donor screening, eligibility determination, and testing for compatibility match to the recipient, evaluating medical records and testing for relevant communicable agents or diseases (RCDADs), vendor qualification, confirmation of the certificate of analysis and independent verification and testing of reagents used in the manufacture of LANTIDRA. Reagents derived from animals and humans are controlled to ensure the absence of microbial contaminants and adventitious agents.

Critical process parameters are established for unit operations based on in-process monitoring. Controls are implemented throughout the process to support process consistency. In-process testing includes: (b) (4)

Lot release testing is performed on the final LANTIDRA product prior to placing into the final container closure system (CryoMACS bags). Samples are removed to perform the sterility, viability, endotoxin, identity, purity, and potency tests. Lot release test methods are suitability validated (except the visual inspection Appearance test, which is a qualified assay). The LANTIDRA specifications are adequate to ensure product quality and consistency.

Process Validation

The suitability of the manufacturing of LANTIDRA drug substance (DS) and drug product (DP) was assessed by CellTrans, Inc. using pancreas from deceased donors. The process validation batches were not administered to patients; however, these batches were used to assess final container closure stability, transport to clinical site and compatibility of delivery devices used to infuse LANTIDRA to the hepatic portal vein.

There were numerous deviations that occurred during the initial process validation, specifically related to operator training on performing lot release testing. Root causes were identified, and appropriate Corrective and Preventative Actions (CAPAs) were implemented to correct the deviations and prevent future recurrences. Further, during the review of the original BLA submission, the Applicant indicated they will be changing a critical gradient centrifugation reagent used in the manufacturing. The Applicant performed an additional new process validation study to address complete response deficiencies related to manufacturing facility changes, lack of operational proficiency and changes in manufacturing reagents. The process validation was conducted using pancreas from deceased donors obtained from OPTN. The process validation was assessed against established process parameters and predefined release criteria.

(b) (4) batches were manufactured, and (b) (4) of the (b) (4) batches were clinical lots that were administered to patients under an expanded access protocol under IND11807. The process validation lots met all prespecified critical process parameters and lot release criteria. The LANTIDRA manufacturing process was successfully validated. Additional validation of aseptic process simulation was performed. Lastly, the process of carrying the LANTIDRA in an insulated cooler from the CellTrans manufacturing facility to the Radiology department (a 5-minute walk) was also validated.

Manufacturing Risks, Potential Safety Concerns and Management

The pancreas, which is the starting material for the manufacture of LANTIDRA, is controlled through donor screening and testing and is procured by OPTN. Organs are screened by review of medical records and acceptance requirements. Transmission of relevant infectious agents and diseases is controlled by testing reagents and control of the manufacturing process. Further, at any given time, only one pancreatic organ is processed at the CellTrans manufacturing facility to generate (b) (4) lot of LANTIDRA. The risk of cross contamination is minimal. All aseptic operations are performed in positive pressure laminar flow biosafety cabinets within the manufacturing facility clean rooms with qualified and trained operators using personal protective equipment, sterile single use materials. Some equipment is reused after cleaning and sterilization with validated cleaning and sterilization procedures. Environmental monitoring is also performed.

Drug Product Stability and Shelf life

LANTIDRA is supplied as a cellular suspension in a CryoMACS infusion bag. The stability of LANTIDRA has been determined to be six (6) hours at 15°C to 24°C from time of packaging into the CryoMACS bags. The product is walked from the manufacturing facility to the clinical site (5-minute walk within the same building).

Comparability

The current manufacturing process occurs at the CellTrans facility on the campus of UIH. The product lots for the clinical trials UIH 001 and UIH-002 were also manufactured at the same facility. The process validation was conducted based on process validation protocol with predefined requirements to assess the critical process parameters and critical quality attributes. LANTIDRA lots manufactured to support process validation all passed the prespecified acceptance criteria for in-process and final lot release testing. The process validation studies provided assurance that CellTrans, Inc. can consistently manufacture LANTIDRA for use at the UI Health hospital.

CMC Post marketing commitments

Deficiencies were noted in the Applicant's complete response provided to address the leachables and extractables pre-license inspection observations for the final container closure system. The Leachables and Extractables study pertains to the final containers closure systems that consist of two Miltenyi CryoMACS, 510(k) cleared bags that contains LANTIDRA and the second Rinse bag containing transplant media used to rinse the LANTIDRA product bag and the infusion line post LANTIDRA infusion to the patient to ensure complete delivery of LANTIDRA. The study report had deficiencies related to inadequate limits of quantification of the analytical methods used in the leachable study and a toxicological assessment of the leachables detected. The CryoMACS bags are 510(k) cleared and the drug product is stored for a relatively short time (six hours), compared to other approved products that use these CryoMACS bags. However, the Applicant will address these CMC concerns in a PMC. As summarized above, all issues have been addressed, except the extractables and leachables study report and leachables toxicological assessment, which should be addressed via a PMC. A PMC for leachables and extractables is outlined in Section 3.e. "Container/Closure System" and in Section 11.c. "Recommendation for Postmarketing Activities."

b. Testing Specifications

The analytical methods and their validations and/or qualifications were reviewed for LANTIDRA and were found to be adequate for their intended purpose.

The lot release specifications for LANTIDRA are shown below in Table 2.

Table 2: LANTIDRA Lot Release Specifications indicating quality parameter measured, analytical test method and acceptance criteria.

Quality Parameter	Test Method	Acceptance Criteria
Container Closure Integrity	Visual Inspection	No evidence of tampering or damage to drug product container
Appearance	Visual appearance Inspection	No visible foreign objects or turbidity
Safety - Sterility	(b) (4) aerobic and anaerobic	No growth in 14 days
Safety - Fungal	Culture	No growth in 28 days
Safety - Gram stain	Gram Stain and Microscopic Evaluation	Negative for presence of contamination
Safety - Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe	Each transplant will contain ≤ 5 EU per kg of patient weight per Hour
Identity - Estimated Tissue volume	Visual Quantification of Pelleted Islets (packed tissue volume)	≤ 10 cc
Identity - Islet morphology	Dithizone stain (DTZ) Stain and Microscopic Evaluation	Islet Present – color/shape/islet size
Potency - Glucose Static Incubation (GSI)	ELISA Quantification of Glucose Stimulated Islets	Ratio of insulin secretion under high glucose stimulation to that under low glucose stimulation ≥ 1
Potency - Islet yield	DTZ Stain and Microscopic Quantification (Islet Yield)	$\geq 5,000$ EIN per kg for initial transplant. $\geq 4,500$ EIN per kg for subsequent transplants (in same patient who received the first transplant)
Potency - Viability	SYTO [®] 13 Green/Ethidium Bromide Staining and Microscopic Evaluation	$\geq 70\%$ viable islets

Quality Parameter	Test Method	Acceptance Criteria
Purity - Endotoxin	Endotoxin (Limulus Amebocyte Lysate), EndoSafe Endotoxin	Each transplant will contain ≤ 5 EU per kg of patient weight per Hour
Purity - Islet purity	Dithizone (DTZ) Stain and Microscopic Quantification	≥ 30%

Dose is determined by the estimated tissue volume, islet yield and islet viability. The maximum dose per transplant is dictated by the estimated tissue volume, which should not exceed 10 cc per transplant, and the total EIN present in the infusion bag (up to a maximum of 1 x 10⁶ EIN per bag).

c. CBER Lot Release

CBER Lot release and testing, including the submission of product samples to CBER, is not required. The basis for this decision is that each lot of LANTIDRA will treat a single patient. Lot release testing would negatively impact the often-limited quantity of islet cells available to the patient, and failure of a single lot will have minimal potential impact on public health.

d. Facilities Review / Inspection

Facility information and data provided in the BLA were reviewed by CBER and found to be acceptable. The facility involved in the manufacture of LANTIDRA (Purified Allogeneic Islets of Langerhans for Transplant), activities performed, and inspection history are summarized in the following Table 3.

Table 3: CellTrans, Inc Manufacturing Facility Information

Name/Address	FEI number	DUNS number	Inspection	Justification /Results
CellTrans Incorporation Islet Isolation Facility 1740, West Taylor Street, Building (b) (4) STE C200, University of Illinois Hospital, Chicago IL 60612 Drug substance and drug product manufacturing; in-process and release testing; final packaging and labeling	3019202665	117774787	Pre-license inspection (PLI)	CBER DMPQ June 07 to 11, 2021 VAI

Acronym key: VAI – Voluntary Action Indicated.

CBER DMPQ conducted a pre-license inspection (PLI) of CellTrans Islet Isolation facility from June 7 - 11, 2021. All FDA Form 483 issues were resolved, and the inspection was classified as voluntary action indicated (VAI). Another PLI did not occur during the resubmission review cycle; instead CBER-DMPQ recommended follow-up of the corrective actions to the FDA Form 483

observations during the next routine FDA manufacturing site inspection.

e. Container/Closure System

LANTIDRA consists of two CryoMACS freezing bags. The LANTIDRA bag consists of a 1000ml Miltenyi CryoMACS bag (Miltenyi Biotec, catalog number 200-074-404, FDA-cleared under BK090020) filled with a cellular suspension of the drug product containing not more than 10cc estimated packed islet cells, formulated in 400ml buffered transplant media. The LANTIDRA bag is aseptically connected to a smaller second rinse bag consisting of a 750 ml CryoMACS bag (Miltenyi Biotec, Catalog # 200-074-403) filled with 200 ml of transplant media for use in rinsing the LANTIDRA bag and infusion line during infusion to the patient's portal vein to assure complete transfer of the product to the patient.

Both the LANTIDRA bag and rinse bag are connected via a sterile (b) (4) spike adapter, one spike to one spike sterile connector (SCD) tubing and pinch clamp. The LANTIDRA bag and the rinse bag are packaged into a flexible sterile outer package, that is placed in a secondary flexible sterile overwrap that is placed in an insulated cooler to avoid temperature extremes during transport to the radiology department where transplantation takes place.

The applicant evaluated the container/closure integrity during the process validation study, and all acceptance criteria were met. Further, the applicant evaluated the extractables and leachables of the CryoMACS bags and tubing with transplant media in a "Simulated extractable and leachable study" performed by (b) (4). The Extractable and Leachable study report had inadequate validation of the limits of quantification (LOQs) for the analytical methods used in the leachable study. Further, the applicant did not take into consideration the contribution of leachables from the second bag for the rinse. A reassessment of the leachables data with validated LOQ is needed that also takes leachables from the second bag for the rinse bag into account. If the organic leachable compound levels are above the monitoring level, a toxicological reassessment will be needed. The applicant will address this CMC concern in a PMC, as outlined in Section 11.c.

f. Environmental Assessment

The BLA included a request for categorical exclusion from an Environmental Assessment under 21 CFR 25.31. The FDA concluded that this request is justified, and no extraordinary circumstances exist that would require an environmental assessment.

4. Nonclinical Pharmacology/Toxicology

No nonclinical studies were conducted with LANTIDRA. The applicant included references to published studies evaluating the biological activity as well as the hepatic distribution and safety of transplanted allogeneic or syngeneic islets in combination with various immunosuppressive agents in diabetic rodent (mice, rats) and nonhuman primate models. These studies support inclusion of immunosuppression as a critical

component for successful islet engraftment and survival following transplant in diabetic animals.

5. Clinical Pharmacology

The data supporting the clinical pharmacology of LANTIDRA is based on two clinical studies (UIH-001 and UIH-002) that included pharmacodynamic and immunogenicity assessments.

Dose-Response:

- No formal clinical dose finding, or dose-response exploration studies have been performed during the development of LANTIDRA for treatment of T1D
- In both UIH-001 & UIH-002 studies a target islet dose of 10,000 EIN/kg was proposed based on the findings of previous experience with Edmonton Protocol for allogeneic islet transplantation.
- From a total of 30 subjects, 11 (37%), 12 (40%) and 7 (23%) were treated with single, two and three dose of islet infusions, respectively.
- For subject who received multiple infusions, the mean inter-dose interval between the first and the second infusion was 279 days (range 25 to 1029 days), and between the second and third infusions was 984 days (range 62-2815 days).
- The mean administered dose per infusion was 7207 EIN/kg (range 4186-13624). The mean total administered dose per subject was 13,453 EIN/kg (range 4208-29,404).

Pharmacodynamics:

The primary mechanism of action of LANTIDRA is believed to be secretion of insulin by transplanted β - cells. The pharmacodynamic effects of LANTIDRA 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 subject's last transplant during Studies UIH-001 and UIH-002 using a mixed meal tolerance test (MMTT). The pharmacodynamic profile of the allogeneic islet cells is most clearly demonstrated in subjects who are free from the requirement of exogenous insulin. The MMTT result is summarized below for subjects with insulin-independent 1-year following treatment with LANTIDRA:

- The baseline glucose basal was 178 ± 76 mg/dL and at 1-year it was 106 ± 17 mg/dL.
- The baseline glucose 90-min (stimulated) was 357 ± 91 mg/dL and at 1-year it was 142 ± 40 mg/dL.
- There were no age-related or sex-related differences in basal and stimulated glucose level.

Immunogenicity:

Human leukocyte antigen (HLA) sensitization also called development of donor-specific antibodies following islet transplantation is considered a potential risk as it might be a barrier against future transplantation (either islet or whole organ such as future kidney transplantation). HLA sensitization can be because of the use of multiple islet infusions to achieve enough engrafted islet mass that may expose an islet recipient to several

mismatched HLA alleles. In studies #UIH-001 and UIH-002, panel-reactive antibodies (PRA) were determined by analysis of anti-human antibodies. T1D autoimmunity was assessed by measuring antibodies against islet antigens or insulin.

- For the combined UIH-001 & 002, 6 out of 28 (21%) patients tested transitioned from panel-reactive antibodies (PRA Class I, Class II, or both) <20% at baseline to $\geq 20\%$ following islet transplant.
- A trend for increased risk for PRA (either Class I or II) with multiple vs single infusion was observed. For example, about 11%, 25% and 29% of subjects transitioned to $\geq 20\%$ PRA when infused with one, two or three islet transplantation, respectively. Also, two out of the 3 (67%) patients who transitioned from Class II PRA <20% at baseline to $\geq 20\%$ posttransplant did so only after receiving more than one transplant (second infusion in both cases).
- Antibodies against islet cells, glutamic acid decarboxylase 65 (GAD65), islet antigen 2 (IA2) and insulin did not increase at 48 weeks after last transplant as compared to the baseline levels.

6. Clinical/Statistical

a. Clinical Program

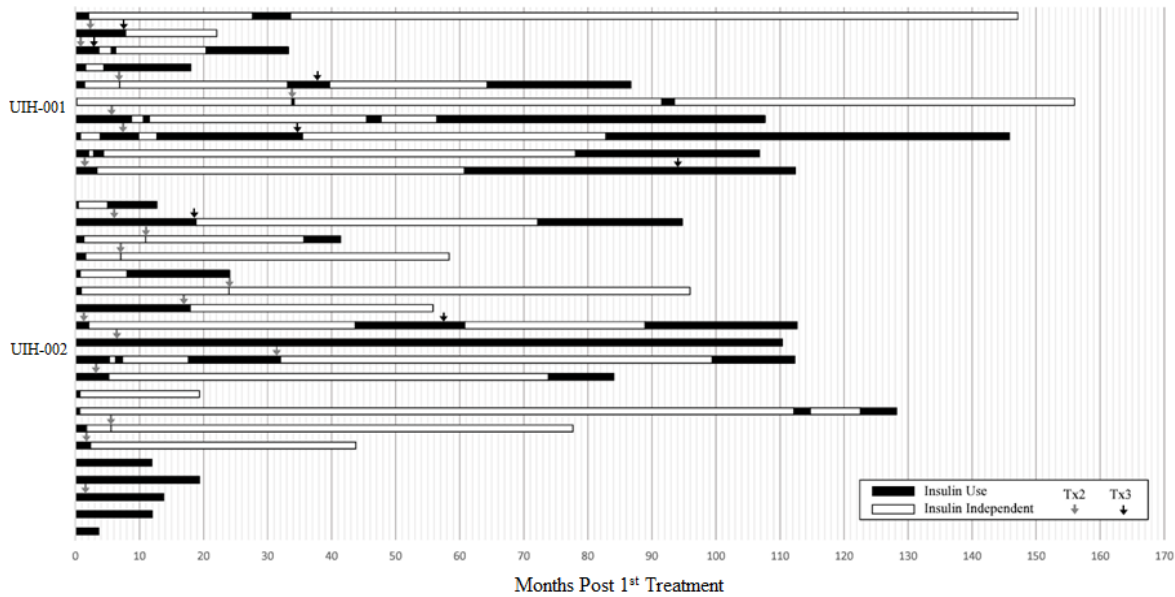
The Applicant's primary evidence of effectiveness and safety was generated from two open-label studies, UIH 001 (Phase 1/2) and UIH-002 (Phase 3) which were combined in a primary efficacy analysis. The primary efficacy analysis used a composite endpoint consisting of an HbA1c $\leq 6.5\%$ and absence of severe hypoglycemic events (SHE) through one year after the subject's last transplant, but this was not interpretable based on substantial missing data and the enrolled population at baseline had met or nearly met the primary endpoint at enrollment.

Efficacy

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. Additionally, 10 out of 30 (33%) subjects had insulin independence for at least 5 years with a maximum reported insulin independence of 12.8 years. See Figure 1 for a graphical representation on outcomes of insulin independence for all treated subjects.

Restoration of endogenous insulin production that results in insulin independence restores glucose homeostasis and avoids clinically significant hypoglycemia and hyperglycemia. Insulin independence is a substantial clinical benefit to patients.

Figure 1: Periods of Insulin Use and Insulin Independence following Initial Infusion, by Patient (Pooled Population UIH-001 and UIH-002)



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.

Safety

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

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

Serious adverse events related to the 56 portal infusions of LANTIDRA in the clinical trials included one life-threatening liver laceration, one intraabdominal hemorrhage, and two perihepatic hematomata resulting in prolonged hospitalization. Three subjects required blood transfusions due to procedural adverse events. Infusion of pancreatic islets and other cells into the portal venous system results in microembolization. Thus, there is a potential for these micro emboli to cause portal hypertension. Portal vein branch thrombosis may also occur following islet transplantation procedures. During administration of LANTIDRA, the median peak portal blood pressure increase from baseline was 3 mmHg (range -3 to 18 mmHg). Elevated portal pressures \geq 22 mmHg were reported during procedures for two subjects requiring cessation of the procedure, and incomplete delivery of LANTIDRA for one subject.

Concomitant medications for immunosuppression are required for β -cell survival. Patients receiving immunosuppressants are at increased risk of developing lymphomas and other malignancies, particularly of the skin; developing bacterial, viral, fungal, and

parasitic infections, including opportunistic infections; and anemia, sometimes requiring transfusion. Over the entire course of follow-up (0.3 to 13.2 years), sixteen adverse events of malignancy were reported for 11 subjects; three events were life-threatening (post-transplant lymphoproliferative disease, melanoma and papillary thyroid cancer). The most commonly reported malignancy was skin cancer (n=12). Serious infections occurred in 83% of subjects. One subject died of multi-organ failure from sepsis in the second year after LANTIDRA. In total, 211 infections were reported for 26 subjects; one was life-threatening, 22 reactions severe, and 115 events moderate in severity. Eight subjects had to discontinue immunosuppression due to severe infections, and discontinuation of immunosuppression results in loss of islet cells and endogenous insulin production. Additionally, anemia was reported in 24 (80%) of subjects and two subjects required blood transfusions due to non-procedural related anemia.

b. Bioresearch Monitoring (BIMO)

A BIMO inspection was conducted for the Applicant in support of this application, with specific focus on study UIH-002. The inspection did not reveal substantive issues that impact the data submitted in support of this original Biologics License Application (BLA).

c. Pediatrics

Pediatric Research Equity Act (PREA) is not applicable to LANTIDRA for the treatment of adults with Type 1 diabetes (T1D) who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education, because LANTIDRA was granted orphan drug designation for the indication.

Only adult subjects were enrolled in LANTIDRA clinical trials.

d. Other Special Populations

None.

7. Safety and Pharmacovigilance

The Applicant submitted a pharmacovigilance plan for LANTIDRA. The Important Identified Risks associated with LANTIDRA include Sensitization to Donor Antigens, Graft Failure, Bleeding, Portal Vein Hypertension, Increased Liver Function Tests, Blood Cell Disorders, Blood Chemistry Disorders, Cardiovascular Disorders, Infections, Neoplasms, Renal and Urinary Disorders. Important Potential Risks include Donor Disease Transmission, Microbial Contamination, Portal Vein Thrombosis, and Developmental Reproductive Pathology. Postmarketing safety monitoring will include:

- Routine pharmacovigilance: Adverse event reporting in accordance with 21 CFR 600.80 and quarterly periodic safety reports for 3 years and annual thereafter.

Data available at this time do not suggest any safety signals that warrant a Risk Evaluation and Mitigation Strategy or safety-related postmarketing requirement study. There is no safety-related postmarketing commitment study for this product.

8. Labeling

The proposed proprietary name, LANTIDRA, was re-reviewed by the Advertising and Promotional Labeling Branch (APLB) on March 6, 2023, and remains acceptable. CBER communicated the acceptability of the proprietary name to the applicant on March 6, 2023.

The Advertising and Promotional Labeling Branch (APLB) reviewed the proposed prescribing information on June 14, 2023, and found it acceptable from a promotional and comprehension perspective.

9. Advisory Committee Meeting

On April 15, 2021, at 10:00 a.m. Eastern Standard Time (EST), the 69th meeting of the Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) took place in open session to discuss biologics license application (BLA) 125734 for LANTIDRA also known as donislecel (purified allogeneic deceased donor pancreas derived Islets of Langerhans). Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP).

The meeting comprised of two sessions dedicated to CMC and Clinical.

In the CMC session, the Applicant presented on “Introduction and Manufacturing Process” and “Potency and Purity Assays and Relationships to Clinical Outcomes,” followed by FDA presentation on “Product Characterization.” Following these presentations, there was a CMC Clarifying Questions and Answers session with the Presenters. The following discussion questions were presented to the committee:

CMC Discussion Question 1:

- a) What is the contribution of endocrine, exocrine, or other cell types expected to be in the final drug product to the clinical outcomes and product potency?
- b) How might the relative proportions of endocrine, exocrine, or other cell types in the product play a role in clinical outcomes and product potency?
- c) What are the specific types of non- β cells that the Applicant should characterize and/or, possibly, control for in the product?

FDA Summary of Discussion Question 1:

The Committee acknowledged that there was great variability in the final product and raised concerns regarding the presence of ductal and non-beta cells in the final product. The ductal cells present in the final drug product could differentiate into beta cells and could damage other cells via inflammatory actions. Retrospective evaluation of ductal cells and non-beta cells in the final product could be informative to determine if the ratio of endocrine versus exocrine cells affects the clinical outcomes. The Committee suggested rapid testing methods, such as flow cytometry and measurement of oxygen consumption rate, to characterize the final product and potentially be implemented post-approval.

CMC Discussion Question 2:

- a) Are the product quality attributes of purity and potency sufficient to evaluate lot-to-lot consistency in manufacturing, product quality, and product strength?
- b) If not, what additional product characteristics, not previously identified as CQAs for LANTIDRA (donislecel), would provide more meaningful measures to assess lot-to-lot product consistency?

FDA Summary of Discussion Question 2:

The Committee discussed that it is difficult to have consistent product lots because each lot is derived from a different donor pancreas. In addition, the Committee noted that it would be good to have better quality control of the product to avoid administration of multiple doses. The committee suggested adding rapid quality control assays to aid in controlling lot-to-lot variability. The Committee members also discussed the issue of human leukocyte antigen (HLA) desensitization and suggested retrospective HLA analysis.

Clinical 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, LANTIDRA (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).

Clinical Topic for Discussion #2

The applicant has proposed "Treatment of Brittle T1D" as the indication for cadaveric allogenic pancreatic islet cells, LANTIDRA (donislecel). Given that there is no specific definition for "brittle T1D" 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 T1D as the appropriate target population.

FDA Summary of Discussion:

The two 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, LANTIDRA (donislecel) should be limited to a very small subset of patients with T1D for whom available therapy and technology are insufficient at preventing life-threatening complications from insulin induced hypoglycemia. Some committee members voiced that LANTIDRA (donislecel)

would be appropriate for patients who are not surgical candidates but would otherwise be candidates for whole pancreas transplant.

Discussion and Voting Question

Does LANTIDRA (donislecel) delivered by intraportal administration have an overall favorable benefit-risk profile for some patients with T1D? 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 LANTIDRA (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.

10. Other Relevant Regulatory Issues

N/A

11. Recommendations and Benefit/Risk Assessment

a. Recommended Regulatory Action

Consistent with 21 USC 355, substantial evidence of effectiveness for LANTIDRA for this rare population with an unmet is based on 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 T1D to compose a single adequate and well controlled investigation. 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 Consortium of Islet Transplants (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.

Thus, the review team recommends traditional approval of LANTIDRA, an allogeneic pancreatic islet cellular therapy indicated for the treatment of adults with Type 1 diabetes (T1D) who are unable to approach target HbA1c because of current repeated episodes of severe hypoglycemia despite intensive diabetes management and education and for use in conjunction with concomitant immunosuppression.

b. Benefit/Risk Assessment

There is a favorable benefit-risk profile for LANTIDRA with the required concomitant use of immunosuppression for a limited population of adults with T1D 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 preserve the viability of the islet cells.

c. Recommendation for Postmarketing Activities

The Applicant agreed to the following CMC PMC:

CellTrans, Inc. commits to reassess the analytical levels of organic leachables from the container closure system (two units, 750- and 1000-mL bags) using a methodology with validated limit of quantification (LOQ) values that are reliably below the reporting limit of (b) (4) (monitoring level, calculated based on the toxicological concern threshold). Based on this analytical reassessment, for compounds found above the reporting limit, CellTrans, Inc. also commits to perform a toxicological assessment and will submit the final reassessment of the organic leachables analytical levels and their toxicological assessment as a Post Marketing Commitment.

Final Study Report Submission: February 29, 2024.