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Applicant	CellTrans Inc
Established Name	Allogeneic Human Pancreatic Islets of Langerhans
(Proposed) Trade Name	DONISLECEL
Pharmacologic Class	
Formulation(s), including Adjuvants, etc	
Dosage Form(s) and Route(s) of Administration	A cellular suspension for infusion into the hepatic portal vein only.
Dosing Regimen	Depends upon the total number of islets packaged for infusion.
Indication(s) and Intended Population(s)	Indicated for the treatment of brittle Type 1 diabetes (labile diabetes) in adults.

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GLOSSARY

AC	Advisory committee
AE	Adverse event
BLA	Biologics license application
BMI	Body mass index
CI	Confidence interval
CSR	Clinical study report
EST	Eastern Standard Time
FDA	Food and Drug Administration
HbA1c	Hemoglobin A1c; glycated hemoglobin
IE	Islet equivalent
PMISP	Particular Matter Involving Specific Parties
PK	Pharmacokinetic
SAE	Serious adverse event
SD	Standard deviation
SHE	Severe hypoglycemic events
T1D	Type 1 diabetes
UI	University of Illinois
UIC	University of Illinois at Chicago
UIH	University of Illinois Hospital and Health Sciences System

1. EXECUTIVE SUMMARY

This biologics license application (BLA) is for approval of an allogeneic pancreatic islet cellular therapy indicated for the treatment of brittle Type 1 diabetes (labile diabetes, T1D) in adults whose symptoms are not well controlled despite intensive insulin therapy. At the time of review and at the April 15, 2021 Advisory Committee meeting, the product was known by a proposed trade name, DONISLECEL. This name will be used throughout this memo, although it may not be the final trade name if the product is licensed.

The primary evidence to support the safety and effectiveness of the product is based on the results of two clinical studies, UIH-002 (Phase 3) and UIH-001 (Phase1/2). Both studies were nonrandomized, open-label, single-center studies in which one to three allogeneic pancreatic islet transplants were administered to subjects with brittle T1D.

Twenty-one subjects were enrolled in UIH-002 and the composite primary endpoint was hemoglobin A1c (HbA1c) $\leq 6.5\%$ and free of severe hypoglycemic events (SHEs) at one year after the first transplant and at one year after the last transplant. Eight (38.1%) subjects met the primary endpoint (95% confidence interval (CI): 18.1%, 61.6%). After removing one subject (b) (6) who was

previously enrolled in study UIH-001, 7 (35%) of the 20 subjects met the primary endpoint (95% CI: 15.4%, 59.2%). The sample size justification for study UIH-002 was based on a test of the null hypothesis that the success rate is less than 50%. However, it is not clear that the sponsor ever intended to perform this hypothesis test, and there was no agreement with FDA regarding a performance goal for the primary endpoint that would establish substantial evidence of effectiveness.

Ten subjects were in enrolled in UIH-001 and the primary endpoint was insulin independence and $HbA1c \leq 6.5\%$ at one year after the last transplant. Three (30%) subjects met the primary endpoint (95% CI: 6.7%, 65.3%).

After combining these two clinical studies, the integrated dataset consisting of 30 treated distinct subjects was evaluated. The primary endpoint for the integrated analysis was $HbA1c \leq 6.5\%$ and free of SHE at one year after the last transplant. Nineteen (63.3%) of the 30 subjects met the primary endpoint (95% CI: 43.9%, 80.1%). The secondary endpoint was insulin independence at one year after the last transplant. Twenty (66.7%) of the 30 subjects met the secondary endpoint (95% CI: 47.2%, 82.7%). Sixteen of these 20 subjects also met the primary endpoint. There was no prespecified performance goal for the primary endpoint in this pooled analysis.

In terms of safety, no subjects reported inhibitory effects in the studies. There were no treatment-emergent adverse event leading to death within the specified follow-up window. One death was reported during long-term follow-up in study UIH-002.

Because success criteria were not defined for any endpoints, there is no inferential statistical procedure to apply to the efficacy data. This review will evaluate the data on a descriptive basis; the sufficiency of these data to provide substantial evidence of effectiveness is deferred to the clinical review team.

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

T1D is a disease characterized by the autoimmune-mediated loss of insulin-producing β -cells within the islets of Langerhans in the pancreas. The disease results in the complete deficiency of insulin, causing several potentially life-threatening conditions such as hyper- and hypoglycemia, ketoacidosis, and dehydration. "Brittle" T1D is a particularly difficult form of T1D to treat and is characterized by severe instability of blood glucose levels with frequent and unpredictable episodes of hypoglycemia that disrupt quality of life, often requiring frequent or prolonged hospitalizations. It is estimated that 1.25 million Americans have brittle T1D.

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

Currently, there are limited alternative treatment options to help patients for whom insulin therapy is insufficient. Whole pancreas transplantation has traditionally been the intervention of choice for T1D patients with intractable hypoglycemia unawareness, but this approach requires major surgery. Although mortality and morbidity following pancreas transplantation have improved over the years, whole pancreas transplantation still involves significant procedural risk and is not appropriate for all brittle T1D patients.

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

The pre-BLA meeting was held on August 3, 2016. During the meeting the FDA preliminarily agreed that the two University of Illinois (UI) Health studies (IND number: 11807), UIH-001 and UIH-002, and the planned efficacy analyses were sufficient in scope and that the number of subjects were sufficient in size to support the proposed indication and label. The FDA also requested the applicant to provide an integrated efficacy report for all subjects who received their product and the applicant agreed.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The submission was adequately organized for conducting a complete statistical review without unreasonable difficulty.

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

5.1 Review Strategy

Six clinical studies were submitted in support of this application. Two are phase 1/2 studies, UIH-001 and UC-12176A, one is a phase 2 study, CIT-02, and three are phase 3 studies, UIH-002, CIT-06, and CIT-07. Because the latter two phase 3 studies are ongoing and do not yet have enough subjects for analysis, study UIH-002 was intended to be the primary source of evidence of safety and effectiveness study and study UIH-001 provides supportive evidence. Therefore, study UIH-002 is reviewed in detail and UIH-001 is briefly reviewed in this memo. Because the label contains the integrated efficacy results from these two studies, the integrated summary of efficacy is discussed in Section 7, Integrated Overview of Efficacy.

5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review

The following documents and datasets for the BLA were reviewed. All data sources are included in the applicant's electronic Common Technical Document (eCTD) submission located in the FDA/CBER Connect.

BLA	125734/0	
	Module 1.14	Labeling
	Module 2.7.3	Summary of Clinical Efficacy
	Module 5.2	Tabular Listing of all Clinical Studies
	Module 5.3.5.2	Study Reports
		UIH-001: study report body, protocol, statistical analysis plan.
		UIH-002: study report body, protocol, statistical analysis plan.
	Module 5.3.5.2	Data Files
		UIH-001: dm.xpt, tx.xpt, lb.xpt
		UIH-002: dm.xpt, tx.xpt, lb.xpt

5.3 Table of Studies/Clinical Trials

Table 1 Summary of clinical studies in the BLA

Type of Study	Study Identifier	Objective(s)	Study Design and Type of Control	Test Product(s); Dose Regimen; Route of Administration	Number of Subjects	Diagnosis	Duration of Treatment
Safety and Efficacy	UIH-001	To demonstrate the safety and effectiveness of allogeneic islet transplantation performed at UI Health for the treatment of patients with T1D.	Phase 1/2, prospective, nonrandomized, single-arm, single-center uncontrolled (historical controls added in BLA)	Purified allogeneic islets of Langerhans; Single infusion with variable dosage; Intrahepatic (portal vein infusion)	10	Type 1 diabetes mellitus	Single infusion; possibility of additional infusions based upon eligibility
Safety and Efficacy	UIH-002	To demonstrate the safety and efficacy of allogeneic islet transplantation in patients with T1D performed at UI Health.	Phase 3, prospective, nonrandomized, single-arm, single-center uncontrolled (historical controls added in BLA)	Purified allogeneic islets of Langerhans; Single infusion with variable dosage; Intrahepatic (portal vein infusion)	21	Type 1 diabetes mellitus	Single infusion; possibility of additional infusions based upon eligibility

Efficacy	CIT-02	To determine the proportion of subjects who were insulin independent after a single islet transplant at 75 ± 5 days posttransplant in patients treated with Lisofylline added to a standard islet transplant regimen.	Phase 2, prospective, randomized, single-arm, multicenter uncontrolled (historical controls added in BLA)	Purified allogeneic islets of Langerhans; Single infusion with variable dosage; Intrahepatic (portal vein infusion)	2	Type 1 diabetes mellitus	Single infusion; possibility of additional infusions based upon eligibility
Efficacy	CIT-06	To test the hypothesis that islet transplantation in T1D patients with established kidney transplants leads to a reduced risk of diabetes related complications as assessed by improved metabolic control measured by serial HbA1c levels and/or reduced occurrence of hypoglycemic events compared with intensive insulin therapy.	Phase 3, prospective, nonrandomized, single-arm, multicenter uncontrolled (historical controls added in BLA)	Purified allogeneic islets of Langerhans; Single infusion with variable dosage; Intrahepatic (portal vein infusion)	4	Type 1 diabetes mellitus	Single infusion; possibility of additional infusions based upon eligibility

Efficacy	CIT-07	To demonstrate the safety and efficacy of allogeneic islets transplantation for the treatment of T1D in subjects with hypoglycemia unawareness and a history of severe hypoglycemic episodes, as demonstrated by glycemic control and elimination of severe hypoglycemic episodes.	Phase 3, prospective, nonrandomized, single-arm, multicenter uncontrolled (historical controls added in BLA)	Purified allogeneic islets of Langerhans; Single infusion with variable dosage; Intrahepatic (portal vein infusion)	4	Type 1 diabetes mellitus	Single infusion; possibility of additional infusions based upon eligibility
Safety	UC-12176A	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.	Phase 1/2, prospective, nonrandomized, single-arm, single-center uncontrolled (historical controls added in BLA)	Purified allogeneic islets of Langerhans; Single infusion with variable dosage ; Intrahepatic (portal vein infusion)	3	Type 1 diabetes mellitus	Single infusion; possibility of additional infusions based upon eligibility (patients only received a single islet transplant using UI Health-manufactured islets)

Source: Original BLA 125734/0; Module 5.2 Tabular Listing of all Clinical Studies.

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

The Advisory Committee (AC) virtual meeting took place on April 15, 2021 at 10:00 a.m. Eastern Standard Time (EST). Given the topic of this meeting, it was determined to be a Particular Matter Involving Specific Parties (PMISP). Two clinical questions were discussed in the meeting and listed as follows.

Discussion Question 1:

- a. 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 one 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 might support the efficacy of cadaveric allogenic pancreatic islet cells (donislecel).
- b. 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).

Discussion Question 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 two endocrinologists on the panel 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 subjects with type 1 diabetes for whom available therapy and technology are insufficient at preventing life-threatening complications from insulin induced hypoglycemia. Some committee members voiced opinions that DONISLECEL would be appropriate for subjects who are not surgical candidates but would otherwise be candidates for whole pancreas transplant.

Following the Committee discussion, the Committee was asked to vote on the following voting question:

Does DONISLECEL delivered by intraportal administration have an overall favorable benefit-risk profile for some subjects 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.

There were no statistical issues that came up for the meeting.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial UIH-002

6.1.1 Objectives (Primary, Secondary, etc)

The primary objective was to demonstrate the safety and efficacy of allogeneic islet transplantation in T1D subjects performed at University of Illinois at Chicago (UIC).

6.1.2 Design Overview

This was a phase 3, nonrandomized, single-center study in which at least 50 study subjects with brittle T1D were planned for one to three allogeneic pancreatic islet transplants per subject.

Potentially eligible subjects with diabetes underwent a two-part screening phase to determine eligibility, followed by a waiting list period (as needed). Pre-transplant, transplant, and early post-transplant periods were followed by a post-transplant period up to one year after transplant for the primary assessment. Longer term follow-ups of up to 5 or 10 years were also planned for those subjects opting to continue in the study.

6.1.3 Population

Subjects who met the following criteria were eligible for the study:

1. Age between 18-75 years.
2. Diagnosed with T1D for more than 5 years, and with their T1D complicated by the following situations that persisted despite intensive insulin management efforts:
 - At least one episode of severe hypoglycemia in the past 3 years.
 - Reduced awareness of hypoglycemia.

Subjects were excluded if at least one of the following conditions was present:

- Body mass index (BMI) > 27 kg/m²
- C-peptide response to glucagon stimulation (1 mg IV), with any C-peptide ≥ 0.3 ng/mL
- Insulin requirement > 0.7 IU/kg/day
- HbA1c > 12%

6.1.4 Study Treatments or Agents Mandated by the Protocol

DONISLECEL consists of isolated allogenic human islets of Langerhans formulated in serum free transplant medium (indicator-free CMRL 1066 medium with HEPES, without sodium bicarbonate, and supplemented with human albumin). Islet injections were administered via portal vein delivery to reach the target total of 10,000 islet equivalent (IE)/kg of the recipient's body weight. Up to three injections could have been administered if insulin independence was not achieved by the fourth week after each infusion.

6.1.6 Sites and Centers

Only one study site, University of Illinois Hospital and Health Sciences System (UI Health), formerly known as UIC, participated this study.

6.1.7 Surveillance/Monitoring

The study was monitored in compliance with the relevant parts of 21 CFR and according to International Council for Harmonisation GCP Guidelines. An independent monitor, knowledgeable in GCP guidelines and regulations, visited the study site prior to study initiation and was to visit periodically thereafter to monitor the acceptability of the facilities, the agreement between CRF entries and original source documentation, adherence to the clinical protocol including documentation of study procedures and adherence to the treatment plan, adherence to GCP and to applicable FDA regulations, and the maintenance of adequate clinical records.

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint:

The composite primary endpoint was the proportion of successful subjects, defined as HbA1c \leq 6.5% and free of SHE at one year after the first transplant and at one year after the last transplant.

Failure to achieve the favorable outcome was summarized in two subgroups: the rate of subjects having an HbA1c $>$ 6.5% at Day 365, and the rate of subjects who experienced any SHE from Day 28 to Day 365. If a subject's HbA1c results were reported on visit days that did not fall on the exact Day 365, records from the date that was the closest to and within 4 weeks (28 days) before or after Day 365 were used.

Secondary Endpoints:

- Absence of exogenous insulin (insulin independence) reported at one year after the last transplant.
- Fasting capillary glucose in a week
- Fasting plasma glucose \leq 126 mg/dL
- Post-prandial capillary glucose in a week
- C-peptide (fasting or stimulated) \geq 0.5 ng/mL

6.1.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size:

Originally the planned sample size was 50 subjects, determined according to the assumptions that 80% of the transplant population will achieve the primary endpoint under a two-sided test of the null hypothesis that the proportion of successes was 50% with 5% type 1 error rate. However, after getting the updated information in Table 2, the applicant re-estimated the sample size. They changed the assumption to one-sided test with 5% type 1 error rate and reduced the sample size to 21 subjects.

Table 2 Power of a Single-arm Trial at a One-sided Significance Level 0.05

	Sample Size			
	15	20	30	50
Observed Favorable Outcome Rate (%)	Power for the true improvement of the favorable outcome rate to be at least 50% (%)			
65	32	39	51	70
70	50	60	75	91.5
75	71	81	93	99.1
80	88	95	99.2	>99.9

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 6.

Reviewer Comment:

According to the clinical study report (CSR) of UIH-002 in module 5.3.5.2, the change of sample size was made sometime after 2012 (Section 9.8.1). The protocol in the same module under APPENDICES is dated Aug 7, 2014 which should be the most recent version and it states 50 subjects in Sections 4 and 11.2.1. The summary of protocol changes at the beginning of this protocol does not mention a sample size change either. It appears the applicant did not officially change the sample size in the protocol, but that it was done after 2012. Although the original sample size justification of 50 subjects was based on a test of the null hypothesis that the success rate is less than 50%, it is not clear that the sponsor ever intended to perform this hypothesis test, and there was no agreement with FDA regarding a performance goal for the primary endpoint that would establish substantial evidence of effectiveness.

Analysis Populations:

The following analysis sets were considered:

Intent-to-treat (ITT) Population: The ITT population comprised all subjects who were enrolled in this study. This is the analysis population for the efficacy endpoints.

Safety Population (SAF): The Safety population comprised all subjects who were enrolled in this study. All safety analyses were conducted on this population.

Statistical Methods

Primary Endpoint Analysis:

An exact (Clopper-Pearson) two-sided 95% confidence interval was constructed for the primary endpoint testing.

Secondary Endpoint Analysis:

Number and percent of subjects attaining each outcome listed above were to be summarized. No formal testing was planned.

Missing Data:

Missing data could have occurred due to death, or if the subject withdrew consent to be followed, or if immunosuppression had been started but the subject never received a transplant. In these cases, the endpoint was classified as a failure to achieve a favorable outcome. Should the primary endpoint not be evaluated for a subject for other reasons, a failure was to be imputed unless data existed from a time beyond one year after transplant, in which case the later value would be imputed to be the value at one year post-transplant.

6.1.10 Study Population and Disposition

6.1.10.1 Populations Enrolled/Analyzed

Table 3 Populations Enrolled

Population		Subjects
ITT	Population	21
Safety	Population	21

Source: Adapted from – Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 8 & 12.

6.1.10.1.1 Demographics

Of the 21 subjects in the Safety population, 15 (71%) were female and 21 (100%) were Caucasian. The mean (standard deviation, SD) age was 47.8 (12.6) years. The other baseline characteristics and demographic data at the time of first transplant for the Safety population are described in Table 4 and Table 5, respectively.

Table 4 Baseline Characteristics, Safety Population (N=21)

Parameter	Subjects N=21
Age (years)	
Mean (SD)	47.8 (12.6)
Median (Min, Max)	47.0 (21, 67)
Weight (kg)	
Mean (SD)	64.5 (8.8)
Median (Min, Max)	63.8 (52.5, 83.4)
Height (cm)	
Mean (SD)	166.5 (7.6)
Median (Min, Max)	165.0 (150.9, 181.9)
BMI (kg/m ²)	
Mean (SD)	23.4 (2.0)
Median (Min, Max)	23.5 (20.2, 27.3)

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 8.

Table 5 Demographics, Safety Population (N=21)

Parameter	Subjects N=21
Sex n (%)	
Female	15 (71%)
Male	6 (29%)
Race n (%)	
Caucasian	21 (100%) ^a
Black	0
Asian	0
Native American	1 (5%) ^a
Other	0
Ethnicity n (%)	
Hispanic	1 (5%)
Non-Hispanic	20 (95%)

^a One subject identified as both Caucasian and Native American.

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 8.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

A summary of baseline T1D control is provided in Table 6. The mean baseline of HbA1c was 7.37% and the mean baseline rate of SHE was 1.14 episodes/month.

Table 6 Baseline Diabetes Control (N=21)

Parameter	Subjects
Insulin Requirement (unit/kg/day)	
N	21
Mean (SD)	0.47 (0.134)
Median (Min, Max)	0.50 (0.1, 0.8)
Missing; N (%)	0 (0.0)
HbA1c (%)	
N	21
Mean (SD)	7.37 (0.867)
Median (Min, Max)	7.30 (5.7, 9.0)
Missing; N (%)	0 (0.0)
Frequency of SHE (episodes/month) ^a	
N	11
Mean (SD)	1.14 (1.48)
Median (Min, Max)	0.357 (0.05, 4.24)
Missing; N (%)	10 (47.6%)
HYPO Score ^a	
N	12
Mean (SD)	428 (492)
Median (Min, Max)	266 (2.4, 1638)
Missing; N (%)	9 (42.9%)
Fasting Plasma Glucose (mg/mL)	
N	20
Mean (SD)	172 (61.2)
Median (Min, Max)	173 (78, 291)
Missing; N (%)	1 (4.8)
90-min Glucose Post-Glucose Challenge (mg/dL)	
N	20
Mean (SD)	368 (69.9)
Median (Min, Max)	366 (279, 559)
Missing; N (%)	1 (4.8)
Reduced Awareness of Hypoglycemia ^b	
N (%)	21 (100%)
Mixed Meal Test	
Fasting C-peptide < 0.1 ng/mL; N (%) ^c	19 (90.5%)
90-min C-peptide post glucose challenge < 0.1 ng/mL; N (%) ^c	19 (90.5%)
Missing; N (%)	1 (4.8)

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

^a Baseline values were calculated based on hypoglycemic events self-reported by a patient during the screening/waiting period between enrollment and initial transplant, which varied in length by patient.

^b Reported qualitatively only at enrollment.

^c 0.1 ng/mL is the undetectable lower limit for C-peptide.

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 11.

6.1.10.1.3 Subject Disposition

Nineteen out of 21 transplanted subjects (90%) completed the study through one year after their last transplant. One subject, (b) (6) was previously enrolled in another study, UIH-001, as subject (b) (6), where he received two prior

transplants; he was re-enrolled in UIH-002 for a third transplant. The transplant received during UIH-002 is considered a first transplant for this subject. Two subjects (10%) discontinued early. The reasons for discontinuation were AE-related (due to immunosuppression) for one subject and the inability to comply with immunosuppression regimen and study visits for another subject.

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The summary of the composite primary endpoint is provided in Table 7. Eight (38.1%) subjects met the primary endpoint.

Table 7 Summary of Primary Efficacy Endpoint (all enrolled subjects)

Parameter	One Year after First Tx	One Year after Last Tx	One Year after First and Last Tx
Total Transplanted, N	21	21	21
Total Evaluable, N	21	21	21
Success (HbA1c \leq 6.5% + Free of SHE) N (%)	8 (38.1%)	11 (52.4%)	8 (38.1%)
95% C.I.	18.11%, 61.56%	29.78%, 74.29%	18.11%, 61.56%

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 12.

Reviewer Comment:

(1) In the CSR of UIH-002, the applicant only presented the results of one year after first treatment and one year after the last treatment individually. As stated in section 6.1.8 of this memo, the primary endpoint is defined as ‘... at one year after the first transplant and at one year after the last transplant,’ I think they should also look at the results based on success at both one year after the first transplant and one year after the last transplant. Therefore, I added a third column to present the results.

(2) One subject, (b) (6) was previously enrolled in UIH-001 as subject (b) (6) where he received two transplants. He received a third transplant in UIH-002. After discussing with the clinical reviewer, this subject should be excluded from this efficacy analysis. Table 8 presents the updated results after removing (b) (6) which are similar to Table 7.

Table 8 Summary of Primary Efficacy Endpoint after Removing (b) (6)

Parameter	One Year after First Tx	One Year after Last Tx	One Year after First and Last Tx
Total Transplanted, N	20	20	20
Total Evaluable, N	20	20	20
Success (HbA1c \leq 6.5% + Free of SHE) N (%)	7 (35%)	10 (50%)	7 (35%)
95% C.I.	15.39%, 59.22%	27.20%, 72.80%	15.39%, 59.22%

6.1.11.2 Analyses of Secondary Endpoints

The summary of the secondary endpoints is provided in Table 9. Twelve (57.1%) subjects were insulin independent at one year after the last transplant.

Table 9 Summary of Secondary Efficacy Endpoints

	One Year after Last Tx	Missing
Total Evaluable: N=21		
Absence of exogenous insulin	12 (57.1)	2 (9.5) ^a
Among subjects fulfilling the primary efficacy outcome at last transplant (N=11)^b		
Absence of exogenous insulin	9 (81.8)	0 (0.0)
Fasting capillary glucose in a week	4 (36.4)	7 (63.6)
Fasting plasma glucose ≤ 126 mg/dL	11 (100.0)	0 (0.0)
Post-prandial capillary glucose in a week:	3 (27.3)	8 (72.7)
C-peptide (fasting or stimulated) ≥ 0.5 ng/mL	10 (90.9)	0 (0.0)

a Patients who discontinued early.

b Percentages within this subgroup were based on this group N.

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 13.

6.1.11.3 Subpopulation Analyses

The applicant did not conduct any subgroup analyses as part of this study.

Reviewer Comment:

I conducted the following subgroup analyses for age and sex. (Because there is only one subject who is non-white, the subgroup analysis for race is not included.) The results indicate no substantial age effects on primary efficacy following islet transplantation.

Table 10 Subgroup Analyses Results of Primary Endpoint (N=21)

Parameter	One Year after First Tx	One Year after Last Tx	One Year after First and Last Tx
Success (HbA1c $\leq 6.5\%$ + Free of SHE)			
N (%)			
Age			
Age ≤ 47 Years (n=10)	4 (40%)	6 (60%)	4 (40%)
Age > 47 Years (n=11)	4 (36.36%)	5 (45.45%)	4 (36.36%)
Sex			
Male (n=6)	4 (66.67%)	4 (66.67%)	4 (66.67%)
Female (n=15)	4 (26.67%)	7 (46.67%)	4 (26.67%)

6.1.11.4 Dropouts and/or Discontinuations

As discussed in Section 6.1.10.1.3, there were two subjects who discontinued early from the study and they were treated as failure in the final analysis of the primary endpoint.

6.1.12 Safety Analyses

6.1.12.3 Deaths

There were no treatment-emergent adverse event leading to death within the specified follow-up window, but one death, (b) (6) was reported during long-term follow-up.

6.1.12.4 Nonfatal Serious Adverse Events (SAEs)

Within the first year after last transplant, 18 SAEs were observed in 11 subjects. Overall, the majority of SAEs were considered probably related to treatment, specifically immunosuppression. The most common treatment-related SAE classes were infections (5 events, including cytomegalovirus viremia and pneumonia), benign neoplasms (5 events), and cardiac disorders (4 events, including myocardial ischemia and left ventricular dysfunction).

6.1.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events, sepsis or bacteremia were not reported during the study.

6.2 Trial UIH-001

6.2.1 Objectives (Primary, Secondary, etc)

The primary objective was to demonstrate the safety of allogeneic islet transplantation in T1D patients, as performed at UI Health.

6.2.2 Design Overview

This was a phase 1/2, open-label, single-center study of allogeneic islet transplantation in subjects with brittle T1D. Ten subjects received up to three islet transplantations to assess safety and obtain initial efficacy data.

Subjects interested in participating in the study provided informed consent to answer a questionnaire regarding their medical history as part of a pre-screening process. Subjects with diabetes who were potentially eligible based on questions asked during pre-screening and continued to express interest continued with the screening process to determine eligibility. Following the screening period, subjects underwent a waiting list period (as needed), as they awaited their first transplant and had periodic reevaluations.

6.2.3 Population

Enrolling subjects had T1D mellitus for more than five years, complicated by at least one of the following situations that persisted despite intensive insulin management efforts:

1. Reduced awareness of hypoglycemia
2. Metabolic lability/instability

6.2.4 Study Treatments or Agents Mandated by the Protocol

DONISLECEL consists of isolated allogeneic human islets of Langerhans, formulated in serum-free transplant media (indicator-free CMRL containing (b) (4) HEPES and (b) (4) human albumin).

6.2.6 Sites and Centers

Only one study site, UI Health, formerly known as UIC, participated this study.

6.2.8 Endpoints and Criteria for Study Success

Primary Endpoint:

The composite primary endpoint was the proportion of subjects with an HbA1c \leq 6.5% and independence from insulin at 30 days after the last islet cell infusion. This composite primary endpoint was also evaluated at 90 days, 180 days and one year (365 days) after the last islet cell infusion.

Secondary Endpoints:

- Subjects' attaining HbA1c \leq 6.1% up to one year after last transplant
- Subjects' oral glucose tolerance test at one year after last transplant

6.2.9 Statistical Considerations & Statistical Analysis Plan

Determination of Sample Size:

No rationale for a sample size of 10 subjects was provided in the protocol.

Analysis Populations:

The following analysis sets were considered:

Intent-to-treat (ITT) Population:

The ITT population included any subjects in whom protocol-directed therapy (e.g., pretransplant immunosuppression) was initiated. All efficacy analyses were on this ITT population, regardless of whether transplantation occurred or not.

Safety Population (SAF):

The Safety population included any subject in whom protocol-directed therapy was initiated. All safety analyses were on this Safety population.

Statistical Methods:

Primary Endpoint Analysis:

An exact (Clopper-Pearson) two-sided 95% confidence interval was constructed.

Secondary Endpoint Analysis:

Number and percent of subjects attaining each outcome listed above were summarized.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Table 11 Populations Enrolled

Population	Subjects
ITT Population	10
Safety Population	10

Source: Adapted from – Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-001 Table 14 & 15.

6.2.10.1.1 Demographics

Of the 10 subjects in the Safety population, 9 (90%) were female and 10 (100%) were Caucasian. The mean (SD) age was 46.4 (10.16) years. The other baseline characteristics and demographic data at the time of first transplant for the Safety population are described in Table 12 and Table 13, respectively.

Table 12 Baseline Characteristics, Safety Population (N=10)

Parameter	Subjects N=10
Age (years)	
Mean (SD)	46.4 (10.16)
Median (Min, Max)	45 (35, 63)
Weight (kg)	
Mean (SD)	62.4 (4.47)
Median (Min, Max)	61.8 (55.6, 71.4)
Height (cm)	
Mean (SD)	166.6 (5.56)
Median (Min, Max)	166 (155.2, 175.4)
BMI (kg/m ²)	
Mean (SD)	22.5 (0.95)
Median (Min, Max)	22.5 (20.9, 24.1)

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 14.1.2.

Table 13 Demographics, Safety Population (N=10)

Parameter	Subjects N=10
Sex n (%)	
Female	9 (90%)
Male	1 (10%)
Race n (%)	
Caucasian	10 (100%)
Ethnicity n (%)	
Non-Hispanic	10 (100%)

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-002 Table 14.1.2.

6.2.10.1.3 Subject Disposition

Ten out of 10 enrolled subjects (100%) completed the study through one year after their last transplant. No subjects discontinued early.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

The summary of the composite primary endpoints is provided in Table 14. Three (30%) subjects were determined as successful at one year after the last transplant.

Table 14 Summary of Primary Efficacy Endpoints (ITT=10)

Parameter	30 Days after Last Tx	90 Days after Last Tx	180 Days after Last Tx	1 Year after Last Tx
Success (HbA1c \leq 6.5% + Insulin Independence) N (%)	1 (10%)	3 (30%)	2 (20%)	3 (30%)
95% C.I. ^a				6.7%, 65.3%
Partial Success (Reduced Insulin, HbA1c, & HYPO Score) N (%)	0	5 (50%)	6 (60%)	6 (60%)
Failure, N (%)	9 (90%)	2 (20%)	2 (20%)	1 (10%)

^a 95% Confidence Interval only estimated for Full Success at one year (Day 365).

Source: Original BLA 125734/0; Module 5.3.5.2 CSR Study UIH-001 Table 15.

6.2.11.3 Subpopulation Analyses

The applicant did not conduct any subgroup analyses as part of this study.

Reviewer Comment:

I performed the following subgroup analyses. (Since there is only one subject who is male and all subjects are Caucasian, the subgroup analysis is only performed for age group.) All the successes are in the younger group.

Table 15 Subgroup Analysis for Primary Efficacy Endpoint (ITT=10)

Parameter	30 Days after Last Tx	90 Days after Last Tx	180 Days after Last Tx	1 Year after Last Tx
Success (HbA1c \leq 6.5% + Insulin Independence) N (%)				
Age < 45 Years (n=5)	1 (20%)	3 (60%)	2 (40%)	3 (60%)
Age \geq 45 Years (n=5)	0	0	0	0

6.2.11.5 Exploratory and Post Hoc Analyses

I re-analyzed the data using the endpoint of HbA1c \leq 6.5% and free of SHE at one year after the last transplant which is also the primary endpoint for the integrated analysis in Section 7. Nine (90%) subjects met the endpoint.

6.2.12 Safety Analyses

6.2.12.3 Deaths

No deaths were reported in subjects who participated in this clinical study.

6.2.12.4 Nonfatal Serious Adverse Events (SAEs)

Nineteen SAEs occurred through one year after the last transplant in five subjects, including three subjects receiving a single transplant and two subjects receiving three transplants.

6.2.12.5 Adverse Events of Special Interest (AESI)

Thromboembolic events, sepsis or bacteremia were not reported during the study.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

For the treatment of brittle Type 1 diabetes (labile diabetes) in adults whose symptoms are not well controlled despite intensive insulin therapy.

7.1.1 Methods of Integration

Data from studies UIH-001 and UIH-002 were combined for the integrated analysis of efficacy. Please refer to Section 6 for the details of these two studies. No other inclusion or exclusion criteria were applied for the integrated analysis.

Reviewer Comment:

One subject previously enrolled in UIH-001 (subject ID (b) (6)) was reenrolled in UIH-002 (subject ID (b) (6)) and was counted as a single subject in this integrated analysis.

The primary endpoint was $\text{HbA1c} \leq 6.5\%$ and free of SHE at one year after the last transplant and the secondary endpoint was insulin independence at one year after the last transplant.

Reviewer Comment:

Both endpoints were proposed by the applicant and the clinical reviewer presented the results in the AC meeting. There was no prespecified hypothesis testing or performance goal for either endpoint.

7.1.2 Demographics and Baseline Characteristics

Tables 16 and 17 present the baseline characteristics and demographics of the integrated data. The mean (SD) age was 46.8 (11.6) years old. Twenty-four (80%) subjects were female and all subjects were Caucasian.

Table 16 Baseline Characteristics, Safety Population (N=30)

Parameter	Subjects N=30
Age (years)	
Mean (SD)	46.8 (11.6)
Median (Min, Max)	46.5 (21, 67)
Weight (kg)	
Mean (SD)	63.8 (7.8)
Median (Min, Max)	62.4 (52.5, 83.4)
Height (cm)	
Mean (SD)	166.6 (6.9)
Median (Min, Max)	166.0 (150.9, 181.9)
BMI (kg/m ²)	
Mean (SD)	23.1 (1.8)
Median (Min, Max)	23.0 (20.2, 27.3)

Source: Original BLA 125734/0; Module 2.7.3 Summary of Clinical Efficacy Table 13.

Table 17 Demographics, Safety Population (N=30)

Parameter	Subjects N=30
Sex n (%)	
Female	24 (80%)
Male	6 (20%)
Race n (%)	
Caucasian	30 (100%) ^a
Black	0
Asian	0
Native American	1 (3.3%) ^a
Other	0
Ethnicity n (%)	
Hispanic	1 (3.3%)
Non-Hispanic	29 (97%)

^a One patient in UIH-002 identified as both Caucasian and Native American.

Source: Original BLA 125734/0; Module 2.7.3 Summary of Clinical Efficacy Table 13.

7.1.4 Analysis of Primary Endpoint(s)

Table 18 presents the results of the integrated efficacy analysis. Nineteen (63.3%) subjects met the primary endpoint. The 95% CI was (43.9%, 80.1%).

Table 18 Analysis Results of the Integrated Data (ITT=30)

Parameter	One Year after Last Tx
Success (HbA1c ≤ 6.5% + Free of SHE) N (%)	19 (63.3%)
95% C.I.	43.9%, 80.1%
Failure	
Total Deemed Failure; N (%)	11 (36.7%)
HbA1c > 6.5%; N (%)	5 (16.7%)
Any SHE; N (%)	7 (23.3%)
Missing	
N (%)	1 (3.3%)

Source: Original BLA 125734/0; Module 2.7.3 Summary of Clinical Efficacy Table 15.

7.1.5 Analysis of Secondary Endpoints

Out of the 30 subjects in the integrated efficacy analysis, 20 (66.7%, 95% CI: 47.2%, 82.7%) subjects were insulin independent at one year after the last transplant. Sixteen of these 20 subjects were also a success for the primary endpoint.

7.1.7 Subpopulations

Because the subjects were all identified as Caucasian, a subgroup analysis by race was not performed. The analyses by age and sex are provided in Tables 19 and 20. The results indicate no substantial age or sex effects on primary efficacy following islet transplantation. The median of the age is 46.5, so the cut-point of age analysis was 47 years-old.

Table 19 Analysis Results of the Integrated Data by Age (ITT=30)

Parameter	Age ≤ 47 Years N=18	Age > 47 Years N=12
Success (HbA1c ≤ 6.5% + Free of SHE) N (%)	12 (66.7%)	7 (58.3%)
95% C.I.	40.99%, 86.66%	27.67%, 84.83%
Failure		
Total Deemed Failure; N (%)	6 (33.3%)	5 (41.7%)
HbA1c > 6.5%; N (%)	4 (22.2%)	1 (8.3%)
Any SHE; N (%)	3 (16.7%)	4 (33.3%)
Missing		
N (%)	1 (5.6%)	0

Source: Original BLA 125734/0; Module 2.7.3 Summary of Clinical Efficacy Table 18.

Table 20 Analysis Results of the Integrated Data by Sex (ITT=30)

Parameter	Female N=24	Male N=6
Success (HbA1c ≤ 6.5% + Free of SHE) N (%)	15 (62.5%)	4 (66.7%)
95% C.I.	40.59%, 81.20%	22.28%, 95.67%
Failure		
Total Deemed Failure; N (%)	9 (37.5%)	2 (33.3%)
HbA1c > 6.5%; N (%)	4 (16.7%)	1 (16.7%)
Any SHE; N (%)	6 (25.0%)	1 (16.7%)
Missing		
N (%)	0	1 (16.7%)

Source: Original BLA 125734/0; Module 2.7.3 Summary of Clinical Efficacy Table 21.

7.1.11 Efficacy Conclusions

After combining the data from the two clinical studies, 30 treated subjects were evaluated and 19 (63.3%) of them were determined as a success: HbA1c ≤ 6.5% and free of SHE at one year after the last transplant. The Clopper-Pearson two-sided 95% CI was (43.9%, 80.1%).

Because success criteria were not defined for any endpoints, there is no inferential statistical procedure to apply to the efficacy data. This review will evaluate the data on a descriptive basis; the sufficiency of these data to provide substantial evidence of effectiveness is deferred to the clinical review team.

10. CONCLUSIONS

10.1 Statistical Issues and Collective Evidence

This BLA submission includes the final analysis of two clinical studies: Study UIH-002 (Phase 3) and Study UIH-001 (Phase 1/2). Both studies were nonrandomized, open-label, single-center studies in which one to three allogeneic pancreatic islet transplants were administered to subjects with brittle T1D. Because both studies are single-center trial at the same site, the results may not be generalizable.

Twenty-one subjects were enrolled in UIH-002 and the composite primary endpoint was the proportion of successful subjects, defined as hemoglobin A1c (HbA1c) $\leq 6.5\%$ and free of SHEs at one year after the first transplant and at one year after the last transplant. Eight (38.1%) subjects met the primary endpoint (95% CI: 18.1%, 61.6%). One subject (b) (6) was previously enrolled in study UIH-001. After discussing with the clinical reviewer, this subject should be removed from the analysis of UIH-002. After removing the subject, seven (35%) of the 20 subjects met the primary endpoint (95% CI: 15.4%, 59.2%). The sample size justification for study UIH-002 was based on a test of the null hypothesis that the success rate is less than 50%. However, it is not clear that the sponsor ever intended to perform this hypothesis test, and there was no agreement with FDA regarding a performance goal for the primary endpoint that would establish substantial evidence of effectiveness.

Ten subjects were in enrolled in UIH-001 and the primary endpoint was insulin independence and HbA1c $\leq 6.5\%$ at one year after the last transplant. Three (30%) subjects met the primary endpoint (95% CI: 6.7%, 65.3%).

After combining these two clinical studies, the integrated dataset consisting of 30 treated unique subjects was evaluated. The primary endpoint for the integrated analysis was HbA1c $\leq 6.5\%$ and free of SHE at one year after the last transplant. Nineteen (63.3%) of the 30 subjects met the primary endpoint (95% CI: 43.9%, 80.1%). The secondary endpoint was the proportion of subjects who were insulin independent at one year after the last transplant. Twenty (66.7%) of the 30 subjects met the secondary endpoint (95% CI: 47.2%, 82.7%); Sixteen of these 20 subjects also met the primary endpoint. There was no prespecified performance goal for the primary endpoint of this pooled analysis.

The safety evaluation revealed that no subject reported inhibitory effects in the studies. One death was reported during long-term follow-up in study UIH-002.

10.2 Conclusions and Recommendations

In integrated analysis, the proportion of subjects who had an HbA1c $\leq 6.5\%$ and were free of SHE at one year after the last transplant was 63% (19/30 subjects). 66.7% (20/30) of subjects were insulin independent at one year after the last transplant. However, because success criteria were not defined for any endpoints, there is no inferential statistical procedure to apply to the efficacy data. The sufficiency of these data to provide substantial evidence of effectiveness is deferred to the clinical review team.