



Our STN: BL 125734/0

**MID-CYCLE COMMUNICATION
SUMMARY**

December 11, 2020

CellTrans, Inc.
Attention: Dr. Jose Oberholzer
2242 W. Harrison St., Suite (b) (4)
Chicago, IL 60612

Dear Dr. Oberholzer:

Attached is a copy of the summary of your November 12, 2020, Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN BL 125734/0 in your future submissions related to the subject product.

If you have any questions, please contact Edward Thompson at edward.thompson@fda.hhs.gov or by phone at (240) 402-8443.

Sincerely,

Raj K. Puri, MD, PhD
Director
Division of Cellular and Gene Therapies
Office of Tissues and Advanced Therapies
Center for Biologics Evaluation and Research

Mid-Cycle Communication Teleconference Summary

Application type and number: BLA 125734/0
Product name: Donislecel (Purified Allogeneic Islets of Langerhans for Transplant)
Proposed Indication: to treat Brittle type I diabetes mellitus
Applicant: CellTrans Inc.
Meeting date & time: November 12, 2020 at 5 PM [Eastern Time]
Committee Chair: Sukhanya Jayachandra, PhD
RPM: Edward Thompson


FDA Attendees:

Rachael Anatol, PhD, CBER/OTAT
Patricia Beaston, MD, PhD, CBER/OTAT/DCEPT
Kimberly Benton, PhD, CBER/OTAT
Wilson Bryan, MD, CBER/OTAT
Melanie Eacho, PhD, CBER/OTAT/DCGT
Sukhanya Jayachandra, PhD, CBER/OTAT/DCGT
Elizabeth Hart, MD, CBER/OTAT/DCEPT
Ilan Irony, MD, CBER/OTAT/DCEPT
Wei Liang, PhD, CBER/OTAT/DCEPT
Anthony Lorenzo, CBER/OCBQ/DMPQ
Timothy Martin, PhD, OCBG/DMPQ
Randa Melhem, PhD, CBER/OCBQ/DMPQ
Steven Oh, PhD, CBER/OTAT/DCGT
Raj Puri, MD, PhD, CBER/OTAT/DCGT
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT
Laura Ricles, PhD, CBER/OTAT/DCGT
Irina Tiper, PhD, CBER/OTAT/DCGT
Lori Tull, CBER/OTAT/DRPM
Edward Thompson, CBER/OTAT/DRPM
Zehra Tosun, PhD, CBER/OTAT/DCGT

CellTrans Inc. Attendees

José Oberholzer, MD, MHCM, FACS, CellTrans, Inc.
James McGarrigle, PhD, CellTrans, Inc.
Giovanna La Monica, PhD, CellTrans, Inc.
Yi Li, MS, CellTrans, Inc.
Jennifer Cook, CPA, CellTrans, Inc.

(b) (4)



Agenda:

Provide discipline review updates including any issues of concern that necessitates a discussion.

Discussion Summary:

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

- a. Chemistry, Manufacturing and Controls (CMC)

- i. Raw Materials and Reagents: There is a lack of independent identity verification of all critical reagents used in the manufacturing process, which is a regulatory requirement per 21 CFR 211.84.

Meeting discussion:

The applicant referred to the pre-BLA meeting (dated September 2, 2016) on the raw materials and reagents testing and noted that they cannot perform this assessment as it is not feasible. FDA noted that independent identity verification of all critical reagents is an important aspect that needs to be addressed in the BLA and an informal meeting will be scheduled with the applicant to further discuss.

- ii. Potency Assay: The sampling for the potency assay is only performed on pre-culture islet- fraction. As per the submission, once the COBE fractions are combined into top, middle, and bottom pools, each pool is suspended into culture media and only top pool is sampled for potency (3.2.S.2. Manufacture page 20). You are not sampling all fractions at pre-culture stage and are not performing potency on the final product, making it difficult to determine the potency of the final drug product. Note: Based on islet numbers, the final drug product can be formulated from all three pools. We plan to send an Information Request (IR) on this issue.

Meeting discussion: The applicant stated that the middle and bottom fractions each contain less than (b) (4) of islets cells, and are therefore, unreliable for their potency assay. The percentage from the top layer is most meaningful for potency, which on average makes up (b) (4) of the final product. The applicant noted that additional testing would not be feasible for the completed studies for the BLA. FDA noted that a detailed information request will be sent to the applicant for clarification.

- iii. Stability studies: As part of stability and compatibility studies, you evaluated the stability of final formulated drug product in the final container closure (Miltenyi cryobags) for up to 6 hours, then passed the

stored islets through (b) (4) representative delivery devices by gravity, and collected the islets for testing. The validation results showed a (b) (4) (b) (4) islet yield loss. Given the Islet purity specification is set at >30% and there may be up to a (b) (4) loss of islets, the therapeutic infusion dose consistency remains unclear.

Meeting discussion: The applicant stated that loss of purity to below 30% is theoretically possible but have not occurred in their studies. FDA noted that an information request will be sent.

- iv. Delivery Device: We plan to send an IR regarding how the delivery devices used in the clinical study and bench testing (e.g., compatibility testing studies) supports your current labeling strategy.

Meeting discussion: Applicant appreciated the notification.

b. Clinical

- i. Primary efficacy analysis: While your October 19, 2020 response to our October 5, 2020 request for additional information remains under review, we are concerned that the provided data do not allow a meaningful analysis of your primary efficacy endpoint, namely the proportion of subjects who achieve a composite of HbA1c \leq 6.5% and freedom from severe hypoglycemic events (SHE) at 1-year after the last transplant. In the combined studies UIH-001 and UIH-002, 15/30 (50%) of subjects did not have baseline SHE, and review of narratives suggest that some subjects with reported SHE had hypoglycemia episodes rather than SHE. In Study UIH-002, HbA1c at the time of first transplant was <6.5% in 3/21 (14%) subjects and <7% in 9/21 (43%) of subjects. In Study UH-001, 1 subject (10%) did not have a baseline HbA1c and 2/10 (20%) had HbA1c <6.5 and 5/10 (50%) had HbA1c <7%. Data interpretability of the primary endpoint is limited since subjects have met or nearly met the primary endpoint prior to administration of the investigational treatment.

Meeting discussion: Applicant stated the response to the information request should address these issues. FDA stated this information is still under review.

- ii. Secondary efficacy analysis: The duration of insulin independence and changes in insulin use are not well characterized at this time. Information request to support additional analysis will be forthcoming.

Meeting discussion: Applicant stated that in response to the October information request, tables were provided that should address this

issue. FDA stated that the information is still under review, but additional information may be requested.

- iii. Dosing: Many subjects received multiple islet cell transplants. The specific criteria for additional islet cell transplant require clarification. An information request is forthcoming.

Meeting discussion: FDA will send an information request . Applicant acknowledged.

2. Information regarding major safety concerns.

There are no major safety concerns identified at this time.

Meeting discussion: No further discussion.

3. Preliminary Review Committee thinking regarding risk management.

Routine pharmacovigilance is recommended.

Meeting discussion: No further discussion.

4. Any information requests sent and responses not received.

Not at this time

Meeting discussion: No further discussion.

5. Any new information requests to be communicated.

a. CMC plans to request information on the following topics:

- i. Sampling timepoints for the potency (Glucose stimulation index (GSI) assay) for drug substance and drug product.
- ii. Validation data to ensure that the potency (GSI assay) acceptance criteria pre-culture and after final formulation are the same.
- iii. Clarification on manufacturing process step times.
- iv. Details of how the post-culture islets are harvested from flasks and undergo final formulation.
- v. Delivery devices proposed for use in the labelling and those used in the clinical and compatibility studies.

- vi. Islet loss and the effect on the therapeutic dose.

Meeting discussion: FDA will be sending information requests on above with a potency assay clarification as noted in 1.a.ii. Applicant acknowledged.

- b. DMPQ plans to request information regarding the following topics:

- i. The qualification and controls of the decontamination process of the incoming pancreas.
- ii. Aseptic Process Simulation studies to include simulations of non-routine interventions with justification.
- iii. Manual equipment cleaning processes to clarify periodic verification; and studies to evaluate cleaning effectiveness over time on the (b) (4) (b) (4) used for the digestion process step.
- iv. Critical equipment qualification reports for the Ricordi Chamber and associated components; BSCs; COBE cell processor; and tube sealer.
- v. HVAC system equipment qualification and preventive maintenance; integration with the University of Illinois HVAC; and change control procedures.

Meeting discussion: FDA will be sending information requests. Applicant acknowledged.

- 6. Proposed date(s) for the Late-Cycle meeting (LCM).

- a. The LCM between you and the Review Committee is currently scheduled for April 1, 2021 from 3 pm to 5 pm, Eastern Time.
- b. We intend to send the LCM meeting materials to you approximately 20 days in advance of the LCM on March 12, 2021.

Meeting discussion: No further discussion.

- 7. Updates regarding plans for the AC meeting.

We are currently planning to hold an advisory committee meeting to discuss this application. At this time, we are still assessing and expect to notify you of the date for this meeting.

Meeting discussion: No further discussion.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

Pending proposals for post marketing commitments/requirements by July 19, 2021 and proposal with your prescribing information label by July 19, 2021.

Meeting discussion: No further discussion.

End