

**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research (CBER)  
Office of Biostatistics and Pharmacovigilance (OBPV)  
Division of Pharmacovigilance (DPV)**

**PHARMACOVIGILANCE ORIGINAL BLA MEMORANDUM**

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**Through:** Christopher Jason, MD  
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**Subject:** Review of Pharmacovigilance Plan for  
Lantidra/Donislecel; Pancreatic Islet Cell  
transplantation

**Applicant:** CellTrans, Inc.

**Product:** Donislecel, Purified Allogenic Islets of Langerhans  
Cells for Transplant

Proprietary Name: Lantidra

**Application Type/Number:** 125734/0. Original BLA

**Indication:** 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.

**Action Due Date:** 6/28/2023

## **1 Objective**

CellTrans Inc. submitted a BLA for its product, purified allogeneic islets of Langerhans (generic name: donislecel, trade name: Lantidra), for marketing approval for the treatment of brittle type 1 diabetes (T1D).

The purpose of this review memorandum is to evaluate the sponsor's proposed plan for postmarketing safety monitoring and to identify potential safety concerns associated with the use of Donislecel that may need to be addressed through additional post-marketing safety surveillance, studies, or other pharmacovigilance activities, should the product be approved.

## **2 Product Information**

### **2.1 Clinical Background**

Diabetes Mellitus type I (T1D) is a significant public health concern. It is estimated that 1.25 million Americans have T1D.<sup>1</sup> Type 1 Diabetes is associated with mortality and significant morbidity including blindness, heart disease, and renal failure. The cost associated with managing the morbidity of type 1 diabetes is estimated to exceed \$16,000 per patient per year.<sup>2</sup>

The standard of care for managing type 1 diabetes is insulin injection combined with frequent evaluation of blood sugar levels. This therapy is not effective in every patient, and there are patients with diabetes who continue to demonstrate inadequate serum glucose control despite optimal medical management and education. Even when effective autologous insulin injection is implemented the risk of hypoglycemia and cardiovascular events remain. For these patients with poor glucose control on maximal therapy, pancreas transplantation has been employed.<sup>3</sup>

Pancreatic transplantation has a high morbidity and mortality.<sup>4</sup> For this reason, transplantation of purified islet cells has been proposed and studied as a treatment for type 1 diabetes in adults that continue to demonstrate glycemic pathology despite optimal medical therapy and intensive education.

### **2.2 Product Description**

The CellTrans product is a human allogeneic cellular suspension intended for intravascular administration within the portal vein of the liver. The product consists of a suspension of allogeneic pancreatic islets of Langerhans in Connaught Medical Research Laboratories (CMRL) 1066 transplant medium. The active ingredient is the allogeneic islets of Langerhans that are derived from a deceased donor's pancreas.

Should donislecel be approved under BL 125734/0, note that the manufacturing and administration will be limited to a single site, University of Illinois Health Hospital.

### **2.3 Proposed Indication**

Donislecel is 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.

### **2.4 Pertinent Regulatory History**

On February 1, 2017, the preparation of islet cells for transplant to be used for brittle diabetes by this application was designated as an orphan drug.

The original BLA Application for this product was submitted in May 2017 under BLA number 125651 but withdrawn in July 2017. The sponsor, CellTrans Inc., applied for a new BLA number in 2021 – STN 125734/0.

The updated submission under BL 125734/0 included basic scientific data from the original submission relating to the preparation of the commercial product as well as additional data whose purpose was to address the concerns the FDA relayed to the sponsor in 2017.

The new application also included new unreviewed information: including new health database studies used to support the product's safety and effectiveness. These IND studies were conducted under the auspices of the University of Illinois Health Science Center (noted by initials UIH). These IND numbers are available in the cover letter dated May 19, 2020.

Upon receipt of the new application, the file was reviewed by the FDA and the relevant findings as well as the sponsor's presentation of the data was presented at a meeting of the Cellular Tissue and Gene Therapies Advisory Committee (CTGTAC) on April 15, 2021. The committee voted 12-4 that the overall safety profile for this product is favorable.

However, the product was ultimately subject to a complete response letter on August 18, 2021. This letter stated that approval could not be granted due to deficiencies in chemistry, manufacturing and controls (CMC). The applicant has since resubmitted the application after responding to the FDA and improving their CMC practices.

### **2.5 Known Safety Information for this Class of Product**

Because this therapy is proposed as a first in its class product there is no other safety information besides the clinical studies which are submitted to support this application.

## **3 Documents Reviewed**

The following documents were reviewed in support of this application:

Table 1: Documents Reviewed

Source	STN Number	Description
Applicant	125734/0/36	Cover letters regarding submission of PVP and referenced below
Applicant	125734/0/36	Risk Management Plan
Applicant	125734/0/01	Documents relevant to original submission, refer to cover letter of May 19, 2020
Reviewer	Pharmacovigilance Plan Review Memorandum	Previous PVP review, dated August 5, 2021
Applicant	125734/0/50	Safety Update IR

## 4 Clinical Studies Submitted in Support of this Application

### 4.1 Clinical Trial Overview

The applicant submitted data from 5 trials that comprise the analyzed safety population: 3 trials in phase 1 or phase 2 and 2 trials in phase 3. They are listed in Table 2 below.

Table 2: Clinical Trial Overview

Designation	Title	Number of patients/Number of transplants	Description of Study/Results
UIH-001	Islet Transplantation in Type 1 Diabetic Patients Using the Edmonton Protocol of Steroid Free Immunosuppression	10/21	Pilot study Phase 1/2. Endpoint: insulin independence. 3/10 subjects full success criteria
UIH-002	Islet Transplantation in Type 1 Diabetic Patients Using the UIC Protocol, Phase 3	21/35	Endpoints: HbA1c $\leq$ 6.5% and absence of significant hypoglycemia (see safety analysis)
Other Studies: UC-12176A, CIT-02, CIT-06, CIT-07	Islet Transplantation in Type I Diabetic Patients Using the UIC Protocol, Phase 3	6,3 24, 24 (with 24 control patients)	Results not included in this analysis because of differences in product preparation

Note: at the Cellular Tissue and Gene Therapies Advisory Committee meeting referred to above, studies done at centers other than UIH were excluded from FDA safety and efficacy analysis because the preparation of the islet cells for transplant was not standardized, and the products were prepared differently than in UIH-001 and UIH-002. These results are included in some of their analyses.

The total number of patients included in the safety analysis from UIH-001 and UIH-002 is 30 patients who received 56 transplant procedures. The difference from the chart above is due to one patient being counted twice. Additional patients enrolled recently under the Expanded Access Protocol are discussed below. As part of the resubmission of the product from CR, there were no new studies submitted with the submission. Follow up of subjects from studies UIH-001 and UIH 002 was submitted. For a full review of the safety data submitted in the original submission 125734/0/1, please refer to the initial OBPV pharmacovigilance plan review memorandum.

## **4.2 Interval Safety Analysis**

### **4.2.1 Patient Enrollment, Follow-Ups, and Withdrawals Overview**

The 30 patients were all followed by the investigators for at least one year after transplantation. After that they had a five-year follow-up and a 10-year follow-up. In the interim, the patients were evaluated by outside medical personnel and referred as needed to the investigators.

The average length of follow-up was slightly less than 5 years.

All patients were followed by the investigators for the first year; this period of follow up constituted the primary safety evaluation period. 6/30 patients refused follow-up after one year.

Of the remaining 24 patients:

- 9/24 patients were followed for less than 5 years. These 9 patients were lost to follow-up at 2 years (n=2), 3 years (n=3), 4 years (n=2), and between 4 and 5 years (n=2).
- 15/24 patients were long-term follow-up patients (>5 years). Of these 15 patients, 12 were followed between 5 and 10 years and 3 were followed longer than 10 years.

### **4.2.2 Additional safety information**

There were two additional patients enrolled under the Expanded Access Protocol since the 125734/0 was submitted.

According to an IR response (125734/51) received April 27, 2023, there was an additional death reported in 2022. The patient was more than 10 years post-

transplant and the death was not adjudicated to be secondary to the procedure. There have been no new cases of cancer.

#### **4.2.3 Safety assessment**

The evidence supporting safety of this preparation of islet cells is limited. It consisted of 30 patients who received 56 transplant procedures. Of these patients, 3 have died and 5 are still insulin independent. The two recently enrolled patients have very limited information because both of their transplants are within the last year.

*Reviewer Comment:* A pancreatic islet cell transplant and immunosuppression in a population of type 1 diabetics who are refractory to long-term exogenous insulin therapy is expected to result in significant morbidity and mortality. The profile noted above is neither unexpected nor excessive and the labeling appears to be adequate to inform providers and patients of these risks.

This profile was presented to the Cellular Tissue and Gene Therapies Advisory Committee in April 2021. The Committee voted the safety profile was acceptable. Updates to the profile since that presentation do not change the safety profile significantly.

Of note, the OTP clinical team has raised the issue of specialized training for islet cell transplantation. At this time, there is review team consensus that given the product will be manufactured and distributed at a single site (University of Illinois Health Hospital) where staff have training in the manufacture and administration of this product, there is no new safety signal that would trigger a Risk Evaluation and Mitigation Strategies (REMS) to ensure the benefits outweigh the risks.

However, should the applicant submit a future sBLA to expand manufacturing to include additional site(s), then the review team will discuss the need for specialized training for islet cell transplantation, and whether such training will be required under a REMS to ensure that benefits outweigh risks of the procedure. The review team plans to send a comment to the applicant regarding a potential REMS in the context of expanding manufacturing to additional site(s).

#### **4.3 Deaths**

As noted above there have been 3 patient deaths. Two deaths were included in the original submission. Since then, a death was reported due to a heart failure in a patient who was more than 10 years status-post transplantation (subject (b) (6) ).

*Reviewer Comment:* The additional death reported in the two year interval since the presentation at the CTGTAC meeting does not change the product's safety profile.

### **5 Post-market data**

This product is not currently licensed in the U.S. and there is no foreign postmarketing experience for this product.

## 6 Pharmacovigilance Plan

The pharmacovigilance plan was received on May 21, 2021. It recommends routine pharmacovigilance; including review and submission of adverse event reports in accordance with 21 CFR 600.80, the preparation and submission of periodic safety reports to FDA, and safety review including signal detection and benefit-risk analysis.

Individual patient safety reports (i.e., case processing of adverse events/adverse drug reactions) will be handled in accordance with US FDA requirements for expedited and non-expedited safety reports, including the collection, processing, triaging and reporting of adverse events (AEs)/adverse drug reactions (ADRs) from healthcare professionals, clinical trials, consumer spontaneous adverse events, and adverse events from other sources (e.g., literature).

The PVP enumerated the following identified and potential risks and proposed the following pharmacovigilance strategy. For the eleven identified risks, the action proposed, objectives, rationale, and milestones were identical. There were differences in the potential risks which are delineated in table 4. For all risks and adverse events: If new safety data provide evidence of an increase in severity or frequency of the safety concern, the Risk Management Plan will be revised. The product label will be updated as appropriate based upon statutory requirements. CellTrans will notify the FDA immediately if new information leads to a change in the benefit-risk balance of Donislecel.

Table 3:  
Identified Risks:

Identified Risks	Action Proposed	Objectives	Rationale	Milestones
Sensitization to Donor Antigens, Graft Failure Bleeding, Portal Vein Hypertension, Increased LFTs, Blood Cell Disorders, Blood Chemistry D/O, Cardiovascular D/O, Infections, Neoplasms, Renal and Urinary D/O	Routine PV, Risk minimization,	Avoid recurrent adverse events as noted as identified risks	Sponsor advocates standard regulatory guidance, best practices to mitigate risk, routine pharmacovigilance, and described risk minimization procedures.	Safety signals will be reviewed as specified in the protocol. Pharmacovigilance reports will be sent to the FDA in accordance with statutory requirements.

Table 4: Potential Risks

Potential Risks	Action Proposed	Objectives	Rationale	Milestones
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Donor Disease Transmission	Routine pharmacovigilance, risk minimization, follow procedures from organ procurements agencies	Avoid donislecel disease transmission by proper testing of transplant material and recipient follow-up.	Communication with organ procurement agencies, routine pharmacovigilance and described risk minimization procedures are appropriate.	Safety signals will be reviewed as specified in the protocol. PV reports will be sent to the FDA in accordance with statutory requirements.
Microbial Contamination	Routine pharmacovigilance; all safety signals will be followed up by PS Officer (or designee) using the procedures described in the protocol. Risk minimization procedures as described previously	Avoid donislecel microbial contamination by identifying areas for potential contamination to occur	Standard regulatory to mitigate the risk of this safety concern; routine pharmacovigilance along with risk minimization procedures are appropriate.	As noted above
Portal Vein Thrombosis	As noted above	Safety concern is an operative complication, routine PV is appropriate	As noted above	As noted above
Developmental Reproductive Pathology	As noted above	Monitor, evaluate, and characterize risk	Usually due to concomitant medication use, routine PV is appropriate	As noted above

PS Officer: Public safety officer

*Reviewer Comment:* The applicant's proposed PVP is acceptable.

## 7 Labeling

There is no Post-marketing Experience section in the proposed label with this product.



## 8 Conclusion

OBPV has reviewed the data provided by the applicant. The proposed pharmacovigilance plan is acceptable. Safety data accumulated in the interval between the complete response letter and last PVP memo and this review reveals no new safety concerns and reflects the previously described risks of donisleucel. No additional pharmacovigilance actions, Risk Evaluation and Mitigation Strategy or postmarketing studies such as postmarketing requirements (PMRs) or postmarketing commitments (PMCs), are indicated.

## 9 DPV Recommendations

Should this submission be approved, the safety labeling and PVP are acceptable. Based on review of the premarket clinical safety database and the Applicant's proposed PVP, OBPV/DPV recommends the following for post-marketing safety monitoring:

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

Refer to the final version of the U.S. Prescribing Information (USPI) submitted by the applicant for the final agreed-upon language for the label.

## 10 References

<sup>1</sup> Centers for Disease Control and Prevention, *National Diabetes Statistics Report: Estimates of Diabetes and Its Burden in the United States*, U.S.D.o.H.a.H. Services, Editor. 2014: Atlanta, GA, USA.

<sup>2</sup>American Diabetes Association, The Cost of Diabetes, [The Cost of Diabetes | ADA](#)

<sup>3</sup> Orchard, T.J., et al., *Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality*. *Jama*, 2015. **313**(1): p. 45-53.

<sup>4</sup> Gruessner, A.C. and D.E. Sutherland, *Pancreas transplant outcomes for United States (US) and non-US cases as reported to the United Network for Organ Sharing (UNOS) and the International Pancreas Transplant Registry (IPTR) as of October 2002*. *Clin Transpl*, 2002: p. 41-77.