Cellular, Tissue, and Gene Therapies Advisory Committee Meeting

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ERRATA TO THE BRIEFING DOCUMENT FOR LANTIDRA™ (DONISLECEL) FOR THE TREATMENT OF BRITTLE TYPE 1 DIABETES MELLITUS FOR THE CELLULAR, TISSUE, AND GENE THERAPIES ADVISORY COMMITTEE MEETING

15 APRIL 2021

APPLICANT: CELLTRANS, INC.

1. INTRODUCTION

The following errors have been identified in the CellTrans, Inc. briefing document prepared for the Cellular, Tissue, and Gene Therapies advisory committee. The identified errors do not carry through to other sections of the briefing materials and do not affect the overall safety and efficacy conclusions as stated in the briefing document. Errors are identified by grey highlight and strikethrough with corrections identified in bold text below.

2. IDENTIFIED ERRORS

2.1. Error 1: Page 16, Section 1.3.5 Dosage and Administration. The term "glucagon-like peptide-1 (GLP-1) inhibitor" is not correct. It should be "glucagon-like peptide-1 (GLP-1) analog."

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

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

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

2.2. Error 2: Page 38, Section 2.5.4 Dosage and Administration and Page 71, Section 5.1.1 Donislecel. The summary statistics reported for the number of transplanted islets (IE) and the number of transplanted islets per patient body weight (IE/kg) were incorrect and have been updated to reflect the correct values.

Text on Page 38:
Patients in the donislecel Phase 1/2 and Phase 3 studies (UIH-001 and UIH-002, respectively) received a median islet dose of ~~6,570 IE/kg~~ **6643 IE/kg** (range 4,186 IE/kg to 13,633 IE/kg), for a median total islet number of ~~399,178 IE~~ **411,107 IE** (range 253,924 IE to ~~858,856 IE~~ **877,677 IE**) per transplant. Cumulatively, patients received a median total islet dose of 724,184 IE (range 260,902 to 1,831,236) across all transplants.

Text on Page 70:
For patients in Studies UIH-001 and UIH-002, the median islet number per transplant was ~~399,178 IE~~ **411,107 IE** (range 253,924 IE to ~~858,856 IE~~ **877,677 IE**), or ~~6,570 IE/kg~~ **6643 IE/kg** (range 4,186 IE/kg to 13,633 IE/kg). Cumulatively, patients received a median total islet dose of 724,184 IE (range 260,902 to 1,831,236) across all transplants.

2.3. Error 3: Page 50, Section 4.1.3 Baseline Diabetes Care and Control. Table 13 was updated to reflect the correct percentage of patients with data for frequency of SHE. The percentage value and associated SHE footnote were updated.

Table 1. Baseline Diabetes Control Characteristics for Patients in Studies UIH-001, UIH-002, and the Pooled Population

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population [a] N=30
Insulin Requirement (units/kg/day), n (%)	10 (100)	21 (100)	29 (96.7)
Mean (SD)	0.52 (0.135)	0.47 (0.134)	0.51 (0.142)
Median (Min, Max)	0.55 (0.3, 0.7)	0.50 (0.1, 0.8)	0.53 (0.3, 0.8)
Missing, n (%) [b]	0	0	1 (3.3)
HbA1c (%), n (%)	9 (90.0)	21 (100)	29 (96.7)
Mean (SD)	7.21 (1.205)	7.37 (0.867)	7.35 (0.918)
Median (Min, Max)	6.90 (5.9, 9.5)	7.30 (5.7, 9.0)	7.30 (5.7, 9.5)
Missing, n (%) [b]	1 (10.0)	0 (0.0)	1 (3.3)
Frequency of SHE (episodes/month), n (%) [c]	5 (50.0)	11 (52.4)	16 ~~(55.2)~~ **(53.3)**
Mean (SD)	0.16 (0.054)	1.138 (1.477)	0.832 (1.294)
Median (Min, Max)	0.13 (0.1, 0.2)	0.36 (0.05, 4.24)	0.22 (0.05, 4.24)
Missing, n (%) [b]	5 (50.0)	10 (47.6)	14 (46.7)
HYPO Score, n (%) [c]	7 (70.0)	12 (57.1)	18 (60.0)
Mean (SD)	88.18 (67.987)	428.49 (491.671)	319.06 (429.43)
Median (Min, Max)	88.05 (11.1, 211.9)	265.87 (2.4, 1638.0)	109.14 (2.4, 1638.0)
Missing, n (%) [b]	3 (30.0)	9 (42.9)	12 (40.0)

Parameter	UIH-001 N=10	UIH-002 N=21	Pooled Population [a] N=30
Fasting Plasma Glucose (mg/dL), n (%)	9 (90.0)	20 (95.2)	28 (93.3)
Mean (SD)	143.3 (87.87)	171.8 (61.18)	165.1 (70.50)
Median (Min, Max)	105.0 (69, 348)	172.5 (78, 291)	168.0 (69, 348)
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)
90-min Glucose, post glucose challenge (mg/dL), n (%)	9 (90.0)	20 (95.2)	28 (93.3)
Mean (SD)	312.1(94.18)	368.4 (69.90)	352.6 (81.94)
Median (Min, Max)	305.0 (122, 438)	365.5 (279, 559)	365.0 (122, 559)
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)
Reduced awareness of hypoglycemia, n (%) [d]	10 (100)	21 (100)	30 (100)
Missing, n (%) [b]	0	0	0
MMT: Fasting C-peptide <0.1 ng/mL, n (%) [e]	9 (90.0)	19 (90.5) [f]	27 (90.0) [f]
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)
MMT: 90-min C-peptide, post glucose challenge, <0.1 ng/mL, n (%) [e]	8 (80.0) [f]	19 (90.5) [f]	26 (86.7) [f]
Missing, n (%) [b]	1 (10.0)	1 (4.8)	2 (6.7)

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

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

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

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

c Baseline values were calculated based on hypoglycemic events self-reported by the patient during the screening/waiting period between enrollment and initial transplant, which varied in length for each patient. **Number of subjects includes only patients for whom frequency data were available during the screening/waiting period.**

d Reported qualitatively only at enrollment.

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

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

2.4. Error 4: Page 66, Section 4.1.10 Exposure-Efficacy Relationships. Text and Figure 15 included incorrect insulin independence data. The text and figure have been updated to reflect the correct data.

Insulin independence at 1 year after last transplant was observed with greater frequency with increased **cumulative** donislecel dose ~~(cumulative) up to a total dose of between 750,000 and 1,000,000 IE~~ (Figure 15). While ~~22% (2/9)~~ **44% (4/9)** of patients receiving fewer than 500,000 IE achieved insulin independence, this increased to ~~43% (3/7)~~ **57% (4/7)** for those receiving 500,000-750,000 IE, ~~and~~ to 83% (5/6) for those receiving 750,000-1,000,000 IE**, and to 88% (7/8) for those receiving more than 1,000,000 IE**. ~~Beyond 1,000,000 IE, insulin independence decreased slightly to 62.5% (5/8) but was still more frequent than in patients receiving <750,000 IE.~~ Together, these results support the conclusion that **cumulative** doses ~~≥750,000 IE are favorable for promoting~~ **≥500,000 IE promote** insulin independence in most patients.

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

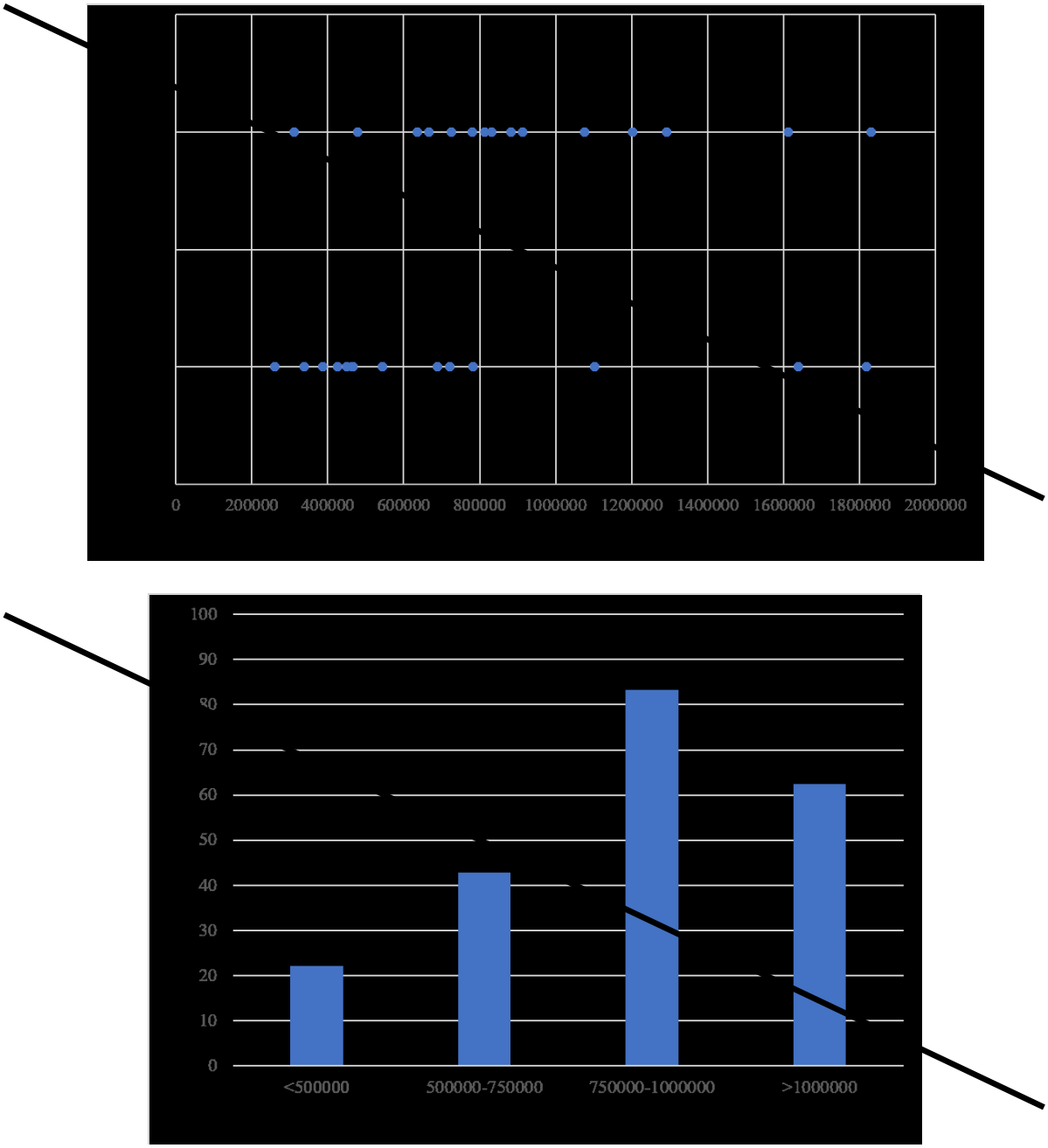
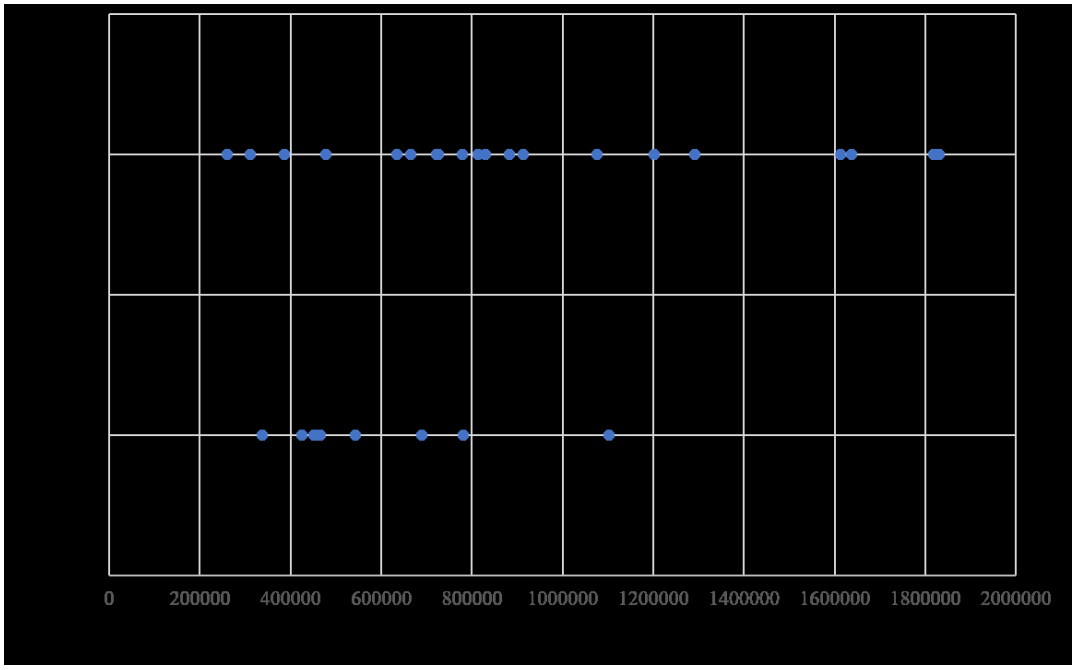
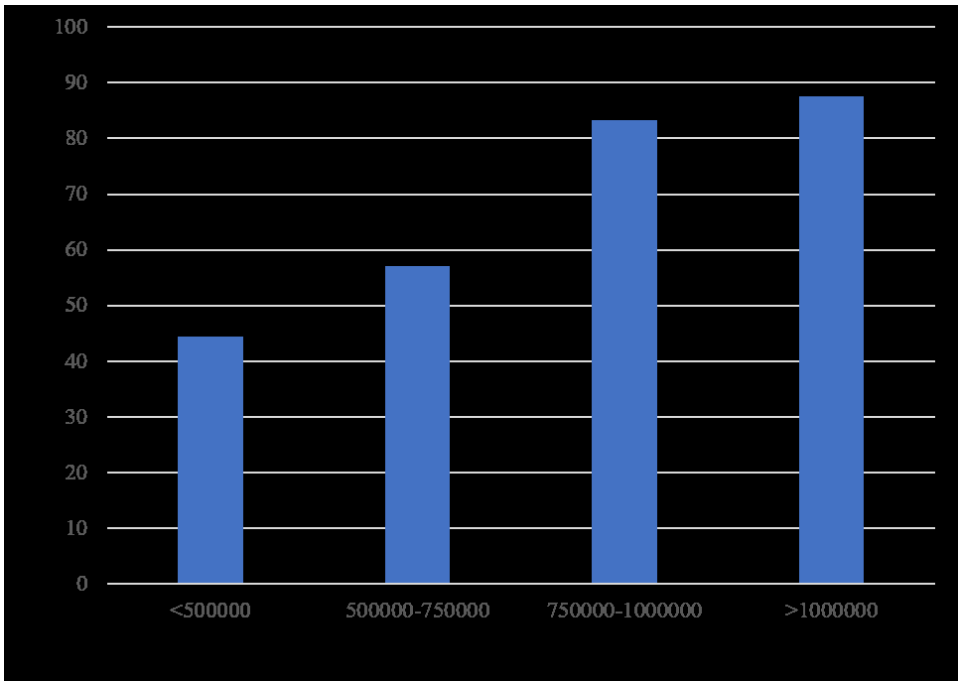


Figure 2. Insulin Independence at 1 Year after Last Transplant, by Cumulative Dose (Pooled Population)





2.5. Error 5: Page 69, Section 4.2.2 Other Historical Comparators. Table 27 was updated to reflect the corrected SHE baseline values from Table 13.

Table 2. Comparison of Efficacy Outcomes for Donislecel (Pooled Population), Islet Transplantation at Other Transplant Centers, and Insulin Therapy

Study		HbA1c (%)	Patients with SHEs (%)	Insulin Ind. (%) [a]
Donislecel (CellTrans)				
Pooled Population	Baseline	7.4±0.9	~~100~~ **53** [b]	0
	1 year post-last transplant [bc]	6.0±0.7	23	67
Islet Transplantation				
CITR	Baseline	7.9±0.0	80	0
	1 year post-last transplant	~6.5±NR	6	52
TRIMECO	Baseline	8.1 (7.4, 8.9)	72 [e d]	0
	6 months post-first transplant	5.6	8	44
	1 year post-first transplant	5.8	15	59
UBC	Baseline	8.1±1.2	NR	0
	Assessment time not stated	6.7±0.2	NR	38
Insulin Therapy				
DCCT	Baseline (all patients)	9.1±1.6 [d c]	NR	0
	Conventional insulin [e f]	9.1±1.3	35	0
	Intensive insulin [e f]	7.2±0.9	65	0
TRIMECO	Baseline	8.1 (7.7, 8.6)	82 [e d]	0
	6 months	8.2	64	0
UBC	Baseline	8.1±1.2	NR	0
	Assessment time not stated	7.8±0.3	NR	0

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

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

a Defined as lack of exogenous insulin use

b **Baseline values were calculated based on hypoglycemic events self-reported by the patient during the screening/waiting period between enrollment and initial transplant, which varied in length for each patient. Frequency of SHEs were only reported for the 16 patients who had SHE frequency data available during the screening/waiting period.**

~~b~~ c Primary follow-up

~~c~~ d ≥2 SHEs in year prior to randomization

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

e f Average 6.5 years of follow-up

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

2.6. Error 6: Page 121, Table 45. The number of UIH patients under the "Primary Efficacy Endpoint(s) and Results" column was corrected from 4 to 3.

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

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

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